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ORIGINAL PAPER

A meta-analysis of the association between induced abortion and breast cancer risk among Chinese females

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Abstract

Objective To evaluate the association between induced abortion (IA) and breast cancer risk among Chinese females.

Methods We searched three English databases (PubMed, ScienceDirect, and Wiley) and three Chinese databases (*CNKI*, *WanFang*, and *VIP*) for studies up to December 2012, supplemented by manual searches. Two reviewers independently conducted the literature searching, study selection, and data extraction and quality assessment of included studies. Random effects models were used to estimate the summary odds ratios (ORs) and the 95 % confidence intervals (CIs).

Results A total of 36 articles (two cohort studies and 34 case–control studies) covering 14 provinces in China were included in this review. Compared to people without any history of IA, an increased risk of breast cancer was observed among females who had at least one IA (OR = 1.44, 95 % CI 1.29–1.59, $I^2 = 82.6$ %, $p < 0.001$, $n = 34$). No significant publication bias was found among the included studies (Egger test, $p = 0.176$). The risk increased to 1.76 (95 % CI 1.39–2.22) and 1.89 (95 % CI 1.40–2.55) for people who had at least two IAs and at least three IAs, respectively. Subgroup analyses showed similar results to the primary results. Meta-regression analysis of the included studies found that the association between IA and breast cancer risk attenuated with increasing percent of IA in the control group ($\beta = -0.022$, $p < 0.001$).

Conclusion IA is significantly associated with an increased risk of breast cancer among Chinese females, and the risk of breast cancer increases as the number of IA increases. If IA were to be confirmed as a risk factor for breast cancer, high rates of IA in China may contribute to increasing breast cancer rates.

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Introduction

Chinese females historically had a lower risk of breast cancer compared to their counterparts in the USA and other Western countries. However, the incidence of breast cancer in China had increased at an alarming rate over the past two decades (from 36.17/100,000 to 51.24/100,000 in urban areas and from 10.39/100,000 to 19.61/100,000 in rural areas) [1]. The marked change in breast cancer incidence was parallelled to the one-child-per-family policy, which became legal in China since the early 1980s [2]. Averagely 8.2 million medical terminations of pregnancy were reported yearly (14.4 million in 1983 and 6.4 million in 2010) [3]. It is estimated that one in four Chinese females have at least one induced abortion (IA) during their reproductive lives, and approximately 40 pregnancies are aborted for every 100 living births [2].

Experimental data suggested that there was a plausible association between IA and breast cancer [4–6]. During the first trimester of pregnancy, hormonal changes propel newly produced breast cells through a state of differentiation, a natural maturing process which greatly reduces the risk of breast cancer in the future. An interruption of this process by abortion will arrest this process before differentiation occurs, greatly raising the future risk of breast cancer in the future.

Recent studies on the association between IA and breast cancer risk got conflicting results. The first systematic review by Brind et al. [7] reported a 30 % increased risk of breast cancer for any IA exposure. However, another systematic review of 53 studies concluded that IAs did not increase women's risk of developing breast cancer [8]. In China, two studies conducted in Shanghai found no association between IA and breast cancer risk [9, 10], but another recent study from Jiangsu reported a very strong association with both the premenopausal and the postmenopausal women [11].

Many concerns have been raised because of the difficulty of drawing definite conclusions on IA [12, 13]. For example, biases, particularly those related to the case–control design and inadequate choices of the reference group [9, 14], can create spurious associations or obscure relations.

As one of the countries with the highest prevalence of IA, in China, it is particularly important to clarify the association between IA and breast cancer risk. The lack of social stigma associated with IA in China may limit the amount of underreporting and present a more accurate picture of this association [10]. Although the two reviews mentioned above [7, 8] had focused on the association between IA and breast cancer, they did not include several important studies, such as the study from Jiangsu [11]. Omission of these important studies undoubtedly biased the summary results. Moreover, neither of the two reviews explored the effect of IA on breast cancer in different subgroups, for example, the demographic characteristics of the participants, the quality assessment of the included studies, and the percent of IA in the control group, etc.

In order to update the current evidence on IA and its effect on breast cancer among Chinese females, we performed this systematic review and meta-analysis to help resolve these uncertainties and further define the effect of IA on breast cancer.

Methods

This systematic review was conducted according to the MOOSE guideline [15].

Eligibility criteria

Cohort studies and case–control studies investigating the associations between IA and breast cancer risk among Chinese females were initially reviewed. Studies that reported risk estimates [odds ratios (ORs) or relative risks (RRs)] and 95 % confidence intervals (CIs) or cross-table data were included. Studies with benign breast disease selected as controls, studies focused on spontaneous abortion, and studies with incomplete data of interest were excluded.

Data sources and searching strategy

The published literatures were independently searched by two reviewers in three English databases (PubMed, ScienceDirect, and Wiley) and three Chinese databases (*CNKI, WanFang,* and *VIP*) up to December 2012, complemented by manual searches. Authors of potential literatures were contacted when more information or clarification was needed. Three groups of keywords were used in the Chinese searching strategy: (1) case–control study, cohort study, and prospective study; (2) breast cancer, breast carcinoma, breast tumor, breast neoplasm, mammary cancer, mammary carcinoma, mammary tumor, and mammary neoplasm; and (3) risk factor, etiology, abortion, polymorphism and susceptibility. Other keywords were also used in the English searching strategy: Chinese, China, and the Han population. In the PubMed database, all the keywords were used with medical subject headings (Mesh).

Assessment of the methodological quality of included studies

The methodological quality of included studies was independently assessed by two reviewers according to Newcastle–Ottawa Scale (NOS) based on three broad perspectives [16]: (1) the selection of the study groups; (2) the comparability of the groups; and (3) the ascertainment of exposure or outcome of interest, with scores ranging from 0 to 9. To minimize the bias due to the judgment of NOS, any disagreement in this assessment was adjudicated by a third reviewer.

Study selection and data extraction

Two review authors, working independently and in parallel, scanned the abstracts for information concerning the association between IA and breast cancer and obtained the

Table 1 Characteristics of included studies

References	Region of China	Type of study	Number of case	Number of control	NOS score*
Sanderson et al. [10]	Shanghai	Case–control	1385	1,459	A
Ye et al. [9]	Shanghai	Cohort	652	694	A
Yuan et al. [57]	Shanghai	Case–control	534	534	B
Xu et al. [56]	Multi-center	Case–control	416	1,156	B
Gao [55]	Jiangsu	Case–control	505	524	B
Bai [54]	Gansu	Case–control	425	1,108	B
Li et al. [53]	Liaoning	Case–control	620	620	B
Liu et al. [52]	Jiangsu	Case–control	515	515	B
Li and Wang [51]	Shandong	Case–control	102	102	B
Zhang et al. [50]	Heilongjiang	Case–control	232	452	C
Li et al. [49]	Shanghai	Case–control	448	448	B
Li [48]	Shandong	Case–control	154	308	A
Zhai [47]	Jiangsu	Case–control	488	482	B
Li et al. [46]	Liaoning	Case–control	449	363	B
Lin and Yu [45]	Zhejiang	Case–control	237	237	B
Zeng et al. [44]	Shenzhen	Case–control	232	232	B
Shi et al. [43]	Jiangsu	Case–control	223	223	B
Shi et al. [42]	Fujian	Case–control	145	145	B
Huang et al. [41]	Guangdong	Case–control	133	133	B
Pang et al. [40]	Sichuan	Case–control	119	119	B
Yu et al. [39]	Shandong	Case–control	103	309	B
Wang et al. [38]	Gansu	Case–control	102	102	B
Jian et al. [37]	Heilongjiang	Case–control	232	452	C
Li et al. [36]	Multi-center	Case–control	3332	3,332	B
Rong et al. [35]	Hebei	Case–control	150	150	B
Zhu et al. [34]	Tianjin	Case–control	1,523	1,599	B
Li et al. [33]	Sichuan	Case–control	104	154	B
Wang et al. [32]	Sichuan	Case–control	400	400	A
Qiu et al. [31]	Hubei	Case–control	500	500	A
Xing et al. [30]	Liaoning	Case–control	1,417	1,587	B
Ji [29]	Jiangsu	Case–control	206	214	B
Ren [28]	Liaoning	Case–control	200	200	B
Wang [27]	Zhejiang	Cohort	84	269	A
Cao [26]	Tianjin	Case–control	836	946	B
Jiang et al. [23]	Jiangsu	Case–control	669	682	A
Zhang [25]	Shanghai	Case–control	1,495	1,573	A

* A, NOS score = 8–9; B, NOS score = 5–7; C, NOS score ≤ 4

full texts of the studies when necessary. After obtaining the full texts, the review authors independently assessed the eligibility of the studies. In the case of multiple publications or overlapping data sets, only studies with the largest or the most updated results were included.

Information on the baseline characteristics (type of study, year of publication, first author, regions of China, sample size in each arm, and source of population), the methodological quality of included studies, and the risk estimates (ORs or RRs) and their 95 % CIs or cross-table data were collected. ORs calculated from both the univariate and multivariate logistic regression models were used in the final analysis.

Any disagreement in study selection and data collection was adjudicated by a third reviewer.

Data analysis

The I^2 statistic was calculated to determine the size of heterogeneity [17]. The summary ORs and 95 % CIs were calculated using a random effects model based on cross-table data and ORs, weighting with the inverse of the variance. Pre-specified subgroup meta-analyses were used to explore potential sources of heterogeneity according to type of study, NOS scores, regions of China, source of study population (population-based or hospital-based), sample size (≥800 vs. <800), year of publication (≥2007 vs. <2007). Potential publication bias was assessed with the Egger tests and represented graphically with funnel plots of the OR versus its standard error [18, 19].

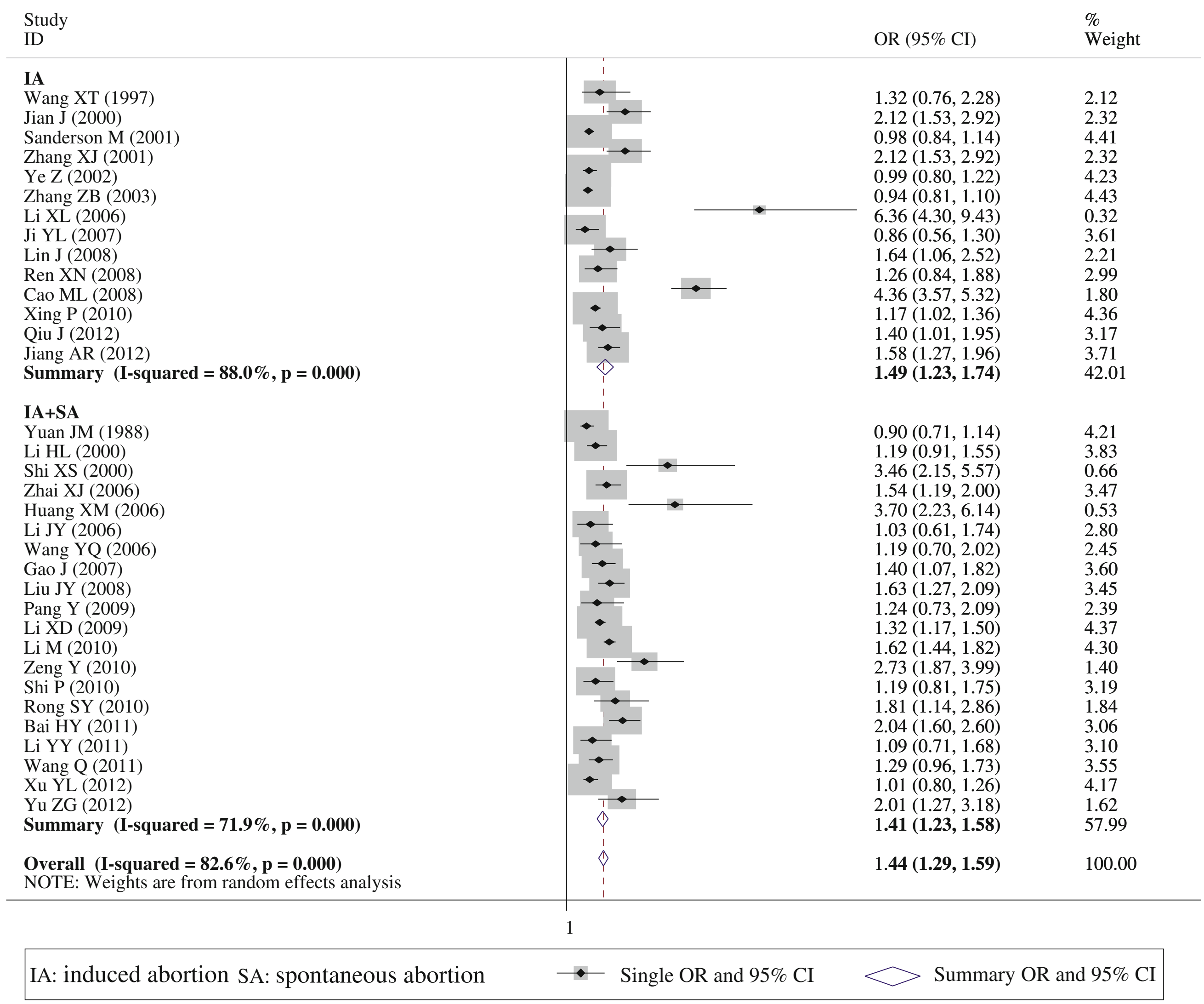


Fig. 1 Forest plot of studies on the association between breast cancer and at least one IA based on cross-table data in combination with crude ORs

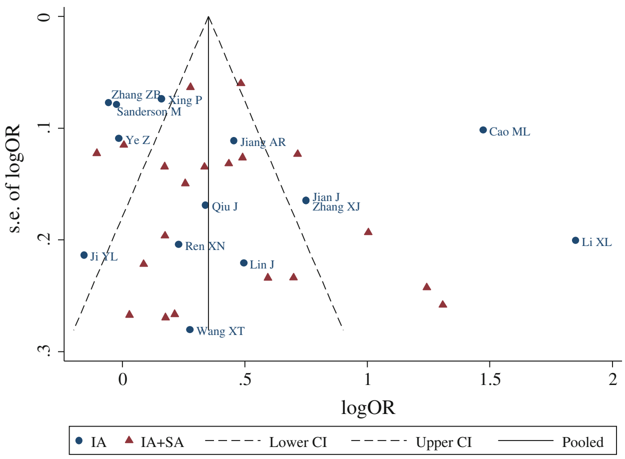


Fig. 2 Funnel plot of all studies on the association between breast cancer and IA (≥1 time) based on cross-table data in combination with ORs

Sensitivity analysis on studies reporting multivariate adjusted ORs was conducted to explore the effect of the potential confounding factors. Sensitivity analysis was also conducted to test whether the primary results were affected by the studies which fell outside of the funnel plot. Additional analysis was conducted to explore the association between breast cancer risk and two or more IAs, and three or more IAs.

Several studies did not separate IA from total abortion. The reported prevalence of spontaneous abortion (SA) ranged from 4.26 to 5.27 % in China [21, 22]. However, most of the prevalence of abortion in the control groups of the included studies was >50 %, suggesting that abortions tended to be primarily IA rather than SA. Therefore, we included these studies in this meta-analysis for a supplementary analysis.

Last, in order to explore whether inadequate choice of referent group could bias the real association between IA and breast cancer risk, meta-regression was used to explore whether the magnitude of the association between IA and breast cancer attenuated as the percent of IA in the reference group increased [20].

All the statistical analyses were performed with STATA 12.0.

Results

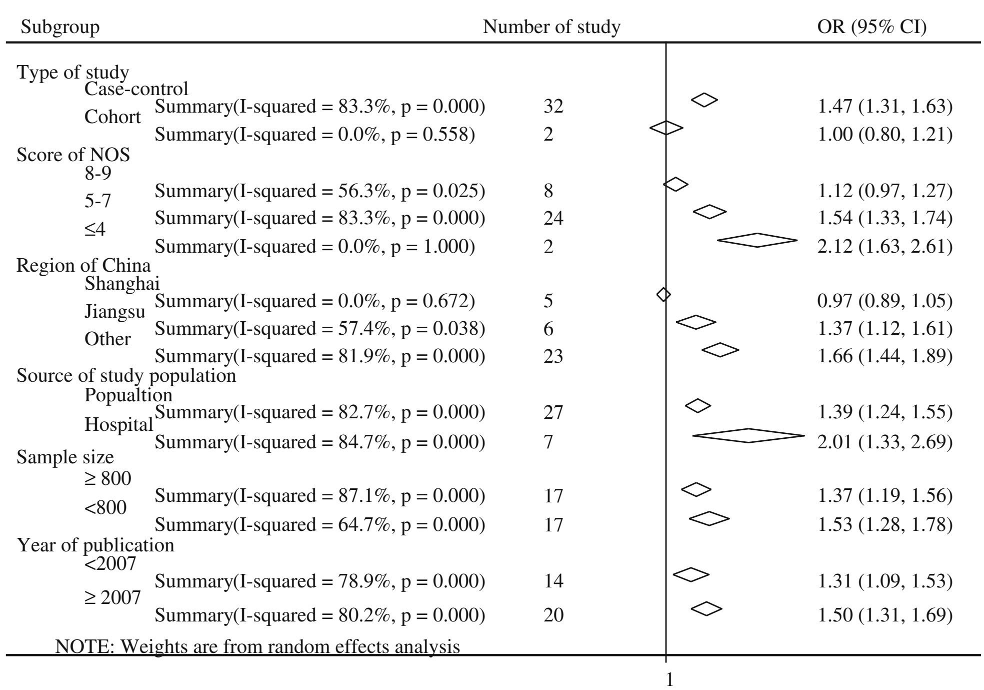
Study selection

A total of 38 articles were initially identified as case–control studies or cohort studies on the risk factors of breast cancer among Chinese females. After discarding two studies of duplicate publication [23, 24], 36 articles (two cohort studies [9, 27] and 34 case–control studies) were finally included in this systematic review [9–11, 25–57], covering 14 provinces of China (Table 1).

Syntheses of results

Based on cross-table data and crude ORs (95 % CIs), the summary ORs of IA alone and IA together with SA were 1.49 (95 % CI 1.23–1.74, $I^2 = 88.0$ %, $p < 0.001$, $n = 14$) and 1.41 (95 % CI 1.23–1.58, $I^2 = 71.9$ %, $p < 0.001$,

Fig. 3 Subgroup analysis of associations between IA and breast cancer



$n = 20$), respectively (Fig. 1). The summary OR based on all studies was 1.44 (95 % CI 1.29–1.59, $I^2 = 82.6$ %, $p < 0.001$, $n = 34$) (Fig. 1). Egger test based on all studies got a p value of 0.176, together with the funnel plot showed in Fig. 2; no evidence of publication bias was found among the included studies.

Subgroup analyses

As shown in Fig. 3, most of the results from the subgroup analysis showed an increased risk of breast cancer, with the ORs ranging from 1.31 to 2.12. However, no significant associations between IA and breast cancer were found in cohort studies, studies with a NOS score of 8–9, or studies conducted in Shanghai.

Sensitivity analysis

Among the 36 studies included, 13 had reported adjusted ORs. Sensitivity analysis based on these 13 adjusted ORs had got a summary OR of 1.59 (95 % CI 1.28–1.90) (**Supplement 1**). Sensitivity analysis excluding the 16 studies fell outside of the funnel plot in the primary analysis got a summary OR of 1.35 (95 % CI 1.26–1.45), with no heterogeneity ($I^2 = 0$) (**Supplement 2**) and no publication bias (Egger test, p value = 0.986) among the remaining studies (**Supplement 3**).

Additional analysis

For women who had at least two IAs, additional analysis showed that the risk of breast cancer increased to 1.76 (95 % CI 1.39–2.22, $I^2 = 89.1$ %, $p < 0.001$, $n = 19$) when including studies of both IA and SA. (Fig. 4). For women who had at least three IAs, the risk of breast cancer increased to 1.89 (95 % CI 1.40–2.55, $I^2 = 82.9$ %, $p < 0.001$, $n = 18$) when including studies of both IA and SA (Fig. 5). Meta-regression showed that lower percent of IA in the control group was associated with higher risk of breast cancer ($\beta = -0.022$, $p < 0.001$) (Fig. 6).

Discussion

Overall, this systematic review of 36 studies with different designs and conducted across a wide range of regions in China revealed that IA was significantly associated with an increased risk of breast cancer among Chinese females.

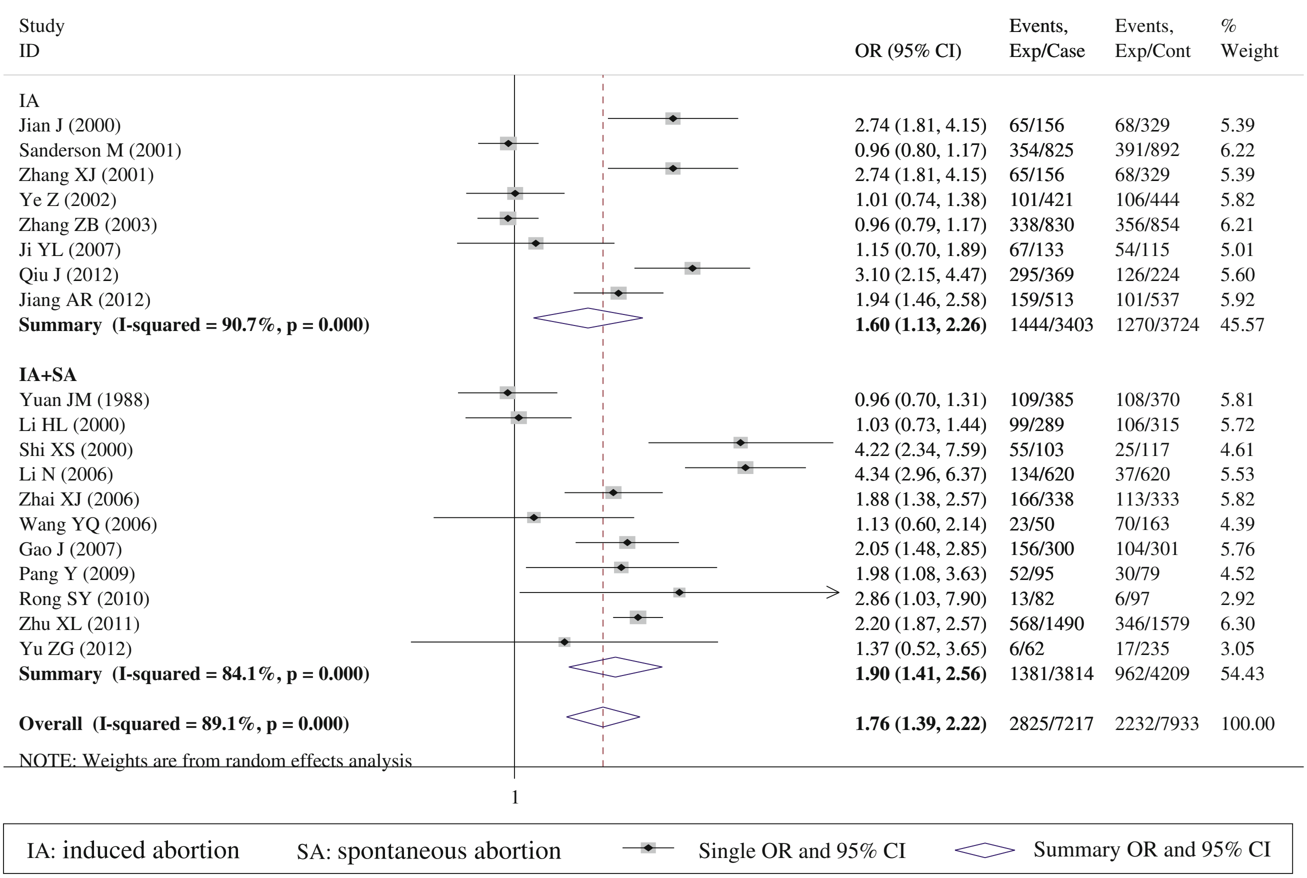


Fig. 4 Forest plot of studies on the association between breast cancer and at least two IAs

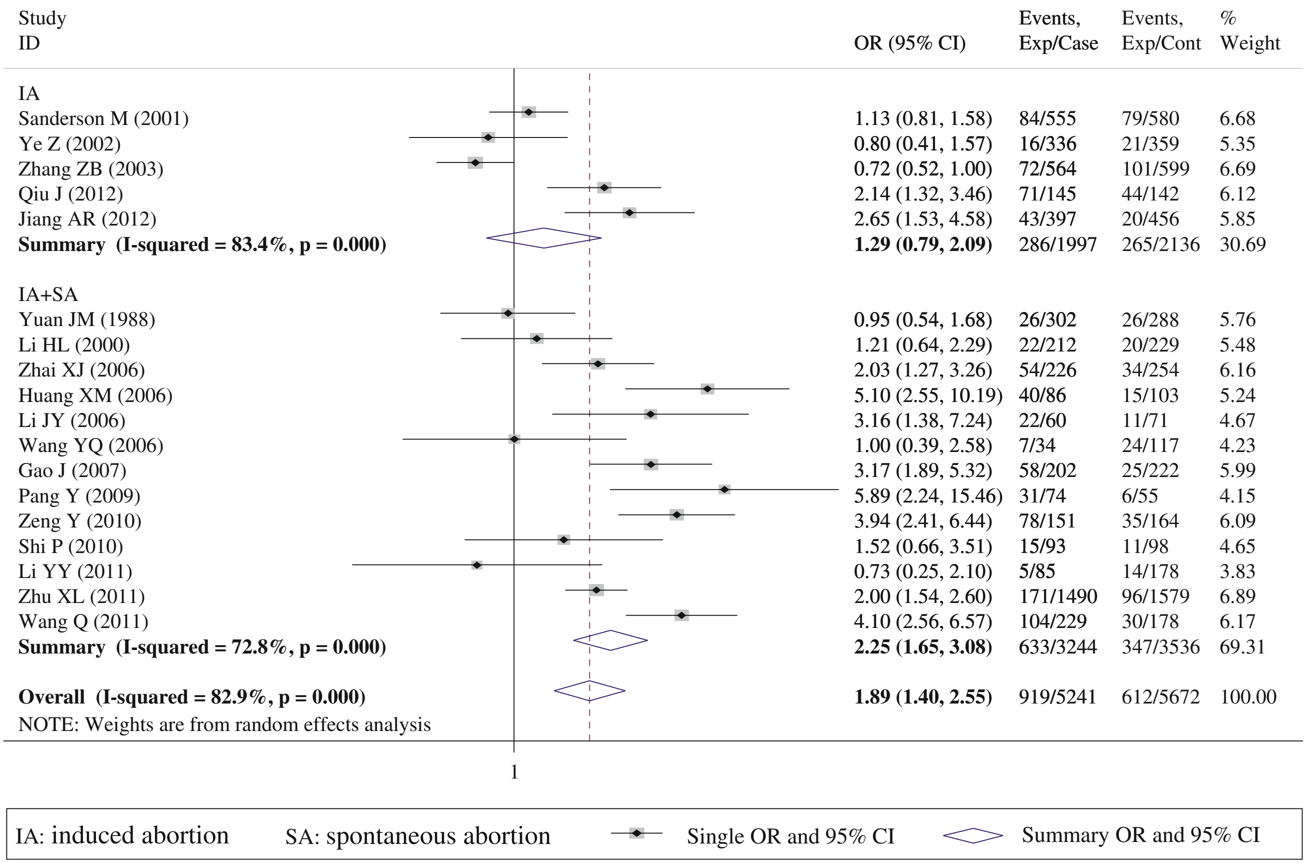


Fig. 5 Forest plot of studies on the association between breast cancer and at least three IAs

The risk increased as the number of IA increased. These findings were different from a recent meta-analysis of 53 studies carried out in 16 countries [8], but were consistent with a previously published systematic review [7].

Since the positive association between IA and incident breast cancer was first presented by Segi et al. in [58], several studies supported this association [59–62]. However, some other studies, including two important studies from Shanghai [9, 10], found a null or similar association. Inadequate choices of the reference group might be one of the most important determinants of the different results. In fact, the prevalence of IA in the control group were more than 50 % among both the two Shanghai studies (51 % in Ye et al. [9], and 66 % in Sanderson et al. [10]), and among several other included studies with NOS of 8–9 (80.4 % in Qiu et al. [31], 68.3 % in Zhang [25], 63.0 % in Wang et al. [32], and 62.7 % in Wang [27]). As argued by Brind and Chinchilli [14], once the prevalence of a given exposure rises to a level of predominance in the control group, statistical adjustment cannot remove all the confounding caused by the adjustment terms. This was well exemplified by the meta-regression analysis in our study (Fig. 6). It was also the main reason why we did not observe an increased risk of breast cancer in the subgroup analysis based on

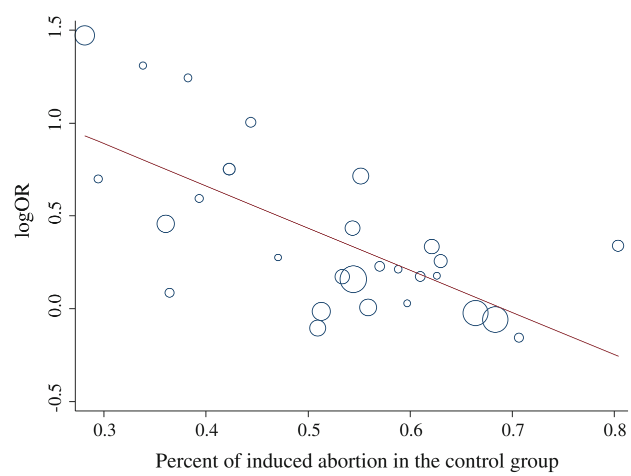


Fig. 6 Meta-regression of percent of IA in the control group with odds ratio of individual study

Shanghai studies, studies with a NOS score of 8–9, and cohort studies, because both studies of Sanderson and Ye were conducted in Shanghai [9, 10] and with a NOS score of 8–9, and the study of Ye was one of the two cohort studies.

In our study, an increased risk of breast cancer was observed as the number of IA increased. The significant dose–response relationship was also observed in previous studies both in China [11] and in other countries [63]. However, for women who had at least three IAs, the association was suggested non-significant in studies including only IA, but significant in studies including both IA and SA. The result was reasonable in China. First, different from USA where abortion is used predominantly to postpone first childbirth [7, 14], almost all IAs in China were performed to limit family size after the first child. Therefore, more IAs may imply an early age of childbirth. The protective effects of early childbirth will probably dilute the harmful effect of more IAs. Second, the self-reported number of IA will probably be underestimated, as the stigma of abortion still exists in China, especially when a woman has more than two IAs. Therefore, this underestimation will inevitably create spurious associations between IA and breast cancer, especially for more IAs.

Our results might be confounded by additional factors. First, some abortions performed before marriage might be included. However, these abortions were very few, and probably would not be reported in China [9], as they are less socially acceptable and are associated with more stigmas. Second, though inadequate choices of the reference group might be the main reason why there was no association in the strongest studies, i.e., cohorts, NOS of 8–9, and those conducted in Shanghai, the positive result of association between IA and breast cancer risk still might be overstated. Third, the pooled ORs might be confounded by other factors, including age, parity, and age at first birth. Although meta-analysis based on adjusted ORs could theoretically get a clearer conclusion, crude ORs from univariate logistic regression were used in the primary analysis based on the following three reasons: (1) some of the included studies did not report the adjusted ORs, including those not focusing on IA and those concluding negative ORs after multiple adjusting due to small sample size or inadequate choices of the reference group. In fact, only 13 of the 36 studies had reported the adjusted ORs, and summary based on these 13 adjusted ORs was similar to the primary result, suggesting that the primary result was not substantially confounded by the un-adjusted factors. (2) The adjustment terms varied greatly in the included studies. Summarizing these results from different calculation methods would inevitably incur more confounding rather than get a clearer result. (3) ORs from cross-table were also crude ORs equal to ORs calculated from univariate logistic regression. In order to get a more comparable result with cross-table, crude ORs from univariate logistic regression rather than adjusted ORs from multivariate logistic regression should be used. Therefore, these results should be interpreted with caution, and future prospective cohort studies with more adequate reference group were needed to investigate the association further.

There were several strengths in our study. First, we searched not only studies focusing on abortion, but also extended the searching on studies focusing on all potential risk factors of breast cancer, including genetic polymorphisms. This strategy greatly extended our targeted studies. Second, studies included in this review were not limited to studies with complete cross-table data, but extended to the studies with ORs and 95 % CIs. In fact, according to the results of Egger test and the funnel plot, we did not find a significant publication bias among included studies. Therefore, we concluded that the results based on the current evidences were relatively convincible.

Conclusions

In summary, the most important implication of this study is that IA was significantly associated with an increased risk of breast cancer among Chinese females, and the risk of breast cancer increases as the number of IA increases. If IA were to be confirmed as a risk factor for breast cancer, high rates of IA in China may contribute to increasing breast cancer rates.

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