Systematic Review and Meta-Analysis

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No association between abortion and risk of breast cancer among nulliparous women

Evidence from a meta-analysis

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Abstract

Background: Various epidemiological studies have demonstrated the association between abortion and risk of breast cancer among nulliparous women; however, results remain inconclusive. This meta-analysis assessed the association based on previous studies.

Methods: PubMed, EMBase, China National Knowledge Infrastructure, Chongqing VIP, and Wanfang databases were searched for relevant articles until February 2018. In this meta-analysis, fixed-effects models were used to estimate the combined effect size and the corresponding 95% confidence interval (CI). All statistical data were analyzed using STATA 12.0.

Results: A total of 14 articles consisting of 6 cohort studies and 8 case-control studies were included in this review. All articles were of high quality, as determined based on the Newcastle Ottawa Scale assessment. The combined risk ratio (RR) indicated no significant association between abortion and breast cancer among nulliparous women (RR = 1.023, 95%CI = 0.938–1.117; $Z = 0.51$, $P = .607$). Subgroup analyses revealed no significant associations between risk of breast cancer and induced abortion or between risk of breast cancer and spontaneous abortion (SA) among nulliparous women (RR = 1.008, 95% CI = 0.909-1.118 and RR = 1.062, 95%CI = 0.902-1.250, respectively). Neither 1 nor >2 abortions increased the risk of breast cancer among nulliparous women. Sensitivity analysis showed that our results were reliable and stable.

Conclusion: Current evidence based on epidemiological studies showed no association between abortion and risk of breast cancer among nulliparous women.

Abbreviations: CI = confidence interval, IA = induced abortion, NOS = Newcastle Ottawa scale, OR = odds ratio, RR = risk ratio, SA = spontaneous abortion.

Keywords: induced abortion, meta-analysis, nulliparous, spontaneous abortion

Editor: Martin S. Staege.

HT and YW contributed equally to this manuscript.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The authors have no conflicts of interest to disclose.

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How to cite this article: Tong H, Wu Y, Yan Y, Dong Y, Guan X, Liu Y, Lu Z. No association between abortion and risk of breast cancer among nulliparous women: evidence from a meta-analysis. Medicine 2020;99:19(e20251).

Received: 30 September 2018 / Received in final form: 22 March 2020 / Accepted: 14 April 2020

http://dx.doi.org/10.1097/MD.0000000000020251

1. Introduction

Breast cancer is the most commonly occurring cancer among women regardless of race or ethnicity[1] and is the sixth leading cause of cancer-related deaths.[2,3] World Cancer Research Fund International reported nearly 1.7 million new breast cancer cases in 2012.[4] Breast cancer in women represented 12% of all new cancer cases and 25% of all cancer cases.[4] In the United States, about 1/8 of the female population suffer from breast cancer during their lifetime, and 40,000 women die from breast cancer annually.[5] Breast cancer has become a major public health problem worldwide.

Previous studies reported that several factors could increase the risk of breast cancer, such as early menarche,[6] family history,[7] number of births,[8] obesity,[9] increasing age,[10] and genetic mutation.[11] Several epidemiological studies also revealed the relationship between abortion and breast cancer. Paoletti[12] performed a large-scale cohort study through a ten-year period, including 100,000 females aged 40 to 65 years; no relationship was found between breast cancer and induced abortion (IA), but a potential association between breast cancer and spontaneous abortion (SA) depending on menopausal status was suggested. In Denmark, a cohort study among women aged >50 years conducted through a twelve-year period showed that IA exerted no long-term effects on the risk of breast cancer (HR 0.95, 95% confidence intervals [CI] 0.83–1.09).[13] Another prospective cohort study[8] with 970,437 person-years among predominantly premenopausal population in Scandinavia found that breast cancer risk was not associated with either IA or SA.

In addition, several comprehensive meta-analysis described the relationship between breast cancer and abortion. Guo[14] pooled 15 prospective studies that revealed no sufficient evidence to support a positive association between either IA and breast cancer risk or SA and breast cancer risk. However, another meta-analysis involving Chinese females suggested that IA could significantly increase the risk of breast cancer.[15]

Thus far, analysis of the risk of abortion among nulliparous women with breast cancer is rarely conducted. In addition, previous studies have led to inconsistent results,[16–18] and no systematic comprehensive review has been performed to examine the relation between breast cancer and abortion. Thus, the current study is the first meta-analysis to determine the relation between breast cancer and abortion among nulliparous women.

2. Materials and methods

2.1. Literature search

The meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis recommendations. Two investigators independently searched several large databases, including PubMed Medline (1966 to Feb 2018), EMBase (1966 to Feb 2018), China National Knowledge Infrastructure (1994 to Feb 2018), Wanfang Data (1980 to Feb 2018), and Chongqing VIP (1989 to Feb 2018) for all relevant studies. The following terms were searched in the article titles, abstracts, and keywords: "induced abortion"/"spontaneous abortion", "nulliparous"/"nonparous" and "breast cancer"/"breast carcinoma"/"breast tumor." Relevant studies were also selected based on the reference list of identified articles.

2.2. Inclusion and exclusion criteria

Two reviewers (M Li and L Xu) independently selected the potential articles based on inclusion and exclusion criteria. In case of a divergence of opinion between the 2, a third reviewer was selected to evaluate whether the article in question was eligible. All selected studies were subjected to the following inclusion criteria:

(1) An observational design based on human population is adopted in the studies;
(2) The types of abortion include SA and IA;
(3) Sufficient information is provided to calculate the effect size;
(4) The articles are written in English or Chinese.

Any study that failed to meet these criteria was excluded.

2.3. Data extraction

Data on the study were independently extracted by 2 review authors using a standard form for each study. The extracted information included the first author, year of publication, country, study design, odds ratio (OR) or risk ratio (RR), and 95%CI. If required, information that had been omitted was retrieved via communication with the authors of the studies. During data collection, the third reviewer adjudicated on any divergence.

2.4. Quality assessment

In this review, Y Liu and X Guan independently evaluated the quality of the included studies by using the Newcastle Ottawa Scale (NOS) in accordance with the Cochrane Collaboration. The NOS checklist included 3 items: selection, comparability, and outcomes. The scale ranged from 0 to 9 stars with NOS score >= 7 stars considered as high quality, 4 to 6 stars as moderate quality, and <=3 stars as low quality.

2.5. Ethical approval

Ethical approval was not required because all data were extracted from previously published articles.

2.6. Statistical analyses

The results of the meta-analysis were analyzed using Stata 12.0 (Stata Corporation, College Station, TX). Although different studies provided different measures of effects like RR or OR, as the incidence of breast cancer was low, these 2 effect measures should give similar estimates.[19,20] The pooled outcomes were assessed using the RR, along with the 95% CI. To assess the heterogeneity among the included studies, Cochran Q test and I^2 were applied. $I^2>50\%$ indicated heterogeneity, and the random-effects model was applied. Conversely, the fixed-effect model was applied. In this meta-analysis, the funnel plot and Egger test were performed to detect possible publication bias. To further explore the source of heterogeneity, subgroup analysis was conducted. In addition, sensitivity analysis was carried out by omitting each study and recalculating the pooled effect size for the remaining studies to validate the credibility of outcomes. When $P \leq .05$, the difference was considered statistically significant.

3. Results

3.1. Search results

A total of 656 articles were initially generated based on the search strategy. Removal of 107 duplicate articles ultimately resulted in 549 articles for further assessment. After screening the abstracts, 87 articles were assessed based on their full texts. Further screening led to the exclusion of 73 articles from the meta-analysis. Ultimately, 14 articles[8,12,16–18,21–29] met the rigid screening criteria (Fig. 1).

Table 1 lists basic information on the articles included in this review. Two types of abortion, IA and SA, were deduced from 7 articles in which case each of them was considered as 2 distinct articles. Thus, 21 studies were included in this meta-analysis.

3.2. Characteristics of included studies

All selected articles were published in English. The field sites of all included articles covered over 6 countries, including United States,[8,16,18,21,22,24,25,27,28] Greece,[23] China,[17] Denmark,[26] France,[12] and Slovenia.[29] A cohort study design was adopted in 6 studies,[8,12,16,21,26,28] and a case-control study design was used in 8 studies.[17,18,22–25,27,29] All included studies reported on the association of IA with breast cancer risk among nulliparous women. Seven studies[8,12,16,23,24,27,29] reported on the relationship between SA and risk of breast cancer among nulliparous women.

3.3. Methodological quality

Using the NOS checklist, we assessed the methodological quality of the included studies and identified 4 moderate-quality

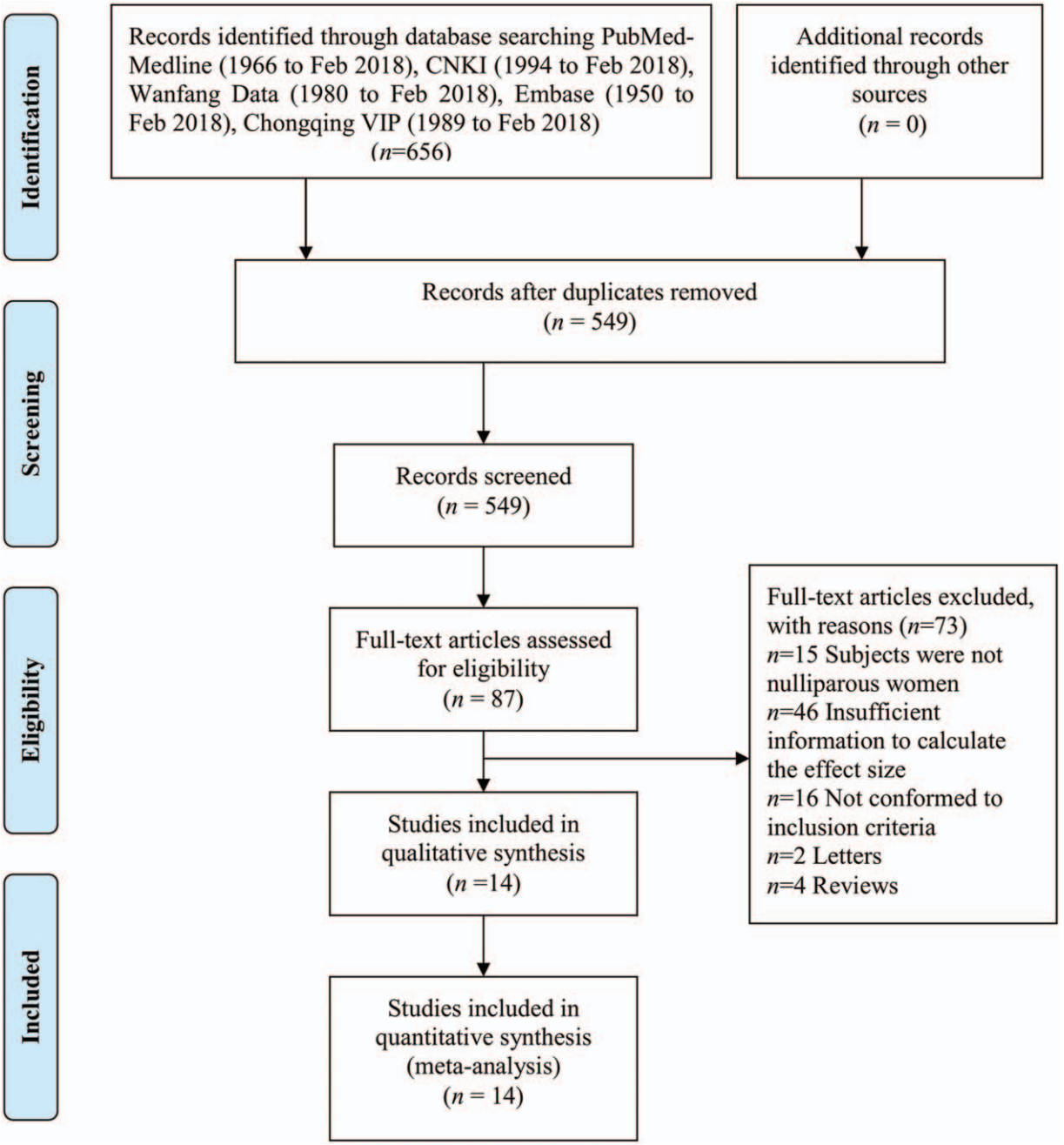

Figure 1. Flow diagram of the screening process.

articles[24,26,27,29] and 10 high-quality articles[8,12,16–18,21–23,25,28] (Table 1). Therefore, the included 14 articles were of good quality.

Table 2

3.4. Association of breast cancer risk with abortion

No significant heterogeneity was found ($Q=15.29$, $P=.759>.05$; $I^2=0.1\%$). Thus, we used a fixed-effects model to pool the effect size (Fig. 2). The pooled effect size indicated no significant association between abortion and breast cancer among nulliparous women (pooled RR = 1.023, 95%CI = 0.938–1.117; $Z=0.51$, $P=.607$).

3.5. Publication bias

The funnel plot, which was used to visually identify publication bias, was generally symmetric (Fig. 3). In addition, neither Begg test nor Egger test showed a significant risk of publication bias ($z=0.75$, $P=.450>.05$; $t=0.41$, $P=.686>.05$).

3.6. Subgroup analysis

A total of 14 studies reported on the risk of breast cancer among nulliparous women with IA, and the pooled effect size revealed no significant difference (pooled RR = 1.008, 95%CI: 0.909–1.118); 7 studies analyzed the risk of breast cancer among nulliparous

Table 1

Characteristics of the included studies.

ID	Author	Year	Country	Design study	Sample	Age	Number of abortion	OR[95%CI] for induced abortion	OR[95%CI] for spontaneous abortion	Quality assessment
							total	0.90 [0.50,1.40]	–	
1	Palmer J	2004	USA	CS	80	21-69	only 1	0.80 [0.40,1.50]		H
							2+	1.00 [0.50,1.90]		
2	Lipworth L	1995	Greece	CC	820 cases and 753 controls	under 35	total	0.98 [0.56,1.73]	1.17 [0.64,2.13]	H
3	Rosenberg L	1988	USA	CC	820 cases and 1688 controls	median: case: 52; control: 40	total	1.30 [0.80,2.20]	0.90 [0.50,1.50]	M
							total	0.95 [0.76,1.19]	1.04 [0.8,1.35]	
4	Henderson K	2008	USA	CS	29390	20-79	only 1	0.98 [0.77,1.25]	1.17 [0.89,1.54]	H
							2+	0.86 [0.57,1.30]	0.68 [0.41,1.13]	
5	Wu J	2014	China	CC	133	<60	total	0.75 [0.24,2.32]	-	H
6	Rookus M	1996	USA	CC	159 cases and 117 controls	20-54	total	0.90 [0.40,2.30]	-	H
7	Melbye M	1997	Danmark	CS	95	>=12	total	1.04 [0.83,1.31]	-	M
							total	0.69 [0.46,1.04]	1.33 [0.64,2.77]	
8	Giangreo M	2003	USA	CC	273 cases and 274 controls	<=40	only 1	0.84 [0.52,1.35]	0.59 [0.22,1.63]	M
							2+	0.54 [0.28,1.04]	3.47 [1.03,11.66]	
							total	0.92 [0.68,1.25]	1.31 [0.93,1.86]	
9	Paoletti X	2003	France	CS	651	40-65	only 1	0.95 [0.67,1.34]	1.28 [0.84,1.96]	H
							2+	0.87 [0.52,1.46]	1.37 [0.79,2.36]	
							total	1.19 [0.9,1.58]	0.82 [0.55,1.21]	
10	Michels K	2007	USA	CS	622	25-42	only 1	1.21 [0.89,1.64]	-	H
							2+	1.12 [0.62,2.02]	-	
							total	1.40 [0.90,2.10]	-	
11	Daling J	1996	USA	CS	303 cases and 244 controls	under 45	only 1	1.50 [1.00,2.50]	-	H
							2+	1.20 [0.60,2.10]	-	
							total	2.51 [0.61,10.29]	1.41 [0.22,9.01]	
12	Robertson C	2001	Slovenia	CC	46 cases and 38 controls	25-54	only 1	3.30 [0.64,17.04]	-	M
							2+	0.94 [0.06,15.7]	-	
13	Newcomb P	2000	USA	CC	50 cases and 82 controls	20-69	total	0.80 [0.10,6.30]	-	H
14	Ma H	2017	USA	CC	55 cases and 208 controls	20-64	total	0.91 [0.60,1.38]	-	H

CC = case-control study, CI = confidence interval, CS = cohort study, H = high quality, M = moderate quality, OR = odds ratio.

women with SA, and the pooled RR was 1.062 (95%CI: 0.902–1.250).

On the basis of the cohort studies, nulliparous women with a history of abortion had a pooled risk of breast cancer equal to 1.041 (95%CI: 0.942–1.150). With regard to the case-control studies, the relationship between abortion and risk of breast cancer among nulliparous women was not determined, and the combined RR was 0.966 (95%CI: 0.804–1.159).

With regard to the influence of the number of abortions on the risk of breast cancer among nulliparous women, 10 studies reported on the relationship between 1-time abortion and risk of breast cancer, and the pooled RR was 1.081 (95%CI: 0.958-1.221).

Table 2

Results of subgroup analysis.

Subgroup	Number of publication	Effect size			Chi-square	*P*	I^2 (%)	*Z*	*P*	Begg test		Egger test	
		OR	Lower	Upper						*Z*	*P*	*t*	*P*
Total	21	1.023	0.938	1.117	15.29	.759	0.0	0.51	.607	0.75	.450	0.41	.686
Type of abortion													
IA	14	1.008	0.909	1.118	11.02	.609	0.0	0.15	.880	0.66	.511	0.09	.874
only 1	7	1.051	0.909	1.214	7.15	.307	16.1	0.67	.503	0.15	.881	0.79	.483
2+	7	0.901	0.719	1.128	3.83	.700	0.0	0.91	.364	0.30	.764	0.09	.931
SA	7	1.062	0.902	1.250	3.99	.678	0.0	0.72	.470	0.30	.764	0.28	.727
Only 1	3	1.159	0.926	1.451	1.96	.375	0.0	1.29	.196	−0.52	.602	−1.51	.427
2+	3	1.051	0.737	1.500	7.46	.024	73.2	0.28	.783	1.04	.296	4.02	.408
Study design													
Cohort study	9	1.041	0.942	1.150	7.42	.492	0.0	0.79	.430	0.89	.373	0.72	.222
Case-control study	12	0.966	0.804	1.159	7.37	.769	0.0	0.38	.707	0.73	.466	0.46	.743
Number of abortion													
only 1	10	1.081	0.958	1.221	9.63	.381	6.6	1.26	.207	0.09	.929	0.09	.921
2+	10	0.942	0.779	1.139	11.80	.225	23.7	0.62	.535	0.89	.371	1.15	.310

IA = induced abortion, SA = spontaneous abortion, OR = odds ratio.

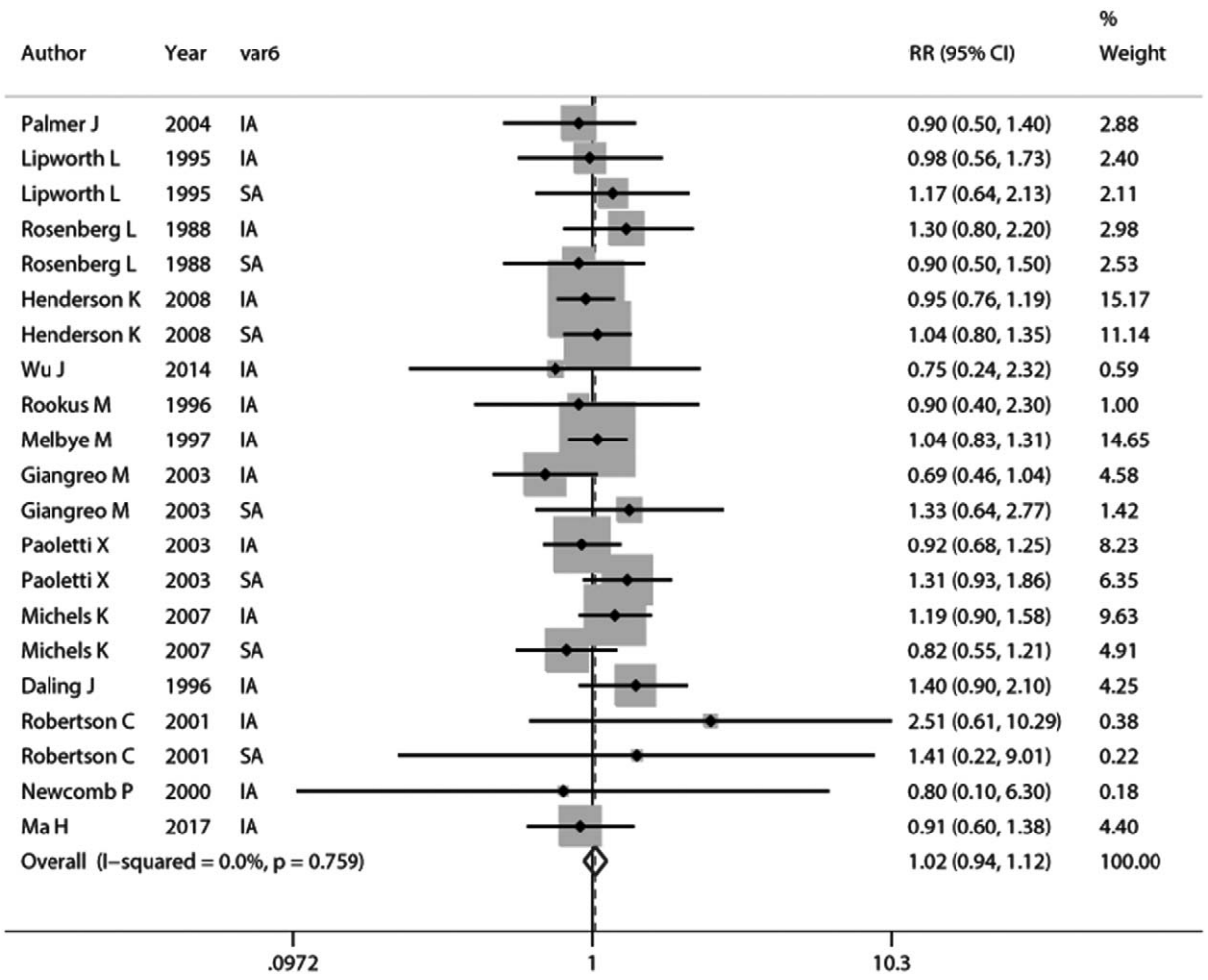

Figure 2. Forest plot of association between abortion and risk of breast cancer among nulliparous women.

Moreover, 10 studies showed indicated the relationship between abortion occurring ≥2 times and risk of breast cancer, and the pooled RR was 0.942 (95%CI: 0.779–1.139). To ensure that similar results were obtained among nulliparous women with different types of abortion, we further conducted a subgroup analysis. Indeed, similar results were found for the women with only 1-time abortion or ≥2 times abortion, provided that they had neither IA nor SA

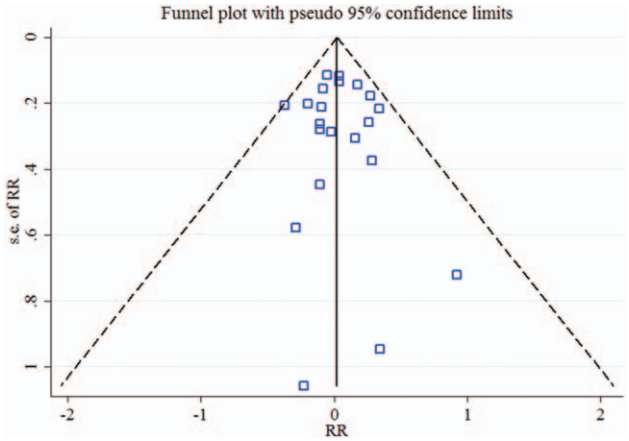

Figure 3. Funnel plot of the included studies in this meta-analysis.

3.7. Sensitivity analysis

Sensitivity analysis was performed to assess the reliability and stability of the results. Fig. 4 showed that no significant change in the pooled effect size was observed when any 1 study was removed.

4. Discussion

Nulliparous women are those who have experienced IA or SA before the midpoint of pregnancy but not those who have experienced pregnancy loss after 20 weeks. This occurrence has thus far been observed in a growing number of women worldwide, particularly in the developed countries. Considerable attention has been devoted toward the health of nulliparous women, for instance, breast cancer.[30–34] Deng[3] performed a meta-analysis to explore the association of IA with breast cancer, with no finding of significant difference between breast cancer and IA among nulliparous women. However, several deficiencies should be considered. This meta-analysis was based on case-

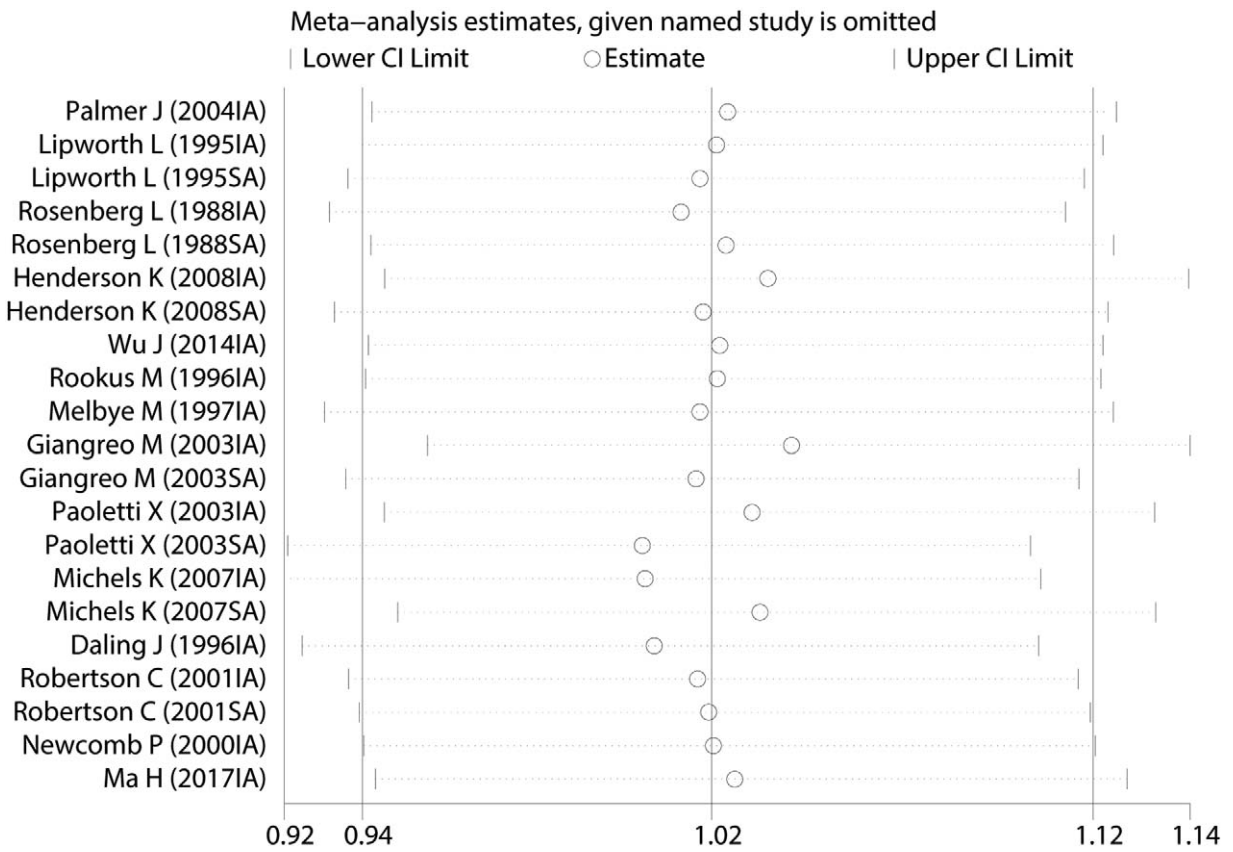

Figure 4. Sensitivity analysis of the included studies in this meta-analysis.

control studies but did not include cohort studies. In addition, the study did not reveal the relationship between breast cancer and SA among nulliparous women. Thus, we performed this current more comprehensive meta-analysis to examine the relationship between abortion and breast cancer among nulliparous women on the basis of the case-control and cohort studies.

For this review, we analyzed 14 articles with 21 studies meeting the rigid screening criteria. All included articles employed proper methodology, which were assessed using the NOS checklists. The pooled OR of all studies was 1.023 [95%CI: 0.938–1.117], which suggested that no association was found between abortion and breast cancer among nulliparous women.

To further explore the different relationships between breast cancer and IA or breast cancer and SA, subgroup analysis was conducted. No significant difference was found in either IA or SA among nulliparous women. Our findings with regard to IA were consistent with the meta-analyses by Deng[3] and Guo[14] but not with the review by Huang.[15] The difference could be attributed to the variation in population of the different studies. Deng[3] and Guo[14] did not limit the countries where the participants came from, whereas Huang[15] included only Chinese females. This observation led us to conclude that race was the main reason.

In the United States, the number of new cases of females with breast cancer is 126.0 per 100,000 women annually. Compared with any chronic disease, breast cancer has a lower incidence. The OR in case-control studies should be close to the RR. Thus, we pooled the total RR based on the effect size (OR) of case-control studies and the effect size (RR) of cohort studies. Considering the influence of study design on the results, we also calculated the relationship between breast cancer and abortion for the 2 types of study design. On the basis of the 6 cohort studies, the pooled RR was 1.041 [95%CI: 0.942–1.150], which suggested that there was not sufficient proof to support the risk of breast cancer for abortion. To date, a cohort study[16] with the largest sample size (29,390 individuals), which used the California State Teachers Retirement System, found no statistically significant association between abortion and breast cancer risk among nulliparous women after Cox multivariable regression. This strong evidence proves that abortion and breast cancer risk are not associated. On the basis of the 8 case-control studies, the pooled effect size indicated that no relationship between abortion and breast cancer risk among nulliparous women was determined. The result was consistent with a previous systematic review.[3]

Several studies have suggested that 2 or more abortions can increase the risk of breast cancer among women.[27,35] However, other studies hold the opposite view. The subgroup analysis in our study revealed no association between breast cancer risk and the number of abortions among nulliparous women who had neither SA nor IA.

Although our meta-analysis demonstrated that no association was found between the risk of breast cancer and abortion among nulliparous women on the basis of the case-control studies and cohort studies, several flaws should be considered. First, some studies identified age as an important factor affecting the risk of breast cancer. However, owing to the variation in age in all included studies, the association of age with the risk for breast cancer was not analyzed in this review. Second, the sample size was small in all included studies, except for the study by

Henderson.[16] Therefore, studies with a larger sample size need to be conducted in the future to further determine the relationship between abortion and the risk of breast cancer among nulliparous women.

Acknowledgments

Z Lu designed the study, H Tong, Y Wu, and Y Yan wrote the manuscript. Y Dong and X Guan performed the statistical analysis. Y Liu discussed the results.

Author contributions

Conceptualization: Zhihui Lu.
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Project administration: Yun Liu, Zhihui Lu.
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Software: Yonghai Dong.
Supervision: Xihong Guan.
Writing – original draft: Huazhang Tong, Yifan Wu, Yin Yan, Yonghai Dong, Zhihui Lu.
Writing – review and editing: Huazhang Tong, Yifan Wu, Zhihui Lu.

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