Review Article

# Menstrual and Reproductive Factors and Risk of Breast Cancer in Iranian Female Population: A Systematic Review and Meta-Analysis


## Abstract

**Background:** Breast cancer (BC) is the most frequent cancer in Iranian females. Due to the changes in lifestyle and reproductive risk factors, the BC incidence rate has been rapidly increasing. Knowing risk factors of BC could significantly contribute to improve preventive behaviors. To investigate the relationship between menstrual and reproductive factors and BC in Iranian female population. **Methods:** Web of Science, PubMed, Scopus, and SID as well as references of included studies were searched. Among relevant published observational studies, 27 studies met the inclusion criteria. Pooled risk estimates for the risk factors were determined using random-effects models due to the presence of substantial heterogeneity ($P < 0.05$). **Results:** All of the selected studies had case–control design. There was a positive relationship between maternal age at first pregnancy and risk of BC (OR = 1.79 95% CI: 1.36–2.35). Also, menopausal status was associated with higher risk of BC (OR = 1.60 95% CI: 1.18–2.17), whereas, there was no association between menarche age and increased risk of BC (OR = 0.55 95% CI: 0.29–1.03). History of abortion (OR = 1.21 95% CI: 0.97–1.5), nulliparity (OR = 1.43 95% CI: 0.89–2.31), and breastfeeding history (OR = 0.68 95% CI: 0.42–1.09) were not associated with BC risk. **Conclusions:** Our findings suggest that age at the first pregnancy and menopausal status were significantly associated with BC risk among Iranian women, whereas menarche age, nulliparity, and history of breastfeeding were not. In regard to the history of abortion, our findings revealed no association with BC, but in high-quality studies, this relationship was significant.


**Keywords:** *Abortion (induced, spontaneous), breast neoplasm, breastfeeding, menopause, reproductive history*


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## Introduction

Breast cancer (BC) is one of the most serious health problems among women worldwide.[1] BC is also the most common cancer in Iranian female population and its incidence rate has doubled throughout three past decades.[2] BC is a multifactorial disease and various factors are involved in its development.[3] It is notable that not all women have the same risk of BC throughout their lives, but specific risk factors could increase their chances to experience the disease.[4] The role of reproductive factors such as menarche age, age at first childbirth, age at menopause, parity, breastfeeding, number of pregnancies, and number of abortion as risk factors for BC has been reported in several epidemiological studies conducted around the world.[5-7] According to available literature, changes in reproductive patterns including low parity, late pregnancies, and shorter breastfeeding increase the risk of BC in women.[8] Previous studies have also shown that prolonged exposure to endogenous estrogen due to early menarche, late age at first delivery, and late menopause or exogenous exposure mainly due to hormone replacement therapy or use of oral contraceptive pills are associated with BC.[5] The association of some factors, such as spontaneous and induced abortion, with BC is still controversial.[5,9] Also, evidence indicates that women who have their first full-term pregnancy after the age of 25 have a higher risk of BC than women who have their first pregnancy before the age of 25.[10-12] The incidence rate of BC is growing fast, especially in Asian countries, caused by changes in lifestyle and reproductive risk factors.[13] According to data from the national cancer registry system of Iran from 2005 to 2014 (10 years), BC is the most common cancer in women and includes



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26% of women cancers and 12% of cancers in both sexes. The cause of increased incidence of cancer in Iranian women aged 25 to 55 is breast cancer.[14] In Iran, 67.6% of affected women are in the age range of 35–60 years.[15] In addition to the higher direct costs forced on patients and providers, the conflict of more years of life and failure to undertake social activities in these women causes a great economic burden on society.[16,17]

According to the evidence, variations in the patterns of risk factors illustrate the international variation in the burden of BC.[18] Therefore, awareness of BC risk factors could improve the prevention of this cancer.[19] Despite the importance of BC as the most common cancer in the Iranian female population, there is a dearth of systematic review (SR) and meta-analysis (MA) on risk factors of BC in Iran. The present study aimed to investigate the relationship between menstrual and reproductive factors and BC in Iranian women. To the best of our knowledge, this is the first SR and MA on the menstrual and reproductive risk factors of BC in Iran.

## Methods

PRISMA guidelines were used to report this SR and MA.[20]

**Search strategy:** To identify the relevant studies, we used computer-based search in databases of PubMed, Web of Science, Scopus, and Persian databases including SID and Magiran until February 23, 2020. Cochrane database was also searched and no article was found and the papers that were extracted from "Web of Science" and "Magiran" were duplicates. The search terms used to identify the studies were: "risk factor" OR "reproductive factors" OR "menstrual factors" OR "reproductive history" AND "breast cancer" OR "breast carcinoma" OR "breast neoplasm" AND "Iran" OR "Persian" and their Persian equivalents. Hand searching of articles referenced by the retrieved studies was performed to increase the search sensitivity. The steps of study selection are shown in Figure 1.

**Screening (inclusion and exclusion criteria):** The retrieved studies were eligible for inclusion in this SR and MA if they 1) were observational studies; 2) the full text of article was accessible; 3) quantified the reproductive or menstrual risk factors; 4) reported risk ratios, odds ratios, hazard ratios, and 95% CIs; and 5) BC incidence was confirmed by histopathology in hospitalized sample or being registered as case of diagnosed BC in cancer registry in Iranian females. There were no limitations on language or publication date. Excluded studies were 1) animal or genetic articles and 2) review articles, editorials, letters, case reports, meeting abstracts, and nonpeer-reviewed articles.

**Study selection:** Two authors independently checked the titles and abstracts for each study and collected and analyzed potentially relevant studies for eligibility; disagreements were addressed by discussion and otherwise were settled by a third author.

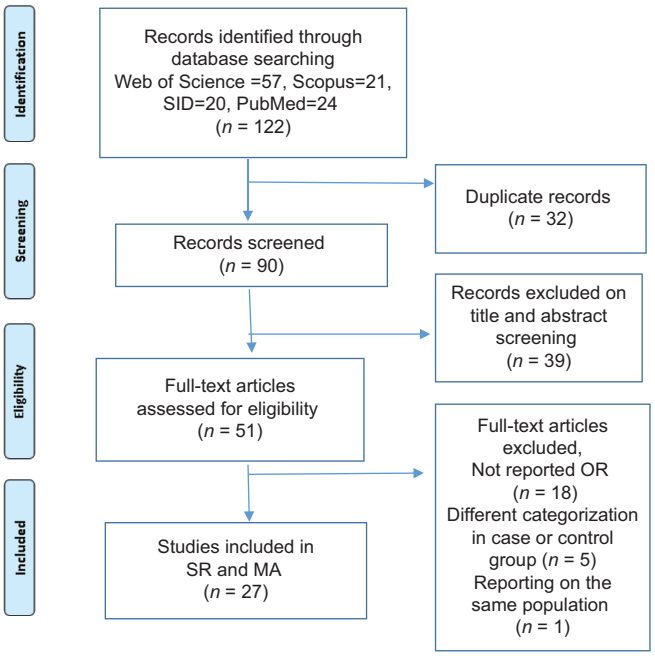


**Figure 1: PRISMA flowchart of study selection**

**Data extraction:** The data were extracted by two researchers (EM and an assistant) independently. The extracted items included authors' name, publication year, study design, sample size, number of BC cases and controls, data collection, sources of BC-related information, and adjusted covariate(s). The included menstrual and reproductive risk factors were age at first live childbirth, age at menarche, history of abortion, nulliparity, having a history of breastfeeding, and menopausal status.

**Quality assessment:** Two researchers (EM and an assistant) evaluated independently the methodological quality of individual studies with the Newcastle-Ottawa Scale (NOS) to assess the quality of nonrandomized studies, with all disagreements settled by a third author. NOS implemented the star system with a maximum of nine stars scoring from 0 to 9. In this way, 7–9 stars indicated high quality, 4–6 stars showed moderate quality, and 0–3 stars meant low quality.[21]

### Data synthesis and statistical methods

The following exposures were extracted from eligible articles: menopausal status (menopausal status means whether a woman has experienced menopause or not) and age at menarche (<12 years and ≥12 years) as menstrual factors. Also, age at first live childbirth (<20 years and ≥20 years), parity (parous vs. nulliparous), breastfeeding (yes/no), and history of abortion (yes/no) deemed as reproductive factors. This study included all forms of BC regardless of their pathological aspects or tumor stage. We selected the most recent study if data from the same population were used in multiple articles.[22]

Because all of the included studies were case–control, odds ratios (ORs) were used to evaluate the association of menstrual as well as reproductive risk factors and BC. The pooled measure was determined as the inverse variance weighted mean of the natural logarithm of OR with 95% CI. Adjusted OR was preferred over crude measures whenever it was available. If more than one measure of association between each of prognostic factors and the odds of BC was available in a study, the approach of combining effect sizes through multiple comparisons in individual studies introduced by Borenstein. *et al.*[23] was used. We used random effects model and combined study specific OR (95% CI), which considers both within-study and between-studies variation.[24] If the Q-test, a standardized measure of the deviation of the effect of each study from the overall effect, was statistically significant ($P < .05$), or if the variance between studies as a percentage of the total variance ($I^2$ statistic) was more than 20%, there was heterogeneity of effect size between studies.[25,26] Subgroup analyses were conducted so as to further assess ORs in the subset of studies. Publication bias was explored visually with funnel plots, and quantitatively using the Egger[27] and Begg[28] statistical tests. The trim and fill approach was used to further investigate publication bias.[29,30] Statistical significance was considered as $P < 0.05$. Stata version 11.2 (StataCorp, College Station, Texas) was used for all analyses.

## Results

### Identification and description of studies

In the initial search, 134 studies were identified, of which 44 studies were duplicates and 39 studies were removed after assessing the title and abstract. The remaining 51 studies were carefully reviewed and 24 articles were excluded for the reasons demonstrated in Figure 1. Finally, 27 studies fulfilled all the inclusion criteria [Figure 1].

Except of five studies,[12,31-34] one or more risk factors of BC were adjusted in all included studies. All studies were published during 2002–2019, and most were published in 2011.[35-38] Six studies had "high"[10,12,35,37,39,40] and 21 articles[9,11,12,31-34,36,38,41-52] had moderate quality assessment score [Table 1].

### Association between menstrual factors and BC

The data of 7 studies with a sample size of 15260 (1754 cases and 13506 controls) revealed that menarche age (with control group < 12 years)) OR = 0.55 95% CI: 0.29–1.03, $P < 0.001$, $I^2 = 84.9\%$, $P = 0.062$ (was not associated with increased risk of BC [Table 2, Figure 2]. According to the data of 15 studies with a sample size of 44046 (3043 cases and 41003 controls), menopausal status (with premenopause as control group) was associated with higher risk of BC (OR = 1.60 95% CI: 1.18–2.17, $P < 0.001$, $I^2 = 92.9\%$, $P = 0.002$) [Table 2, Figure 3].

### Association between reproductive factors and BC

In reproductive factors, according to the results of 12 studies with a sample size of 5513 (2221 cases and 3292 controls), there was no association between the history of abortion with an increased risk of BC (OR = 1.21 95% CI: 0.97–1.5, $P < 0.001$, $I^2 = 79.3\%$, $P = 0.1$) [Table 2, Figure 4]. Also, nulliparity did not increase the risk of BC (OR = 1.43 95% CI: 0.89–2.31, $P < 0.005$, $I^2 = 65.7\%$, $P = 0.141$) (8 studies, sample size 16098, 2112 cases and 13986 controls) [Table 2, Figure 5]. There was an increased risk of BC in first pregnancy after 20 years old (OR = 1.79 95% CI: 1.36–2.35, $P < 0.001$, $I^2 = 79.6\%$, $P = 0.001$) in 10 studies with a sample size of 4716 (2239 cases and 2477 controls) [Table 2, Figure 6]. Also, the history of breastfeeding was not related to higher BC risk (OR = 0.68 95% CI: 0.42–1.09, $P < 0.001$, $I^2 = 81.3\%$, $P = 0.108$) based on 8 studies with a sample size of 4209 (1694 cases and 2515 controls) [Table 2, Figure 7].

### Subgroup analyses

Subgroup analyses were conducted based on quality score (high or moderate), adjustment of studies for risk factors (yes or no), source of BC information (hospital-based or registry), and geographical area (north, south, west, east, and center of Iran) regarding each of examined menstrual and reproductive risk factors, separately. A significant increase in BC risk was identified in some of the subgroups [Table 2].

### Publication bias

The funnel plots and Egger and Begg tests for abortion did not provide substantial evidence on the publication bias (Egger: $P = 0.27$; Begg: $P = 0.22$). Also, Egger and Begs tests (Egger: $P = 0.80$; Begg: $P = 0.46$) and the funnel plot for Breastfeeding did not provide evidence for the publication bias. Furthermore, based on the results of Egger and Begg tests and funnel plots, there was no publication bias for menarche age (Egger: $P = 0.28$; Begg: $P = 0.29$) and nulliparity (Egger: $P = 0.22$; Begg: $P = 0.46$). However, Egger and Begs tests and the funnel plot for menopausal status (Egger: $P < 0.001$; Begg: $P = 0.66$) and age at first pregnancy (Egger: $P < 0.001$; Begg: $P = 0.93$) provided evidence for the publication bias (Appendix). For further assessment on publication bias for menopausal status and age at first pregnancy, we used trim and fill approach.[29,30] In this imputation method, no study was imputed in menopausal status but for age at first pregnancy, two hypothetically missing studies were imputed and the "adjusted" point estimate suggested similar OR compared with the original analysis (OR = 1.63, 95% CI = 1.29–2.07).

## Discussion

The present SR and MA focused on some menstrual and reproductive factors effect on the risk of BC in Iranian female population. The results showed that there is no significant relationship between menarche age and BC in

**Table 1: Case-control studies included in the meta-analysis**

| Author/year | Sample size Case/control | Data source | Source of BC information | Reported risk factor (s) | Covariate adjustment | Quality score |
|---|---|---|---|---|---|---|
| Sharifzadeh *et al.*/2011[35] | 85/85 | Face-to-face interview, medical records | Hospital-based | Abortion | Age, occupation, education | High |
| Razmara *et al.*/2010[32] | 197/197 | Questionnaire, interview | Hospital-based | Menarche age, abortion, first pregnancy age | - | Moderate |
| Ebrahimi and Montazeri/2002[31] | 321/300 | Questionnaire, interview | Hospital-based | Nulliparity, first pregnancy age | - | Moderate |
| Keihanian *et al.*/2010[41] | 60/60 | Questionnaire, face-to-face interview | Hospital-based | Menopausal status, abortion | Age | Moderate |
| Jafarinia *et al.*/2016[42] | 170/170 | Questionnaire | Registry | Breastfeeding | Age | Moderate |
| Pesaran *et al.*/2003[45] | 176/176 | Questionnaire, face-to-face interview | Hospital-based | Nulliparity, first pregnancy age | Age, geographic area | Moderate |
| Amini Sani *et al.*/2003[46] | 105/105 | Questionnaire | Hospital-based | Abortion | Age, place of residence | Moderate |
| Marzbani *et al.*/2017[43] | 202/398 | Questionnaire, face-to-face interview, medical records | Hospital-based | Menarche age | Age | Moderate |
| Zayeri *et al.*/2016[44] | 303/303 | Questionnaire, face-to-face interview | Hospital-based | Menopausal status, first pregnancy age | Age | Moderate |
| Dianatinasab *et al.*/2017[10] | 526/526 | Questionnaire, face-to-face interview, medical record | Hospital-based | Menopausal status | Age | High |
| Montazeri *et al.*/2008[12] | 116/116 | Medical record | Hospital-based | First pregnancy age | Menopausal status | High |
| Akbari *et al.*/2011[38] | 376/425 | Questionnaire, face-to-face or telephone interview, medical records | Hospital-based | Abortion, breastfeeding | Demographic variables, SES status | Moderate |
| Yavari *et al.*/2005[48] | 303/303 | Questionnaire, face-to-face interview | Hospital-based | Menopausal status, abortion, nulliparity, first pregnancy age, breastfeeding | Age | Moderate |
| Holakouie Naieni *et al.*/2007[47] | 250/500 | Face-to-face interview | Registry | Menopausal status, abortion | Age, place of residence | Moderate |
| Ebrahimi *et al.*/2002[11] | 286/249 | Questionnaire | Hospital-based | Menopausal status, nulliparity, first pregnancy age | Place of residence | Moderate |
| Hajian-Tilaki and Kaveh-Ahangar/2011[36] | 100/200 | Questionnaire, face-to-face interview | Hospital-based | Menarche age, menopausal status, abortion, first pregnancy age, breastfeeding | Age | Moderate |
| Ghiasvand *et al.*/2011[37] | 521/521 | Questionnaire | Registry | Menarche age, nulliparity | Age, province of residence | High |
| Mahouri *et al.*/2007[40] | 168/504 | Questionnaire | Hospital-based | Menopausal status, abortion, nulliparity, breastfeeding | Age | High |
| Lotfi *et al.*/2008[50] | 80/80 | Questionnaire | Hospital-based | Menopausal status | Age, place of residence | Moderate |
| Montazeri *et al.*/2004[12] | 243/486 | Interview | Hospital-based | Menopausal status | - | Moderate |
| Tehranian *et al.*/2010[49] | 312/312 | Interview, Questionnaire | Hospital-based | Menarche age | Age, ethnicity | Moderate |
| Jokar *et al.*/2016[51] | 225/225 | Telephone interview | Hospital-based | Menarche age, menopausal status, abortion, first pregnancy age, breastfeeding | Age | Moderate |

*Contd...*

**Table 1: Contd...**

| Author/year | Sample size Case/control | Data source | Source of BC information | Reported risk factor (s) | Covariate adjustment | Quality score |
|---|---|---|---|---|---|---|
| Moradi-nazar *et al.*/2019[39] | 212/408 | Face-to-face interview, Questionnaire, medical records | Hospital-based | Abortion, first pregnancy age, breastfeeding | Demographic variables, BMI | High |
| Sepandi *et al.*/2014[33] | 197/11653 | Face-to-face interview, questionnaire | Hospital-based | Menarche age, menopausal status, nulliparity | - | Moderate |
| Zare *et al.*/2013[34] | 111/25481 | Face-to-face interview | Hospital-based | Menopausal status | - | Moderate |
| Hosseinzade *et al.*/2014[9] | 140/280 | Face-to-face interview, questionnaire | Hospital-based | Menopausal status, abortion, nulliparity, breastfeeding | Age | Moderate |
| Mousazade *et al.*/2019[52] | 51/153 | Questionnaire | Hospital-based | Menopausal status | Age | Moderate |

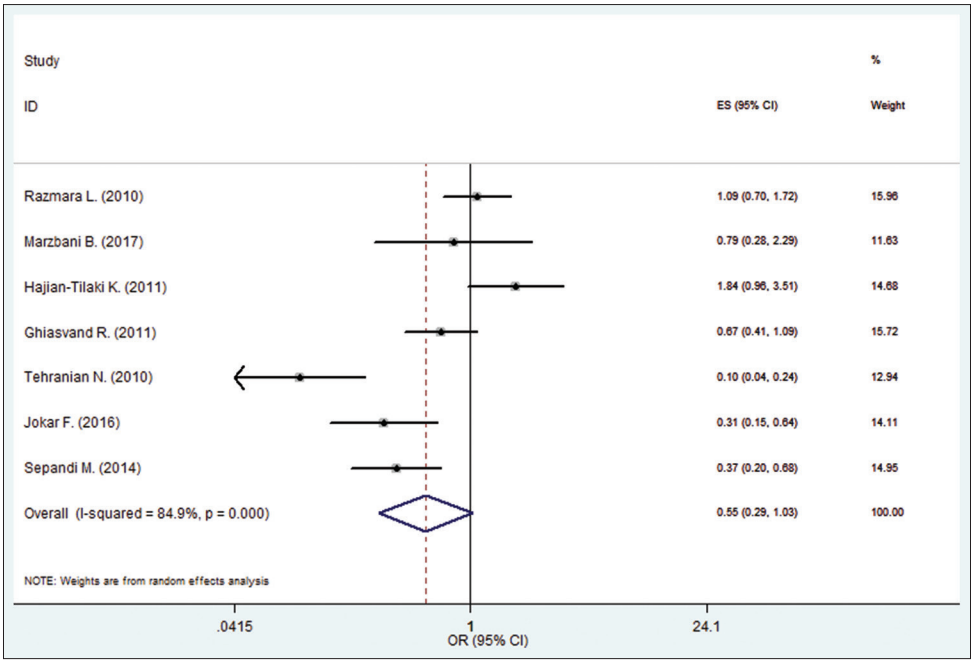


**Figure 2: Forest plot of the relationship between age at menarcheal and breast cancer using the random effects model**

Iranian women. But postmenopausal women were at higher risk for BC than premenopausal women. In a MA conducted to assess the relationship between early menarche and menopausal status with BC in Iranian women, the data of 12 case–control studies revealed that the odds of BC was significantly higher in the women with early menarche and the data of twenty case–control studies showed that the relationship between menopausal status and BC was not statistically significant.[53] But in studies by Namiranian *et al.*[54] and Besharat *et al.*,[55] the relationship between early menarche and BC was not statistically significant. Another MA of Iranian studies reported no relationship between menstrual factors (age of menarche; menopausal status) and BC risk.[56] As it can be seen, different results have been obtained in similar populations. The reason for inconsistency in our results and study by Zahmatkesh *et al.*[57] might be due to the difference in reviewed databases, included studies, and time range of published studies in meta-analyses. In a MA conducted on Indian women, early age at menarche and menopause had 85% and 35% more risk of BC, respectively. A MA of Southeast Asian women also showed that menopausal status was a risk factor for BC.[58] Different findings may be due to differences in ethnicity, different lifestyles in countries, and the method of the study. Some studies in Turkey,[59,60] Bahrain, and Kuwait[61] have identified early menarche as a risk factor for BC. But in other studies in Turkey,[62,63] Pakistan,[64] and Saudi Arabia,[5] as in the present study, early menarche was not reported as a risk factor for BC. Also, some studies in Pakistan,[64] Turkey,[63] and Iraq,[65] similar to the present study, have reported postmenopausal status as a risk factor for BC, while some studies in Turkey have reported inconsistent results.[60]

Our results showed the only reproductive factor associated with an elevated risk of BC was older age at first pregnancy. But, there was no clear statistical relationship

**Table 2: Overall and subgroup pooled odds ratios for the association of BC with menstrual and reproductive factors**

| Menstrual and reproductive factors | Parameters | All studies | Adjusted for BC risk factors | | Quality category | |
|---|---|---|---|---|---|---|
| | | | Yes | No | High | Moderate |
| Menarche age | No. of studies | 7[32,33,36,37,43,49,51] | 4[33,36,37,43] | 3[32,37,49,51] | 1[37] | 6[32,33,36,37,43,49,51] |
| | OR (95% CI) | 0.55 (0.29-1.03) | 0.77 (0.39-1.52) | 0.34 (0.08-1.35) | 0.67 (0.41-1.09) | 0.53 (0.24-1.15) |
| | $I^2$,% | 84.9 | 76.7 | 92.2 | - | 87.4 |
| | *P* | 0.001 | 0.005 | 0.001 | - | 0.001 |
| Menopausal status | No. of studies | 15[9-12,33,34,36,40,41,44,47,48,50-52] | 10[9,10,33,34,36,41,44,47,48,52] | 5[11,12,40,50,51] | 2[10,40] | 13[9,11,12,33,34,36,41,44,47,48,50-52] |
| | OR (95% CI) | 1.6 (1.18-2.17) | 1.8 (1.1-2.93) | 1.24 (0.97-1.60) | 1.02 (0.74-1.41) | 1.71 (1.22-2.41) |
| | $I^2$% | 92.9 | 94.7 | 49.7 | 0 | 93.9 |
| | *P* | <0.001 | <0.001 | 0.093 | 0.864 | <0.001 |
| Abortion history | No. of studies | 12[9,32,35,36,38-41,46-48,51] | 5[9,36,41,46-48] | 7[32,35,38-40,51] | 3[35,39,40,47] | 9[9,32,36,38,41,46,48,51] |
| | OR (95% CI) | 1.21 (0.97-1.50) | 1.48 (1.07-2.04) | 1.06 (0.7-1.59) | 1.38 (1.02-1.87) | 1.16 (0.9-1.51) |
| | $I^2$% | 79.3 | 78.9 | 81.9 | 0 | 83.4 |
| | *P* | 0.001 | 0.001 | 0.001 | 0.501 | 0.001 |
| Nulliparity | No. of studies | 8[9,11,31,33,37,40,45,48] | 4[9,33,37,45,48] | 4[11,31,40] | 2[37,40] | 6[9,11,31,33,45,48] |
| | OR (95% CI) | 1.43 (0.89-2.31) | 0.94 (0.53-1.65) | 2.12 (1.42-3.17) | 1.15 (0.20-6.65) | 1.60 (1.14-2.25) |
| | $I^2$% | 65.7 | 54.5 | 0 | 82.4 | 17.6 |
| | *P* | 0.005 | 0.086 | 0.528 | 0.017 | 0.3 |
| First pregnancy age | No. of studies | 10 [11,31,32,36,39,44,45,48,51] | 7[36,44,45,48] | 3[11,31,32,39,51] | 2[39] | 8[36,45,48,51][11,31,32,44] |
| | OR (95% CI) | 1.79 (1.36-2.35) | 1.88 (1.28-2.77) | 1.60 (1.26-2.04) | 2.02 (1.39-2.93) | 1.75 (1.30-2.35) |
| | $I^2$% | 79.6 | 83.1 | 0 | 2.9 | 79.1 |
| | *P* | 0.001 | 0.001 | 0.701 | 0.31 | 0.001 |
| Breastfeeding history | No. of studies | 8[9,36,38-40,42,48,51] | 4[9,36,42,48] | 4[38-40,51] | 2[39,40] | 6[9,36,38,42,48,51] |
| | OR (95% CI) | 0.68 (0.42-1.09) | 0.57 (0.24-1.36) | 0.75 (0.40-1.42) | 1.11 (0.58-2.12) | 0.56 (0.32-0.98) |
| | $I^2$% | 81.3 | 79.6 | 86.3 | 72.4 | 79.1 |
| | *P* | 0.001 | 0.002 | 0.001 | 0.057 | 0.001 |

| Menstrual and reproductive factors | Source of BC information | | Geographic area | | | | |
|---|---|---|---|---|---|---|---|
| | Hospital-based | Registry | North | South | West | East | Center |
| Menarche age | 6[32,33,36,37,43,49,51] | 1[37] | 2[36,51] | 2[33,37] | 2[32,43] | - | 1[49] |
| | 0.53 (0.24-1.15) | 0.67 (0.41-1.09) | 0.76 (0.13-4.36) | 0.51 (0.28-0.92) | 1.04 (0.69-1.58) | - | 0.1 (0.04-0.24) |
| | 87.4 | - | 92.2 | 55.9 | 0 | - | - |
| | 0.001 | - | 0.001 | 0.132 | 0.586 | - | - |
| Menopausal status | 14[9-12,33,34,36,40,41,44,48,50-52] | 1[47] | 5[36,41,47,51,52] | 3[10,33,40] | 1[9] | 1[34] | 5[11,12,44,48,50] |
| | 1.49 (1.11-1.98) | 4.18 (2.56-6.82) | 1.44 (0.89-2.33) | 1.06 (0.81-1.38) | 2.54 (1.41-4.56) | 1.23 (0.71-2.14) | 2.12 (1.35-3.33) |
| | 91.6 | - | 93.5 | 0 | - | - | 83.1 |
| | <0.001 | - | <0.001 | 0.916 | - | - | <0.001 |
| Abortion history | 11[9,32,35,36,38-41,46,48,51] | 1[47] | 4[36,41,47,51] | 1[40] | 3[9,32,39] | 2[35,46] | 2[38,48] |
| | 1.22 (0.94-1.58) | 1.21 (0.94-1.56) | 1.07 (0.83-1.38) | 1.14 (0.52-2.49) | 1.61 (1.14-2.27) | 2.06 (1.32-3.2) | 0.73 (0.27-1.94) |
| | 80.6 | - | 69.7 | - | 19.9 | 0 | 94.5 |
| | 0.001 | - | 0.019 | - | 0.287 | 0.914 | 0.001 |

*Contd...*

**Table 2: Contd...**

| Menstrual and reproductive factors | Source of BC information | | Geographic area | | | | |
|---|---|---|---|---|---|---|---|
| | Hospital-based | Registry | North | South | West | East | Center |
| Nulliparity | 7[9,11,31,33,40,45,48] | 1[37] | 0 | 3[33,37,40] | 1[9] | 0 | 4[11,31,45,48] |
| | 1.65 (1.19-2.30) | 0.52 (0.31-0.89) | - | 0.98 (0.46-2.11) | 1.34 (0.58-3.1) | - | 2.16 (1.42-3.27) |
| | 14.8 | - | - | 73.1 | - | - | 0 |
| | 0.317 | - | - | 0.024 | - | - | 0.771 |
| First pregnancy age | 10[11,31,32,36,39,44,45,48,51] | - | 2[36,51] | 0 | 2[32,39] | 0 | 6[11,12,31,44,45,48] |
| | 1.79 (1.36-2.35) | - | 2.41 (1.47-3.94) | - | 1.81 (1.21-2.73) | - | 1.63 (1.16-2.29) |
| | 79.6 | - | 0 | - | 55.5 | - | 76.1 |
| | 0.001 | - | 0.355 | - | 0.134 | - | 0.001 |
| Breastfeeding history | 7[9,36,38-40,48,51] | 1[42] | 2[36,51] | 1[40] | 3[9,39,42] | 0 | 2[38,48] |
| | 0.71 (0.42-1.20) | 0.46 (0.23-0.94) | 0.49 (0.24-0.99) | 1.55 (0.95-2.53) | 0.59 (0.38-0.92) | - | 0.84 (0.18-3.82) |
| | 83.3 | - | 28.7 | - | 29.1 | - | 95.2 |
| | 0.001 | - | 0.236 | - | 0.244 | - | 0.001 |

between abortion, nulliparity, and breastfeeding with BC. However, in the subgroup analysis for the history of abortion, high-quality studies and adjusted studies for BC risk factors showed a positive relationship between abortion and BC. According to a study by Besharat *et al*.,[55] nulliparity was not associated with the risk of BC. Also, in women who had more than a total of about 5 years of breastfeeding, the chance of developing BC was not statistically significant. Other independent studies also supported these results.[56,66,67] Another MA by Mao *et al*. (2019)[68] on Chinese women found an overall lower risk of BC for parous women, compared with nulliparous women. Also, this study indicated that early age at first childbirth is a protective factor for BC that is consistent with our study. A MA on Indian women has reported that age at first childbirth, breastfeeding, and nulliparity are all related to increased risk of BC.[57] The results of the mentioned study are not consistent with our study in terms of the relationship between breastfeeding and nulliparity with BC. On the other hand, according to the results of this study, in women with late first pregnancy, the risk of BC is increased, which is consistent with the current study. In meta-analyses, which were done on the data related to the Korean[69] and Southeast Asian women,[58,70] age at first pregnancy and the total period of breastfeeding and nulliparity were associated with an elevated risk of BC. In an SR and MA by Namiranian *et al*. (2014)[54] on the Eastern Mediterranean Region, the highest risk factor for BC was having no live birth. Also, age at first pregnancy more than 30 years old increased the risk of BC, which is congruent with the results of the present study. In subgroup analysis, breastfeeding had a preventive relationship with BC in studies conducted in north and west of Iran. Maybe the different breastfeeding patterns of the mothers must be considered in different regions.

Also, the results of the studies in Middle Eastern countries on the relationship between old age at first pregnancy and BC are contradictory. In some studies in Turkey,[59,60,71] older age at first pregnancy has been reported as a risk factor for BC, which is consistent with the present study, whereas some studies in Turkey,[62,63] Pakistan,[64] and Saudi Arabia[5] have yielded conflicting results. Overall, it seems that there are possible geographical differences in incidence and risk factors of BC due to racial variations, family history, and disease background, stress level, nutritional culture, environmental pollutions, and lifestyle.

About the relationship between abortion and BC, in an SR conducted by Yeganeh *et al*. (2018),[72] out of 25 articles examining abortion, 15 reported positive and 10 reported no relation between abortion and BC. The Collaborative Group on Hormonal Factors in BC published a MA that showed no difference in the risk of BC development in women who had one or more spontaneous or induced abortions.[73] These results were further supported by another cohort study in women from California.[74] The findings of these

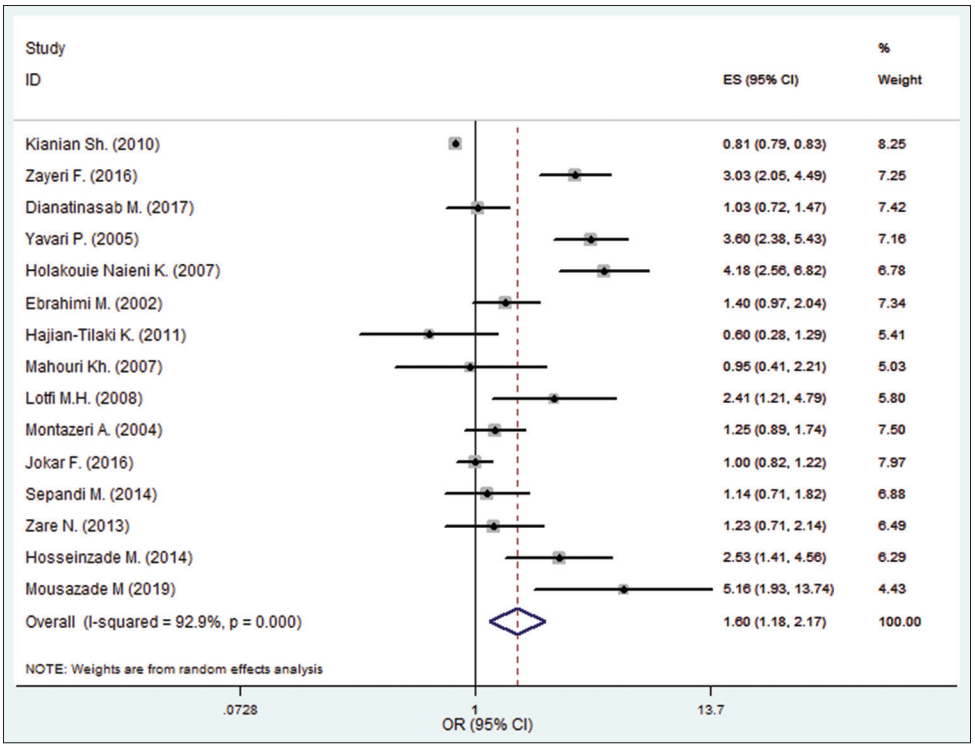


**Figure 3: Forest plot of the relationship between menopausal status and breast cancer using the random effects model**

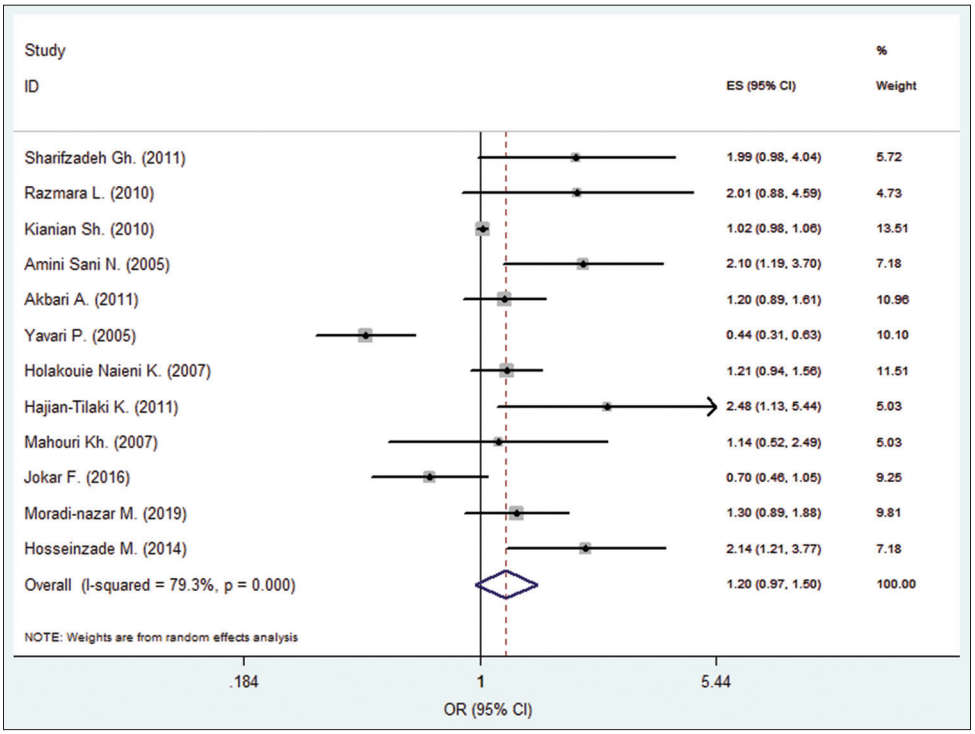


**Figure 4: Forest plot of the relationship between abortion and breast cancer using the random effects model**

studies and another study of Saudi Arabia are in line with the current study. However, many studies from Asia and Middle Eastern countries maintain the existence of a strong link between first-trimester abortions and BC risk.[75-77] But two MA studies[78,79] and Expert committee opinions by both American College of Obstetricians and Gynecologists[80] and National Cancer Institute[81] revealed that there was no significant relationship between induced abortion and BC in Chinese women. The considerable problem in studies about abortion is that abortion is illegal in some

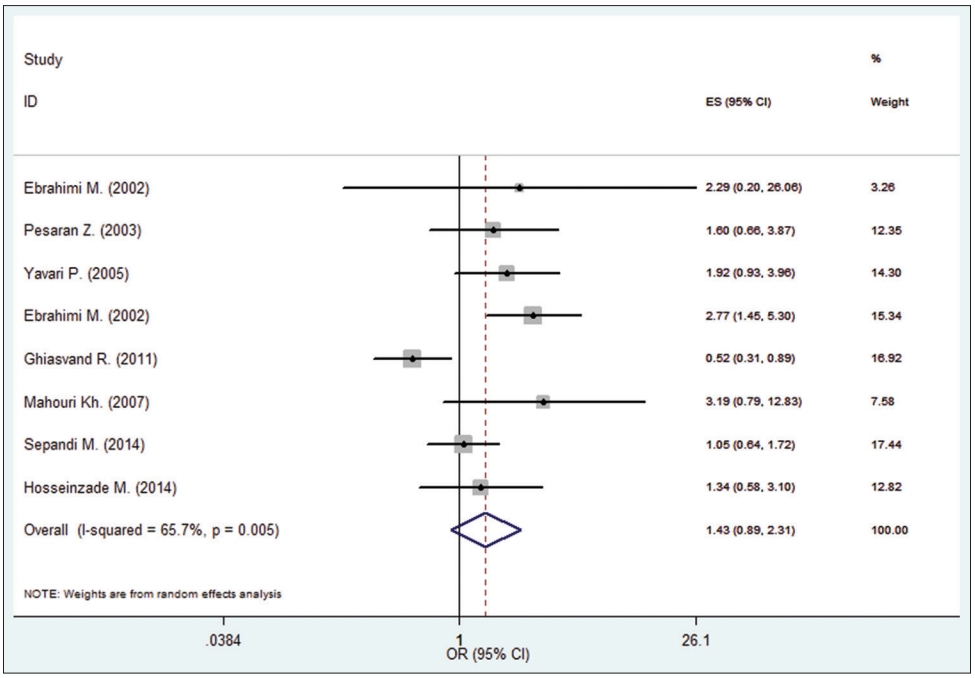


**Figure 5: Forest plot of the relationship between nulliparity and breast cancer using the random effects model**

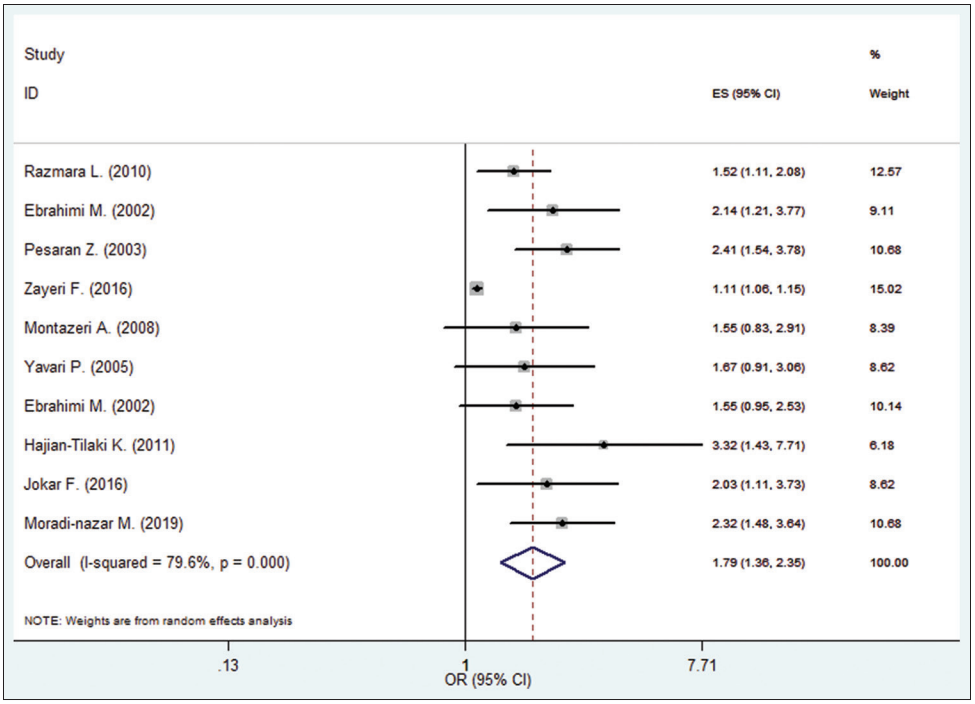


**Figure 6: Forest plot of the relationship between first pregnancy age and breast cancer using the random effects model**

countries, so studies conducted in these countries may report abortion rate less than its real rate. Therefore, in the present MA, given that the study population is from Iran, a country with restrictive regulations regarding abortion, the findings should be considered with caution. At the same time, in the subgroup with high-quality studies and the studies conducted in the west and east areas of Iran, this relationship was significant. According to the present study, although abortion and nulliparity were not considered risk factors for BC, abortion in the eastern and western regions of Iran and nulliparity in the central regions of Iran showed a significant relationship with BC. Also, in the northern and western regions of Iran, breastfeeding showed a preventive relationship with BC. In explaining this issue, we should mention the differences in access to screening and diagnostic services, genetic and racial differences,

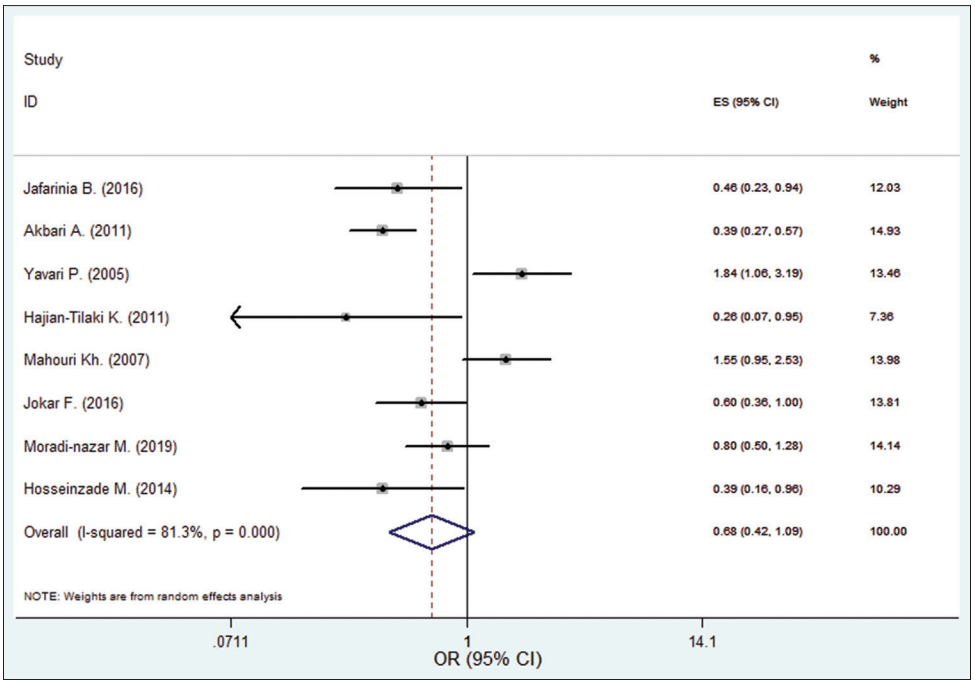


**Figure 7: Forest plot of the relationship between breastfeeding and breast cancer using the random effects model**

differences in household size, and access to reproductive health services in Iran provinces.

**Strength:** Previous meta-analyses focused on a risk factor and its various levels of exposure; however, our results focus on several factors regarding its identical exposure in Iranian women. Also, in the present MA, the risk factors of BC were examined by geographical regions of Iran, separately.

**Limitation:** This SR had several limitations. The first limitation was the availability and quality of the published data. Many studies did not include some statistical parameters (i.e., OR, CI), and the control groups of each risk factor were different. Hence, we had to exclude some studies of MA. Second, all of the included studies in this MA were case–control, so we need trials with high methodological quality including prospective cohort studies, as those are less susceptible to bias. It seems that in studies on these issues in Iran, there is a need for higher accuracy and quality in the method of performing and reporting the results of individual studies. Third, in most of the included studies in this MA, the sampling was hospital-based which may be convenient and inexpensive to collect but may be biased by factors such as age, socioeconomic status, and physical condition, that affect the likelihood of hospitalization for cases and controls. It is recommended that information of cancer registry or population-based control groups be used in future studies.

## Conclusions

Our findings revealed that menopausal status and first pregnancy age were shown to be significantly associated with increased BC risk, whereas menarche age, nulliparity, and breastfeeding were not associated with higher BC risk among Iranian females. In regard to the history of abortion, our findings revealed no association with abortion and BC, but in high-quality studies and adjusted studies for risk factors of BC, the relationship between abortion and BC was significant. The inconsistencies between our findings and other studies from other countries might be due to differences in race, stress level, nutritional culture, environmental pollutions, and lifestyle.

### Ethical approval

The present SR and MA is part of the first author's Ph.D. thesis under code of ethics: IR.MUMS.NURSEREC.1397.034, (Grant ID: 970008).

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This manuscript is part of Ph.D. thesis of the first author approved by Mashhad University of Medical Sciences, Mashhad, Iran, under the code of IR.MUMS.NURSEREC.1397.034 (Grant ID: 970008).

### Conflicts of interest

There are no conflicts of interest.

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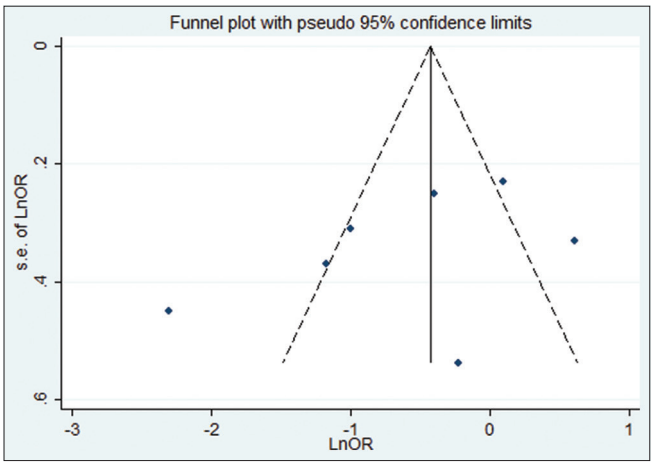
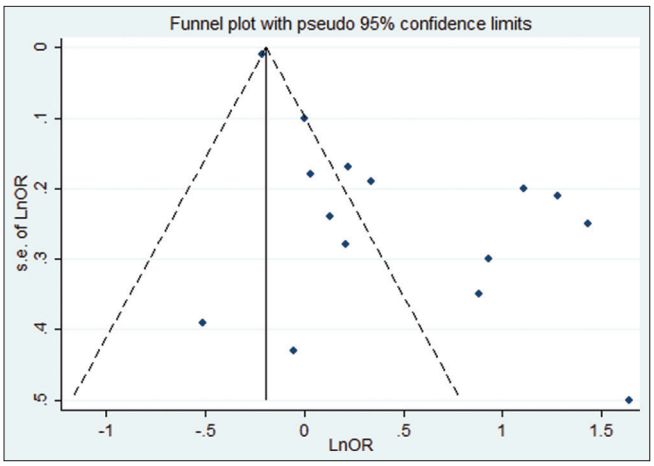
# Appendix

## Funnel Plots for publication bias

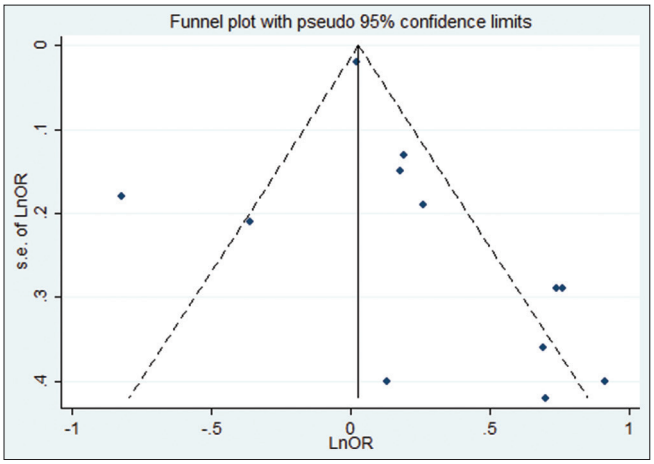
Articles performing **age of menarche** analysis



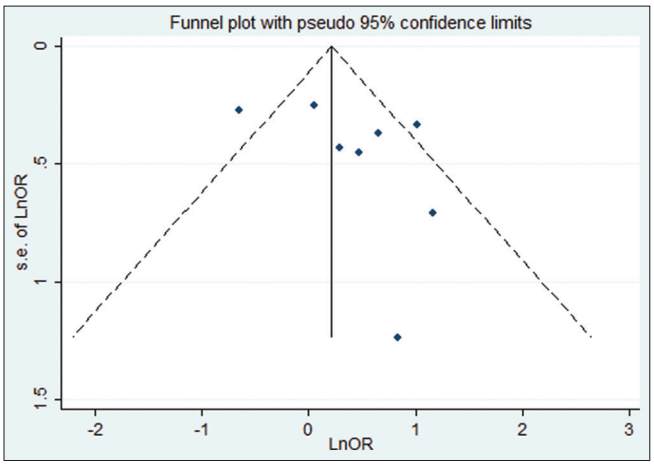

Articles performing menopause status analysis



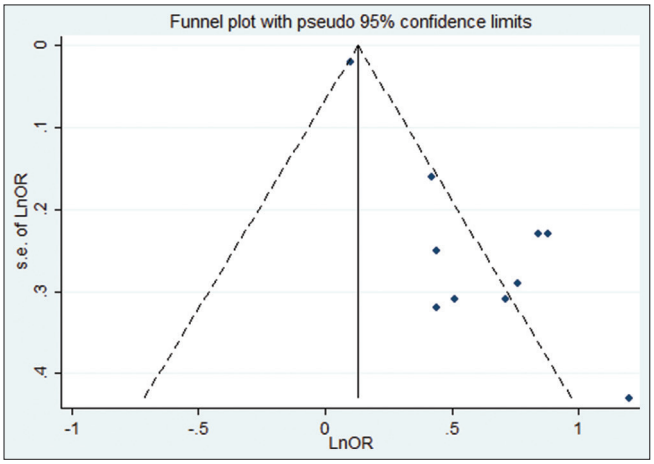

Articles performing abortion analysis



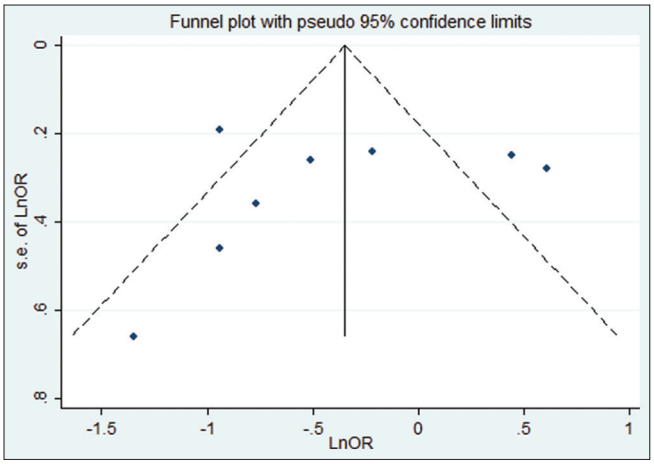
Articles performing nulliparous status analysis




Articles performing age of first pregnancy analysis




Articles performing breastfeeding analysis



**Quality assessment of included articles in the meta-analysis based on NOS**

| No. | Author (Ref.) | Selection | | | | Comparability | Exposure | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Sharifzadeh Gh. | * | * | * | * | ** | c | * | c | 7 |
| 2 | Razmara L. | * | * | * | * | -- | c | * | b | 5 |
| 3 | Ebrahimi M. | * | * | * | * | -- | c | * | b | 5 |
| 4 | Keihanian Sh. | * | * | * | * | * | c | * | b | 6 |
| 5 | Jafarinia B. | * | * | * | * | * | c | * | b | 6 |
| 6 | Pesaran Z. | * | b | * | b | ** | c | * | b | 5 |
| 7 | Amini Sani N. | c | * | * | * | ** | c | * | b | 6 |
| 8 | Marzbani B. | * | * | * | * | * | c | * | b | 6 |
| 9 | Zayeri F. | * | * | * | * | * | c | * | b | 6 |
| 10 | Dianatinasab M. | * | * | b | * | * | * | * | * | 7 |
| 11 | Montazeri A. (2008) | * | * | * | * | * | * | * | b | 7 |
| 12 | Akbari A. | c | * | * | b | ** | c | * | b | 5 |
| 13 | Yavari P. | * | b | b | * | * | c | * | b | 4 |
| 14 | Holakouie Naieni K. (2007) | b | * | * | b | ** | c | * | b | 5 |
| 15 | Ebrahimi M. | * | * | b | * | * | c | * | c | 5 |
| 16 | Hajian-Tilaki K. | * | * | * | * | * | c | * | b | 6 |
| 17 | Ghiasvand R. | * | * | * | * | ** | c | * | b | 7 |
| 18 | Mahouri Kh. | * | * | * | * | * | c | * | * | 7 |
| 19 | Lotfi M.H. | * | b | * | b | * | c | * | b | 4 |
| 20 | Montazeri A. (2004) | c | * | * | b | -- | * | * | b | 4 |
| 21 | Tehranian N. | c | b | * | * | ** | c | * | b | 5 |
| 22 | Jokar F. | * | * | * | * | * | c | * | c | 6 |
| 23 | Moradi-nazar M. | * | * | * | * | ** | * | * | * | 9 |
| 24 | Sepandi M. | * | * | * | b | -- | c | * | b | 4 |
| 25 | Zare N. | * | * | * | b | -- | c | * | c | 4 |
| 26 | Hosseinzade M. | * | * | * | * | * | c | * | b | 6 |
| 27 | Mousazade M | b | * | * | b | * | c | * | c | 4 |

Note: A study can be awarded a maximum of one star for each numbered item within the selection and exposure categories. A maximum of two stars can be given for comparability. In selection and exposure items: *adequately reported, "“b"” inadequately reported, "“c"” no reported. In comparability item: ** adequately reported, *inadequately reported