Preterm Birth and Breast Cancer Risk: A Systematic Review and Meta-Analysis

CURRENT STATUS: POSTED

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DOI:
10.21203/rs.3.rs-16045/v1

SUBJECT AREAS
Maternal & Fetal Medicine

KEYWORDS
Premature Birth; Breast Neoplasms; Parity; Meta-Analysis; Systematic Review
Abstract
Background: The characteristics of pregnancy, such as gestational age are related to the level of maternal hormones, which levels of these hormones can be associated with breast cancer (BC) risk. Therefore, the aim of this study was to determine the relationship between the preterm birth (PB) and BC risk in women in a systematic review and meta-analysis.

Methods: In this systematic review and meta-analysis, published studies were located back to the earliest available publication date (1983), using the Medline/PubMed, Embase, Scopus and Web of Science (Clarivate analytics) bibliographic databases. Eligibility, methodological quality, and data extraction were done by two independent reviewers, and finally, to calculate the pooled estimates, Meta-analysis was performed.

Results: Thirteen studies including a total of 2,845,553 women were included in this meta-analysis. Pooled results suggested that PB could increase the risk of BC (RR = 1.03, 95% CI: 1.00, 1.07; I² = 62.5%). Risk was significantly increased in women with a PB at >37 gestational weeks (RR = 1.03, 95% CI: 1.01, 1.06) and 26-31 gestational weeks (RR = 1.03, 95% CI: 1.01, 1.06) compared to those with 40-41 gestational weeks. A significant increment in the risk of BC in uniparous women with a PB (RR = 1.05, 95% CI = 1.01, 1.08) and women with >45 years (RR = 1.12, 95% CI = 1.01, 1.24) was observed.

Conclusions: The results of this study supported the higher risk of BC in all woman with PB, primiparous women and women with >45 years. Therefore, more care and screening for early detection of the disease is recommended in these women.

Background
According to GLOBOCAN's 2018 report, more than 18 million new cases of cancer, as well as 9.6 million deaths from cancer have been reported worldwide [1]. Meanwhile, breast cancer (BC) is the most common cancer among women in most countries of the world, accounting for 25% of cases of cancer and 12% of deaths due to cancer among women [2–6]. In 2016, BC is known as the most common cancer with 1.68 million cases (and 535,000 deaths and 15.1 million DALYs) [7].

A number of studies in different countries have shown that numerous factors, such as genetics,
lifestyle, obesity, reproductive factors and anthropometric factors, have an impact on BC and have contradictory results in this regard [1, 5, 8–15]. The results of some studies have shown that the number of previous pregnancies, as well as the age at first pregnancy and delivery, is associated with the risk of BC in women. Changes observed in estrogen levels during pregnancy [16, 17] as well as histologic changes in breast tissue can justify this relationship [18]. On the other hand, the characteristics of pregnancy, such as gestational age and birth weight are related to the level of maternal hormones, which levels of hormones can be associated with the risk of BC [19–22].

Swerdlow et al. [23] have shown in their study that gestational age is inversely associated with BC (especially before menopause), and the risk in women with gestational age of 26–31 weeks was 2.4 times compared to 40–41 weeks. However, M Kaijser et al. [24] suggested that PB and low birth weight are not associated with an increased risk of BC. Another study concluded that preterm labor cannot increase the risk of premenopausal BC, except for women with gestational age less than 32 weeks [25]. Therefore, there is no general consensus on this relationship.

In several other studies, conflicting results have been reported, which may be due to low sample size, methodological problems (in the design, analysis, and reporting of results) or the difference in risk factors in diverse populations. On the other hand, the primary studies in compared to meta-analysis study were hampered by low statistical power because of low sample size. Therefore, the aim of this study was to conduct a systematic review and meta-analysis of the relationship between the PB and BC risk in women.

Methods
Study design
This was a systematic review and meta-analysis. To design, run and report the findings, we followed the PRISMA Statement [26] (Preferred reporting items for systematic reviews and meta-analyses).

Data sources, search strategy, and selection criteria
Published studies were located back to the earliest available publication date (1983), using the Medline, Embase, Scopus, Web of Science bibliographic databases, and by hand-searching of reference lists of identified studies and pertaining review papers. We also checked the citation lists of relevant publications to find additional pertinent studies. As recommended in the Meta-Analysis of
Observational Studies in Epidemiology (MOOSE) guideline [27], we searched unpublished studies using gray literature databases. The literature search was made with no language or publication date restrictions. Search details are available in Appendix s1. The search results of different sources were combined, and duplicates were removed. The search results were evaluated by two independent reviewers (M.S and A.A-H) by screening titles and abstracts, followed by a full-text review. Consensus was reached by discussion or third party opinion (S.V).

Eligibility criteria
In the present systematic review and meta-analysis, studies were included if they met the following inclusion criteria: (1) observational studies (cohort, case-control, nested case-control or case-cohort studies) that evaluated the associations of PB with the risk of developing BC, (2) and they reported any form of effect size estimate (odds ratio (OR), hazard ratio (HR), standardized incidence ratio (SIR) or rate ratio (RR)). We excluded studies if: (1) they had cross-sectional design, (2) we were not able to extract the exact details about research method or results; (3) and presented only as abstracts, conference paper, letters to the editor and editorials.

Data extraction and risk of bias assessment:
All eligible studies were reviewed, and the following data was extracted by two investigators independently: (1) authors; (2) year of publication; (3) location; (4) study population; (5) duration of follow-up; (6) the number of cancer cases; (7) risk estimates with CIs; (8) confounders adjusted for in multivariate analysis. Methodological quality assessment for the included studies was done independently by two reviewers (M.S and J.H) using criteria as outlined in the Newcastle–Ottawa scaling for case-control and cohort studies. Explicit judgment regarding the following items was done: selection of the study groups, comparability of the groups and ascertainment of exposure and outcome. Any disagreement was resolved by discussion or third party opinion (S.V).

Statistical analyses
All effect size estimates (HRs, ORs and RRs) were treated as equivalent measures of risk. We calculated the pooled risk of BC associated with PB stratified by parity and menopausal status. Extracted risk estimates from primary studies were pooled using inverse-variance weighted DerSimonian-Laird random-effect models which incorporates between-study variability into the
calculations. To investigate whether the results of the meta-analysis were depend on a particular trial or group of trials, we recomputed the meta-analysis statistic after omitting one study at a time(sensitivity analysis). Additionally, we assessed the probability of publication bias with Egger's test, with P-value < 0.10 considered representative of statistically significant publication bias. All comparisons were two-tailed, and 95% confidence intervals (CI) were described where applicable. The Stata software (Version 13.0) (Stata Corp, College Station, Texas) was used for Meta-analysis.

Results

The Literature search

A flow diagram of the systematic review showing the study selection is presented in Fig. 1. The initial search identified 3,426 potentially relevant articles (315 from PubMed, 153 from Embase, 949 from Scopus, 499 from Web of Science and 25 from other sources), of which 606 articles were excluded because they were duplicates. Briefly, we identified 13 potentially relevant studies for meta-analysis.

Study characteristics

Table 1 outlines the main characteristics of the included studies. These six studies were conducted between 1998 and 2018, of which six studies were conducted after 2010. The studies were conducted in the United States (6 studies), Sweden (3 studies), United Kingdom (1 study), Denmark (1 study), Norway (1 study) and one in Iraq. In terms of study design, five of the thirteen studies were designed as a cohort, seven were case-control and one nested case-control study. Sample size ranged from 22,758 to 694,657 participants in cohort studies and 300 to 41,255 in case-control studies. The summary of methodological quality appraisal of the included studies is shown in additional file 2. All studies classified as good quality. All studies adopted appropriate approach to account for potential confounders. All cohort studies selected their exposed and nonexposed participants from the same community sample. Two of seven included case-control studies used hospital control and classified as moderate risk of selection bias. All studies provided adequate criteria for diagnosis of the outcomes of interest and provided a proper description of how the outcomes were measured.

| Author | Location | Design       | Sample size | Breast cancer ascertainment | Exposure source | Factors adjusted for in analyses |
|--------|----------|--------------|-------------|-----------------------------|-----------------|----------------------------------|
| Troisi, 1998 | USA | Case-control | Cases = 1,669 | Hospital | Hospital | Race, |
| Study | Country | Study Design | Cases | Controls | Database | Variables |
|-------|---------|--------------|-------|----------|----------|-----------|
| Troisi, 1998 | USA | Case-control | 1,669 | 1,505 | Hospital records | Race, education, parity, age, previous spontaneous and induced abortion, site of tumor |
| Hsieh, 1999 | Sweden | Nested case-control | 2318 | 10,199 | National Cancer Registry | Age, age at first birth |
| Melbye, 1999 | Denmark | Cohort | 474,156 | | Danish Cancer Registry | Age, age at first birth, parity, stillbirths, preterm and term deliveries, history of spontaneous and induced abortion |
| Innes, 2000 | USA | Case-control | 484 | 2,904 | Computerized Cancer registry | Woman’s social security number, full maiden, date of birth, race, county of residence |
| Vatten, 2002 | Norway | Cohort | 694,657 | | Norwegian Cancer Registry | Age, calendar period of diagnoses, total number of births |
| Innes, 2004 | USA | Case-control | 2,522 | 10,052 | Computerized Cancer registry | Maternal race (black, non-Hispanic white, Hispanic and other), marital status, maternal education |
| Cnattingius, 2005 | Sweden | Cohort | 314,019 | | Cancer Register | Age, placental weight, birth weight, gestational age, infant sex, family situation, smoking habits, mother’s country of birth, height, BMI, pregnancy induced hypertensive diseases, vaginal bleeding in late pregnancy, diabetes mellitus, and parity |
| Nechuta, 2010 | USA | Case-control | 8,251 | 33,004 | Michigan Cancer Surveillance Program’s statewide cancer registry | Age at first and last birth, education at first birth, infant’s gender at first and last birth, parity, maternal birth year race |
| Sanderson, 2012 | USA | Case-control | Cases = 979 Controls = 974 | Rio Grande Valley located at the southern tip of Texas | Rio Grande Valley located at the southern tip of Texas | Age, family history of breast cancer, age at menarche, menopausal status, parity, BMI, use of oral contraceptives, use of hormone replacement therapy, alcohol intake, number of mammograms in past 6 years, physical activity |
| Altaha, 2013 | Iraq | Case control | Cases = 100 Controls = 200 | Oncology clinic in AL-Ramadi General Hospital | Al-Anbar governorate | Age of the women in years, residence of women whether urban or rural, marital status, education level, occupation of women, age at menarche, age at first full term delivery, number of live births, number of stillbirths, number of previous abortions before the 24th week of pregnancy, whether it is spontaneous or induced |
| Troisi, 2013 | USA | Case-control | 22,758 | Cancer Surveillance System (CSS) of western Washington | Washington State Cancer Registry (WSCR) | Parity, calendar year of delivery, age at delivery, race, ethnicity |
| Hajiebrahimi, 2016 | Sweden | Cohort | Cases = 8,327 Controls = 8,327 | Swedish Cancer Register | Medical Birth Register | Age at latest pregnancy, parity, educational level and calendar time of offspring birth, age at latest pregnancy, parity, educational level, calendar year, gestational age |
| Swerdlow, 2018 | UK | Cohort | 83,451 | National Health Service Central Registers | National Health Service Central Registers | Age, time since recruitment to cohort, benign breast |
Overall association between PB and BC

Thirteen studies including a total of 2,845,553 women were included in this meta-analysis. Pooled results suggested that PB could increase the risk of BC (RR = 1.03, 95% CI: 1.00, 1.07; I² = 62.5%, Fig. 2). There was an evidence for publication bias (Egger’s regression intercept: 0.68, 95%CI: 0.01 to 1.35, P = 0.045, Fig. 3). Sensitivity analysis showed that the estimates of the pooled SMD range from 1.02 (95% CI: 0.98 to 1.06) to 1.04 (95% CI: 1.00 to 1.07), suggesting that no one study is substantially influencing the pooled estimate.

Subgroup analysis
PB < 37 compared to > 37 gestational weeks

Three (one cohort and two case-control) studies including a total of 487,835 women evaluated the association between PB and BC. When the studies were combined, there was no difference in the risk of BC between women with a PB at < 37 gestational weeks and who with a PB > 37 gestational weeks (RR = 1.13, 95% CI: 0.86, 1.39; I² = 54.7%, Fig. 2).

PB 32–36 compared to > 37 gestational weeks

Six studies comprising 2,036,812 participants investigated the risk of BC in women with a PB at 32–36 compared to women with a PB at > 37 gestational weeks. The summary RR of BC for the 32–36
compared with > 37 gestational weeks categories was 1.01 (95% CI, 0.98, 1.04) with low heterogeneity ($I^2 = 27.7\%$, $P$ for heterogeneity $= 0.19$) (Fig. 2).

PB < 32 compared to > 37 gestational weeks
A total of seven studies (including 2,037,112 participants and 150,902 cases) were included in the meta-analysis. When the studies were combined, there was no difference in the risk of BC between women with a PB at < 32 gestational weeks and those with > 37 gestational weeks (RR = 0.99, 95% CI: 0.81, 1.17; $I^2 = 83.2\%$, Fig. 2).

PB 37–39 compared to 40–41 gestational weeks
Three studies including 794,762 women assessed the risk of BC. Risk was, significantly increased in women with a PB at > 37 gestational weeks compared to those with 40–41 gestational weeks (RR = 1.03, 95% CI: 1.01, 1.06; $I^2 = 0\%$, Fig. 2).

PB 32–36 compared to 40–41 gestational weeks
There were three studies with 794,762 participants (two cohort and one case-control) that compared the risk of BC in women with a PB at 32–36 compared to women with 40–41 gestational weeks. The pooled analysis revealed that the PB was not associated with BC risk (RR = 1.04, 95% CI: 0.89, 1.19) using a random-effects model, and significant heterogeneity was observed among individual studies ($I^2 = 67.1\%$, $P$ for heterogeneity $= 0.01$).

PB 26–31 compared to 40–41 gestational weeks
Three studies including 794,762 women assessed the risk of BC. A significant increment in the risk of BC (RR = 1.03, 95% CI: 1.01, 1.06) was observed in women with a PB at 26–31 gestational weeks compared to those with 40–41 gestational weeks, with non-significant heterogeneity ($I^2 = 0\%$, $P$ heterogeneity $= 0.42$) (Fig. 2).

Uniparous compared to multiparous
Four studies including 2,444,775 participants assessed the risk of BC in uniparous women. The overall summary RRrs of the uniparity versus the multiparity category show that parity modify the association between PB and BC. A significant increment in the risk of BC in uniparous women with a PB (RR = 1.05, 95% CI = 1.01, 1.08) was observed, while this relationship in multiparous women was not significant (RR = 1.03, 95% CI = 1.00, 1.07).
BC diagnosis age

All studies were included in the meta-analysis of PB and BC risk by age status. The relationship between PB and BC risk showed a significant increment (RR = 1.12, 95% CI = 1.01, 1.24) in women with > 45 years category but in women with < 45 years category (RR = 0.95, 95% CI = 0.83, 1.07).

Discussion

To assess the relationship of gestational age and BC risk, we carried out a systematic review and meta-analysis in which, out of 3,426 potentially relevant articles, 13 relevant studies were included in the meta-analysis. The main result of this study revealed that there is mild evidence that support the relationship between PB and women BC risk, since the risk in women with PB were on average at a 3% greater risk of BC. And also, this meta-analysis provided some mild evidence of higher BC risk in women with a birth at 26–31 and 37–39 weeks compared to 40–41 weeks. The main findings of our study recognized that the PB increases the risk of BC in women with > 45 years. And also the results showed that PB in primiparous women could lead to an increased risk of BC, while in multiparous women, this relationship was not observed. However, it should be noted that in these analyzes, the effect of other effective variables on the relationship between PB and the risk of BC has not been adjusted, therefore, the interpretation and generalization of the findings must be done with caution.

The present systematic review and meta-analysis suggested an increase in the BC risk (RR = 1.03) in women with a PB 26–31 gestational weeks compared to 40–41 gestational weeks. Similar to our study, Swerdlow et al. [23] have shown in their study that the risk in women with gestational age of 26–31 weeks was 2.4 times compared to 40–41 weeks. Previous studies as well as the results of this study showed that early delivery may increase the risk of BC. Swerdlow et al. [23] have suggested that hormonal stimulation and breast proliferation at the beginning of pregnancy and the lack of enough opportunity for differentiation that occurs at the end of pregnancy are the cause of this relationship. Mammary cells in human and animals differentiate in the third trimester [28–30] and therefore a full term pregnancy is considered as a protective factor for BC [31]. Therefore, term or post-term pregnancy may be expected to increase the degree of differentiation, which will reduce the risk of BC.
Oestrogens are one of the effective factors in BC etiology [32], and increased concentrations of oestrogens during pregnancy may affect the risk of BC in daughters. Babies born before the 28th week of pregnancy have high levels of estrogen after birth and the previous studies have shown that birth before 32 weeks of pregnancy is a major risk factor for BC [24, 33, 34]. Therefore, the relationship between preterm delivery and the risk of BC can be explained by changes observed in levels of these hormones.

In our study, the risk of BC in women with preterm delivery at 26–31 weeks compared with compared with delivery at 41–41 weeks did not have a significant difference in risk of breast cancer. As same as our results, Innes KE and Byers TE in their study [35] concluded that very or extreme PB is related to higher risk of maternal BC risk. In another similar study by Melbye M et al. [25], the results showed a higher risk of BC in women with gestational age less than 32 weeks. Some studies have contradicted our findings. M Kaijser et al. [24] reported that PB are not associated with an increased risk of breast cancer.

Some studies have reported the relationship between the induced abortion and BC risk [36, 37]. Probably a part of the relationship between abortion and BC risk can be attributed to the duration of pregnancy. On the other hand, “Collaborative Group on Hormonal Factors in Breast Cancer” in a meta-analysis of 53 studies suggested that abortion is not associated with increased risk of BC [38]. Therefore, this relationship is still ambiguous and further studies are needed.

The findings of this meta-analysis were in line with this, with the higher BC risk for PB, significantly for post-menopausal BC and primiparous women and also borderline significantly for BC overall. Some studies evaluated the association of PB and BC risk in parous and nulliparous women. Melbye M et al. [25] reported a higher risk of BC in parous women with preterm delivery below 32 weeks compared with women with term delivery. Yongchun Deng et al. [36] in a meta-analysis study revealed that in parous women, induced abortion can increase the BC risk, but it was not significant in the nulliparous women.

Our study documented that the PB increases the risk of BC in women with > 45 years, but not in women with < 45 years. As accord to our results, Melbye M et al. [25] concluded that preterm labor
cannot increase the risk of premenopausal breast cancer.

In terms of generalizability of our results, it seems the results are generalizable to various populations because it was a systematic review and meta-analysis and pooled the different results from different countries. It should also be mentioned that there was no significant heterogeneity between primary studies.

There are some limitations in this study. The most important limitation of this study was that the gestational age had different categories in primary studies, making it difficult to extract needed data and analysis, and led to different subgroups analyzes. Another limitation of this study was that there are some potential confounder variables in the relationship between PB and BC risk, which in this study was not possible to adjust their effect.

Conclusion
In summary, the results of this study showed that the risk of BC in women with very early PB is significantly higher. Also, PB in women with > 45 years, as well as primiparous women has a significant relationship with the increased risk of breast cancer.

Abbreviations
BC:Breast Cancer, OR:Odds Ratio, RR:Risk Ratio, HR:Hazard Ratio, SIR:Standardized Incidence Ratio, CI:Confidence Interval, PB:Preterm Birth, MeSH:Medical Subject Headings, PRISMA:Preferred Reporting Items for Systematic Review and Meta-Analysis, MOOSE:Meta-Analysis of Observational Studies in Epidemiology.

Declarations

Ethics approval and consent to participate
This work did not require any written patient consent.

Consent for publication
Not applicable.

Availability of data and material
The datasets of this article are included within the article.

Competing interests
All authors declared no conflict of interest.

**Funding**

Not applicable

**Authors' contributions**

MR, MS, AM-H, SV, AA-H and AE conceived the study. MS, AA-H, SV and AM-H collected the data. All authors contributed equally to draft the manuscript. MS, AA-H, MR and AE analyzed the data and all authors revised the manuscript and approved the final version.

**Acknowledgements**

We would like to thank the authors of included studies who sent required row data if needed.

**References**

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A: *Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries*. *CA: A Cancer Journal for Clinicians* 2018, *68*(6):394-424.

2. DeSantis CE, Fedewa SA, Goding Sauer A, Kramer JL, Smith RA, Jemal A: *Breast cancer statistics, 2015: Convergence of incidence rates between black and white women*. *CA: a cancer journal for clinicians* 2015.

3. Siegel RL, Miller KD, Jemal A: *Cancer statistics, 2017*. *CA: A Cancer Journal for Clinicians* 2017, *67*(1):7-30.

4. Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, Allen C, Hansen G, Woodbrook R, Wolfe C: *The global burden of cancer 2013*. *JAMA oncology* 2015, *1*(4):505-527.

5. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A: *Global cancer statistics, 2012*. *CA: A Cancer Journal for Clinicians* 2015, *65*(2):87-108.

6. Alsharif U, El Bcheraoui C, Khalil I, Charara R, Moradi-Lakeh M, Afshin A, Collison M, Chew A, Krohn KJ, Daoud F et al: *Burden of cancer in the Eastern Mediterranean Region, 2005-2015: findings from the Global Burden of Disease 2015 Study*. *International Journal of*
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1. Ghiasvand R, Maram ES, Tahmasebi S, Tabatabaee SHR: Risk factors for breast cancer among young women in southern Iran. *International journal of cancer* 2011, 129(6):1443-1449.

2. Gibson LJ, Hery C, Mitton N, Gines-Bautista A, Parkin DM, Ngelangel C, Pisani P: Risk factors for breast cancer among Filipino women in Manila. *International journal of cancer* 2010, 126(2):515-521.

3. Mørch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard Ø: Contemporary Hormonal Contraception and the Risk of Breast Cancer. *New England Journal of Medicine*
2017, 377(23):2228-2239.

4. Nelson HD, Zakher B, Cantor A, Fu R, Griffin J, O'Meara ES, Buist DSM, Kerlikowske K, van Ravesteyn NT, Trentham-Dietz A et al: Risk Factors for Breast Cancer for Women Age 40 to 49: A Systematic Review and Meta-analysis. Annals of internal medicine 2012, 156(9):635-648.

5. Palmer JR, Wise LA, Horton NJ, Adams-Campbell LL, Rosenberg L: Dual effect of parity on breast cancer risk in African-American women. Journal of the National Cancer Institute 2003, 95(6):478-483.

6. Clapp JF, 3rd, Schmidt S, Paranjape A, Lopez B: Maternal insulin-like growth factor-I levels (IGF-I) reflect placental mass and neonatal fat mass. American journal of obstetrics and gynecology 2004, 190(3):730-736.

7. Hill M, Parizek A, Kancheva R, Duska M, Velikova M, Kriz L, Klimkova M, Paskova A, Zizka Z, Matucha P et al: Steroid metabolome in plasma from the umbilical artery, umbilical vein, maternal cubital vein and in amniotic fluid in normal and preterm labor. The Journal of steroid biochemistry and molecular biology 2010, 121(3-5):594-610.

8. Russo J, Russo IH: Development of the human breast. Maturitas 2004, 49(1):2-15.

9. Boyne MS, Thame M, Bennett FJ, Osmond C, Miell JP, Forrester TE: The relationship among circulating insulin-like growth factor (IGF)-I, IGF-binding proteins-1 and -2, and birth anthropometry: a prospective study. The Journal of clinical endocrinology and metabolism 2003, 88(4):1687-1691.

10. Bukowski R, Chlebowski RT, Thune I, Furberg A-S, Hankins GDV, Malone FD, D’Alton ME: Birth weight, breast cancer and the potential mediating hormonal environment. PloS one 2012, 7(7):e40199-e40199.

11. Mucci LA, Lagiou P, Tamimi RM, Hsieh CC, Adami HO, Trichopoulos D: Pregnancy estriol, estradiol, progesterone and prolactin in relation to birth weight and other birth size
variables (United States). Cancer causes & control : CCC 2003, 14(4):311-318.

2. Troisi R, Potischman N, Roberts J, Siiteri P, Daftary A, Sims C, Hoover RN: Associations of maternal and umbilical cord hormone concentrations with maternal, gestational and neonatal factors (United States). Cancer causes & control : CCC 2003, 14(4):347-355.

3. Swerdlow AJ, Wright LB, Schoemaker MJ, Jones ME: Maternal breast cancer risk in relation to birthweight and gestation of her offspring. Breast cancer research : BCR 2018, 20(1):110-110.

4. Kaijser M, Akre O, Cnattingius S, Ekbom A: Preterm birth, birth weight, and subsequent risk of female breast cancer. British journal of cancer 2003, 89(9):1664-1666.

5. Melbye M, Wohlfahrt J, Andersen AM, Westergaard T, Andersen PK: Preterm delivery and risk of breast cancer. Br J Cancer 1999, 80(3-4):609-613.

6. Moher D, Liberati A, Tetzlaff J, Altman DG: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine 2009, 6(7):e1000097.

7. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB: Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Jama 2000, 283(15):2008-2012.

8. Ferguson DJ, Anderson Tj: A morphological study of the changes which occur during pregnancy in the human breast. Virchows Archiv A, Pathological anatomy and histopathology 1983, 401(2):163-175.

9. Russo J, Tay LK, Russo IH: Differentiation of the mammary gland and susceptibility to carcinogenesis. Breast cancer research and treatment 1982, 2(1):5-73.

10. Russo J, Balogh GA, Heulings R, Mailo DA, Moral R, Russo PA, Sheriff F, Vanegas J, Russo IH: Molecular basis of pregnancy-induced breast cancer protection. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)
2006, 15(4):306-342.

1. Russo J, Mailo D, Hu YF, Balogh G, Sheriff F, Russo IH: Breast differentiation and its implication in cancer prevention. Clinical cancer research : an official journal of the American Association for Cancer Research 2005, 11(2 Pt 2):931s-936s.

2. Travis RC, Key TJ: Oestrogen exposure and breast cancer risk. Breast cancer research : BCR 2003, 5(5):239-247.

3. Ekbom A, Erlandsson G, Hsieh C, Trichopoulos D, Adami HO, Cnattingius S: Risk of breast cancer in prematurely born women. Journal of the National Cancer Institute 2000, 92(10):840-841.

4. Trichopoulos D: Hypothesis: does breast cancer originate in utero? Lancet (London, England) 1990, 335(8695):939-940.

5. Innes KE, Byers TE: First pregnancy characteristics and subsequent breast cancer risk among young women. International journal of cancer 2004, 112(2):306-311.

6. Deng Y, Xu H, Zeng X: Induced abortion and breast cancer: An updated meta-analysis. Medicine 2018, 97(3):e9613-e9613.

7. Carroll P: Breast cancer risk and induced abortion: the debate continues. The Lancet Oncology 2002, 3(5):267.

8. Breast cancer and abortion: collaborative reanalysis of data from 53 epidemiological studies, including 83 000 women with breast cancer from 16 countries. The Lancet 2004, 363(9414):1007-1016.

Supplementary Files Legend
Supplementary 1: Search Strategy
Supplementary 2: Table s2: Results of the critical appraisal of the included case control studies
Figures
Figure 1 Flow diagram of the literature search for studies included in meta-analysis

Figure 1
Flow diagram of the literature search for studies included in meta-analysis
Figure 2 Forest plot describing the association between preterm birth and breast cancer risk.
Figure 2

Forest plot describing the association between preterm birth and breast cancer risk
Figure 3 The Funnel plot of included primary studies
Figure 3

The Funnel plot of included primary studies
**Figure 4** Forest plot describing the association between preterm birth and breast cancer risk on the basis of parity status.
Figure 4
Forest plot describing the association between preterm birth and breast cancer risk on the basis of parity status
Figure 5 Forest plot describing the association between preterm birth and breast cancer risk on the basis of age categories
Figure 5

Forest plot describing the association between preterm birth and breast cancer risk on the basis of age categories

Supplementary Files

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PRISMA 2009 checklist.doc
Appendix s1.doc
Supplementary 2.docx