REVIEW

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

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Abstract

Backgrounds: Changes in estrogen levels during pregnancy as well as histologic changes in breast tissue can justify the relationship of preterm birth (PTB) and the risk of BC. Therefore, there is a hypothesis that the duration of pregnancy can be associated with BC, so the aim of this study was to find out whether PTB is a risk factor for BC. **Methods:** Published studies were located back to the earliest available publication date (1983), using the Medline/ PubMed, Embase, Scopus, and Web of Science bibliographic databases. This review included the cohort or case control studies that assessed the association between PTB and BC. Pooled effect sizes with corresponding 95% confidence intervals (CI) were calculated using random-effects models. **Results:** Thirteen studies including a total of 2,845,553 women were included in this meta-analysis. Pooled results suggested that PTB could increase the risk of BC (RR: 1.03, 95% CI: 1.00, 1.07; I2= 62.5%). The risk was significantly increased in women who delivered at 37-39 (RR: 1.03, 95% CI: 1.01, 1.06) and 26-31 weeks of gestation (RR: 1.25, 95% CI: 1.04, 1.47) compared to women who delivered at 40-41 weeks of gestation. A significant increment in the risk of BC was observed in primiparous (RR: 1.05, 95% CI: 1.01, 1.08) and women older than 45 years (RR = 1.12, 95% CI: 1.01, 1.24). There was no difference between other gestational age categories. **Conclusions:** Our findings add to evidence that short gestation pregnancies may increase the risk of BC, especially in primiparous and women older than 45 years. Considering the methodological weaknesses existed in included studies, minor clinical differences, and the complexity of the exact pathophysiology of PTB on BC, the precise position of PTB as a risk factor for BC in clinical practice is undetermined. Further studies are still needed.

Keywords: Preterm birth- breast cancer- systematic review- meta-analysis

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Introduction

According to GLOBOCAN's 2020, more than 19 million new cases of cancer, as well as 9.95 million deaths from cancer have been reported worldwide (Bray et al., 2018). Breast cancer (BC) is the most common cancer among women in most countries of the world, accounting for 11.7% of cases of cancer and 6.9% of deaths due to cancer among women (DeSantis et al., 2015; C. Fitzmaurice et al., 2018; Christina Fitzmaurice et al., 2015; Siegel et al., 2017; Torre et al., 2015). BC is known as the most common cancer with 2.26 million cases, 684,996 deaths, and 17,708,600 DALYs in 2017 (C. Fitzmaurice et al., 2018).

A number of studies in different countries showed that numerous factors had a significant impact on BC, and there are contradictory results in this regard such as older age, family history of breast cancer, early menarche, late menopause, high body mass index, being obese or overweight, exposure to tobacco smoke, and high dietary intake of fats or fatty foods (Anothaisintawee et al., 2013; Antoniou et al., 2006; Bray et al., 2018; Collaborative Group on Hormonal Factors in Breast, 2012; Ghiasvand et al., 2011; Gibson et al., 2010; Mørch et al., 2017; Nelson et al., 2012; Palmer et al., 2003; Torre et al., 2015). One of the most important influencing factors is reproductive factors. The results of some studies have shown that the number of previous pregnancies, age at first pregnancy, and age at first delivery was associated with the risk of BC in women. Changes observed in estrogen levels

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during pregnancy (Clapp et al., 2004; Hill et al., 2010) and histologic changes in breast tissue can justify this relationship (Russo et al., 2004). On the other hand, the characteristics of pregnancy, such as gestational age and birth weight, are related to the level of maternal hormones, which can be associated with the risk of BC (Boyne et al., 2003; Bukowski et al., 2012; Mucci et al., 2003; Troisi et al., 2003). Therefore, there is a hypothesis that the duration of pregnancy can be associated with BC.

Various studies have reported conflicting results on the association between PTB and BC. In some studies, inverse relationship (especially before menopause) has been reported (Swerdlow et al., 2018) and the results of some studies have shown that there is no significant relationship (Kaijser et al., 2003; Melbye et al., 1999). Therefore, there is no consensus on this relationship. On the other hand, the primary studies compared to meta-analysis were disadvantaged by low statistical power because of low sample size. Consequently, due to the contradictory results of the primary studies and the lack of a systematic review, our goal is to conduct a systematic review and meta-analysis in order to aggregate the findings of previous studies to assess the relationship between PTB on the risk of BC.

Materials and Methods

Study design

This was a systematic review and meta-analysis. To design, run, and report the findings, we followed the PRISMA Statement (Moher et al., 2009) (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) until Jun 2020, 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 (Stroup et al., 2000), we searched unpublished studies using gray literature databases, such as “worldcat”, “ntis”, “ahrq”, and “opengrey”. Furthermore, we contacted with experts for additional information and unpublished studies. 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 assessed 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 examine the influence of preterm deliveries on the risk of breast cancer, (2) the BC detected by objective techniques such as t molecular pathology, digital mammography, computer-aided detection (CAD) systems, ultrasound imaging, and magnetic resonance imaging (MRI), (3) gestational age categorized into six groups: <32 weeks, 32-36 weeks, 37-39 weeks, 40-41 weeks and >42 weeks, (4) and reports of 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, case series, case report, or ecologic design, (2) we were not able to extract the exact details about research method or results; (3) and they were 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 were 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. A ‘star system’ judgment regarding eight items in three broad perspectives was done: selection of the study groups, comparability of the groups, and ascertainment of exposure and outcome. Stars awarded for each quality item serve as a quick visual assessment. Stars are awarded such that the highest quality studies are awarded up to nine stars. Any disagreement was resolved by discussion or third-party opinion (S.V).

Statistical analysis

All studies reported adjusted RR with 95% CI. All adjusted effect size estimates (HRs, ORs, and RRs) were treated as equivalent measures of risk. We calculated the pooled adjusted risk of BC associated with PTB stratified by parity and menopausal status. Extracted risk adjusted 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 depending 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 searches

A flow diagram of the systematic review showing the study selection is presented in Figure 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 Table 2. All studies were 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. As per NOS assessment, two of seven case-control studies showed an evidence of moderate selection bias, regarding their hospital-based controls. All studies provided adequate criteria for diagnosis of the outcomes of interest, and provided a proper description of how the outcomes were measured.

Overall association between preterm birth and breast cancer

Thirteen studies including a total of 2,845,553 women were included in this meta-analysis. Pooled results suggested that PTB could increase the risk of BC (RR= 1.03, 95% CI: 1.00, 1.07; I^2= 62.5%, p-value for heterogeneity< 0.001, Figure 2). There was an evidence for publication bias (Egger's regression intercept: 0.68, 95%CI: 0.01 to 1.35, P= 0.045, Figure 3). Sensitivity analysis showed that the estimates of the pooled RR ranged 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 was substantially influencing the pooled estimate.

Subgroup analysis

Women who delivered at <37 compared to those delivered at >37 weeks of gestation

Three (one cohort and two case-control) studies including a total of 487,835 women assessed the association between PTB and BC. When the studies were combined, there was no difference in the risk of BC between women who delivered at <37 compared to those delivered at >37 weeks of gestation (RR = 1.13, 95% CI: 0.86, 1.39; I^2= 54.7%, p-value for heterogeneity= 0.051,

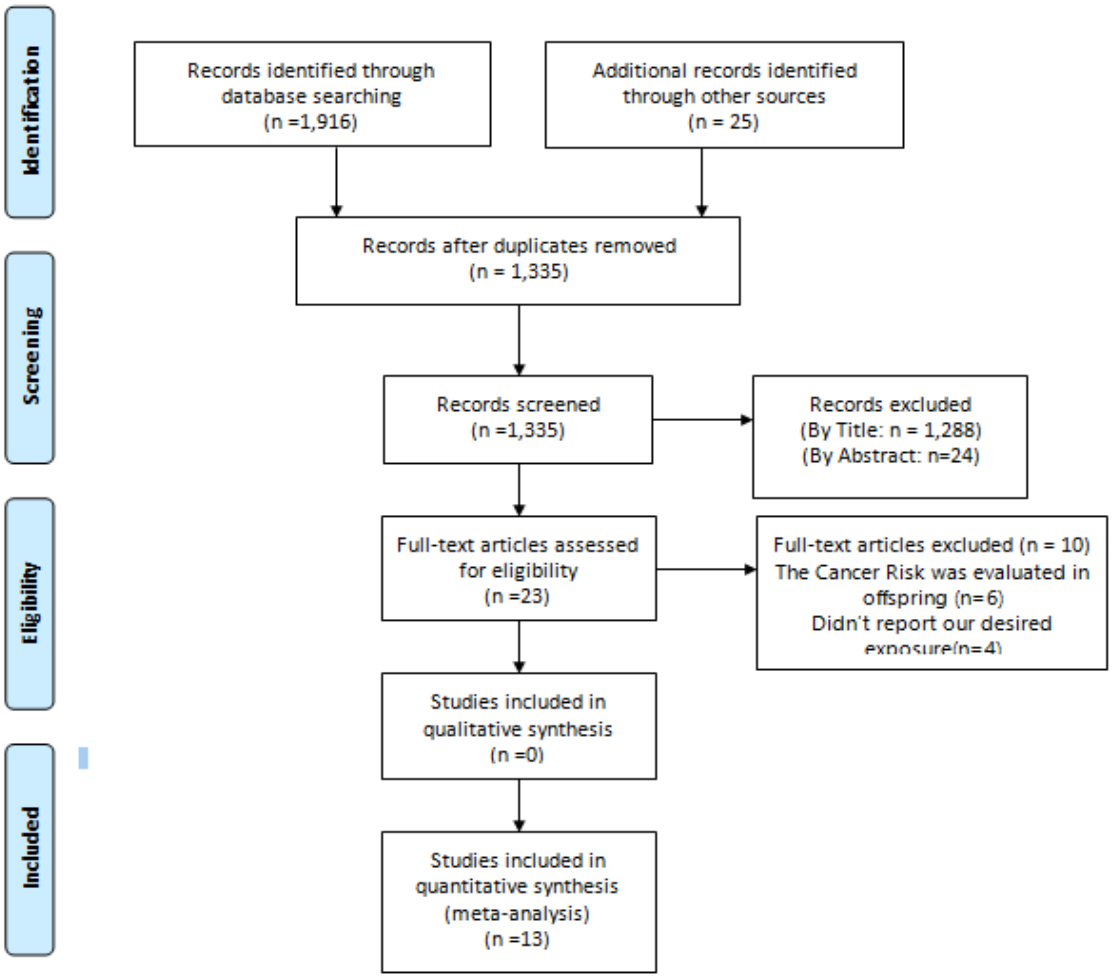

Figure 1. Flow Diagram of the Literature Search for Studies Included in Meta-Analysis

Table 1. The Characteristics of Included Primary Studies

Author	Location	Design	Sample size	Breast cancer ascertainment	Exposure source	Factors adjusted for in analyses
Troisi, 1998	USA	Case-control	Cases= 1,669 Controls= 1,505	Hospital records	Hospital records	Race, education, parity, age, previous spontaneous and induced abortion, site of tumor
Hsieh, 1999	Sweden	Nested case-control	Cases= 2318 Control= 10,199	National Cancer Registry	Swedish National Board	Age, age at first birth
Melbye, 1999	Denmark	Cohort	474,156	Danish Cancer Registry	Danish Civil Registration System	Age, age at first birth, parity, stillbirths, preterm and term deliveries, history of spontaneous and induced abortion.
Innes, 2000	USA	Case-control	Cases= 484 Controls= 2,904	Computerized Cancer registry	Birth registry data	Woman's social security number, full maiden, date of birth, race, county of residence
Vatten, 2002	Norway	Cohort	694,657	Norwegian Cancer Registry	Medical Birth Registry	Age, calendar period of diagnoses, total number of births
Innes, 2004	USA	Case-control	Cases= 2,522 Controls= 10,052	Computerized Cancer registry	Birth registry data	Maternal race (black, non-Hispanic white, Hispanic and other), marital status, maternal education
Cnattingius, 2005	Sweden	Cohort	314,019	Cancer Register	Swedish National Board of Health And Welfare and Statistics Sweden	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	Cases= 8,251 Controls= 33,004	Michigan Cancer Surveillance Program's statewide cancer registry	Michigan Birth Registry	Age at first and last birth, education at first birth, infant's gender at first and last birth, parity, maternal birth year race, gestational age
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 disease, family history of breast cancer in first-degree relatives, socioeconomic score, own birth weight, age at menarche, parity, age at first pregnancy, cumulative duration of breast feeding, current oral contraceptive use before menopause height at age 20, alcohol consumption, age started smoking, pre or post-menopausal BMI and hormones

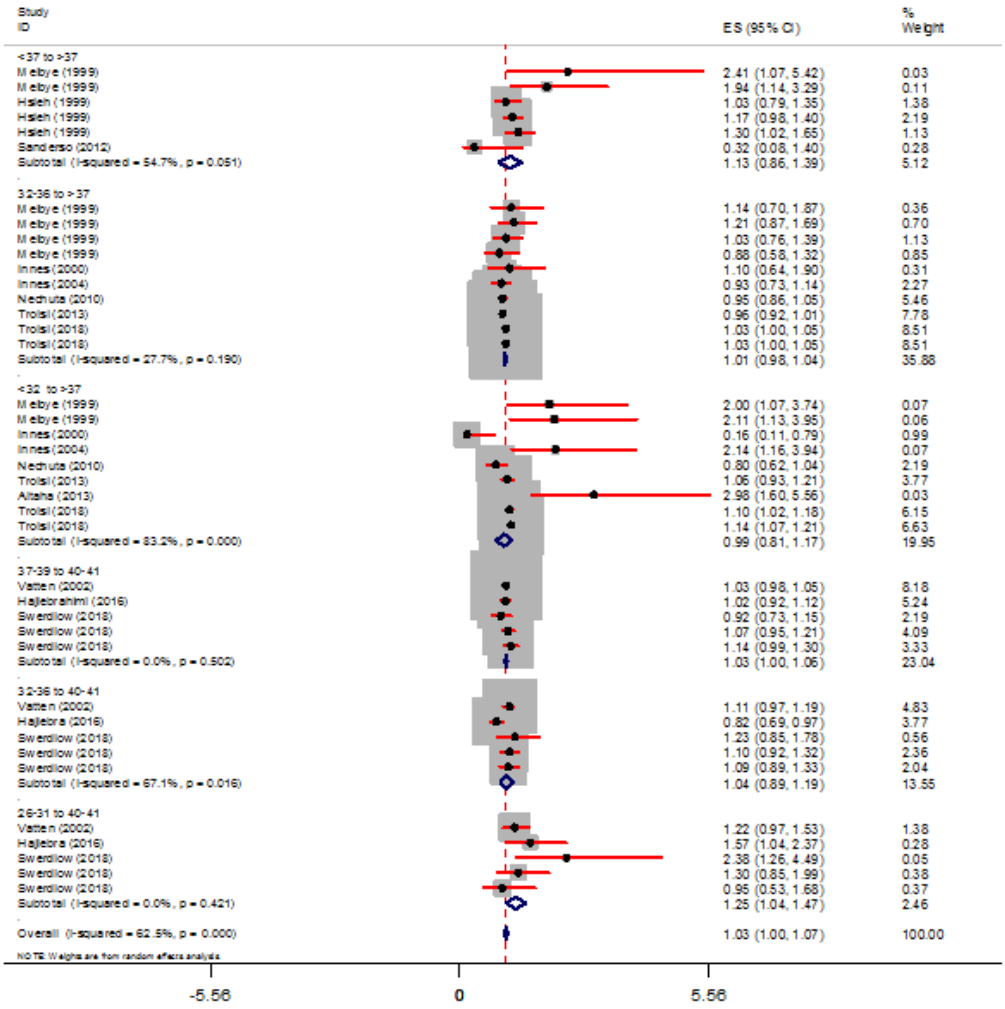

Figure 2. Forest Plot Describing the Aassociation between Preterm Birth and Breast Cancer Risk

Figure 2).

Women who delivered at 32-36 compared to those delivered at >37 weeks of gestation

Six studies (one cohort and three case-control) comprising 2,036,812 participants investigated the risk of BC in women who delivered at 32-36 compared to those delivered at >37 weeks of gestation. The summary RR was 1.01 (95% CI, 0.98, 1.04) with low heterogeneity (I^2 = 27.7%, p-value for heterogeneity= 0.190) (Figure 2).

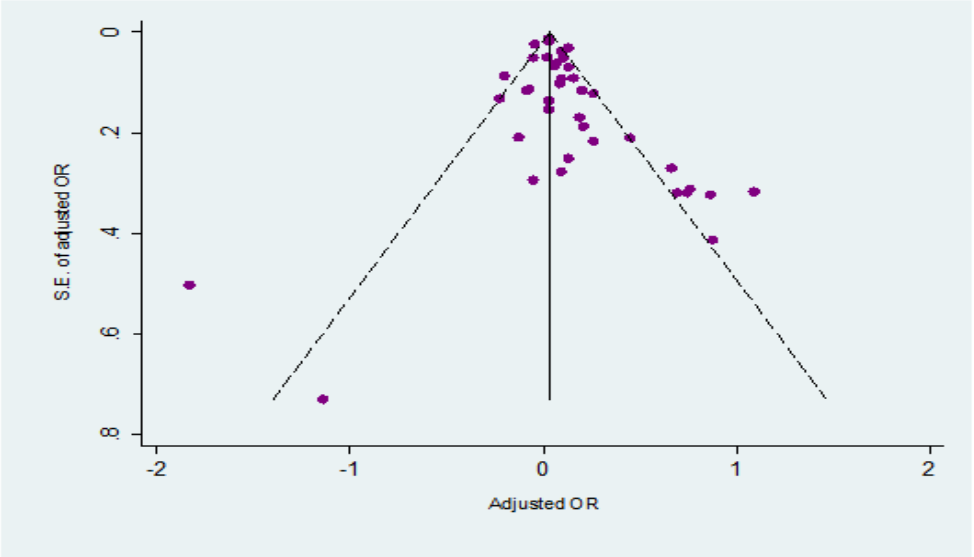

Figure 3. The Funnel Plot of Included Primary Studies

Table 2. Results of the Critical Appraisal of the Included Studies

Case control studies									
Study (first author)	Selection of the study groups				Comparability of the groups	Ascertainment of exposure			Score
	Is the case definition adequate	Representativeness of the cases	Selection of Controls	Definition of Controls	Based on design and analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Troisi, 1998	*	*	*	*	**	*	*	*	9
Innes, 2000	*	*	*	*	**	*	*		8
Innes, 2004	*	*	*	*	**	*	*		8
Nechuta, 2010	*	*	*	*	**	*	*		8
Sanderson, 2012	*	*		*	**	*	*		7
Altaha, 2013	*	*		*	**	*	*		7
Troisi, 2013	*	*	*	*	**	*	*		8

Cohort studies									
udy (first author)	Selection of the study groups				Comparability of the groups	Ascertainment of outcome			Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Based on design and analysis	Ascertainment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Hsieh, 1999	*	*	*		**	*	*	*	8
Melbye, 1999	*	*	*		*	*	*	*	7
Vatten, 2002	*	*	*		**	*		*	7
Cnattingius, 2005	*	*	*		**	*	*	*	8
Hajiebrahimi, 2016	*	*	*	*	**	*	*	*	9
Swerdlow, 2018	*	*	*	*	**	*	*	*	9

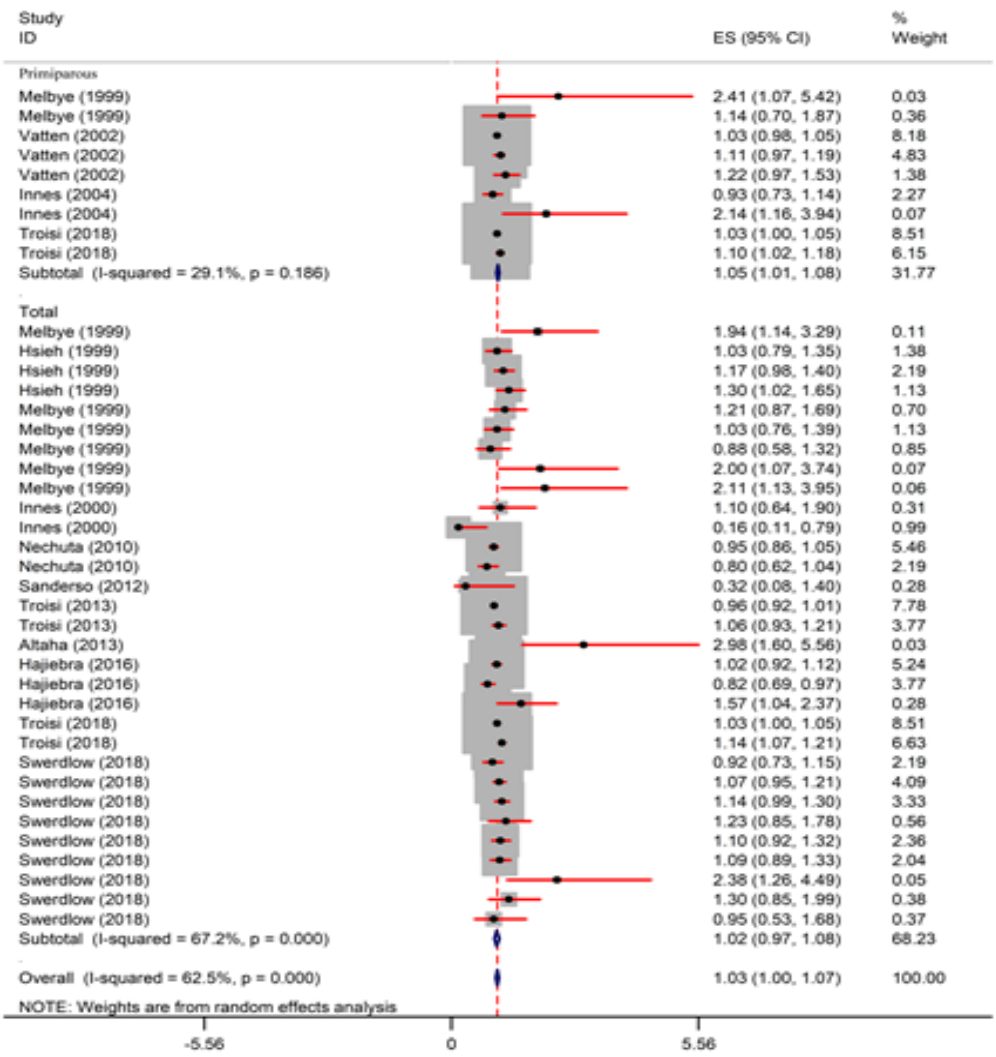

Figure 4. Forest Plot Describing the Association between Preterm Birth and Breast Cancer Risk on the Basis of Parity Status

Women who delivered at <32 compared to those delivered at >37 weeks of gestation

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 who delivered at <32 compared to those delivered at >37 weeks of gestation (RR = 0.99, 95% CI: 0.81, 1.17; I^2= 83.2%, p-value for heterogeneity< 0.001, Figure 2).

Women who delivered at 37-39 compared to those delivered at 40-41 weeks of gestation

Three studies including 794,762 women assessed the risk of BC. Risk was, significantly increased in women who delivered at 37-39 compared to those delivered at 40-41 weeks of gestation (RR = 1.03, 95% CI: 1.01, 1.06; I^2= 0%, p-value for heterogeneity= 0.502, Figure 2).

Women who delivered at 32-36 compared to those delivered at 40-41 weeks of gestation

There were three studies with 794,762 participants (two cohort and one case-control) that compared the risk of BC in women who delivered at 32-36 compared to those delivered at 40-41 weeks of gestation. The pooled analysis revealed that the PTB was not associated with BC risk (RR = 1.04, 95% CI: 0.89, 1.19) using a random-effects model, with non-significant heterogeneity among individual studies (I^2 = 67.1%, p-value for heterogeneity= 0.016, Figure 2).

Women who delivered at 26-31 compared to those delivered at 40-41 weeks of gestation

Three studies including 794,762 women assessed the risk of BC. A significant increment in the risk of BC (RR = 1.25, 95% CI: 1.04, 1.47) was observed in women who delivered at 26-31 compared to those delivered at 40-41 weeks of gestation, with non-significant heterogeneity (I^2 =0%, p-value for heterogeneity= 0.421) (Figure 2).

Primiparous women who delivered at <37 compared to multiparous women delivered at > 37 weeks of gestation

Four studies including 2,444,775 participants assessed the risk of BC in primiparous women who delivered at

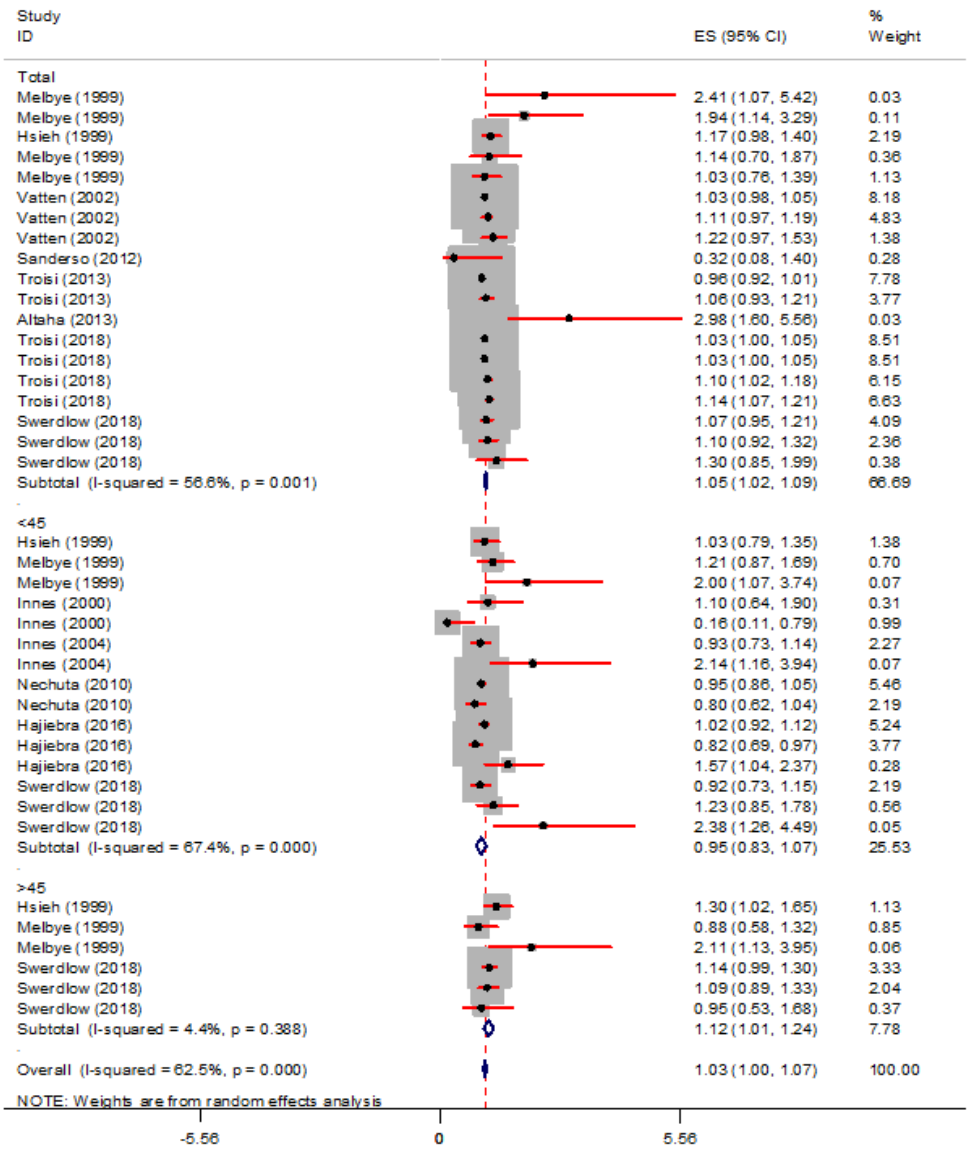

Figure 5. Forest Plot Describing the Association between Preterm Birth and Breast Cancer Risk on the Basis of Age Categories

<37 weeks of gestation. The overall summary RR of the uniparity versus the multiparity show that parity modify the association between PTB and BC. A significant increment in the risk of BC was observed in primiparous women who delivered at <37 (RR = 1.05, 95% CI = 1.01, 1.08, I^2= 29.1%, p-value for heterogeneity= 0.186), while this association in multiparous women was not significant (RR = 1.02, 95% CI = 0.97, 1.08, I^2= 67.2%, p-value for heterogeneity< 0.001) (Figure 4).

Age at breast cancer diagnosis

All studies were included in the meta-analysis of PTB and BC risk by age status. Women older than 45 years who delivered at <37 weeks of gestation were at a significantly higher risk of developing BC compared to women with pregnancies progressed beyond 37 weeks of gestation (RR = 1.12, 95% CI: 1.01, 1.24, I^2= 4.4%, p-value for heterogeneity= 0.388). We haven't seen the association for women under 45 years who delivered at <37 weeks of gestation (RR = 0.95, 95% CI: 0.83, 1.07, I^2= 67.4%, p-value for heterogeneity< 0.001) (Figure 5).

Discussion

The results of this study showed that the risk of BC in women with very early PTB was significantly higher. PTB in women with >45 years, as well as primiparous women had a significant relationship with the increased risk of breast cancer.

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 the risk in women with PTB were on average at a 3% greater risk of BC (RR= 1.03, 95% CI: 1.00, 1.07). This meta-analysis also provided some 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 PTB increases the risk of BC in women with >45 years. The results showed that PTB in primiparous women could lead to an increased risk of BC but 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 PTB 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 PTB 26-31 gestational weeks compared to 40-41 gestational weeks. Similar to our study, Swerdlow et al. (Swerdlow et al., 2018) 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 in line with the results of this study showed that early delivery may increase the risk of BC. Swerdlow et al., (2018) 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 (Ferguson et al., 1983; Russo et al., 2006; Russo et al., 1982) and a full term pregnancy is considered as a protective factor for BC (Russo et al., 2005). 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 (Travis et al., 2003), 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 (Ekbom et al., 2000; Kaijser et al., 2003; Trichopoulos, 1990). 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 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 (Innes et al., 2004) concluded that very or extreme PTB was related to higher risk of maternal BC risk. In another similar study by Melbye M et al. (Melbye et al., 1999), the results showed a higher risk of BC in women with gestational age less than 32 weeks. Some studies have contradicted our findings. Kaijser et al., (2003) reported that PTB were not associated with an increased risk of breast cancer.

Some studies have reported the relationship between the induced abortion and BC risk (Carroll, 2002; Deng et al., 2018). 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 was not associated with increased risk of BC (Beral et al., 2004). Therefore, this relationship is still ambiguous and further studies are needed.

The findings of this meta-analysis were in line with the higher BC risk for PTB, significantly for post-menopausal BC and primiparous women, and also borderline significantly for BC overall. Some studies assessed the association of PTB and BC risk in parous and nulliparous women. Melbye et al., (1999) reported a higher risk of BC in parous women with preterm delivery below 32 weeks compared with women with term delivery. Deng et al., (2018) in a meta-analysis study revealed that in parous women, induced abortion could increase the BC risk, but it was not significant in the nulliparous women.

Our study documented that the PTB increased the risk of BC in women with >45 years, but not in women with <45 years. As accord to our results, Melbye et al., (1999) concluded that preterm labor could not 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.

Limitations

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 PTB and BC risk, which in this study was not possible to adjust their effect.

Another limitation of this study was that PTB was an extremely heterogeneous outcome measure as it summarized spontaneous and iatrogenic components for which several different underlying etiologies were described. Since none of included studies reported the etiology of their preterm, it is impossible to us to carry out a subgroup analysis in this regard.

Because the risk of preterm delivery is higher in women who are pregnant with assisted reproductive techniques, and hormone therapy is also higher in these women, it is recommended that subgroup analysis be performed in women with PTB and IVF / ICSI but because of lack of data, it is not possible in this study and recommended to further studies.

In addition to the above, given that the definition and diagnostic methods of breast cancer have changed in recent decades, there is a possibility of diagnosis bias in this study that should be considered by readers.

There are confounding variables in examining the association between PTB and BC. Because it is not possible to adjust the confounding variables in meta-analysis studies, it is recommended to perform an individual patient data (IPD) meta-analysis.

The last one is that, parous women are usually older than nulliparous women. Considering that the necessary data were not reported in the primary studies, it was not possible to perform subgroup analysis based on parous or nulliparous in this study.

In conclusions, the results of this study showed that the risk of BC in women with very early PTB was significantly higher. PTB in women with >45 years, as well as primiparous women had a significant relationship with the increased risk of breast cancer. Considering the methodological weaknesses existed in included studies, minor clinical differences, and the complexity of the exact pathophysiology of PTB on BC, the precise position of PTB, as a risk factor for BC, in clinical practice is undetermined. Further studies are still needed.

Abbreviations

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

Author Contribution Statement

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, NN, MR and AE analyzed the data and all authors revised the manuscript and approved the final version.

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Declarations

Ethics approval and consent to participate

This work did not require any written patient consent.

Availability of data and material

The datasets of this article are included within the article.

Conflict of interest

All authors declared no conflict of interest.

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