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REVIEW

Obstetrical outcomes in women with history of breast cancer: a systematic review and meta-analysis

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Abstract

Purpose Potential risk of adverse obstetrical outcomes has been shown among breast cancer survivors. Therefore, the aim of this systematic review and meta-analysis was to evaluate the relationship between history of breast cancer (BC) and obstetrical outcomes.

Methods PubMed, EMBASE, and Medline were searched from the inception of each database to April 2019. Selection criteria included prospective and retrospective cohort studies of BC pregnant survivors. The meta-analysis was performed by computing odds ratios (ORs) using both fixed and random-effects models. Quality assessment of the included studies was performed using the Newcastle–Ottawa Scale and the review was registered with PROSPERO number CRD42019127716.

Results Four studies, including 1466 cases of BC survivors and 6,912,485 controls, were included. Compared with controls, a higher incidence of obstetrical complication was found in women with history of BC. The incidence of preterm birth (PTB) in the study group was 11.05% compared with 7.79% in the control group (1.68, 95% confidence interval 1.43–1.99). Breast cancer history was also associated with low birth weight (LBW) (study group: 9.26% vs. control group: 5.54%, 1.88, CI 95% 1.55–2.27), cesarean section (CS) (study group: 19.76% vs. control group 10.81%, 1.78, CI 95% 1.39–2.27), intrauterine fetal death (IUFD) (study group: 0.004% vs. control group 0.36%, of 1.25 CI 95% 0.36–4.35), and fetal anomalies (study group: 5.8% vs. control group: 4.26%, 1.45 CI 95% 1.01–2.09).

Conclusions History of BC was associated with adverse obstetrical outcomes.

Keywords Breast cancer · Preterm birth · Perinatal outcomes · Obstetric outcomes

Abbreviations

BC	Breast cancer
PTB	Preterm birth
LBW	Low birth weight
CS	Cesarean section
IUFD	Intrauterine fetal death
NOS	Newcastle–Ottawa Scale
ORs	Odds ratios
CIs	Confidence intervals
MeSH	Relevant medical subject heading

Introduction

Breast cancer (BC) is the most frequent malignancy occurring in women, with 1.7 million new cases diagnosed every year. It represents about 25% of new cases of female cancer and about 12% in the general population [1]. Incidence rates vary widely among different regions, with the main incidence registered in high-income countries (92 per 100,000 in North America) [2–4]. About one in eight women will be diagnosed with BC in their life [5, 6] with about 10% of women facing a diagnosis of BC in reproductive age [7]. New treatments increased survival rates and remission time in all age groups, mainly in women aged 20–39 years [5]. Therefore, the number of women in reproductive age with a history of BC is significantly increasing, and many BC

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survivors desire fertility and become pregnant. Fertility rate has been reported to be about three times lower than in woman without history of BC [8] mostly due to the direct gonadotoxic effects of treatments or the need to delay conception until the end of the therapies [9]. Beyond the risk of infertility, potential risk of adverse obstetrical outcomes has been shown among BC survivors [10–13]. Therefore, the aim of this systematic review and meta-analysis was to evaluate the relationship between history of BC and obstetrical outcomes.

Methods

Protocol, eligibility criteria, information sources, and search strategy

This review was performed according to a priori designed protocol recommended for systematic review and meta-analyses [14–16].

PubMed, Medline, Embase, Cinahl, and Clinicaltrials.gov databases were searched electronically from the inception of each database to April 2019, utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "BC" and "obstetrical outcomes." No restriction about date of publication was posed for our research.

We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines to perform search strategy and selection processes [17]. Before data extraction, the review was registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number CRD42019127716).

Study selection and data extraction

Only studies reporting and describing the prevalence of obstetrical outcomes in pregnant women with BC history were considered eligible for the inclusion in the present systematic review. History of BC was defined as a BC diagnosis at any time before pregnancy. Obstetrical outcomes recorded included the following:

- preterm birth (PTB): gestational age < 37 weeks at delivery;
- low birth weight (LBW): birth weight < 2500 g;
- cesarean section (CS);
- intrauterine fetal death (IUFD): fetal demise after 20 weeks of pregnancy;
- fetal anomalies: minor and major malformations, including chromosomal anomalies.

Prospective and retrospective cohort studies were considered eligible for inclusion if the above criteria were met. Only full-text articles were considered eligible for inclusion; personal communications, case reports, reviews, conference abstracts, and case series with < 3 cases were also excluded to avoid publication bias. We excluded studies omitting at least one inclusion criterion or presenting data reported in graph or percentage form rather than proportional rates.

Two authors (FV and IF) independently reviewed all abstracts. Full-text copies of those papers were obtained, and the same reviewers independently extracted relevant data regarding study characteristics and pregnancy outcomes. Inconsistencies were discussed by the reviewers and consensus reached or by discussion with a third author (VDA). If more than one study was published on the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. For those articles in which information was not reported but the study methodology supposed that this information would have been recorded initially, the authors were contacted to obtain missing data.

Assessment of risk of bias

Quality assessment of the included studies was performed using the Newcastle–Ottawa Scale (NOS) for cohort studies (Table 1). The evaluation system included eight literature evaluation entries for a total of nine possible points including the selection of the study population, the comparability, exposure assessment, and the results of the evaluation. The NOS scale validity rating criteria are as follows: 8–9, high quality; 6–7, medium quality; < 5, low quality [18].

Data synthesis and outcomes

The aim of this systematic review and meta-analysis was to evaluate the strength of association between history of BC and obstetrical outcomes. Statistical analysis was performed using Review Manager 5.0 (http://www.cochrane.org).

Extracted results were pooled in a meta-analysis. The meta-analysis was performed by computing odds ratios

Table 1 Quality assessment of the included studies, according to Newcastle–Ottawa Scale (NOS)

Author	Year	Selection	Comparability	Outcome
Dalberg	2006	★★	★	★★
Langagergaard	2006	★★	★	★★
Jacob	2017	★★	★	★★
Hartnett	2017	★★	★	★★

A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability

(ORs) using both fixed and random-effects models (weighting by inverse of variance). Between-study heterogeneity was assessed using tau2, χ^2 (Cochrane Q), and I2 statistics.

Forest plots were used for graphical representation of each study and pooled analysis. The size of each box represents the weight that the corresponding study exerts in the meta-analysis; confidence intervals (CIs) for each study are displayed as a horizontal line through the box. The pooled OR is symbolized by a solid diamond at the bottom of the forest plot, and the width of the square represents the 95% CI of the OR. A significant two-way p value for comparison was defined as $p < 0.05$. Statistical heterogeneity among studies was examined using both the Cochrane Q statistic (significant at $p < 0.1$) and the I2 value. A value of 0% indicates no observed heterogeneity, whereas I2 values $\geq 50\%$ indicate a substantial level of heterogeneity. Given the inherent heterogeneity (different designs and definitions), a random effect model was used, regardless of the I2 value [19]. Publication bias was examined using analyses described by Egger et al. [20, 21].

Results

General characteristics

Our preliminary literature search identified 991 publications. 980 studies were excluded based on title or abstract. We selected 11 potentially eligible studies. Seven studies were excluded after a careful, qualitative analysis; the list of excluded studies and reason for exclusion are available in Table S1. In total, we included four qualifying studies in our analysis (Fig. 1) [10, 11, 22, 23].

Included studies were published between 2006 and 2017 (Table 1); three studies were conducted in Europe [10, 11, 22] and one in Asia [23].

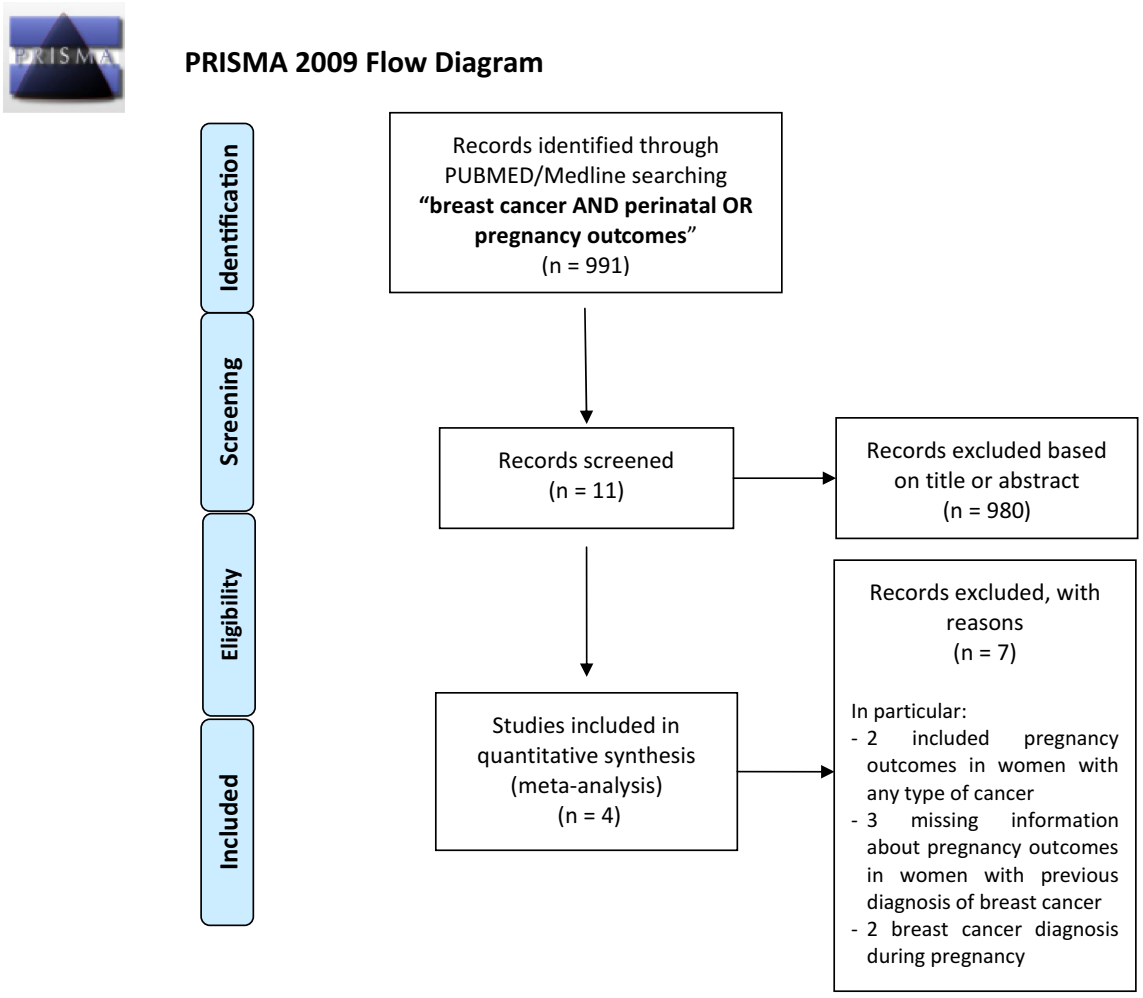

Fig. 1 Flow chart for study selection

The population sizes of the studies ranged from 165 to 4,031,349. Table 2 shows the characteristics of the four included studies. Mean maternal age of study group and control group was, respectively, 34.3 (range 34–34.6) and 28.4 (range 27–30) years.

The median interval between BC diagnosis and first pregnancy was 2.21 years, with a minimum of 1.5 and a maximum of 3.08 years [10, 11, 22].

Synthesis of the results

In these studies, 1466 pregnant women with history of BC (study group) and 6,912,485 without history of BC (control group) were described. The detection rate (DR) and the false-positive rate (FPR), for the ability of prior BC to detect cases of adverse pregnancy outcomes, were reported for each study.

Compared with controls, a higher incidence of obstetrical complications was found in women with history of BC (Table 3):

- *Preterm birth* (PTB) (study group: 11.05% 162/1466 vs. control group: 7.79% 538,682/6,912,485) with an OR of 1.68 (CI 95% 1.43–1.99) $p < 0.00001$ (Fig. 2) [10, 11, 22, 23].
- *Low birth weight* (LBW) (study group: 9.26% 119/1285 vs. control group: 5.54% 382,498/6,903,051) with an OR of 1.88 (CI 95% 1.55–2.27) $p < 0.00001$ (Fig. 3) [10, 11, 23].
- *Cesarean section* (CS) (study group: 19.76% 98/496 vs. control group: 10.81% 310,451/2,870,683) with an OR of 1.78 (CI 95% 1.39–2.27) $p < 0.00001$ (Fig. 4) [11, 22].
- *Intrauterine fetal death* (IUFD) (study group: 0.004% 2/547 vs. control group: 0.36% 10,346/2,880,971) with

Table 2 Characteristics of the included studies

	Dalberg [11]	Langagergaard [10]	Jacob [22]	Hartnett [23]
Population	331 women in pregnancy with a previous diagnosis of breast cancer	216 women in pregnancy with a previous diagnosis of breast cancer	165 women in pregnancy with a previous diagnosis of breast cancer between the ages 18 and 45	754 women in pregnancy with a previous diagnosis of breast cancer between the ages 20 and 45
Comparison	Singleton pregnancies in women without breast cancer	Singleton pregnancies in women without breast cancer	Singleton pregnancies in women without breast cancer	Singleton pregnancies in women without breast cancer
Outcomes	PTB, LBW, CS, APGAR < 7, FD, fetal anomalies	PTB, LBW, FD, fetal anomalies	PTB, CS, miscarriage, IUGR	PTB, LBW, SGA, CS, APGAR < 7
Study design	Retrospective	Retrospective	Retrospective	Retrospective

PTB preterm birth, *LBW* low birth weight, *CS* cesarean section, *FD* fetal demise, *IUGR* intrauterine growth restriction, *SGA* small for gestational age

Table 3 Obstetrical outcomes

	Dalberg [11]	Langareraard [10]	Jacob [22]	Hartnett [23]	OR (95% CI)	*p* Value
PTB	36/331 (10.9%) vs. 148,825/2,870,518 (5.2%)	14/216 (6.5%) vs. 507/10,453 (4.9%)	2/165 (1.2%) vs. 1/165 (0.6%)	110/754 (14.6%) vs. 389,349/4,031,349 (1%)	1.68 (1.43, 1.99)	**< 0.00001**
LBW	20/329 (6.1%) vs. 103,464/2,861,817 (36.2%)	3/202 (1.5%) vs. 137/9885 (1.4%)	NR	96/754 (12.7%) vs. 278,897/4,031,349 (6.9%)	1.88 (1.55, 2.27)	**< 0.00001**
CS	70/331 (21.1%) vs. 310,419/2,870,518 (10.8%)	NR	28/165 (17%) vs. 32/165 (19.4%)	NR	1.78 (1.39, 2.27)	**< 0.00001**
IUFD	2/331 (0.6%) vs. 10,307/2,870,518 (0.4%)	0/216 (0%) vs. 39/10,453 (0.4%)	NR	NR	1.25 (0.36, 4.35)	0.72
Fetal anomalies	24/331 (7.3%) vs. 122,305/2,870,518 (4.3%)	7/203 (3.4%) vs. 369/9775 (3.8%)	NR	1/214 (0.5%) vs. 2/220 (0.9%)	1.45 (1.01, 2.09)	**0.04**

Data are presented as number in the intervention group versus number in the control group with percentage

PTB preterm birth, *LBW* low birth weight, *CS* cesarean section, *IUFD* intrauterine fetal demise

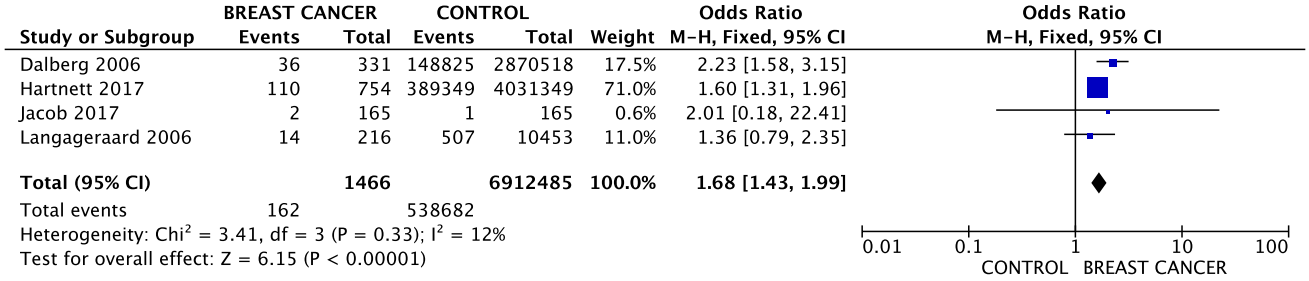

Fig. 2 Meta-analysis for PTB

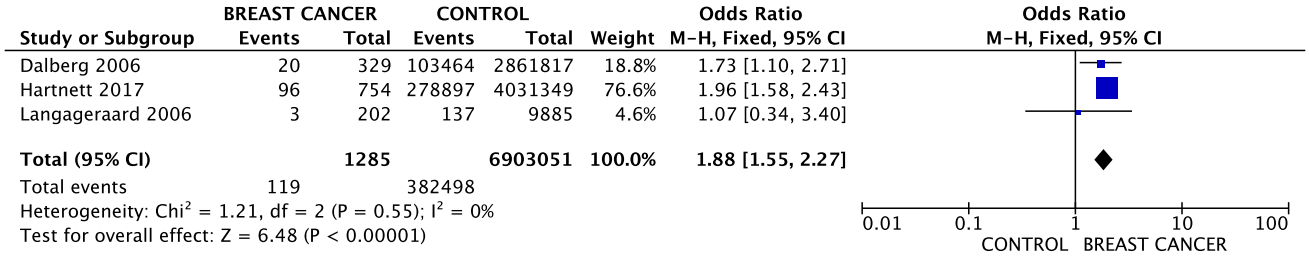

Fig. 3 Meta-analysis for LBW

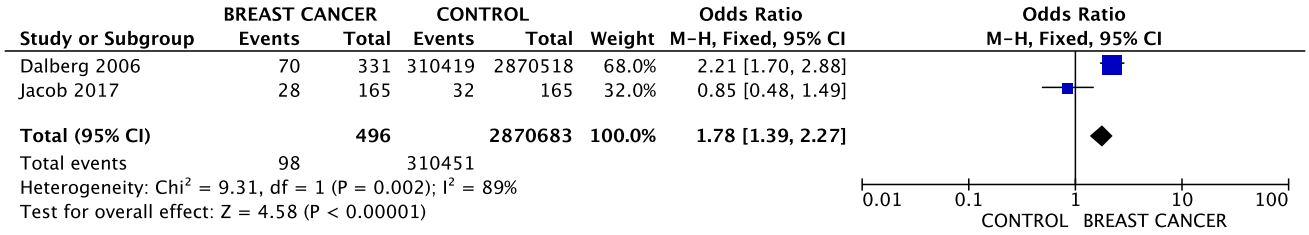

Fig. 4 Meta-analysis for CS

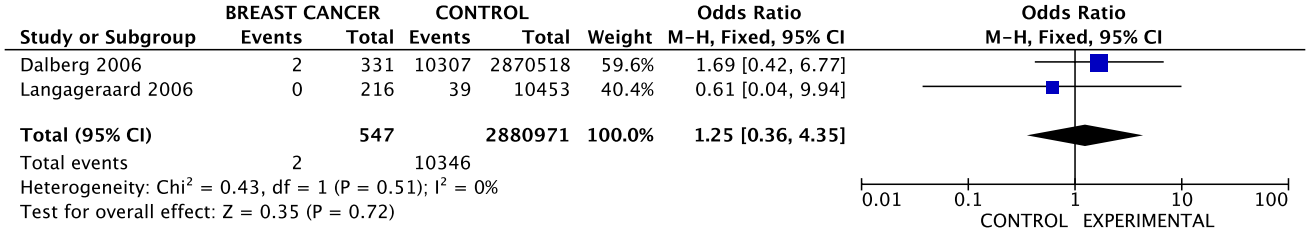

Fig. 5 Meta-analysis for IUFD

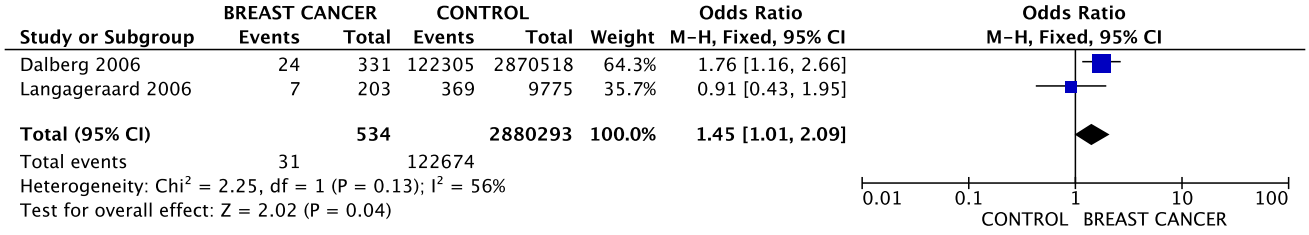

Fig. 6 Meta-analysis for fetal anomalies

an OR of 1.25 $p = 0.72$(CI 95% 0.36–4.35) (Fig. 5) [10, 11].

– *Fetal anomalies* (study group: 5.8% 31/534 vs. control group: 4.26% 122,674/2,880,293) with an OR of 1.45 (CI 95% 1.01–2.09) $p = 0.04$ (Fig. 6) [10, 11].

For most of analyzed variables, results showed low heterogeneity.

Discussion

The findings from this systematic review showed that history of BC was associated with a significantly higher risk of PTB, LBW, CS, and fetal anomalies.

For women with history of BC, a subsequent pregnancy has been shown not to affect overall survival, mainly when pregnancy occurs 6 months or more after BC diagnosis [24] and no detrimental effect of pregnancy in BC survivors has been reported, regardless of estrogen receptor status [25].

On the other hand, women should be clearly counseled that they might be at higher risk for pregnancy complications, and therefore a close longitudinal assessment from the first trimester should be carried out in a maternal–fetal center in order to rule out any potential adverse obstetrical condition.

Our findings are concordant with the current literature, as the increased risk of PTB and LBW has been already described in large birth registry studies [26], particularly if women underwent chemotherapy or delivered within 2 years from the diagnosis of BC. Previous studies have also shown an elevated risk of PTB in survivors of different cancers compared with women with no history of cancer.

Compelling clinical and biochemical evidence suggest that an inflammatory response to intrauterine infection is one of the main determinants of PTB [27], and previous chemotherapy may play a role in maintaining a proinflammatory condition even long after withdrawal of therapy.

In fact, a depletion of lymphocytes and the associated immune deficiency has been shown in BC survivors, with CD4 + cells remaining 50% below baseline 12–14 months after treatment. Lymphocytes are more susceptible to apoptosis on stimulation, leading thus to post-chemotherapy immune dysfunction [28]. An abnormal immune condition after chemotherapy has also been demonstrated by a weaker response to vaccines in BC survivors up to 2.6 years after a cytotoxic therapy [29].

Nevertheless, it is likely that a closer surveillance may also increase the rate of iatrogenic PTB, as well as the rate of consequent CS and LBW neonates.

The strength of association between congenital anomalies and history of cancer is not completely elucidated yet, as in the literature there are both reassuring [30–32] and concerning studies evaluating offspring of cancer survivors [33, 34].

Our data showed a significantly higher rate of fetal anomalies in BC survivors.

In animal models, there is an indisputable evidence for mammalian germ cell mutagenicity induced by chemotherapy at human doses [35]. Furthermore, although a causal relationship has not been established between treatment with tamoxifen and pregnancy outcome, the relatively high frequency of severe congenital abnormalities suggests that tamoxifen may be related to potential teratogenic effects [36]. Few mechanisms other than the direct role of chemotherapy have been proposed to explain the development of anomalies in the offspring of cancer survivors: in particular, cancer and congenital malformations may share similar pathological substrates in terms of maternal metabolic, hormonal, and nutritional exposure [37].

To our knowledge, no systematic review about the association between history of BC and obstetrical outcomes is as large and comprehensive up to date. The population included is sufficiently numerous, and the statistical heterogeneity within the studies was low for all outcomes analyzed.

The small number of included studies, their retrospective, non-randomized design, differences between the included populations, and dissimilar approach for the BC management are the major limitations of this systematic review. Furthermore, in some of the included studies, the strength of association between history of BC and adverse obstetrical outcomes might have been affected by several co-factors which were not balanced between cases affected and not affected by BC before pregnancy, even if all the included studies were case–control series reporting matched populations. Finally, the overall sample sizes might be unbalanced, with 0.02% in the study group and 99.98% in the control group.

Conclusion

In summary, this study showed that history of BC was associated with adverse obstetrical outcomes. When planning a pregnancy, a BC survivor should refer to a maternal–fetal medicine specialist to be counseled about potential risks of previous treatments on pregnancy outcomes, and therefore to plan a close, longitudinal antenatal monitoring for a dedicated surveillance. Nevertheless, future large prospective studies sharing objective protocols of BC management and subsequent pregnancy are needed to better elucidate the actual association between history of BC and adverse obstetrical outcomes.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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