review articles

Pregnancy After Breast Cancer: A Systematic Review and Meta-Analysis

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abstract

PURPOSE Many patients and physicians remain concerned about the potential detrimental effects of pregnancy after breast cancer (BC) in terms of reproductive outcomes and maternal safety. This systematic review and meta-analysis aimed at providing updated evidence on these topics.

METHODS A systematic literature review was conducted to identify studies including patients with a pregnancy after BC (PROSPERO number CRD42020158324). Likelihood of pregnancy after BC, their reproductive outcomes, and maternal safety were assessed. Pooled relative risks, odds ratios (ORs), and hazard ratios (HRs) with 95% CIs were calculated using random effects models.

RESULTS Of 6,462 identified records, 39 were included involving 8,093,401 women from the general population and 112,840 patients with BC of whom 7,505 had a pregnancy after diagnosis. BC survivors were significantly less likely to have a subsequent pregnancy compared with the general population (relative risk, 0.40; 95% CI, 0.32 to 0.49). Risks of caesarean section (OR, 1.14; 95% CI, 1.04 to 1.25), low birth weight (OR, 1.50; 95% CI, 1.31 to 1.73), preterm birth (OR, 1.45; 95% CI, 1.11 to 1.88), and small for gestational age (OR, 1.16; 95% CI, 1.01 to 1.33) were significantly higher in BC survivors, particularly in those with previous chemotherapy exposure, compared with the general population. No significantly increased risk of congenital abnormalities or other reproductive complications were observed. Compared to patients with BC without subsequent pregnancy, those with a pregnancy had better disease-free survival (HR, 0.66; 95% CI, 0.49 to 0.89) and overall survival (HR, 0.56; 95% CI, 0.45 to 0.68). Similar results were observed after correcting for potential confounders and irrespective of patient, tumor, and treatment characteristics, pregnancy outcome, and timing of pregnancy.

CONCLUSION These results provide reassuring evidence on the safety of conceiving in BC survivors. Patients' pregnancy desire should be considered a crucial component of their survivorship care plan.

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INTRODUCTION

Among patients of reproductive age, breast cancer (BC) is the most commonly diagnosed malignancy,[1] and women with prior history of breast tumor represent the largest group of cancer survivors.[2] With the availability of more effective anticancer treatments, addressing their potential long-term toxicities has gained substantial attention.[3,4] Returning to a normal life following treatment completion should be considered a crucial ambition in cancer care in the 21st century.[5] In patients diagnosed during their reproductive years, this includes the possibility to complete their family building plans.

For many patients with BC, pregnancy-related issues represent a main area of concern.[6] Because of the rise in age at first pregnancy over the past few years, an increased number of women are diagnosed with BC before completing their reproductive plans.[7-9] Among the potential long-term side effects of anticancer treatments, premature ovarian insufficiency and subsequent impaired fertility are of particular concern.[10,11] Moreover, patients with hormone receptor–positive BC are administered adjuvant endocrine therapy for up to 5-10 years after diagnosis[6,12]; while on treatment, conception is contraindicated.[13,14] In addition, many women and their treating physicians remain concerned about the safety for both offspring and mother of pregnancy following BC diagnosis and treatment.[15,16] The main reasons for this distress are the possibility that a previous exposure to anticancer therapies might have negative effects on the fetus by increasing the risk of congenital abnormalities, obstetric, or birth complications.[17] Furthermore, as BC is a hormonal-driven tumor and considering the surge in female hormones during pregnancy, there is a general concern that pregnancy could increase patients' risk of recurrence.[17]

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Few women conceive following treatment completion for breast cancer (BC). Concerns persist among patients and physicians about the potential detrimental effects of pregnancy after BC in terms of reproductive outcomes and maternal safety. This systematic review and meta-analysis aimed at providing updated evidence on these topics.

Knowledge Generated

These results provide reassuring evidence on the safety of conceiving in women with previous BC. BC survivors had 60% reduced likelihood of having a subsequent pregnancy compared with the general population. However, no alarming signals in the majority of analyzed reproductive outcomes were observed, including no significantly increased risk of congenital abnormalities. Pregnancy after BC was not associated with any detrimental prognostic effect.

Relevance

These data strongly support the need for a deeper consideration of patients' pregnancy desire as a crucial component of their survivorship care plan and expectation to return to a normal life.

Current guidelines do not discourage having a pregnancy following treatment completion for BC and an adequate period of follow-up.[6,18] However, only a small number of patients with BC do conceive.[19] To refine the evidence surrounding this topic to guide patients and physicians during oncofertility counseling, we performed a systematic review and meta-analysis aiming to assess likelihood of pregnancy in women with prior history of BC, their reproductive outcomes, and maternal safety.

METHODS

Search Strategy and Selection Criteria

The systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[20]

A systematic literature search of Medline, Web of Science, and Cochrane databases was performed on January 31, 2020, with no language or date restriction using the following text: Breast Neoplasms [MeSH] AND (pregnancy or pregnancies or conception or conceiving or gestation or pregnancy [MeSH]). The search strategy was repeated before final analysis on October 31, 2020, to confirm the retrieval of all possible studies. Furthermore, a review of conference proceedings from both the European Society for Medical Oncology and the ASCO annual meetings, and the San Antonio Breast Cancer Symposium was performed to include relevant unpublished studies. Relevant articles were cross-referenced to confirm that all possible pertinent records were identified.

Eligible studies had to satisfy the following criteria: (1) retrospective or prospective case-control or cohort studies and clinical trials reporting on pregnancy after BC; (2) studies with available information on one or more of the three outcomes of interest (likelihood of pregnancy after BC, reproductive outcomes, and/or maternal safety); and (3) availability or possibility to estimate data on relative risk (RR), odds ratio (OR), and hazard ratio (HR), according to the analyzed outcome, with their 95% CIs.

Exclusion criteria were (1) case reports and case series including less than 10 patients; (2) studies reporting on pregnancy-associated BC (ie, BC diagnosed during pregnancy or within 5 years after pregnancy) with no data on pregnancy following BC diagnosis; and (3) ongoing studies with the results not presented nor published at the time of the literature search.

The systematic literature search was carried out independently by two authors (E.B. and M.P.), and any discrepancies were solved by discussion with a third author (M.L.).

This study is registered with the PROSPERO registration number CRD42020158324; the full protocol is available on the PROSPERO website.

Data Analysis

The following variables were extracted independently by two authors (E.B. and M.P.) from all included studies, if available: first author; year of publication; study design and methodology; number of women included in each cohort; number of women with a subsequent pregnancy; type of conception, pregnancy, fetal, and obstetrical outcomes; and survival outcomes. For studies with more than one publication or having a superimposable population, only the most updated and/or the largest study was included.

This meta-analysis aimed to compare the following:

1. Likelihood of pregnancy defined as the comparison between the proportion of patients who had a pregnancy after prior history of BC versus the proportion of healthy women from the general population who had a pregnancy and the proportion of survivors who had a pregnancy after prior history of other malignancies (expressed as RRs).

2. Reproductive outcomes in patients with prior history of BC versus those in healthy women from the general population, in terms of pregnancy completion, induced abortion, spontaneous abortion, low birth weight, preterm birth, intrauterine fetal death, small for gestational age, pre-eclampsia, congenital abnormalities, elective delivery, emergency caesarean section, and postpartum bleeding.
3. Maternal safety by comparing survival outcomes between BC patients with or without a subsequent pregnancy, in terms of disease-free survival (DFS) and overall survival (OS).

Subgroup analyses were conducted to assess the following:

1. Reproductive outcomes according to the use of chemotherapy (yes *v* no) and interval between diagnosis and pregnancy (early *v* late, defined as using cutoffs one or 2 years after BC diagnosis);
2. Maternal survival outcomes (DFS and/or OS) according to nodal status (negative *v* positive), hormone receptor status (positive *v* negative), use of chemotherapy (yes *v* no), interval between diagnosis and pregnancy (early *v* late, defined as using cutoffs one, 2, or 5 years after BC diagnosis), pregnancy outcomes (completed pregnancy *v* abortion), and germline *BRCA* status.

Adjusted RRs, ORs, and HRs with their 95% CI were extracted from included studies. When the above measures were not reported but the number of events for each group could be derived, RRs or ORs were computed as the ratio of proportions or odds of events between groups, whereas HRs were estimated using the method reported by Watkins and Bennett.[21] When RRs, ORs, and HRs were not available or could not be computed for a specific outcome, the studies were excluded from that analysis. For maternal safety, two main analyses were conducted by including (1) all studies with available information on DFS and/or OS and (2) only the studies with information on DFS and/or OS adjusted for the potential guarantee-time bias or healthy mother effect. Survival analyses on maternal safety were then repeated by excluding computed HRs and including only the studies reporting the HRs.

Pooled RRs, ORs, and HRs with their 95% CI were calculated using the method of DerSimonian and Laird[22] using the random effects model. The quantitative measure of the degree of inconsistency in the results of the included studies was computed using the Higgins I^2 index.[23] The likelihood of publication bias was assessed by Egger's asymmetry test.[24] Pooled RRs, ORs, and HRs were considered statistically significant with a P value of $< .05$ (two-sided). To assess whether the pooled RR, OR, and HR estimates were stable or dependent on one single included study, sensitivity analyses were conducted.

Statistical analyses were performed by M.B. and M.C. using Stata 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

RESULTS

Of 6,462 identified records, 39 studies were included in the meta-analysis (Fig 1).[25-63] Among the 8,263,980 women included in these studies, 8,093,401 were from the general population, 57,739 had malignancies other than BC, and 112,840 had breast tumors. Among the 112,840 patients with BC, 7,505 had a pregnancy after diagnosis. One study did not report the number of included women from the general population,[57] and another the number of patients with BC who had a pregnancy after diagnosis.[49]

Likelihood of Pregnancy

Seven records were included in this analysis (Data Supplement, online only).[42,46,47,49,56,57,59] Of 3,393,632 women included in these studies, 3,289,113 were from the general population, 57,739 had malignancies other than BC, and 46,780 had breast tumors.

Overall, patients with cancer had 35% reduced likelihood of having a subsequent pregnancy compared with the general population (RR, 0.65; 95% CI, 0.55 to 0.77); the lowest likelihood of pregnancy was observed in patients with previous cervical cancer (Fig 2; Data Supplement).

Among the 46,780 patients with BC included in the analysis, 2,026 (4.2%) had a subsequent pregnancy. Compared with the general population, BC survivors had a 60% reduced likelihood of having a subsequent pregnancy (RR, 0.40; 95% CI, 0.32 to 0.49; Data Supplement).

Reproductive Outcomes

Nine records were included in this analysis (Data Supplement).[38,39,50-53,57,59,62] A total of 4,817,692 women with a pregnancy were included, of whom 4,814,452 from the general population and 3,240 had previous BC.

Summary of the pooled results on reproductive outcomes is reported in Figure 3, and publication bias and sensitivity analysis for all outcomes are given in the Data Supplement.

No difference was observed between patients with BC and the general population in terms of completed pregnancies (OR, 1.21; 95% CI, 0.48 to 3.03; Data Supplement), spontaneous (OR, 1.04; 95% CI, 0.86 to 1.26; Data Supplement) or induced (OR, 1.40; 95% CI, 0.71 to 2.76; Data Supplement) abortions, developing pre-eclampsia (OR, 1.03; 95% CI, 0.27 to 3.98; Data Supplement), and postpartum bleeding (OR, 0.88; 95% CI, 0.57 to 1.37; Data Supplement).

An increased risk of caesarean section was observed in patients with BC (OR, 1.14; 95% CI, 1.04 to 1.25; Data Supplement). Offspring of patients with BC was at increased risk of low birth weight (OR, 1.50; 95% CI, 1.31 to 1.73; Data Supplement), preterm birth (OR, 1.45; 95% CI, 1.11 to 1.88; Data Supplement), and small for gestational age (OR, 1.16; 95% CI, 1.01 to 1.33; Data Supplement) compared with the general population. No significantly increased risk of congenital abnormalities was observed for

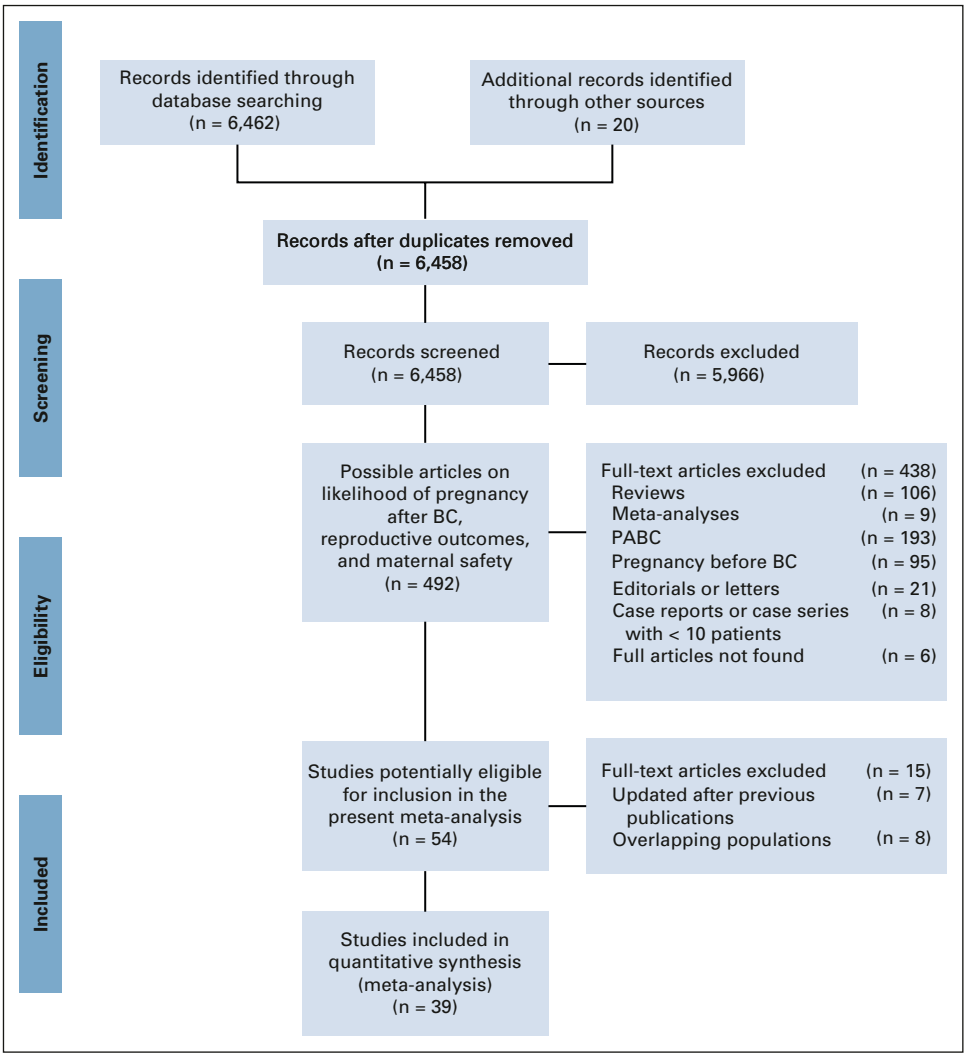

FIG 1. The PRISMA flowchart summarizing the process for the identification of eligible studies. BC, breast cancer; PABC, pregnancy-associated breast cancer; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

the offspring of BC survivors (OR, 1.63; 95% CI, 0.89 to 2.98; Data Supplement).

Subgroup analyses of reproductive outcomes according to previous exposure to chemotherapy and timing of pregnancy after BC were performed by including two studies.[53,57] As compared with offspring of women from the general population, the increased risk of low birth weight and small for gestational age appeared to be restricted to BC patients with previous exposure to chemotherapy (Data Supplement). The results did not vary substantially from those of the main analyses for the offspring of patients with early or late pregnancies after BC (Data Supplement).

Maternal Safety

Disease outcomes were reported in 25 studies (Data Supplement),[25-37,40,41,43-45,48,54,55,58,60,61,63] of which 19 adjusted the results for the potential guarantee-time bias.[25-27,29-31,35-37,40,41,43,45,48,54,58,60,61,63] Of 63,968 patients with BC included, 3,387 (5.3%) had a pregnancy after BC.

DFS. DFS between patients with or without a pregnancy after BC was reported in 11 studies.[30,31,33,37,43,45,55,58,60,61,63] Among them, four studies reported relapse-free survival,[33,37,45,61] one study distant recurrence-free interval,[43] and one study distant DFS.[31]

As compared to patients with BC without subsequent pregnancy, those with a post-treatment pregnancy showed better DFS (HR, 0.66; 95% CI, 0.49 to 0.89; Fig 4A and Data Supplement). Similar results were observed in the studies correcting for the potential guarantee-time bias (HR, 0.68; 95% CI, 0.51 to 0.91; Fig 4B and Data Supplement) and in the analyses after excluding computed HRs (Data Supplement).

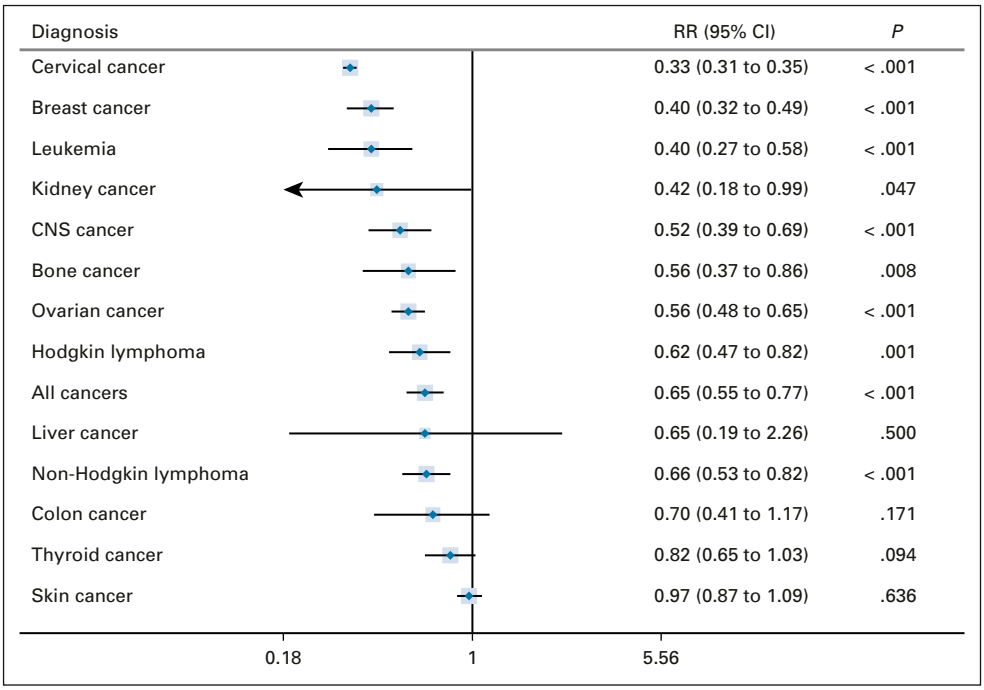

FIG 2. Likelihood of pregnancy after cancer diagnosis. RR, relative risk.

Two studies reported the DFS results according to hormone receptor status.[58,63] No detrimental effect of pregnancy after BC was observed in patients with hormone receptor–positive (HR, 1.10; 95% CI, 0.73 to 1.66; Fig 4C) or hormone receptor–negative (HR, 0.72; 95% CI, 0.55 to 0.95; Fig 4D) disease.

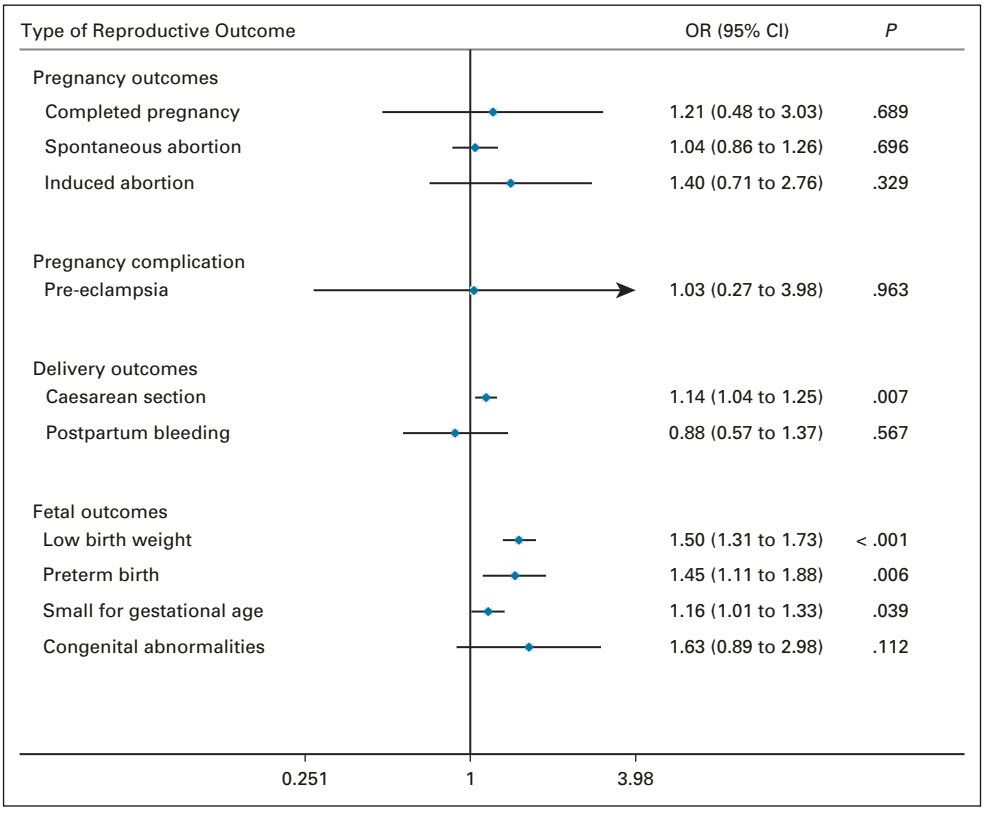

FIG 3. Reproductive outcomes of patients with a pregnancy after breast cancer. OR, odds ratio.

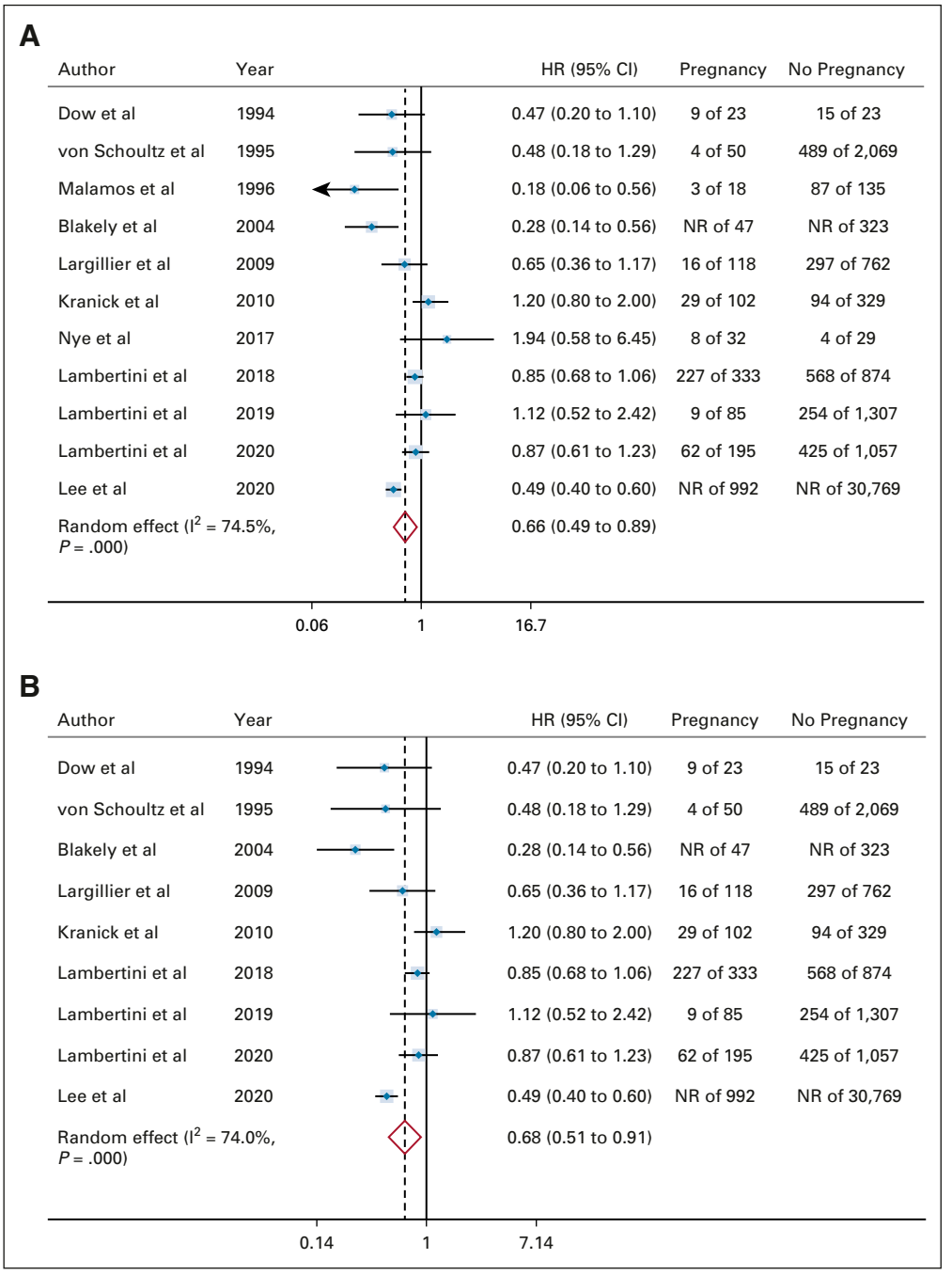

FIG 4. Disease-free survival comparing patients with or without a pregnancy after breast cancer: (A) in all studies (*P* for random effect = .007), (B) by including only studies correcting for the potential guarantee-time bias (*P* for random effect = .008), (C) in women with hormone receptor–positive disease (*P* for random effect = .659), and (D) in women with hormone receptor–negative disease (*P* for random effect = .019). HR, hazard ratio; NR, not reported.

The lack of detrimental effect of pregnancy after BC was also observed irrespective of pregnancy outcome (Data Supplement)[45,58,61] and timing of pregnancy after BC (Data Supplement).[45,58]

OS. OS between patients with or without a pregnancy after BC was reported in 21 studies.[25-29,32,34-37,40,41,43-45,48,54,58,60,61,63]

As compared to patients with BC without subsequent pregnancy, those with a post-treatment pregnancy showed better OS (HR, 0.56; 95% CI, 0.45 to 0.68; Fig 5A and Data Supplement). Similar results were observed in the studies adjusting for the potential guarantee-time bias (HR, 0.53; 95% CI, 0.42 to 0.67; Fig 5B and Data Supplement) and in the analyses after excluding computed HRs (Data Supplement).

At the subgroup analyses, the lack of detrimental effect of pregnancy after BC was observed irrespective of nodal

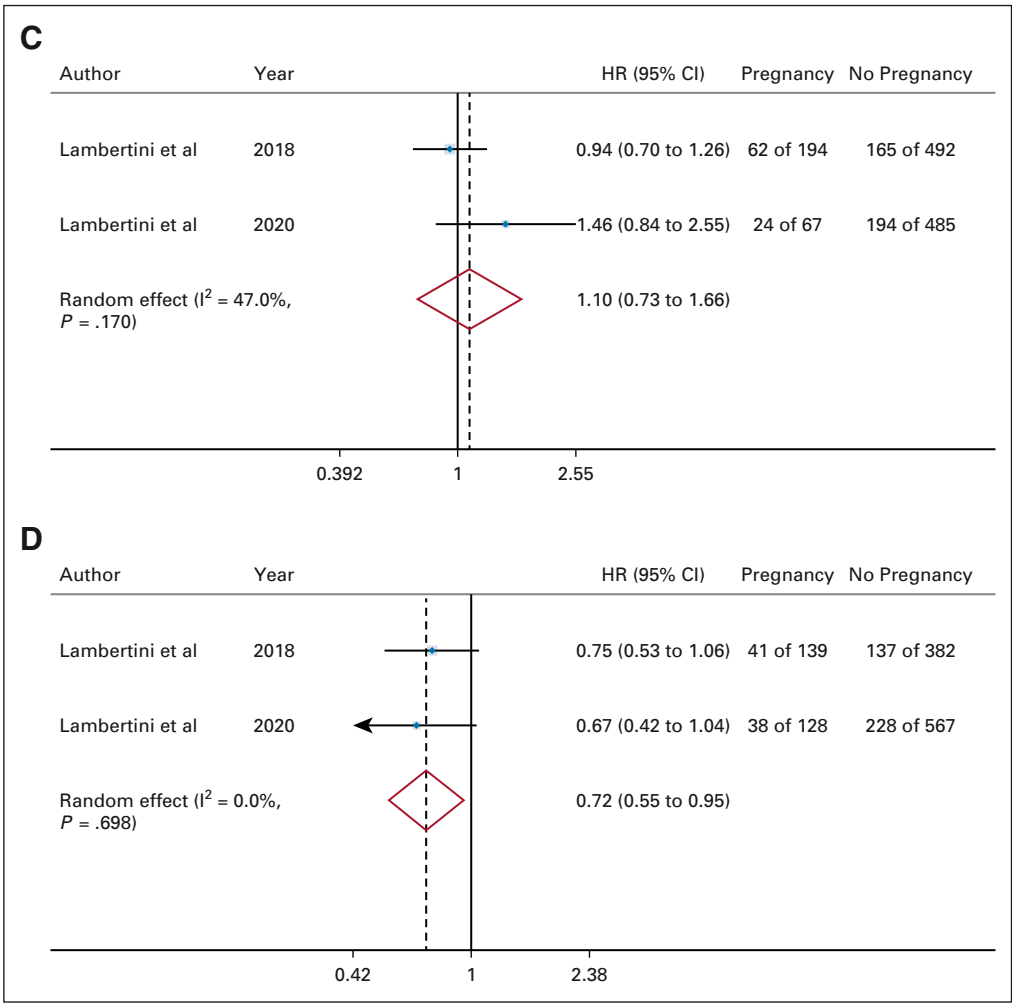

FIG 4. (Continued).

status (Data Supplement),[29,36,45] previous treatment (Data Supplement),[36,58] pregnancy outcome (Data Supplement),[41,45,58,61] and timing of pregnancy after BC (Data Supplement).[29,40,45] No detrimental effect of pregnancy after BC was observed in *BRCA*-mutated patients (HR, 0.85; 95% CI, 0.51 to 1.43; Data Supplement).[48,63] Subgroup analysis on the basis of hormone receptor status could not be conducted considering that only one study reported OS results separately in patients with hormone receptor–positive and hormone receptor–negative disease.[58]

DISCUSSION

This comprehensive systematic review and meta-analysis provides updated evidence regarding likelihood of pregnancy in women with prior history of BC, their reproductive outcomes, and maternal safety. BC survivors had 60% reduced likelihood of having a subsequent pregnancy compared with the general population. Patients with BC, particularly those exposed to previous chemotherapy, had an increased risk of caesarean section and having offspring with low birth weight, preterm birth, and small for gestational age as compared with women from the general population. However, no alarming signals in other reproductive outcomes were observed, including no significantly increased risk of congenital abnormalities. Pregnancy after BC was not associated with any detrimental prognostic effect irrespective of tumor characteristics, previous treatment, pregnancy outcome, timing of pregnancy after BC, and *BRCA* status.

These findings provide crucial information for improving the oncofertility counseling of patients with BC, guiding them and their treating physicians in making evidence-based decisions on future family planning.

Despite being the most commonly diagnosed malignancy in women of reproductive age and one of the solid tumors with the highest survival rates,[1] several studies over the past few years have raised awareness on the low likelihood of future conception in BC survivors.[64] This meta-analysis quantifies the impact of previous cancer diagnosis in this regard, showing that BC survivors have a low likelihood of

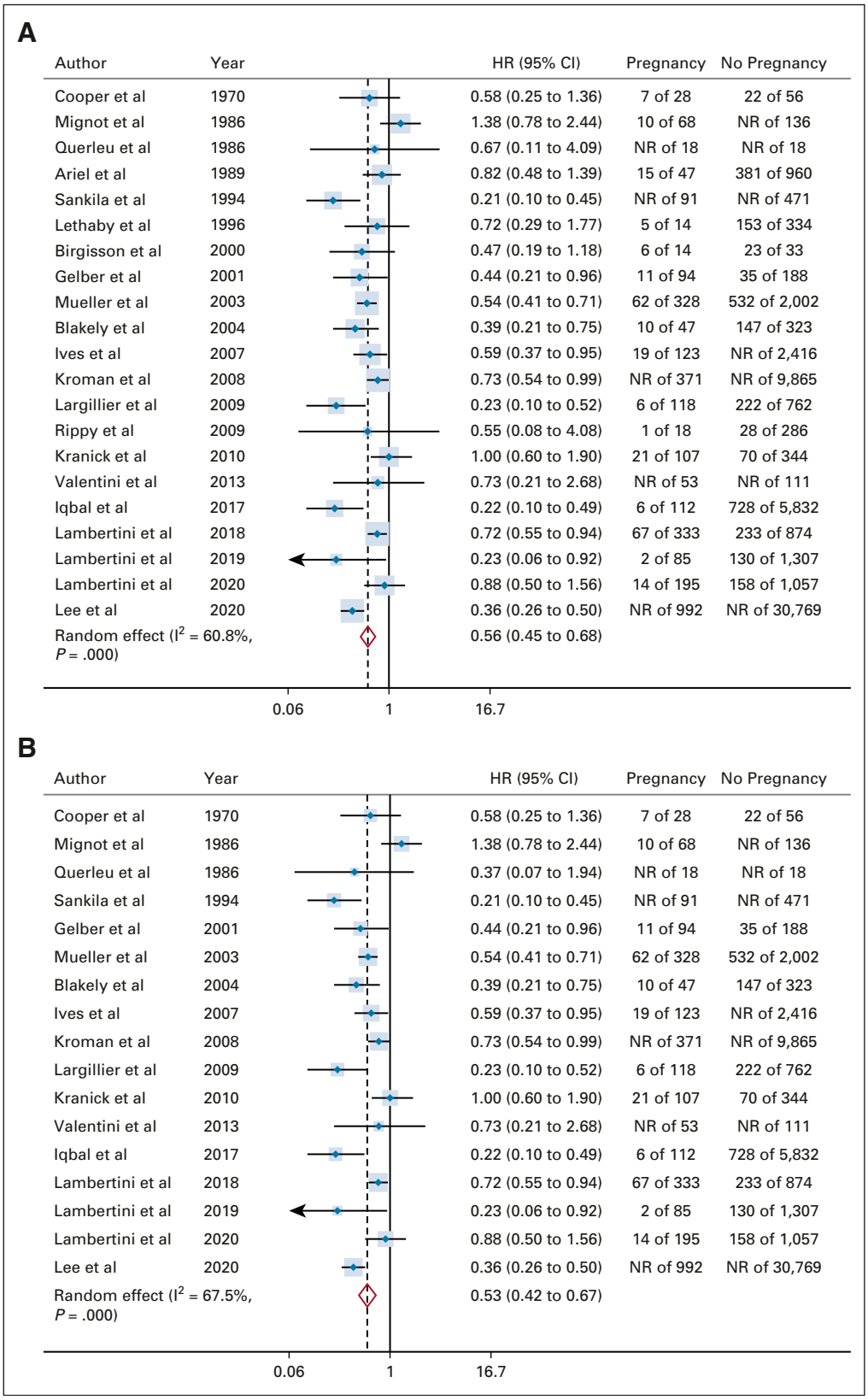

FIG 5. Overall survival comparing patients with or without a pregnancy after breast cancer: (A) in all studies (P for random effect < .001) and (B) by including only studies correcting for the potential guarantee-time bias (P for random effect < .001). HR, hazard ratio; NR, not reported.

achieving a subsequent pregnancy, second only to women with prior history of cervical cancer. There are different potential explanations. First, BC is diagnosed at a relatively older age compared with other malignancies arising during reproductive years.[1] Second, premenopausal women with BC are frequently administered potentially gonadotoxic therapies (eg, cyclophosphamide-based chemotherapy regimens),[6,10,11,65] and those with hormone receptor–positive disease receive adjuvant endocrine treatment for a prolonged duration of 5-10 years.[13,14] Therefore, proper and timely referral of patients interested in future conception to fertility units is crucial.[18] Strengthening oncofertility programs and overcoming the barriers for their implementation (including financial burden) should be considered a priority to improve patients' care and survivorship.[66,67] Although nulliparity is known to be associated with increased interest in future pregnancies,[68] all newly diagnosed patients should receive oncofertility counseling to make sure that they fully understand the implications of developing treatment-induced premature ovarian insufficiency.[18] Of note, the lower likelihood of future conception in BC survivors was also observed in the three studies included in this meta-analysis that controlled for parity[46,47,49] and in a further study analyzing previously nulliparous women.[56] Finally, patients' and physicians' concerns about a potential negative impact of previous BC diagnosis and treatment on reproductive outcomes and maternal safety might have played a major role in discouraging many survivors from attempting pregnancy.[15,16] These highly relevant issues have been dispelled by the present meta-analysis.

Previous studies have raised safety concerns regarding a potentially higher risk of adverse reproductive outcomes in cancer survivors previously exposed to anticancer therapies.[69,70] The present meta-analysis focusing specifically on BC survivors provides reassuring evidence on this important issue. For the majority of analyzed outcomes including risk of spontaneous abortion and congenital anomalies, no significant differences were observed as compared with the general population. The trend for an increased risk of congenital abnormalities observed for the offspring of BC survivors did not reach statistical significance (OR, 1.63; 95% CI, 0.89 to 2.98), and it should be interpreted with caution. No difference between minor and major malformations was made in all but one of the studies entering this analysis, and defects like undescended testes or unspecified limb malformations were also included in the definition of congenital abnormalities. One of the largest studies included in this analysis reported a rate of congenital abnormalities of approximately 3% among the whole cohort of cancer survivors,[50] ie, similar to the rate expected in the general population.[71] The higher rate observed in the subgroup of BC survivors was discussed by the authors as potentially chance findings, considering the small numbers and the fact that it was observed in different parity groups.[50] Notably, recent evidence,[63] including secondary analyses of randomized studies (that could not be included in the present meta-analysis because of lack of comparison with the general population),[60,72,73] is reassuring in this regard reporting a rate of congenital abnormalities in offspring of BC survivors lower than 3%. This finding might also be an example of Simpson's paradox, by which effects observed in cohorts can separately even reverse when they are combined.[70] Nevertheless, this meta-analysis showed that BC survivors had increased risks of 14% of caesarean section, 50% of having offspring with low birth weight, 45% of preterm birth, and 16% of small for gestational age as compared with the general population. Notably, the risk of developing these complications was mostly observed in patients previously exposed to chemotherapy. These data provide additional evidence to support the expert opinion–based recommendation to monitor more closely pregnancies of cancer survivors in experienced units.[18] Considering the current and upcoming availability of several targeted agents and immunotherapy in the early BC setting, further research to understand their potential impact on reproductive outcomes is needed in the coming years.[74]

Because of the fact that BC is a hormonally driven tumor, concerns of a potential detrimental prognostic effect of pregnancy in these patients have discouraged many women from attempting conceiving over the past few years.[15-17] In contrast to previous meta-analyses,[75,76] the present updated meta-analysis included all the recent largest studies exploring this issue and allowed several subgroup analyses, thus providing solid evidence on maternal safety. No detrimental prognostic effect in terms of DFS or OS was observed for BC patients with a subsequent pregnancy. The safety of pregnancy after BC was shown irrespective of tumor characteristics (including among women with hormone receptor–positive disease and nodal involvement), previous treatment, pregnancy outcome, timing of pregnancy after BC, and *BRCA* status. It should be noted that the evidence in this field derives mostly from retrospective studies and may be prone to guarantee-time bias.[77] However, to provide proper answers to this relevant but challenging clinical question also considering the difficulties of conducting prospective studies, it is considered acceptable to rely on well-conducted retrospective studies.[78] Secondary analyses focusing on studies that controlled for guarantee-time bias confirmed the lack of detrimental prognostic effect of pregnancy after BC. These data reinforce the current recommendation that pregnancy in BC survivors, after completing adequate treatment and period of follow-up, should not be discouraged.[18] Notably, only two studies reported on the safety of pregnancy after BC in patients with hormone receptor–positive disease.[58,63] Although the tendency for improved outcomes in patients with a pregnancy after BC seemed to be restricted only to the cohort of patients with hormone receptor–negative

disease, no detrimental prognostic effect was observed also among women with hormone receptor–positive BC. In these studies, the median duration of adjuvant endocrine therapy before conception ranged between 50 and 60 months.[58,63] The results from the prospective POSITIVE trial (ClinicalTrials.gov identifier: NCT02308085) assessing the safety of a temporary interruption of adjuvant endocrine therapy to attempt pregnancy are awaited to provide evidence on this crucial issue.[79,80] Additional research efforts are needed in this area. No adequate evidence exists on the safety of having multiple pregnancies following treatment completion and on conceiving after prior history of BC diagnosed during pregnancy. Moreover, there are limited data reporting on the safety of assisted reproductive technologies in BC survivors not subsequently exposed to anticancer therapies.[81]

Among study limitations, it should be considered that this meta-analysis was based on abstracted data and most of the included studies were retrospective observational analyses. Some matching criteria differed in the included studies. In addition, limited data were available for several reproductive outcomes. Moreover, not all the preplanned subgroup analyses could be conducted because of lack of details in the included studies on the effect of administered anticancer therapies, tumor size, and patients' age on the results as well as because of the nonhomogenous definition of early or late pregnancies. This highlights the need to pursue further research in this area. Finally, in some of the analyses, the heterogeneity was high; this could be attributable to the inclusion of studies with different design, sample size, inclusion criteria, period of conduction, and controlling factors. High heterogeneity was observed in all analyses assessing maternal safety, with one study conducted exclusively in the Asian population being an important driver of this result (as shown in the sensitivity analyses in the Data Supplement) because of its low variability (narrow CI) and extreme HRs.[61] When a high heterogeneity is present, the reliability of the pooled estimate can be questioned; however, if the majority of studies report similar results confirmed by the pooled estimate, the observed heterogeneity can be defined more as quantitative than qualitative. As a consequence, the presence of high heterogeneity may affect the accuracy of the pooled estimate, but it is unlikely to affect its validity. In this regard, for the analyses assessing maternal safety, all but three studies for DFS and two for OS reported an HR < 1 pointing in the same direction as the pooled estimate to support the lack of detrimental prognostic effect of pregnancy after BC. In addition, as suggested by DerSimonian and Laird, the use of the random effects model allows us to obtain reliable pooled estimated and consistent CI also in the presence of a certain amount of heterogeneity.[82] Moreover, sensitivity analyses and the additional efforts to take into account these issues provided consistent results with the main analyses further supporting the overall conclusions.

In conclusion, the results of the present meta-analysis provide reassuring updated evidence on the safety of conceiving in women with previous BC. These findings are of paramount importance to raise awareness on the need to provide oncofertility counseling to all young patients with newly diagnosed BC to increase their likelihood of future conception. The higher risk of delivery and fetal complications (but not of congenital abnormalities) calls for ensuring a closer monitoring of these pregnancies in experienced units. The lack of detrimental prognostic effect of pregnancy after BC strongly supports the need for a deeper consideration of patients' pregnancy desire as a crucial component of their survivorship care plan and expectation to return to a normal life.

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DISCLAIMER

The contents of this article are solely the responsibility of the authors. The financial sponsors of the study (AIRC and 5x1000) had no role in study design, data collection, analysis, interpretation, or writing of the report, and they had no access to the data.

EQUAL CONTRIBUTION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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