TITLE PAGE

Prevalence of pregnancy after breast cancer, reproductive outcomes and maternal safety: a systematic review and meta-analysis

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Running head

Feasibility and safety of pregnancy after breast cancer

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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). Prevalence of pregnancy after BC, their reproductive outcomes and maternal safety were assessed. Pooled relative risks (RRs), odds ratios (ORs), and hazard ratios (HRs) with 95% confidence intervals (CI) 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 114,573 BC patients of whom 7,505 had a pregnancy after diagnosis.

BC survivors were significantly less likely to have a subsequent pregnancy compared to the general population (RR=0.40, 95%CI 0.32-0.49).

Risks of caesarean section (OR=1.14, 95%CI 1.04-1.25), low birth weight (OR=1.50, 95%CI 1.31-1.73), preterm birth (OR=1.45, 95%CI 1.11-1.88), and small for gestational age (OR=1.16, 95%CI 1.01-1.33) were significantly higher in BC survivors, particularly in those with prior chemotherapy exposure, compared to the general population. No significant increased risk of congenital abnormalities or other reproductive complications was observed.

Compared to BC patients without subsequent pregnancy, those with a pregnancy had better disease-free survival (HR=0.66, 95%CI 0.49-0.89) and overall survival (HR=0.56, 95%CI 0.45-0.68). Similar

results were observed after correcting for potential confounders and irrespective of patient, tumor, and treatment characteristics, pregnancy outcome and timing of pregnancy.

CONCLUSIONS

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.

MANUSCRIPT

Introduction

Among patients of reproductive age, breast cancer 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 breast cancer patients, pregnancy-related issues represent a main area of concern.[6] Due to the rise in age at first pregnancy over the past years, an increased number of women are diagnosed with breast cancer before completing their reproductive plans.[7–9] Among the potential long-term side effects of anticancer treatments, premature ovarian insufficiency (POI) and subsequent impaired fertility are of particular concern.[10,11] Moreover, patients with hormone receptor-positive breast cancer 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 breast cancer diagnosis and treatment.[15,16] The main reasons for this distress are the possibility that a prior exposure to anticancer therapies might have negative effects on the fetus by increasing the risk of congenital abnormalities, obstetric, or birth complications. Furthermore, as breast cancer 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.[15,16]

Current guidelines do not discourage having a pregnancy following treatment completion for breast cancer and an adequate period of follow-up.[6,17] However, only a small number of breast cancer

patients do conceive.[18] To refine the evidence surrounding this topic in order to guide patients and physicians during oncofertility counselling, we performed a systematic review and meta-analysis aiming to assess prevalence of pregnancy in women with prior history of breast cancer, their reproductive outcomes and maternal safety.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19]

A systematic literature search of Medline, Web of Science, and Cochrane databases including the keywords 'breast cancer' and 'pregnancy' was performed on January 31, 2020 with no language or date restriction. 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 (ESMO) and the American Society of Clinical Oncology (ASCO) annual meetings, and the San Antonio Breast Cancer Symposium (SABCS) was performed in order 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: (i) retrospective or prospective case-control or cohort studies, as well as clinical trials reporting on pregnancy after breast cancer; (ii) studies with available information on one or more of the three outcomes of interest (prevalence of pregnancy after breast cancer, reproductive outcomes, and/or maternal safety); (iii) availability or possibility to estimate data on relative risk (RR), odds ratio (OR), and hazard ratio (HR), according to the analysed outcome, with their 95% confidence intervals (CI).

Exclusion criteria were: (i) case-reports and case series including less than ten patients; (ii) studies reporting on pregnancy-associated breast cancer (i.e. breast cancer diagnosed during pregnancy or within five years after pregnancy) with no data on pregnancy following breast cancer diagnosis; (iii) ongoing studies with results not presented nor published at the time of the literature search.

The systematic literature search was carried out independently by two authors (EB and MP) and any discrepancies were solved by discussion with a third author (ML).

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 (EB and MP) 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; 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:

- prevalence of pregnancy in patients with prior history of breast cancer versus healthy women from the general population and survivors of other malignancies.
- reproductive outcomes in patients with prior history of breast cancer 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 post-partum bleeding.

- maternal safety by comparing survival outcomes between breast cancer patients with or without a subsequent pregnancy, in terms of disease-free survival (DFS) and overall survival (OS).

Subgroup analyses were conducted to assess:

- reproductive outcomes according to use of chemotherapy (yes vs. no), and interval between diagnosis and pregnancy (early vs. late, defined using as cut-offs one or two years after breast cancer diagnosis);
- maternal survival outcomes (DFS and/or OS) according to nodal status (negative vs. positive), hormone receptor status (positive vs. negative), use of chemotherapy (yes vs. no), interval between diagnosis and pregnancy (early vs. late, defined using as cut-offs one, two or five years after breast cancer diagnosis), pregnancy outcomes (completed pregnancy vs. 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, while HRs were estimated using the method reported by Watkins and Bennett.[20] 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: (i) all studies with available information on DFS and/or OS; (ii) only the studies with information on DFS and/or OS adjusted for the potential guarantee-time bias/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 with the method of DerSimonian and Laird using the random effects model.[21] The quantitative measure of the degree of inconsistency in the results of the included studies was computed using the Higgins I^2 index.[22] The likelihood of publication bias was assessed by Egger's asymmetry test.[23] Pooled RRs, ORs, and HRs were considered statistically significant with a P value of <0.05 (two-sided). In order to assess whether the pooled RR, OR, and HR estimates were stable or depended on one single included study, sensitivity analyses were conducted.

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

Results

Out of 6,462 identified records, 39 studies were included in the meta-analysis (Figure 1).[24–62] Among the 8,265,713 women included in these studies, 8,093,401 were from the general population, 57,739 had malignancies other than breast cancer, and 114,573 had breast tumors. Among the 114,573 breast cancer patients, 7,505 had a pregnancy after diagnosis. One study did not report the number of included women from general population,[56] and another the number of breast cancer patients that had a pregnancy after diagnosis.[48]

Prevalence of pregnancy

Seven records were included in this analysis (appendix Table S1).[41,45,46,48,55,56,58] Out of 3,395,365 women included in these studies, 3,289,113 were from the general population, 57,739 had malignancies other than breast cancer, and 48,513 had breast tumors.

Overall, cancer patients had 35% reduced likelihood of having a subsequent pregnancy compared to the general population (RR=0.65; 95% CI 0.55-0.77); the lowest prevalence of pregnancy was

observed in patients with prior cervical cancer (Figure 2; appendix Figures S1-S13 and Table S2-S11).

Among the 48,513 breast cancer patients included in the analysis, 2,026 (4.2%) had a subsequent pregnancy. Compared to the general population, breast cancer survivors had a 60% reduced likelihood of having a subsequent pregnancy (RR=0.40, 95% CI 0.32-0.49; appendix Figure S14 and Table S12).

Reproductive outcomes

Nine records were included in this analysis (appendix Table S13).[37,38,49–52,56,58,61] 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 prior breast cancer. One study did not report the number of included women from the general population.[56]

Summary of the pooled results on reproductive outcomes are reported in Figure 3, publication bias and sensitivity analysis for all outcomes in the supplementary material.

No difference was observed between breast cancer patients and the general population in terms of completed pregnancies (OR=1.21, 95% CI 0.48-3.03; appendix Figure S15), spontaneous (OR=1.04, 95% CI 0.86-1.26; appendix Figure S16), or induced (OR=1.40, 95% CI 0.71-2.76; appendix Figure S17) abortions, developing pre-eclampsia (OR=1.03, 95% CI 0.27-3.98; appendix Figure S18), and postpartum bleeding (OR=0.88, 95% CI 0.57-1.37; appendix Figure S19 and Table S14).

An increased risk of caesarean section was observed in breast cancer patients (OR=1.14, 95% CI 1.04-1.25; appendix Figure S20 and Table S15). Offspring of breast cancer patients were at increased risk of low birth weight (OR=1.50, 95% CI 1.31-1.73; appendix Figure S21 and Table S16), preterm birth (OR=1.45, 95% CI 1.11-1.88; appendix Figure S22 and Table S17), and small for gestational age (OR=1.16, 95% CI 1.01-1.33; appendix Figure S23 and Table S18) compared to the general

population. No significant increased risk of congenital abnormalities was observed for the offspring of breast cancer survivors (OR=1.63, 95% CI 0.89-2.98; appendix Figure S24 and Table S19).

Subgroup analyses of reproductive outcomes according to prior exposure to chemotherapy and timing of pregnancy after breast cancer were performed by including two studies.[52, 56] As compared to offspring of women from the general population, the increased risk of low birth weight and small for gestational age appeared to be restricted to breast cancer patients with prior exposure to chemotherapy (appendix Figures S25-30). Results did not vary substantially from those of the main analyses for the offspring of patients with early or late pregnancies after breast cancer (appendix Figures S31-36).

Maternal safety

Disease outcomes were reported in 25 studies (appendix Table S20),[24–36,39,40,42–44,47,53,54,57,59,60,62] of which 19 adjusted the results for the potential guarantee-time bias.[24–26,28–30,34–36,39,40,42,44,47,53,57,59,60,62] Out of 63,968 breast cancer patients included, 3,387 (5.3%) had a pregnancy after breast cancer.

Disease-free survival

DFS between patients with or without a pregnancy after breast cancer was reported in 11 studies.[29,30,32,36,42,44,54,57,59,60,62] Among them, four studies reported relapse-free survival,[32,36,44,60] one study distant recurrence-free interval,[42] and one study distant DFS.[30]

As compared to breast cancer patients without subsequent pregnancy, those with a post-treatment pregnancy showed better DFS (HR=0.66, 95% CI 0.49-0.89; Figure 4A and appendix Table S21). Similar results were observed in the studies correcting for the potential guarantee-time bias (HR=0.68, 95% CI 0.51-0.91; Figure 4B and appendix Table S22), and in the analyses after excluding computed HRs (appendix Figures S37-38 and Tables S23-24).

At the subgroup analyses, the lack of detrimental effect of pregnancy after breast cancer was observed irrespective of hormone-receptor status (appendix Figure S39 and Figure S40),[57,62] pregnancy outcome (appendix Figures S41-S42 and Tables S25-S26),[44,57,60] and timing of pregnancy after breast cancer (appendix Figures S43-S44).[44,57]

Overall survival

OS between patients with or without a pregnancy after breast cancer was reported in 21 studies.[24–28,31,33–36,39,40,42–44,47,53,57,59,60,62]

As compared to breast cancer patients without subsequent pregnancy, those with a post-treatment pregnancy showed better OS (HR=0.56, 95% CI 0.45-0.68; Figure 5A and appendix Table S27). Similar results were observed in the studies adjusting for the potential guarantee-time bias (HR=0.53, 95% CI 0.42-0.67; Figure 5B and appendix Table S28), and in the analyses after excluding computed HRs (appendix Figures S45-46 and Tables S29-30).

At the subgroup analyses, the lack of detrimental effect of pregnancy after breast cancer was observed irrespective of nodal status (appendix Figures S47-S48 and Tables S31-S32),[28,35,44] prior treatment (appendix Figures S49-S50),[35,57] pregnancy outcome (appendix Figures S51-S52 and Tables S33-S34),[40,44,57,60] and timing of pregnancy after breast cancer (appendix Figures S53-S54 and Tables S35-S36).[28,39,44] No detrimental effect of pregnancy after breast cancer was observed in *BRCA*-mutated patients (HR=0.85, 95% CI 0.51-1.43; appendix Figure S55).[47,62]

Discussion

This comprehensive systematic review and meta-analysis provides updated evidence regarding prevalence of pregnancy in women with prior history of breast cancer, their reproductive outcomes, and maternal safety. Breast cancer survivors had 60% reduced likelihood of having a subsequent

pregnancy compared to the general population. Breast cancer patients, particularly those exposed to prior chemotherapy, had an increased risk of caesarean section, having offspring with low birth weight, preterm birth, and small for gestational age as compared to women from the general population. However, no alarming signals in other reproductive outcomes were observed, including no significant increased risk of congenital abnormalities. Pregnancy after breast cancer was not associated with any detrimental prognostic effect irrespective of tumor characteristics, prior treatment, pregnancy outcome, timing of pregnancy after breast cancer, and *BRCA* status.

These findings provide crucial information for improving the oncofertility counselling of breast cancer patients 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 last years have raised awareness on the low likelihood of future conception in breast cancer survivors.[63] This meta-analysis quantifies the impact of prior cancer diagnosis on prevalence of post-treatment pregnancy showing that breast cancer survivors have a low likelihood of achieving a subsequent pregnancy, second only to women with prior history of cervical cancer. There are different potential explanations. Firstly, breast cancer is diagnosed at a relatively older age compared to other malignancies arising during reproductive years.[1] Secondly, the frequent need to administer potentially gonadotoxic therapies (e.g. cyclophosphamide-based chemotherapy regimens),[10,11] and the prolonged duration of adjuvant endocrine treatment in patients with hormone receptor-positive disease.[13,14] Therefore, proper and timely referral of patients interested in future conception to fertility units is crucial.[17] Strengthening oncofertility programs and overcoming the barriers for their implementation (including financial burden) should be considered a priority to improve patients' care and survivorship.[64,65] Finally, patients' and physicians' concerns about a potential negative impact of prior breast cancer diagnosis and treatment on reproductive outcomes and maternal safety may 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 potential higher risk of adverse reproductive outcomes in cancer survivors previously exposed to anticancer therapies.[66,67] The present meta-analysis focusing specifically on breast cancer survivors provides reassuring evidence on this important issue. For the majority of the analyzed outcomes, no differences were observed as compared to the general population. Importantly, there was no significant difference in risk of spontaneous abortion and congenital anomalies. Nevertheless, this meta-analysis showed that breast cancer 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 to 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.[17] Considering the current and upcoming availability of several targeted agents and immunotherapy in the early breast cancer setting, further research to understand their potential impact on reproductive outcomes is needed in the coming years.[68]

Due to the fact that breast cancer 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 years.[15,16] In contrast to prior meta-analyses,[69,70] 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 breast cancer patients with a subsequent pregnancy. The safety of pregnancy after breast cancer was shown irrespective of tumor characteristics (including among women with hormone receptor-positive disease and nodal involvement), prior treatment, pregnancy

outcome, timing of pregnancy after breast cancer, 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.[71] 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.[72] Secondary analyses focusing on studies that controlled for guarantee-time bias, confirmed the lack of detrimental prognostic effect of pregnancy after breast cancer. These data reinforce the current recommendation that pregnancy in breast cancer survivors, after completing adequate treatment and period of follow-up, should not be discouraged.[17] Results from the prospective POSITIVE trial (NCT02308085) assessing the safety of a temporary interruption of adjuvant endocrine therapy to attempt pregnancy are awaited to provide evidence on this crucial issue.[73,74]

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 and for performing subgroup analyses (including lack of precise details on the administered anticancer therapies) highlighting the need to pursue further research in this area. Finally, the heterogeneity was high in some of the analyses; this could be attributable to the inclusion of studies with different design, sample size, inclusion criteria, and controlling factors, with one study being an important driver of such heterogeneity.[60] When a high heterogeneity is present, the reliability of the pooled estimate can be questioned; however, if the majority of the studies report the same result (i.e. HR<1) confirmed by the pooled estimate, the presence of high heterogeneity may affect the accuracy of the pooled estimate but is unlikely to affect its validity. In addition, 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, results of the present meta-analysis provide reassuring updated evidence on the safety of conceiving in women with prior breast cancer. These findings are of paramount importance to raise awareness on the need to provide oncofertility counselling to all newly diagnosed young breast cancer patients in order 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 breast cancer strongly supports the need for a deeper consideration of patients' pregnancy desire as a crucial component of their survivorship care plan and wish to return to a normal life.

TITLE PAGE

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Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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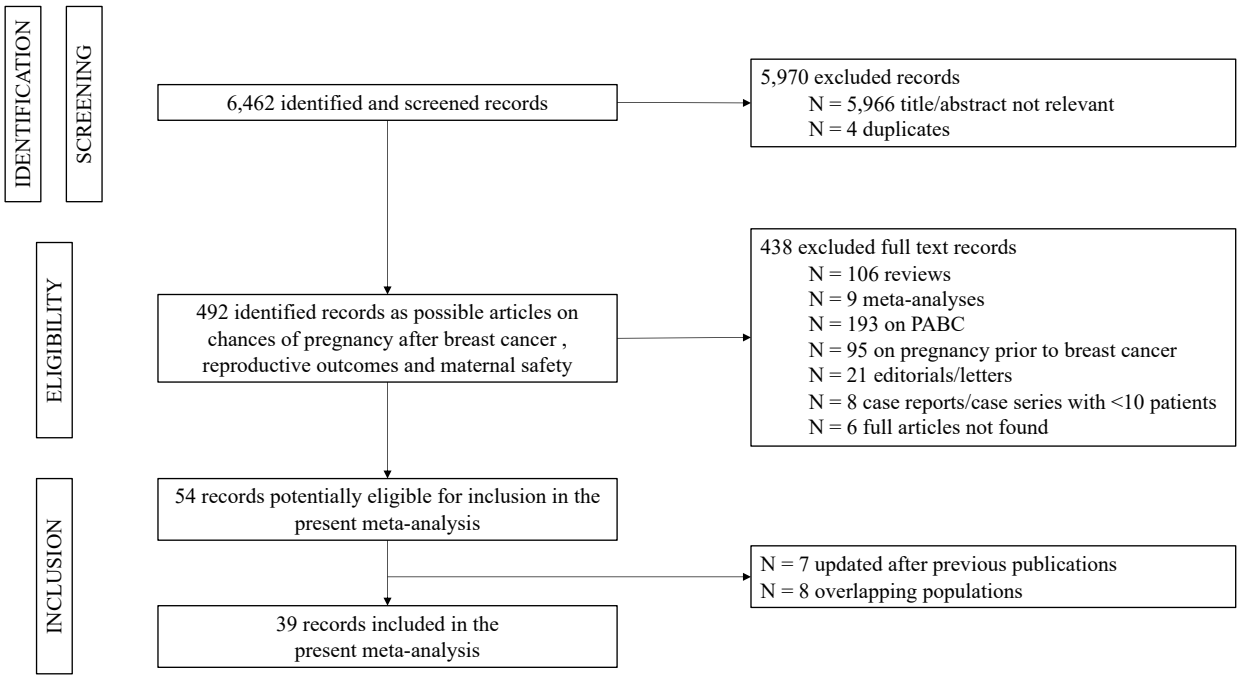
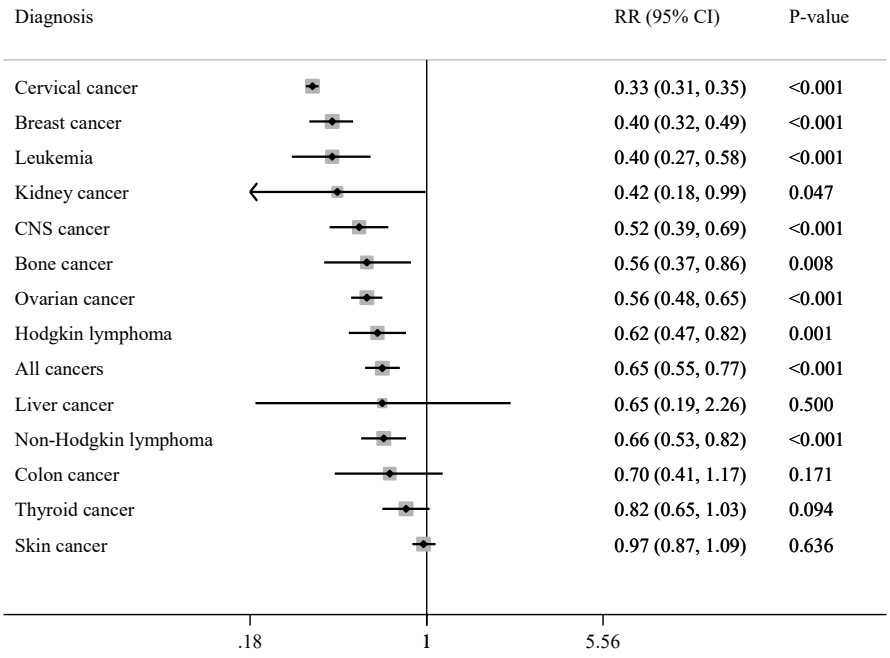
FIGURE LEGENDS

Figure 1 - The PRISMA flow chart summarizing the process for the identification of eligible studies.



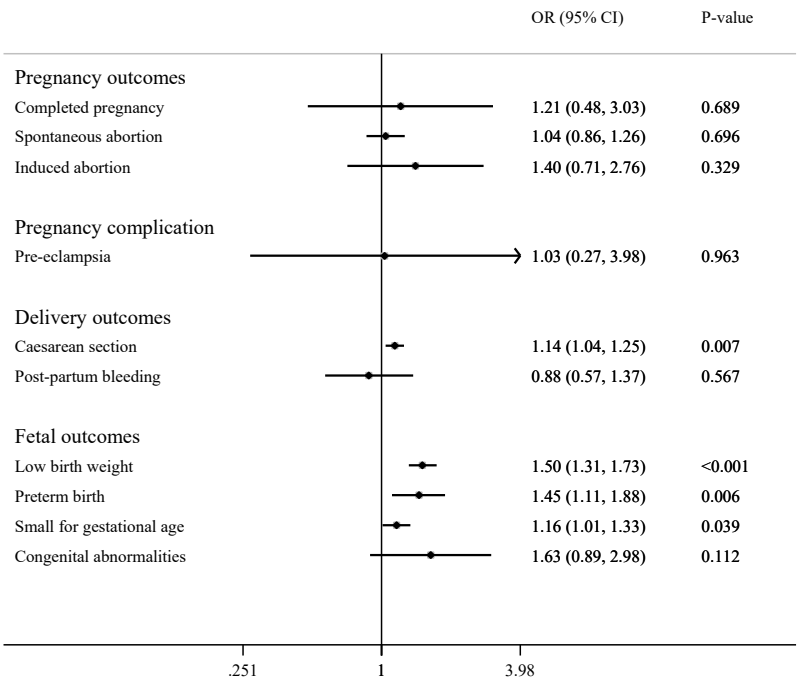
Abbreviations: PABC pregnancy associated breast cancer, BC breast cancer

Figure 2 - Prevalence of pregnancy after cancer diagnosis.



Abbreviations: RR relative risk, CI confidence interval

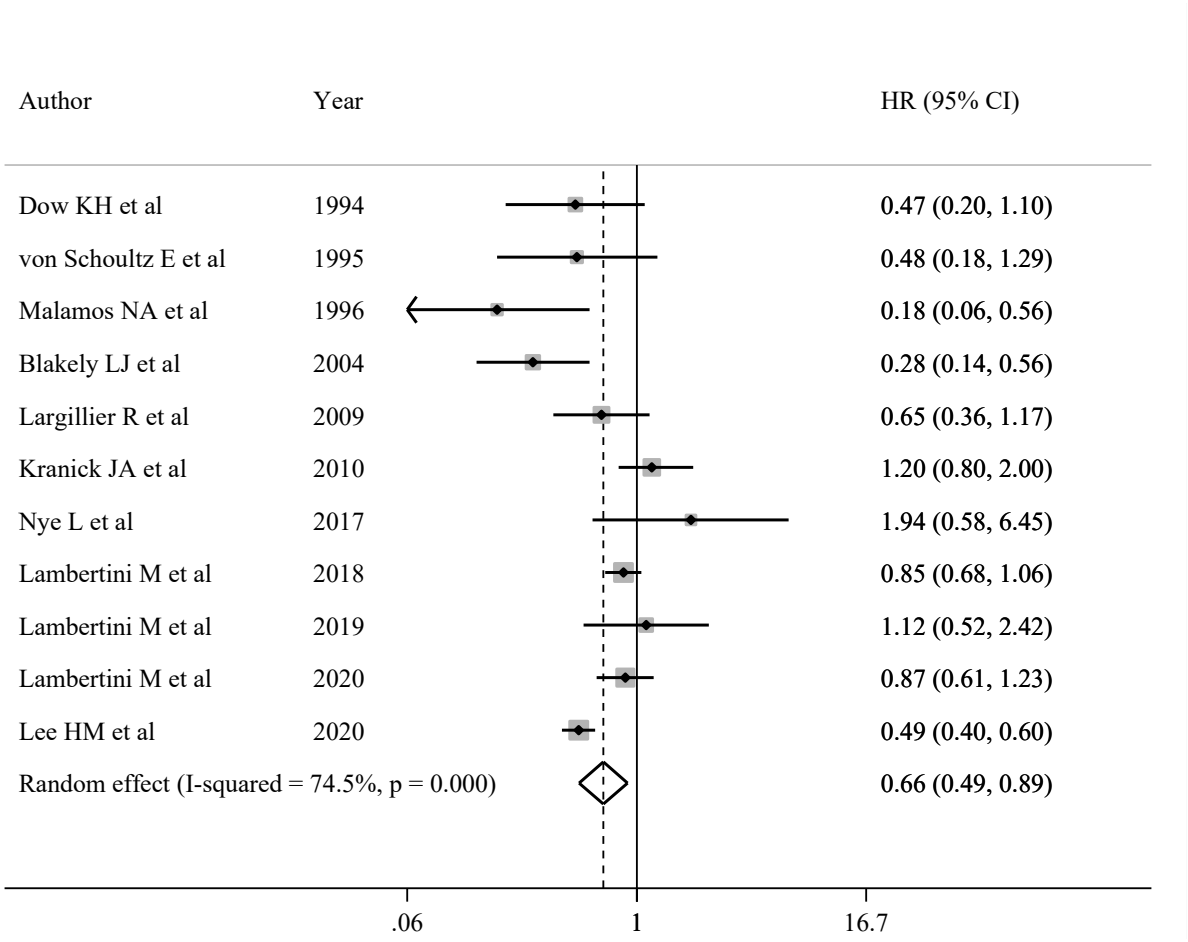
Figure 3 - Reproductive outcomes of patients with a pregnancy after breast cancer.



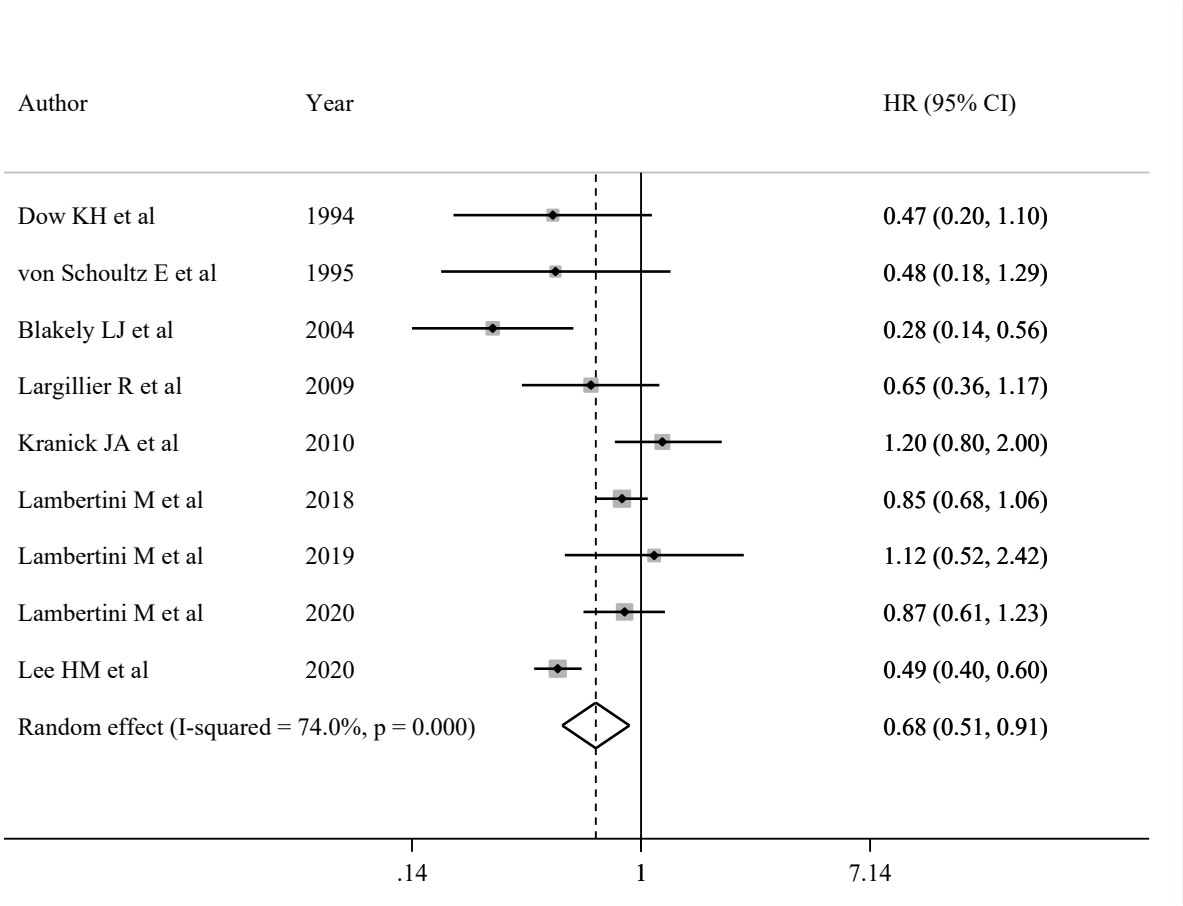
Abbreviations: OR odds ratio, CI confidence interval

Figure 4 - Disease-free survival by comparing between patients with or without a pregnancy after breast cancer in all studies (A) and by including only studies correcting for the potential guarantee-time bias (B).

4A



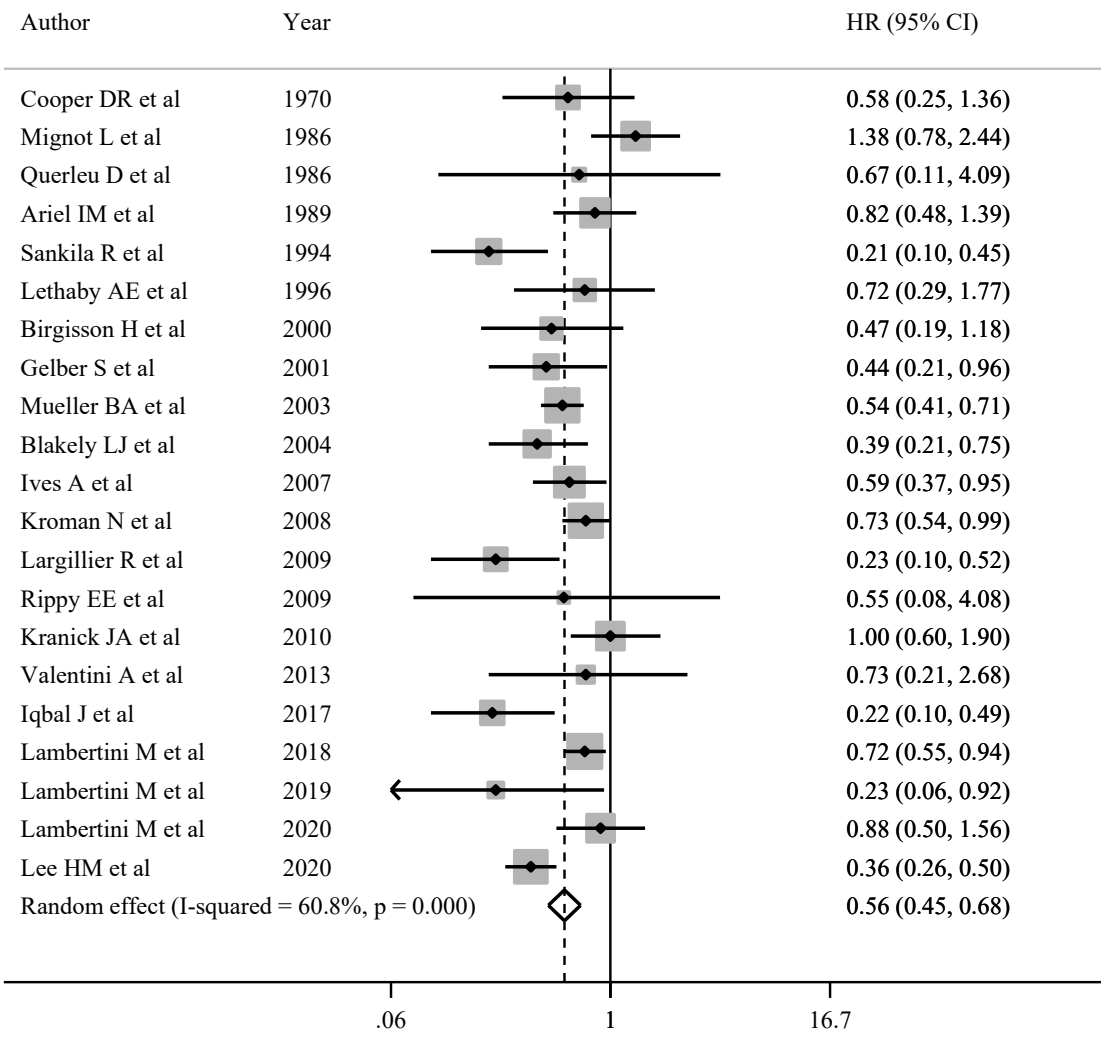
4B



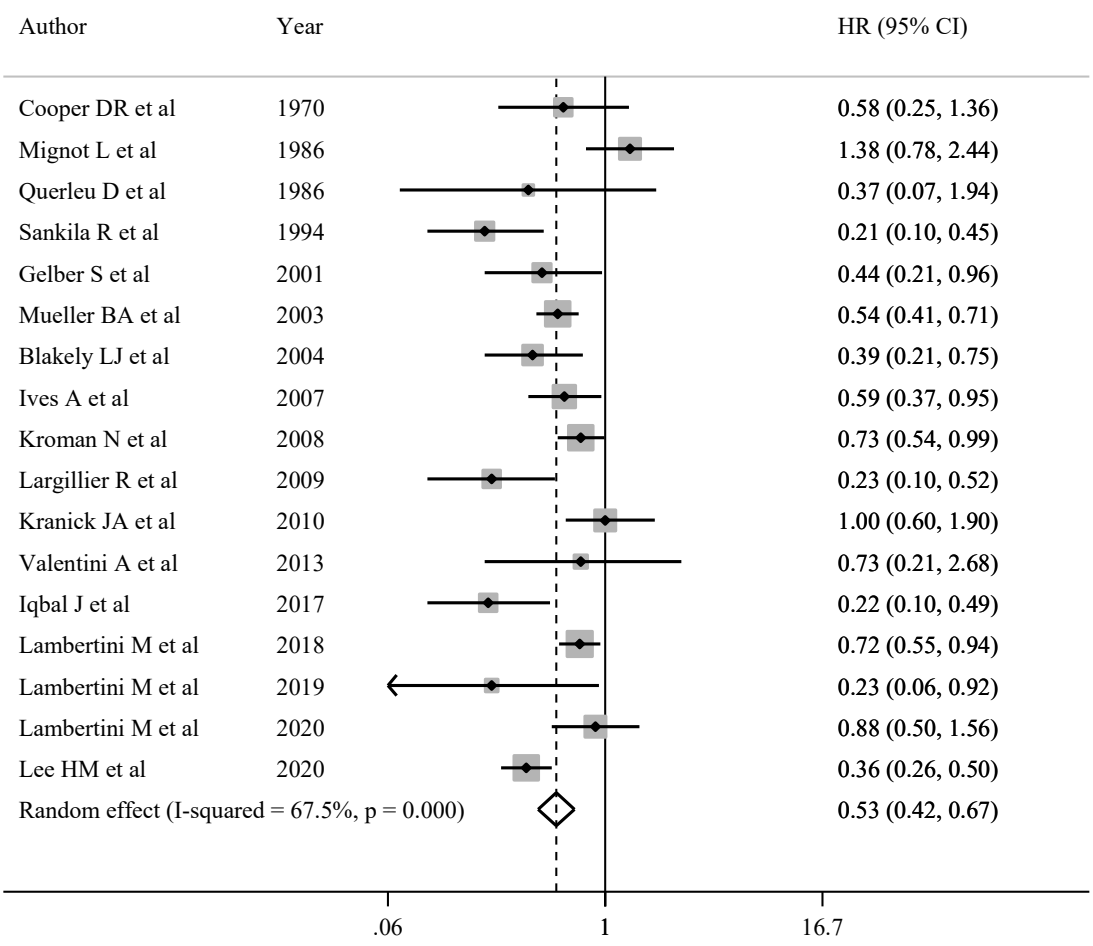
Abbreviations: HR hazard ratio, CI confidence interval

Figure 5 - Overall survival by comparing between patients with or without a pregnancy after breast cancer in all studies (A) and by including only studies correcting for the potential guarantee-time bias (B).

5A


Author
Year
HR (95% CI)
Cooper DR et al 1970 0.58 (0.25, 1.36)
Mignot L et al 1986 1.38 (0.78, 2.44)
Querleu D et al 1986 0.67 (0.11, 4.09)
Ariel IM et al 1989 0.82 (0.48, 1.39)
Sankila R et al 1994 0.21 (0.10, 0.45)
Lethaby AE et al 1996 0.72 (0.29, 1.77)
Birgisson H et al 2000 0.47 (0.19, 1.18)
Gelber S et al 2001 0.44 (0.21, 0.96)
Mueller BA et al 2003 0.54 (0.41, 0.71)
Blakely LJ et al 2004 0.39 (0.21, 0.75)
Ives A et al 2007 0.59 (0.37, 0.95)
Kroman N et al 2008 0.73 (0.54, 0.99)
Largillier R et al 2009 0.23 (0.10, 0.52)
Rippy EE et al 2009 0.55 (0.08, 4.08)
Kranick JA et al 2010 1.00 (0.60, 1.90)
Valentini A et al 2013 0.73 (0.21, 2.68)
Iqbal J et al 2017 0.22 (0.10, 0.49)
Lambertini M et al 2018 0.72 (0.55, 0.94)
Lambertini M et al 2019 0.23 (0.06, 0.92)
Lambertini M et al 2020 0.88 (0.50, 1.56)
Lee HM et al 2020 0.36 (0.26, 0.50)
Random effect (I-squared = 60.8%, p = 0.000) 0.56 (0.45, 0.68)
.06
1
16.7

5B



Abbreviations: HR hazard ratio, CI confidence intervals

APPENDIX

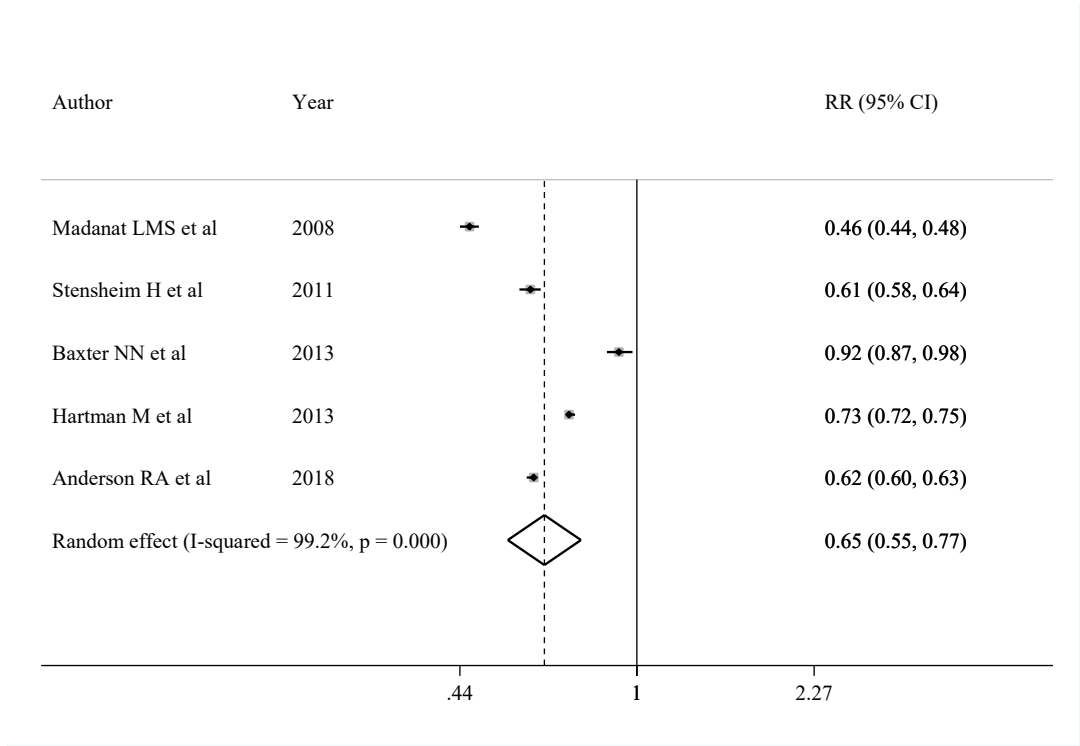
Table S1 - Studies comparing prevalence of pregnancy in cancer patients and in healthy women from the general population.[1–7]

Four were case-control studies,[2–4,7] and three cohort studies.[1,5,6] Two studies reported results of chances of pregnancy only for breast cancer patients.[6,7] Matching criteria for choosing controls were different among studies, with four of them controlling for age.[2,3,5,7]

Reference	Country	Study design	Breast cancer patients (n)	Pregnant breast cancer patients (n)	Matching criteria for choosing controls	Outcomes
Madanat LMS et al 2008	Finland	Cohort study	1,591	83	Siblings of cancer patients	Postdiagnosis parenthood
Stensheim H et al 20111/11/22 3:07:00 PM	Norway	CC	4,061	124	Age and sex	Postcancer pregnancy rates
Hartman M et al 2013	Sweden	CC	12,139	124	Attained age and year of birth	Postcancer standardized birth ratios
Baxter NN et al 2013	Canada	CC	558	N.R.	Year of birth and geographic location	Childbirth occurring at least one year after the date of diagnosis (survivors) / referent date (controls).
Anderson RA et al 2018	Scotland	Retrospective cohort study	5,173	547	Age, deprivation quintile and year of diagnosis	Postdiagnosis standardized incidence ratios for pregnancy
Anderson C et al 2018	North Carolina – USA	Cohort study	4,685	293	N.R.	Incidence of postdiagnosis live births
Lee HM et al 2019	South Korea	Prospective CC	18,280	855	Age	Postcancer childbirth rates

Abbreviations: CC case-control; N.R. not reported

Figure S1 - Prevalence of pregnancy after cancer in the overall population.



Random effect: p<0.001
Egger's test: p=0.862

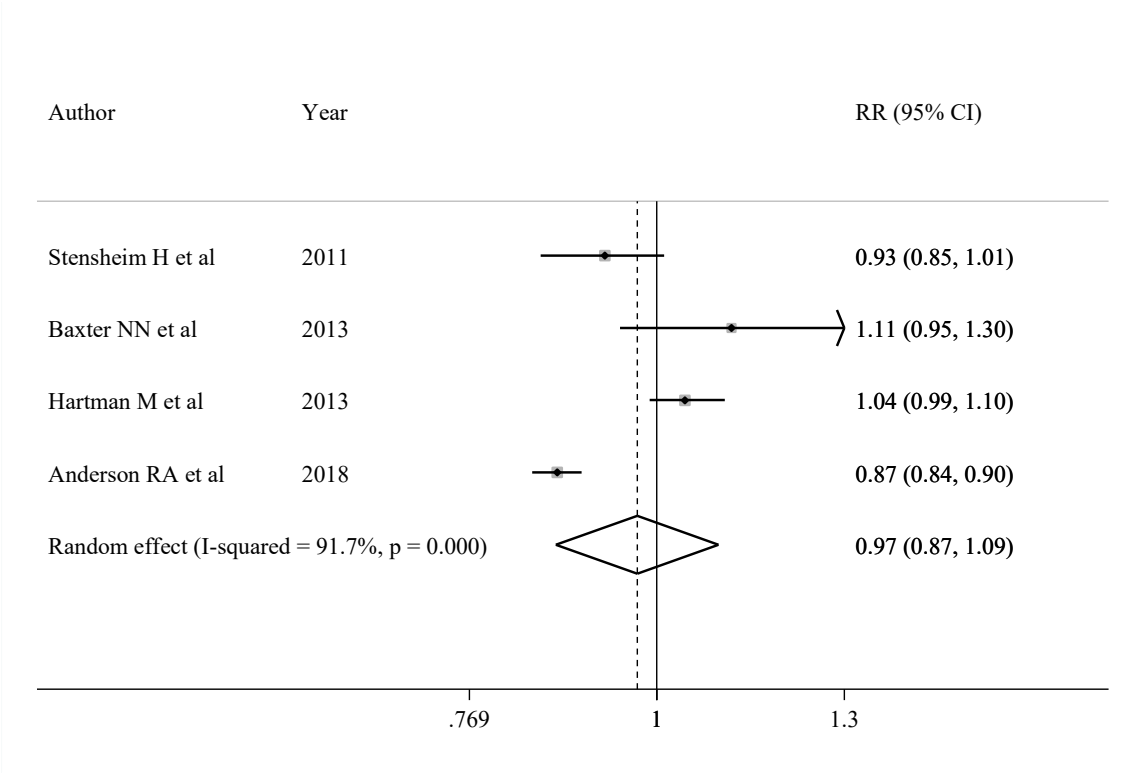
Abbreviations: RR, relative risk; CI, confidence intervals.

Table S2 - Sensitivity analysis for prevalence of pregnancy after cancer in the overall population.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	RR	95% CI	P-value		
Madanat LMS et al 2008	0.71	0.62-0.81	<0.001	98.6	<0.001
Stensheim H et al 2011	0.66	0.54-0.81	<0.001	99.4	<0.001
Baxter NN et al 2013	0.60	0.50-0.71	<0.001	99.2	<0.001
Hartman M et al 2013	0.63	0.51-0.79	<0.001	99.1	<0.001
Anderson RA et al 2018	0.66	0.51-0.85	0.001	99.4	<0.001

Abbreviations: RR, relative risk; CI, confidence intervals.

Figure S2 - Prevalence of pregnancy after skin cancer.



Random effect: p=0.636
Egger's test: p=0.318

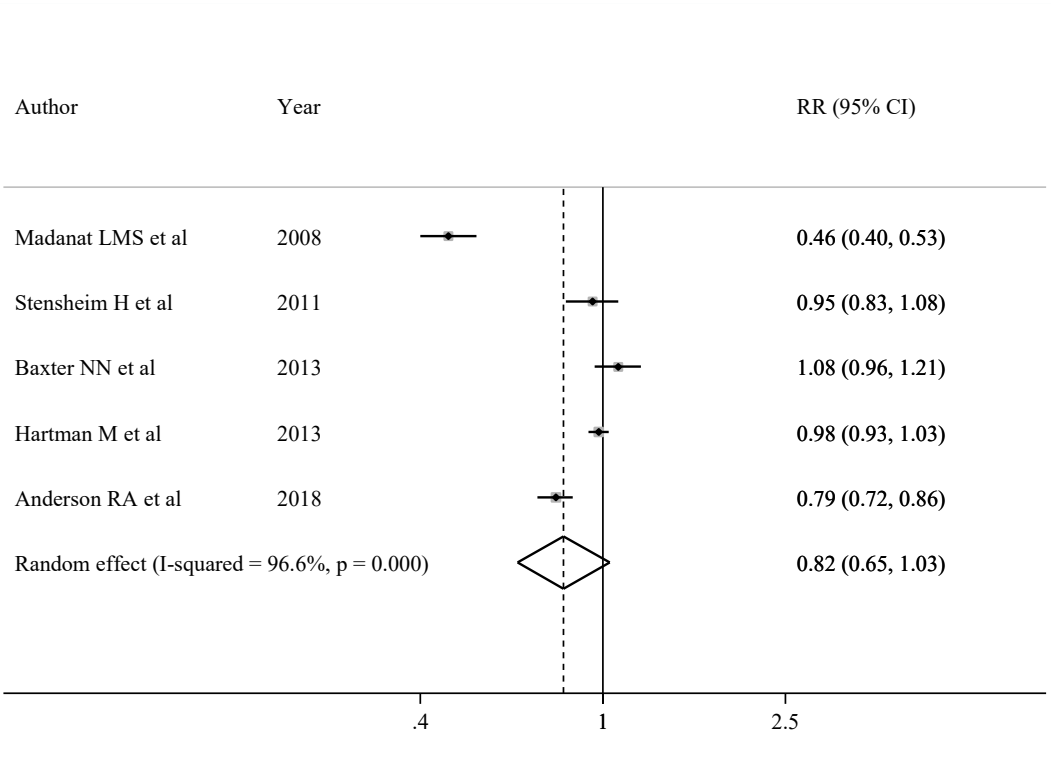
Abbreviations: RR, relative risk; CI, confidence intervals.

Table S3 - Sensitivity analysis for prevalence of pregnancy after skin cancer.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	RR	95% CI	P-value		
Stensheim H et al 2011	0.99	0.85-1.15	0.903	94.5	<0.001
Baxter NN et al 2013	0.94	0.83-1.07	0.354	93.5	<0.001
Hartman M et al 2013	0.94	0.84-1.05	0.286	80.4	0.006
Anderson RA et al 2018	1.01	0.92-1.11	0.780	66.8	0.049

Abbreviations: RR, relative risk; CI, confidence intervals.

Figure S3 - Prevalence of pregnancy after thyroid cancer.



Random effect: p=0.094
Egger's test: p=0.364

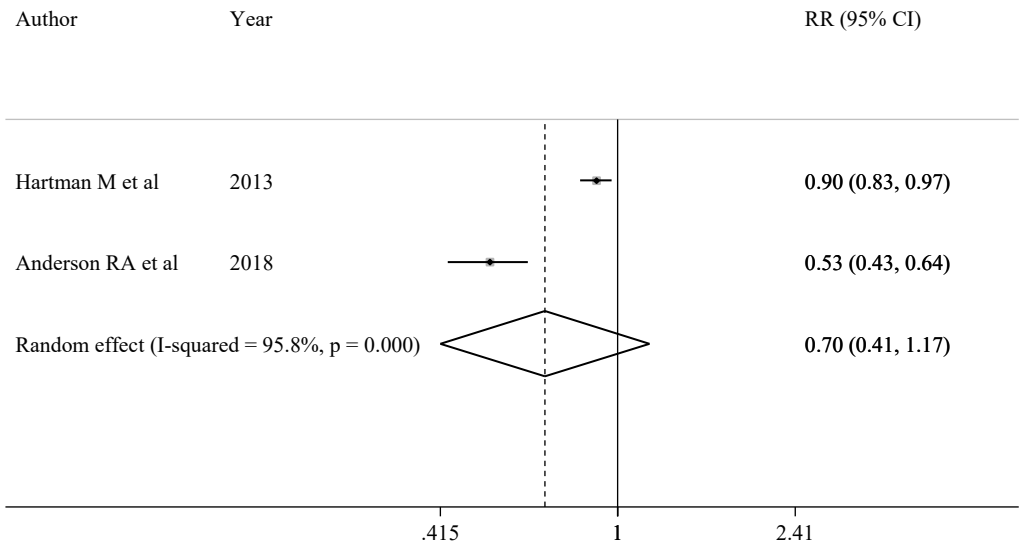
Abbreviations: RR, relative risk; CI, confidence intervals.

Table S4 - Sensitivity analysis for prevalence of pregnancy after thyroid cancer diagnosis.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	RR	95% CI	P-value		
Madanat LMS et al 2008	0.94	0.83-1.07	0.348	86.8	<0.001
Stensheim H et al 2011	0.79	0.60-1.05	0.104	97.4	<0.001
Baxter NN et al 2013	0.77	0.58-1.01	0.060	97.2	<0.001
Hartman M et al 2013	0.78	0.57-1.08	0.137	96.7	<0.001
Anderson RA et al 2018	0.83	0.61-1.12	0.225	97.2	<0.001

Abbreviations: RR, relative risk; CI, confidence intervals.

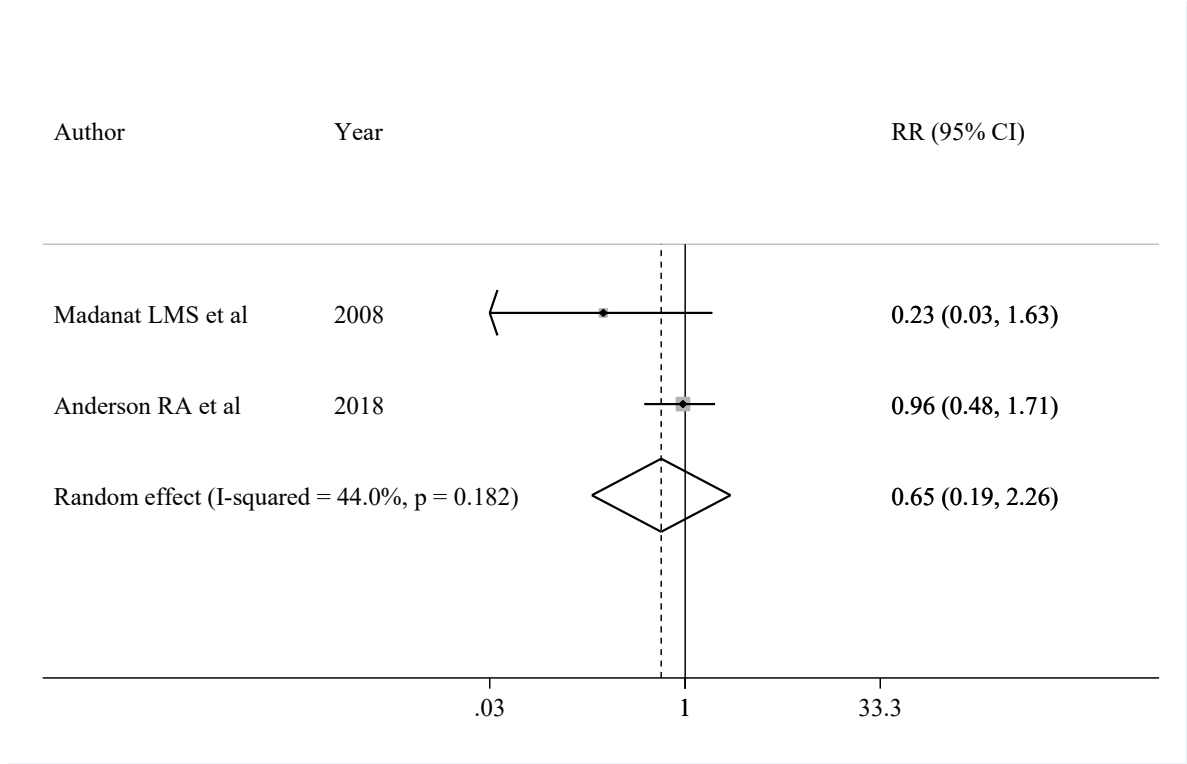
Figure S4 - Prevalence of pregnancy after colon cancer.



Random effect: p=0.171
Egger's test: not calculable

Abbreviations: RR, relative risk; CI, confidence intervals.

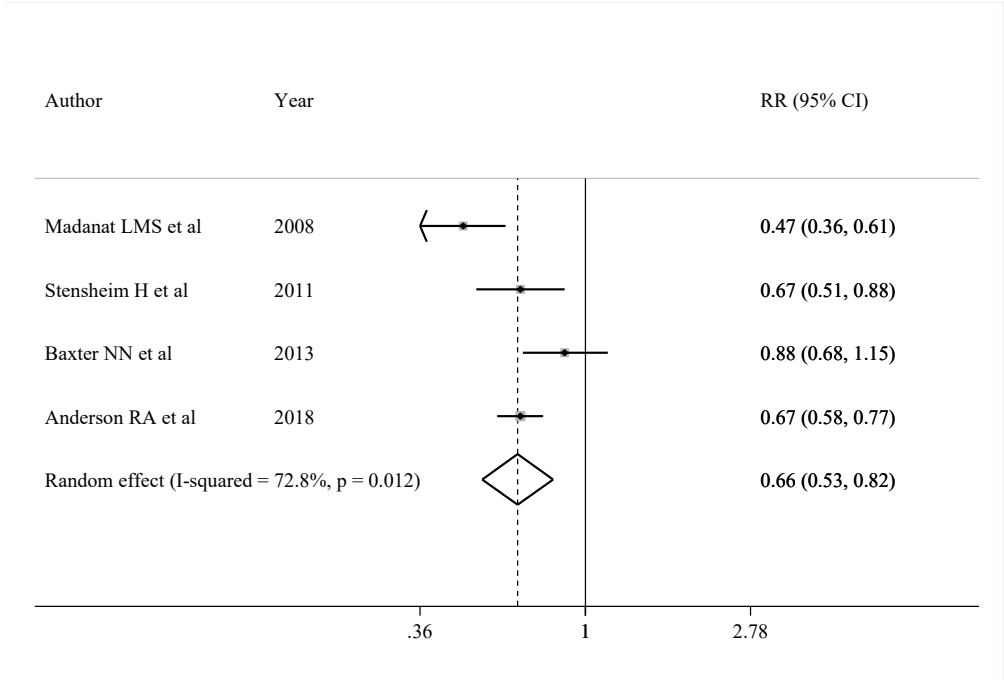
Figure S5 - Prevalence of pregnancy after liver cancer.



Random effect: p=0.500
Egger's test: not calculable

Abbreviations: RR, relative risk; CI, confidence intervals.

Figure S6 - Prevalence of pregnancy after non-Hodgkin lymphoma.



Random effect: p<0.001
Egger's test: p=0.938

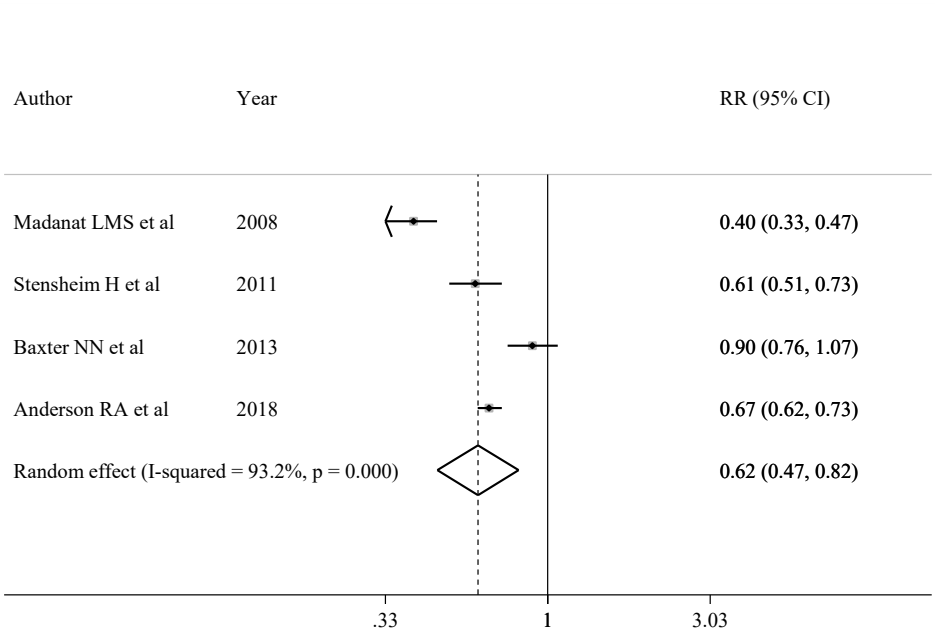
Abbreviations: RR, relative risk; CI, confidence intervals.

Table S5 - Sensitivity analysis for prevalence of pregnancy after non-Hodgkin lymphoma.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	RR	95% CI	P-value		
Madanat LMS et al 2008	0.72	0.61-0.85	<0.001	40.6	0.186
Stensheim H et al 2011	0.65	0.48-0.88	0.005	81.8	0.004
Baxter NN et al 2013	0.60	0.49-0.75	<0.001	64.7	0.059
Anderson RA et al 2018	0.65	0.45-0.93	0.020	81.8	0.004

Abbreviations: RR, relative risk; CI, confidence intervals.

Figure S7 - Prevalence of pregnancy after Hodgkin lymphoma.



Random effect: p=0.001
Egger's test: p=0.812

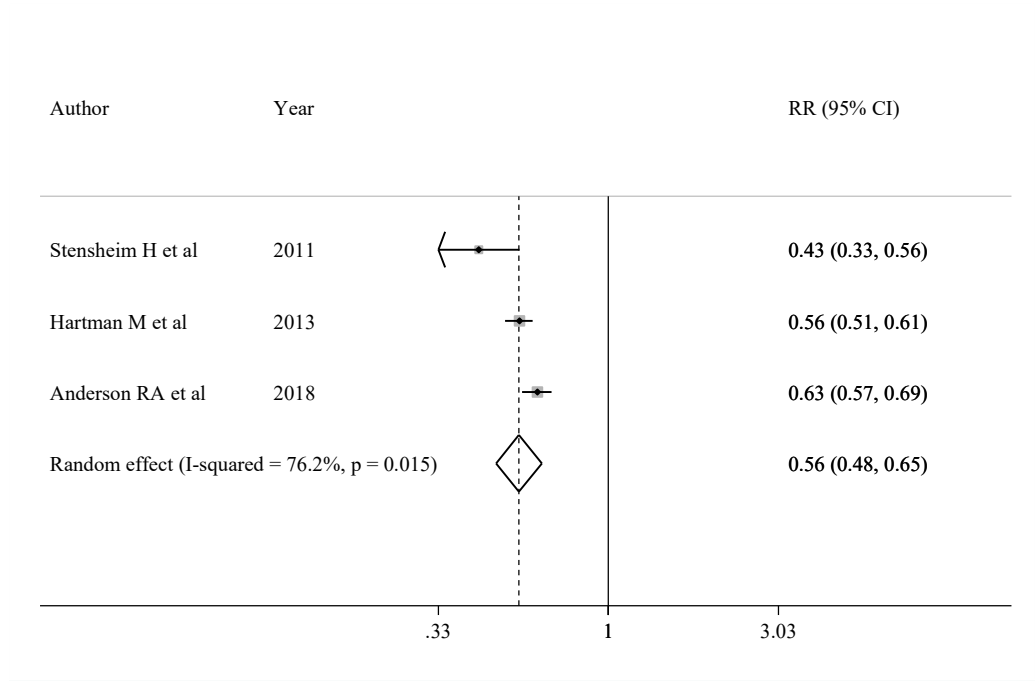
Abbreviations: RR, relative risk; CI, confidence intervals.

Table S6 - Sensitivity analysis for prevalence of pregnancy after Hodgkin lymphoma.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	RR	95% CI	P-value		
Madanat LMS et al 2008	0.71	0.59-0.87	0.001	82.7	0.003
Stensheim H et al 2011	0.62	0.43-0.91	0.014	95.4	<0.001
Baxter NN et al 2013	0.55	0.41-0.74	<0.001	92.6	<0.001
Anderson RA et al 2018	0.60	0.38-0.96	0.033	95.2	<0.001

Abbreviations: RR, relative risk; CI, confidence intervals.

Figure S8 - Prevalence of pregnancy after ovarian cancer.



Random effect: p<0.001
Egger's test: p=0.473

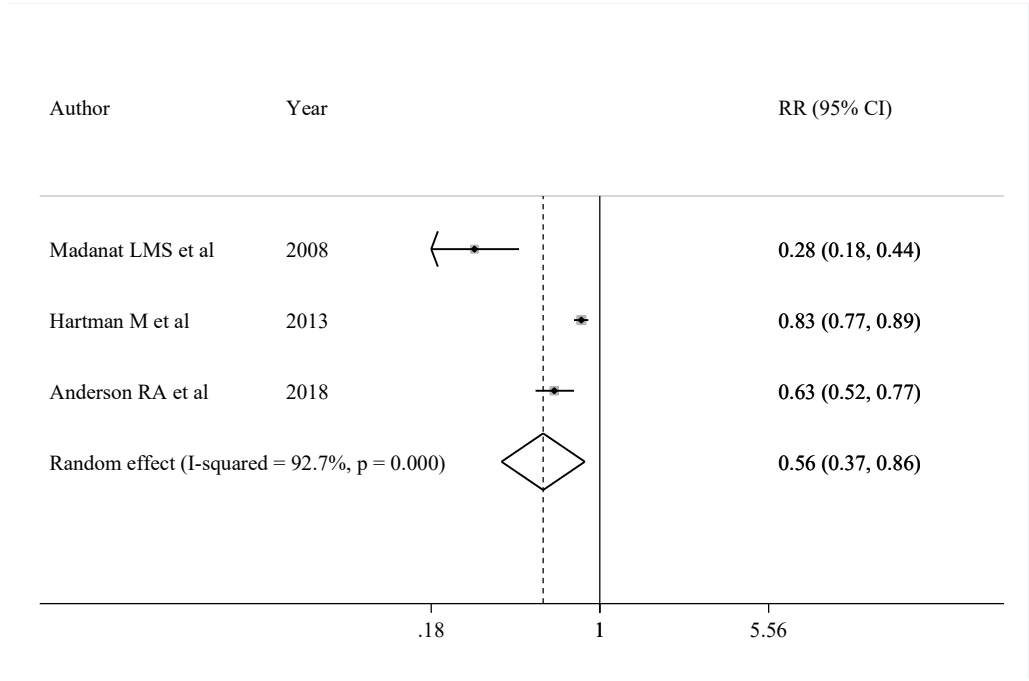
Abbreviations: RR, relative risk; CI, confidence intervals.

Table S7 - Sensitivity analysis for prevalence of pregnancy after ovarian cancer.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	RR	95% CI	P-value		
Stensheim H et al 2011	0.59	0.53-0.67	<0.001	67.8	0.078
Hartman M et al 2013	0.53	0.37-0.77	0.001	85.9	0.008
Anderson RA et al 2018	0.51	0.39-0.65	<0.001	70.9	0.064

Abbreviations: RR, relative risk; CI, confidence intervals.

Figure S9 - Prevalence of pregnancy after bone cancer.



Random effect: p=0.008
Egger's test: p=0.090

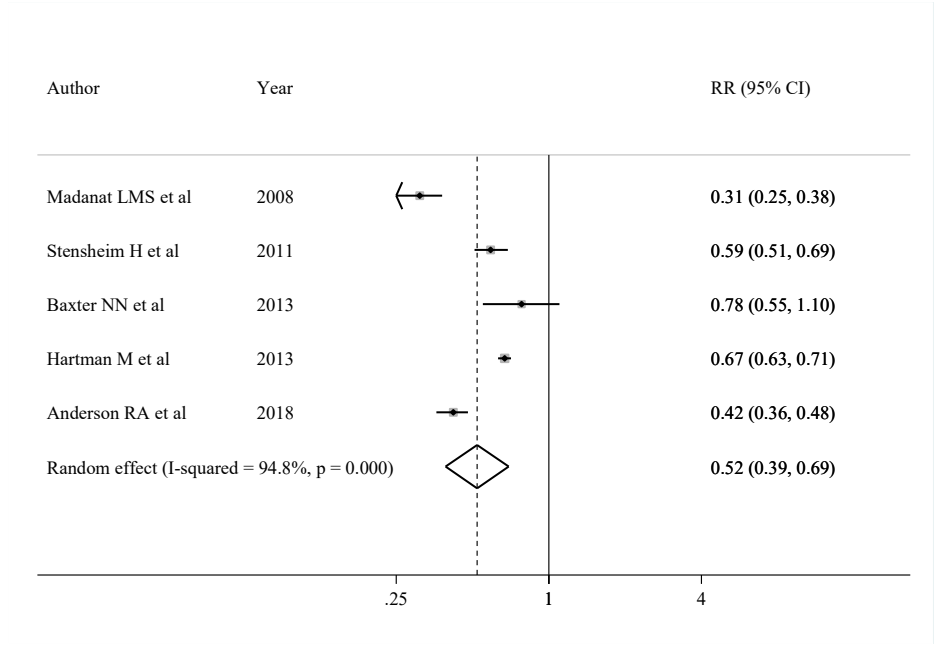
Abbreviations: RR, relative risk; CI, confidence intervals.

Table S8 - Sensitivity analysis for prevalence of pregnancy after bone cancer.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	RR	95% CI	P-value		
Madanat LMS et al 2008	0.73	0.56-0.96	0.024	85.0	0.010
Hartman M et al 2013	0.43	0.19-0.95	0.038	90.6	0.001
Anderson RA et al 2018	0.49	0.17-1.43	0.193	95.5	<0.001

Abbreviations: RR, relative risk; CI, confidence intervals.

Figure S10 - Prevalence of pregnancy after central nervous system cancer.



Random effect: p<0.001
Egger's test: p=0.315

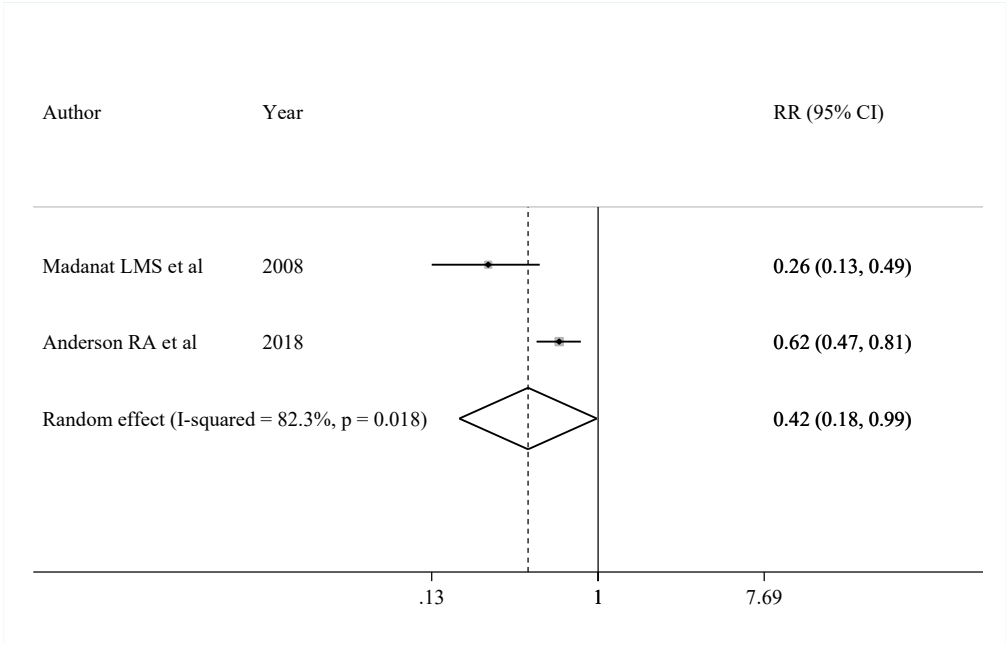
Abbreviations: RR, relative risk; CI, confidence intervals.

Table S9 - Sensitivity analysis for prevalence of pregnancy after central nervous system cancer.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	RR	95% CI	P-value		
Madanat LMS et al 2008	0.59	0.46-0.75	<0.001	91.8	<0.001
Stensheim H et al 2011	0.51	0.34-0.75	0.001	96.1	<0.001
Baxter NN et al 2013	0.48	0.35-0.66	<0.001	96.0	<0.001
Hartman M et al 2013	0.49	0.35-0.67	<0.001	91.3	<0.001
Anderson RA et al 2018	0.55	0.40-0.76	<0.001	94.0	<0.001

Abbreviations: RR, relative risk; CI, confidence intervals.

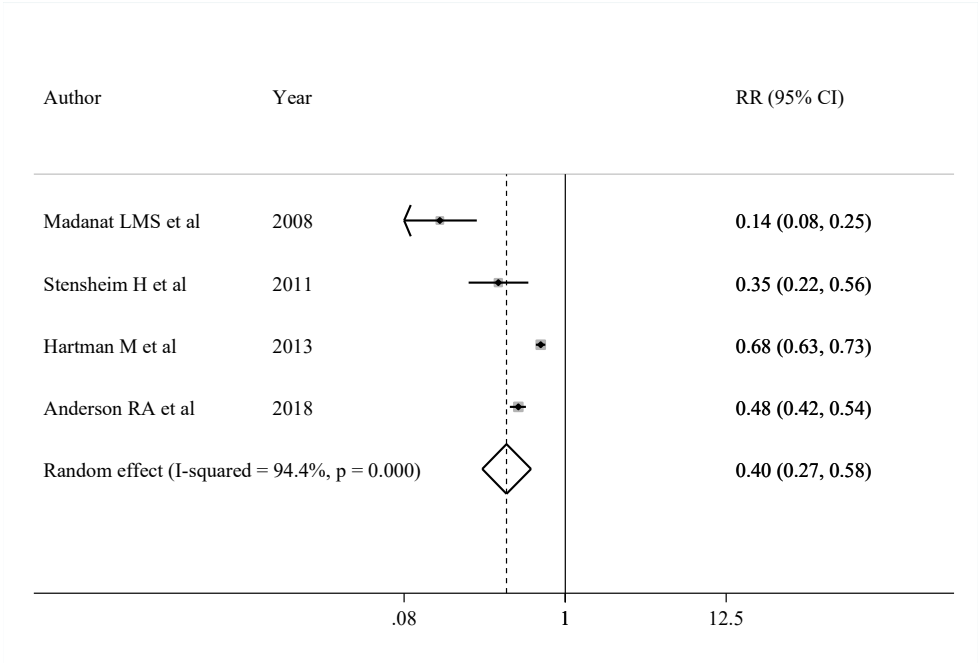
Figure S11 - Prevalence of pregnancy after kidney cancer.



Random effect: p=0.047
Egger's test: not calculable

Abbreviations: RR, relative risk; CI, confidence intervals.

Figure S12 - Prevalence of pregnancy after leukemia.



Random effect: p<0.001
Egger's test: p=0.138

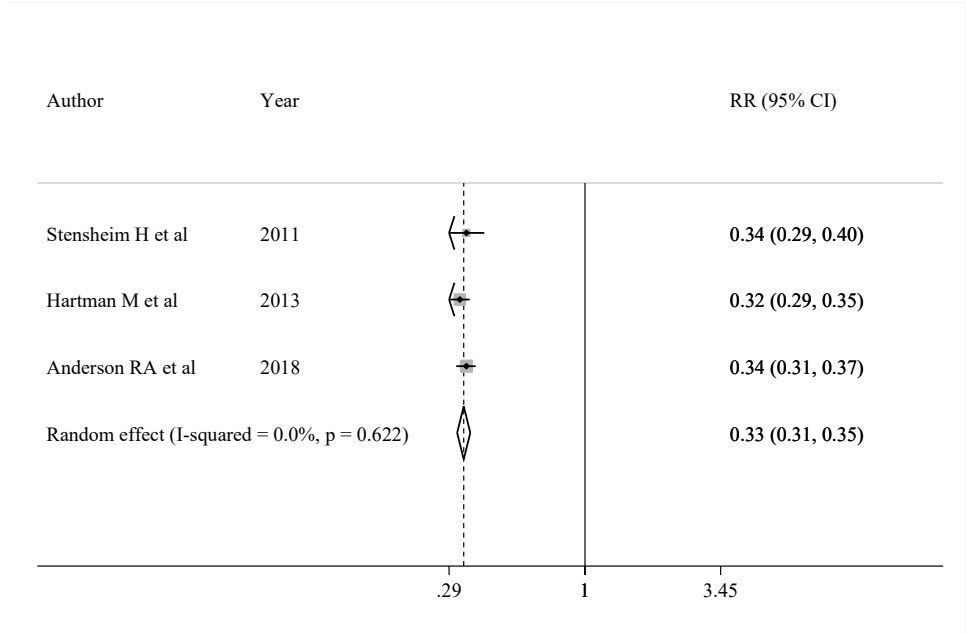
Abbreviations: RR, relative risk; CI, confidence intervals.

Table S10 - Sensitivity analysis for prevalence of pregnancy after leukemia.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	RR	95% CI	P-value		
Madanat LMS et al 2008	0.51	0.37-0.71	<0.001	92.8	<0.001
Stensheim H et al 2011	0.41	0.27-0.63	<0.001	95.8	<0.001
Hartman M et al 2013	0.30	0.15-0.58	<0.001	89.0	<0.001
Anderson RA et al 2018	0.33	0.13-0.82	0.017	94.5	<0.001

Abbreviations: RR, relative risk; CI, confidence intervals.

Figure S13 - Prevalence of pregnancy after cervical cancer.



Random effect: p<0.001
Egger's test: p=0.855

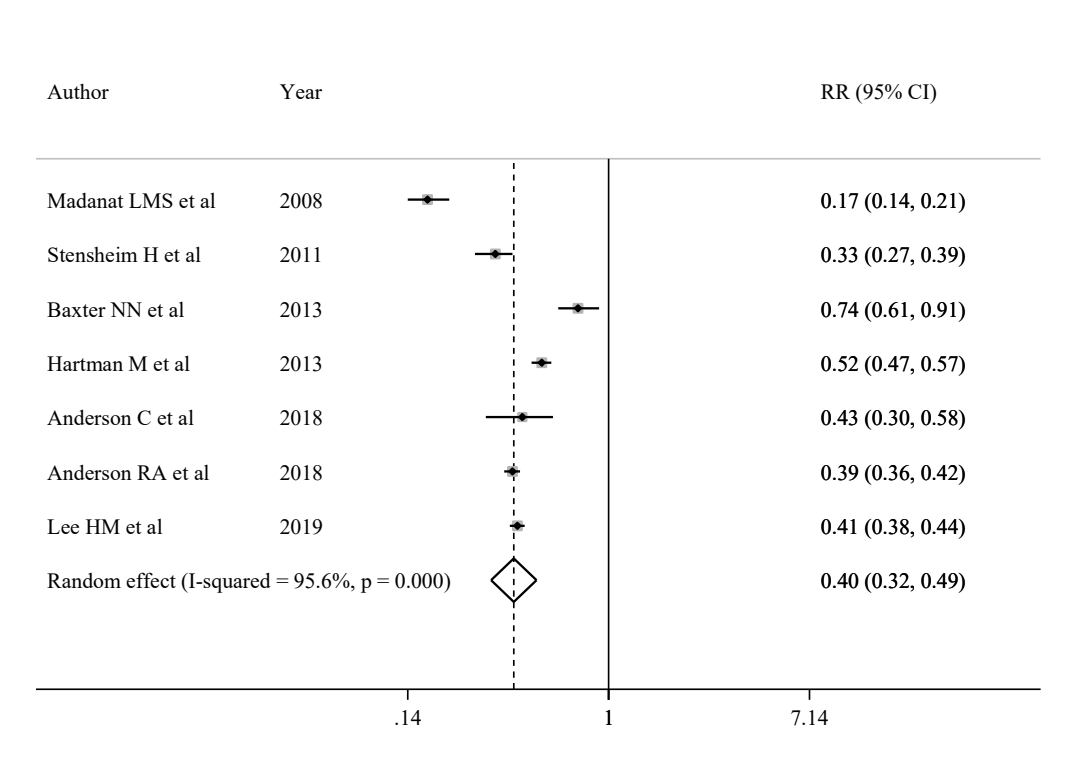
Abbreviations: RR, relative risk; CI, confidence intervals.

Table S11 - Sensitivity analysis for prevalence of pregnancy after cervical cancer.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	RR	95% CI	P-value		
Stensheim H et al 2011	0.33	0.31-0.35	<0.001	0.0	0.357
Hartman M et al 2013	0.34	0.31-0.37	<0.001	0.0	1.000
Anderson RA et al 2018	0.32	0.30-0.35	<0.001	0.0	0.524

Abbreviations: RR, relative risk; CI, confidence intervals.

Figure S14 - Prevalence of pregnancy after breast cancer.



Random effect: p<0.001
Egger's test: p=0.735

Abbreviations: RR, relative risk; CI, confidence intervals.

Table S12 - Sensitivity analysis for prevalence of pregnancy after breast cancer.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	RR	95% CI	P-value		
Madanat LMS et al 2008	0.45	0.38-0.53	<0.001	91.5	<0.001
Stensheim H et al 2011	0.41	0.32-0.52	<0.001	96.2	<0.001
Baxter NN et al 2013	0.36	0.29-0.44	<0.001	95.1	<0.001
Hartman M et al 2013	0.38	0.29-0.48	<0.001	95.4	<0.001
Anderson C et al 2018	0.39	0.31-0.50	<0.001	96.3	<0.001
Anderson RA et al 2018	0.40	0.29-0.53	<0.001	96.2	<0.001
Lee HM et al 2019	0.39	0.29-0.53	<0.001	96.3	<0.001

Abbreviations: RR, relative risk; CI, confidence intervals.

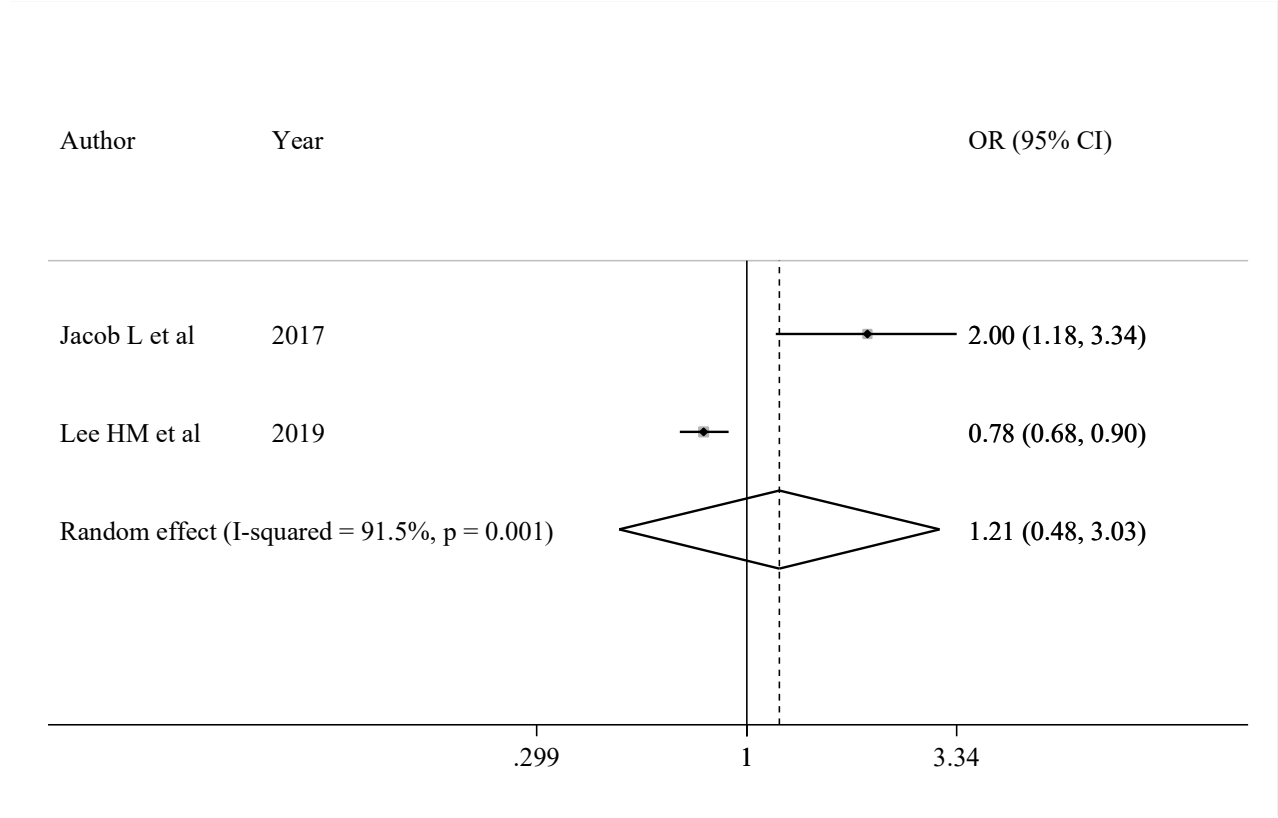
Table S13 - Studies comparing pregnancy outcomes in breast cancer patients and in healthy women from the general population. [6–14]

For the two studies reporting results also for patients with pregnancy-associated breast cancer, only data in patients with pregnancy after breast cancer were considered for the purpose of this analysis.[8,14] *One study was included despite reporting only relative risks considering its large sample size that makes the values superimposable to those of odds ratios.*[11] *Among the 9 included records, 5 were case-control studies,*[6,7,10,12,14] *and 4 were cohort studies.*[8,9,11,13] *Except for 2 studies,*[8,13] *all the others corrected for maternal age; other controlling factors were considered in the different studies.*

Reference	Country	Study design	Pregnant breast cancer patients (n)	Pregnant women without cancer history (n)	Matching criteria/controlling factors	Outcomes
Langagergaard V et al* 2006	Denmark	Cohort study	216	10,453	Month and year of birth, county of mother's residence	Preterm birth, low birth weight at term, stillbirth, and birth weight.
Dalberg K et al 2006	Sweden	Cohort study	331	2,870,518	Age of the mother, parity, year of delivery	Infant health and mortality, delivery complications, preterm birth, rates of instrumental delivery and cesarean section
Stensheim H et al 2013	Norway	Population-based CC	101	505	Age and sex	Perinatal death, preterm birth, low birth weight, and major congenital anomalies
Jacob L et al 2017	Germany	CC	165	165	Age, center, diagnosis of obesity and documented referral to a fertility center	Delivery of a live-born child, early and late pregnancy loss, pre-term birth, pre-eclampsia
Hartnett KP et al 2017	USA	Retrospective cohort study	754	3,770	Mother's age at delivery, race and ethnicity, parity and maternal education	Preterm birth, low birth weight, low birth weight at term, SGA, cesarean section, and admission to NICU
Black KZ et al** 2017	USA	Cohort study	512	1,911,757	N.R.	Preterm birth, low birth weight, and SGA
Anderson C et al** 2018	USA	CC	293	N.R.	Year of delivery and maternal age	Preterm birth, low birth weight, SGA and cesarean delivery
Lee HM et al 2019	South Korea	Prospective CC	855	10,164	Age	Natural vaginal delivery, induced delivery, breech delivery, vacuum extraction, cesarean section, full-term delivery, premature delivery, miscarriage, preeclampsia, preterm labor, premature rupture of membranes, obstetric hemorrhage, plural birth, hydramnios/oligoamnios.
Ma KK et al* 2020	USA	CC	13	360	Age at pregnancy, parity, body mass index, race	Pregnancy completion, induced abortion, spontaneous abortion, intrauterine fetal death

Abbreviations: CC, case-control; SGA, small for gestational age; NICU, neonatal intensive care unit; N.R., not reported; N.A., not applicable; CT, chemotherapy.
*= included only data from pregnancy subsequent to breast cancer
**=partial population overlapping

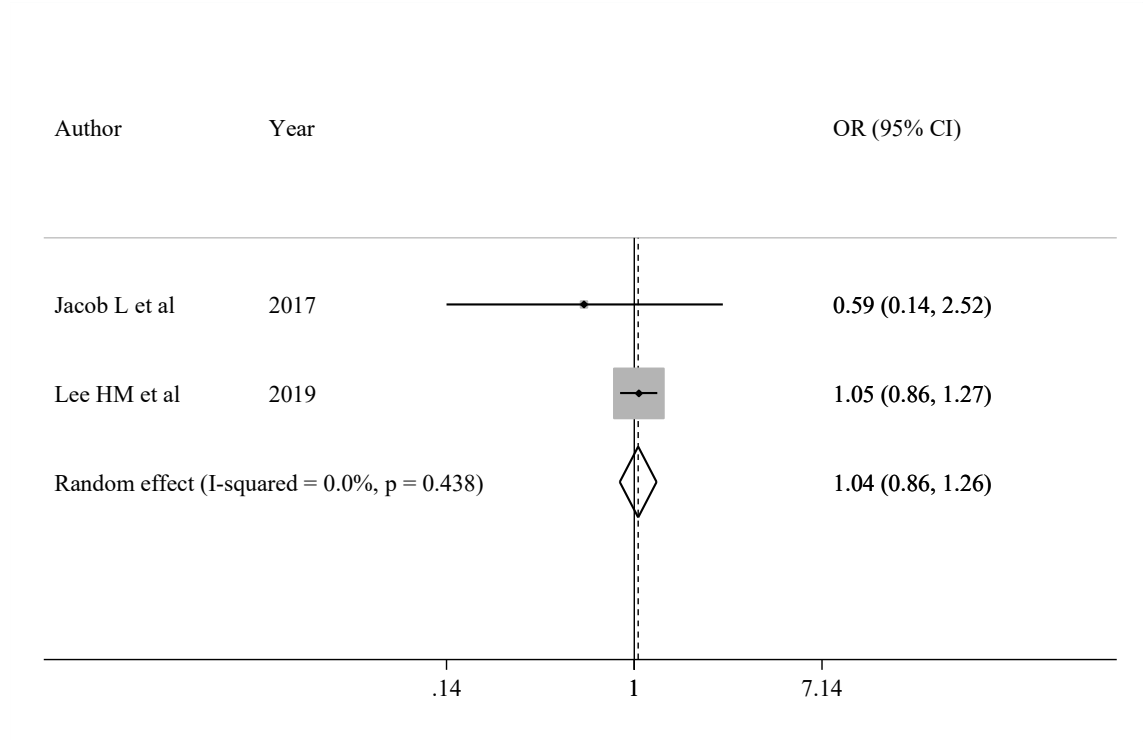
Figure S15 - Pregnancy outcomes - completed pregnancy comparing between breast cancer patients and healthy women from the general population.



Random effect: p=0.689
Egger's test: not calculable

Abbreviations: OR, odds ratio; CI, confidence intervals

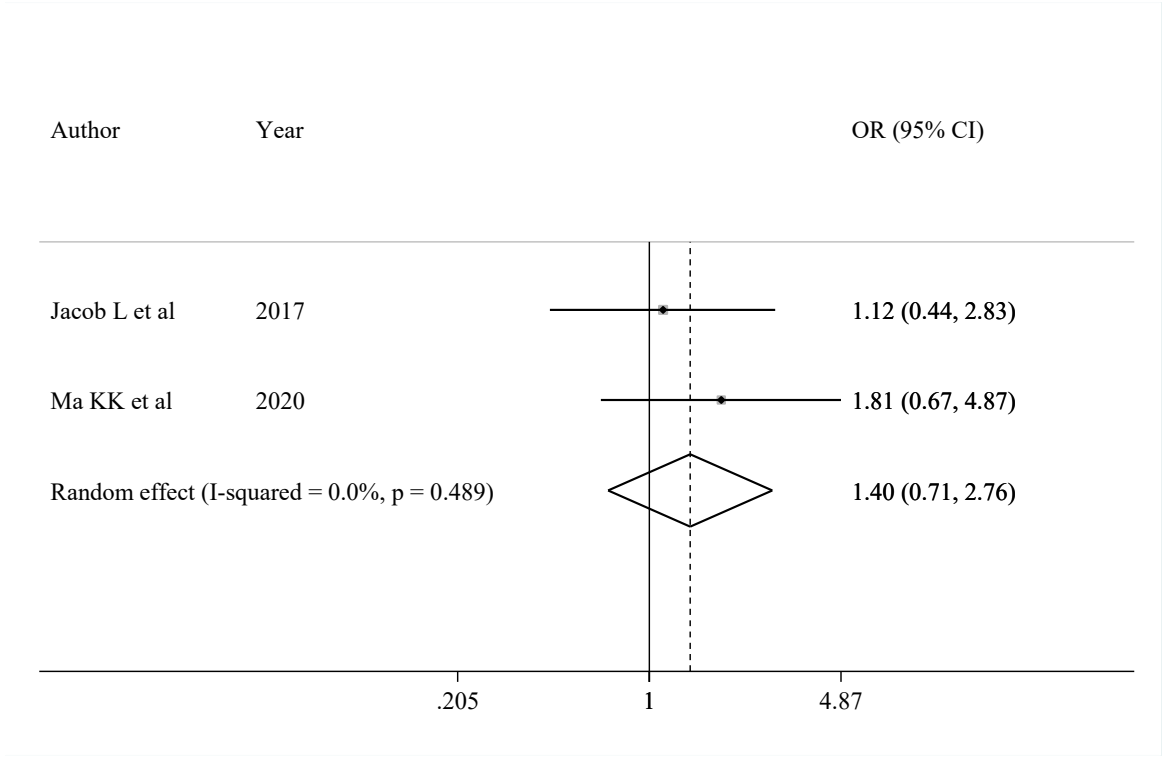
Figure S16 - Pregnancy outcomes - spontaneous abortion comparing between breast cancer patients and healthy women from the general population.



Random effect: p=0.696
Egger's test: not calculable

Abbreviations: OR, odds ratio; CI, confidence intervals

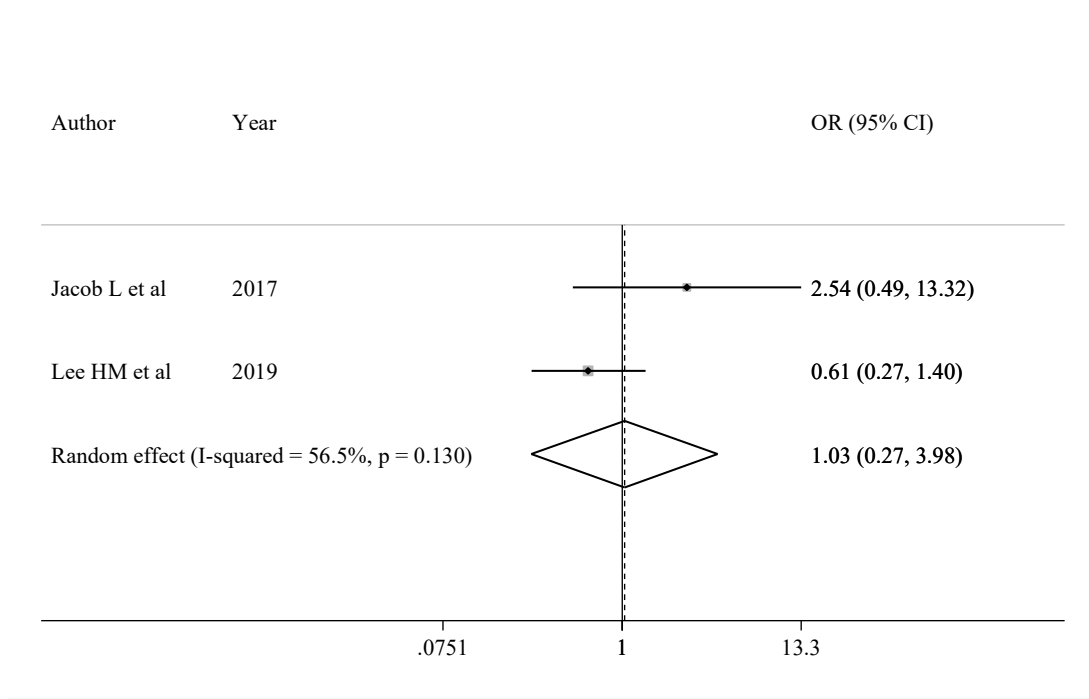
Figure S17 - Pregnancy outcomes - induced abortion comparing between breast cancer patients and healthy women from the general population.



Random effect: p=0.329
Egger's test: not calculable

Abbreviations: OR, odds ratio; CI, confidence intervals

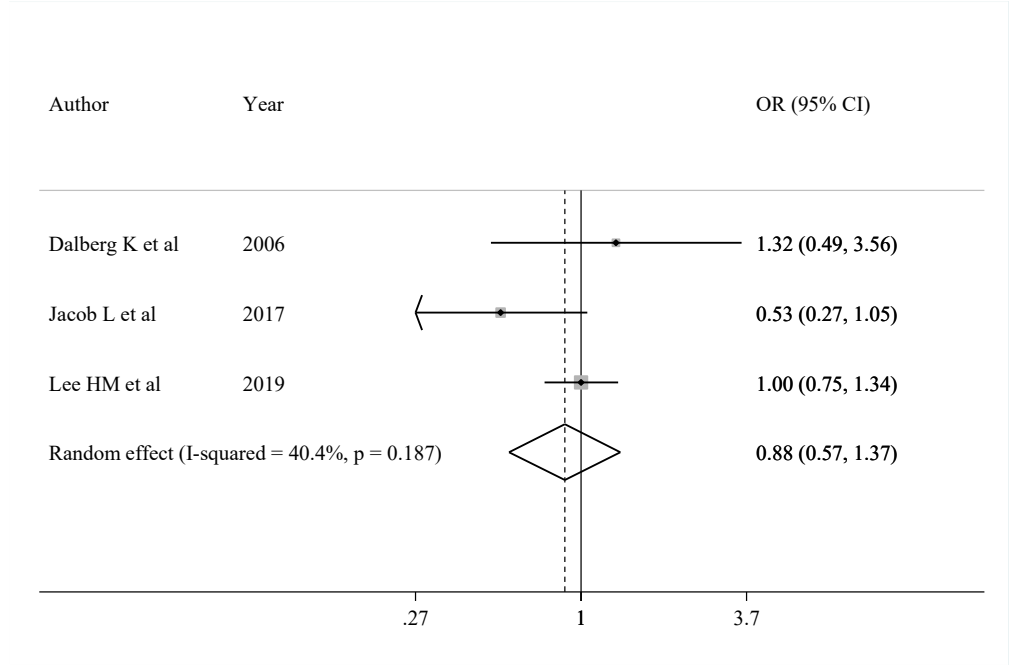
Figure S18 - Pregnancy outcomes - developing pre-eclampsia comparing between breast cancer patients and healthy women from the general population.



Random effect: p=0.963
Egger's test: not calculable

Abbreviations: OR, odds ratio; CI, confidence intervals

Figure S19 - Pregnancy outcomes - postpartum bleeding comparing between breast cancer patients and healthy women from the general population.



Random effect: p=0.567
Egger's test: p=0.811

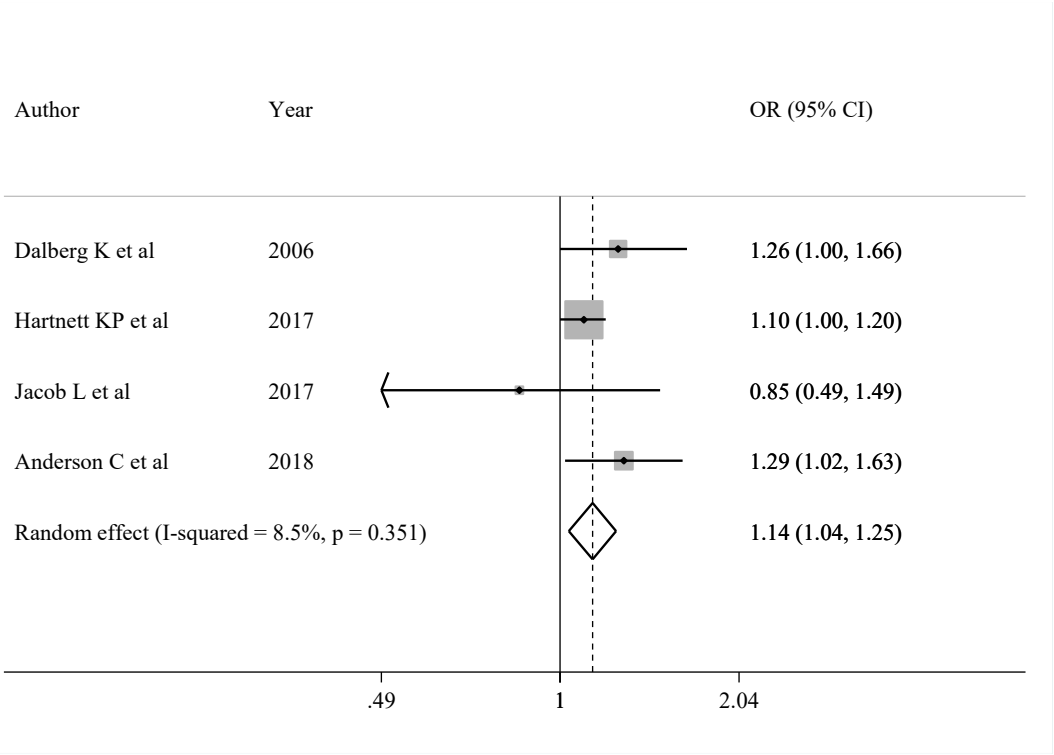
Abbreviations: OR, odds ratio; CI, confidence intervals

Table S14 - Sensitivity analysis of pregnancy outcomes - postpartum bleeding comparing between breast cancer patients and healthy women from the general population.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	OR	95% CI	P-value		
Dalberg K et al 2006	0.79	0.43-1.44	0.435	64.8	0.092
Jacob L et al 2017	1.02	0.77-1.35	0.878	0.0	0.598
Lee HM et al 2019	0.78	0.32-1.88	0.574	54.8	0.137

Abbreviations: OR, odds ratio; CI, confidence intervals

Figure S20 - Pregnancy outcomes - undergoing elective or emergency cesarian section comparing between breast cancer patients and healthy women from the general population.



Random effect: p=0.007
Egger's test: p=0.787

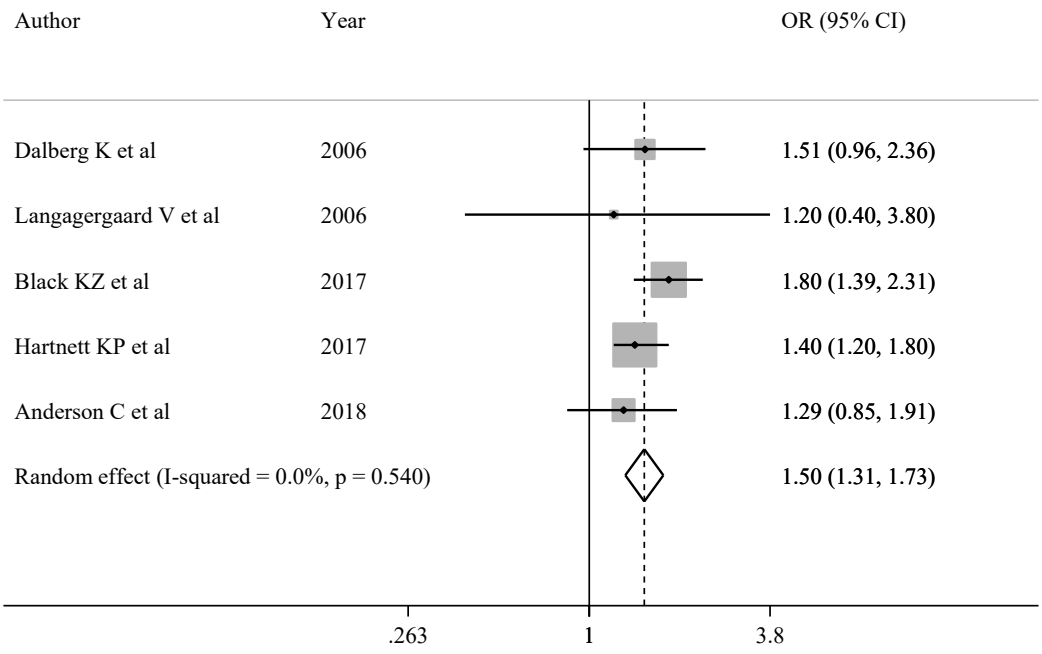
Abbreviations: OR, odds ratio; CI, confidence intervals

Table S15 - Sensitivity analysis of pregnancy outcomes - undergoing elective or emergency cesarian section comparing between breast cancer patients and healthy women from the general population.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	OR	95% CI	P-value		
Dalberg K et al 2006	1.13	0.99-1.28	0.060	0.0	0.586
Hartnett KP et al 2017	1.23	1.04-1.45	0.013	0.0	0.438
Jacob L et al 2017	1.15	1.04-1.26	0.005	0.0	0.595
Anderson C et al 2018	1.11	1.02-1.21	0.016	0.0	0.390

Abbreviations: OR, odds ratio; CI, confidence intervals

Figure S21 - Pregnancy outcomes - low birth weight comparing between breast cancer patients and healthy women from the general population.



Random effect: p<0.001
Egger's test: p=0.480

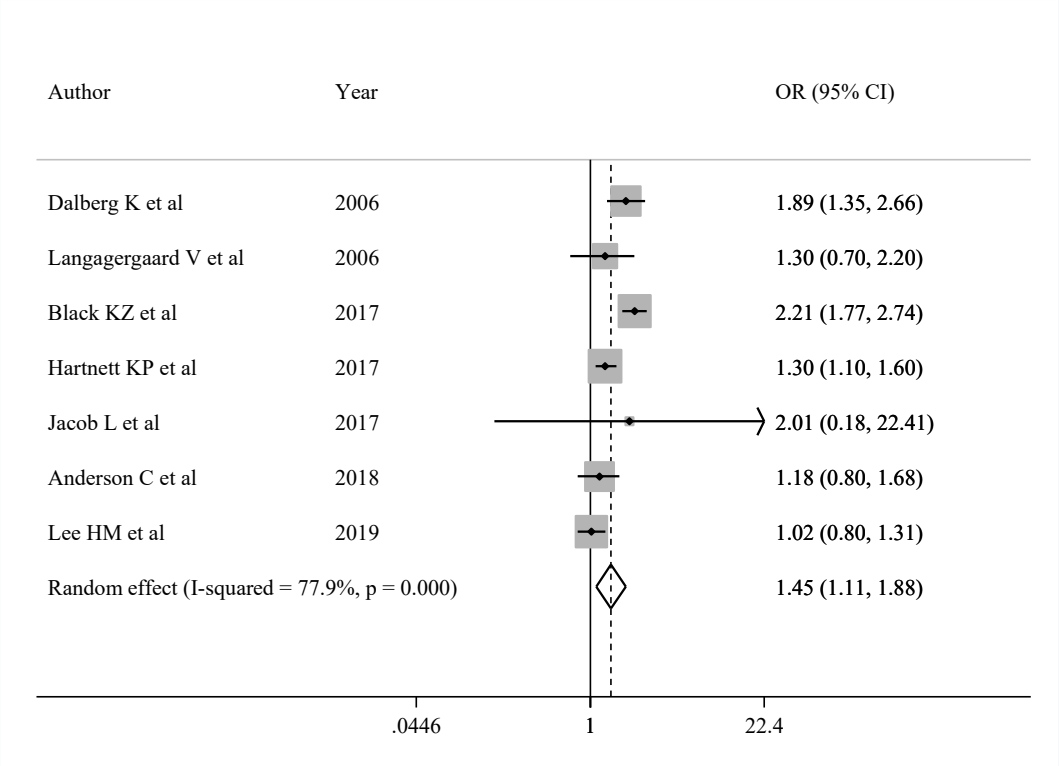
Abbreviations: OR, odds ratio; CI, confidence intervals

Table S16 - Sensitivity analysis of pregnancy outcomes - low birth weight comparing between breast cancer patients and healthy women from the general population.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	OR	95% CI	P-value		
Dalberg K et al 2006	1.50	1.29-1.75	<0.001	0.0	0.563
Langagergaard V et al 2006	1.51	1.31-1.73	<0.001	0.0	0.557
Black KZ et al 2017	1.39	1.18-1.64	<0.001	0.0	0.686
Hartnett KP et al 2017	1.60	1.32-1.94	<0.001	0.0	0.542
Anderson C et al 2018	1.53	1.32-1.78	<0.001	0.0	0.948

Abbreviations: OR, odds ratio; CI, confidence intervals

Figure S22 - Pregnancy outcomes - pre-term birth comparing between breast cancer patients and healthy women from the general population.



Random effect: p=0.006
Egger's test: p=0.897

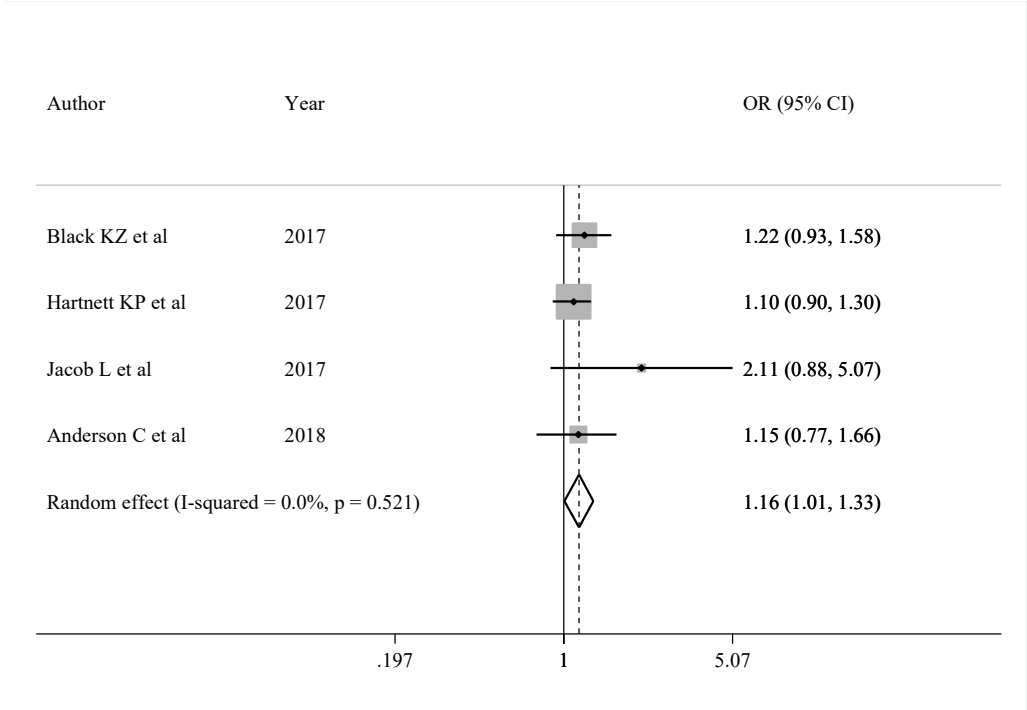
Abbreviations: OR, odds ratio; CI, confidence intervals

Table S17 - Sensitivity analysis of pregnancy outcomes - pre-term birth comparing between breast cancer patients and healthy women from the general population.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	OR	95% CI	P-value		
Dalberg K et al 2006	1.37	1.02-1.85	0.038	61.9	0.022
Langagergaard V et al 2006	1.46	1.09-1.96	0.010	69.6	0.006
Black KZ et al 2017	1.29	1.07-1.56	0.008	45.6	0.102
Hartnett KP et al 2017	1.48	1.05-2.09	0.025	68.2	0.008
Jacob L et al 2017	1.44	1.10-1.89	0.008	69.5	0.006
Anderson C et al 2018	1.50	1.11-2.03	0.008	65.4	0.013
Lee HM et al 2019	1.57	1.20-2.05	0.001	45.1	0.105

Abbreviations: OR, odds ratio; CI, confidence intervals

Figure S23 - Pregnancy outcomes - small for gestational age comparing between breast cancer patients and healthy women from the general population.



Random effect: p=0.039
Egger's test: p=0.104

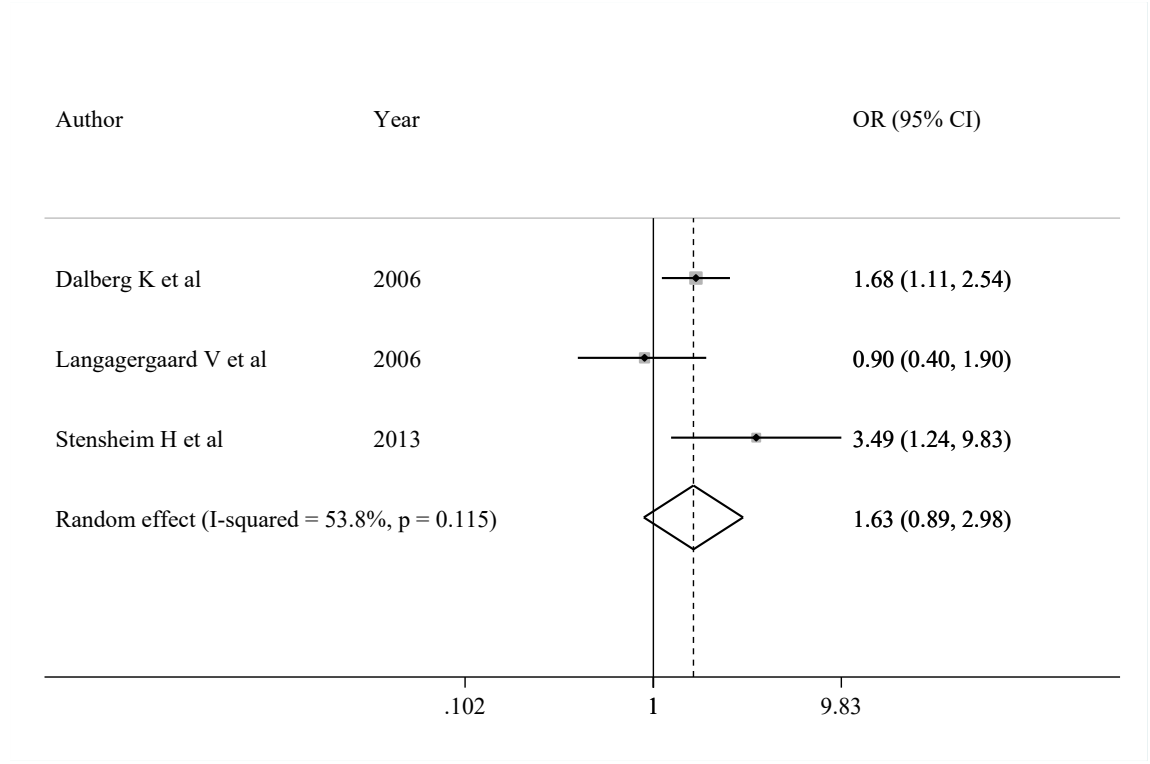
Abbreviations: OR, odds ratio; CI, confidence intervals

Table S18 - Sensitivity analysis of pregnancy outcomes - small for gestational age comparing between breast cancer patients and healthy women from the general population.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	OR	95% CI	P-value		
Black KZ et al 2017	1.14	0.96-1.35	0.138	2.1	0.360
Hartnett KP et al 2017	1.24	1.01-1.53	0.049	0.0	0.454
Jacob L et al 2017	1.14	0.99-1.31	0.069	0.0	0.819
Anderson C et al 2018	1.17	0.99-1.38	0.072	11.2	0.324

Abbreviations: OR, odds ratio; CI, confidence intervals

Figure S24 - Pregnancy outcomes - congenital abnormalities comparing between breast cancer patients and healthy women from the general population.



Random effect: p=0.112
Egger's test: p=0.896

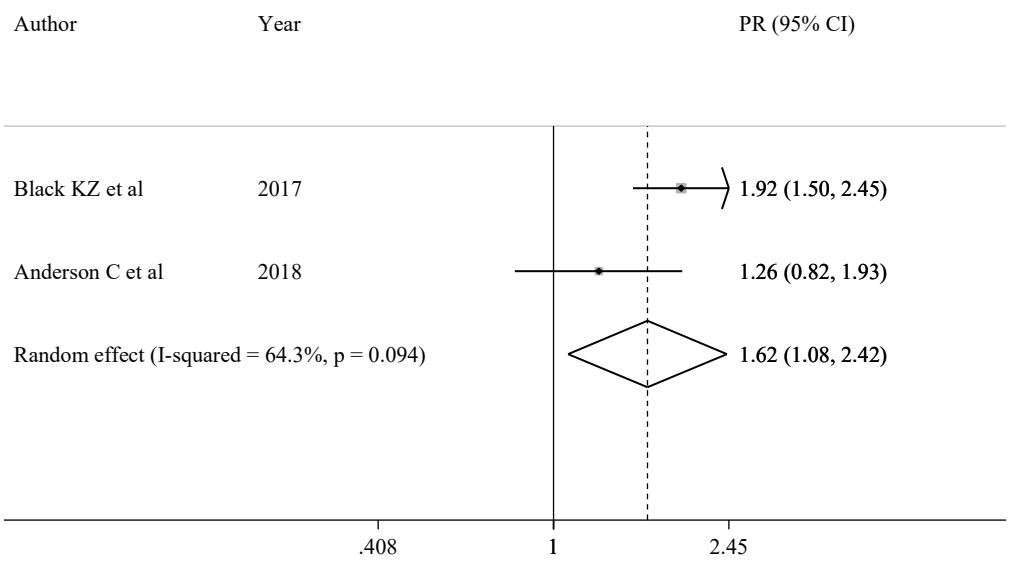
Abbreviations: OR, odds ratio; CI, confidence intervals

Table S19 - Sensitivity analysis of pregnancy outcomes - congenital abnormalities comparing between breast cancer patients and healthy women from the general population.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	OR	95% CI	P-value		
Dalberg K et al 2006	1.69	0.45-6.38	0.435	76.2	0.040
Langagergaard V et al 2006	2.06	1.08-3.93	0.028	39.5	0.199
Stensheim H et al 2013	1.35	0.75-2.42	0.319	48.0	0.166

Abbreviations: OR, odds ratio; CI, confidence intervals

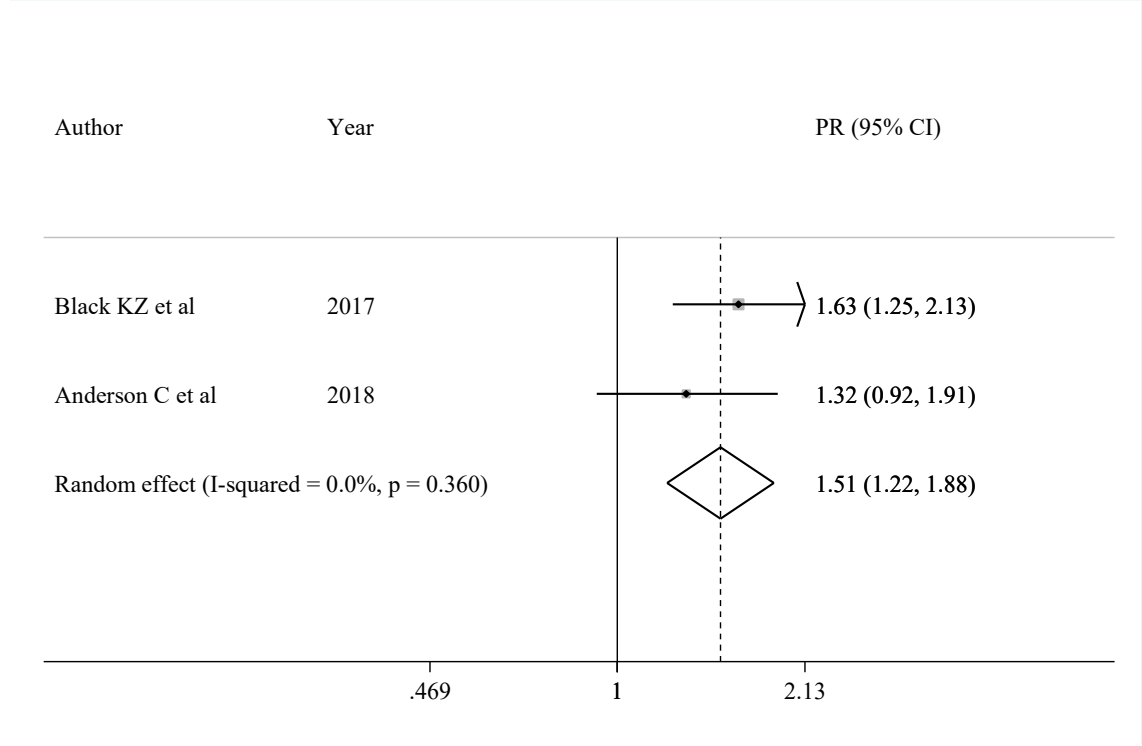
Figure S25 - Pregnancy outcome according to therapy - low birth weight comparing between breast cancer patients who received chemotherapy and healthy women from the general population.



Random effect: p=0.021
Egger's test: not calculable

Abbreviations: PR, prevalence ratio; CI, confidence intervals

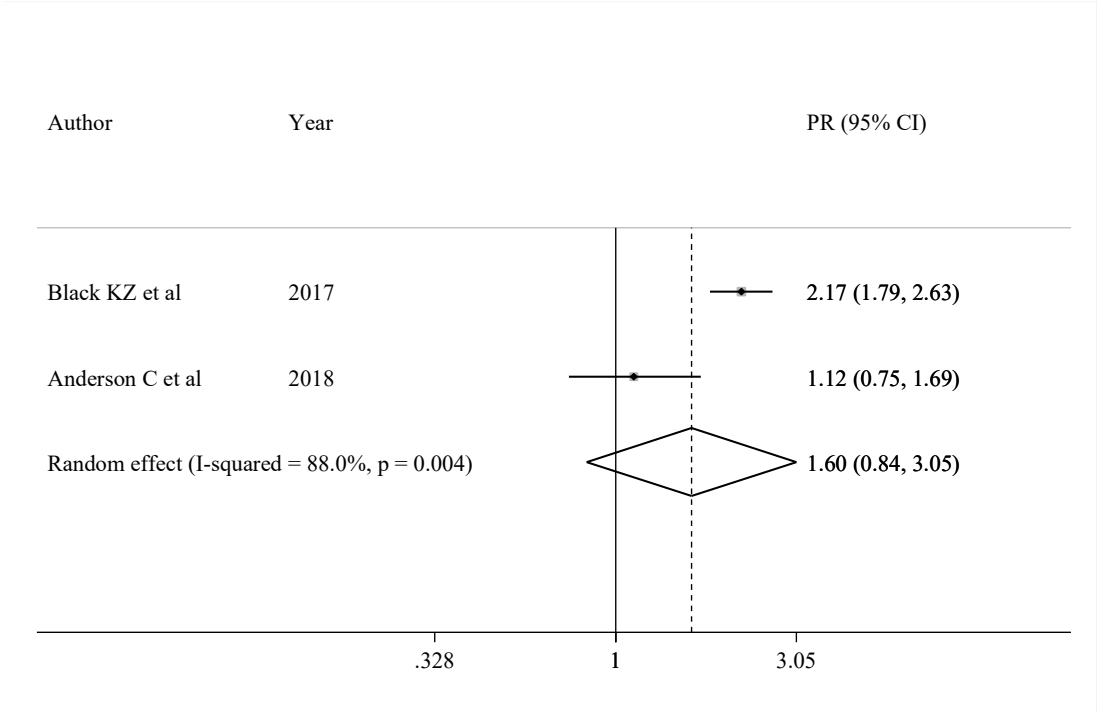
Figure S26 - Pregnancy outcome according to therapy - small for gestational age comparing between breast cancer patients who received chemotherapy and healthy women from the general population.



Random effect: $p<0.001$
Egger's test: not calculable

Abbreviations: PR, prevalence ratio; CI, confidence intervals

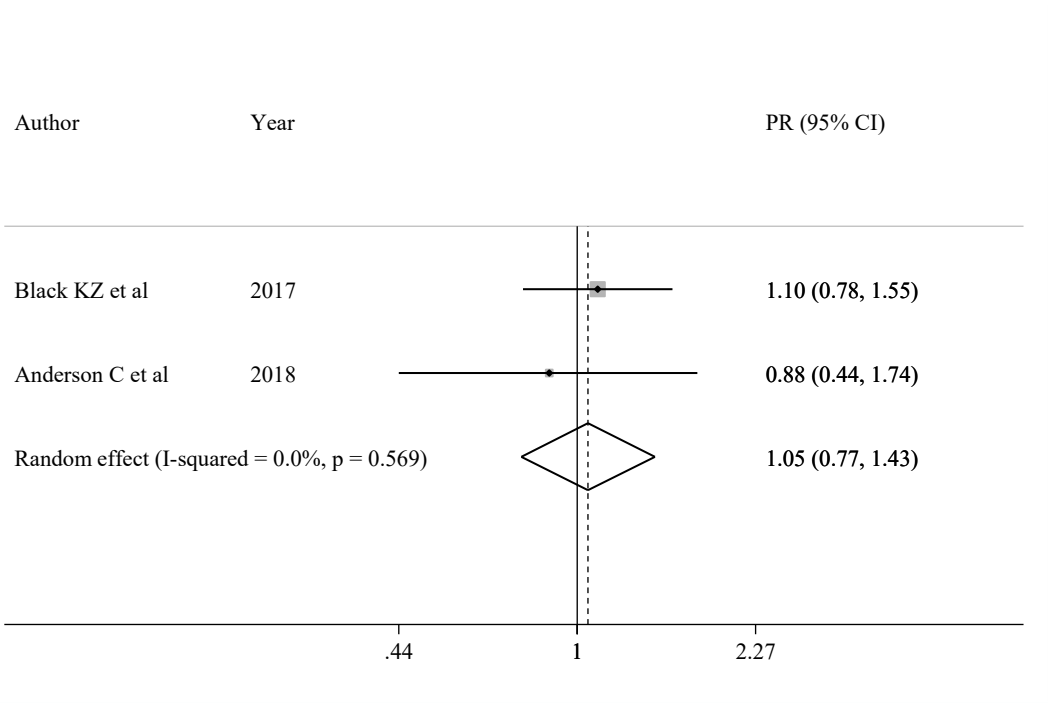
Figure S27 - Pregnancy outcome according to therapy – preterm birth comparing between breast cancer patients who received chemotherapy and healthy women from the general population.



Random effect: p=0.155
Egger's test: not calculable

Abbreviations: PR, prevalence ratio; CI, confidence intervals

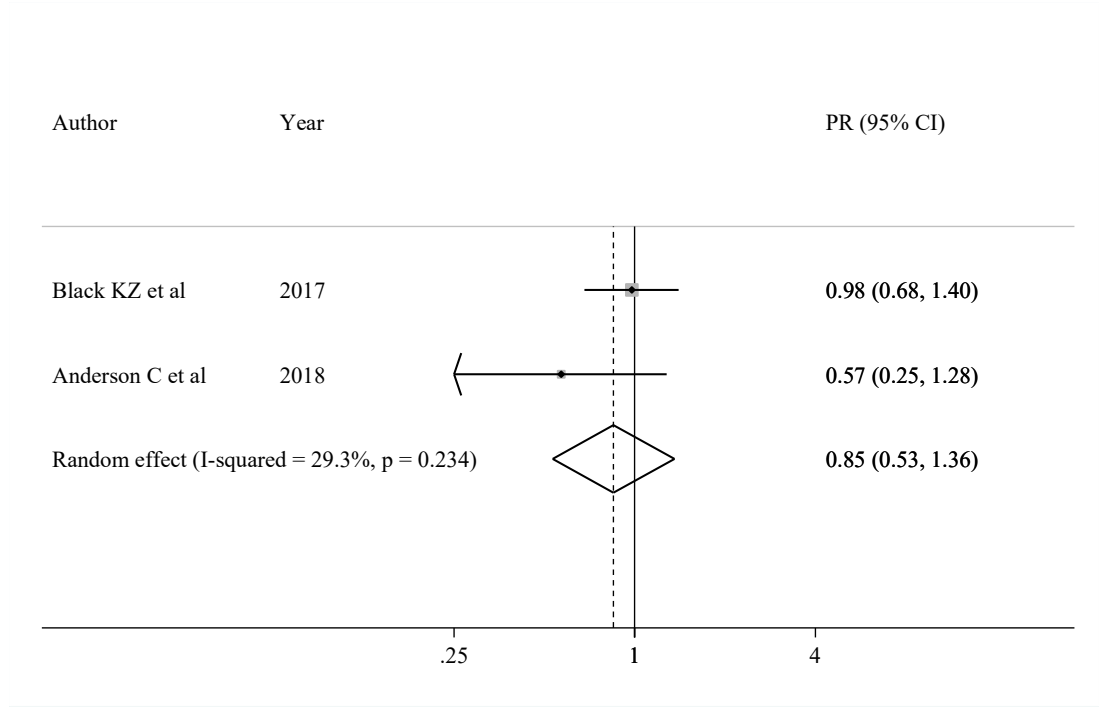
Figure S28 - Pregnancy outcome according to therapy - low birth weight comparing between breast cancer patients who did not receive chemotherapy and healthy women from the general population.



Random effect: p=0.746
Egger's test: not calculable

Abbreviations: PR, prevalence ratio; CI, confidence intervals

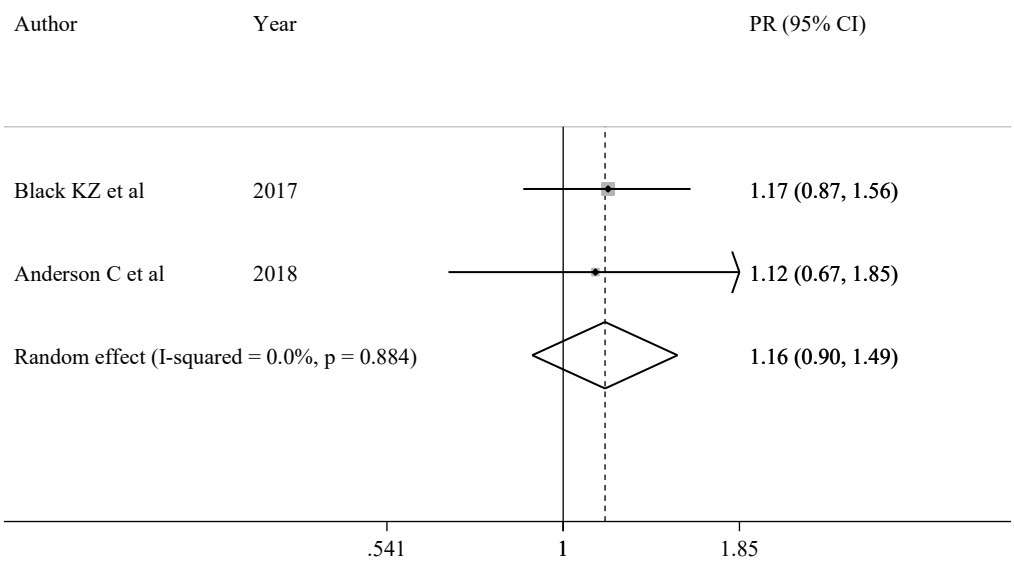
Figure S29 - Pregnancy outcome according to therapy - small for gestational age comparing between breast cancer patients who did not receive chemotherapy and healthy women from the general population.



Random effect: p=0.496
Egger's test: not calculable

Abbreviations: PR, prevalence ratio; CI, confidence intervals

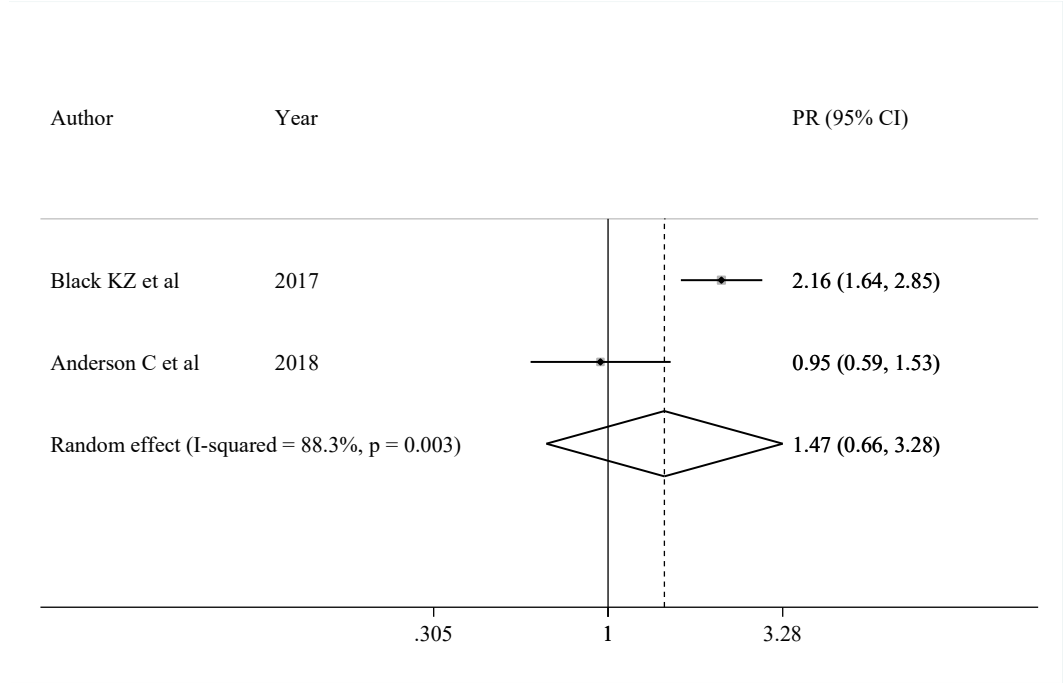
Figure S30 - Pregnancy outcome according to therapy - preterm birth comparing between breast cancer patients who did not receive chemotherapy and healthy women from the general population.



Random effect: p=0.258
Egger's test: not calculable

Abbreviations: PR, prevalence ratio; CI, confidence intervals

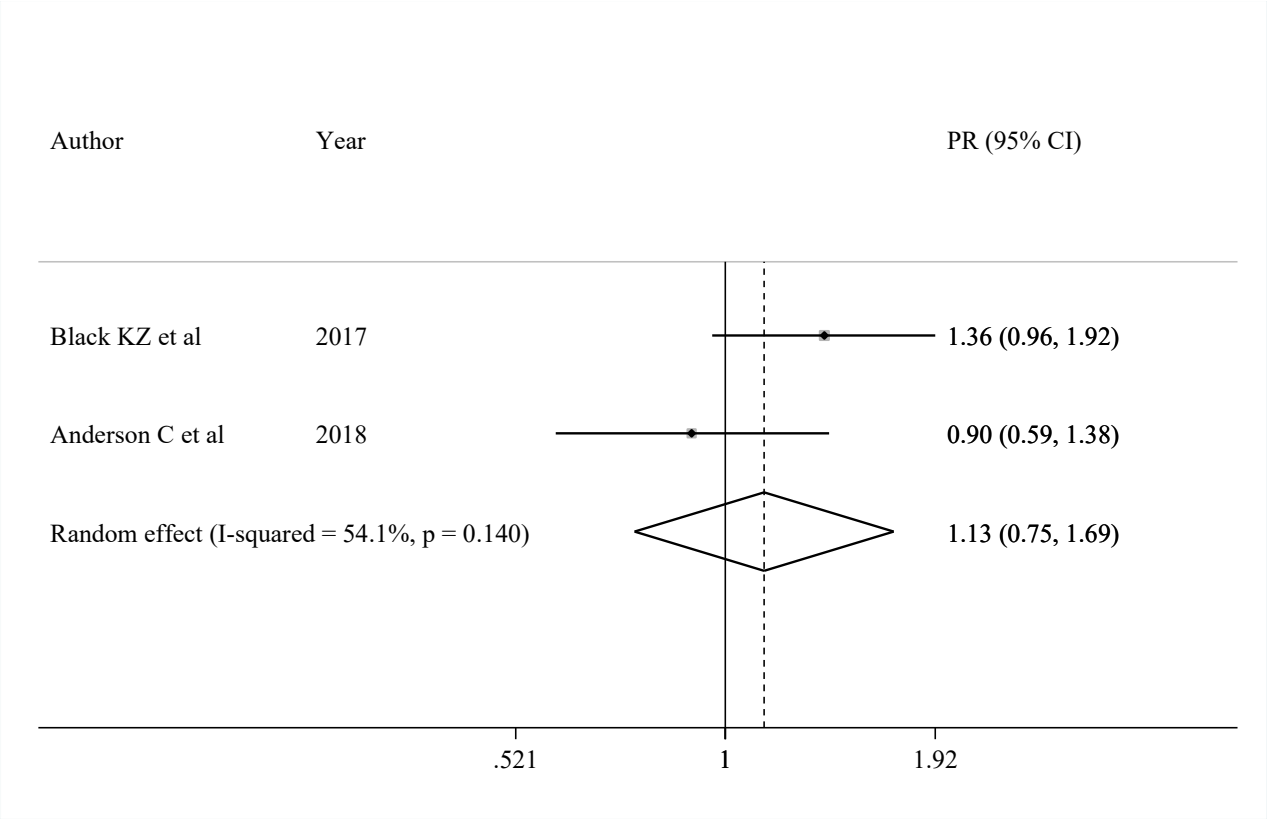
Figure S31 - Pregnancy outcome according to timing of pregnancy - low birth weight comparing between breast cancer patients achieving an early pregnancy and healthy women from the general population (the cut-off for timing of pregnancy after breast cancer was five years in one study, and two years in the other).



Random effect: p=0.350
Egger's test: not calculable

Abbreviations: PR, prevalence ratio; CI, confidence intervals

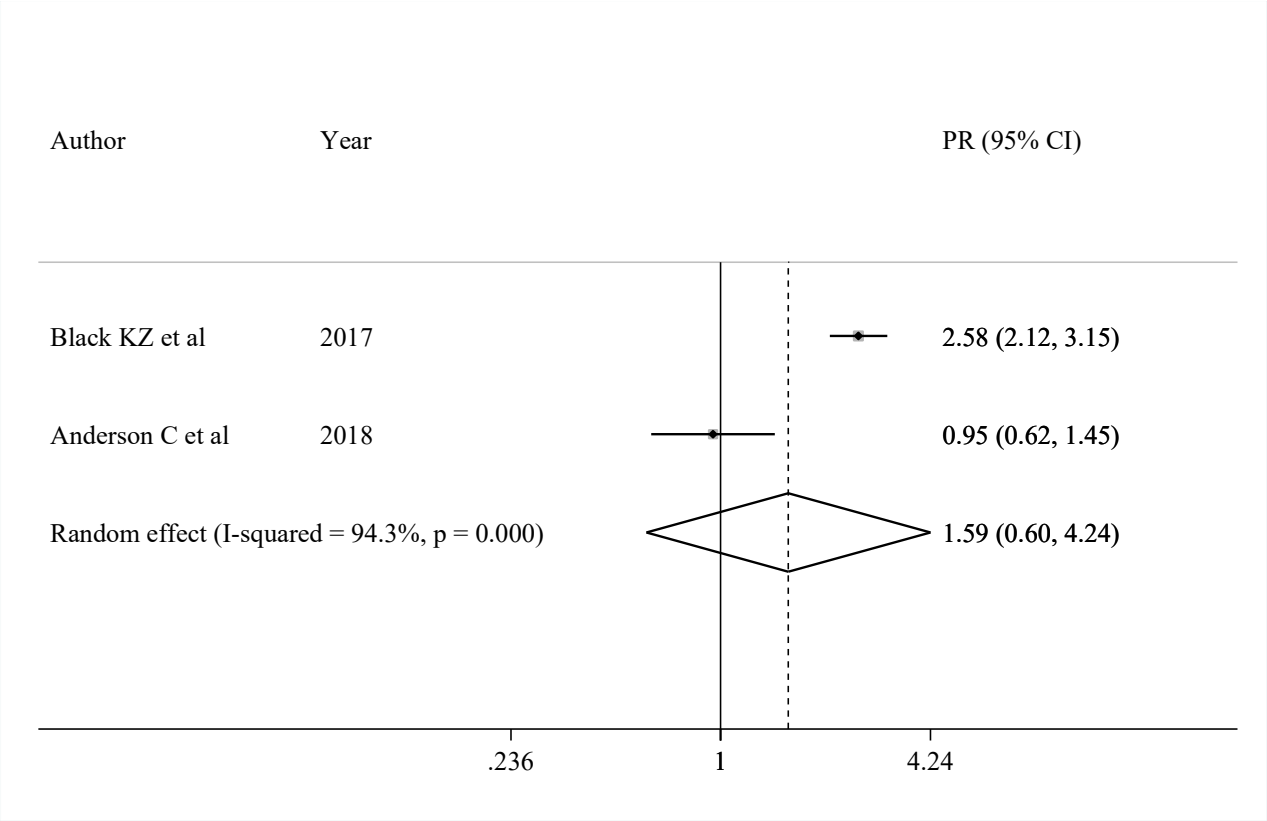
Figure S32 - Pregnancy outcome according to timing of pregnancy - small for gestational age comparing between breast cancer patients achieving an early pregnancy and healthy women from the general population (the cut-off for timing of pregnancy after breast cancer was five years in one study, and two years in the other).



Random effect: p=0.559
Egger's test: not calculable

Abbreviations: PR, prevalence ratio; CI, confidence intervals

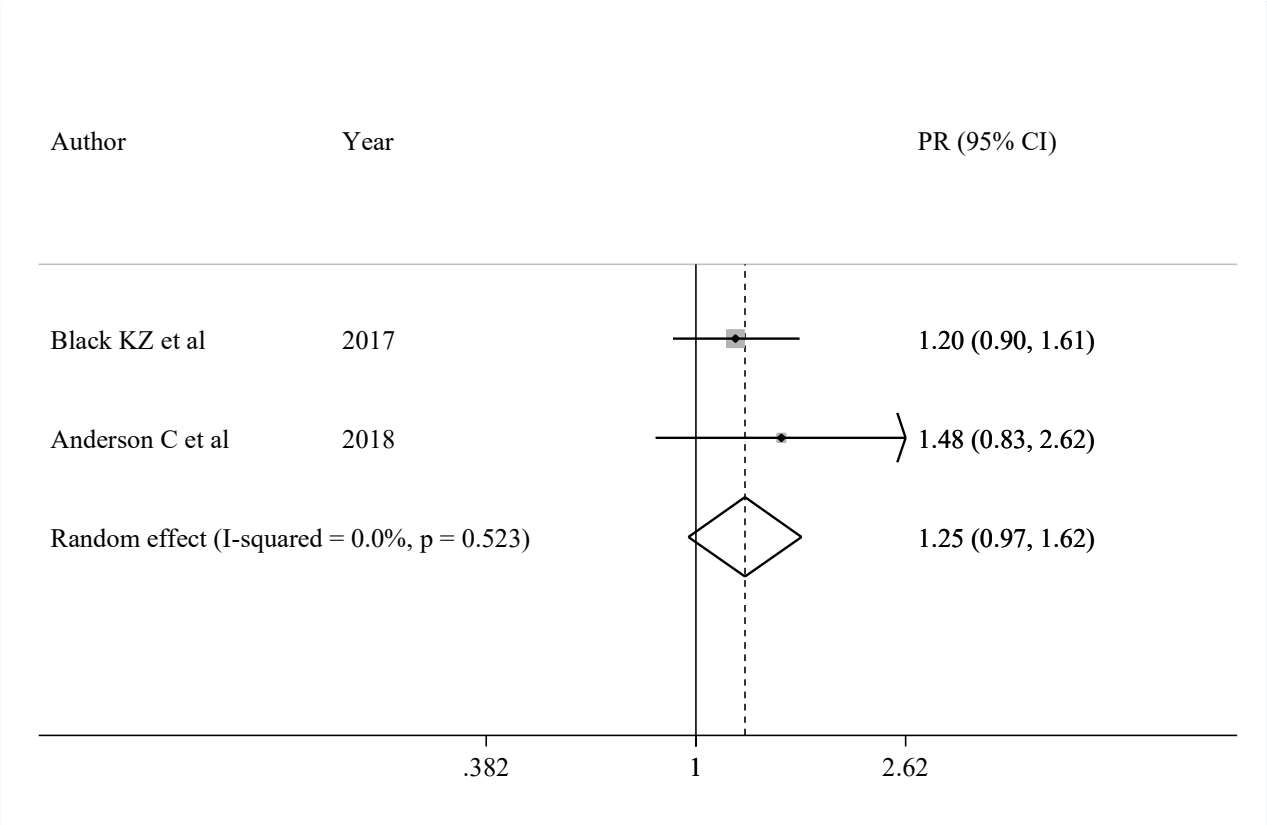
Figure S33 - Pregnancy outcome according to timing of pregnancy - preterm birth comparing between breast cancer patients achieving an early pregnancy and healthy women from the general population (the cut-off for timing of pregnancy after breast cancer was five years in one study, and two years in the other).



Random effect: p=0.350
Egger's test: not calculable

Abbreviations: PR, prevalence ratio; CI, confidence intervals

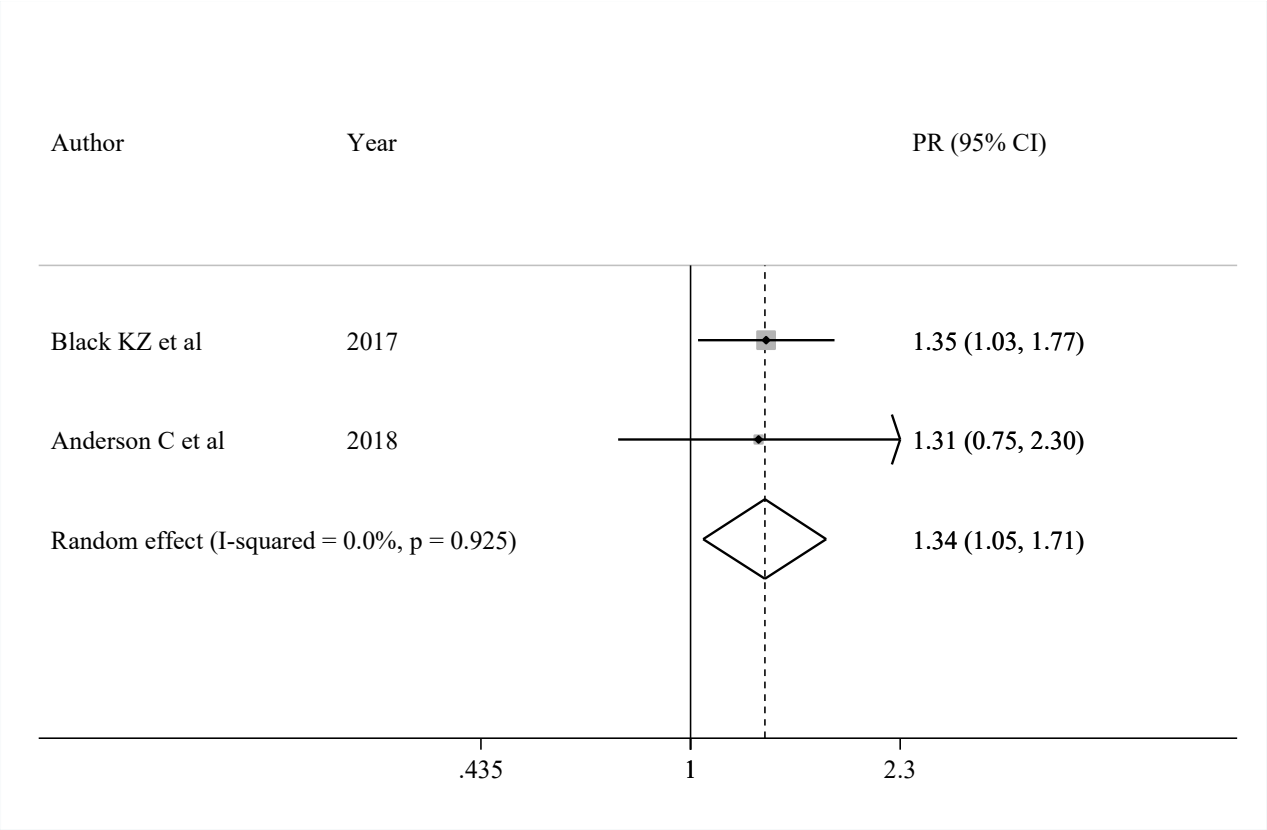
Figure S34 - Pregnancy outcome according to timing of pregnancy - low birth weight comparing between breast cancer patients achieving a late pregnancy and healthy women from the general population (the cut-off for timing of pregnancy after breast cancer was five years in one study, and two years in the other).



Random effect: p=0.089
Egger's test: not calculable

Abbreviations: PR, prevalence ratio; CI, confidence intervals

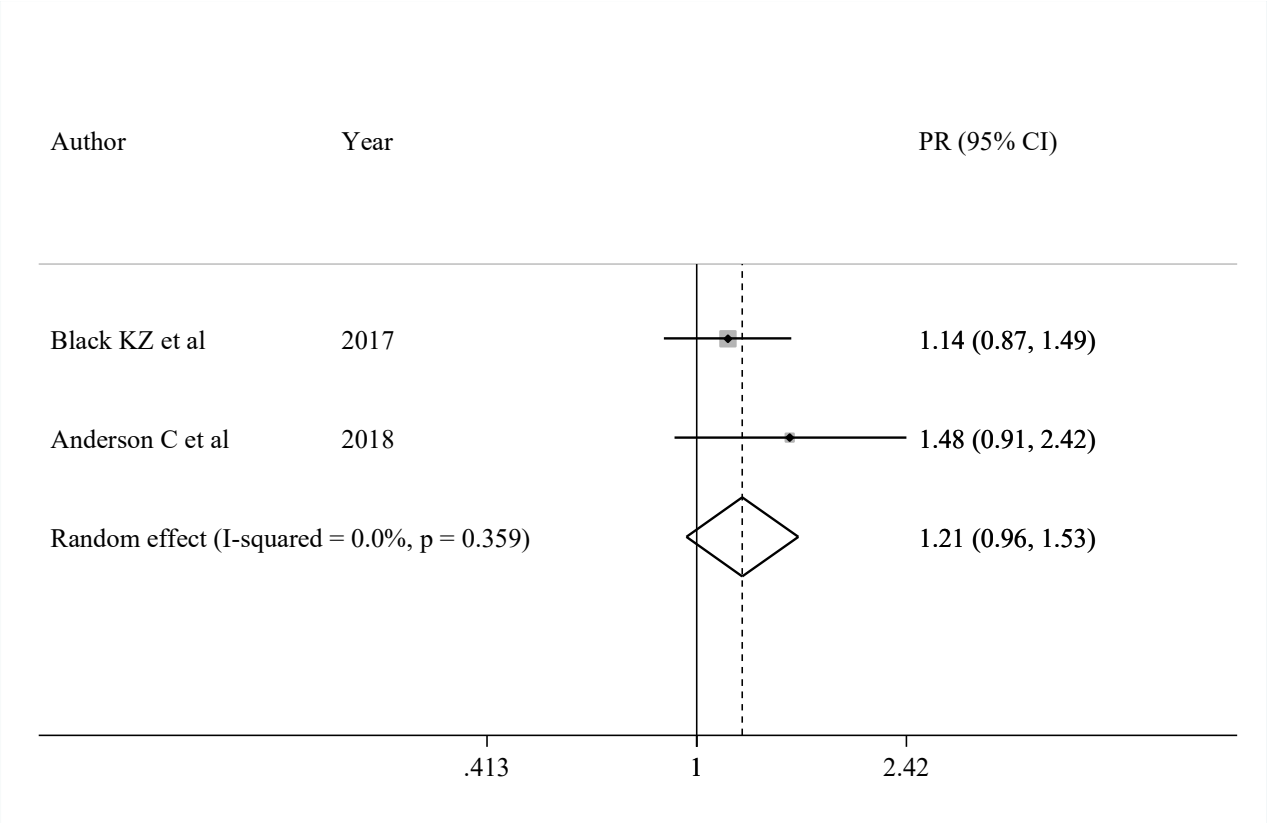
Figure S35 - Pregnancy outcome according to timing of pregnancy - small for gestational age comparing between breast cancer patients achieving a late pregnancy and healthy women from the general population (the cut-off for timing of pregnancy after breast cancer was five years in one study, and two years in the other).



Random effect: p=0.018
Egger's test: not calculable

Abbreviations: PR, prevalence ratio; CI, confidence intervals

Figure S36 - Pregnancy outcome according to timing of pregnancy - preterm birth comparing between breast cancer patients achieving a late pregnancy and healthy women from the general population (the cut-off for timing of pregnancy after breast cancer was five years in one study, and two years in the other).



Random effect: p=0.111
Egger's test: not calculable

Abbreviations: PR, prevalence ratio; CI, confidence intervals

Table S20 - Studies comparing maternal outcomes in patients with or without a pregnancy after breast cancer.[15–39]

For the three studies reporting results also for patients with pregnancy-associated breast cancer, only data in patients with pregnancy after breast cancer were considered for the purpose of this analysis.[30,33,34] Among the 25 studies included, 8 were case-control studies,[15–17,20,24,32,33,35] and 17 cohort studies.[18,19,21–23,25–31,34,36–39] The majority of the studies reported results corrected for maternal age and disease stage at diagnosis. A total of 19 studies corrected the results for the potential "healthy mother effect".[15–17,19–21,25–30,32–34,36–39] *Median follow-up of the included trials ranged from 5 to 13 years.*

Reference	Country	Study design	Pregnant breast cancer patients (n)	Non-pregnant breast cancer patients (n)	Matching criteria/controlling factors	Correction for HME	Follow-up (years)	Outcomes
Cooper DR et al 1970	USA	CC	32	64	Clinical stage of disease, nodal status, and age	yes	N.R.	OS
Mignot L et al** 1986	France	CC	68	136	Age, year of diagnosis, stage	yes	6	OS
Querleu D et al** 1986	France	CC	18	18	Stage, year of diagnosis, age	yes	N.R.	OS, DFS
Ariel IM et al 1989	USA	Cohort study	47	960	N.R.	no	N.R.	OS
Sankila R et al 1994	Finland	Population-based cohort study	91	471	Stage,age, and year of diagnosis	yes	N.R.	OS
Dow KH et al 1994	USA	CC	23	23	Age, stage, time from the end of treatment to the onset of full-term pregnancy	yes	N.R.	DFS
von Schoultz et al 1995	Sweden	Cohort study	50	2,069	N.R.	yes	7	DDFS
Malamos NA et al 1996	Greece	Cohort study	21	222	N.R.	no	N.R.	OS, RFS
Lethaby AE et al 1996	New Zealand	Cohort study	14	334	N.R.	no	10.2	OS
Birgisson H et al 2000	Iceland	CC	14	33	Tumour size, axillary lymph node status and years of birth and diagnosis.	no	11.9	OS
Gelber S et al 2001	Patients enrolled in IBCSG trials	Retrospective cohort study	94	188	DFI, nodal status, tumor size, age at diagnosis, year of diagnosis	yes	7.4	OS
Mueller BA et al 2003	USA	Population-based cohort study	329	2,088	Age, race/ethnicity, diagnosis year, disease stage, and presence of a previous non breast primary tumor	yes	N.R.	OS
Blakely LJ et al 2004	USA	Retrospective cohort study	47	323	N.R.	yes	13	RFS, OS
Ives A et al 2007	Australia	Population-based cohort study	123	2,416	Age at diagnosis, tumour size, lymph node status, and time from diagnosis of cancer to approximate time of conception	yes	10.7	OS
Kroman N et al 2008	Denmark	Prospective cohort study	371	9,865	Tumour characteristics, time between diagnosis and most recent previous childbirth, age, year of treatment, protocol allocation, full-term pregnancy after diagnosis, induced abortion after diagnosis, and spontaneous abortion after diagnosis	yes	10	OS
Largillier R et al*** 2009	France	Retrospective cohort study	118	762	N.R.	yes	7.25	DRFI, OS
Rippy EE et al 2009	United Kingdom	Cohort study	18	286	N.R.	no	5	OS
Kranick JA et al 2010	USA	CC	107	344	Stage at diagnosis, age, months of survival from date of diagnosis to last menstrual period prior to conception, recurrence status at time of conception of first subsequent pregnancy, and year of diagnosis	yes	12.7 year for pregnancy group and 11.4 year for no-pregnancy group	OS, RFS

Valentini A et al *** 2013	Several American, Asian and European countries	CC	53	111	Age, BRCA mutation type, country of residency, date of breast cancer diagnosis, and date of completion of baseline questionnaire	yes	N.R.	OS
Iqbal J et al*** 2017	Canada	Population-based, retrospective cohort study	112	5,832	Year of diagnosis, age, cancer stage, ER, PR, and HER2 status, radiotherapy, chemotherapy.	yes	5.2	OS
Nye L et al 2017	USA	Retrospective CC	32	29	Age and stage	no	9.2y for cases; 6.5y for controls	DFS
Lambertini M et al 2018	Belgium, Spain, Italy, Denmark	Retrospective cohort study	333	874	Estrogen receptor, nodal status, adjuvant chemotherapy, adjuvant hormonal therapy, age, and year of diagnosis.	yes	9.6	DFS, OS
Lee MH et al 2020	Korea	Population-based, retrospective cohort study	992	30,769	Age at breast cancer diagnosis, adjuvant hormonal therapy, chemotherapy, and radiotherapy	yes	N.R.	OS, RFS
Lambertini M et al 2019	Several Asian, European, African and American countries	Exploratory analysis within a RCT (ALTTO trial)	85	1,307	N.A.	yes	6.23	DFS, OS
Lambertini M et al 2020	Several European countries, Israel, USA, Mexico, Brazil	Retrospective cohort study	195	1,057	Year at diagnosis, nodal status, hormone receptor status, type of BRCA mutation, DFI	yes	8.3	DFS, OS

Abbreviations: HME, healthy mother effect; DFI, disease free interval; OS, overall survival; RFS, relapse free survival; DFS, disease-free survival; N.R., not reported; N.A., not applicable; DDFS, distant disease-free survival; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor 2; DRFI, distant recurrence free interval; RCT, randomized controlled trial

*=previous analysis, included only non-updated outcomes

**=partial population overlapping

***=included only data from pregnancy subsequent to breast cancer

Table S21 - Sensitivity analysis for disease-free survival comparing between patients with or without a pregnancy after breast cancer.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	HR	95% CI	P-value		
Dow KH et al 1994	0.68	0.50-0.93	0.015	76.6	<0.001
von Schoultz E et al 1995	0.68	0.50-0.92	0.013	76.7	<0.001
Malamos NA et al 1996	0.71	0.53-0.95	0.020	73.3	<0.001
Blakely LJ et al 2004	0.72	0.54-0.96	0.028	72.6	<0.001
Largillier R et al 2009	0.66	0.48-0.91	0.012	77.0	<0.001
Kranick JA et al 2010	0.62	0.45-0.84	0.002	72.3	<0.001
Nye L et al 2017	0.63	0.47-0.85	0.003	75.1	<0.001
Lambertini M et al 2018	0.63	0.45-0.90	0.010	72.6	<0.001
Lambertini M et al 2019	0.63	0.47-0.87	0.004	75.9	<0.001
Lambertini M et al 2020	0.64	0.46-0.89	0.008	75.5	<0.001
Lee HM et al 2020	0.70	0.52-0.96	0.025	64.0	0.003

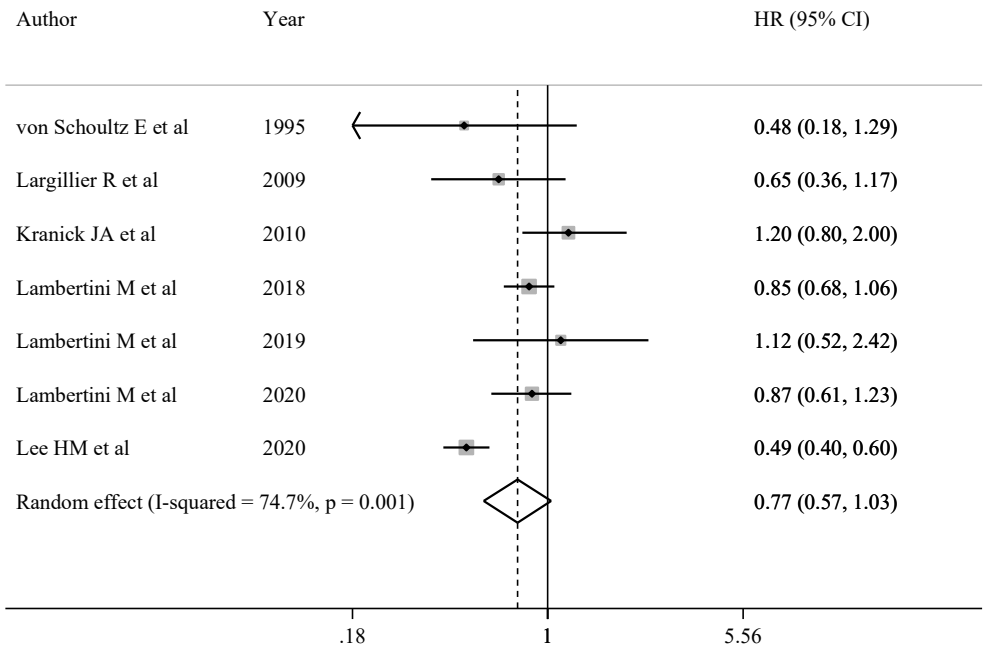
Abbreviations: HR, hazard ratio; CI, confidence intervals.

Table S22 - Sensitivity analysis for disease-free survival adjusted for the potential guarantee-time bias comparing between patients with or without a pregnancy after breast cancer.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	HR	95% CI	P-value		
Dow KH et al 1994	0.70	0.51-0.95	0.020	76.8	<0.001
von Schoultz E et al 1995	0.69	0.51-0.94	0.018	76.9	<0.001
Blakely LJ et al 2004	0.74	0.56-0.98	0.036	71.4	0.001
Largillier R et al 2009	0.68	0.49-0.93	0.017	77.3	<0.001
Kranick JA et al 2010	0.63	0.47-0.84	0.002	71.1	0.001
Lambertini M et al 2018	0.65	0.46-0.91	0.012	71.6	0.001
Lambertini M et al 2019	0.65	0.48-0.88	0.005	75.9	<0.001
Lambertini M et al 2020	0.65	0.47-0.90	0.010	75.4	<0.001
Lee HM et al 2020	0.74	0.56-0.97	0.033	56.4	0.025

Abbreviations: HR, hazard ratio; CI, confidence intervals.

Figure S37 - Disease-free survival comparing between patients with or without a pregnancy after breast cancer excluding the studies with computed hazard ratios.



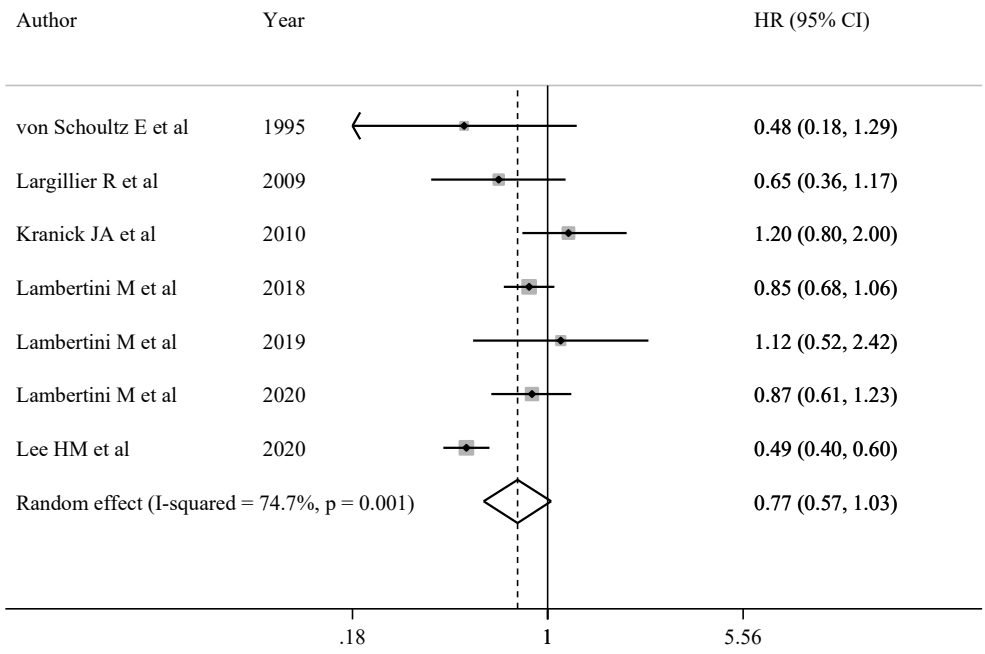
Random effect: p=0.080
Egger's test: p=0.441

Table S23 - Sensitivity analysis for disease-free survival comparing between patients with or without a pregnancy after breast cancer excluding the studies with computed hazard ratios.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	HR	95% CI	P-value		
von Schoultz E et al 1995	0.79	0.58-1.08	0.147	78.4	<0.001
Largillier R et al 2009	0.79	0.56-1.10	0.156	78.8	<0.001
Kranick JA et al 2010	0.71	0.52-0.96	0.025	72.0	0.003
Lambertini M et al 2018	0.75	0.52-1.09	0.130	74.0	0.002
Lambertini M et al 2019	0.74	0.54-1.01	0.058	77.5	<0.001
Lambertini M et al 2020	0.75	0.53-1.06	0.105	77.2	0.001
Lee HM et al 2020	0.87	0.74-1.02	0.091	0.0	0.455

Abbreviations: HR, hazard ratio; CI, confidence intervals.

Figure S38 – Disease-free survival adjusted for the potential guarantee-time bias comparing between patients with or without a pregnancy after breast cancer excluding the studies with computed hazard ratios.



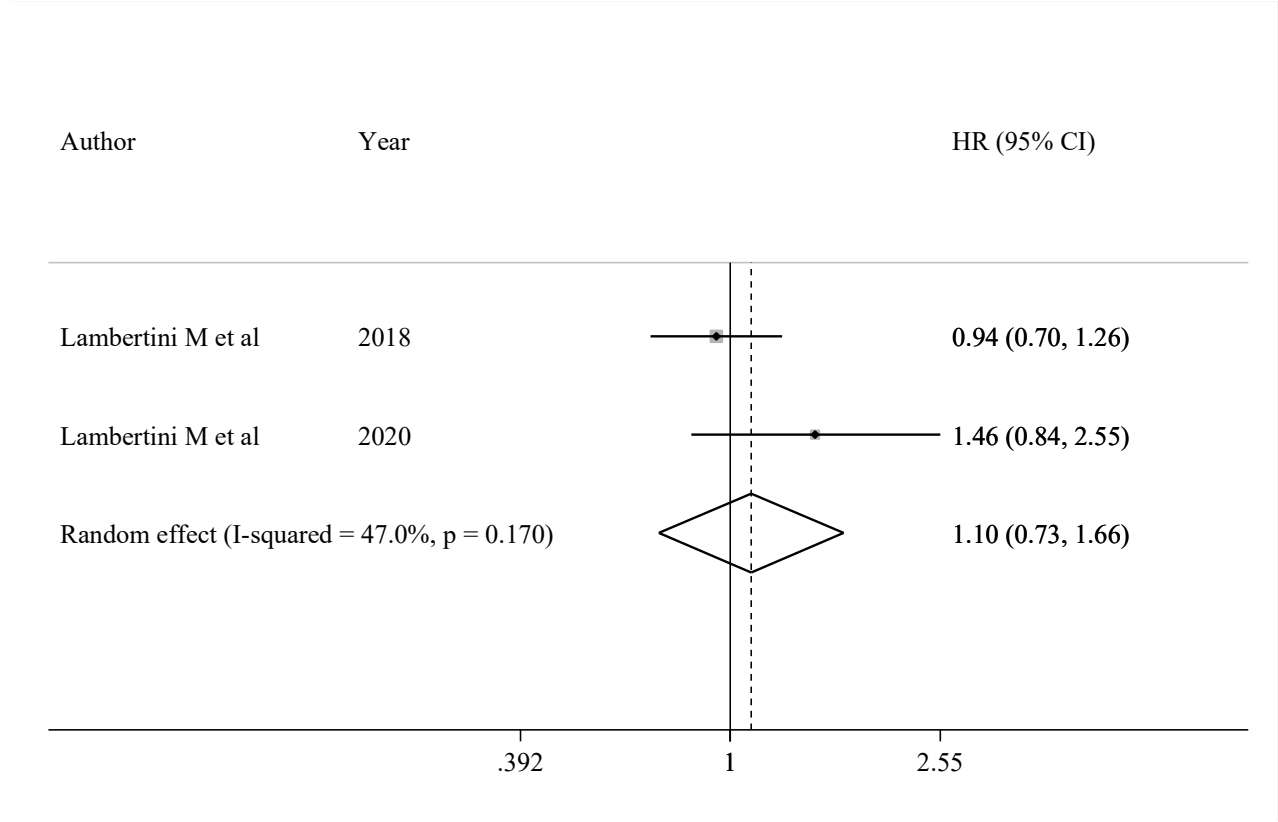
Random effect: p=0.080
Egger's test: p=0.441

Table S24 - Sensitivity analysis for disease-free survival adjusted for the potential guarantee-time bias comparing between patients with or without a pregnancy after breast cancer excluding the studies with computed hazard ratios.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	HR	95% CI	P-value		
von Schoultz E et al 1995	0.79	0.58-1.08	0.147	78.4	<0.001
Largillier R et al 2009	0.79	0.56-1.10	0.156	78.8	<0.001
Kranick JA et al 2010	0.71	0.52-0.96	0.025	72.0	0.003
Lambertini M et al 2018	0.75	0.52-1.09	0.130	74.0	0.002
Lambertini M et al 2019	0.74	0.54-1.01	0.058	77.5	<0.001
Lambertini M et al 2020	0.75	0.53-1.06	0.105	77.2	0.001
Lee HM et al 2020	0.87	0.74-1.02	0.091	0.0	0.455

Abbreviations: HR, hazard ratio; CI, confidence intervals.

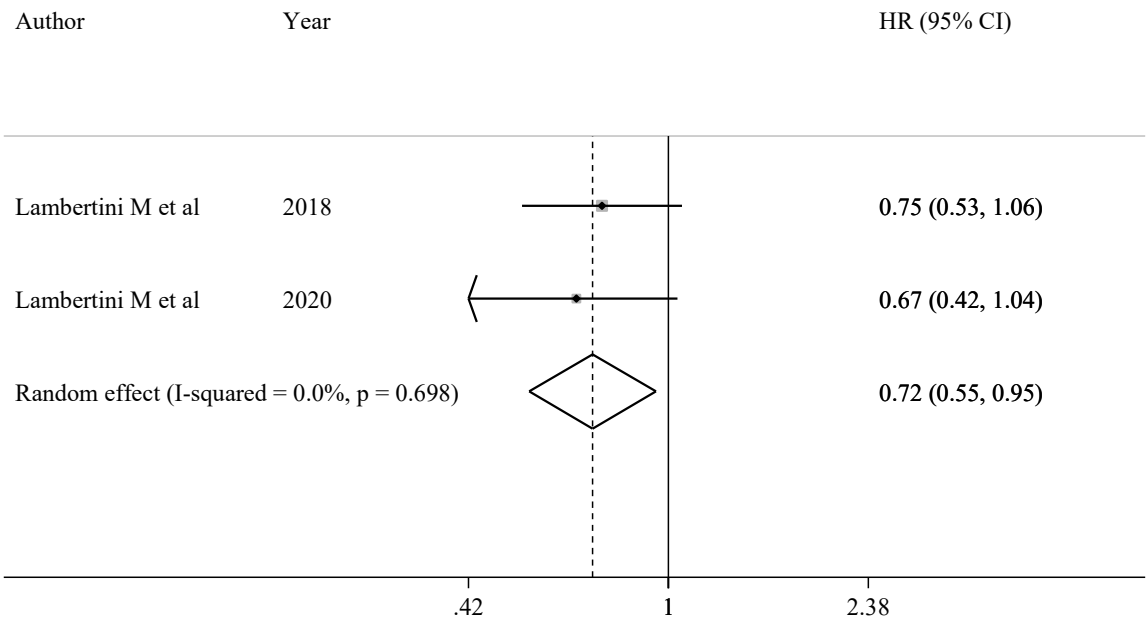
Figure S39 - Maternal safety according to hormone-receptor status: disease-free survival in patients with hormone receptor-positive breast cancer.



Random effect: p=0.659
Egger's test: not calculable

Abbreviations: HR, hazard ratio; CI, confidence intervals.

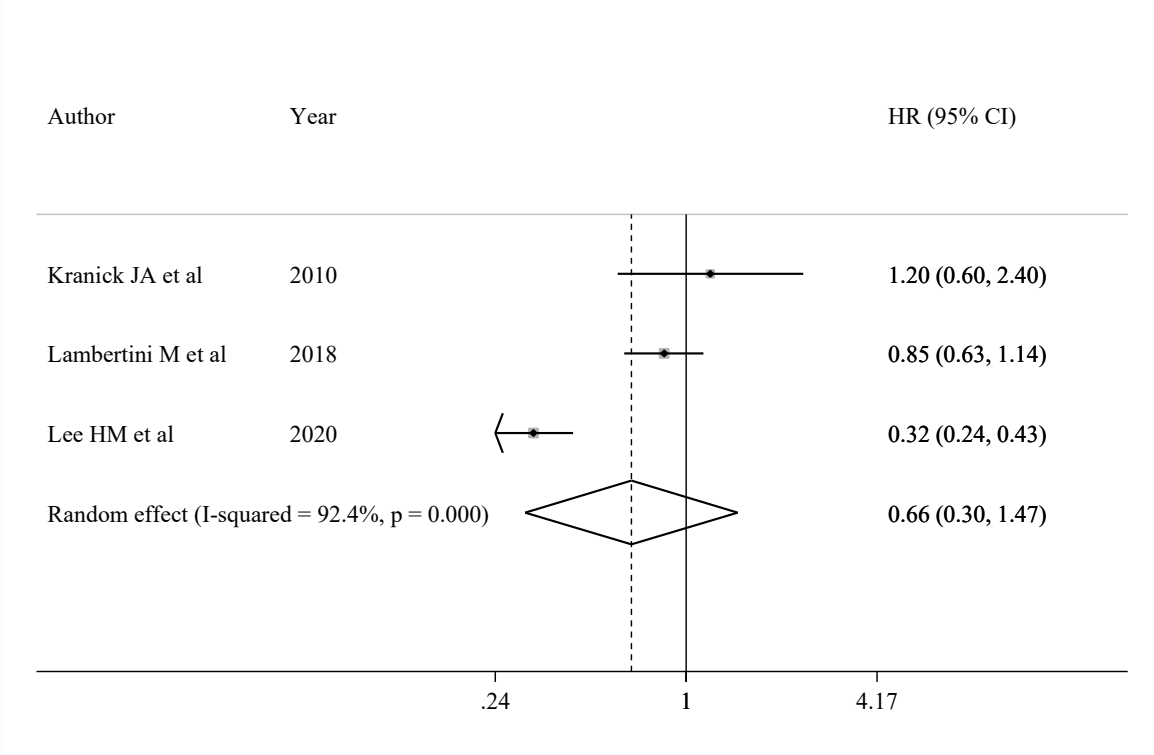
Figure S40 - Maternal outcomes according to hormone-receptor status: disease-free survival in patients with hormone receptor-negative breast cancer.



Random effect: p=0.019
Egger's test: not calculable

Abbreviations: HR, hazard ratio; CI, confidence intervals.

Figure S41 - Maternal outcomes according to pregnancy outcome: disease-free survival in patients that completed pregnancy.



Random effect: p=0.312
Egger's test: p=0.716

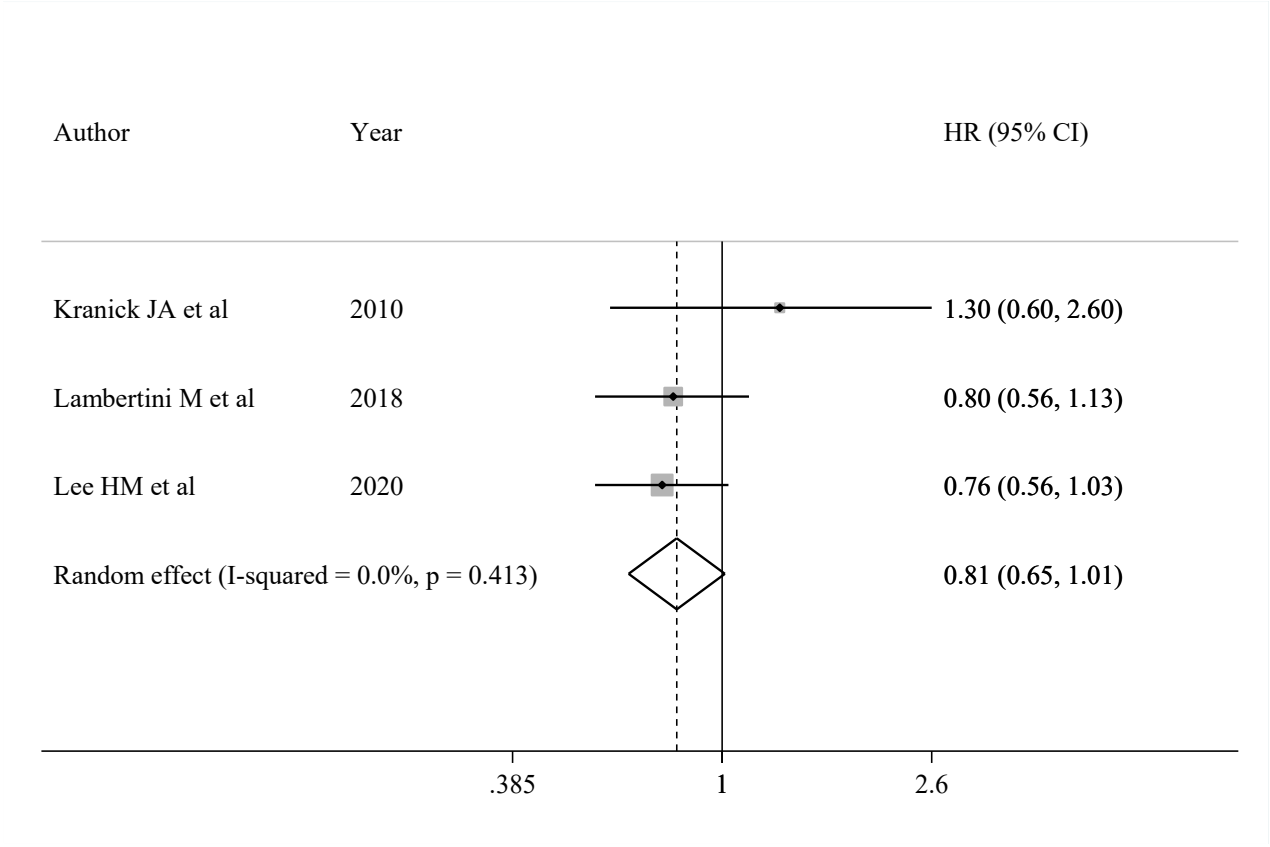
Abbreviations: HR, hazard ratio; CI, confidence intervals.

Table S25 - Sensitivity analysis maternal outcomes according to pregnancy outcome: disease-free survival in patients that completed pregnancy.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	HR	95% CI	P-value		
Kranick JA et al 2010	0.52	0.20-1.36	0.182	95.3	<0.001
Lambertini M et al 2018	0.60	0.16-2.17	0.433	91.6	0.001
Lee HM et al 2020	0.90	0.68-1.18	0.433	0.0	0.370

Abbreviations: HR, hazard ratio; CI, confidence intervals.

Figure S42 - Maternal outcomes according to pregnancy outcome: disease-free survival in patients that had an abortion.



Random effect: p=0.066
Egger's test: p=0.012

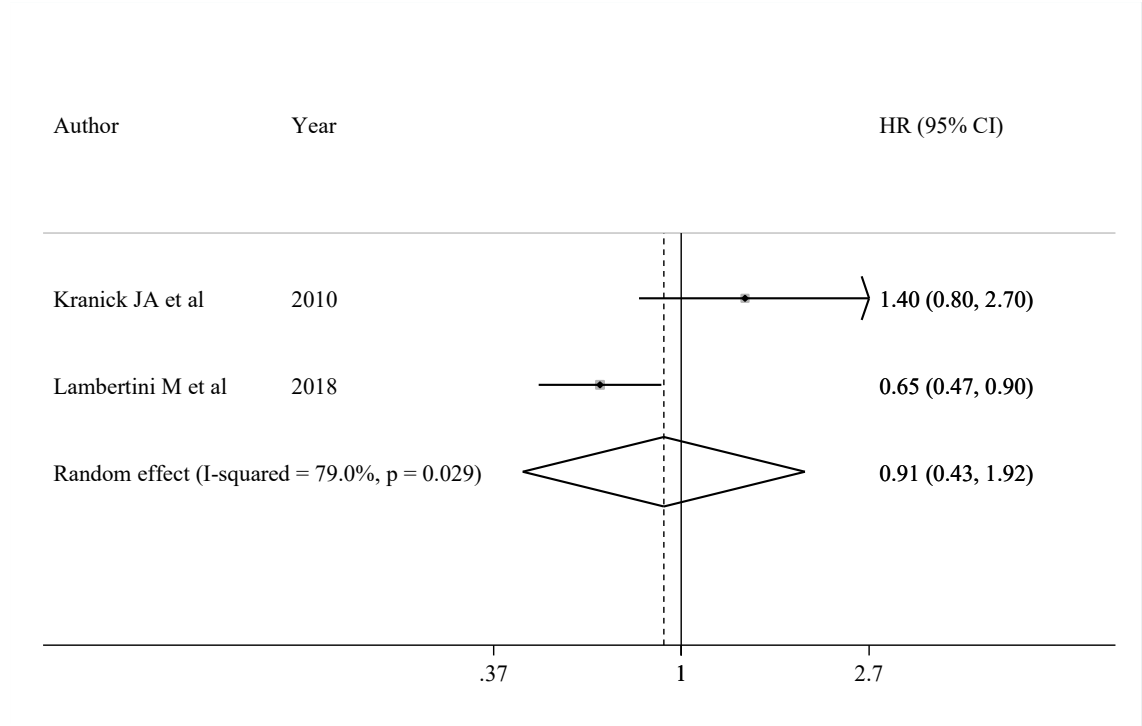
Abbreviations: HR, hazard ratio; CI, confidence intervals.

Table S26 - Sensitivity analysis maternal outcomes according to pregnancy outcome: disease-free survival in patients that had an abortion.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	HR	95% CI	P-value		
Kranick JA et al 2010	0.78	0.62-0.98	0.032	0.0	0.829
Lambertini M et al 2018	0.89	0.55-1.44	0.643	43.1	0.185
Lee HM et al 2020	0.91	0.60-1.39	0.672	27.0	0.242

Abbreviations: HR, hazard ratio; CI, confidence intervals.

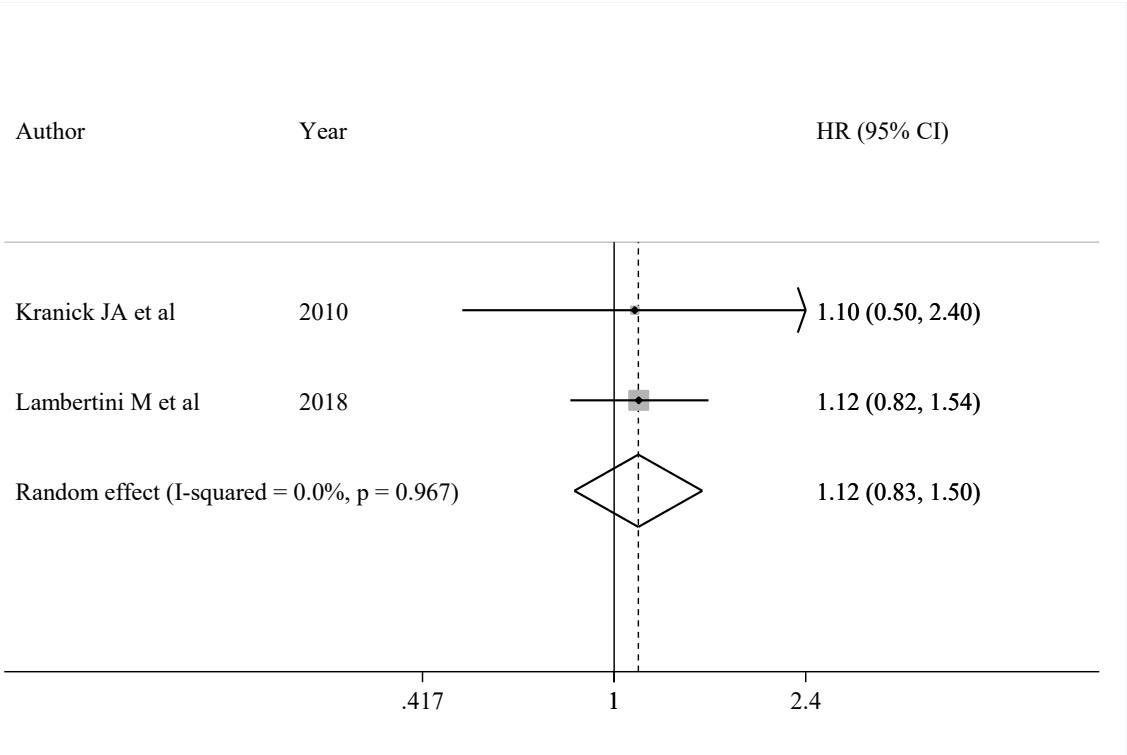
Figure S43 - Maternal outcomes according to pregnancy timing: disease-free survival in patients with an early pregnancy (the cut-off for timing of pregnancy after breast cancer was one year in one study and two years in the other).



Random effect: p=0.809
Egger's test: not calculable

Abbreviations: HR, hazard ratio; CI, confidence intervals.

Figure S44 - Maternal outcomes according to pregnancy timing: disease-free survival in patients with a late pregnancy (the cut-off for timing of pregnancy after breast cancer was one year in one study and two years in the other).



Random effect: p=0.458
Egger's test: not calculable

Abbreviations: HR, hazard ratio; CI, confidence intervals.

Table S27 - Sensitivity analysis for overall survival comparing between patients with or without a pregnancy after breast cancer.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	HR	95% CI	P-value		
Cooper DR et al 1970	0.55	0.45-0.69	<0.001	62.8	<0.001
Mignot L et al 1986	0.53	0.43-0.65	<0.001	54.7	0.002
Querleu D et al 1986	0.55	0.45-0.68	<0.001	62.8	<0.001
Ariel IM et al 1989	0.54	0.44-0.67	<0.001	61.5	<0.001
Sankila R et al 1994	0.58	0.48-0.71	<0.001	56.6	0.001
Lethaby AE et al 1996	0.55	0.44-0.68	<0.001	62.6	<0.001
Birgisson H et al 2000	0.56	0.45-0.69	<0.001	62.6	<0.001
Gelber S et al 2001	0.56	0.45-0.69	<0.001	62.4	<0.001
Mueller BA et al 2003	0.55	0.44-0.70	<0.001	62.5	<0.001
Blakely LJ et al 2004	0.57	0.46-0.70	<0.001	61.6	<0.001
Ives A et al 2007	0.55	0.44-0.69	<0.001	62.8	<0.001
Kroman N et al 2008	0.54	0.43-0.68	<0.001	60.9	<0.001
Largillier R et al 2009	0.58	0.47-0.71	<0.001	58.7	<0.001
Rippy EE et al 2009	0.55	0.45-0.68	<0.001	62.8	<0.001
Kranick JA et al 2010	0.54	0.43-0.66	<0.001	60.1	<0.001
Valentini A et al 2013	0.55	0.45-0.68	<0.001	62.7	<0.001
Iqbal J et al 2017	0.58	0.47-0.71	<0.001	57.9	0.001
Lambertini M et al 2018	0.54	0.43-0.68	<0.001	60.6	<0.001
Lambertini M et al 2019	0.56	0.46-0.70	<0.001	61.4	<0.001
Lambertini M et al 2020	0.54	0.44-0.67	<0.001	61.2	<0.001
Lee HM et al 2020	0.58	0.47-0.71	<0.001	54.2	0.002

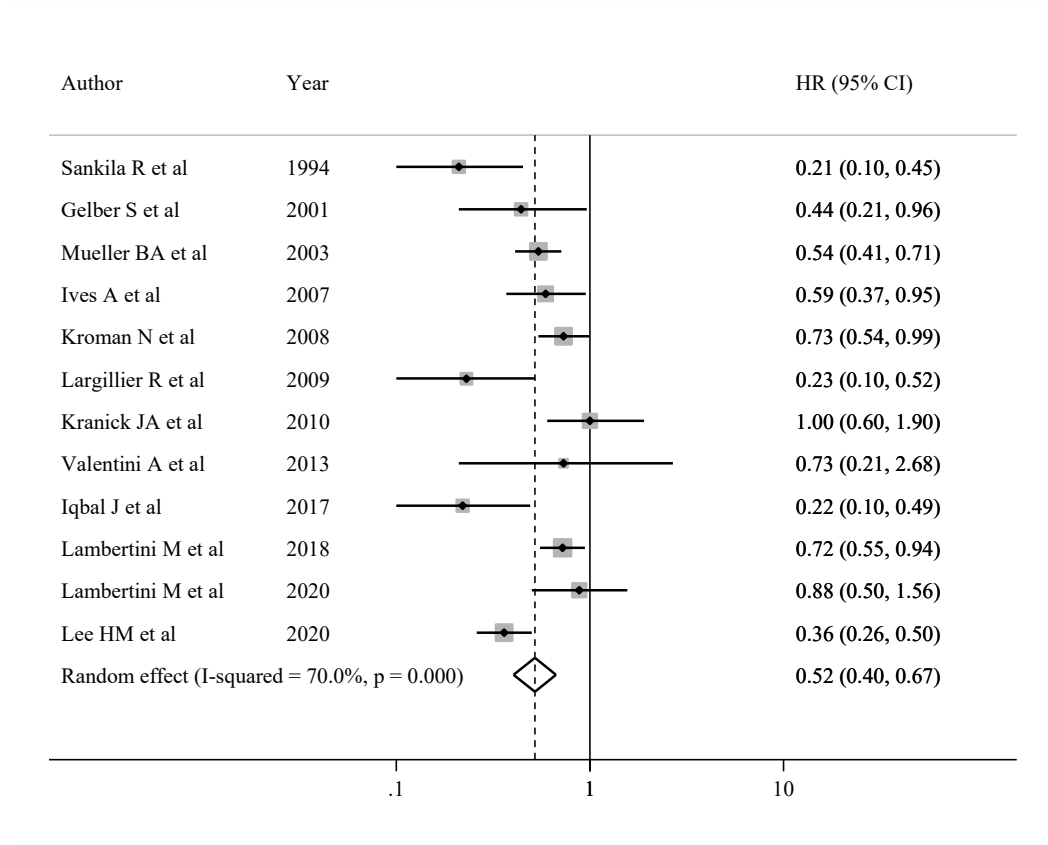
Abbreviations: HR, hazard ratio; CI, confidence intervals.

Table S28 - Sensitivity analysis for overall survival adjusted for the potential guarantee-time bias comparing between patients with or without a pregnancy after breast cancer.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	HR	95% CI	P-value		
Cooper DR et al 1970	0.53	0.41-0.67	<0.001	69.5	<0.001
Mignot L et al 1986	0.50	0.40-0.63	<0.001	62.2	0.001
Querleu D et al 1986	0.53	0.42-0.68	<0.001	69.4	<0.001
Sankila R et al 1994	0.56	0.45-0.70	<0.001	64.5	<0.001
Gelber S et al 2001	0.53	0.42-0.68	<0.001	69.2	<0.001
Mueller BA et al 2003	0.52	0.40-0.68	<0.001	69.4	<0.001
Blakely LJ et al 2004	0.54	0.42-0.69	<0.001	68.6	<0.001
Ives A et al 2007	0.52	0.41-0.67	<0.001	69.5	<0.001
Kroman N et al 2008	0.51	0.40-0.66	<0.001	67.6	<0.001
Largillier R et al 2009	0.55	0.44-0.70	<0.001	66.2	<0.001
Kranick JA et al 2010	0.51	0.40-0.65	<0.001	67.0	<0.001
Valentini A et al 2013	0.53	0.41-0.67	<0.001	69.4	<0.001
Iqbal J et al 2017	0.56	0.44-0.70	<0.001	65.5	<0.001
Lambertini M et al 2018	0.51	0.40-0.66	<0.001	67.2	<0.001
Lambertini M et al 2019	0.54	0.43-0.69	<0.001	68.4	<0.001
Lambertini M et al 2020	0.51	0.40-0.65	<0.001	68.0	<0.001
Lee HM et al 2020	0.55	0.44-0.70	<0.001	62.8	<0.001

Abbreviations: HR, hazard ratio; CI, confidence intervals.

Figure S45 - Overall survival comparing between patients with or without a pregnancy after breast cancer excluding the studies with computed hazard ratios.



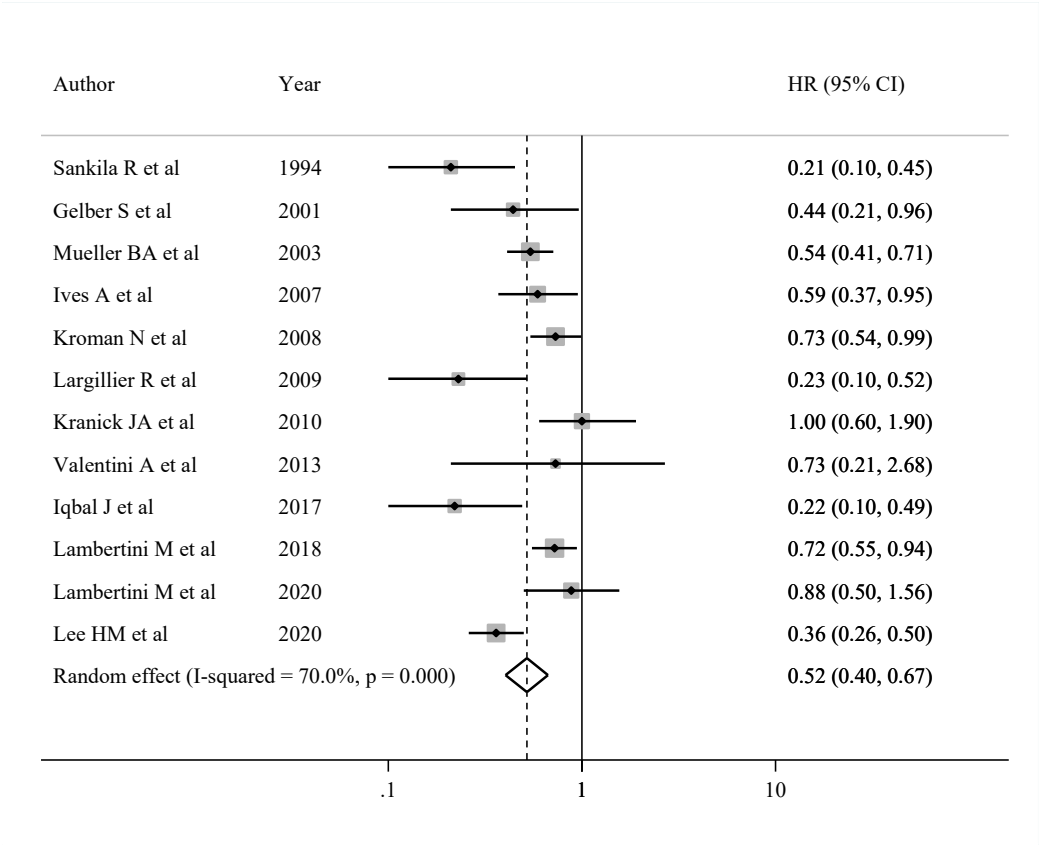
Random effect: p<0.001
Egger's test: p=0.286

Table S29 - Sensitivity analysis for overall survival comparing between patients with or without a pregnancy after breast cancer excluding the studies with computed hazard ratios.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	HR	95% CI	P-value		
Sankila R et al 1994	0.55	0.43-0.71	<0.001	66.5	0.001
Gelber S et al 2001	0.52	0.40-0.68	<0.001	72.4	<0.001
Mueller BA et al 2003	0.51	0.38-0.69	<0.001	72.6	<0.001
Ives A et al 2007	0.51	0.38-0.67	<0.001	72.7	<0.001
Kroman N et al 2008	0.49	0.37-0.65	<0.001	69.9	<0.001
Largillier R et al 2009	0.55	0.42-0.70	<0.001	68.7	<0.001
Kranick JA et al 2010	0.49	0.38-0.63	<0.001	69.4	<0.001
Valentini A et al 2013	0.51	0.39-0.66	<0.001	72.6	<0.001
Iqbal J et al 2017	0.55	0.43-0.70	<0.001	67.9	0.001
Lambertini M et al 2018	0.49	0.37-0.65	<0.001	69.3	<0.001
Lambertini M et al 2020	0.49	0.38-0.64	<0.001	70.7	<0.001
Lee HM et al 2020	0.55	0.42-0.71	<0.001	64.6	0.002

Abbreviations: HR, hazard ratio; CI, confidence intervals.

Figure S46 - Overall survival adjusted for the potential guarantee-time bias comparing between patients with or without a pregnancy after breast cancer excluding the studies with computed hazard ratios.



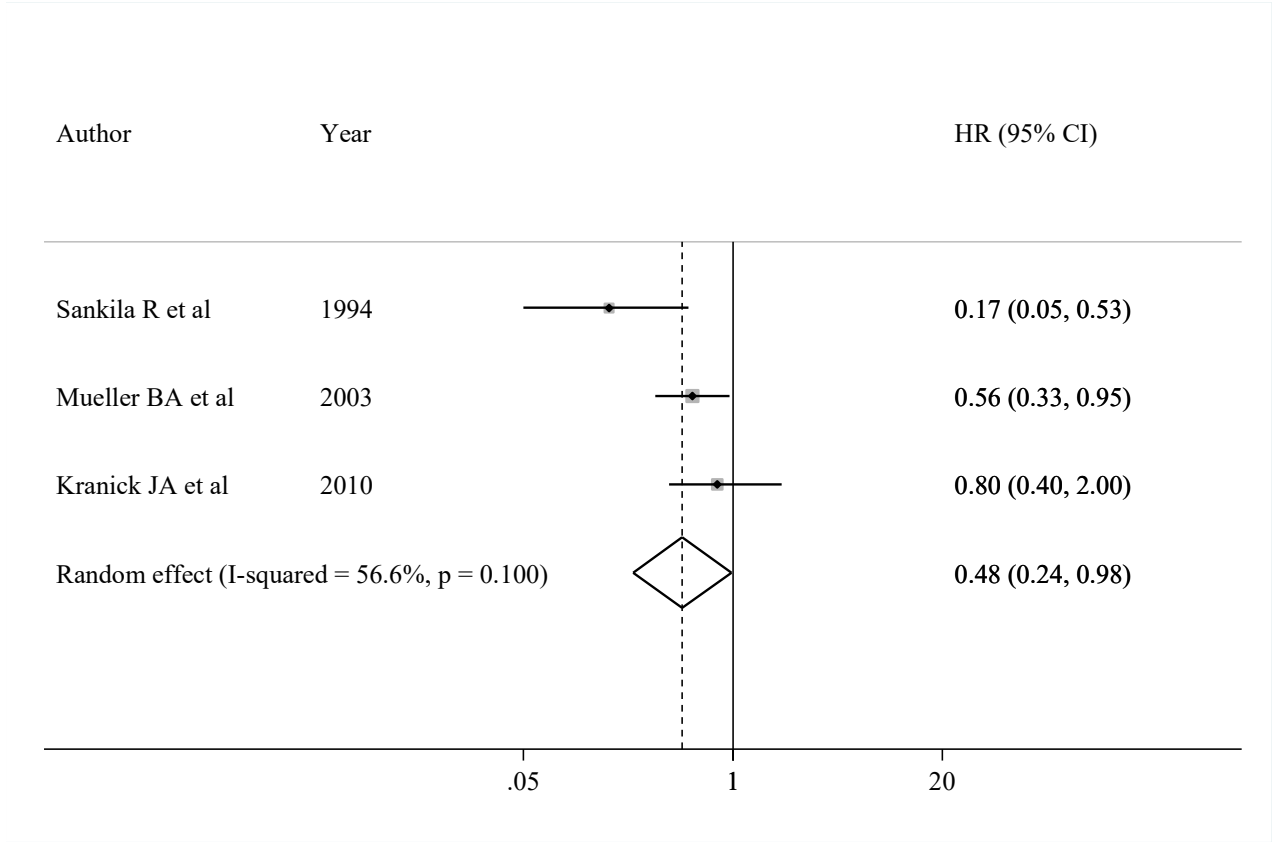
Random effect: p<0.001
Egger's test: p=0.286

Table S30 - Sensitivity analysis for overall survival adjusted for the potential guarantee-time bias comparing between patients with or without a pregnancy after breast cancer excluding the studies with computed hazard ratios.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	HR	95% CI	P-value		
Sankila R et al 1994	0.55	0.43-0.71	<0.001	66.5	0.001
Gelber S et al 2001	0.52	0.40-0.68	<0.001	72.4	<0.001
Mueller BA et al 2003	0.51	0.38-0.69	<0.001	72.6	<0.001
Ives A et al 2007	0.51	0.38-0.67	<0.001	72.7	<0.001
Kroman N et al 2008	0.49	0.37-0.65	<0.001	69.9	<0.001
Largillier R et al 2009	0.55	0.42-0.70	<0.001	68.7	<0.001
Kranick JA et al 2010	0.49	0.38-0.63	<0.001	69.4	<0.001
Valentini A et al 2013	0.51	0.39-0.66	<0.001	72.6	<0.001
Iqbal J et al 2017	0.55	0.43-0.70	<0.001	67.9	0.001
Lambertini M et al 2018	0.49	0.37-0.65	<0.001	69.3	<0.001
Lambertini M et al 2020	0.49	0.38-0.64	<0.001	70.7	<0.001
Lee HM et al 2020	0.55	0.42-0.71	<0.001	64.6	0.002

Abbreviations: HR, hazard ratio; CI, confidence intervals.

Figure S47 - Maternal outcomes according to nodal status: overall survival in patients with node-negative breast cancer.



Random effect: p=0.043
Egger's test: p=0.657

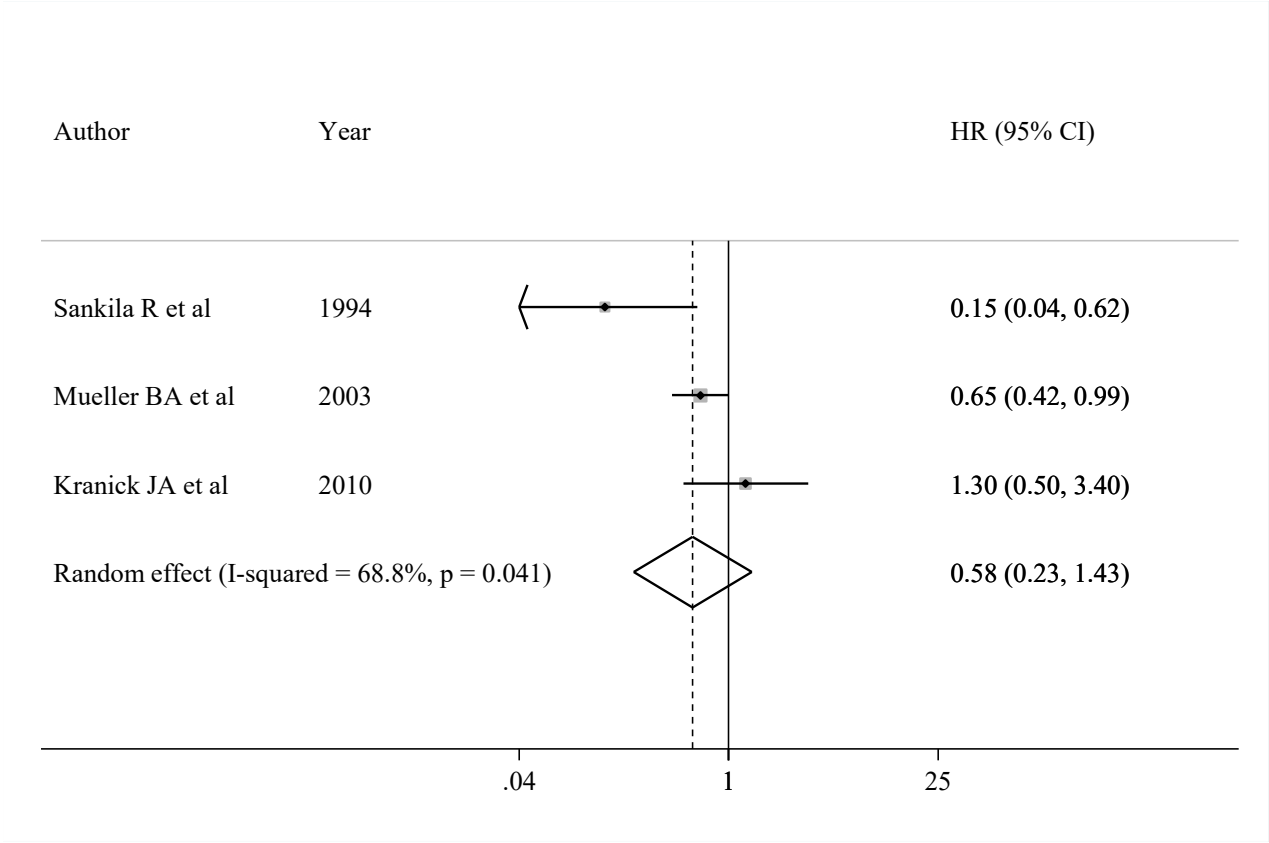
Abbreviations: HR, hazard ratio; CI, confidence intervals.

Table S31 - Sensitivity analysis maternal outcomes according to nodal status: overall survival in patients with node-negative breast cancer.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	HR	95% CI	P-value		
Sankila R et al 1994	0.62	0.40-0.97	0.036	0.0	0.468
Mueller BA et al 2003	0.39	0.09-1.78	0.226	77.9	0.034
Kranick JA et al 2010	0.35	0.11-1.09	0.071	69.4	0.071

Abbreviations: HR, hazard ratio; CI, confidence intervals.

Figure S48 - Maternal outcomes according to nodal status: overall survival in patients with node-positive breast cancer.



Random effect: p=0.234
Egger's test: p=0.793

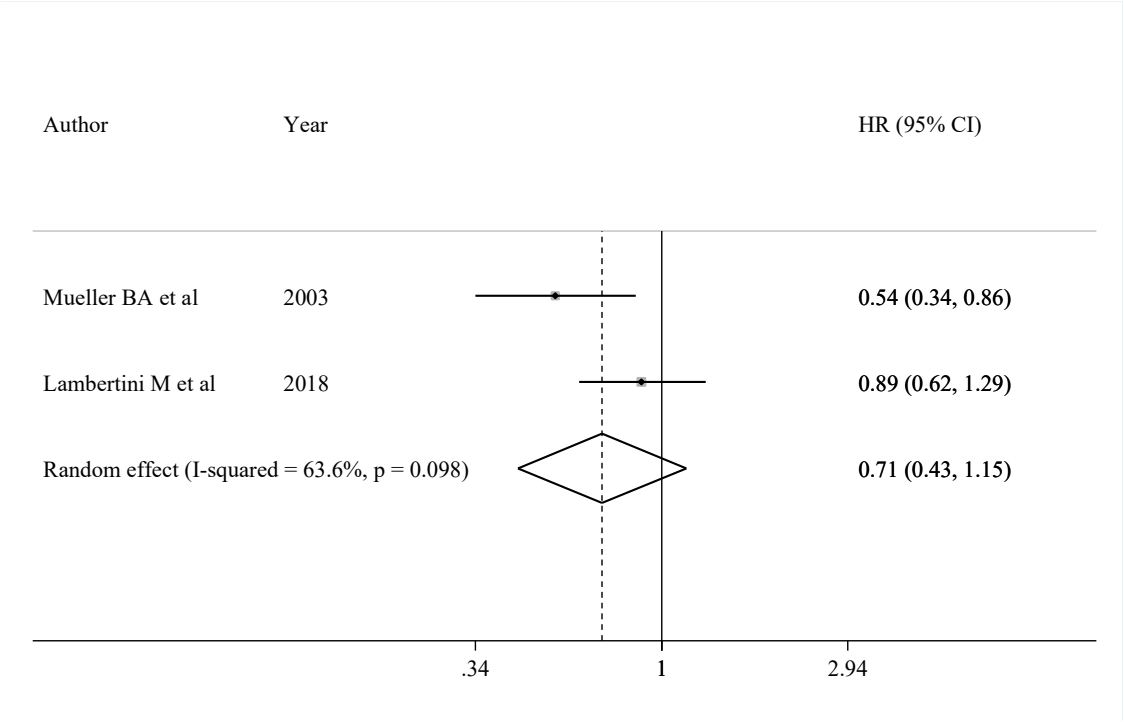
Abbreviations: HR, hazard ratio; CI, confidence intervals.

Table S32 - Sensitivity analysis maternal outcomes according to nodal status: overall survival in patients with node-positive breast cancer.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	HR	95% CI	P-value		
Sankila R et al 1994	0.80	0.43-1.49	0.485	40.3	0.196
Mueller BA et al 2003	0.47	0.06-3.87	0.481	84.4	0.011
Kranick JA et al 2010	0.36	0.09-1.48	0.158	75.0	0.045

Abbreviations: HR, hazard ratio; CI, confidence intervals.

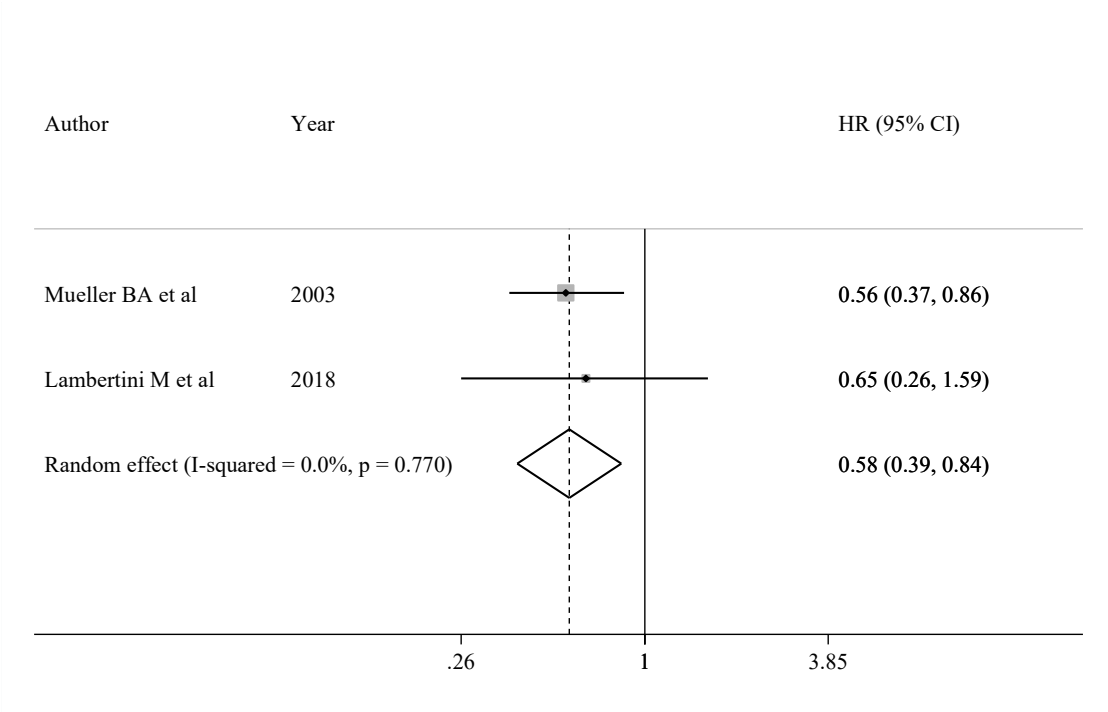
Figure S49 - Maternal outcomes according to therapy: overall survival in patients who received prior chemotherapy.



Random effect: p=0.165
Egger's test: not calculable

Abbreviations: HR, hazard ratio; CI, confidence intervals.

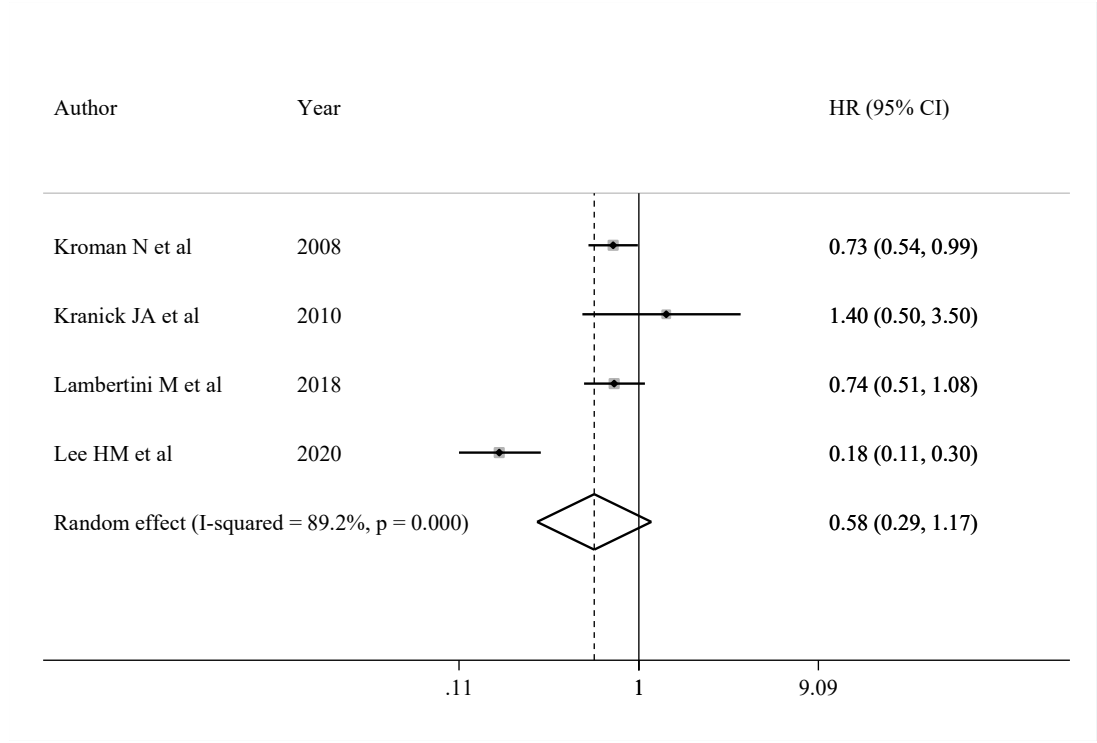
Figure S50 - Maternal outcomes according to therapy: overall survival in patients who did not receive prior chemotherapy.



Random effect: p=0.005
Egger's test: not calculable

Abbreviations: HR, hazard ratio; CI, confidence intervals.

Figure S51 - Maternal outcomes according to pregnancy outcome: overall survival in patients that completed pregnancy.



Random effect: p=0.126
Egger's test: p=0.877

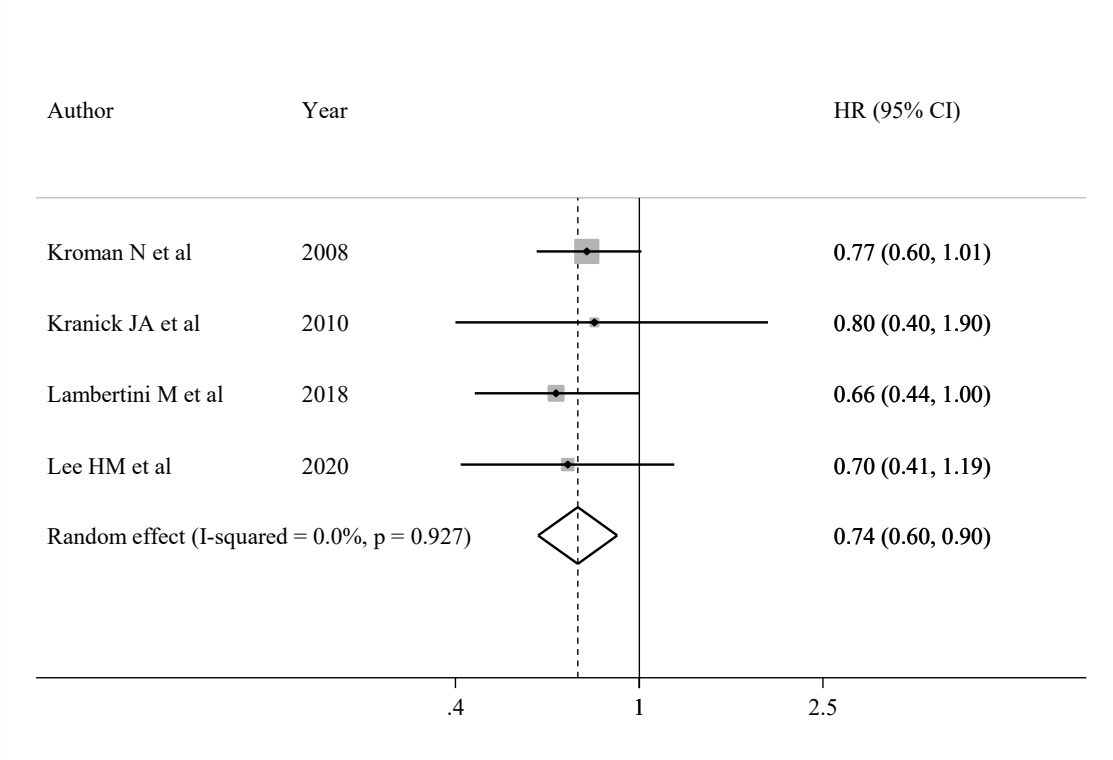
Abbreviations: HR, hazard ratio; CI, confidence intervals.

Table S33 - Sensitivity analysis maternal outcomes according to pregnancy outcome: overall survival in patients that completed pregnancy.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	HR	95% CI	P-value		
Kroman N et al 2008	0.54	0.18-1.68	0.292	91.8	<0.001
Kranick JA et al 2010	0.47	0.21-1.03	0.059	91.9	<0.001
Lambertini M et al 2018	0.54	0.18-1.63	0.275	92.3	<0.001
Lee HM et al 2020	0.76	0.60-0.96	0.019	0.0	0.449

Abbreviations: HR, hazard ratio; CI, confidence intervals.

Figure S52 - Maternal outcomes according to pregnancy outcome: overall survival in patients that had an abortion.



Random effect: p=0.002
Egger's test: p=0.755

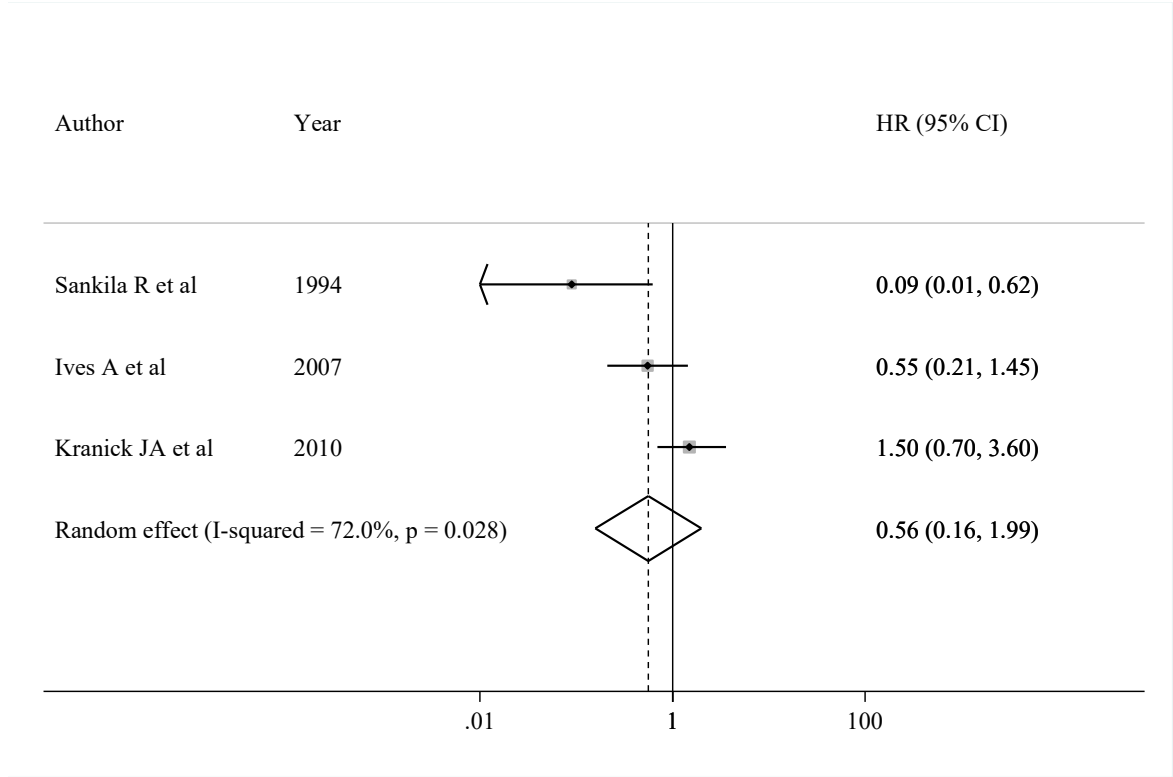
Abbreviations: HR, hazard ratio; CI, confidence intervals.

Table S34 - Sensitivity analysis maternal outcomes according to pregnancy outcome: overall survival in patients that had an abortion.

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	HR	95% CI	P-value		
Kroman N et al 2008	0.69	0.51-0.93	0.016	0.0	0.911
Kranick JA et al 2010	0.73	0.60-0.90	0.003	0.0	0.812
Lambertini M et al 2018	0.76	0.61-0.95	0.016	0.0	0.943
Lee HM et al 2020	0.74	0.60-0.92	0.006	0.0	0.808

Abbreviations: HR, hazard ratio; CI, confidence intervals.

Figure S53 - Maternal outcomes according to pregnancy timing: overall survival in patients with an early pregnancy (the cut-off for timing of pregnancy after breast cancer was one year in one study, and two years in the others).



Random effect: p=0.373
Egger's test: p=0.281

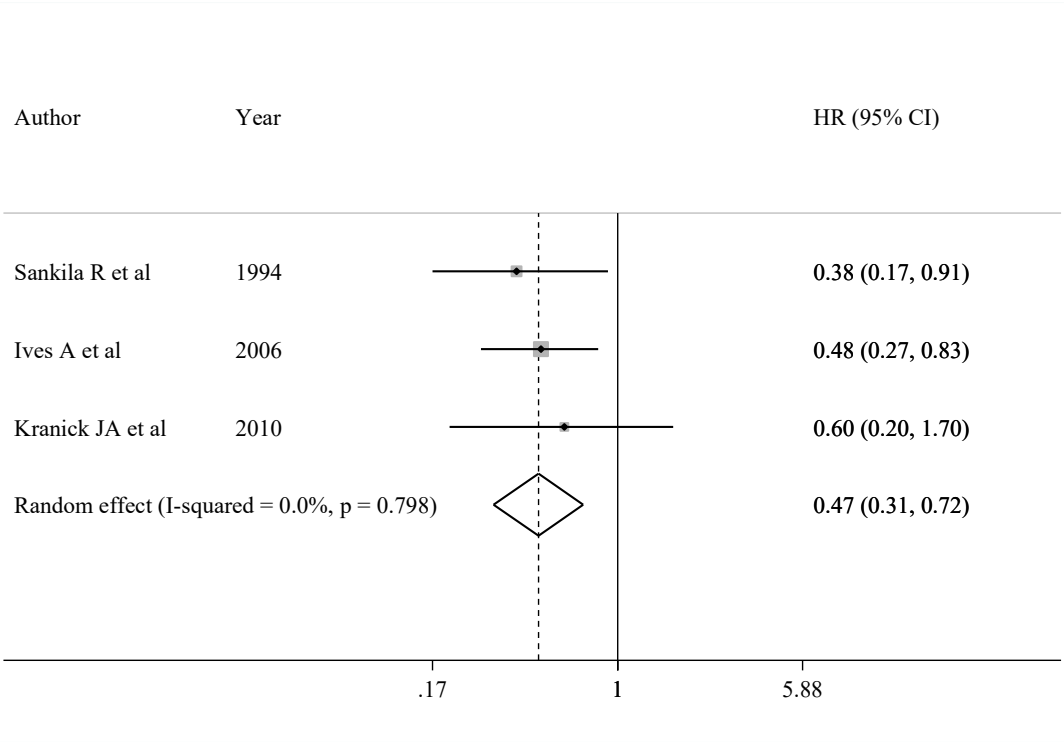
Abbreviations: HR, hazard ratio; CI, confidence intervals.

Table S35 - Sensitivity analysis maternal outcomes according to pregnancy timing: overall survival in patients with an early pregnancy (the cut-off for timing of pregnancy after breast cancer was one year in one study, and two years in the others).

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	HR	95% CI	P-value		
Sankila R et al 1994	0.94	0.35-2.51	0.901	58.5	0.120
Ives A et al 2007	0.43	0.03-6.70	0.550	83.8	0.013
Kranick JA et al 2010	0.28	0.05-1.56	0.148	58.8	0.119

Abbreviations: HR, hazard ratio; CI, confidence intervals.

Figure S54 - Maternal outcomes according to pregnancy timing: overall survival in patients with a late pregnancy (the cut-off for timing of pregnancy after breast cancer was one year in one study, and two years in the others).



Random effect: p=0.001
Egger's test: p=0.930

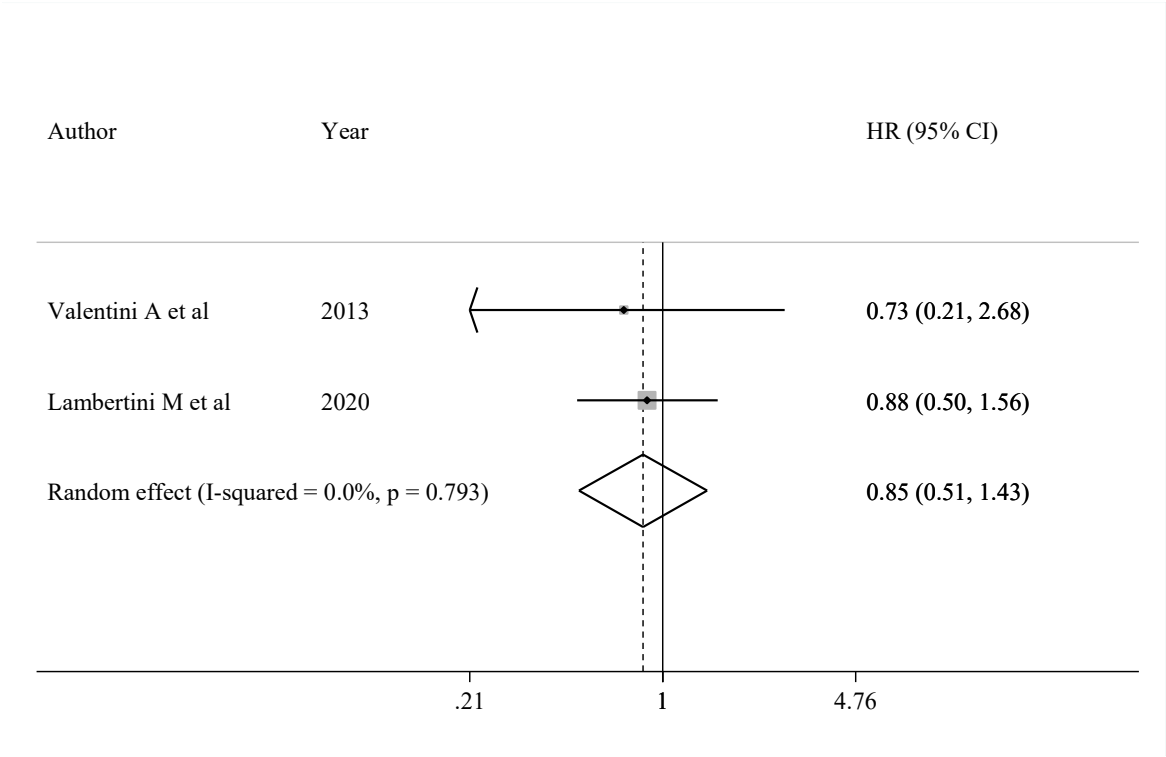
Abbreviations: HR, hazard ratio; CI, confidence intervals.

Table S36 - Sensitivity analysis maternal outcomes according to pregnancy timing: overall survival in patients with a late pregnancy (the cut-off for timing of pregnancy after breast cancer was one year in one study, and two years in the others).

Study excluded	Random effect			I-squared (%)	I-sq. P-value
	HR	95% CI	P-value		
Sankila R et al 1994	0.50	0.31-0.83	0.007	0.0	0.717
Ives A et al 2007	0.45	0.23-0.87	0.018	0.0	0.510
Kranick JA et al 2010	0.45	0.28-0.71	0.001	0.0	0.650

Abbreviations: HR, hazard ratio; CI, confidence intervals.

Figure S55 - Maternal outcomes according to *BRCA* status: overall survival in patients carrying germline *BRCA* pathogenic variants.



Random effect: p=0.549
Egger's test: not calculable

Abbreviations: HR, hazard ratio; CI, confidence intervals.

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