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Safety of pregnancy following breast cancer diagnosis: A meta-analysis of 14 studies

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ABSTRACT

Background: Due to the rising trend of delaying pregnancy to later in life, more women are diagnosed with breast cancer before completing their families. Therefore, enquiry into the feasibility and safety of pregnancy following breast cancer diagnosis is on the rise. Available evidence suggests that women with a history of breast cancer are frequently advised against future conception for fear that pregnancy could adversely affect their breast cancer outcome. Hence, we conducted a meta-analysis to understand the effect of pregnancy on overall survival of women with a history of breast cancer.

Methods: Two of the authors independently performed a literature search up to September 2009 with no language restrictions. Eligible studies were published retrospective control-matched, population-based and hospital-based studies that have addressed the impact of pregnancy on the overall survival of women with history of breast cancer. Pooling of data was done using the random effect model. Unpublished statistics from three studies were obtained to perform further subgroup and sensitivity analyses. This included examining the effect of pregnancy according to age at diagnosis, healthy mother effect, type of study, nodal status and other parameters.

Results: Fourteen studies were included in this meta-analysis (1244 cases and 18,145 controls). Women who got pregnant following breast cancer diagnosis had a 41% reduced risk of death compared to women who did not get pregnant [PRR: 0.59 (90% confidence interval (CI): 0.50–0.70)]. This difference was seen irrespective of the type of the study and particularly in women with history of node-negative disease. In a subgroup analysis, we compared the outcome of women with history of breast cancer who became pregnant to breast cancer patients who did not get pregnant and were known to be free of relapse. In this analysis, we did not find significant differences in survival between either group [PRR: 0.85; 95% CI: 0.53–1.35].

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Conclusions: This study confirms that pregnancy in women with history of breast cancer is safe and does not compromise their overall survival. Hence, breast cancer survivors should not be denied the opportunity of future conception.

1. Introduction

Around 10% of patients in the developed world and 25% of patients in the developing world are diagnosed with breast cancer below the age of 40.[1,2] These young women have poorer survival and a higher risk of recurrence compared to their older counterparts.[3] However, advances in the field of adjuvant therapies have improved breast cancer survival and significantly reduced the risk of recurrence with 400,000 breast cancer survivors below the age of 40 estimated in the United States in 2010.[4]

Given the rising trend of delaying pregnancy to later in life,[5] more women are diagnosed with breast cancer before completing their families. Therefore, patient enquiry into the possibility of subsequent pregnancy is increasingly encountered in breast cancer clinics.

Current evidence suggests that breast cancer survivors are frequently counselled against future conception, even those who have completed their treatment course.[6] Some reports have shown that induced abortion rate is quite high, ranging from 20 to 40%,[7] which probably reflects the uncertainties of patients and physicians regarding the safety of pregnancy following breast cancer diagnosis. In an earlier study by Gelber and colleagues, 23 of 33 induced abortions (69%) were reported as recommended by the treating physician.[8] It is believed that the hormonal milieu of pregnancy could stimulate breast cancer recurrence and consequently worsen the survival of these women. It is a matter of regret that some women are denied the opportunity to resume a normal life based on an assumption made in the absence of strong supporting evidence. This fact urges the medical community to provide more robust conclusions on the safety of pregnancy in breast cancer survivors.

Several studies were conducted to address this question. Some studies have suggested that pregnancy is associated with a better prognosis. However, these studies may have had selection bias, what has been described as the 'healthy mother effect'[9]. This refers to the fact that although the pregnancy exposed group was matched with controls of similar age and stage, women who became pregnant still represent a group which is particularly healthier and free of relapse. Hence, we conducted a meta-analysis to investigate the effect of pregnancy on overall survival of women with history of breast cancer diagnosis. We performed several sensitivity analyses using previously unpublished statistical information of three of the largest studies to better define our results.

2. Methods

The study design was a quantitative synthesis of retrospective control-matched, population-based and hospital-based studies that contribute to the evaluation of the impact of pregnancy on the overall survival (OS) of women with history of breast cancer. The primary end-point was OS, which was defined as time from breast cancer diagnosis to death or last follow-up.

2.1. Data sources and search strategy

The search was carried out independently by two authors (H.A.A. Jr. and F.A.P.) and no language restrictions were applied. The literature up to September 2009 was searched using the Medline database. Studies not reported in full text (abstract only) were not considered eligible. To identify the target population, 'breast cancer patients' and the intervention 'pregnancy', search was carried out using the combination key words 'breast cancer, pregnancy' and 'breast cancer, gestation'. In order to ensure that all studies dealing with pregnancy following breast cancer were captured, no selective keywords referring to the study design were introduced in the search strategy. Cross referencing from relevant studies was performed to confirm retrieval of all possible studies.

2.2. Selection of articles

We set minimum criteria based on which the studies were deemed eligible for this meta-analysis. These are as follows:

- Presence of a 'case' group of patients who became pregnant anytime following breast cancer diagnosis (irrespective of pregnancy outcome) and a 'comparator' group of breast cancer patients who did not become pregnant.
- Independence from other studies to avoid giving double weight to estimates derived from the same study.
- Studies that compared outcomes in terms of OS, number of deaths, or any other way to evaluate impact on survival.
- Studies that provided sufficient information to estimate hazard ratio (HR) or odds ratio (OR) as measures of relative risk (RR), and 95% confidence interval (CI). This means that eligible studies had to provide either the HR or the OR or crude data and corresponding standard errors, variance, CIs or *p*-value of the significance of the estimates. Where such information was not reported, we estimated the HR from the published survival curves, where available.

Authors of studies published since 1996 were contacted to provide unpublished statistics within subgroups of their studies to allow more accurate analysis and minimise publication bias.

2.3. Description of the studies retrieved

A total number of 6132 records were retrieved using the key words mentioned earlier. Of these 6132 records, 107 articles

were related to pregnancy in breast cancer survivors. We then excluded review articles, case reports, editorials or studies not addressing breast cancer outcome following pregnancy. After applying the secondary exclusion criteria, 30 studies were potentially eligible. We then excluded studies that did not have a control group, or had an inadequate control group and/or studies with insufficient statistical information to estimate survival. In studies that were updated more than once, we used the latest version for our analysis. Lists of the excluded studies are summarised in Appendix 1. Fig. 1 summarises the PRISMA flow chart.

Out of 30 potentially eligible studies, 14 met the eligibility criteria and were included in this meta-analysis.[8–21] Seven studies were control-matched studies,[8–11,15–17] four were population-based studies,[12,14,19,20] and three were hospital-based studies.[13,18,21] Twelve of the 14 studies were published in English, and the remaining 2 were published in French[11] and Icelandic.[16] The results of 12 trials were provided from their original publication whilst updated versions of original papers were used in two studies[11,20] in order to provide longer follow-up results.

2.4. *Statistical analysis*

Every published measure of association and the corresponding 95% CI (if available), were log-transformed and the corresponding variance and standard error were calculated using the formula proposed by Greenland.[22] When estimates were not available from the paper, we calculated them from the published crude data in terms of OR. To obtain the standard error of the log OR, Woolf's formula was used.[23] If only the *p*-value was published then a 'test-based' estimate was considered.[22] Finally if only survival curves were available, the HR, its log-transformation and its standard error were indirectly extracted using the Parmar method.[24]

We used both HR and OR as measures of relative risk (RR). The association between pregnancy and mortality across the selected studies was then computed as pooled RR (PRR) with 95% CI. The PRR was considered statistically significant if the 95% CIs did not include 1.0. PRR was estimated by pooling the study-specific estimates by random effect models fitted using SAS (proc Mixed) with maximum likelihood estimate. These models provided estimates adjusted for the potential correlation within studies as well as the heterogeneity between studies.

The homogeneity of the effect across studies was assessed by using the large sample test based on the Cochrane's Q statistics, which is approximately distributed as a χ^2 statistics. A p-value < 0.10 was used to indicate lack of homogeneity amongst effects. I^2 statistics was also provided to quantify the percentage of total variation across studies that were attributable to heterogeneity rather than to chance.[25] The method of Macaskill et al. was used for assessing publication bias.[26] It consists of a funnel-plot regression of the log HR or log OR on the sample size, weighted by the inverse of the pooled variance.

Subgroup analyses and meta-regression were carried out to investigate heterogeneity between studies focusing on the study characteristics including the country, year of publication, type of study, type of surgery and the health status of the comparator. Further analyses were performed within different subgroups including age categories (<35 and $\geqslant$35 years), nodal status (positive and negative) and time elapsed since breast cancer to diagnosis (6–24 months and >24 months).

In case the published paper did not provide the needed measure of association, they were requested from the corresponding author of studies published since 1996. Only three authors agreed to share their data.[8,20,21] In one study, Kroman and colleagues provided a new version of the Cox model for

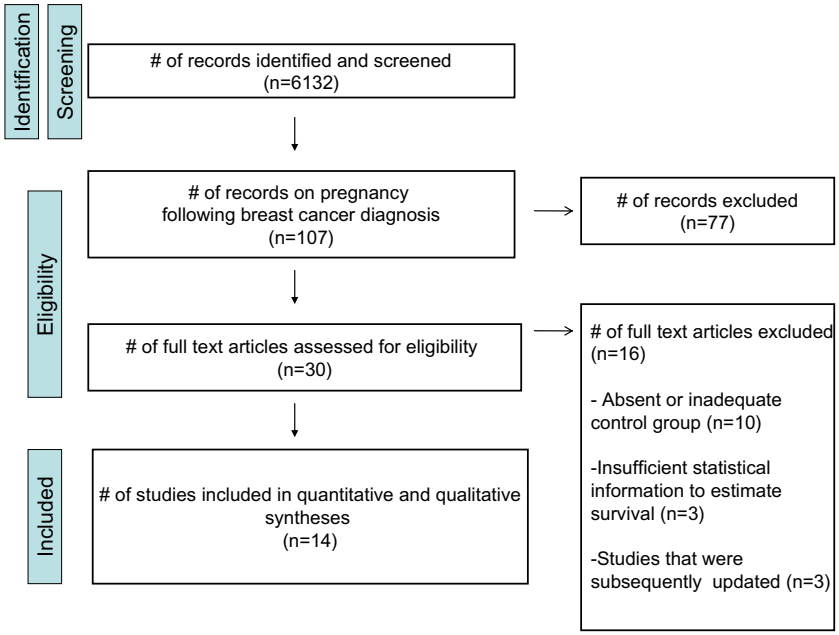

Fig. 1 – PRISMA flow chart.

patients with available information on relapse and with adjustment for relapse as a time-dependent covariate.[20]

To evaluate the influence of individual studies on the PRR, sensitivity analyses were performed by excluding each study individually and recalculating the PRR (data not shown). Further sensitivity analyses were performed by excluding two outliers,[9,21] excluding the largest study[20] and by excluding the studies in which patients were exposed to mastectomy.[10,12,13]

3. Results

3.1. *Characteristics of the trials*

Fourteen studies published between 1970 and 2009 met the inclusion criteria and were included in our analysis.[8–21] A total of 1244 women who became pregnant following breast cancer diagnosis were compared with a control group of 18,145 patients. The number of subjects analysed in the different studies varied from 14-328 in the pregnancy group to 33-10037 in the control group. Table 1 summarises the characteristics of the studies.

Seven studies were control-matched studies.[8–11,15–17] Matching criteria were mainly according to stage, age and year of diagnosis in seven, five and five studies respectively. In four studies,[9,10,16,17] the control group had to have survived a period $\geqslant$ the time to pregnancy of their matching cases. In the remaining three studies,[8,11,15] the control group had to have a recurrence-free survival time $\geqslant$ the time to pregnancy of their matching cases. None of the studies controlled for oestrogen receptor (ER) or HER2 status.

Age at diagnosis was specified in all studies. One study included patients <50,[16] seven studies specified an age $\leqslant$45,[11,12,14,15,17,19,20] one study $\leqslant$42,[8] two studies $\leqslant$40,[9,10] and the remaining three studies included only patients $\leqslant$35 years old.[13,18,21]

Table 1 – Studies comparing overall survival in pregnant and non-pregnant patients.

Study	Year of publication	Country	No. Pregnant	No. Non-pregnant	Outcome of pregnancy	Age at diagnosis	Study design	Matching criteria for choosing controls
Cooper[10]	1970	USA	28	56	Full-term (delivery)	$\leqslant$40	Matched CC	Stage (I/III); N(+/–); age
Mignot[11]	1986	France	68	136	All[c]	$\leqslant$45	Matched CC	Age, year of tumour treatment, TNM status, histology
Ariel[12]	1989	USA	46	900	Unspecified	22–45	Population based	NA
Sankila[9]	1994	Finland	91	471	Full-term (delivery)	<40	Matched CC	Stage (I/III); age; year of BC diagnosis
Malamos[13]	1996	Greece	21	222	All[c]	<35	Hospital based	NA
Lethaby[14]	1996	New Zealand	14	334	Unspecified	<45	Population based	NA
Velentgas[15]	1999	USA	53	265	All[c]	<45	Matched CC	Stage of disease
Birgisson[16]	2000	Iceland	14	33	Full-term (delivery)	<50	Matched CC	Tumour size, nodal status, year of BC diagnosis
Gelber[8]	2001	International	94	188	All[c]	16–42[a]; 22–53[b]	Matched CC	Nodal status, tumour size, age, year of BC diagnosis
Mueller[17]	2003	USA	328	2002	Full-term (Live birth)	<45	Matched CC	Age, race/ethnicity, year of BC diagnosis, stage
Blakely[18]	2004	USA	47	323	All[c]	<35	Hospital based	NA
Ives[19]	2007	Australia	123	2416	All[c]	<45	Population based	NA
Kroman[20]	2008	Denmark	199	10,037	Full-term	<45	Population based	NA
Largillier[21]	2009	France	118	762	Unspecified	<35	Hospital based	NA
Total			1244	18,145				

NR: not reported; CC: case–control; BC: breast cancer; NA: not applicable.

[a] CASES

[b] CONTROLS.

[c] Full term (live birth) and at least one amongst the following: preterm (spontaneous or elective) abortion, miscarriage, ectopic, stillbirth.

3.2. *Overall survival*

Out of the 14 analysed studies, 8 presented the HRs estimated from the Cox model adjusted for several covariates. Three studies presented crude date of the OR calculation, two presented Kaplan–Meier curves and one presented comparison of the median survival and the *p*-value for their difference (Table 2).

Women who became pregnant following breast cancer diagnosis had a significant improvement in OS compared with those who did not become pregnant [PRR: 0.59; CI: 0.50–0.70] (Fig. 2). A look at the individual studies indicates that eight studies demonstrated a significant survival advantage for subsequent pregnancy[8,9,13,17–21] whilst the remaining six had a trend favoring pregnancy but did not reach statistical significance. There was evidence of heterogeneity between the studies ($p = 0.04$; $I^2 = 43.1$) mainly related to the results of two studies that showed marked survival benefit of women who became pregnant following breast cancer.[9,21] When excluded, the results remained the same [PRR: 0.64; CI: 0.55–0.74] with no evidence of heterogeneity ($p = 0.60$; $I^2 = 0$). No evidence of publication bias was detected ($p = 0.47$).

Table 2 – Overall Survival; follow-up duration and RR estimation.

Study	Follow-up duration	RR estimated by	RR within subgroups: from paper	RR within subgroups: obtained from authors
Cooper[10]	5-year OS	Crude data	Nodal status	
Mignot[11]	10-year OS	KM curves		
Ariel[12]	10-year OS	Crude data	Nodal status	
Sankila[9]	15-year OS	Cox's model	Tumour stage, age at diagnosis, time diagnosis-pregnancy	
Malamos[13]	14-year OS[a]	Median survival and *p*-value		
Lethaby[14]	17-year OS	Crude data and *p*-value (Cox)	Nodal status	
Velentgas[15]	15-year OS[a]	Cox's model	Tumour stage	
Birgisson[16]	20-year OS	Crude data from KM curves		
Gelber[8]	10-year OS	Cox's model		Age at diagnosis, time diagnosis-pregnancy
Mueller[17]	17 year-OS[a]	Cox's model	Tumour stage, age at diagnosis, nodal status	
Blakely[18]	22-year OS	Crude data		
Ives[19]	21-year OS	Cox's model	Time diagnosis-pregnancy	
Kroman[20]	30+ year OS	Cox's model		Age at diagnosis, nodal status, time diagnosis-pregnancy
Largillier[21]	10-year OS	Cox's model		Time diagnosis-pregnancy

OS: overall survival; RR: relative risk; KM: Kaplan–Meier.
[a] Reported as maximum follow-up duration.

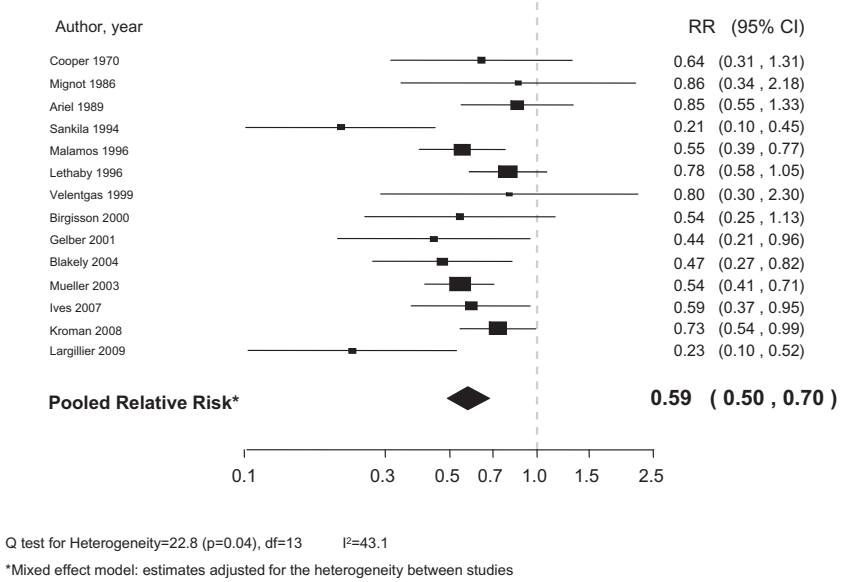

Fig. 2 – Overall survival analysis.

3.3. Subgroup and sensitivity analyses

Several factors that may have induced differences in outcome were investigated with subgroup and meta-regression analyses. The results are summarised in Table 3. The most important source of heterogeneity was the 'healthy mother effect'. Three control-matched studies compared the outcome of women with history of breast cancer who became subsequently pregnant to breast cancer controls who did not get pregnant and were known to be free of relapse.[8,11,15] In addition, we

Table 3 – Heterogeneity subgroups and sensitivity analysis.

Trial	No. of studies	PRR (95% CI)	p-value[a]	I^2 parameter, %	χ^2 for heterogeneity p-value
Sensitivity analysis					
Exclusion of the studies reporting the best results[9,21]	12	0.64 (0.55–0.74)		0	0.6
Exclusion of the largest study[20]	13	0.57 (0.47–0.69)		43.2	0.05
Exclusion of the studies with mastectomy[10,12,13]	11	0.56 (0.44–0.70)		50.5	0.03
Subgroup analysis					
Country					
USA	5	0.60 (0.45–0.80)		0.9	0.4
Europe	6	0.49 (0.30–0.80)		66.2	0.01
Oceania + International	3	0.69 (0.41–1.16)	0.473	17.5	0.3
Year of publication					
<2000	7	0.64 (0.46–0.89)		53.6	0.04
⩾2000	7	0.56 (0.45–0.70)	0.229	27.7	0.22
Outcome of pregnancy[c]					
Only full-term	5	0.55 (0.37–0.81)		58.3	0.05
Full-term + abortion	9	0.62 (0.49–0.77)	0.488	37.3	0.12
Type of studies					
Case–control	7	0.50 (0.37–0.68)		24.8	0.24
Hospital based	3	0.48 (0.26–0.88)		45.7	0.16
Population based	4	0.74 (0.56–0.99)	0.03	0	0.71
Type of estimate					
Crude	5	0.71 (0.56–0.89)		0	0.44
Adjusted	9	0.56 (0.47–0.66)	0.09	49.2	0.046
Follow-up duration (years)					
⩽10	5	0.57 (0.32–1.03)		54.5	0.067
>10	9	0.59 (0.49–0.72)	0.87	43	0.08
Controlling for health status at pregnancy					
Yes[b]	4	0.85 (0.53–1.35)		15.4	0.31
No	10	0.56 (0.44–0.70)	0.038	54	0.02
Age at diagnosis					
<35 years	7	0.55 (0.44–0.68)		38.4	0.14
⩾35 years	3	0.79 (0.34–1.84)	0.226	0	0.97
Time since BC diagnosis to pregnancy (months)					
6–24	5	0.34 (0.13–0.90)		71.5	0.007
>24	5	0.55 (0.36–0.84)	0.584	39.2	0.16
Lymph nodal status at diagnosis					
Negative	5	0.63 (0.41–0.96)		0	0.745
Positive	5	0.96 (0.67–1.37)	0.091	20.8	0.282
Tumour stage at diagnosis					
Local	3	0.40 (0.09–1.77)		57.2	0.097
Regional	3	0.54 (0.25–1.15)	0.921	61.1	0.076

CI, confidence interval; PRR, pooled relative risk.

[a] Significance of factors from meta-regression analysis. The I^2 represents the percentage of total variation across studies that is attributable to heterogeneity rather than chance.

[b] Three matched control studies (Mignot, Velentgas, Gelber): controls were chosen with a recurrence free survival time ⩾interval between diagnosis and pregnancy of cases; 1 population-based study (Kroman). RR for Full-term pregnancy (time-dependent covariate) derived from a Cox model for pt with available information on relapse and with adjustment for relapse (time-dependant covariate).

[c] Full term includes also Live Birth and Delivery; Full-Term + abortion includes full term (live birth) and at least one amongst the following: preterm (spontaneous or elective) abortion, miscarriage, ectopic, stillbirth.

obtained from the Danish group the unpublished RR on restricting the analysis to women with available information on relapse.[20] Introducing relapse in the multivariate analysis as a time-dependent covariate provided a RR of dying for patients with a subsequent pregnancy of 0.98 [95% CI: 0.69–1.39].

The combined analysis of these four studies showed a 15% non-significant reduction in the risk of death for women who subsequently became pregnant [PRR: 0.85; 95% CI: 0.53–1.35] (Fig. 3). This pooled estimate was significantly greater (meta-regression p-value = 0.038) than the one from the

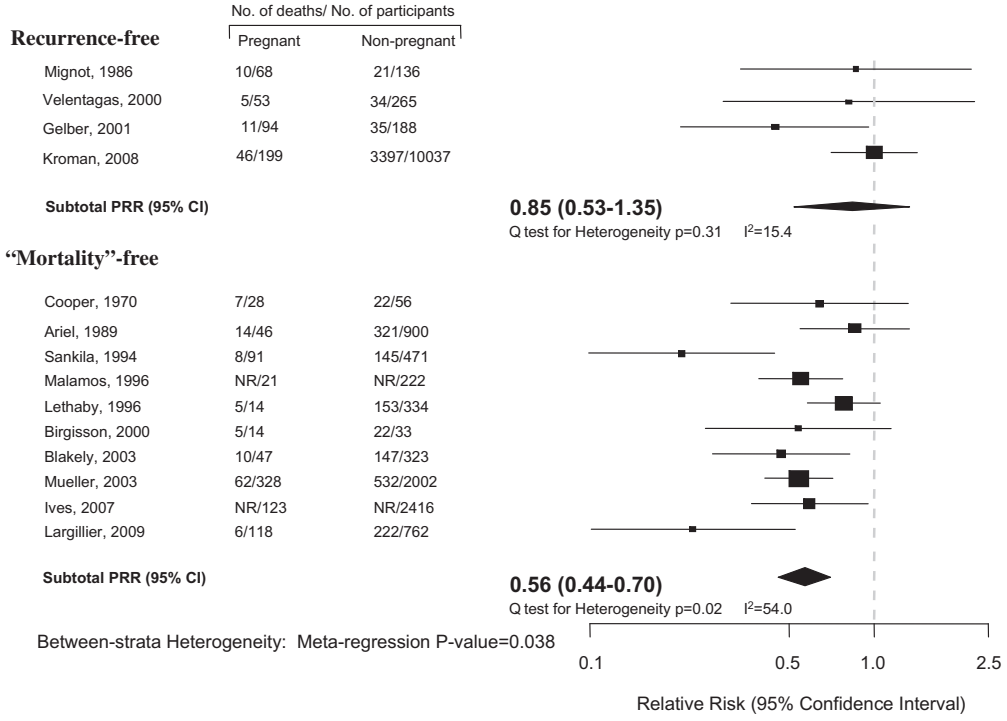

Fig. 3 – Healthy Mother Effect subgroup analysis.

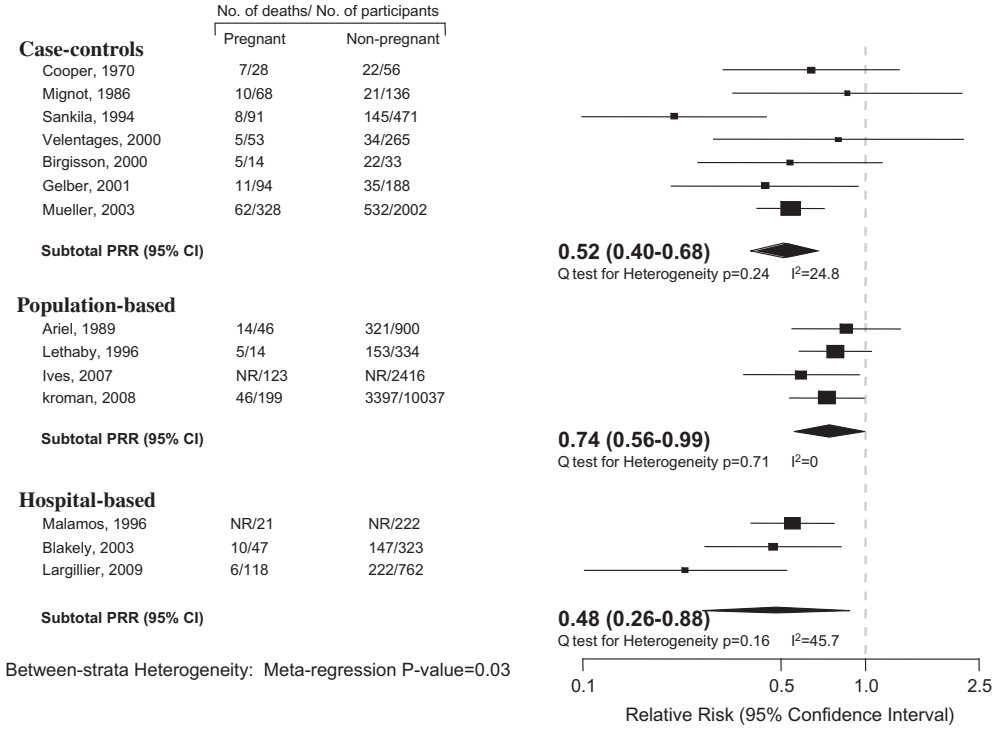

Fig. 4 – Subgroup analysis according to the type of study.

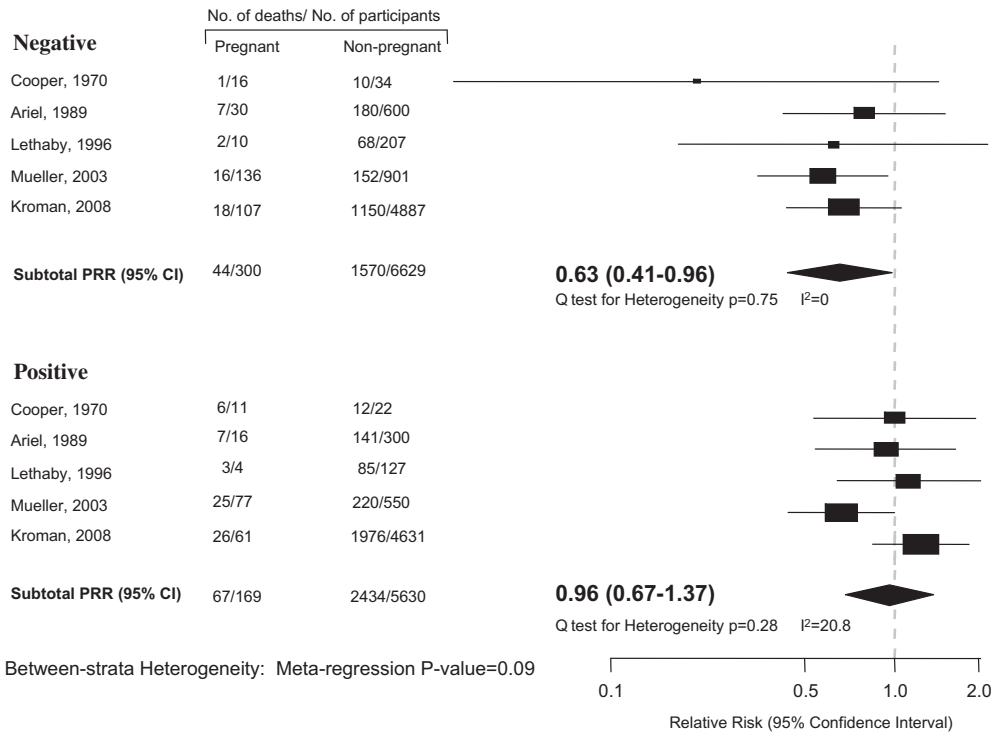

Fig. 5 – Impact of pregnancy on overall survival according to nodal status.

remaining studies where comparators had to 'only' survive at least the interval between diagnosis and pregnancy of the corresponding cases [PRR: 0.56; 95% CI: 0.44–0.70]. Another important source of heterogeneity was the type of study (Fig. 4). Population-based studies presented a significantly (meta-regression p-value = 0.03) higher pooled estimate [PRR: 0.74; 95% CI: 0.56–0.99] than both hospital-based [PRR: 0.48; 95% CI: 0.26–0.88] and control-matched studies [PRR: 0.50; 95% CI: 0.37–0.68]. A minor source of heterogeneity was the follow-up duration ($p = 0.09$), whilst the heterogeneity within the type of estimate (crude versus adjusted) was much higher than the heterogeneity between the strata ($p = 0.087$).

No other factors amongst the study characteristics were found to be potential sources of heterogeneity. Amongst the patients' and tumour characteristics, nodal status was the only source of heterogeneity (Fig. 5). The relative risk of death of patients who became pregnant following breast cancer was remarkably lower amongst those with history of node-negative breast cancer [PRR = 0.63; 95% CI: 0.41–0.96] than those with node-positive disease [PRR = 0.96; 95% CI: 0.67–1.37] (meta-regression p-value = 0.09). The within-subgroup heterogeneity was very small in both strata ($I^2 = 0$ and $I^2 = 20.8\%$ for node-negative and node-positive respectively).

4. Discussion

This meta-analysis evaluated the effect of pregnancy on the OS of women with a history of breast cancer. We found that breast cancer survivors who became pregnant had a significantly reduced risk of death compared with women who were diagnosed with breast cancer but did not become pregnant afterwards. The subgroup analyses have shown that only three factors appear to be able to modify the observed association, which are the 'healthy mother effect', study type and the lymph node status.

In 1994, Sankila and colleagues introduced the term 'healthy mother effect' as a possible explanation for the potential protective effect of pregnancy.[9] To address this concern, we performed a subgroup analysis and restricted the analysis to non-relapsing breast cancer controls. We found that patients who became pregnant following breast cancer diagnosis had a trend towards improved survival but did not reach statistical significance. These results confirm the safety of pregnancy and stimulate the generation of hypotheses that could explain a possible protective effect.

The hormonal milieu of pregnancy represents a mean whereby pregnancy could provide a protective value. Whilst high levels of oestrogen during pregnancy were thought to be a reason to deny breast cancer survivors the opportunity of subsequent conception for fear of stimulating breast cancer recurrence, it is important to realise that hormonal changes during pregnancy are very complex and not solely limited to rise in oestrogen levels. In this context, Asztalos and colleagues have recently provided some insights through analysing the gene expression patterns in the breast following pregnancy.[27] In this study, they showed that parous women have significantly reduced expression of ER-alpha, progesterone receptor and HER2 and a twofold higher ER-beta expression compared with nulliparous subjects. These changes were seen in parous women shortly (0–2 years) and remotely (5–10 years) following pregnancy. These results suggest that pregnancy might confer a protective effect in patients with ER-positive breast cancer. Unfortunately, the lack of information regarding ER-status in the studies analysed hampers the drawing of solid conclusions.

Another hypothesis has been proposed, which has been referred to as 'alloimmunization'[28]. It has been shown previously that foetal cells and breast cancer cells share common antigens. During pregnancy, as the foetal cells circulate normally in the maternal circulation,[29] it is postulated that the immune response exerted by maternal immunity against these cells could act against the dormant cancer cells.[30] However, this remains speculative requiring further validation.

We performed a subgroup analysis to address the optimal time to become pregnant, which remains a very crucial point. We used data from five studies,[10,12,14,17,20] including 187 and 353 patients who became pregnant within 6–24 months and after 2 years of breast cancer diagnosis respectively. We found that pregnancy within 6–24 months following breast cancer diagnosis or beyond did not have an effect on the overall outcome apart from significant heterogeneity observed in the results of the earlier group [I^2: 71.5; $p = 0.007$]. In this context, it is important to point out that epidemiological studies in the general population have shown that pregnancy seems to exert a bidirectional, time-dependent effect on breast cancer. It is protective in the long-term, but in the short-term, tumour incidence and aggressiveness are increased.[31–34] The reason behind the transient increase in breast cancer risk is not very well understood. Some have suggested that the process of breast remodelling following pregnancy is associated with angiogenesis, inflammation and extracellular matrix alterations, which could have stimulatory effects on incipient lesions in the breast.[35] Others have shown that there is a transient increase in the mammary stem cell content following pregnancy reaching up to 11-fold.[36] It is not clear how to integrate this information within the results encountered in our study. Most of the studies analysed in the current analysis had an OS analysis of at least 10 years. Thus, our results mainly reflect the long-term effects of pregnancy. Owing to the reassuring results of patients who got pregnant >2 years following breast cancer diagnosis, and the possible adverse effects of pregnancy and high incidence of tumour recurrence during the first 2 years,[37] a minimum period of 2 years following diagnosis should be allowed before attempting to get pregnant. This would also allow patients to recover from the chemotherapy-induced ovarian toxicity.

For patients with history of ER-positive breast cancer, 5 years of adjuvant hormonal therapy remains the current standard of care and women should complete their treatment period and then consider becoming pregnant. A conflict always remains in those women with ER-positive disease who are willing to interrupt hormonal therapy to become pregnant. These women should be counselled that interruption of hormonal therapy could be detrimental to their breast cancer outcome and therefore is discouraged.

Our study suffers from some limitations that should be taken into consideration when interpreting its results. First, it is based on published data rather than original patient data. Although we tried to collect original information, we were only successful in obtaining data from three studies. Also, none of the studies were controlled for important biological parameters like ER and *HER2*- status. These data were also missing from the original patient records as most of the analysed patients were treated in an era before routine implementation of these markers. To address this point, we are currently conducting a new multi-centric case–control study to investigate the effect of pregnancy on breast cancer outcome according to the ER and *HER2*-status.

Two important relevant issues that deserve emphasis but were not addressed in our study are the pregnancy outcome and the safety of breastfeeding following breast cancer diagnosis. An earlier study by the Danish group showed no excess risk of adverse birth outcome for 216 newborns of women with breast cancer before pregnancy compared with women without breast cancer.[38] A later study from Sweden involving 331 newborns confirmed these findings, but highlighted a higher incidence of preterm birth and low birth weight infants suggesting that pregnancies in women with history of breast cancer should be regarded as 'high risk pregnancies'.[39] On the other hand, the effect of breastfeeding on breast cancer outcome was only addressed in two small studies.[40,41] In both of them, having breastfed after breast cancer was not shown to be detrimental on survival.

In conclusion, while acknowledging that selection bias partly contributes to the reduced risk of death exerted by pregnancy occurring after breast cancer; it is still reasonable to conclude that pregnancy is safe in women with a history of breast cancer. Thus, counselling against pregnancy in these women remains unjustified. We believe that these results could influence the way these women are counselled in breast cancer clinics. Hence, more efforts should be directed towards preserving the fertility of young women who are willing to consider pregnancy following completion of their adjuvant therapies. Patients' preferences regarding their future fertility, and the desire to have a biological child should be critical factors during the decision-making process.[42] As stressed by the American Society of Clinical Oncology (ASCO) recommendation, oncologists dealing with young women with breast cancer should be aware of these concerns and address fertility issues early in the disease course.[43]

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2010.09.007.

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