VOLUME 31 · NUMBER 1 · JANUARY 1 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Prognostic Impact of Pregnancy After Breast Cancer According to Estrogen Receptor Status: A Multicenter Retrospective Study

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Published online ahead of print at www.jco.org on November 19, 2012.

Supported by grants from Les Amis de l'Institut Bordet (Grant No. 2012-09) and the European School of Oncology. H.A.A. Jr and L.D.M.-A. are supported by fellowship grants from the European Society for Medical Oncology. The International Breast Cancer Study Group trial, which provided patient information for this study, was partially funded by the National Institutes of Health (Grant No. CA-753562).

Presented in part at the European Breast Cancer Conference, Vienna, Austria, March 21-24, 2012.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/13/3101-73/$20.00

DOI: 10.1200/JCO.2012.44.2285

## ABSTRACT

### Purpose
We questioned the impact of pregnancy on disease-free survival (DFS) in women with history of breast cancer (BC) according to estrogen receptor (ER) status.

### Patients and Methods
A multicenter, retrospective cohort study in which patients who became pregnant any time after BC were matched (1:3) to patients with BC with similar ER, nodal status, adjuvant therapy, age, and year of diagnosis. To adjust for guaranteed time bias, each nonpregnant patient had to have a disease-free interval at least equal to the time elapsing between BC diagnosis and date of conception of the matched pregnant one. The primary objective was DFS in patients with ER-positive BC. DFS in the ER-negative cohort, whole population, and overall survival (OS) were secondary objectives. Subgroup analyses included DFS according to pregnancy outcome and BC–pregnancy interval. With a two-sided $\alpha = 5\%$ and $\beta = 20\%$, 645 ER-positive patients were required to detect a hazard ratio (HR) = 0.65.

### Results
A total of 333 pregnant patients and 874 matched nonpregnant patients were analyzed, of whom 686 patients had an ER-positive disease. No difference in DFS was observed between pregnant and nonpregnant patients in the ER-positive (HR = 0.91; 95% CI, 0.67 to 1.24, $P = .55$) or the ER-negative (HR = 0.75; 95% CI, 0.51 to 1.08, $P = .12$) cohorts. However, the pregnant group had better OS (HR = 0.72; 95% CI, 0.54 to 0.97, $P = .03$), with no interaction according to ER status ($P = .11$). Pregnancy outcome and BC–pregnancy interval did not seem to impact the risk of relapse.

### Conclusion
Pregnancy after ER-positive BC does not seem to reduce the risk of BC recurrence.

*J Clin Oncol 31:73-79. © 2012 by American Society of Clinical Oncology*

## INTRODUCTION

With advancements in local and systemic adjuvant therapies, there has been a continuous decline in recurrence rates and risk of death secondary to breast cancer (BC).[1] This has led to more attention given to quality of life and survivorship issues, particularly for those diagnosed at a relatively young age.[2,3]

Over the past decade, there has been an increasing trend of women delaying childbearing.[4] This has resulted in more patients with BC inquiring about fertility-related issues and whether a subsequent pregnancy could alter their risk of disease recurrence after completion of adjuvant therapy.[5] Recent evidence suggests that 40% to 50% of women with history of BC may wish to have a subsequent pregnancy.[6] However, only 4% to 7% manage to become pregnant,[7] which emphasizes the need to improve the quality of available evidence to help counseling these women.

Recently, we conducted a large meta-analysis and found that pregnancy after BC diagnosis reduces the risk of death by 41%.[8] However, such reduced risk is likely confounded by a selection bias, known as the "healthy mother effect."[9] Indeed, patients who become subsequently pregnant are mostly patients with no evidence of relapse. Hence the improved outcome observed in the pregnant group could be a reflection of selecting nonrelapsing patients and not due to a true effect of pregnancy on BC outcome.

Nevertheless, few biologic hypotheses were suggested favoring a real protective effect of subsequent pregnancy. Preclinical models have shown that high estrogen levels after estrogen deprivation induces apoptosis in ER-positive BC cell lines.[10] In addition, fetal michrochimerism was suggested to act as an immunologic boost for patients previously exposed to tumor-associated antigens.[11] Despite that, there are still concerns about a possible negative impact of subsequent pregnancy, particularly in patients with history of an endocrine-sensitive BC. None of the previous studies had the information or the power to allow a subgroup analysis according to estrogen receptor (ER) status. These uncertainties have contributed to more BC survivors being advised against pregnancy, with induced abortion rates reported to be in the range of 30%.[12-14] This reflects the doubt and fear faced not only by patients, but also by their treating physicians.

In this study, we tried to address the limitations highlighted earlier by conducting an a priori powered matched study in patients with known ER status, which was corrected as much as possible for selection bias.

## PATIENTS AND METHODS

### Study Design

This was a retrospective cohort study in which patients with known ER status who became pregnant anytime after BC diagnosis were matched with patients with BC who did not become subsequently pregnant. This study took place in five European hospitals (European Institute of Oncology [Milan], Jules Bordet Institute [Brussels], Vall D'Hebron University Hospital [Barcelona], Macerata Hospital [Macerata] and La Paz University Hospital [Madrid]), in addition to the Danish Breast Cancer Cooperative Group (DBCG). We also collected original information from a previously published study that had a similar design to the current study,[13] although in the former, outcome according to ER status was not investigated.

A retrospective search was carried out in the databases of all participating sites before December 31, 2007, to identify women who were younger than 50 years at the time of BC diagnosis. Potentially eligible patients had to have had primary nonmetastatic BC with known ER status. Patients who were diagnosed with BC during pregnancy or those who experienced relapse before subsequent pregnancy were excluded. Patients were then divided into two groups: (1) patients who became pregnant after BC diagnosis (ie, exposed; will be referred to as "pregnant"); and (2) patients who did not become subsequently pregnant (ie, nonexposed; will be referred to as "nonpregnant").

To reduce the impact of selection bias (in other words; guaranteed time bias), we ensured that each nonpregnant patient had a disease-free interval (DFI) equal to or longer than the interval between BC diagnosis and conception of the matched pregnant one. The following events were considered in defining DFI: local relapse, distant relapse, secondary cancer, and death from any cause.

To investigate the independent effect of pregnancy on outcome, we attempted to control for the following factors in a descending order: ER, nodal status, adjuvant chemotherapy, adjuvant hormonal therapy, age ($< 35$ or $\geq 35$ years), and year of diagnosis (difference up to 5 years).

Matching was performed within each institution with the aim to obtain three nonpregnant patients for each pregnant one. If there were only one or two nonpregnant patients available, matching criteria were relaxed until other patients were found. If three matches were not found even after relaxing the criteria, we allowed two or even one patient, in an effort to include as many pregnant women in the study. Patients identified as nonpregnant were contacted by telephone or mail to confirm that they did not become pregnant any time after BC diagnosis. In case the patient was dead at the time of contact, available family members provided the needed information. In case of the DBCG, the status of the nonpregnant patients was confirmed using the files linked to the Danish National Registry.

All information was collected using a unified case report form and was provided to the data center at the Jules Bordet Institute in Brussels for data cleaning and statistical analysis. The study was approved by the ethics committee of the Jules Bordet Institute, which acted as the central ethics committee for the study. Per their local regulations, all institutions provided approval to use the required data for the sake of this study.

### Sample Size Calculation and Statistical Analysis

The primary objective was disease-free survival (DFS) between pregnant and nonpregnant patients with ER-positive BC. Secondary objectives included DFS in the ER-negative cohort and overall population, in addition to overall survival (OS). Predefined subgroup analyses included differences in DFS according to pregnancy outcome (ie, completed pregnancy $\nu$ abortion), BC–pregnancy interval (ie, $< 2$ $\nu$ $\geq 2$ years), and breastfeeding status (ie, yes $\nu$ no).

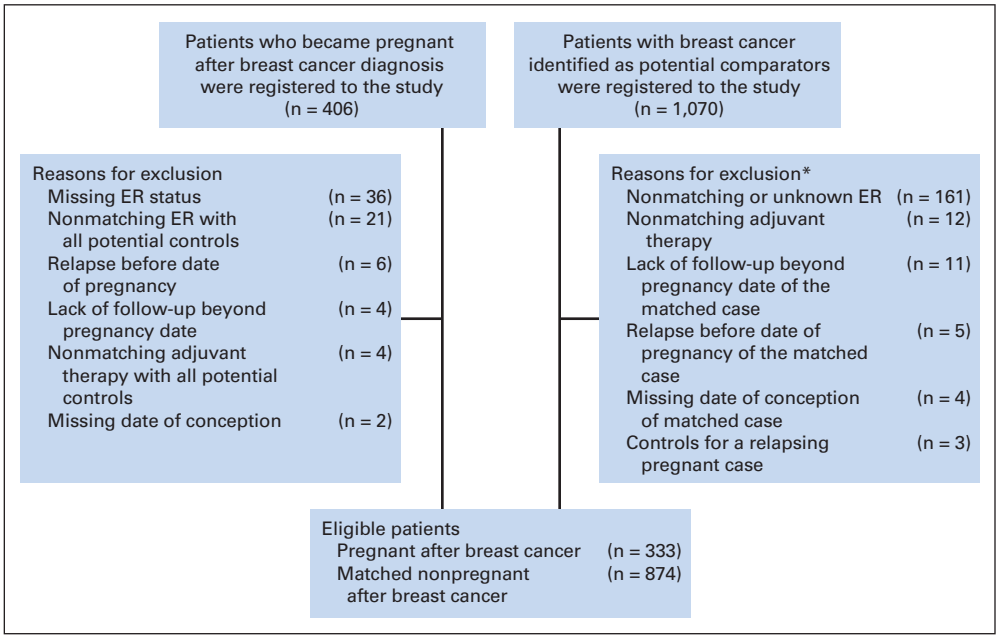


**Fig 1.** CONSORT diagram summarizing patients eligible for the study. (*) Some patients in the comparator group had more than one reason for exclusion but were considered once. ER, estrogen receptor.

It was difficult to determine a realistic assumption for the hazard ratio (HR) between the pregnant and nonpregnant cohorts, as previous studies were mostly confounded by selection bias and have mainly used OS rather than DFS as an outcome. Hence we reverted to a combined analysis of four studies that was adjusted for selection bias, which showed an HR for OS of 0.85 in favor of the pregnant group,[8] yet this was not adjusted for receptor status. We opted to power the study to observe a protective effect in pregnant patients with ER-positive BC, which would allow us to examine the effect of pregnancy on BC outcome according to ER status. We estimated the required sample size to be able to detect an HR less than 1 for DFS in favor of the pregnant cohort with ER-positive disease. A power of 80% was targeted in case of a true HR of $\leq 0.65$ using a two-sided significance level of 5%. Based on this model, 226 events were required. Assuming that approximately 35% of patients will develop a DFS event, we sought to include at least 645 patients with ER-positive BC. According to the study design, this would allow the inclusion of 161 pregnant patients with ER-positive disease.

On the basis of the inclusion criteria of the study, all patients who became pregnant were to be disease-free at the time of conception. To examine the prognostic impact of pregnancy, DFS was calculated from the date of conception until a local, regional, or distant recurrence; the development of secondary cancer; or death. In the nonpregnant patients, DFS was calculated from the date of diagnosis, adding the time elapsing between diagnosis and conception of the matched pregnant case. All institutions provided the dates of BC diagnosis, conception (in pregnant women), and relapse or death or end of follow-up. If any of these dates were missing, the case was excluded.



**Table 1.** Patients Characteristics

| Characteristic | Pregnant | | Nonpregnant | | *P* |
|---|---|---|---|---|---|
| | No. | % | No. | % | |
| No. of patients | 333 | | 874 | | |
| Year of diagnosis, range | 1977-2007 | | 1978-2007 | | |
| Age, years | | | | | < .001 |
| Mean | 32 | | 35 | | |
| Standard deviation | 4 | | 5 | | |
| Median | 31 | | 34 | | |
| Range | 21-44 | | 22-48 | | |
| Tumor size, cm | | | | | .90 |
| ≤ 2 | 185 | 55.5 | 500 | 57 | |
| > 2 | 135 | 40.5 | 359 | 41 | |
| Unknown | 13 | 4 | 15 | 2 | |
| Nodal status | | | | | .91 |
| Negative | 188 | 57 | 498 | 57 | |
| Positive | 144 | 43 | 376 | 43 | |
| Histologic grade | | | | | .68 |
| 1 | 37 | 11 | 103 | 12 | |
| 2 | 96 | 29 | 253 | 29 | |
| 3 | 114 | 34 | 346 | 39 | |
| Unknown | 86 | 26 | 172 | 20 | |
| Estrogen receptor status | | | | | .54 |
| Negative | 139 | 42 | 382 | 44 | |
| Positive | 194 | 58 | 492 | 56 | |
| HER2 status | | | | | .58 |
| Negative | 32 | 9.5 | 70 | 8 | |
| Positive | 35 | 10.5 | 90 | 10 | |
| Unknown | 266 | 80 | 714 | 82 | |
| Adjuvant chemotherapy | | | | | .34 |
| No | 69 | 21 | 160 | 18 | |
| Yes | 264 | 79 | 714 | 82 | |
| Adjuvant hormonal therapy | | | | | .97 |
| No | 210 | 63 | 584 | 67 | |
| Yes | 86 | 26 | 238 | 27 | |
| Unknown | 37 | 11 | 52 | 6 | |
| Duration, months | () | | () | | |
| Median | 60 | | 60 | | |
| Range | 6-69 | | 7-96 | | |
| Type of breast surgery | | | | | .02 |
| Mastectomy | 167 | 50 | 503 | 58 | |
| Conservative breast surgery | 166 | 50 | 371 | 42 | |
| Follow-up from time of conception in years | | | | | .47 |
| Median | 4.7 | | 4.7 | | |
| 95% CI | 4.4 to 5.3 | | 4.3 to 5.1 | | |
| Interquartile range | 3.1-6.9 | | 2.5-7.2 | | |

Abbreviation: HER2, human epidermal growth factor receptor 2.

Analysis was done by fitting the data in Cox regression semiparametric models in the different planned subgroups and estimating the HRs for pregnant patients compared with nonpregnant with the maximum likelihood method (an observed HR < 1 means that the pregnant patients have a lower risk of relapse or death compared with the nonpregnant patients). CIs at 95% were reported together with point estimations of the HRs. Homogeneity tests on the HRs obtained in the planned subgroups were carried out to assess the possible interactions between pregnancy status and any of the following factors: ER status, nodal status, age, delay between diagnosis and pregnancy, adjuvant chemotherapy, and adjuvant hormonal therapy.

Survival plots were drawn using the Kaplan-Meier method, and the differences were evaluated using the log-rank test. Reported *P* values are two sided, with *P* values less than .05 considered as statistically significant. Statistical analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC).

## RESULTS

### Patient Characteristics

A total of 1,476 patients were registered to the study, of whom 406 patients became pregnant after BC diagnosis. After data cleaning, 269 patients were excluded for various reasons (Fig 1), resulting in 1,207 patients (333 pregnant and 874 nonpregnant) eligible for the analysis. Patient characteristics are summarized in Table 1.

Nearly 60% of the patients were recruited from the DBCG registry (Appendix Table A1, online only). Patients who became subsequently pregnant were younger (median age, 31 *v* 34 years; $P < .001$) and were more likely to have undergone breast-conserving surgery (50% *v* 42%; $P = .02$). A total of 686 patients (57%) had ER-positive BC, 194 and 492 in the pregnant and nonpregnant groups, respectively. No information was available on previous parity or the use of assisted reproductive technologies (ART).

### Survival Analysis

In the pregnant group, the median time from BC diagnosis to conception was 2.4 years. The median follow-up from conception for the pregnant group or a similar time point for the nonpregnant group was 4.7 years (interquartile range, 3.1 to 6.9 years) and 4.7 years (interquartile range, 2.5 to 7.2 years), respectively, with no differences according to ER status. Overall, 354 patients (29.3%) experienced a DFS event, with no differences in event rates observed between the ER-positive (n = 199; 29%) and ER-negative (n = 153; 30%) cohorts.

In patients with ER-positive BC, no difference in DFS was observed between those who became pregnant after BC diagnosis and the matched nonpregnant group (HR = 0.91; 95% CI, 0.67 to 1.24; $P = .55$; Fig 2A). The same observation was made when the analysis was restricted to patients with ER-negative disease (HR = 0.75; 95% CI, 0.51 to 1.08; $P = .12$) or when considering all patients irrespective of ER status (HR = 0.84; 95% CI, 0.66 to 1.06, $P = .14$; Figs 2B and 2C).

Regarding the OS analysis, the pregnant group showed a better OS (HR = 0.72; 95% CI, 0.54 to 0.97, $P = .03$), with no interaction observed according to ER status ($P = .11$; Figs 3A to 3C).

### Subgroup Analysis

*Pregnancy outcome.* Pregnancy outcome was unknown in 10 patients, and hence 323 patients (97%) were eligible for this analysis and were compared with 856 patients (98%) who did not become subsequently pregnant. We did not find any difference in DFS between patients who completed their pregnancy to term and their matched group (HR = 0.79; 95% CI, 0.57 to 1.08; $P = .14$; Fig 4A).

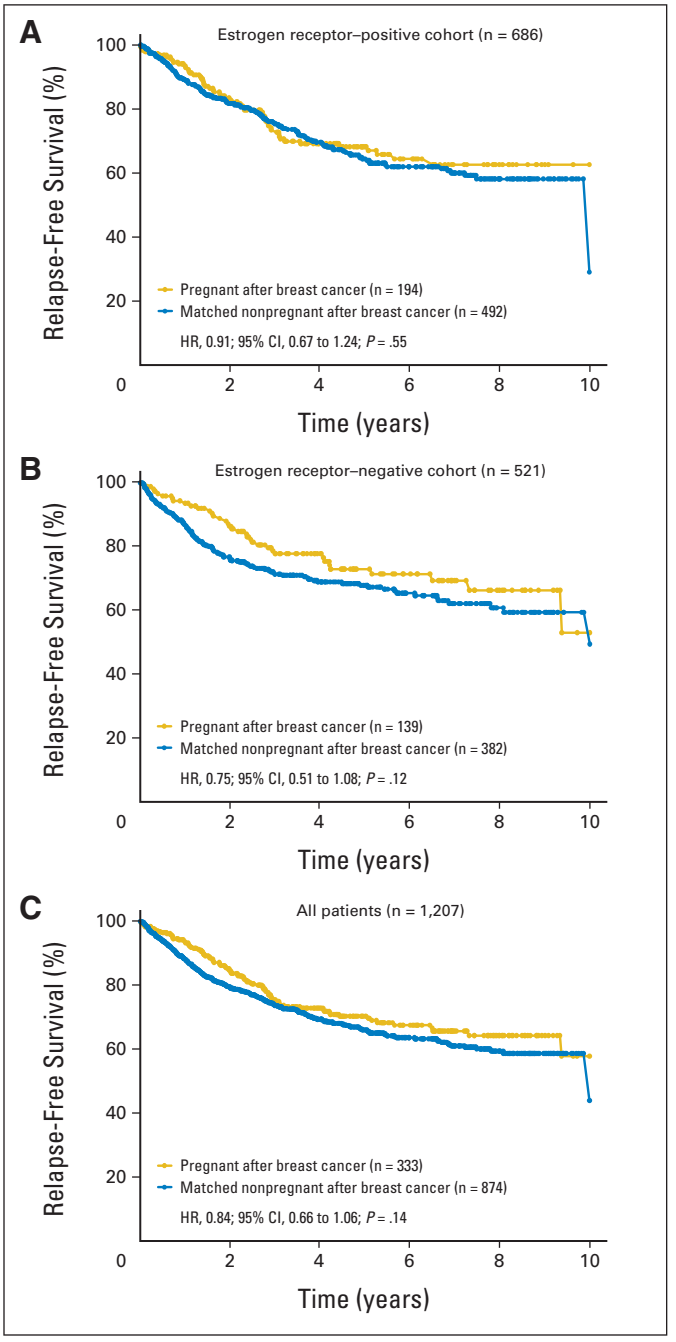


**Fig 2.** Differences in disease-free survival between the pregnant group and matched nonpregnant group. (A) Estrogen receptor (ER) –positive cohort; (B) ER-negative cohort; (C) all patients. Hazard ratios (HRs) with 95% CIs are provided. *P* values are calculated using the log-rank test.

The same results were observed when comparing the outcome of patients who had an abortion or miscarriage and their matched group (HR = 0.87; 95% CI, 0.58 to 1.31; $P = .5$).

*Time to pregnancy after BC diagnosis.* We found no difference in DFS between patients who became pregnant ≥ 2 years from BC diagnosis and their matched group (HR = 1.13; 95% CI, 0.64 to 1.98; $P = .68$; Fig 4B). To the contrary, those who became pregnant within 2 years of BC diagnosis had a better DFS (HR = 0.56; 95% CI, 0.34 to

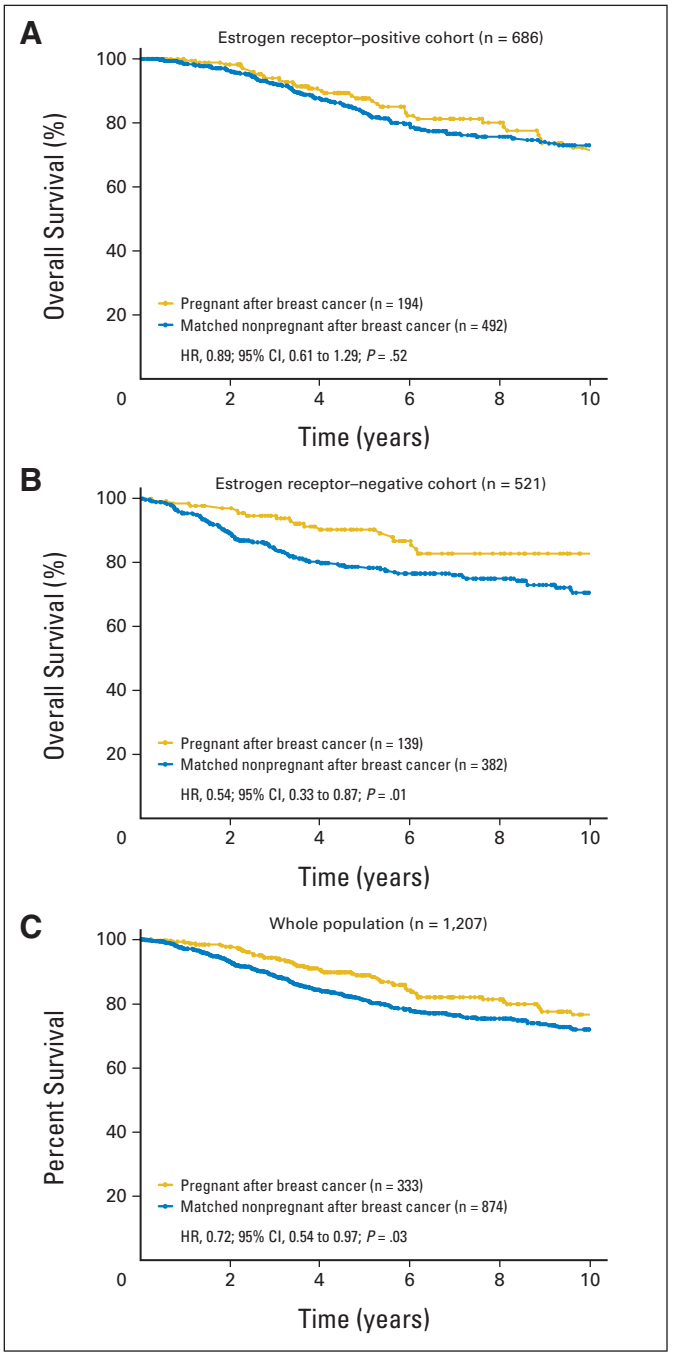


**Fig 3.** Differences in overall survival between the pregnant group and the matched nonpregnant group. (A) Estrogen receptor (ER) –positive cohort; (B) ER-negative cohort; (C) all patients. Hazard ratios (HRs) with 95% CIs are provided. *P* values are calculated using the log-rank test.

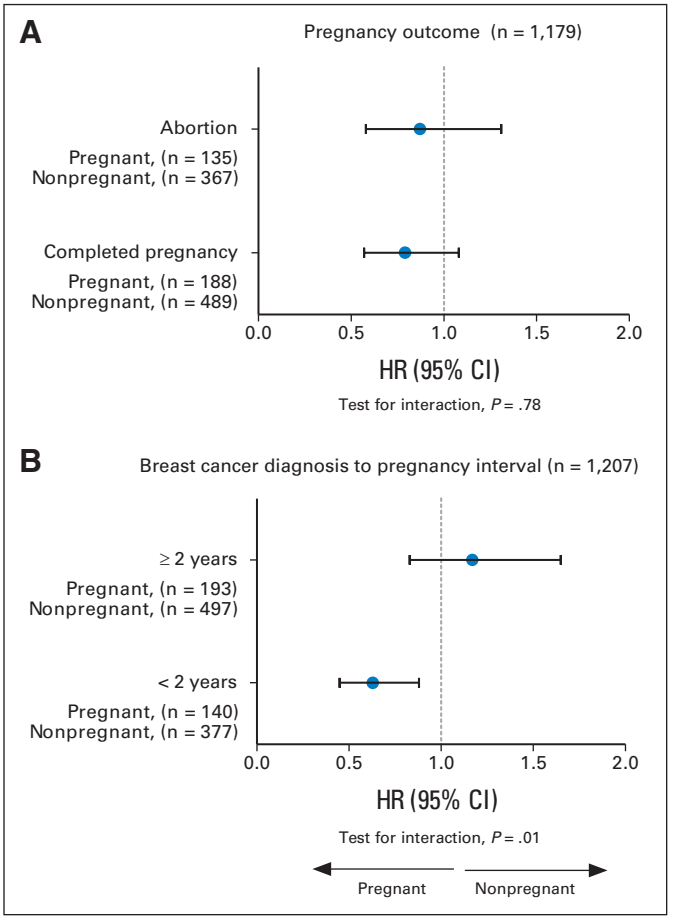


**Fig 4.** Forest plots of predefined subgroup analyses. Dotted lines represent a hazard ratio (HR) of 1.0, and error bars represent 95% CI. (A) Pregnancy outcome (completed pregnancy *v* induced abortion and miscarriage); (B) breast cancer diagnosis to pregnancy interval (< 2 *v* ≥ 2 years). The *P* value of interaction is provided.

0.92; $P = .02$) with a significant interaction ($P = .01$) but no interaction according to ER status ($P = .84$).

To determine whether this was a true protective effect of early pregnancy or the result was confounded by some sort of bias, we compared the DFS of the nonpregnant patients who were matched to women who became pregnant before or after 2 years from BC diagnosis. We found that the nonpregnant group who were matched to the early pregnancy cohort (ie, < 2 years) had a significantly lower DFS ($P < .001$) even after adjustments for ER, tumor size, nodal status, histologic grade, and use of adjuvant chemotherapy (HR = 2.2; 95% CI, 1.7 to 2.8; $P < .001$; Appendix Fig A1, online only). Although the selection of the nonpregnant patients was random, it seemed that those with relatively long DFI were more likely to be matched with patients who became pregnant after 2 years since BC diagnosis.

We performed a similar analysis in the pregnant patients, but no difference in DFS was observed ($P = .45$), even after adjustment for the same covariates (HR = 1.1; 95% CI, 0.78 to 1.7; $P = .43$; Appendix Fig A1). These analyses suggest that the improved outcome in the early pregnancy group could be the result of selection bias rather than a true protective effect.

*Breastfeeding status.* We had information on breastfeeding only for 64 patients, of whom 25 breastfed their newborns, whereas 39 did not. The low number of patients did not allow adequate statistical analysis.

## DISCUSSION

In this study, we addressed for the first time the prognostic impact of subsequent pregnancy in women with a history of an endocrine-sensitive BC. The main analysis indicated that pregnancy did not seem

to be protective against BC recurrence in patients with an endocrine-sensitive disease. Although we included a higher number than planned of pregnant patients with ER-positive disease (194 *v*161), the event rate was lower than expected (29% instead of 35%), which slightly reduced the power of the study (75% instead of 80%). However, the DFS analysis in the ER-positive population indicated that subsequent pregnancy is not detrimental. In addition, the pregnant group had a better OS independent of ER status. These findings point out that pregnancy after BC diagnosis could be considered safe in women with history of an ER-positive disease.

Apart from the safety of subsequent pregnancy, previous studies failed to show convincing evidence regarding other relevant questions such as the therapeutic role of induced abortion and the optimal time to become subsequently pregnant. Consistent with earlier studies,[12-14] we found that approximately 30% of patients who became pregnant after BC diagnosis had an induced abortion. However, we did not find that abortion had an effect on BC outcome, irrespective of ER status. Hence, based on these findings, abortion should not be promoted for therapeutic reasons. On the other hand, we found no difference in DFS between patients who became pregnant within 2 years of BC diagnosis and those who became pregnant afterward. Of note, the study was not powered to provide a definitive answer for these end points, which should be taken into account. However, to the best of our knowledge, this is the largest matched study that addresses these questions.

Limited information was available about breastfeeding in our study. Previous reports have shown that breastfeeding after BC seems to be associated with relatively low rate of BC-related events.[15,16] However, neither included a comparator group to allow proper evaluation of the safety of breastfeeding. Hence further studies are needed to elucidate the impact of breastfeeding on BC outcome in these patients.

Our study nevertheless has some limitations. The study was designed to show a protective effect of pregnancy rather than equivalence or absence of harmful effect, which is probably more clinically relevant. However, the feasibility of conducting a noninferiority trial in this setting is low. In addition, we wanted to confirm whether a true protective effect exists. Although our results failed to demonstrate any definite protective effect from pregnancy subsequent to the diagnosis of BC, there was no evidence of a deleterious effect either. Another limitation was the large number of patients who had missing information on HER2 status (80%). This is secondary to inclusion of patients who were diagnosed before routine testing of HER2.

The retrospective nature of the study hindered us from accurately registering the number of required events and from completely ruling out the impact of selection bias. However, it is important to note that addressing the impact of subsequent pregnancy on BC prognosis in a prospective randomized trial is impossible, and thus we will have to rely on data from large, well-conducted retrospective studies.

No information was available on the use of ART in patients who became subsequently pregnant in our study. However, this study included patients who were diagnosed with BC before 2008, the time when none of the participating sites were routinely offering ART for patients with BC. In addition, we lack strong evidence linking the use of ART to BC recurrence[17] or the risk of developing BC in the general population.[18,19] Hence it is unlikely that the absence of information on ART in this study would have significant implications on the interpretation of our findings.

Our study was not designed to address the feasibility and safety of early interruption of hormonal therapy in patients with endocrine-sensitive disease. Patients in both groups (ie, pregnant and nonpregnant) received a median duration of standard 60 months of hormonal therapy. However, not all patients with ER-positive disease received hormonal therapy, which was possibly due to the inclusion of patients diagnosed before routine implementation of adjuvant hormonal therapy in young women. Hence until further data are available, women should be advised to complete adequate hormonal therapy before considering becoming pregnant. This remains rather challenging for some patients, as chances of pregnancy could be low after 5 years of tamoxifen.[20-23] Currently, the Breast International Group and the North American Breast Cancer Group are launching a study to provide guidance about adopting customized strategies for patients who wish to become pregnant before completion of classic endocrine therapy.[23]

In conclusion, this study indicated that pregnancy is not protective against BC recurrence in women with a history of an endocrine-sensitive BC at least during the first 5 years after pregnancy. However, the results are rather reassuring for a lack of detrimental effect irrespective of ER status. We believe that our study adequately addressed many of the limitations of previous studies and hence would be highly relevant to the counseling of young women wishing a pregnancy after BC diagnosis.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

## AUTHOR CONTRIBUTIONS

**Conception and design:** Hatem A. Azim Jr, Marianne Paesmans, Martine J. Piccart, Fedro A. Peccatori
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**Final approval of manuscript:** All authors

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