Society of Medical Education & Research

2024, Volume 4, Issue 1, Page No: 81-92
ISSN: 3108-4834

Archive of International Journal of Cancer and Allied Science

Pregnancy Outcomes and Prognosis in Young Women with Hormone Receptor-Positive Breast Cancer: A Systematic Review and Meta-Analysis

Daniel Patrick O'Connor[1], Sean Michael Byrne[1], Lauren Jane Evans[1]

[1]Department of Oncology, University College Dublin, Dublin, Ireland.

***E-mail** ✉ dan.oconnor.ucd@gmail.com

Abstract

The decision to pursue pregnancy after breast cancer treatment raises concerns, particularly in women with hormone receptor-positive tumors, due to fears of recurrence or compromised survival. Despite growing evidence suggesting safety, uncertainty persists among both patients and clinicians. A comprehensive search of Medline, Embase, and Cochrane Library was performed through 31 March 2023 without restrictions on date or language. Studies eligible for inclusion were retrospective or prospective cohort and case-control studies, as well as clinical trials, comparing survival outcomes in premenopausal women who did or did not experience pregnancy following a diagnosis of hormone receptor-positive breast cancer. Key outcomes analyzed were disease-free survival (DFS) and overall survival (OS). Data were pooled using hazard ratios (HRs) with 95% confidence intervals (CIs). The study protocol was registered in PROSPERO (CRD42023394232).Of 7796 records screened, eight studies met inclusion criteria, totaling 3805 women, including 1285 who became pregnant after breast cancer. Median follow-up ranged from 3.8 to 15.8 years and was similar across pregnancy and non-pregnancy groups. Analysis of three studies (n = 987) reporting DFS revealed no significant difference between the two groups (HR 0.96, 95% CI 0.75–1.24, P = 0.781). In six studies (n = 3504) reporting OS, pregnancy was associated with a significantly lower risk of death compared to women who did not conceive (HR 0.46, 95% CI 0.27–0.77, P < 0.05).These findings indicate that pregnancy after hormone receptor-positive early breast cancer does not compromise survival and may even improve overall outcomes. Women with a history of this breast cancer subtype can be reassured about the safety of post-treatment pregnancy.

Keywords: Breast cancer, Hormone receptor-positive, Pregnancy, Premenopausal, Survival, Oncofertility

Introduction

Breast cancer is the leading malignancy among women of reproductive age, and advances in treatment have significantly increased survival rates, making young breast cancer survivors one of the largest groups among early-onset cancer survivors [1-3]. As a result, long-term survivorship has become a vital focus in the management of these patients [4, 5].

Access this article online https://smerpub.com/

Received: 26 November 2023; **Accepted:** 19 February 2024

How to cite this article: O'Connor DP, Byrne SM, Evans LJ. Pregnancy Outcomes and Prognosis in Young Women with Hormone Receptor-Positive Breast Cancer: A Systematic Review and Meta-Analysis. Arch Int J Cancer Allied Sci. 2024;4(1):81-92. https://doi.org/10.51847/09JqoaN4Lx

For women who wish to have children, anticancer therapies can lead to premature ovarian insufficiency (POI) and reduced fertility, which substantially affect quality of life and limit the likelihood of pregnancy after breast cancer [6-8].

With the trend of delayed first pregnancies and the rising incidence of young-onset breast cancer worldwide, an increasing number of women are diagnosed before completing their reproductive plans [9]. Counseling regarding fertility risks and available preservation strategies is therefore an essential part of oncofertility care for all reproductive-age patients [5].

Recent studies indicate that pregnancy, whether spontaneous or achieved through fertility preservation methods, can generally be safe after breast cancer treatment [8, 10, 11]. However, certain patient populations remain areas of concern. Specifically,

questions persist about the safety of pregnancy after hormone receptor-positive early breast cancer. These patients typically undergo endocrine therapy for 5–10 years, during which pregnancy is not recommended, historically leading to delayed conception and a narrower fertility window [12-18].

In addition, since hormone receptor-positive breast cancer is sensitive to hormonal stimulation and pregnancy induces high levels of estrogen and progesterone, there is concern that pregnancy could increase recurrence risk [19, 20]. This subtype also carries a persistent long-term recurrence risk, necessitating extended follow-up to evaluate safety thoroughly [21, 22].

Several retrospective cohort studies have explored outcomes of pregnancy in women previously treated for hormone receptor-positive early breast cancer [23, 24]. The prospective POSITIVE trial, which examined temporary interruption of adjuvant endocrine therapy to allow pregnancy, recently reported that this approach appears safe during short-term follow-up [25]. However, the trial primarily included patients with stage I–II disease (only 6% stage III) and had limited follow-up (41 months), which may not capture long-term recurrence risks in this population.

Consequently, concerns about potential adverse effects of pregnancy persist, and some patients continue to be advised against conception despite accumulating evidence supporting safety [19, 26].

This systematic review and meta-analysis aim to provide updated evidence on the safety of pregnancy following diagnosis and treatment of hormone receptor-positive early breast cancer.

Materials and Methods

Literature search and eligibility

This study was conducted as a systematic review and meta-analysis following the PRISMA guidelines [27]. We searched Medline, Embase, and the Cochrane Library for all relevant publications up to 31 March 2023, without limiting by language or date. The search strategy included terms related to breast cancer and pregnancy: ("breast neoplasms" [MeSH Terms]) AND (("pregnancy" [MeSH Terms]) OR ("pregnancies" [MeSH Terms]) OR ("conception" [MeSH Terms]) OR ("gestation" [MeSH Terms])). Additional studies were identified by reviewing the references of relevant articles to ensure comprehensive coverage.

To be included, studies needed to meet the following criteria: (i) retrospective or prospective cohort or case-control studies, or clinical trials, comparing survival outcomes between women who experienced a pregnancy after hormone receptor-positive early breast cancer and those who did not; (ii) reporting at least one of the outcomes of interest—overall survival (OS), disease-free survival (DFS), or breast cancer recurrence; and (iii) presenting hazard ratios (HRs) with 95% confidence intervals (CIs) or providing sufficient data to calculate them.

Studies were excluded if they: (i) were case reports or small series with fewer than 10 participants; (ii) focused on breast cancer diagnosed during pregnancy or within one year postpartum without data on post-treatment pregnancies; or (iii) were ongoing studies without available results at the time of the search. The review protocol was registered in PROSPERO (CRD42023394232).

Study aim

The main goal of this analysis was to evaluate whether pregnancy after diagnosis and treatment of hormone receptor-positive early breast cancer affects survival outcomes, specifically OS, DFS, and the risk of recurrence.

Data extraction and management

Two independent reviewers (LA and MML) screened the literature, extracted data, and resolved discrepancies through discussion with a third reviewer (EB). Extracted information included: author, year of publication, study design and methodology, cohort sizes, number of women who became pregnant, survival outcomes, and methods used to control for confounders. For studies with multiple publications, only the most recent data were considered.

Risk of bias assessment

The methodological quality and potential bias of the included studies were evaluated using the Newcastle–Ottawa Scale (NOS) [28]. This tool assigns up to 9 points across three domains of bias for cohort or case-control studies. Based on their scores, studies were categorized as having low, moderate, or high risk of bias.

Statistical analysis

Hazard ratios (HRs) with 95% confidence intervals (CIs) were extracted from the eligible studies. If HRs were not directly reported but sufficient event data were available,

HRs were estimated using the approach described by Watkins and Bennett [29]. Studies lacking HRs or insufficient data for calculation were excluded from that particular analysis.

Pooled HRs and corresponding 95% CIs were calculated using a random-effects model following the DerSimonian and Laird method [30]. Statistical heterogeneity across studies was quantified using the Higgins I^2 statistic [31]. Potential publication bias was assessed with Egger's test [32]. A P value <0.05 (two-sided) was considered statistically significant.

To verify the robustness of the findings, sensitivity analyses were performed to determine whether any single study disproportionately influenced the pooled results. All statistical analyses were conducted using Stata version 13.1 (StataCorp LP, College Station, TX) by MB and EB.

Results and Discussion

From the 7796 records initially identified, 8 studies met all eligibility criteria and were included in the meta-analysis **(Figure 1)** [10, 23, 24, 33-37]. Across these studies, 3805 women with hormone receptor-positive invasive early breast cancer were evaluated, of whom 1285 experienced a post-treatment pregnancy and 2520 did not.

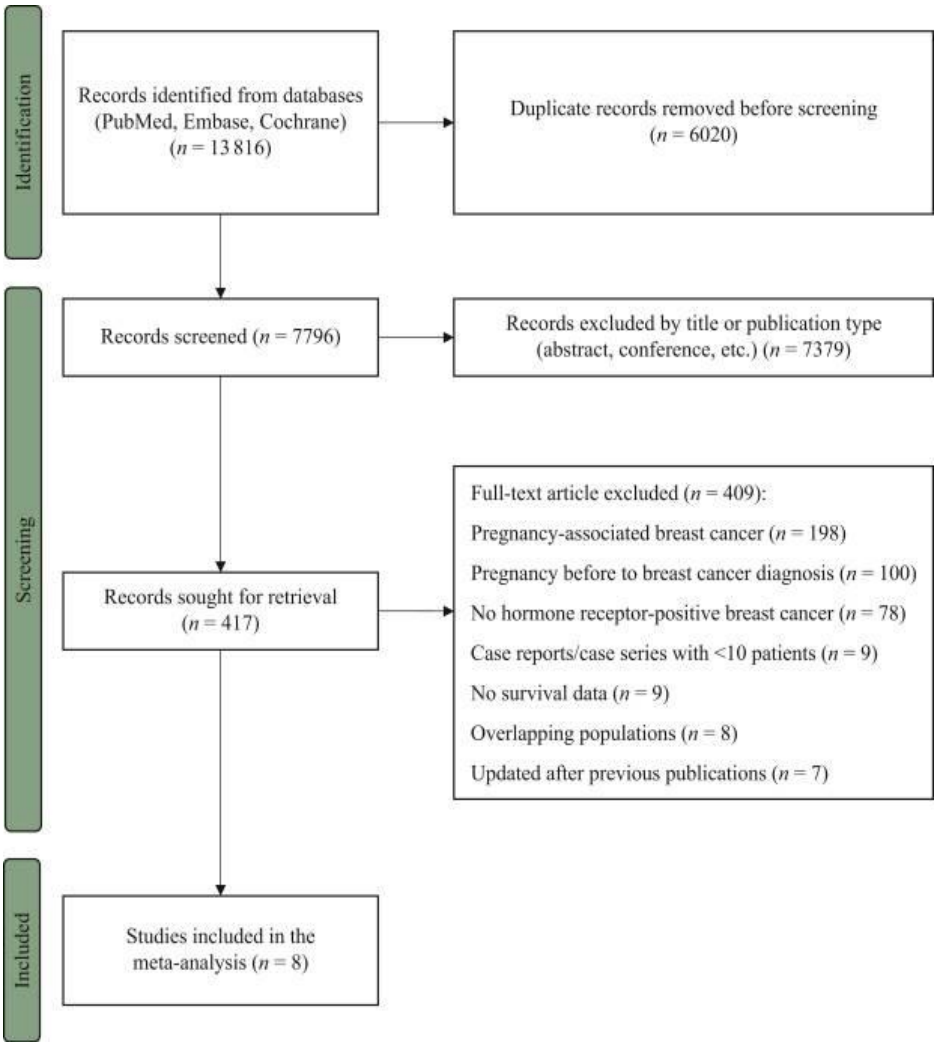

Figure 1. PRISMA flowchart depicting the process of study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

The key features of the studies included in this meta-analysis are summarized in **Table 1**. All included studies were retrospective cohort designs, and each accounted for potential guarantee-time bias in their analyses.

Table 1. Summary of main characteristics of studies incorporated into the meta-analysis.

Reference	Nye and colleagues, 201734	Valentini and colleagues, 201333
Study Location	United States	Canada, United States, Europe, Asia
Time Period	2000-2010	1985-2010
Research Methodology	Backward-looking group analysis	Backward-looking group analysis
Average/Midpoint Age at Initial Diagnosis for Pregnant vs. Non-Pregnant Groups	34.2 compared to 36.1 years	32.5 compared to 33.8 years (not limited to HR+)
Number of Individuals with Pregnancy Following HR+ Breast Cancer	32	21
Number of Individuals without Pregnancy Following Breast Cancer	29	66
Average/Midpoint Duration from Diagnosis to Conception	Within a 5-year period	Average: 2.4 years (not limited to HR+)
Average/Midpoint Observation Period for Pregnant vs. Non-Pregnant Groups	9.2 compared to 6.5 years	10.2 years (not limited to HR+)
Criteria for Pairing Controls or Adjusting Variables	Age, diagnostic stage	Age, BRCA gene variation, residence country, breast cancer diagnosis date, baseline survey completion date
Measured Results	Disease-free survival	Survival rate over 15 years
Assessment of Potential Bias^a	Moderate	High

Lambertini and colleagues, 201822
Europe
Prior to 2007
Backward-looking group analysis
32.0 compared to 35.0 years (not limited to HR+)
194
492
Midpoint: 4.7 years (not limited to HR+)
9.6 years
Estrogen receptor status, lymph node involvement, post-surgical therapies, age, diagnosis year
Disease-free survival in HR+ cases (main outcome)
Low

Rauh-Hain and colleagues, 202236	Chuang and colleagues, 202035	Lambertini and colleagues, 202010
United States	Taiwan	Global
2000-2012	2002-2014	2000-2012
Backward-looking group analysis	Backward-looking group analysis	Backward-looking group analysis
32 compared to 33 years (not limited to HR+)	31.0 compared to 32.3 years (not limited to HR+)	31.0 compared to 36.0 years (not limited to HR+)
240	87	60
273	311	180
Midpoint: 2.72 years (not limited to HR+)	Midpoint: 3.31 years (not limited to HR+)	Midpoint: 6.3 years
9.3 years (not limited to HR+)	4.3 compared to 3.8 years (not limited to HR+)	8.3 years
Age, diagnosis year, stage, tumor grade, ER/PgR/HER2 status, chemotherapy/radiation/surgical treatment, racial/ethnic background, average household earnings, insurance coverage at diagnosis, marital status, Charlson score for comorbidities	Diagnosis age, diagnosis year, propensity score for conception, interval to pregnancy or disease-free survival event	Interval to pregnancy or disease-free survival event, diagnosis year, lymph node involvement, hormone receptor status, BRCA mutation type
Overall survival	Overall survival	Rates of pregnancy, disease-free survival (main outcomes) Outcomes
Moderate	Moderate	Low

Anderson and colleagues, 202224	Scotland	1981-2018	Backward-looking group analysis	31.0 compared to 32.0 years (not limited to HR+)	102	612	Midpoint: 4.1 years (not limited to HR+)	15.8 compared to 14.7 years (not limited to HR+)	Diagnosis year	Overall survival	Low
Bae and colleagues, 202237	Korea	2004-2014	Backward-looking group analysis	32.2 compared to 40.0 years (not limited to HR+)	549	557	Midpoint: 3.3 years (not limited to HR+)	8.2 years	Diagnosis age, post-surgical endocrine/chemotherapy/radiation therapy	Overall survival	High

CT, chemotherapy; DFS, disease-free survival; ER, estrogen receptors; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor-positive breast cancer; OS, overall survival; PgR, progesterone receptors; RT, radiotherapy.

[a]Quality assessment and risk of bias were carried out using the Newcastle–Ottawa Assessment Scale.

In one study, the cohort was composed entirely of women with hormone receptor-positive breast cancer [34]. The remaining seven studies included patients across various breast cancer subtypes; for the purpose of this analysis, only outcomes for hormone receptor-positive cases were extracted. In two studies, tumor receptor status was not explicitly reported; instead, subtype classification was inferred from the administration of adjuvant endocrine therapy [33, 37].

Age at diagnosis varied slightly between groups. Women who subsequently became pregnant were diagnosed at a mean age of 31.0–34.2 years, whereas those who did not conceive ranged from 32.0 to 40.0 years. Median follow-up durations extended from 4.3 to 15.8 years in the pregnancy group and 3.8 to 14.7 years in the non-pregnancy group.

Information regarding adjuvant endocrine therapy was available in over half of the studies [10, 33-35, 37]. Only three studies provided detailed information about the therapy regimens [10, 33, 34]. In two studies, all patients receiving adjuvant therapy were treated exclusively with tamoxifen [33, 34]. In one study, treatment in the pregnancy cohort was more varied: 28.9% received tamoxifen alone, 57.7% received tamoxifen combined with a gonadotropin-releasing hormone agonist (GnRHa), and 7.7% received GnRHa in combination with an aromatase inhibitor [10].

Two studies reported the total duration of endocrine therapy, showing that women who became pregnant generally received shorter treatment than those who did not (50 versus 60 months, $P < 0.001$; 20.9 versus 42.3 months, $P = 0.008$) [10, 34].

Disease-free survival (DFS) was reported in three studies [10, 23, 34], comprising a total of 987 patients, of whom 286 had a post-treatment pregnancy. Pooled analysis indicated that DFS did not significantly differ between the pregnancy and non-pregnancy groups (HR 0.96, 95% CI 0.75–1.24, $P = 0.781$) **(Figure 2).**

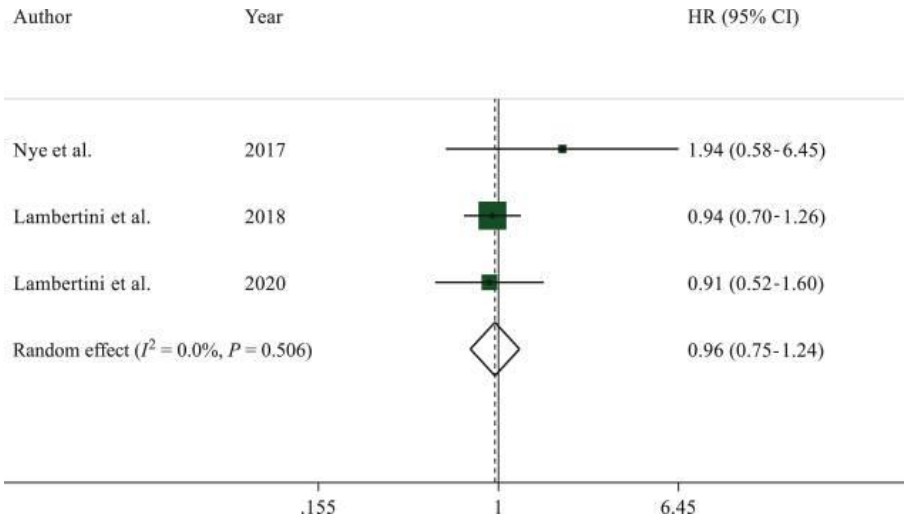

Figure 2. Forest plot showing disease-free survival outcomes in women who conceived after hormone receptor-positive breast cancer compared with those who did not. CI, confidence interval; HR, hazard ratio.

Analysis revealed no significant variability among the included studies (I^2 = 0.0%, P = 0.506), and assessment of publication bias indicated no evidence of systematic reporting (P = 0.406). Overall survival data were reported in six studies [23, 24, 33, 35-37], including 3504 patients in total, with 1193 women experiencing a pregnancy following breast cancer treatment. Pooled results demonstrated a marked survival advantage for the pregnancy cohort compared to the non-pregnancy cohort, with a hazard ratio of 0.46 (95% CI 0.27–0.77, P < 0.005) **(Figure 3).**

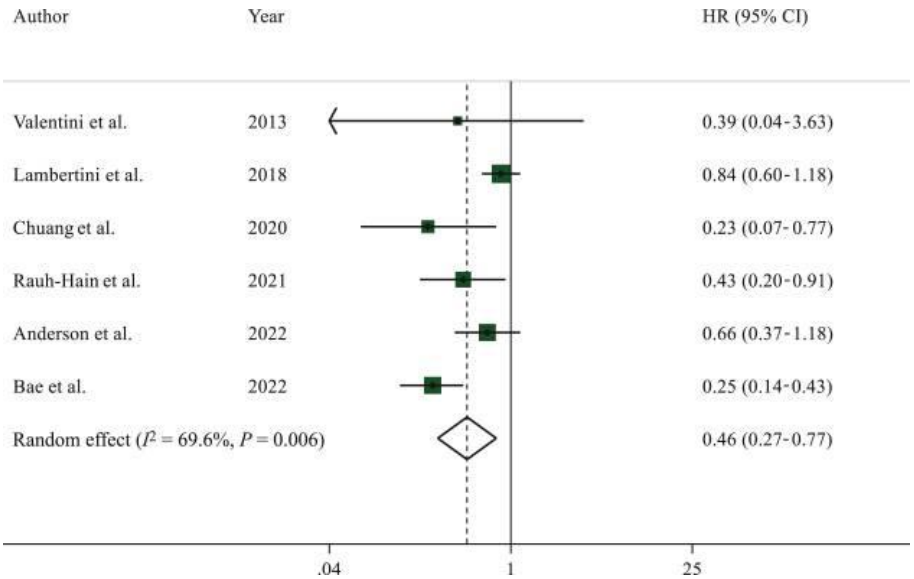

Figure 3. Forest plot illustrating overall survival in women who conceived following hormone receptor-positive breast cancer compared with those who did not. CI, confidence interval; HR, hazard ratio.

Considerable heterogeneity was present in this analysis (I^2 = 69.6%, P = 0.006), but no evidence of publication bias was observed (P = 0.259). This comprehensive review and meta-analysis, integrating eight studies and 3805 young women, suggests that pregnancy after treatment for hormone receptor-positive breast cancer does not compromise prognosis. Disease-free survival (DFS) was comparable between women who became pregnant and those who did not (HR 0.96, 95% CI 0.75–1.24, P = 0.781), while overall survival (OS) was notably

higher in the pregnancy cohort (HR 0.46, 95% CI 0.27–0.77, P < 0.005).

Earlier meta-analyses on this topic were limited, including only two studies [8]. By incorporating six additional studies, our analysis offers a broader and more contemporary perspective on outcomes in women with hormone receptor-positive disease. Sensitivity checks for both DFS and OS confirmed that the findings were robust, with no single study disproportionately influencing the results.

A critical consideration in oncofertility counseling is the management of adjuvant endocrine therapy, which typically precludes pregnancy. Only half of the included studies provided information on therapy regimens, and two reported treatment duration [10, 34]. In these, women who became pregnant generally had shorter exposure to endocrine therapy than those who did not conceive. The median interval from diagnosis to conception in patients with hormone receptor-positive tumors was reported as 6.3 years [10].

Historically, clinicians advised postponing pregnancy for at least two years after breast cancer diagnosis [38], reflecting the higher risk of recurrence in the early post-diagnosis period and the need to recover ovarian function after chemotherapy [39]. For hormone receptor-positive patients, guidance has traditionally recommended delaying conception until completion of adjuvant endocrine therapy, often extending the interval to five years. This conservative approach was based on limited data regarding temporary therapy interruption and the proven benefit of prolonged endocrine treatment, particularly among patients at higher risk who might also receive ovarian suppression for five years [38, 40].

Recent findings from the prospective POSITIVE trial (ClinicalTrials.gov identifier: NCT02308085) have provided new insight into pregnancy after hormone receptor-positive early breast cancer [25]. This study is the first prospective clinical trial to examine the safety of temporarily interrupting adjuvant endocrine therapy to attempt conception in 518 young women (<42 years) who had previously received 18–30 months of endocrine therapy. In this initial analysis, the breast cancer-free interval (BCFI) in participants attempting pregnancy did not significantly differ from a matched cohort derived from the SOFT and TEXT trials (HR 0.81, 95% CI 0.57–1.15) [25]. The 3-year incidence of breast cancer events was similar between the groups: 8.9% (95% CI 6.3–11.6%) in the treatment-interruption group versus 9.2% (95% CI 7.6–10.8%) in the control cohort.

Despite these encouraging early results, the median follow-up of 41 months in the POSITIVE trial is relatively short for assessing late recurrences, which can occur more than a decade after diagnosis in hormone receptor-positive disease [41, 42]. In contrast, the studies included in our meta-analysis reported median follow-ups ranging from 4.3 to 15.8 years, allowing for the capture of some late recurrences.

Another key strength of this meta-analysis is that all included studies accounted for the potential "healthy mother effect." This phenomenon, whereby women who feel healthier are more likely to conceive, could bias outcomes if not corrected. By addressing guarantee-time bias—arising when survival analyses are influenced by the timing of events during follow-up [43]—the included studies reduce the risk of this confounding factor, strengthening the validity of our results [44, 45].

The biological impact of pregnancy on hormone receptor-positive breast cancer has also been a matter of debate. High levels of estrogen, progesterone, and human chorionic gonadotropin during pregnancy may not necessarily be harmful; these hormones can induce apoptosis in hormone receptor-positive breast cancer cells and have historically been employed in breast cancer treatment [46]. Additionally, pregnancy may enhance maternal immune responses against tumor cells, as suggested by the "fetal antigen hypothesis" [47]. These mechanisms align with our finding that pregnancy may even confer a survival benefit in terms of overall survival.

Several limitations of this analysis should be acknowledged. All included studies were retrospective and observational, with differing matching strategies, which may contribute to heterogeneity in the pooled outcomes. Much of the data for hormone receptor-positive patients were derived from subgroups within larger studies encompassing all breast cancer subtypes. Consequently, detailed baseline characteristics, as well as the type and duration of adjuvant endocrine therapy, were often unavailable.

Planned analyses exploring the timing of pregnancy after breast cancer, disease stage at diagnosis, specific endocrine therapies, germline BRCA status, or multiple pregnancies could not be performed due to insufficient data. Furthermore, evidence remains scarce regarding assisted reproductive technologies in this population, as well as pregnancy following breast cancer diagnosed during gestation [11, 48].

Conclusion

This systematic review and meta-analysis of retrospective cohort studies indicates that pregnancy after hormone receptor-positive early breast cancer appears safe and does not adversely affect prognosis. With appropriate treatment and monitoring, conception should not be discouraged in this patient population.

Acknowledgments: None

Conflict of Interest: EB reports research support (to the institution) from Gilead outside the submitted work. EM reports honoraria from Roche, Sevie, Novartis. IVL reports honoraria from AstraZeneca (Inst), Amgen (Inst), Pfizer (Inst), Novartis (Inst), Sandoz (Inst); research funding from Resilience (Inst) and travel support from Novartis outside the submitted work. Executive board member BIG. CS reports grants from AstraZéneca, Daiichi Sankyo, Eisai Europe Ltd., Gilead, Novartis, Pharmalex, Pfizer Inc, Phillips Health Works, Pierre Fabre, PintPharma, Puma Biotechnology Inc, Roche Farma, SA Seagen Int, Solti, Synthon Biopharmaceuticals, Zymeworks; consulting fees from AstraZéneca, Daiichi Sankyo, Eisai Europe Ltd., Gilead, Novartis, Pharmalex, Pfizer Inc, Phillips Health Works, Pierre Fabre, PintPharma, Puma Biotechnology Inc, Roche Farma, SA Seagen Int., Solti, Synthon Biopharmaceuticals, Zymeworks; honoraria from AstraZéneca, Daiichi Sankyo, Eisai Europe Ltd., Gilead, Novartis, Pharmalex, Pfizer Inc, Phillips Health Works, Pierre Fabre, PintPharma, Puma Biotechnology Inc, Roche Farma, SA Seagen Int., Solti, Synthon Biopharmaceuticals, Zymeworks. RAA reports personal fees and non-financial support from Roche Diagnostics, personal fees from Ferring Pharmaceuticals, IBSA and Merck Serono, outside the submitted work. ID reports trial grant and reagents (to the institution) from Roche Diagnostics; academic trial grant from Ferring; speaker's honoraria from Novartis; support for attending meetings from Ferring and Theramex. EdA reports financial honoraria and/or advisory board from Roche/GNE, Novartis, SeaGen, Zodiac, Libbs, Pierre Fabre, Lilly, Astra-Zeneca, MSD, Gilead Sciences. Travel grants from Roche/GNE and Astra-Zeneca. Research grant to my institution from Roche/GNE, Astra-Zeneca, GSK/Novartis, Gilead Sciences. Non-financial: ESMO director of membership 2023-2024; BSMO President 2023-2026. LDM reports grants from Eli lilly, Novartis, Roche, Daiichi Sankyo, Seagen, Astrazeneca, Gilead, Pierre Fabre; consulting fees from Eli lilly, Gilead, Daiichi Sankyo; honoraria from Roche, Novartis, Pfizer, Eli lilly, Astrazeneca, MSD, Seagen, Gilead, Pierre Fabre, Eisai, Exact Sciences, Ipsen, GSK, Agendia, Stemline. AHP reports research grants from Breast Cancer Research Foundation, Susan G. Komen, US NIH/NCI, PCORI; royalties from UpToDate. ML reports advisory role for Roche, Lilly, Novartis, Astrazeneca, Pfizer, Seagen, Gilead, MSD and Exact Sciences, speaker honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz, Libbs, Daiichi Sankyo and Takeda, travel grants from Gilead and Daiichi Sankyo, and research support (to the institution) from Gilead outside the submitted work. All other authors have declared no conflicts of interest.

Financial Support: This work was partially supported by the Italian Association for Cancer Research ('Associazione Italiana per la Ricerca sul Cancro', AIRC) [grant number MFAG 2020 ID 24698] and by Italian Ministry of Health—5 x 1000 funds (years 2021-2022).

Ethics Statement: None

References

1. Fidler M.M., Gupta S., Soerjomataram I., Ferlay J., Steliarova-Foucher E., Bray F. Cancer incidence and mortality among young adults aged 20–39 years worldwide in 2012: a population-based study. Lancet Oncol. 2017;18(12):1579–1589. doi: 10.1016/S1470-2045(17)30677-0
2. Miller K.D., Fidler-Benaoudia M., Keegan T.H., Hipp H.S., Jemal A., Siegel R.L. Cancer statistics for adolescents and young adults, 2020. CA Cancer J Clin. 2020;70(6):443–459. doi: 10.3322/caac.21637
3. Siegel R.L., Miller K.D., Fuchs H.E., Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7–33. doi: 10.3322/caac.21708
4. Shapiro C.L. Cancer survivorship. N Engl J Med. 2018;379(25):2438–2450. doi: 10.1056/NEJMra1712502
5. Lambertini M., Peccatori F.A., Demeestere I., et al. Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2020;31(12):1664–1678. doi: 10.1016/j.annonc.2020.09.006

6. Arecco L., Perachino M., Damassi A., et al. Burning questions in the oncofertility counseling of young breast cancer patients. Breast Cancer (Auckl) 2020;14 doi: 10.1177/1178223420954179
7. Blondeaux E., Massarotti C., Fontana V., et al. The PREgnancy and FERtility (PREFER) study investigating the need for ovarian function and/or fertility preservation strategies in premenopausal women with early breast cancer. Front Oncol. 2021;11 doi: 10.3389/fonc.2021.690320
8. Lambertini M., Blondeaux E., Bruzzone M., et al. Pregnancy after breast cancer: a systematic review and meta-analysis. J Clin Oncol. 2021;39:3293–3305. doi: 10.1200/JCO.21.00535
9. Ely D.M., Hamilton B.E. Trends in fertility and mother's age at first birth among rural and metropolitan counties: United States, 2007-2017. NCHS Data Brief. 2018;(323):1–8.
10. Lambertini M., Ameye L., Hamy A.S., et al. Pregnancy after breast cancer in patients with germline BRCA mutations. J Clin Oncol. 2020;38(26):3012–3023. doi: 10.1200/JCO.19.02399
11. Arecco L., Blondeaux E., Bruzzone M., et al. Safety of fertility preservation techniques before and after anticancer treatments in young women with breast cancer: a systematic review and meta-analysis. Hum Reprod. 2022;37(5):954–968. doi: 10.1093/humrep/deac035
12. Ruddy K.J., Gelber S.I., Tamimi R.M., et al. Prospective study of fertility concerns and preservation strategies in young women with breast cancer. J Clin Oncol. 2014;32(11):1151–1156. doi: 10.1200/JCO.2013.52.8877
13. Burstein H.J., Lacchetti C., Anderson H., et al. Adjuvant endocrine therapy for women with hormone receptor–positive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline Update on Ovarian Suppression. J Clin Oncol. 2016;34(14):1689–1701. doi: 10.1200/JCO.2015.65.9573
14. Lambertini M., Goldrat O., Clatot F., Demeestere I., Awada A. Controversies about fertility and pregnancy issues in young breast cancer patients: current state of the art. Curr Opin Oncol. 2017;29(4):243–252. doi: 10.1097/CCO.0000000000000380
15. Shandley L.M., Spencer J.B., Fothergill A., et al. Impact of tamoxifen therapy on fertility in breast cancer survivors. Fertil Steril. 2017;107(1):243–252.e5. doi: 10.1016/j.fertnstert.2016.10.020
16. Lambertini M., Fontana V., Massarotti C., et al. Prospective study to optimize care and improve knowledge on ovarian function and/or fertility preservation in young breast cancer patients: results of the pilot phase of the PREgnancy and FERtility (PREFER) study. Breast. 2018;41:51–56. doi: 10.1016/j.breast.2018.06.012
17. Buonomo B., Brunello A., Noli S., et al. Tamoxifen exposure during pregnancy: a systematic review and three more cases. Breast Care. 2020;15:148–156. doi: 10.1159/000501473
18. Paluch-Shimon S., Cardoso F., Partridge A.H., et al. ESO-ESMO 4th International Consensus Guidelines for Breast Cancer in Young Women (BCY4) Ann Oncol. 2020;31(6):674–696. doi: 10.1016/j.annonc.2020.03.284
19. Lambertini M., Di Maio M., Pagani O., et al. The BCY3/BCC 2017 survey on physicians' knowledge, attitudes and practice towards fertility and pregnancy-related issues in young breast cancer patients. Breast. 2018;42:41–49. doi: 10.1016/j.breast.2018.08.099
20. Razeti M.G., Spinaci S., Spagnolo F., Massarotti C., Lambertini M. How I perform fertility preservation in breast cancer patients. ESMO Open. 2021;6(3) doi: 10.1016/j.esmoop.2021.100112
21. Metzger-Filho O., Sun Z., Viale G., et al. Patterns of recurrence and outcome according to breast cancer subtypes in lymph node-negative disease: results from international breast cancer study group trials VIII and IX. J Clin Oncol. 2013;31(25):3083–3090. doi: 10.1200/JCO.2012.46.1574
22. Lambertini M., Campbell C., Gelber R.D., et al. Dissecting the effect of hormone receptor status in patients with HER2-positive early breast cancer: exploratory analysis from the ALTTO (BIG 2-06) randomized clinical trial. Breast Cancer Res Treat. 2019;177(1):103–114. doi: 10.1007/s10549-019-05284-y
23. Lambertini M., Kroman N., Ameye L., et al. Long-term safety of pregnancy following breast cancer according to estrogen receptor status. J Natl Cancer Inst. 2018;110(4):426–429. doi: 10.1093/jnci/djx206
24. Anderson R.A., Lambertini M., Hall P.S., Wallace W.H., Morrison D.S., Kelsey T.W. Survival after breast cancer in women with a subsequent live birth:

influence of age at diagnosis and interval to subsequent pregnancy. Eur J Cancer. 2022;173:113–122. doi: 10.1016/j.ejca.2022.06.048
25. Partridge A.H., Niman S.M., Ruggeri M., et al. Interrupting endocrine therapy to attempt pregnancy after breast cancer. N Engl J Med. 2023;388(18):1645–1656. doi: 10.1056/NEJMoa2212856
26. Senkus E., Gomez H., Dirix L., et al. Attitudes of young patients with breast cancer toward fertility loss related to adjuvant systemic therapies. EORTC study 10002 BIG 3-98: fertility attitudes in young patients with breast cancer. Psychooncology. 2014;23(2):173–182. doi: 10.1002/pon.3384
27. Moher D., Liberati A., Tetzlaff J., Altman D.G., PRISMA Group Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Br Med J. 2009;339:b2535.
28. Wells G.A., Shea B., O'Connell D., et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp Available at.
29. Watkins C., Bennett I. A simple method for combining binomial counts or proportions with hazard ratios for evidence synthesis of time-to-event data. Res Syn Meth. 2018;9(3):352–360. doi: 10.1002/jrsm.1301
30. DerSimonian R., Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–188. doi: 10.1016/0197-2456(86)90046-2
31. Higgins J.P.T., Thompson S.G. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539–1558. doi: 10.1002/sim.1186.
32. Egger M., Smith G.D., Schneider M., Minder C. Bias in meta-analysis detected by a simple, graphical test. Br Med J. 1997;315(7109):629–634. doi: 10.1136/bmj.315.7109.629
33. Valentini A., Lubinski J., Byrski T., et al. The impact of pregnancy on breast cancer survival in women who carry a BRCA1 or BRCA2 mutation. Breast Cancer Res Treat. 2013;142(1):177–185. doi: 10.1007/s10549-013-2729-1
34. Nye L., Rademaker A., Gradishar W.J. Breast cancer outcomes after diagnosis of hormone-positive breast cancer and subsequent pregnancy in the tamoxifen era. Clin Breast Cancer. 2017;17(4):e185–e189. doi: 10.1016/j.clbc.2016.12.014
35. Chuang S.C., Lin C.H., Lu Y.S., Hsiung C.A. Mortality of pregnancy following breast cancer diagnoses in Taiwanese women. Oncologist. 2020;25(2):e252–e258. doi: 10.1634/theoncologist.2019-0451
36. .Rauh-Hain J.A., Zubizarreta J., Nitecki R., et al. Survival outcomes following pregnancy or assisted reproductive technologies after breast cancer: a population-based study. Cancer. 2022;128(17):3243–3253. doi: 10.1002/cncr.34371
37. Bae S.Y., Lee J., Lee J.S., et al. Prognosis of pregnancy after breast cancer diagnosis according to the type of treatment: a population-based study in Korea by the SMARTSHIP group. Breast. 2022;63:46–53. doi: 10.1016/j.breast.2022.03.005
38. Paluch-Shimon S., Cardoso F., Partridge A.H., et al. ESO-ESMO fifth international consensus guidelines for breast cancer in young women (BCY5) Ann Oncol. 2022;33(11):1097–1118. doi: 10.1016/j.annonc.2022.07.007
39. Azim H.A., Peccatori F.A., de Azambuja E., Piccart M.J. Motherhood after breast cancer: searching for la dolce vita. Expert Rev Anticancer Ther. 2011;11(2):287–298. doi: 10.1586/era.10.208
40. Sella T., Ruddy K.J., Carey L.A., Partridge A.H. Optimal endocrine therapy in premenopausal women: a pragmatic approach to unanswered questions. JCO Oncol Pract. 2022;18(3):211–216. doi: 10.1200/OP.21.00482
41. Pan H., Gray R., Braybrooke J., et al. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. N Engl J Med. 2017;377(19):1836–1846. doi: 10.1056/NEJMoa1701830
42. Pedersen R.N., Esen B.Ö., Mellemkjær L., et al. The incidence of breast cancer recurrence 10-32 years after primary diagnosis. J Natl Cancer Inst. 2022;114(3):391–399. doi: 10.1093/jnci/djab202
43. Giobbie-Hurder A., Gelber R.D., Regan M.M. Challenges of guarantee-time bias. J Clin Oncol. 2013;31(23):2963–2969. doi: 10.1200/JCO.2013.49.5283
44. Sankila R., Heinävaara S., Hakulinen T. Survival of breast cancer patients after subsequent term pregnancy: "healthy mother effect". Am J Obstet Gynecol. 1994;170(3):818–823. doi: 10.1016/s0002-9378(94)70290-x
45. Valachis A., Tsali L., Pesce L.L., et al. Safety of pregnancy after primary breast carcinoma in young

women: a meta-analysis to overcome bias of healthy mother effect studies. Obstet Gynecol Surv. 2010;65(12):786–793. doi: 10.1097/OGX.0b013e31821285bf

46. Rajkumar L., Guzman R.C., Yang J., Thordarson G., Talamantes F., Nandi S. Prevention of mammary carcinogenesis by short-term estrogen and progestin treatments. Breast Cancer Res. 2004;6(1):R31–R37. doi: 10.1186/bcr734
47. Janerich D.T. The fetal antigen hypothesis: cancers and beyond. Med Hypotheses. 2001;56(1):101–103. doi: 10.1054/mehy.2000.1119
48. Arecco L., Lambertini M. Safety of interrupting adjuvant endocrine therapy to conceive: early data are POSITIVE. Nat Rev Clin Oncol. 2023;20:662–663. doi: 10.1038/s41571-023-00797-4