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► **To cite this version:**

Anne-Sophie Hamy, Agathe Chabassier, Clara Sebbag, Christine Rousset-Jablonski, Clémentine Berkach, et al.. Time-to-pregnancy in patients with previous breast cancer and unexposed women: a prospective exposed-unexposed cohort study. *EClinicalMedicine*, 2025, 86, pp.103392. <10.1016/j.eclinm.2025.103392>. <hal-05209092>

HAL Id: hal-05209092

<https://hal.science/hal-05209092v1>

Submitted on 13 Aug 2025

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Time-to-pregnancy in patients with previous breast cancer and unexposed women: a prospective exposed-unexposed cohort study



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Summary

Background Data on fertility after breast cancer (BC) relative to the general population are lacking. This study aimed to compare the time-to-pregnancy between women with and without prior BC seeking to become pregnant.

Methods We conducted a prospective exposed-unexposed cohort study between March 13, 2018 and June 27, 2019, recruiting participants via the collaborative network Seintinelles. Women aged 18–43 years with a history of localized BC without relapse (exposed) were compared to women without BC (unexposed). Follow-up data were collected every six months over three years. The primary endpoint, time-to-pregnancy, was analyzed using Kaplan–Meier survival analysis with inverse probability weighting. Censoring was performed if women stopped trying to conceive for personal reasons, were lost to follow-up before conception, or completed the study without achieving pregnancy or using assisted reproductive technologies (ART).

Findings Among 4351 women enrolled, 642 sought pregnancy during the study period (76 exposed, 566 unexposed). Among them, 50 exposed (65.8%) and 402 weighted unexposed women (weighted percentage 71.0%) became pregnant at least once. Median time-to-pregnancy was 5.0 months, 95% CI [3.0–7.0] for exposed and 3.0 months, 95% CI [2.0–5.0] for unexposed women (difference in median time-to-pregnancy: 2.0 months, 95% CI [–2.5; 5]). Two years after starting to seek pregnancy, 74.9% of weighted unexposed women and 74.1% of exposed women obtained a pregnancy. Overall, 15 exposed women (19.8%) used either ART methods ($n = 7$, 9.2%) or cryopreserved material ($n = 8$, 10.5%) and 25 unexposed women (4.4%) used ART.

eClinicalMedicine
2025;86: 103392

Published Online xxx
<https://doi.org/10.1016/j.eclinm.2025.103392>

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^sThe members of Seintinelles Research Network are listed in the [Supplementary Material](#).

The median time-to-pregnancy was 3.0 months for both exposed and unexposed women (95% CI [2.0; 5.0] and [2.0; 4.0] respectively) (difference in median time-to-pregnancy: -0.0 months [-2.0 ; 3.0]) in women who sought pregnancy spontaneously, and 14.0 months for exposed (95% CI [6.0–27.0]) and 17.6 months for unexposed women (95% CI [17.6–30.0]) in women seeking pregnancy with ART.

Interpretation In this study from a French collaborative research network, we found no strong evidence of a largely reduced time-to-pregnancy in exposed women seeking to become pregnant compared with unexposed women. Further research on fertility outcomes in the broader population of BC survivors is warranted.

Funding The FEERIC study was funded by *Institut National du Cancer* (InCA), InCA-SHS, grant no. 2016-124, and is part of the Young Breast Cancer Project, funded by Monoprix.

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Keywords: Breast cancer; Pregnancy; Infertility; Survivors; Time-to-pregnancy

Research in context

Evidence before this study

Understanding the fertility outcomes of women with a history of breast cancer (BC) remains a crucial concern, as existing studies have primarily focused on surrogate fertility markers, such as chemotherapy-induced amenorrhea or anti-Müllerian hormone levels. Despite the growing interest in oncofertility, there has been limited exploration of real-world fertility outcomes, particularly time-to-pregnancy in BC survivors relative to the general population. The literature revealed a lack of large-scale, comparative studies focusing on time-to-pregnancy outcomes in BC survivors, emphasizing the need for robust research addressing this knowledge gap.

Added value of this study

This study provides a prospective analysis comparing time-to-pregnancy between women with and without a history of BC using data from the French Seintinelles collaborative network. Our research offers insights into real-world fertility outcomes, demonstrating that time-to-pregnancy is not

significantly prolonged in BC survivors compared to unexposed women. The findings underscore that conception rates remain high among BC survivors and that ART usage, though more prevalent among these women, results in similar time-to-pregnancy outcomes over time.

Implications of all the available evidence

The results offer reassurance regarding the feasibility of natural conception in survivors of breast cancer. These findings support informed, balanced oncofertility counseling, encouraging initial natural conception attempts. Policymakers and healthcare providers should focus on enhancing awareness of real-world fertility outcomes post-BC, ensuring that women are well-informed about their reproductive options and the timing of conception attempts. Future research should aim to further investigate long-term fertility outcomes in diverse populations and explore strategies to optimize fertility counseling and support for BC survivors.

Introduction

Breast cancer (BC) is the most common cancer in women. There have been concerns for decades about the impact on potential recurrence of pregnancy after BC, but there are now large amounts of data suggesting that pregnancy after BC is safe.^{1–3}

Pregnancy rates in women with prior BC range from 3 to 13%,^{3–5} but these rates largely underestimate fertility, as patients who survive BC may not wish to become pregnant, and even if they do, they are confronted with several constraints on their plans: (i) it is recommended to delay pregnancy for at least 18 months after the end of treatment⁶; (ii) pregnancy is contraindicated in patients treated with tamoxifen, due to its known teratogenic effects; (iii) Substantial disruptions in intimate relationships may arise due to

changes in body image, sexual attractiveness, and self-esteem. These challenges can lead to strained relationships, communication difficulties with potential partners, and weaken couple relationships⁷; (iv) Achieving pregnancy through natural conception requires regular sexual intercourse, which can be particularly challenging for cancer survivors. Previous studies suggest that a significant proportion of women who survived cancer—up to two-thirds^{8–11}—experience sexual dysfunction, including low desire, vaginal dryness, and painful intercourse, often exacerbated by estrogen deprivation therapy. Finally, (v) relapse may also compromise pregnancy plans. In addition, these women may have lower fertility due to the physiological decline in fertility if their pregnancy plans are delayed and/or due to chemotherapy-induced damage to the ovaries.

Age is a critical factor influencing fertility outcomes. Fertility naturally declines with age due to a reduction in ovarian reserve and oocyte quality, while the incidence of BC increases with age, particularly after 40 years old. Since BC is relatively rare in younger women, most patients with previous BC who attempt pregnancy tend to be older than the general population of women trying to conceive. This difference may influence both the probability of natural conception and the likelihood of requiring assisted reproductive technologies (ART).

Many studies have investigated the relationship between chemotherapy and surrogate markers of fertility. Anti-Müllerian hormone (AMH) levels have been studied in detail, with the following findings: (i) AMH concentration is lower in BC survivors than in unexposed women^{12–15}; (ii) AMH concentration is lower after chemotherapy than before treatment^{12,13,16–19}; (iii) After chemotherapy for BC, AMH is higher in menstruating women than in patients who are amenorrheic^{15,16}; (iv) AMH concentration before treatment is predictive of ovarian function, as it is based on menstrual function.^{12,18} However, in most of these studies, ovarian reserve evaluations were not linked to reproductive outcomes and pregnancy. Several teams have shown that AMH levels increase again after chemotherapy,^{20,21} suggesting that this parameter is of little value as a dynamic marker of ovarian reserve. Furthermore, several studies have reported spontaneous pregnancies in women without detectable levels of AMH.^{20,21} Evaluations of fertility loss after cancer therefore remain the Achilles' heel of the oncofertility domain.

Published findings concerning the desire for pregnancy and success rates for conception after BC are encouraging. Partridge et al.²² surveyed 440 women and found that 57% of those who attempted to become pregnant were successful. In an American prospective cohort study, 69.2% patients with a history of BC wishing to become pregnant conceived successfully.²³ In the recent POSITIVE study of 497 patients with previous BC interrupting endocrine therapy to attempt to become pregnant for whom pregnancy status data were available,²⁴ 74.0% reported becoming pregnant at least once during the trial. However, pregnancy rates after BC have never been benchmarked against that in the general population, leaving questions about the theoretical effects of BC treatment on fertility unanswered.

The primary objective of the FEERIC study was to compare time-to-pregnancy between women with (exposed) and without prior BC (unexposed) who began seeking pregnancy over a three-year follow-up period.

Methods

Background of the FEERIC study

FEERIC is a nationwide, prospective exposed-unexposed study conducted via the Seintinelles

collaborative research platform, which connects researchers with volunteers across France. Recruitment took place from March 2018 to June 2019. Participants completed baseline and six-monthly follow-up questionnaires for three years, with data collected on fertility intentions, pregnancy attempts, and outcomes. Eligible participants were women aged 18–43 years. The exposed group included women with a previous diagnosis of localized, relapse-free breast cancer who had completed primary treatment. The unexposed group comprised women of similar age with no history of breast cancer. Both groups excluded women with a prior hysterectomy, bilateral oophorectomy, bilateral salpingectomy, or any other prior malignancy. The main analysis focused on women actively seeking pregnancy during the follow-up period, as assessed by self-reported attempts to conceive. The primary endpoint was time-to-pregnancy, defined as the duration from initiation of pregnancy attempts to conception, regardless of pregnancy outcome.

Secondary endpoints included factors associated with time-to-pregnancy; Use and timing of assisted reproductive technologies (ART); Pregnancy outcomes (full-term, miscarriage, other abortions); Obstetric and neonatal outcomes. Comparisons between groups were made for all primary and secondary outcomes. Full details of the study design, population, and statistical analysis are presented in the main manuscript.

Study design

The design of the FEERIC (Fertility, PrEgnancy, contRaception after breast Cancer in France) study has been described extensively elsewhere.²⁵ This study is a prospective exposed-unexposed study aiming to assess the impact of BC on fertility, pregnancy, and contraception in young patients who survived BC in comparison with women without BC.

Ethics

The Seintinelles scientific board approved the FEERIC project on December 7, 2015, and the Sud Ouest Outre Mer II ethics committee approved the project on October 5, 2017 (reference number: 2017: A0218152). All patients included in the study provided electronic consent to participate in the study. The study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies. All participants provided electronic informed consent prior to enrollment in the study, in compliance with ethical and legal requirements.

Study objectives

The primary endpoint of the current work was to compare time-to-pregnancy between women with and without a history of BC who began seeking pregnancy over a three-year follow-up period.

Setting

Seintinelles is a collaborative social network created in 2012 to accelerate the recruitment of French volunteers for cancer research studies, by connecting researchers with men and women of various ages, social and medical backgrounds with or without a history of cancer. In December 2024, the network included more than 40 000 French citizens willing to participate in research studies.^{26,27} Women were recruited in the FEERIC study through the Seintinelles platform from March 13, 2018 to June 27, 2019. Participants were asked to complete a baseline form at inclusion and follow-up forms every 6 months for 3 years. Data were collected via self-administered online questionnaires released through the Seintinelles platform.

Participants

The Seintinelles platform includes both cancer and non-cancer participants. Participants were approached through several approaches. Exposed women were recruited by both: (i) the Seintinelles Research Network; (ii) eight breast care/oncofertility and gynecology centers: Institut Curie, 2 sites (Paris and Saint Cloud), Hôpital Saint-Louis (Paris), Hôpital Cochin (Paris), Centre Léon Bérard (Lyon), Centre Oscar Lambret, Centre Hospitalier Régional Universitaire (Lille), Institut Bergonié (Bordeaux).

Patients were asked to participate in the study at follow-up consultations, or through the display of invitation flyers and posters in waiting rooms. In addition to the direct proposal to participate during follow-up consultations, six centers sent invitations to participate by mailing patients (electronic e-mail addresses when available, otherwise by postal mail) (Institut Curie, Paris and Saint Cloud; Léon Bérard, Lyon; Centre Georges François Leclerc, Dijon; Hôpital Saint-Louis, Paris; Institut du Cancer de Montpellier, Montpellier).

Eligibility criteria were defined as follows:

- **Exposed women** were female aged from 18 to 43 years with a prior diagnosis of localized BC (invasive or *in situ*) who had completed treatment (surgery, chemotherapy, and radiotherapy) at the time of enrollment and were relapse-free. Women who were receiving adjuvant endocrine therapy at the time of eligibility could be included in the study and could decide to temporarily stop it when they sought to get pregnant, consistent with clinical practices.
- **Unexposed women** were women aged from 18 to 43 years free from BC.
- The current study focused on women who were **actively seeking pregnancy**, defined as engaging in unprotected intercourse with the intent to conceive during the time frame of the study. The intention to conceive was assessed longitudinally every 6 months over three years through self-reported data. Women who indicated at least once that they were actively

attempting to conceive were classified as part of the study's target population for the primary endpoint, which aimed to compare time-to-pregnancy between exposed and unexposed women.

- The exclusion criteria for both exposed and unexposed women were prior hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy and/or any prior other malignancy.

Study size

To calculate the sample size, we considered that nearly 20% of the women under 43 years old will have a pregnancy desire during the follow-up period and a 2-fold odds ratio for successfully becoming pregnant in unexposed than in exposed women. The resulting expected pregnancy rates are 8% in the exposed group, and 16% in the unexposed group. Considering a type I error (α) defined by a *p*-value lower than 0.05, a type II error (β) no smaller than 0.2, the planned number of patients was 251 in the exposed and 753 in the unexposed group (total planned number of patients to include: $n = 1004$). Accordingly, the expected number of women attempting to conceive was ~50 among the exposed group ($251 \times 0.20 = 50.2$) and ~151 among the unexposed group ($753 \times 0.20 = 150.6$). As the target number of participants ($n = 1004$) was reached prematurely, authorizations were obtained to pursue participant enrollment until the expected end of the study.

Follow-up

For each follow-up form, women were asked to provide information about:

- Desire for a pregnancy (yes/no/not known).
- Whether they were seeking to become pregnant (defined as current unprotected sexual intercourse with the intent of becoming pregnant); yes/no.
- Occurrence of a pregnancy since last form (yes/no); and if so, pregnancy outcomes.

Follow-up started at the time of seeking pregnancy onset.

Outcomes and exposures

The **exposure variable** was prior BC, defining the exposed (women who survived BC) and unexposed (women without BC) groups.

The **primary outcome** was the occurrence of a pregnancy.

The **secondary outcomes** included:

- Assessment of factors associated with time-to-pregnancy.
- Use of ART, defined as medical procedures used to address infertility, including in vitro fertilization (IVF), intrauterine insemination (IUI), and other

conception-facilitating techniques, such as the use of embryos, oocytes, or ovarian cortex cryopreserved before BC treatment.

- Pregnancy outcomes, categorized into three groups: full-term pregnancy, miscarriage, and other abortive pregnancies (including elective abortion, abortion for medical reasons, ectopic pregnancy, and other pregnancy outcomes).
- Obstetrical outcomes, including mode of delivery (cesarean section *versus* vaginal birth) and presence or absence of delivery complications.
- Neonatal outcomes, categorized based on the presence or absence of fetal malformations.

The primary endpoint was time-to-pregnancy, defined as the time from the start of the attempt to conceive to the start of a pregnancy, regardless of pregnancy outcome. The analysis compared time-to-pregnancy between exposed and unexposed women over the three-year follow-up period.

The secondary endpoints included:

- Assessment of factors associated with time-to-pregnancy.
- Time-to-ART, defined as the time from the start of the attempt to conceive to the first use of an ART method. The event of interest was the first use of any ART method during an attempt to conceive that began after study inclusion. The analysis compared time-to-ART between exposed and unexposed women over the three-year follow-up period.
- Comparison of pregnancy outcomes, obstetrical outcomes, and neonatal outcomes between exposed and unexposed women.

Censorship

Women were subject to right-censoring under the following conditions: (i) not completing a form during the period in which they were trying to conceive, (ii) personal decision to stop attempting pregnancy, and (iii) reaching the end of the three-year study period without conception (Fig. S1). Reasons (i) and (ii) were considered uninformative as they were not systematically linked to the biological likelihood of conception. Relapse should have been treated as a competing risk, but none of the cases experienced a relapse during the period of the study in which they were trying to get pregnant.

Confounding factors and statistical handling

Certain covariates—such as age, marital status, and professional level—were unequally distributed between the groups. While these factors do not inherently determine BC survivorship in the general population, their uneven distribution in our study means they could influence both the likelihood of being in the exposed group and the outcome (time-to-pregnancy). We reweighted the

unexposed population so that the distribution of these covariates would be like the one in the exposed population; thereby enabling a valid comparison.

We identified 14 covariates associated with conception that were not equally distributed between cases and controls and might act as confounders in our dataset: age at which the woman first started trying to get pregnant, nulliparity, professional and educational levels, marital status, body mass index (BMI), smoking status, infertility history, previous use of ART methods, menstrual cycle length and regularity, prior gynecological surgery, prior breast diseases (before cancer for cases), and comorbid conditions. We identified these covariates based on clinical information, and the results obtained with univariable and multivariable Cox models. The directed acyclic graph (DAG) (Fig. S2) clarifies the assumptions underlying the adjustment process.

We used a generalized linear model (GLM) with a logit link function to estimate the propensity score (PS), which represents the probability of receiving the treatment (exposure) given a set of covariates. Inverse probability of weights were computed based on the estimated propensity score (PS). We reweighted the unexposed population so that the distribution of patient characteristics would be similar to that of the exposed population, using weights of 1 for the exposed and $PS/(1-PS)$ for the unexposed. Separate sets of inverse probability of weights were computed for each analytic subset: (i) the full cohort comparison (overall model), (ii) the subgroup of women who did not use ART or cryopreserved material (“No ART-MR” model), and (iii) the subgroup who used ART or cryopreserved material (“ART-MR” model). In each model, weights were estimated using the *WeightIt* package. The sum of the weights in the unexposed group approximated the corresponding exposed group size: 74.4 (overall model), 60.6 (“No ART-MR”), and 19.0 (“ART-MR”), as expected. This approach ensured proper covariate balance within each comparison group. The weights remained within a reasonable range and did not require stabilization or trimming (Specifically, in the time-to-pregnancy (TTP) models, weight ranges were as follows: for the ART-MR model, control weights ranged from 0 to 3.89; for the No ART-MR model, control weights ranged from 0 to 1.81; and for the overall model, control weights ranged from 0 to 2.58. In the time-to-ART model, control weights ranged from 0 to 2.58). We assessed covariate balance after weighting by calculating the standardized mean difference (SMD) and the Kolmogorov–Smirnov (KS) statistic, with balance thresholds of 0.1 and 0.05, respectively.^{28,29} The positivity assumption was assessed variable by variable by looking at their distributions in the exposed and unexposed groups; and by looking at the distribution of the propensity scores in both groups. The confidence intervals for the Kaplan–Meier curves were obtained by

computing 1000 bootstraps.³⁰ We used non-parametric bootstrapping with replacement, and at each time point, the 2.5th and 97.5th percentiles of the survival probabilities across the 1000 bootstrap samples were used to construct the 95% confidence intervals. For the bar charts, proportions were calculated by applying weights to the unexposed group to match the distribution of confounding variables to that in the exposed group. The raw numbers were then determined by taking the closest integer to the product of the weighted proportion and the actual number in each category. This approach ensures that the bar charts accurately reflect the adjusted comparisons between the groups.

Although we used tools and terminology commonly associated with causal inference—such as adjustment for confounders, and inverse probability weighting (IPW)—our aim was not to estimate the causal effect of breast cancer itself, which is not a manipulable exposure. Instead, our goal was to estimate the difference in time-to-pregnancy between women with a history of breast cancer and those without, accounting for differences in baseline characteristics.

We chose inverse probability weighting (IPW) over propensity score matching in order to retain all available participants in our analyses and maximize statistical power, as matching would have excluded unmatched individuals and further reduced the sample size.

Statistics

The study population is described in terms of frequencies and percentages for qualitative variables, and either means with standard deviations (SD) for normally distributed quantitative variables or medians with interquartile range (IQR) for non-normally distributed variables. No data were missing for the continuous variables included in the analyses. For qualitative variables, although some had missing values in the full dataset, the variables retained in the final statistical models and tables did not contain any missing data. Therefore, all models were based on complete-case analyses, which, in this specific context, involved no loss of data due to missingness. For continuous variables (age at inclusion, age started trying to get pregnant), we assessed normality using the Shapiro–Wilk test and Q-Q plots. When normality was not rejected, Welch's t-test was used for comparisons; otherwise, the Wilcoxon–Mann–Whitney test was applied. The association between categorical variables was assessed using Fisher's exact test for two-by-two contingency tables when any expected cell count was below 5. Otherwise, the Chi-squared test of independence was used without continuity correction.

We performed Kaplan–Meier survival analysis to estimate the time-to-pregnancy; and reported the difference in the median time to pregnancy in exposed compared with unexposed women. We ensured that the

data points were independent by considering only the first recorded attempt to become pregnant for each woman. We calculated the 95% CI for the median time-to-pregnancy by determining from the bootstrapped Kaplan–Meier outputs, the exact time values at which the lower and upper confidence bands cross the 0.5 probability level. To build 95% confidence intervals around the weighted Kaplan–Meier curves, we used nonparametric bootstrapping with 1000 resamples. In each resample, inverse probability weights were re-estimated using the same generalized linear model and specifications as in the original sample, using the *weightit* package. The resulting weights were then applied to calculate the Kaplan–Meier curves in each bootstrap iteration. Numbers at risk were shown as unweighted (raw counts at each time point) to preserve transparency about how many participants remained under observation. The IPW-adjusted median time-to-pregnancy is the time at which the weighted survival curve crosses 0.50 on the y-axis; this can be read directly from the abscissa at the 50% mark. Censoring was applied to both the time-to-pregnancy and time-to-ART analyses.

For the time-to-pregnancy analysis, women who stopped trying to conceive for personal reasons, experienced a disease relapse, or did not respond to a form were censored at the date of their last known follow-up (Fig. S1). Women who successfully conceived were no longer followed beyond their first pregnancy, as this was the primary event of interest. For the time-to-ART analysis, women who ceased pregnancy attempts without ART use or were lost to follow-up were censored at the date of their last known follow-up.

We accounted for potential confounding factors by applying inverse probability weighting (IPW) to adjust the Kaplan–Meier conception curves, bar charts and comparative analyses.³¹ The propensity score method involves assigning a weight to each unexposed woman such that the weighted unexposed group has the same overall distribution of each confounding variable as the exposed group. We used a propensity score estimated with a generalized linear model (GLM).^{32,33} In line with best practices in epidemiological research,^{34–37} we reported the median time-to-pregnancy along with the absolute difference in median time-to-pregnancy between exposed and unexposed women, with 95% confidence intervals (CIs). No formal hypothesis testing was conducted, and results were interpreted based on effect sizes and confidence intervals to emphasize clinical relevance.

Subset analyses of time-to-pregnancy were performed (i) among women attempting conception without ART or cryopreserved material; (ii) among women who used ART or cryopreserved material.

We used a Cox multivariable proportional hazards model to evaluate the quantitative influence of various variables on time-to-pregnancy, including the impact of

BC treatments³⁸ with an α risk of 0.05 for hypothesis testing. The multivariable Cox proportional hazards model was built using a stepwise forward selection approach based on the “*add1*” method. Variables were sequentially added to the model until no further improvement in model fit was observed. At each step, a likelihood ratio test (alpha level = 0.05) was performed to compare the model with and without the newly added variable. Variables were included in the model if their addition significantly improved the model fit, as assessed by the likelihood ratio test. Two key variables—exposure status (“exposed or unexposed”) and “age at the start of pregnancy attempts”—were forced into the model, regardless of statistical significance, due to their clinical and methodological importance in the study design. While IPW was used for descriptive statistics and Kaplan–Meier analyses to ensure balance on baseline covariates between groups, we did not apply IPW in the Cox regression, because the multivariable Cox model enables direct adjustment for all relevant confounders within the model itself. All statistical analyses were performed in R. The fitted models included Kaplan–Meier survival analysis, and the multivariable Cox proportional hazards model to analyze time-to-pregnancy. In this analysis, patients were not weighted by IPW, to allow the evaluation of several of the variables among the 14 confounders identified for time-to-pregnancy. The model incorporated a time-dependent variable³⁹ and we addressed the violation of the proportional hazards assumption for one variable (identified by testing the correlation of Schoenfeld residuals with time)⁴⁰ by introducing affine time-dependent coefficients into the model.^{41,42} Additionally, we assessed the linearity assumption for continuous predictors using Martingale residual plots and applied appropriate transformations when necessary.

In this study, we used Kaplan–Meier survival analysis to estimate time-to-pregnancy and time-to-ART use. The Kaplan–Meier method calculates the probability of remaining event-free (*i.e.*, not becoming pregnant or not using ART) at each time point, allowing for right-censored data. Patients could be censored because they (i) stopped trying to conceive for personal reasons, (ii) were lost to follow-up before conception, or (iii) completed the study without achieving pregnancy or using ART. Censored patients were excluded from the risk set. These participants were right censored at their last follow-up date, meaning their data were included up to that point but did not contribute to later time points. Our estimates reflect the probability of a pregnancy occurring over time if both losses to follow-up and the occurrence of a competing event (stopping attempts to conceive, BC recurrence) were to be eliminated (and provided that the censoring arising from those events was not informative). However, we acknowledge that eliminating the competing events from our estimates may

lead to the probability of conceiving being overly interpreted in both groups. To avoid misinterpretation, we reported both Kaplan–Meier estimates and actual crude percentages of women who conceived or used ART.

For ART use, the apparent 100% cumulative incidence does not imply that all women used ART but rather reflects a statistical extrapolation of those who remained at risk. To improve transparency, crude percentages were included in the main text.

Role of the funding source

The funder was not involved in study design, or in the collection, analysis and interpretation of data, the writing of this article or the decision to submit it for publication.

Results

Study participants

From December 2018 through June 2019, 4351 women were enrolled (exposed $n = 517$, unexposed women $n = 3834$) (Fig. 1). In total, 1268 women withdrew from the Sentinelles network or did not complete any of the follow-up forms after inclusion in the study and were excluded from this analysis. There was a low gradual decrease in the number of respondents over the three-year study period (Fig. S2). On inclusion in the study, 2853 (exposed $n = 367$, unexposed women $n = 2486$) had available follow-up data and were not attempting to get pregnant. Among them, 642 (22.5%) of these women (76 exposed [20.7%] and 566 unexposed women [22.8%]) sought pregnancy during the time frame of the study and were included in the time-to-pregnancy analysis.

The characteristics of the exposed and unexposed women were significantly different before adjustment. Exposed women were older than unexposed women at the inclusion in the study (35.0 versus 30.0 years old) (Table S1). Unexposed women were made comparable to exposed women by implementing IPW for 14 key factors in the unexposed group (Fig. S3) (Table 1). After adjustment, age at start trying to get pregnant was 35.0 in exposed and 35.7 in unexposed weighted women, most women had no children (exposed 56.6% versus unexposed weighted women 54.5%). Most unweighted exposed women had prior chemotherapy (82.9%) or endocrine therapy (56.6%), and 59.2% had a fertility preservation procedure before treatment (oocytes 39.5%; embryos 15.8%; and/or ovarian cryopreservation 4%).

For the subsequent comparisons of outcomes between exposed and unexposed women (time-to-pregnancy, modes of conception, use of ART or cryopreserved material, pregnancy outcomes), analyses were performed after weighting the unexposed group only, using inverse probability weights to ensure

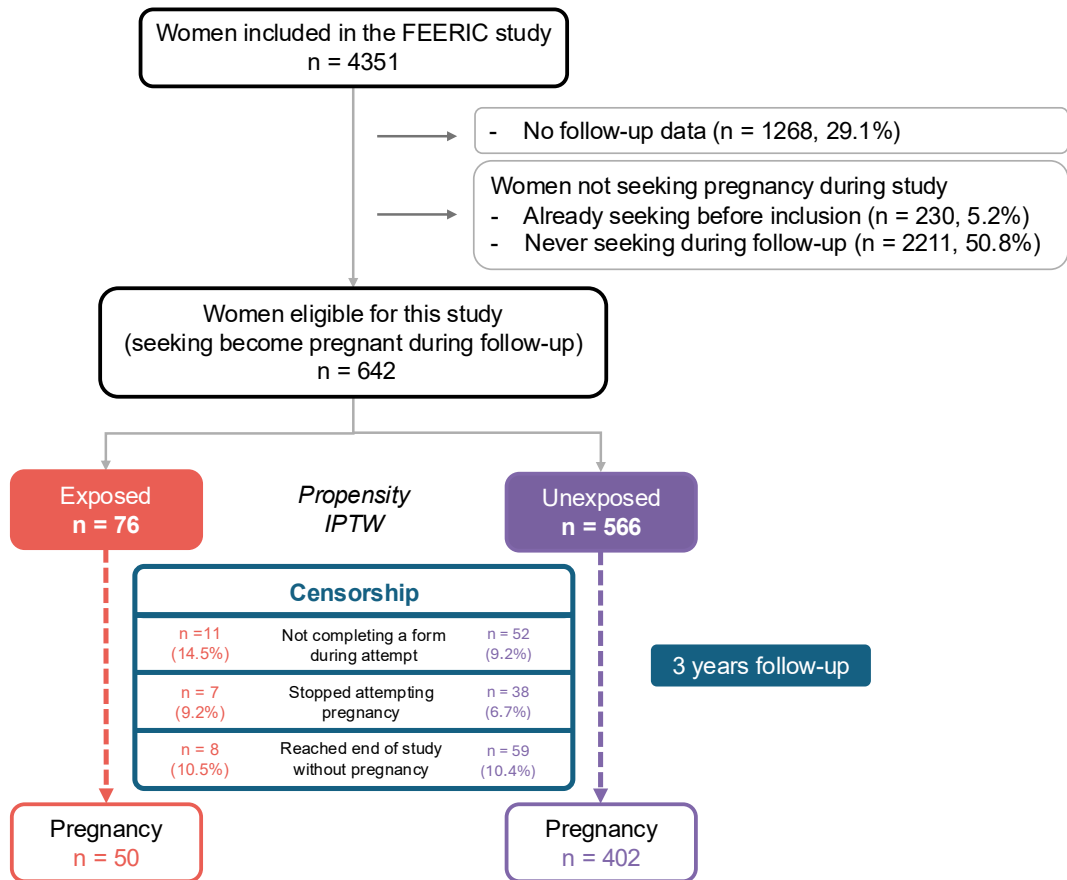


Fig. 1: Flow chart for the study cohort.

comparability with the exposed group on baseline characteristics. Conversely, for models analyzing factors associated with pregnancy success such as multivariable Cox regression, no weighting was applied; instead, all relevant covariates were directly adjusted for within the model.

Comparison of time-to-pregnancy between unweighted exposed and weighted unexposed women

With a median follow-up of 30.0 months, IQR [24.0–36.0], in the population of 76 exposed and 566 unexposed women who attempted to get pregnant after inclusion, 50 exposed (65.8%) and 402 weighted unexposed women (weighted percentage 71.0%) became pregnant at least once. When accounting for censoring (exposed/unexposed respectively: incomplete forms ($n = 11/n = 52$), ceased attempting pregnancy ($n = 7/n = 38$), reaching end of the study endpoint without pregnancy ($n = 8/n = 59$)). The median time-to-pregnancy was 5.0 months, 95% CI [3.0; 7.0] for exposed women and 3.0 months, 95% CI [2.0; 5.0] for unexposed women (difference in median time-to-pregnancy: 2.0 months, 95% CI [-2.5; 5]) (Fig. 2).

One year after the women started trying to get pregnant, the cumulative incidence of pregnancy was 72.7%, 95% CI [59.8; 84.3] for exposed and 78.5%, 95% CI [65.7; 89.1%] for unexposed women. Two years after the women started trying to get pregnant, these incidences had increased to 83.6%, 95% CI [68.4; 100.0%] for exposed and 84.2%, 95% CI [77.0; 96.6] for unexposed women.

Modes of conception and use of ART or cryopreserved material

Overall, 15 exposed women (19.8%) used either ART methods ($n = 7, 9.2%$) or cryopreserved material ($n = 8, 10.5%$; embryo, $n = 4$; oocyte, $n = 3$; ovarian cortex, $n = 1$) in their attempts to get pregnant, and 25 unexposed women (4.4%) used ART. Median time-to-ART was 13.0 months, 95% CI [11.0; 18.0] in exposed and 21.0 months, 95% CI [17.0; 32.0] in unexposed women (difference in median time-to-ART: -8 [-20.0; 1.0]) (Fig. 3). One year after the women started trying to get pregnant, the cumulative incidence of ART use was 41.1% [17.8–62.6%] in exposed versus 3.0% [0.4–8.2] in unexposed women.

Variable	Class	Unexposed women adjusted with IPTW			
		exposed (n=76)	unexposed (n=566)	Total (n =642)	P
Age at inclusion (years)	median [IQR]	35.0 [32.0-37.0]	34.0 [31.0 - 37.0]	34.1 [31.1 - 37.0]	0.83
Age started trying to get pregnant (years)	median [IQR]	35.0 [33.0-38.0]	36.0 [32.0 - 38.0]	35.9 [32.1 - 38.0]	0.59
Time from BC diagnosis to first attempt to get pregnant (months)	median [IQR]	43.0 [33.5-61.5]			
BMI (continuous, kg/m ²)	median [IQR]	22.5 [20.6 - 24.2]	22.7 [20.9 - 24.9]		0.64
BMI, by class (kg/m ²)	Normal weight	59 (77.6%)	431 (76.1%)	490 (76.3%)	0.86
	Underweight	2 (2.6%)	18 (3.2%)	20 (3.1%)	
	Pre-obesity	8 (10.5%)	59 (10.4%)	67 (10.4%)	
	Obesity	7 (9.2%)	58 (10.2%)	65 (10.1%)	
Educational level	High school or lower	4 (5.3%)	47 (8.3%)	51 (7.9%)	0.41
	University	72 (94.7%)	519 (91.7%)	591 (92.1%)	
Profession (class)	Intermediate	26 (34.2%)	199 (35.2%)	225 (35.0%)	0.61
	Low socioprofessional category or unemployed	10 (13.2%)	90 (15.9%)	100 (15.6%)	
	Superior	40 (52.6%)	277 (48.9%)	317 (49.4%)	
Marital status (current)	Single	8 (10.5%)	76 (13.4%)	84 (13.1%)	0.19
	Couple	68 (89.5%)	490 (86.6%)	558 (86.9%)	
Smoking status	Never	41 (53.9%)	288 (50.9%)	329 (51.2%)	0.49
	Current	6 (7.9%)	54 (9.5%)	60 (9.3%)	
	Former	29 (38.2%)	224 (39.6%)	253 (39.4%)	
Comorbid conditions	No	58 (76.3%)	436 (77.0%)	494 (76.9%)	0.20
	Yes	18 (23.7%)	130 (23.0%)	148 (23.1%)	
Comedication	Yes	12 (15.8%)	113 (20.0%)	125 (19.5%)	0.44
	No	64 (84.2%)	453 (80.0%)	517 (80.5%)	
Menstrual cycle length (at inclusion)	Normal	63 (82.9%)	464 (82.0%)	527 (82.1%)	0.61
	Short	4 (5.3%)	37 (6.5%)	41 (6.4%)	
	Long	8 (10.5%)	56 (9.9%)	64 (7.0%)	
	None	0 (0%)	0 (0%)	0 (0%)	
	Not known	1 (1.3%)	9 (1.6%)	10 (1.6%)	
Menstrual cycle regularity (at inclusion)	Regular	68 (89.5%)	503 (88.9%)	571 (88.9%)	0.40
	Irregular	8 (10.5%)	63 (11.1%)	71 (11.1%)	
	None	0 (0%)	0 (0%)	0 (0%)	
Prior gynecological surgery	No	62 (81.6%)	458 (80.9%)	520 (81%)	0.69
	Yes	14 (18.4%)	108 (19.1%)	122 (19%)	
Prior benign breast disease	No	58 (76.3%)	469 (82.9%)	527 (82.1%)	0.28
	Yes	18 (23.7%)	97 (17.1%)	115 (17.9%)	
Prior pregnancy	No	30 (39.5%)	185 (32.7%)	215 (33.5%)	0.93
	Yes	46 (60.5%)	381 (67.3%)	427 (66.5%)	
Number of children	0	43 (56.6%)	308 (54.5%)	351 (54.8%)	0.13
	1	25 (32.9%)	136 (24.1%)	161 (25.1%)	
	More than 1	8 (10.5%)	121 (21.4%)	129 (20.1%)	
History of infertility	Yes	11 (14.5%)	83 (14.7%)	94 (14.6%)	0.24
	No	65 (85.5%)	483 (85.3%)	548 (85.4%)	
Prior use of ART	No	75 (98.7%)	557 (98.4%)	632 (98.4%)	0.53
	Yes	1 (1.3%)	9 (1.6%)	10 (1.6%)	
Chemotherapy	No	13 (17.1%)			
	Yes		63 (82.9%)		
		Number of cycles ≤6	27 (35.5%)		
		Number of cycles ≥7	36 (47.4%)		
Hormonotherapy	No	33 (43.4%)			
	Yes	43 (56.6%)			
Early premature stop ET	No	31 (72.1%)			
	Yes	45 (27.9%)			
Fertility preservation procedure	Yes		45 (59.2%)		
		oocytes	30 (39.5%)		
		embryos	12 (15.8%)		
		ovarian cortex cryopreservation	3 (3.95%)		
	No	19 (40.8%)			

This table compares various characteristics between BC exposed women (n = 76) and unexposed women (n = 566) adjusted with IPW weights. IPW adjustment matches the distributions of confounding variables of the unexposed and exposed groups. The confounding variables included age at which the woman first started trying to get pregnant, nulliparity, professional and educational levels, marital status, BMI, smoking status, infertility history, previous use ART methods, menstrual cycle length and regularity, prior gynecological surgery, prior benign breast diseases, and comorbid conditions. Proportions were calculated by applying IPW weights to the unexposed group and the raw numbers were then determined by taking the closest integer to the product of the weighted proportion and the actual number in each category. p-values comparing distributions of variables between exposed and unexposed women demonstrate that significant differences existed between exposed and unexposed women for some variables before IPW adjustment, but that these differences were no longer significant after adjustment, as no p-values were below the threshold after adjustment. Abbreviation: IPW: inverse probability weighting. Data are presented as median [interquartile range, IQR] or mean (standard deviation, SD) for continuous variables depending on distribution and as number (percentage) for categorical variables. Non normal distribution occurs for the variables age at inclusion (unexposed), age started trying to get pregnant (unexposed), BMI (exposed and unexposed). There was no missing data. In cases when the continuous variable was normal in one exposure group but non-normal in the other, we opted to report median and interquartile range (IQR) consistently across both groups. Time from BC diagnosis to first attempt to get pregnant is only applicable to the exposed group and not defined in the unexposed group. Comparisons between groups were performed using the chi-squared test (or Fisher's exact test when appropriate) for categorical variables, and the Student's t-test (or Mann-Whitney U test for non-normally distributed variables) for continuous variables.

Table 1: Characteristics of the study participants after inverse probability weighting (IPW).

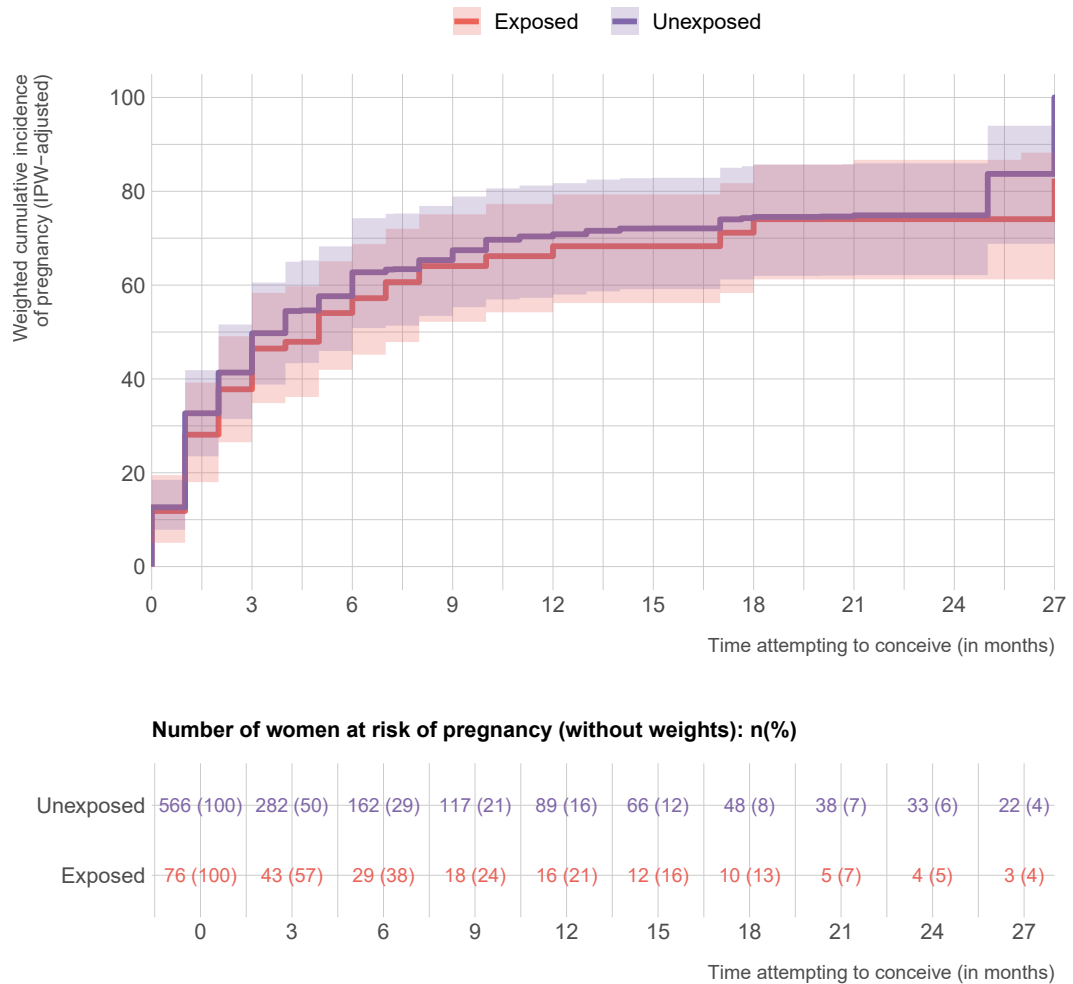


Fig. 2: Time-to-pregnancy comparison between exposed and unexposed women. All 642 women seeking pregnancy during the study period (76 exposed, 566 unexposed) are displayed in this Kaplan Meier curve. These curves depict the proportion of women attempting to get pregnant who became pregnant over time, with confidence intervals derived from 1000 bootstrap samples. The curve was adjusted by inverse probability weighting (IPW). Only the unexposed group was weighted using (IPW), while the exposed group remained unweighted. Numbers at risk are shown as unweighted (raw counts at each time point) to preserve transparency about how many participants remain under observation. The shaded areas represent 95% confidence bands estimated with 1000 bootstraps. This approach balanced the distribution of 14 confounding variables between exposed and unexposed women, making the weighted unexposed group comparable to the exposed group. Most women who attempted to get pregnant succeeded during the study period. In total, 19 exposed and 111 unexposed women were censored due to a lack of response or because they did not become pregnant before the end of the study. An additional 7 exposed and 38 unexposed women were censored because they changed their minds about trying to become pregnant. None of the 76 patients with prior BC who started trying to get pregnant after inclusion in the study experienced a relapse. Considering unweighted numbers, 417 unexposed women conceived during the study. Abbreviation: IPW: inverse probability weighting.

Time-to-pregnancy in the subpopulation of women trying to conceive spontaneously

We performed analyses on the 61 exposed and 541 unexposed women who attempted to get pregnant spontaneously (*i.e.*, without resorting to ART or using cryopreserved material). The median time-to-pregnancy was 3.0 months (95% CI [2.0; 5.0]) for both exposed and unexposed women (95% CI [2.0; 4.0]) (difference in

median time-to-pregnancy: -0.0 months [-2.0; 3.0]) (Fig. 4A). One year after the women had started trying to conceive, the cumulative incidence of pregnancy was 82.2%, 95% CI [67.7; 95.7] for exposed and 82.5%, 95% CI [70.2; 91.9] for unexposed women. Two years after they began trying to conceive, the cumulative incidence of pregnancy reached 91.1%, 95% CI [76.1; 100.0] for exposed and 89.4%, 95% CI [77.1; 99.0] for unexposed women.

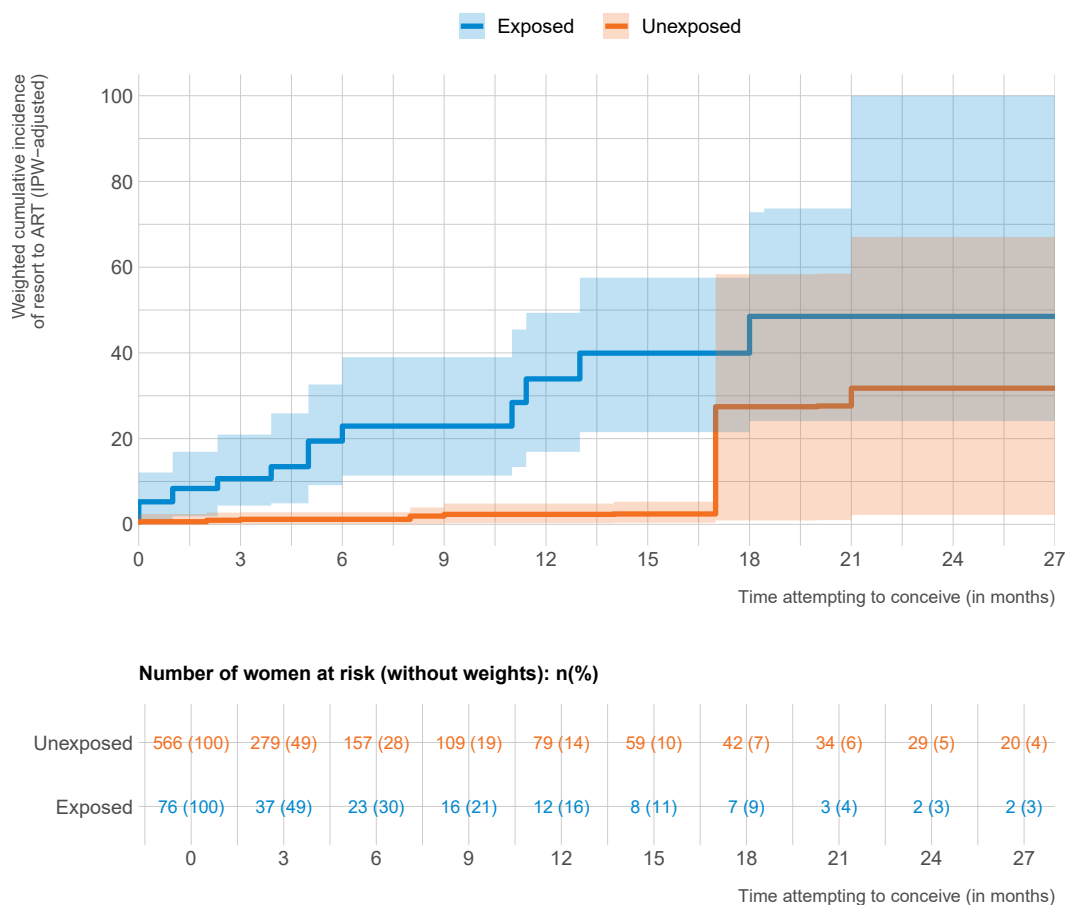


Fig. 3: Comparison of time-to-ART use between exposed and unexposed women. All 642 women seeking pregnancy during the study period (76 exposed, 566 unexposed) are displayed in this Kaplan Meier curve. Follow-up begins at the time women sought pregnancy. In these Kaplan-Meier, only the unexposed group was weighted using (IPW), while the exposed group remained unweighted. Numbers at risk are shown as unweighted (raw counts at each time point) to preserve transparency about how many participants remain under observation. The shaded areas represent 95% confidence bands estimated with 1000 bootstraps. Abbreviation: ART: assisted reproductive technologies.

Time-to-pregnancy in the subpopulation of women attempting to get pregnant using ART or cryopreserved material

Analyses were performed on the 15 exposed and 25 unexposed women who used ART or cryopreserved material. The median time-to-pregnancy was 14.0 months for exposed (95% CI [6.0–27.0]) and 17.6 months for unexposed women (95% CI [17.6–30.0]) (Fig. 4B). Three exposed women became pregnant after the use of cryopreserved material (embryos $n = 2$, oocyte, $n = 1$).

Factors associated with pregnancy success

Analyses of factors associated with pregnancy success were conducted using unweighted regression models, with all relevant covariates included directly in the multivariable analysis. Univariable and multivariable analyses identified age at attempt to get pregnant, parity at inclusion, menstrual cycle regularity, BMI, and ART

use as independent predictors of time-to-pregnancy, whereas no strong evidence of an association was observed for exposed/unexposed status (Table 2).

When considered as a binary variable (yes versus no), the use of ART methods was significantly associated with a lower probability of becoming pregnant ($p < 0.0001$). However, this association was variable over time (Fig. S4): ART use was associated with a lower probability of a rapid pregnancy, but the likelihood of pregnancy then increased over time. These findings applied to both BC patients and unexposed women.

Comparison of pregnancy outcomes between unweighted exposed and weighted unexposed women

Pregnancy outcomes did not differ significantly between exposed and unexposed women ($p = 0.35$). The most frequent outcomes were full-term pregnancies (80.0% for exposed versus 68.5% for unexposed women)

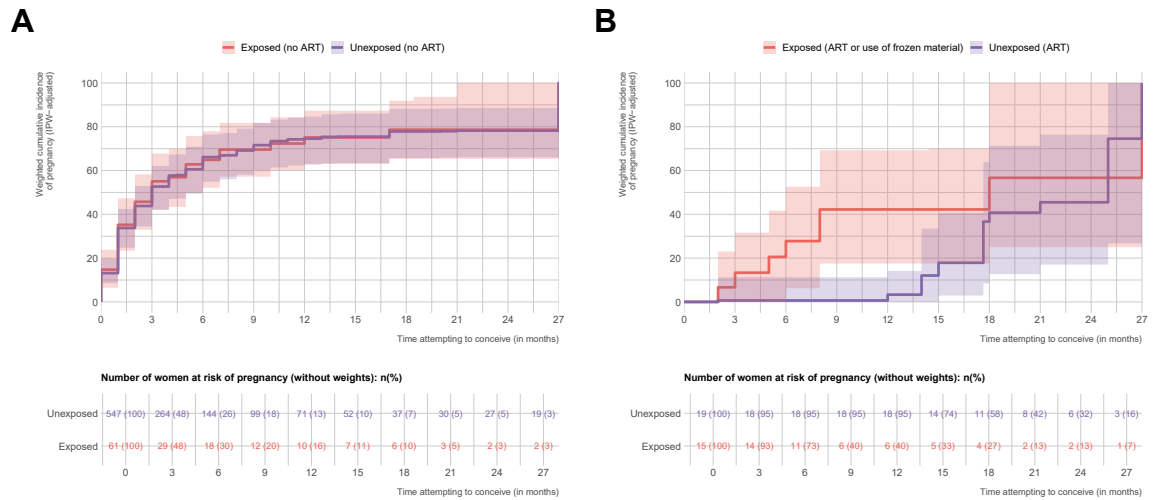


Fig. 4: Time-to-pregnancy comparison between exposed and unexposed women. A: Time-to-pregnancy for women attempting to get pregnant naturally. Only the 608 women who sought pregnancy without resort to ART or cryopreserved material (61 exposed, 547 unexposed) are displayed in this Kaplan Meier curve; B: Time-to-pregnancy for women using ART, including cryopreserved material. Only the 34 women who sought pregnancy with resort to ART or cryopreserved material (15 exposed, 19 unexposed) are displayed in this Kaplan Meier curve. In these Kaplan-Meier, only the unexposed group was weighted using (IPW), while the exposed group remained unweighted. Numbers at risk are shown as unweighted (raw counts at each time point) to preserve transparency about how many participants remain under observation. The shaded areas represent 95% confidence bands estimated with 1000 bootstraps. Abbreviation: ART: assisted reproductive technologies.

and miscarriages (8.0% versus 17.4%, respectively) (Fig. S5). Cesarean section rates did not differ significantly between exposed and unexposed women (24.0% versus 12.9%, respectively, $p = 0.11$; Fig. S6A). Similarly, there were no significant differences between the groups in terms of the rates of delivery complications (6.0% versus 11.1%, respectively, $p = 0.59$; Fig. S6B) and rates of malformations in the offspring (4.0% versus 2.5%, respectively, $p = 0.82$; Fig. S6C).

Discussion

In this prospective study, we assessed time-to-pregnancy in women with a history of BC and unexposed women without such a history. We found no strong evidence of a largely reduced time-to-pregnancy in exposed women seeking to become pregnant compared with unexposed women.

This finding is unprecedented, as most studies in this field have focused on chemotherapy-induced amenorrhea, fertility preservation options, or fertility biomarkers before and after chemotherapy, but to the best of our knowledge, none has assessed time-to-pregnancy in patients with a history of BC relative to a population without such a history. Our findings suggest that the time-to-pregnancy after BC is not significantly impaired relative to the unexposed population.

Over the last decade, there have been significant advances in fertility preservation techniques, including

ovarian tissue cryopreservation, oocyte and embryo freezing, and the use of gonadotropin-releasing hormone analogs. The rapid adoption of fertility preservation techniques was driven by recognition of the potential gonadotoxic effects of cancer treatments and a growing desire of young women to retain their reproductive potential after cancer treatment. The perceived risk and the availability of fertility preservation options led to the widespread use of these techniques, even though direct data linking cancer treatments to infertility remain limited, with most evidence based on clinical or biological proxies rather than clinical infertility definitions. Endorsement by professional societies and incorporation into clinical practice guidelines has normalized the use of fertility preservation, even in the absence of real data for infertility rates.

In parallel, evidence has emerged to suggest that infertility after BC concerns only a minority of patients. In the Young Women’s Breast Cancer multicenter prospective cohort study, 1026 patients with prior BC enrolled from 12 academic and community sites in the United States from 2006 through 2016 were studied; 69.2% of the women wishing to conceive in this study became pregnant within five years after diagnosis.²³ In a retrospective French cohort, 133 patients had 197 pregnancies following BC, and the median time-to-pregnancy was 4.3 months.⁴³ We also analyzed the data available at inclusion for the 517 patients in the cohort studied here with a history of prior BC. Between BC diagnosis and inclusion in the study, 133

Variable	Class	Univariable			Multivariable	
		HR [95% CI]	Log-rank test p	Class versus ref p	HR [95% CI]	Class versus ref p
Age at inclusion (years)		0.99 [0.96-1.00]	0.21			
Age at inclusion (years, by 5 y class)	<30	1	0.19			
	30-35	1.01 [0.82-1.23]		0.960		
	35-40	0.85 [0.65-1.13]		0.270		
	>40	0.57 [0.29-1.11]		0.096		
Age started trying to get pregnant (years, continuous)		0.98 [0.96-1.00]	0.19		0.97 [0.95-0.99]	0.018
Age started trying to get pregnant (years, by 5 y class)	<30	1	0.55			
	30-35	0.99 [0.80-1.22]		0.920		
	35-40	0.92 [0.71-1.20]		0.550		
	>40	0.69 [0.39-1.22]		0.20		
Time from BC diagnosis to first attempt to get pregnant (months)		1.0 [1.00-1.00]	0.8			
BMI, by class (kg/m ²)	Normal weight	1	0.047			
	Underweight	1.2 [0.78-1.80]		0.440	1.3 [0.89-1.90]	0.16
	Pre-obesity	0.84 [0.65-1.10]		0.180	0.79 [0.61-1.00]	0.069
	Obesity	0.67 [0.47-0.95]		0.023	0.59 [0.42-0.83]	0.0024
Educational level	High school or lower	1	0.13			
	University	1.5 [0.87-2.50]				
Profession (class)	Intermediate	1	0.53			
	Low socioprofessional category or unemployed	1.2 [0.87-1.60]				
	Superior	1.1 [0.88-1.30]				
Marital status (current)	Single	1	0.0076			
	Couple	1.6 [1.10-2.20]				
Smoking status	Never	1	0.31			
	Current	0.8 [0.58-1.10]				
	Former	1.3 [0.91-1.90]				
Comorbid conditions	No	1	0.85			
	Yes	0.98 [0.80-1.20]				
Comedication	Yes	1	0.62			
	No	1.1 [0.83-1.40]				
Menstrual cycle length (at inclusion)	Normal	1	0.0022			
	Short	1.2 [0.79-1.90]		0.37		
	Long	0.69 [0.51-0.93]		0.014		
	None	0.5 [0.25-1.00]		0.054		
	Not known	0.64 [0.45-0.92]		0.015		
Menstrual cycle regularity (at inclusion)	Regular	1	<0.0001		1	
	Irregular	0.75 [0.58-0.99]		0.039	0.78 [0.60-1.00]	0.067
	None	0.54 [0.38-0.76]		<0.0001	0.50 [0.36-0.70]	<0.0001
Prior gynecological surgery	No	1	0.16			
	Yes	0.82 [0.62-1.10]				
Prior benign breast disease	No	1	0.27			
	Yes	0.85 [0.64-1.10]				
Prior pregnancy	No	1	<0.0001			
	Yes	1.6 [1.30-2.00]		<0.0001		
Number of children	0	1	0.00083			
	1	1.3 [1.10-1.60]		0.013	1.3 [1.10-1.60]	0.0081
	More than 1	1.6 [1.20-2.10]		<0.0001	1.8 [1.30-2.30]	<0.0001
History of infertility	Yes	1	<0.0001			
	No	0.57 [0.41-0.80]		0.00096		
Prior use of ART	No	1	0.0061			
	Yes	0.41 [0.22-0.77]		0.0055		

(Table 2 continues on next page)

Variable	Class	Univariable			Multivariable	
		HR [95% CI]	Log-rank test p	Class versus ref p	HR [95% CI]	Class versus ref p
(Continued from previous page)						
Use of ART (time-dependent variable)	No [Constant effect]	1	<0.0001	<0.0001	1	<0.0001
	Yes [Constant effect]	0.31 [0.21–0.47]			0.044 [0.011–0.18]	
	No [Time-dependent effect]			1		
	Yes [Time-dependent effect]			2.7 [1.60–4.60]	<0.0001	
Exposed or unexposed	Unexposed	1	0.1		1	
	Exposed	0.79 [0.59–1.10]		0.88 [0.66–1.18]	0.39	
Number of chemotherapy cycles	No chemotherapy	1	0.11			
	Number of cycles ≤ 6	0.59 [0.35–1.00]				
	Number of cycles ≥ 7	0.99 [0.68–1.40]				
Hormonotherapy	No	1	0.018	0.027		
	Yes	0.63 [0.42–0.95]				

The p-values for the models refer to comparisons between each class and the reference, and the overall p-values from the global log-rank test. All p-values are two-sided. There was no missing data. Time from BC diagnosis to first attempt to get pregnant is only applicable to the exposed group and not defined in the unexposed group.

Table 2: Univariable and multivariable analyses of the factors associated with time-to-pregnancy.

pregnancies had occurred in 85 patients, and the median time-to-pregnancy was 3 months.²⁵ In the POSITIVE study,²⁴ for the 497 patients with a history of prior BC who interrupted endocrine therapy to try to get pregnant and for whom pregnancy status data were available, 74.0% reported becoming pregnant at least once during the trial. Notably, premenopausal patients aged 40–42 years had pregnancy rates of almost 50%, providing clear evidence that infertility rates are not particularly high after BC in women from an age class in which pregnancy rates would be expected to be lower.

In our study, women with prior BC were much more likely to use ART or cryopreserved material than unexposed women. A notable limitation of these results is the potential impact of sparse data bias leading to inflated effect estimates and reduced precision,⁴⁴ particularly in the estimation of risk ratios for ART use. The small number of ART users in the unexposed group resulted in very wide confidence intervals, which should be interpreted with caution. However, regardless of whether the pregnancy was spontaneous or resulted from the use of ART or cryopreserved material, time-to-pregnancy was similar in the exposed and unexposed groups. The rates of ART use in this cohort are lower than those reported in the POSITIVE study, in which 43% of patients used ART. These higher rates could be explained by (i) the greater age of the women in the POSITIVE trial (median age of 37 years versus 35.0 years at the start of the attempt to become pregnant in this study); (ii) the study design of the POSITIVE trial, in which the maximum expected duration of the interruption of endocrine therapy—including pregnancy and breastfeeding—was two years after inclusion in the study. Women may therefore have felt obliged to use ART if a spontaneous pregnancy did not occur rapidly.

In our study, the use of ART methods was associated with a lower likelihood of rapid conception, by pregnancy rates gradually increased, reaching those achieved by natural methods. In this cohort, the use of cryopreserved material was rare (8 patients), leading to only three pregnancies. These findings are consistent with those of a recent real-life study⁴⁵ evaluating the long-term results of 844 fertility preservation procedures, which showed that cryopreserved material was used in only 68 and resulted in only eight live births.

Our study, which had a prospective longitudinal design, is the first to compare time-to-pregnancy in patients surviving BC with that in the unexposed population. One methodological limitation of our study is the potential built-in selection bias associated with hazard ratio estimates⁴⁶; hazard ratios are conditional on those who have remained at risk and, as such, are subject to selection bias, even in the absence of censoring. For this reason, we reported differences in median time-to-pregnancy as estimates. We used IPW to align the characteristics of the patients without history of BC to those of patients with a history of BC. However, we cannot rule out the potential for despite this methodological approach, unmeasured and residual confounding inherent differences in the two populations that could not be captured by the observed variables. Also, our estimates are prone to model misspecification bias due to the parametric model we postulated for the propensity score. Selection bias due to informative loss-to-follow-up is another potential limitation of our study, and as with studies relying on self-reported questionnaires, our findings may also be affected by survey response errors and recall bias. Other limits include the recruitment bias inherent in the use of the Seintinelles network, which is based on voluntary participation, resulting in the enrollment of mostly

highly motivated, well-informed women, and may not fully represent more vulnerable groups, such as individuals from lower socioeconomic backgrounds, migrants, or those with limited healthcare access, which could limit the generalizability of our findings. However, both exposed and unexposed women were recruited through the same network, so such biases were probably consistent across the two groups. Plus, because we are targeting a population of women with a history of cancer, our results are not generalizable to another population. Finally, our study was conducted in France, where access to fertility preservation and ART is fully covered by the healthcare system. This unique context may limit the generalizability of our findings to countries where financial barriers impact access to fertility care. While no strong association was observed between BC history and time-to-pregnancy, the wide confidence interval suggests uncertainty in the estimates, which might result in an overall lack of statistical power. Our results should be interpreted in terms of effect sizes and their clinical implications rather than relying solely on statistical significance. Although we used tools and terminology commonly associated with causal inference—such as adjustment for confounders, and inverse probability weighting (IPW)—our aim was not to estimate the causal effect of BC itself, which is not a manipulable exposure. Instead, our goal was to estimate the difference in time-to-pregnancy between women with a history of BC and those without, accounting for differences in baseline characteristics.

This study provides significant insight into the fertility outcomes of BC survivors. By showing that the time-to-pregnancy in women seeking to become pregnant after BC is not largely reduced from that in women without BC, it challenges the long-held belief that BC treatments significantly impair probability of pregnancy and highlights the potential for spontaneous pregnancies in patients who have survived BC. From a clinical perspective, these results highlight the importance of comprehensive oncofertility counseling for young patients with BC. Healthcare providers should inform patients not only about fertility preservation options but also about the high likelihood of achieving pregnancy spontaneously after treatment. This balanced approach can help guide informed decisions regarding fertility preservation methods, considering both their benefits and limitations, and emphasizing the natural fecundity of BC survivors.

Once patients who have had BC decide to try to become pregnant, they could be advised to start by trying to conceive naturally rather than resorting to ART methods directly, as natural conception initially outperforms ART. Only after several months of unsuccessful attempts should patients be advised to use ART methods. The precise time cutoff for referral to fertility specialists is unclear, but probably lies at about 6–12 months, depending on patient age and prior medical history.

These perspectives can foster hope and provide young women faced with BC who hopes to have children with realistic expectations, ultimately improving their overall well-being and quality of life after treatment.

Contributors

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 All authors read and approved the final version of the manuscript. ASH, CS, AC, RB have verified the underlying data.

Data sharing statement

Data accessible upon reasonable request by contacting the corresponding author.

Declaration of interests

None of the authors of the study has any potential conflict of interest to disclose regarding the topic of this study.

Acknowledgements

The authors thank all the study participants from the Sentinelles Research Network.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.eclim.2025.103392>.

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