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Interrupting Endocrine Therapy to Attempt Pregnancy after Breast Cancer

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ABSTRACT

BACKGROUND

Prospective data on the risk of recurrence among women with hormone receptor–positive early breast cancer who temporarily discontinue endocrine therapy to attempt pregnancy are lacking.

METHODS

We conducted a single-group trial in which we evaluated the temporary interruption of adjuvant endocrine therapy to attempt pregnancy in young women with previous breast cancer. Eligible women were 42 years of age or younger; had had stage I, II, or III disease; had received adjuvant endocrine therapy for 18 to 30 months; and desired pregnancy. The primary end point was the number of breast cancer events (defined as local, regional, or distant recurrence of invasive breast cancer or new contralateral invasive breast cancer) during follow-up. The primary analysis was planned to be performed after 1600 patient-years of follow-up. The prespecified safety threshold was the occurrence of 46 breast cancer events during this period. Breast cancer outcomes in this treatment-interruption group were compared with those in an external control cohort consisting of women who would have met the entry criteria for the current trial.

RESULTS

Among 516 women, the median age was 37 years, the median time from breast cancer diagnosis to enrollment was 29 months, and 93.4% had stage I or II disease. Among 497 women who were followed for pregnancy status, 368 (74.0%) had at least one pregnancy and 317 (63.8%) had at least one live birth. In total, 365 babies were born. At 1638 patient-years of follow-up (median follow-up, 41 months), 44 patients had a breast cancer event, a result that did not exceed the safety threshold. The 3-year incidence of breast cancer events was 8.9% (95% confidence interval [CI], 6.3 to 11.6) in the treatment-interruption group and 9.2% (95% CI, 7.6 to 10.8) in the control cohort.

CONCLUSIONS

Among select women with previous hormone receptor–positive early breast cancer, temporary interruption of endocrine therapy to attempt pregnancy did not confer a greater short-term risk of breast cancer events, including distant recurrence, than that in the external control cohort. Further follow-up is critical to inform longer-term safety. (Funded by ETOP IBCSG Partners Foundation and others; POSITIVE ClinicalTrials.gov number, NCT02308085.)

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Breast cancer is the most common type of cancer among women 40 years of age or younger, and the incidence continues to rise, with an estimated 12,000 new cases occurring annually in the United States alone; the incidence is even higher in developing countries.[1,2] Fertility preservation and subsequent childbearing are of paramount importance to many of these patients.[3,4] Fertility concerns affect quality of life and may negatively affect treatment decisions and disease outcomes because some patients may forgo recommended treatments owing to the risk of infertility.[4-6]

Among women with hormone receptor–positive early breast cancer, concerns that subsequent pregnancy might increase the risk of breast cancer recurrence can affect decisions regarding pregnancy. However, retrospective data have shown that subsequent pregnancy is not associated with worse disease outcomes.[7-9] Decision making is further complicated by the recognition that the receipt of adjuvant endocrine therapy for 5 to 10 years substantially reduces the risk of recurrence but that during this time, pregnancy is contraindicated and ovarian reserve is naturally declining.[10,11]

Prospective data regarding pregnancy after breast cancer and interruption of endocrine therapy to attempt pregnancy are lacking. The POSITIVE (Pregnancy Outcome and Safety of Interrupting Therapy for Women with Endocrine Responsive Breast Cancer) trial was designed to address the safety, with respect to a breast cancer event, of temporary interruption of endocrine therapy to attempt pregnancy in premenopausal women with endocrine-responsive early breast cancer. Here, we present results of the prespecified primary analysis of breast cancer outcomes, as well as pregnancy and birth outcomes.

METHODS

TRIAL DESIGN AND OVERSIGHT

The POSITIVE trial is an international, multicenter, investigator-initiated, single-group trial that was collaboratively designed and conducted by the International Breast Cancer Study Group (IBCSG; the coordinating group) and cooperative groups affiliated with the Breast International Group, and the Alliance for Clinical Trials in Oncology (including the National Clinical Trials Network of the National Cancer Institute and others). The trial design and characteristics of the patients at enrollment have been published previously.[12]

IBCSG was responsible for the trial design, data collection, trial management, and statistical analysis. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, which is available with the full text of this article at NEJM.org. Patients were enrolled at 116 centers across 20 countries on 4 continents.[12] The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, the principles of the Declaration of Helsinki, and local clinical research regulations. The protocol was approved by the institutional review board at each participating center. All the patients provided written informed consent. The progress of the trial was reviewed every 6 months by the IBCSG data and safety monitoring committee.

PATIENTS

Women were eligible for the trial if they were 42 years of age or younger; had had stage I, II, or III hormone receptor–positive breast cancer; had received adjuvant endocrine therapy for at least 18 months and for no more than 30 months; and wished to temporarily discontinue therapy to attempt pregnancy. Local results of estrogen-receptor, progesterone-receptor, and human epidermal growth factor receptor 2 testing were used for determination of the receptor status; the cutoff point for hormone-receptor positivity was 1% or higher. Patients could have received previous chemotherapy, with or without fertility preservation, and were required to have no clinical evidence of recurrence.

TRIAL PROCEDURES

Patients discontinued endocrine therapy within 1 month before enrollment. The protocol specified that patients have a 3-month washout period before attempting pregnancy. The duration of interruption of endocrine therapy could be up to 2 years to allow for attempting pregnancy, conception (or failure to conceive), delivery, and breast-feeding (if desired and if feasible). The

use of assisted reproductive technology was allowed. If pregnancy did not occur after 1 year, a fertility assessment was strongly encouraged. After pregnancy and breast-feeding were completed or after unsuccessful conception, resumption of endocrine therapy to complete the planned 5 to 10 years of treatment was strongly recommended. Patient assessments followed a regular schedule (Fig. S1 in the Supplementary Appendix, available at NEJM.org).

END POINTS

The primary end point was the number of breast cancer events (defined as ipsilateral or locoregional invasive disease, distant recurrence, or contralateral invasive breast cancer) observed during the total patient-years of follow-up. The prespecified time-to-event end points were freedom from the occurrence of a breast cancer event and freedom from recurrence of breast cancer at a distant site. Secondary end points for which data are presented in the current report include the ability to become pregnant, pregnancy outcomes, birth outcomes, breast-feeding, the use of assisted reproductive technology, resumption of endocrine therapy, and distant recurrences (see Section 3.5 in the Supplementary Appendix).

STATISTICAL ANALYSIS

We used a group-sequential Poisson approach to design the trial (see Section 3.2 in the Supplementary Appendix). The Endocrine Working Group of the joint Breast International Group–North American Breast Cancer Group collaboration determined that a 2% annual risk of a breast cancer event was acceptable (and that a risk of 4% was unacceptable) on the basis of results from two trials: Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT).[13] The planned sample in the POSITIVE trial was 500 patients. Interim analyses were scheduled to be performed after 270, 600, and 1100 patient-years had accumulated; the primary analysis was planned to be performed after 1600 patient-years of follow-up. If 46 or fewer breast cancer events were observed by the time of the primary analysis, the interruption of endocrine therapy to attempt pregnancy would be considered to be safe in the short term. The probability of declaring treatment interruption unsafe would be 1.00 if the true annual risk of a breast cancer event were 4% and 0.05 if the true annual risk were 2%.

We estimated the cumulative incidence functions for freedom from a breast cancer event in the primary efficacy analysis population (which included all patients for whom data collected after enrollment were available) using the Kaplan–Meier product-limit method. The 3-year cumulative incidence of breast cancer events and corresponding 95% two-sided confidence intervals were calculated.

To supplement the primary analysis, we identified an external control cohort that comprised 1499 patients from SOFT and TEXT[13] (both of which were designed to compare different adjuvant endocrine strategies in premenopausal women with hormone receptor–positive breast cancer) who would have been eligible for the POSITIVE trial.[14] Three methods were used to compare the percentages of patients who were free from breast cancer events and free from distant recurrence of breast cancer in the POSITIVE trial with those in the control cohort. The bootstrap-matching method[15] — the primary method for comparison — averaged results from 5000 bootstrap samples that were matched on the basis of age (<35, 35 to 39, or 40 to 42 years), body-mass index (the weight in kilograms divided by the square of the height in meters; <25 [or unknown] or ≥25), number of positive lymph nodes (0, 1 to 3, 4 to 9, or unknown), previous chemotherapy (yes or no), and previous use of an aromatase inhibitor (yes or no). The second method was a direct-comparison method that compared the results in the treatment-interruption group with the results in the unadjusted control cohort. The third method, the use of multivariable Cox proportional-hazard models, estimated hazard ratios. For both end points, data were censored at the date on which the patient was last known to be free from an event. Additional information is provided in Section 3.3 in the Supplementary Appendix. Time-dependent covariate Cox models and landmark analyses were used to evaluate the effect of pregnancy on breast cancer outcomes; additional information is provided in Section 3.4 in the Supplementary Appendix.

The secondary end points were evaluated in all the patients for whom follow-up data regarding disease, pregnancy, and endocrine-therapy

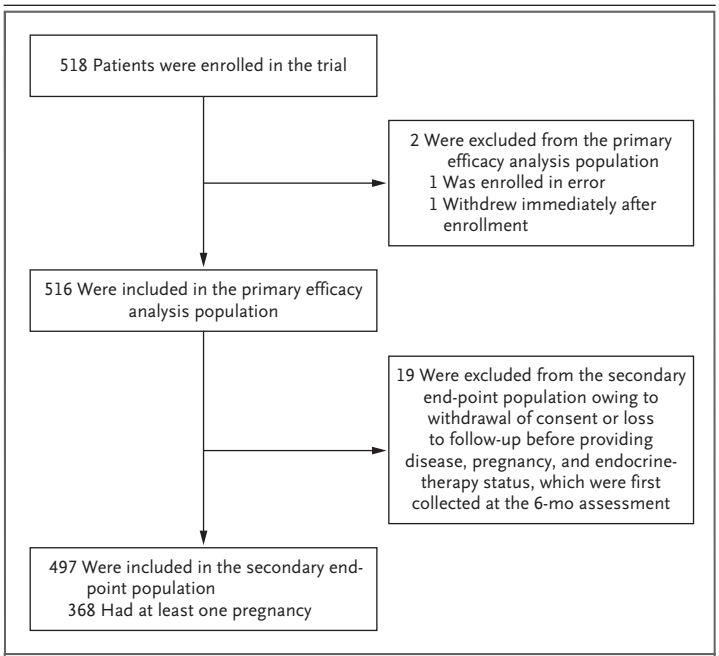

Figure 1. Trial Enrollment and Analysis Populations.

status were provided (the secondary end-point population). There was no adjustment for multiplicity of testing, and secondary end-point analyses were considered to be descriptive. Additional information is provided in Sections 3.5 and 3.6 in the Supplementary Appendix.

RESULTS

PATIENTS

From December 2014 through December 2019, a total of 518 patients were enrolled, 516 of whom were included in the primary efficacy analysis population (Fig. 1). After each interim analysis, the data and safety monitoring committee recommended that the trial continue. As of the database lock on June 1, 2022, a total of 1638 patient-years had been accrued; the median follow-up was 41 months (3.4 years).

The median time from breast cancer diagnosis to enrollment was 29 months (interquartile range, 25 to 32). The median age at enrollment was 37 years (range, 27 to 43), with 34.3% of the patients younger than 35 years of age[12] (Table 1 and Table S1). A majority of the patients (93.4%) had stage I or II disease; 29.3% had 1 to 3 positive nodes and 4.5% had 4 to 9 positive nodes. Most of the patients (62.0%) had received chemotherapy.

BREAST CANCER EVENTS AND DISTANT RECURRENCES

A total of 44 patients in the treatment-interruption group had a breast cancer event, a result that was within the prespecified safety threshold of 46 events (Table S2). The 3-year incidence of breast cancer events was 8.9% (95% confidence interval [CI], 6.3 to 11.6) in the treatment-interruption group and 9.2% (95% CI, 7.6 to 10.8) in the external control cohort (absolute difference, −0.2 percentage points; 95% CI, −3.1 to 2.8), as estimated by the bootstrap-matching method (Fig. 2A). The adjusted hazard ratio in the treatment-interruption group as compared with the control cohort was 0.81 (95% CI, 0.57 to 1.15). There were 22 distant recurrences. The 3-year incidence of distant recurrences was 4.5% (95% CI, 2.7 to 6.4) in the treatment-interruption group and 5.8% (95% CI, 4.5 to 7.2) in the control cohort (absolute difference, −1.4 percentage points; 95% CI, −3.5 to 1.0), as estimated by the bootstrap-matching method, with a hazard ratio of 0.70 (95% CI, 0.44 to 1.12) (Fig. 2B). The results of the comparisons were similar when the direct-comparison method was used (Figs. S2 and S3). Observed differences in the 3-year cumulative incidence of breast cancer events, which was analyzed according to demographic and disease characteristics at enrollment and according to previous treatment, were consistent with expectations for known prognostic factors, although confidence intervals were wide owing to the small numbers of events in many of the subgroups (Fig. 3).

PREGNANCY AND BIRTH OUTCOMES

Information regarding pregnancy status was provided by 497 patients (Fig. 1). Among these patients, 368 (74.0%) reported becoming pregnant at least once during the trial (Table S3). In a multivariate-adjusted Cox model, the hazard ratio for a breast cancer event associated with pregnancy was 0.53 (95% CI, 0.27 to 1.04) (Table S4). Similarly, a landmark analysis showed no increased risk of breast cancer events associated with pregnancy (Fig. S4).

Successful pregnancy was evaluated according to demographic and disease characteristics

at enrollment and according to previous treatment. A logistic-regression model showed that younger age was the only factor that was substantially related to successful pregnancy (Table S5), with 85.7% of the patients younger than 35 years of age becoming pregnant as compared with 76.0% of those 35 to 39 years of age and 52.7% of those 40 to 42 years of age. Among the 497 patients who provided information regarding pregnancy status, 215 (43.3%) reported that they had used assisted reproductive technology during their participation in the trial.

The first occurrence of pregnancy was estimated in a time-to-event analysis, in which resumption of endocrine therapy, no longer attempting to become pregnant, and cancer events were considered to be competing risks. The cumulative incidence of a first pregnancy in the presence of competing risks was 28.8% at 6 months from enrollment, 53.6% at 12 months, and 70.5% at 24 months (Fig. S5).

At the time of the database lock, 317 of the women had had at least one live birth, which constituted 63.8% of the 497 women in the secondary end-point population and 86.1% of the 368 women who had had at least one pregnancy (Table 2). A total of 41 patients (11.1% of the 368 women who had had at least one pregnancy) reported at least one pregnancy complication; the most common complications were hypertension or preeclampsia (3.8%), diabetes mellitus (2.4%), and placental abnormalities (1.6%) (Table S6). Among the 507 pregnancies that occurred during the trial, 350 (69.0%) resulted in live births, 230 (65.7%) of which were vaginal deliveries (Tables S7 and S8).

The 350 pregnancies resulting in live births yielded a total of 365 babies (335 singleton births and 15 sets of twins). Adverse birth outcomes included low birth weight (<2500 g) in 29 babies (7.9%) and birth defects in 8 (2.2%) (Tables S9 and S10). Among the 317 women who had at least one live birth, breast-feeding was reported by 196 (61.8%) (Table S11).

RESUMPTION OF ENDOCRINE THERAPY AND DURATION OF INTERRUPTION

Among 415 patients who were disease-free for at least 2 years, 304 (73.3%) had resumed endocrine therapy at some point after treatment interruption (Table S12). Half the patients had resumed therapy within 26 months after treatment interruption. Among the 111 women who had not yet resumed endocrine therapy at the time of the database lock, 88 (79.3%) reported that they were currently attempting to become pregnant, that they were actively or recently pregnant, or that they were actively or recently breast-feeding (Table S13). The analysis of the cumulative incidence of resumption of endocrine therapy in the presence of competing risks in the secondary end-point population showed that 15.4% of the patients who had been expected to resume this therapy had not done so by 48 months after treatment interruption (Fig. S6).

DISCUSSION

In the current trial, we observed 44 breast cancer events during 1638 patient-years of follow-up, a result that was close to, but did not exceed, the primary analysis safety threshold of 46 breast cancer events during 1600 patient-years. In addition, the 3-year cumulative incidences of breast cancer events and distant recurrences (8.9% and 4.5%, respectively) were similar to those in an external control cohort. These results suggest that although endocrine therapy for a period of 5 to 10 years substantially improves disease outcomes in patients with hormone receptor–positive early breast cancer,[11,13,16,17] a temporary interruption of therapy to attempt pregnancy does not appear to have an appreciable negative short-term effect.

This trial advances our understanding of the effect of subsequent pregnancy on outcomes on the basis of two main factors: only women with hormone receptor–positive disease who desired pregnancy were enrolled, and the effect of temporary interruption (as opposed to discontinuation) of endocrine therapy to attempt to become pregnant was studied prospectively. Previous retrospective data in heterogeneous populations showed no clear evidence of worse survival among women who became pregnant or had a live birth after breast cancer than among those who did not subsequently become pregnant or have a live birth.[7,9] In a meta-analysis involving more than 112,000 patients with breast cancer, disease-free survival and overall survival were higher among those who became pregnant (7505 women) than among those who did not become

Table 1. Demographic and Clinical Characteristics in the Treatment-Interruption Group and the Matched Control Cohort.*

Variable	Unadjusted Cohorts		Bootstrap-Matched Cohorts†	
	Treatment-Interruption Group (N=516)‡	Control Cohort (N=1499)	Treatment-Interruption Group	Control Cohort
	number of patients (percent)		*percent*	
Age group — yr§				
<35	177 (34.3)	286 (19.1)	34.3	34.3
35–39	221 (42.8)	573 (38.2)	42.8	42.8
40–42	118 (22.9)	640 (42.7)	22.9	22.9
Race¶				
White	397 (76.9)	1246 (83.1)	76.9	83.9
Non-White	118 (22.9)	236 (15.7)	22.9	14.6
Black	7 (1.4)	—	1.4	—
Asian	90 (17.4)	—	17.4	—
Other	21 (4.1)	—	4.1	—
Unknown	1 (0.2)	17 (1.1)	0.2	1.5
Body-mass index‖				
<25 or unknown	377 (73.1)	905 (60.4)	73.1	73.1
≥25	139 (26.9)	594 (39.6)	26.9	26.9
Previous births				
None	387 (75.0)	415 (27.7)	75.0	33.3
At least one	129 (25.0)	1068 (71.2)	25.0	65.7
Unknown	0	16 (1.1)	0	1.0
Tumor size — cm				
≤2	331 (64.1)	847 (56.5)	64.2	62.3
>2 to ≤5	161 (31.2)	541 (36.1)	31.2	31.2
>5	21 (4.1)	64 (4.3)	4.1	3.5
Unknown	3 (0.6)	47 (3.1)	0.6	3.1
No. of positive lymph nodes				
0	342 (66.3)	794 (53.0)	66.3	66.3
1–3	151 (29.3)	523 (34.9)	29.2	29.3
4–9	23 (4.5)	175 (11.7)	4.4	4.5
Unknown	0	7 (0.5)	0	0
Tumor histologic grade**				
1	89 (17.2)	223 (14.9)	17.3	17.7
2	252 (48.8)	770 (51.4)	48.9	51.2
3	172 (33.3)	478 (31.9)	33.3	29.5
Unknown	3 (0.6)	28 (1.9)	0.6	1.5
Adjuvant endocrine therapy††				
SERM alone	215 (41.7)	315 (21.0)	41.7	24.5
SERM and OFS	184 (35.7)	578 (38.6)	35.7	53.0

Table 1. (Continued.)

Variable	Unadjusted Cohorts		Bootstrap-Matched Cohorts†	
	Treatment-Interruption Group (N=516)‡	Control Cohort (N=1499)	Treatment-Interruption Group	Control Cohort
	number of patients (percent)		*percent*	
AI and OFS	82 (15.9)	495 (33.0)	15.9	18.4
Other	35 (6.8)	111 (7.4)	6.8	4.1
Previous neoadjuvant or adjuvant chemotherapy	320 (62.0)	1140 (76.1)	62.0	63.9

* Data for some characteristics of the control cohort have not been included owing to a lack of comparable data collection or relevance. Percentages may not total 100 because of rounding. AI denotes aromatase inhibitors, OFS ovarian function suppression, and SERM selective estrogen-receptor modulator.

† For each bootstrap iteration, the treatment-interruption group was sampled with replacement. In addition, the control cohort was sampled with replacement to match the bootstrap treatment-interruption group on the basis of the proportional frequencies of the relevant patient, disease, and treatment characteristics of the bootstrap treatment-interruption group. This process was repeated 5000 times (see Section 3.3.2 in the Supplementary Appendix). The percentages shown are the percentages of all patients across all bootstrap iterations according to group and cohort.

‡ Among the 516 patients in the primary efficacy analysis population, 316 (61.2%) were enrolled at a European site, 116 (22.5%) at a North American site, and 84 (16.3%) at a site in the Asia Pacific region. Among the 134 patients who had human epidermal growth factor receptor 2 (HER2)–positive disease, 131 received HER2-targeted treatment.

§ The age used in the analysis in the treatment-interruption group was the age at enrollment. The age used in the analysis in the control cohort was the age after 2 years of adjuvant endocrine therapy.

¶ Race was determined by the investigator.

‖ The body-mass index was unknown in 1.2% of the patients in the treatment-interruption group, in 2.3% of the patients in the control cohort, and in 2.7% of the bootstrap-matched samples.

** Tumor grade was assessed locally as histologic grade 1 (well differentiated), 2 (moderately differentiated), or 3 (poorly differentiated).

†† Adjuvant endocrine therapy for the treatment-interruption group refers to the adjuvant endocrine therapy that patients had received before enrollment. Patients in the control cohort had received adjuvant endocrine therapy for up to 2 years.

pregnant, even after adjustment for potential confounders for which data were available.[7] Similarly, in a cohort of 5181 Scottish women in whom breast cancer was diagnosed at 20 to 39 years of age, overall survival was higher among the 290 women who had a subsequent live birth than among the 1682 women who did not have a subsequent live birth (hazard ratio for death, 0.65; 95% CI, 0.50 to 0.85), regardless of hormone-receptor status, receipt of chemotherapy, the timing of the birth, or the age of the woman.[9]

In the current trial, nearly three quarters of the women had at least one pregnancy, most of which (70.5%) occurred within 2 years after enrollment. More than 40% of the women used assisted reproductive technology during the trial — a relatively high percentage that was probably attributable, at least in part, to the practice of using oocytes or embryos that are banked before gonadotoxic treatment in order to achieve pregnancy and resume endocrine therapy rapidly.[18] In addition, the percentage of women who became pregnant (53.6% at 12 months) appears to be higher than the percentages reported among women of similar age (irrespective of a breast cancer diagnosis).[19,20]

Recent research involving the assessment of pregnancy and birth outcomes after breast cancer has shown increased risks of cesarean section, preterm birth, and low birth weight.[7] However, the timing of pregnancy appears to be critical; women who conceive within 1 year after initiation of chemotherapy for any cancer have a higher risk of preterm birth than women who conceive at least 1 year after starting chemotherapy.[21] In our trial, women were enrolled at least 18 months after initiation of chemotherapy, and the percentages of women with pregnancy complications are consistent with those of populations of women of a similar age who did not have breast cancer.[22] Endocrine therapy —

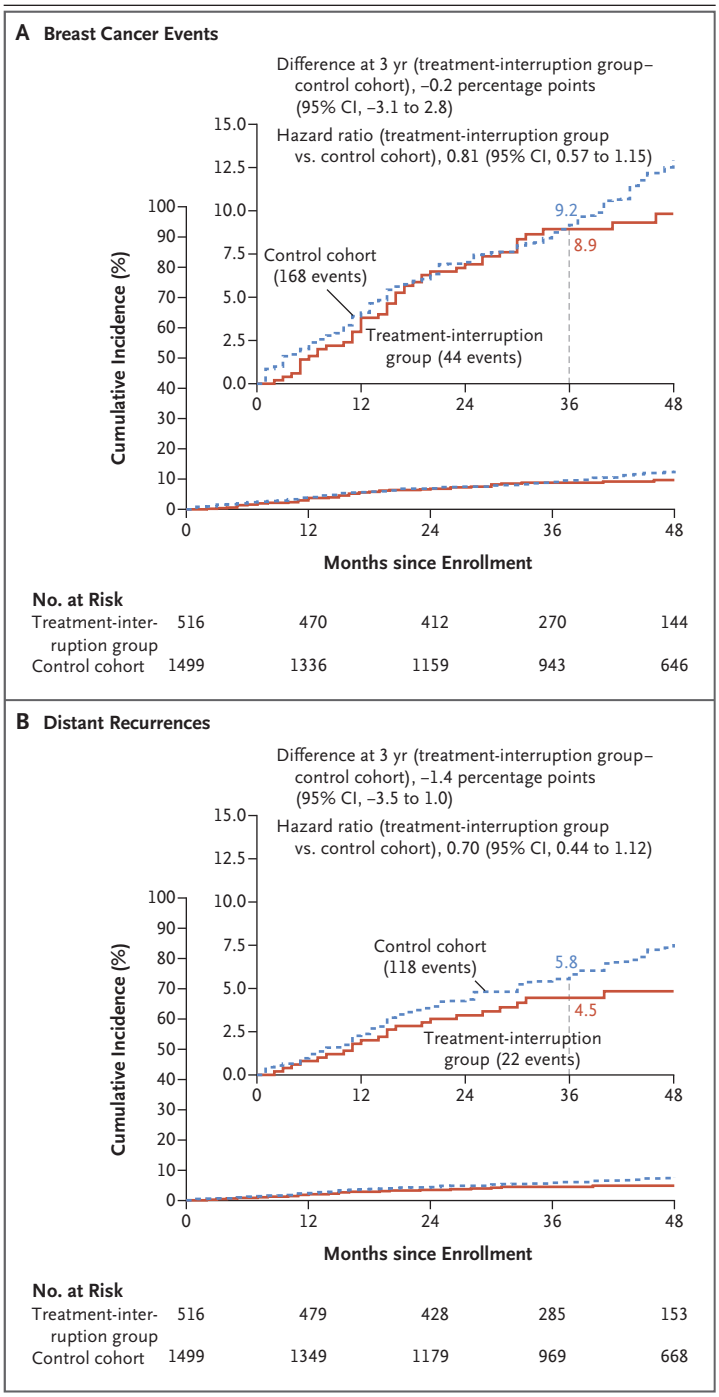

Figure 2. Cumulative Incidence of Breast Cancer Events and Distant Recurrences.

Estimates of the cumulative incidence of breast cancer events (Panel A) and distant recurrences of breast cancer (Panel B) were compared with the use of the bootstrap-matching method. Plots showing the results of both the bootstrap-matching method and the direct-comparison method are provided in Figures S2 and S3. Of the 22 total distant recurrences (Panel B), 21 were the first site of recurrence, and 1 occurred after a local recurrence. The percentage-point differences between the 3-year percentages in the treatment-interruption group in this trial and the external control cohort may not match the absolute differences shown because of rounding. The 0 time point on the x axis for the treatment-interruption group is the date of enrollment after 18 to 30 months of previous endocrine therapy (median duration of previous endocrine therapy, 23 months). The 0 time point on the x axis for the control cohort refers to the date by which the patients had received endocrine therapy for 2 years (see Sun et al.[15]). The insets show the same data on an expanded y axis.

tamoxifen in particular — can be teratogenic and thus should be avoided during pregnancy.[23] The protocol-specified washout period of 3 months between pausing endocrine therapy and attempting pregnancy took into account the median half-lives of selective estrogen-receptor modulators and aromatase inhibitors.[24] The incidence of birth defects was low (2.2% of the 365 offspring) and consistent with general population estimates.[25] Investigations focusing on assisted reproductive technology, birth outcomes, and breast-feeding are under way.

Limitations and challenges of the current trial should be considered. First, the median follow-up was only 3.4 years, and the protocol-specified 10-year follow-up will be critical to inform the safety of interruption of adjuvant endocrine therapy, especially given the long-term risk of recurrence of hormone receptor–positive breast cancer. Longer-term data are also needed to evaluate the effect of the timing of pregnancy as well as the effect of resumption of endocrine therapy on the risk of subsequent breast cancer events. Second, during the design of the trial, we were concerned that women would not resume therapy, despite our intention to study the temporary interruption, rather than the permanent discontinuation, of endocrine therapy. However, the percentage of patients who had not resumed therapy (15.4% at the time of the database lock) appears to be similar to percentages reported among young patients in previous trials (including SOFT and TEXT, in which nearly 20% of women discontinued the protocol-assigned endocrine therapy).[26] Third, although the trial enrolled a substantial number of women with

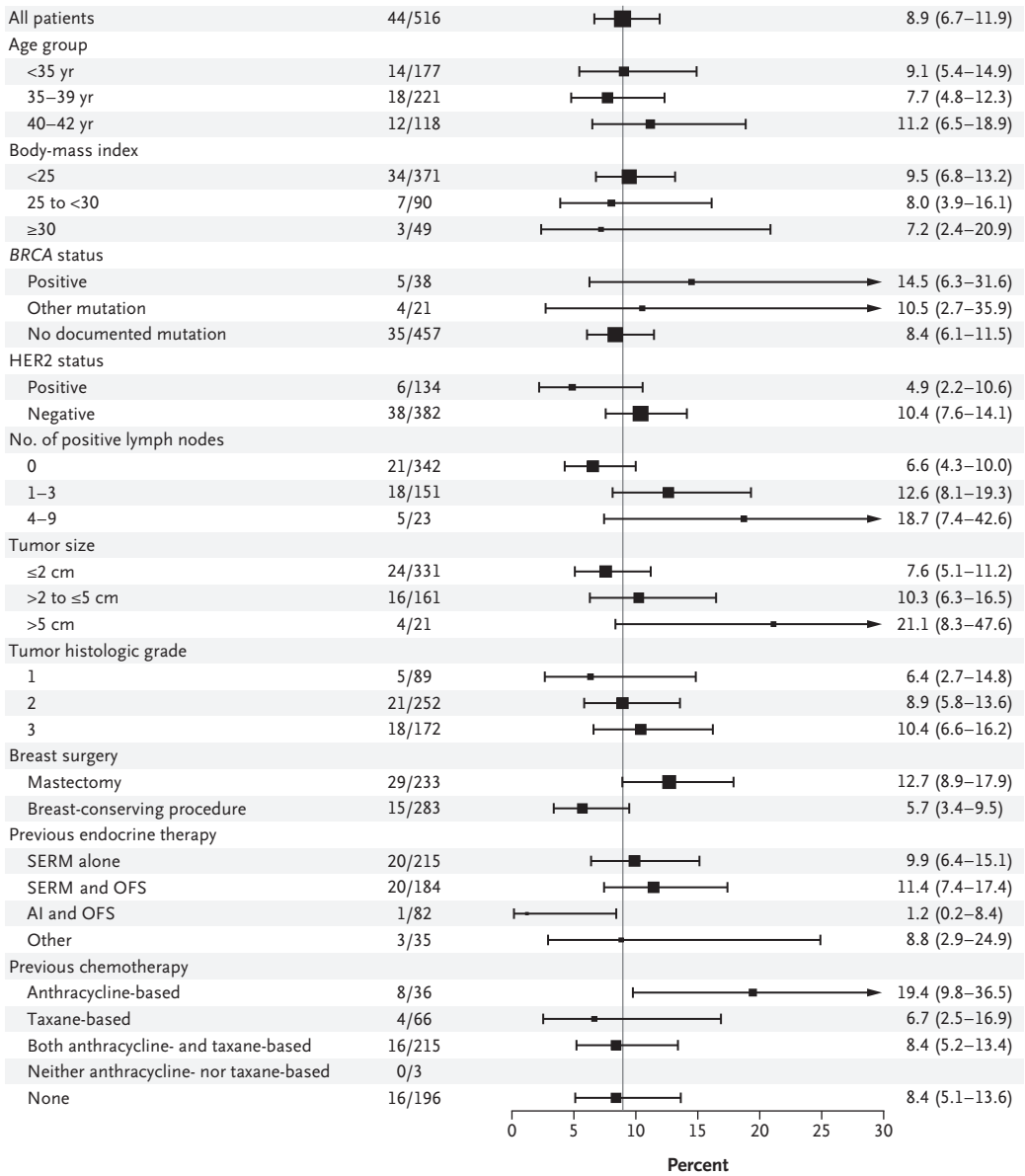

Figure 3. Cumulative Incidence of Breast Cancer Events at 3 Years, According to Demographic and Disease Characteristics and Previous Treatment.

Six patients were excluded from the analysis according to body-mass index owing to missing data. The subgroup labeled "no documented mutation" includes one patient whose *BRCA* mutation status was unknown. Three patients were excluded from the analyses according to tumor size and tumor grade owing to missing data. Tumor grade was assessed locally as histologic grade 1 (well differentiated), 2 (moderately differentiated), or 3 (poorly differentiated). The size of the boxes is proportional to the number of patients in the subgroup, and arrows on the confidence interval bars indicate that the upper boundary of the confidence interval is off the scale. The confidence intervals have not been adjusted for multiplicity, and analyses are considered to be descriptive. AI denotes aromatase inhibitors, HER2 human epidermal growth factor receptor 2, OFS ovarian function suppression, and SERM selective estrogen-receptor modulator.

Table 2. Pregnancy Outcomes in Patients with at Least One Pregnancy during the Trial.*

Outcome That Occurred at Least Once	Patients with ≥1 Pregnancy (N=368)
	no. (%)
Live birth, full-term or preterm	317 (86.1)†
Full-term live birth	292 (79.3)
Preterm live birth	27 (7.3)
Miscarriage	93 (25.3)
Elective abortion	16 (4.3)
Stillbirth	1 (0.3)
Neonatal death	1 (0.3)

* Among the 368 women in whom pregnancy occurred during the trial, a total of 507 pregnancies were reported. A total of 110 women had more than one pregnancy; therefore, some women may be included in more than one outcome category. Overall, 258 women had one pregnancy, 88 had two pregnancies, 16 had three pregnancies, 5 had four pregnancies, and 1 had five pregnancies. Among the 507 pregnancies, 323 (63.7%) resulted in full-term live births, 27 (5.3%) in preterm live births, 114 (22.5%) in miscarriages or spontaneous abortions, 17 (3.4%) in elective abortions, 1 (0.2%) in stillbirth, and 1 (0.2%) in neonatal death; 20 (3.9%) were active (ongoing) pregnancies, and 4 (0.8%) had unknown outcomes.

† These 317 women accounted for 63.8% of the 497 women in the secondary end-point population.

grade 3 disease, large tumors, node positivity, or a combination of these, it is possible that our findings are biased by the "healthy mother" effect. Such an effect in this trial would mean that healthier women with previous breast cancer who had a lower risk of recurrence were more likely than less healthy women at higher risk to be referred for participation (or to participate) in the current trial and to become pregnant, despite the comparison to a control cohort consisting of women who would have met the eligibility criteria of the current trial.[27] Fourth, although the bootstrap-matching method compared groups that were closely matched with respect to several prognostic factors, it is possible that residual imbalances between the groups affected the results. A randomized trial design would have better addressed potential confounding regarding the breast cancer outcomes, as well as the pregnancy and birth outcomes; however, this approach was considered to be neither ethical nor feasible. Fifth, the trial population was not representative of the broader population of premenopausal women with breast cancer with respect to age and race or ethnic group (see Section 6 in the Supplementary Appendix).

In well-matched comparisons to an external control cohort, the POSITIVE trial showed no clear worsening of breast cancer outcomes in the short term after temporary interruption of endocrine therapy to allow for pregnancy in select women with a history of hormone receptor–positive breast cancer. Longer-term follow-up is needed to further inform the safety of this strategy. Nevertheless, these results provide an improved understanding of the effect of subsequent pregnancy on breast cancer outcomes in women.

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APPENDIX

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