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Impact of tamoxifen therapy on fertility in breast cancer survivors

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Impact of tamoxifen therapy on fertility in breast cancer survivors

By

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An abstract of
a thesis submitted to the Faculty of the
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Abstract

Impact of tamoxifen therapy on fertility in breast cancer survivors
By Lisa Shandley

Objective: To determine if tamoxifen use is associated with decreased ovarian reserve and decreased likelihood of having a child following breast cancer diagnosis.

Design: Furthering Understanding of Cancer, Health, and Survivorship in Adult (FUCHSIA) Women Study–a population-based cohort study

Setting: Not applicable.

Patients: Three hundred ninety-seven female breast cancer survivors aged 22-45 years who were diagnosed between ages 20-35 years and were at least 2 years post-diagnosis; 108 survivors also participated in a clinic visit.

Intervention(s): None

Main Outcome Measure(s): Time to first child after cancer diagnosis, clinical measures of ovarian reserve (anti-Müllerian hormone [AMH] and antral follicle count [AFC]) after cancer

Results: Women who ever used tamoxifen were substantially less likely to have a child following breast cancer diagnosis (hazard ratio [HR]=0.29, 95% confidence interval [CI]: 0.16, 0.54) than women who had never used tamoxifen. After adjusting for age at diagnosis, exposure to an alkylating agent, and race, the HR was 0.25 (95% CI: 0.14, 0.47). However, after adjusting for potential confounders, women who had used tamoxifen had an estimated geometric mean AMH level 2.47 (95% CI: 1.08, 5.65) times higher than women who had never taken tamoxifen. AFC was also higher in the tamoxifen group compared to tamoxifen non-users when adjusted for the same variables (risk ratio=1.21, 95% CI: 0.84, 1.73).

Conclusion: Breast cancer survivors who used tamoxifen were less likely to have a child following cancer diagnosis compared to survivors who never used tamoxifen. However, tamoxifen users did not have decreased ovarian reserve compared to tamoxifen non-users.

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Acknowledgments

Table of Contents

INTRODUCTION

Advances in breast cancer screening, detection, and treatment have led to a 5-year breast cancer survival rate of over 80% (1). As survival rates have improved, there has been an increased focus on the complex issues associated with breast cancer survivorship, including fertility and family planning. According to the Young Women's Breast Cancer Study, 50% of women younger than 40 years expressed concerns about future fertility and the possibility of pregnancy following chemotherapy and radiation treatment (2).

Between 55 and 70 percent of women ages 30-50 years old diagnosed with breast cancer have a malignancy that is responsive to and stimulated by hormones (3). Since the 1980s, it has been standard of care to treat hormone sensitive breast cancer with anti-estrogen medications (4). Tamoxifen, a selective estrogen receptor modulator, binds to estrogen receptors and inhibits the action of estrogen in breast tissue. It is the first line agent for premenopausal women diagnosed with early breast cancer (4). Tamoxifen is considered an endocrine disruptor, and thus thought to be cytostatic rather than cytotoxic (5, 6). When taken daily for the recommended 5 years, tamoxifen has been shown to significantly improve survival in women with early breast cancer who remain premenopausal during treatment, reducing breast cancer mortality at 15-years after diagnosis by about one-third (risk ratio [RR] = 0.70, 95% confidence interval [CI]: 0.60, 0.80) compared to women who did not take tamoxifen (7). More recent data from the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial found that 10 years of treatment with tamoxifen can further reduce mortality by an additional 30% when compared to five years of treatment with tamoxifen (RR = 0.71 for 10-years compared to 5-years, 95% CI: 0.58, 0.88) (8).

Despite the survival benefit, a recent study found that 13.4% of women decline initiation of tamoxifen and another 15.5% discontinue it earlier than the recommended 5 years (9). The same study found that 35% of women cited concerns about fertility as a factor in their decision to not take tamoxifen, despite a lack of conclusive epidemiological or experimental evidence regarding tamoxifen's effect on fertility (9). Tamoxifen is more selective than conventional chemotherapies, and therefore assumed to have fewer systemic side effects compared to traditional treatments. Yet, tamoxifen has been shown to induce ovarian cysts (10) and endometrial polyps (11). However, the long-term effects of tamoxifen on fertility remain unknown.

During the past 10 years, anti-Müllerian hormone (AMH) has been used as a clinical marker of fertility that quantifies the number of remaining primordial follicles in the ovaries and has become an accepted, sensitive marker of ovarian reserve (12). Breast cancer survivors exposed to chemotherapy have been shown to have significantly lower AMH compared to women unexposed to chemotherapy (13-19); however, it is not clear whether tamoxifen has an additional, independent or possibly even synergistic effect on reducing ovarian reserve beyond the effect of standard chemotherapy for breast cancer. Additionally, no studies currently investigate the effect of long-term tamoxifen use on later conception and successful pregnancy. The primary objective of this study was to assess how long-term tamoxifen treatment affects rates of child birth and ovarian reserve in breast cancer survivors.

METHODS

Study Population

We used data from the Furthering Understanding of Cancer, Health, and Survivorship in Adult (FUCHSIA) Women's study. The FUCHSIA Women's study is a population-based study examining the effect of cancer treatment during the reproductive years on future fertility. Eligible cancer survivors were identified in collaboration with the Georgia Cancer Registry (GCR). Eligibility criteria included: female; diagnosed with a reportable malignant cancer (20) or ductal carcinoma in situ (DCIS) between the ages of 20-35; diagnosed between 1990-2009; age 22-45 at the time of enrollment in the study between 2012-2013; and at least 2 years since cancer diagnosis at enrollment. Eligible survivors were invited to participate in a detailed telephone interview about their reproductive histories. The present analysis was restricted to the 397 survivors whose first cancer diagnosis recorded in the GCR was breast cancer and who had not had a hysterectomy or bilateral oophorectomy before their cancer diagnosis. A subset of women with a uterus and at least one ovary were invited to participate in a sub-study to assess clinical markers of fertility; 108 breast cancer survivors completed a clinic visit. The Institutional Review Boards of Emory University and the Georgia Department of Public Health approved this study.

Procedures

All study participants completed a computer-assisted telephone interview to ascertain demographics, cancer history, menstrual history, desire for children, infertility history, pregnancy history, surgical history, use of medications including hormonal medications, and lifestyle.

Information regarding cancer diagnosis and treatment, including treatment with tamoxifen, was abstracted from medical records. All available records from diagnosis to present day or end of treatment were reviewed. Tamoxifen exposure was defined as at least 6 months of ever using tamoxifen. Tamoxifen treatment documented in the medical records was compared to self-reported answers in the interview. Participants with discrepant answers who reported never being exposed to tamoxifen but had clearly documented evidence of tamoxifen use in their medical records were reclassified into the tamoxifen group (n = 5). Women who reported taking tamoxifen but whose medical records clearly indicated that tamoxifen was taken for less than 6 months were classified as not taking tamoxifen (n = 12). There were 21 women who reported a history of tamoxifen use but whose duration of use could not be confirmed due to incomplete available medical records; these 21 women remained in the tamoxifen group per self-report. There were also 25 women in the group that reported never taking tamoxifen who did not have available medical records to confirm their self-report. Women who took tamoxifen and women with documented hormone receptor status in the medical records were considered to be hormone-receptor positive (ER/PR+).

Clinic visits took place at participating reproductive clinics across the state of Georgia. Clinic visits included a blood draw and a transvaginal ultrasound. Transvaginal ultrasounds were performed by a trained sonographer who measured ovarian volume for each ovary and antral follicle count (AFC, follicle sizes 2-10 mm). Inter-rater reliability of AFC could not be calculated because only one sonographer scanned each participant; however, all ultrasound reports were reviewed by a single reproductive endocrinologist (JBS). Blood was drawn to measure serum AMH. Serum AMH levels were measured in

duplicate by an enzyme-linked immunosorbent assay (ELISA) (UltraSensitive AMH/MIS ELISA, Ansh Labs, Webster, TX). For participants whose AMH was undetectable by the UltraSensitive assay, samples were measured in duplicate using the Ansh Labs picoAMH ELISA (Ansh Labs, Webster, TX) with an assay sensitivity of 0.006 ng/mL.

Statistical Analysis

Descriptive statistics were used to examine the study population, stratified by history of tamoxifen use. Covariates that were considered to confound the relationship between tamoxifen use and having a live birth after diagnosis were age at interview, age at cancer diagnosis, time since diagnosis, desire for children, childlessness at diagnosis, cancer stage, cancer treatment, and menstrual status after cancer treatment. A logistic model was fit to determine whether women who took tamoxifen were more likely to be childless at the time of the interview. Cox proportional hazard models were used to estimate the hazard ratios (HR) for factors associated with time to having a child after cancer diagnosis among those who were capable of childbearing. Despite treatment guidelines dictating that physicians counsel breast cancer survivors taking tamoxifen on the need for concurrent contraception use (21), studies have shown that reproductive-aged cancer survivors are less likely to use contraception than the general population (22), and sexually active cancer survivors are at considerable risk of unintended pregnancy (23). To account for this, the date of breast cancer diagnosis was chosen as the start of the risk period. Women were followed from breast cancer diagnosis until birth of their first child after diagnosis or until they were censored due to tubal ligation, hysterectomy, bilateral oophorectomy, or the end of follow-up (i.e. time of interview).

Several sub-analyses were performed. First, receptor status was considered. Receptor status was added as a covariate to the adjusted model. Another analysis was performed that excluded women who were hormone receptor negative (and thus not candidates for tamoxifen); 159 women were ER/PR+ and took tamoxifen, and 49 women were ER/PR+ but had never taken tamoxifen. Additionally, a sub-analysis was performed that included only women who were childless at diagnosis, (75 women in the tamoxifen group and 84 women in the no tamoxifen group). Likewise, a sub-analysis that included only women who had not yet met their reproductive goals at the time they were diagnosed with cancer was done; this analysis included 106 women in the tamoxifen group and 131 women in the non-tamoxifen group. Another sub-analysis was performed that excluded women who reported losing their period during cancer treatment and never resuming menses; this analysis included 148 survivors in the tamoxifen group and 182 survivors in the non-tamoxifen group. A supplemental Cox model was also fit to take into account the timing of treatment. Time at risk began when the survivor finished breast cancer treatment or tamoxifen use (see Supplemental Appendix for more information).

To analyze the clinic markers, AMH was log-transformed and a linear regression model controlling for age at clinic visit, cancer stage, exposure to chemotherapy, gonadotropin-releasing hormone (GnRH) agonist use during treatment, and race was fit to evaluate whether serum AMH levels were lower for women treated with tamoxifen versus those not treated with tamoxifen. AMH values that were below the limit of detection (LOD) were assigned a value of LOD/$\sqrt{2}$. A negative binomial model was fit for AFC to determine whether the mean total AFC values were lower for women treated with tamoxifen compared to those not treated with tamoxifen therapy (24). The negative

binomial model was also adjusted for age at clinic visit, cancer stage, exposure to chemotherapy, GnRH agonist use, and race. A sub-analysis was performed that excluded participants who were actively taking tamoxifen at the time of the clinic visit.

SAS 9.4 was used for all statistical analyses (SAS Institute, Cary, N.C.).

RESULTS

Descriptive Statistics

There were 415 women with a primary diagnosis of breast cancer. Of these, 18 were excluded from our analysis for having a hysterectomy or bilateral oophorectomy before cancer diagnosis. Among the 397 women included in our analysis, 179 (45.1%) were classified as tamoxifen users and 218 (54.9%) were classified as not using tamoxifen. Permission was obtained to request medical records for 340 women (85.6%). The characteristics of the sample stratified by tamoxifen use are presented in *Table 1*. The median age at the time of the interview was 39 years in both groups. There was a greater proportion of white women in the tamoxifen group (65.9%) compared to the non-tamoxifen group (56.2%). The groups were similar with respect to age at diagnosis and cancer stage. The median time from cancer diagnosis to interview was 7 years (interquartile range [IQR] 5-10). Both groups desired a median of two children. A similar proportion of survivors in each group reported a history of pregnancy, and a similar proportion in each group was childless at diagnosis.

Sixty-one women (14.7%) reported having at least one child after cancer diagnosis with a smaller proportion of the tamoxifen group (n = 13, 7.3%) having a child after cancer diagnosis compared to the non-tamoxifen group (n = 48, 22.0%). Of the 13 women with a history of tamoxifen who had a child after diagnosis, 6 (46.2%) reported the pregnancy was unintended compared with 21 of the 48 women (43.8%) in the non-tamoxifen group. Five of the 6 unintended pregnancies in the tamoxifen group occurred while the participant was on tamoxifen. A greater proportion of women in the tamoxifen group reported having fewer kids than desired compared to the non-tamoxifen group

(55.9% vs. 48.1%, respectively). Women who took tamoxifen were 65% more likely to be childless at the time of interview (OR = 1.65; 95% CI: 1.07, 2.55).

Time to First Child after Diagnosis

Thirty-one women (7.8%) reported having a tubal ligation prior to cancer diagnosis and were not included in our analysis of time to first child following cancer diagnosis. In the survival analysis, there were 89 women censored after cancer diagnosis and before the study interview for a hysterectomy or oophorectomy and 3 women censored for a tubal ligation. The time to first child after diagnosis differed by tamoxifen status (*Figure 1*), with tamoxifen users consistently taking a longer time to have their first child following diagnosis. Among breast cancer survivors who had a child following diagnosis, the median time between diagnosis and birth of first child after diagnosis was 5 years for those who took tamoxifen compared to 3 years for those who did not take tamoxifen. The pattern of time to first child did not change when we restricted our analysis to women who were childless at the time they were diagnosed or when we restricted the analysis to women who had not yet met their reproductive goals at the time of cancer diagnosis. In both of these sub-analyses, the median time to first child in the tamoxifen and non-tamoxifen groups remained 5 years and 3 years, respectively. When we restricted the analysis to women who were ER/PR+, and thus candidates for adjuvant tamoxifen therapy, the pattern also remained the same but was less pronounced. When the group of tamoxifen non-users was restricted to women who were not candidates for tamoxifen (i.e., ER/PR-) the pattern remained the same. Additionally, when women who reported ongoing amenorrhea were excluded from the analysis, the pattern of the survival curves did not change. When time at risk was calculated using time after breast cancer

treatment, the survival curves followed the same pattern but were less pronounced (*Supplemental Figure 1*).

The unadjusted hazard ratio (HR) for the association between tamoxifen use and having a child following breast cancer diagnosis was 0.29 (95% CI: 0.16, 0.54) (*Table 2*). This association remained in the subset of women who were childless at the time of diagnosis (HR = 0.36, 95% CI: 0.17, 0.76) and in the subset of women who had not yet met their reproductive goals at the time of cancer diagnosis (HR = 0.32, 95% CI: 0.17, 0.60). Among the subgroup of women who were all ER/PR+, the HR was 0.39 (95% CI: 0.15, 0.98). When the group of tamoxifen non-users was restricted to women who were ER/PR-, and thus not candidates for tamoxifen, the HR was 0.26 (95% CI: 0.13, 0.49). In a multivariable model, the three most influential covariates were exposure to an alkylating agent, age at diagnosis, and race; when we adjusted our full model with these three variables, the HR was 0.25 (95% CI: 0.14, 0.47) (*Table 3*). When we added hormone receptor status to the model as a covariate, the HR was 0.20 (95% CI: 0.07, 0.58). When time at risk was calculated using time from treatment, the unadjusted HR was 0.66 (95% CI: 0.35, 1.23); when adjusted for alkylating agent, age at diagnosis, and race, the HR was 0.58 (95% CI: 0.31, 1.08).

Clinical Markers of Ovarian Reserve

One hundred and eight breast cancer survivors participated in a clinic visit; 45 survivors had a history of taking or were currently taking tamoxifen, and 63 survivors had no prior tamoxifen use. Of the 45 women in the tamoxifen group, 29 had taken tamoxifen in the past but were no longer taking it, and 16 were on tamoxifen at the time of the clinic visit. Demographic and cancer characteristics of clinic visitors had similar

distributions to those in *Table 1* (*Table 4*). Two women (1.8%) did not have blood collected for AMH due to difficult intravenous access. Four women (3.7%) had uninterpretable ultrasound reports. The geometric mean (95% CI) AMH levels were 0.26 (0.12, 0.53) ng/mL for survivors who used tamoxifen and 0.15 (0.08, 0.28) ng/mL for survivors who had never used tamoxifen. A similar proportion of survivors in both groups had AMH levels below the LOD (17.7% in the tamoxifen group vs. 15.9% in the no tamoxifen group, p = 0.80). AMH was inversely associated with age at clinic visit (p < 0.0001), chemotherapy exposure (p < 0.0001), and cancer stage (p = 0.012), but was not significantly associated with childlessness at diagnosis (p = 0.63), race (p = 0.50), gravidity (p = 0.62), BMI (p = 0.84), or use of a GnRH agonist during treatment (p = 0.48).

A multivariable model was fit to examine the association between log-transformed AMH and tamoxifen use, while controlling for potential confounders. After adjusting for age at the clinic visit, the estimated geometric mean AMH for women who used tamoxifen was 1.57 (95% CI: 0.67, 3.68) times higher than the estimated geometric mean AMH for women who did not use tamoxifen. *Table 5* depicts the predicted geometric mean AMH levels from this model. After adjusting for age at clinic visit, chemotherapy exposure, cancer stage, GnRH agonist use, and race, the estimated geometric mean AMH for tamoxifen users was 2.47 (95% CI: 1.08, 5.65) times that of nonusers. The three most influential confounders of AMH level were age at clinic visit, cancer stage, and exposure to chemotherapy. When women on tamoxifen at the time of the clinic visit were excluded, the results did not change (*Table 6*). Additionally, when women with polycystic ovaries (PCO) on ultrasound were excluded, the association

remained strong (ratio of the adjusted estimated geometric means comparing tamoxifen to no tamoxifen = 2.74, 95% CI: 1.09, 6.85).

AFC data provided similar results to those for AMH. After adjusting for age at clinic visit, AFC was higher in survivors who took tamoxifen compared to those who did not (RR = 1.18, 95% CI: 0.84, 1.67) (*Table 5*). When the AFC model was adjusted for age at clinic visit, cancer stage, exposure to chemotherapy, GnRH agonist use, and race, the estimate remained higher in those who had taken tamoxifen compared to those who did not (adjusted RR = 1.21, 95% CI: 0.84, 1.73). In the sub-analysis that excluded women on tamoxifen at the time of the clinic visit, the results did not change (*Table 6*). Additionally, when women with PCO were excluded from the AFC analysis, our results did not change (adjusted RR = 1.19, 95% CI: 0.80, 1.78).

DISCUSSION

Our results suggest that breast cancer survivors who took tamoxifen were substantially less likely to have a child following cancer diagnosis compared to women who did not take tamoxifen, but this difference was not a result of a further decreased ovarian reserve in women who took tamoxifen. We adjusted our models for potential confounders of fertility following cancer diagnosis and performed many sub-group analyses to account for scenarios that may have led to confounding. For each sub-analysis, our conclusions remained unchanged with hazard ratios for having a child after diagnosis comparing the tamoxifen group to the no tamoxifen group ranging from 0.16-0.39. Although the small sample size of women who participated in a clinic visit precludes sub-analyses of AMH and AFC, our adjusted models suggest that tamoxifen does not adversely affect markers of ovarian reserve. Our results consistently favored the tamoxifen group having higher ovarian reserve.

The most obvious possible explanation for our findings that women who take tamoxifen are less likely to have a child following diagnosis is that survivors on tamoxifen are following recommendations to not conceive while on tamoxifen. Tamoxifen is a known teratogen (25). It is recommended that women who are on tamoxifen and desire pregnancy stop taking the medication two months prior to attempting to conceive (25). However, beyond the guidelines for the two-month washout period, there are few guidelines for how to interrupt tamoxifen for consideration of reproductive goals. Recent research has indicated that pregnancy is safe for women following breast cancer (26, 27), even for those who are hormone receptor-positive (28), but women are extensively counseled on the benefit of tamoxifen against recurrence and

may be hesitant to discontinue or interrupt treatment. Since the median age at diagnosis for the tamoxifen group in our study was 32, five years of tamoxifen treatment would leave women trying to conceive at age 37 unless advised otherwise. Women who use tamoxifen may find themselves in a situation where their reproductive window is nearly closed at the completion of tamoxifen treatment, which may be further aggravated by exposure to alkylating agents and other gonadotoxins during treatment. However, some women stop tamoxifen treatment early to become pregnant or after becoming pregnant unintentionally, as was seen in the present analysis.

There exist other possible explanations for tamoxifen users being less likely to have a child following diagnosis, which are indirectly supported by the supplemental analysis. One reason may be that women who want to get pregnant are selecting to not take tamoxifen following cancer diagnosis because of concerns regarding fertility. A recent study of tamoxifen initiation and persistence found that fertility concerns were associated with noninitiation of tamoxifen (9). These concerns involve both immediate and future fertility. If this were the case, then there may be a significant proportion of hormone receptor-positive women selecting not to begin tamoxifen due to desired childbearing. It would then be expected that this self-selection of women into the no tamoxifen group would result in more women seeking to become pregnant in the non-tamoxifen group than would be observed if women were randomized to tamoxifen use. However, when the analysis was limited to comparing women who took tamoxifen to women who were not candidates for tamoxifen (ER/PR-), the association remained. Additionally, the proportion of women who had not met their reproductive goals by the time they were diagnosed with cancer was similar between the two groups. There is also

the possibility that receptor status may influence women's childbearing, either biologically or through decision-making. If this were the case, receptor status would confound the relationship between tamoxifen and having a child following diagnosis. When receptor status was added to the model as a covariate, the association between tamoxifen and having a child after diagnosis remained strong.

Despite the findings that women who take tamoxifen are less likely to have a child following diagnosis, it does not appear that this is attributable to a diminishing effect of tamoxifen on ovarian reserve beyond that which is seen in breast cancer survivors with no tamoxifen exposure. Therefore, it should be acknowledged that it does not appear tamoxifen has a direct impact on fertility. Studies in rodent models have shown conflicting results regarding the effect of tamoxifen on ovarian reserve. One study found that tamoxifen significantly reduced ovarian follicular reserve (29), while another found that tamoxifen reduced the number of antral and preantral follicles, but had no effect on the primordial follicle pool, suggesting tamoxifen is an endocrine disruptor rather than a gonadotoxic agent (30). More recently, additional evidence has suggested that tamoxifen can prevent follicle loss when administered concurrently with gonadotoxic agents (e.g. cyclophosphamide) (31); however, concurrent treatment is not used to treat breast cancer due to increased risk of adverse side effects and the possibility of treatment interactions (31).

In 2010, Partridge et al. reported that breast cancer survivors on tamoxifen had lower AMH and AFC compared to survivors who were not on tamoxifen (19). Our results do not support this finding. One potential reason for the difference is that we examined women who had ever had a history of tamoxifen use rather than solely women

who were on tamoxifen at the time of clinic visit. However, when we excluded women who were on tamoxifen at the time of the clinic visit and analyzed only those who had taken tamoxifen in the past but were no longer actively using it, our results did not change. Additionally, we were able to include a larger number of survivors in our analysis compared to Partridge et al. and thus have more power to show an association.

Our study has many strengths. One strength is the large number of breast cancer patients we included in our analysis. We were able to reconstruct extensive reproductive and medical histories, including cancer treatment, on our participants through the use of both a detailed telephone interview and medical record abstraction. The average time from cancer diagnosis to telephone interview was over 7 years in both groups, giving ample time for consideration of reproductive goals following cancer diagnosis. Additionally, our study is strengthened by data from clinic visits that allow us to draw conclusions not only regarding childbearing following diagnosis, but also in regards to ovarian reserve and therefore reproductive potential.

Our study has some limitations. We cannot limit our analysis to women who were actively trying to conceive after cancer diagnosis due to lack of a specific question on attempting pregnancy after cancer. Second, tamoxifen compliance can be poor, especially among young women (9); women who reported taking tamoxifen for only a short period may not have had much exposure if compliance was poor. However, we defined our tamoxifen group as reporting at least 6 months and verified this with medical records to address this issue.

Our study provides preliminary results for future research on the association between tamoxifen use, reproductive outcomes, and post-breast cancer ovarian reserve.

Regardless of the mechanism by which women who take tamoxifen are less likely to have a child after diagnosis, clinicians who care for breast cancer survivors should counsel their patients regarding both their treatment and reproductive options. Women with a history of breast cancer may already be at risk for reduced ovarian reserve, impaired fertility, or a shorter reproductive window (18, 32-34). While it does not appear that tamoxifen additionally reduces ovarian reserve, more research is needed to provide evidence that can guide clinical practice regarding interruption of tamoxifen that takes into consideration both risk of cancer recurrence and ability to meet reproductive goals.

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        reserve- a prospective observational analysis by menstrual history and ovarian

        reserve markers. *Fertility and Sterility* 2008;90(5):1635-9.

TABLES

Table 1. Demographic and cancer characteristics of breast cancer survivors who participated in the telephone interview and who had not had a hysterectomy or bilateral oophorectomy prior to cancer diagnosis, 2012-2013							
	Total (n = 397)		Tamoxifen (n = 179)		No Tamoxifen (n = 218)		
	n	%	n	%	n	%	p-value[a]
Demographics							
Age at interview (years)							0.10
26-35	71	17.9	40	22.4	31	14.2	
36-40	139	35.0	61	34.1	78	35.8	
40-45	187	47.1	78	43.9	109	50.0	
Race							0.01
White	240	60.6	118	65.9	122	56.2	
Black	137	34.6	58	32.4	79	36.4	
Other[b]	19	4.8	3	1.7	16	7.4	
Level of education							0.70
High School or less	20	5.1	7	3.9	13	6.0	
Some college	104	26.3	50	28.1	54	24.8	
College graduate	141	35.6	61	34.3	80	36.7	
Some grad school or grad degree	131	33.1	60	33.7	71	32.6	
Relationship status at interview							0.72
Married, Living with a Partner, or in a Committed Relationship	302	76.3	136	76.4	166	76.1	
Single	90	22.7	41	23.0	49	22.5	
Other[c]	4	1.0	1	0.6	3	1.4	
Pregnancies, Childbirth, and Reproductive Goals							
Pregnancy history at diagnosis							0.42
Nulligravid	127	32.0	61	34.1	66	30.3	
Gravid	270	68.0	118	65.9	152	69.7	
Childless at Diagnosis							0.56
Childless	160	40.3	75	41.9	85	39.0	
Had at least one biological child by diagnosis	237	59.7	104	58.1	133	61.0	
Had a child after diagnosis							<0.0001
Yes	61	15.4	13	7.3	48	25.5	
No	336	84.6	166	92.7	140	74.5	
Had fewer kids than desired							0.12

Yes	203	51.7	99	55.9	104	48.1	
No	190	48.3	78	44.1	112	51.9	
Had a period of infertility before cancer diagnosis							0.85
Yes	144	36.3	64	35.8	80	36.7	
No	253	63.7	115	64.2	138	63.3	
Had a hysterectomy or bilateral oophorectomy by interview							0.10
Yes	108	27.2	56	31.3	52	23.9	
No	289	72.8	123	68.7	166	76.1	
Cancer Diagnosis and Treatment							
Age at Diagnosis (years)							0.41
20-24	12	3.0	7	3.9	5	2.3	
25-29	82	20.7	34	19.0	48	22.0	
30-34	229	57.7	109	60.9	120	55.0	
35	74	18.6	29	16.2	45	20.6	
Time since diagnosis (years)							0.23
2-4	95	23.9	48	26.8	47	21.6	
5-7	127	32.0	62	34.6	65	29.8	
8-10	90	22.7	34	19.0	56	25.7	
>10	85	21.4	35	19.6	50	22.9	
AJCC Stage[d]							0.76
DCIS	48	12.9	18	10.6	30	14.9	
Stage I	95	25.5	44	25.9	51	25.2	
Stage II	166	44.6	80	47.1	86	42.6	
Stage III	55	14.8	24	14.1	31	15.3	
Stage IV	8	2.2	4	2.4	4	2.0	
Surgery							0.47[e]
Less than mastectomy	121	34.7	59	36.6	62	33.0	
Mastectomy or more	228	65.3	102	63.4	126	67.0	
Radiation							0.43[e]
Yes	235	66.6	112	68.7	123	64.7	
No	118	33.4	51	31.3	67	35.3	
Chemotherapy							
Alkylating agent							0.14[e]
Yes	280	78.7	137	82.0	143	75.7	
No	76	21.3	30	18.0	46	24.3	
Topoisomerase Inhibitor							0.97[e]
Yes	236	66.9	111	66.9	125	66.8	
No	117	33.1	55	33.1	62	33.2	

Antimitotic agents							0.08[e]
Yes	222	63.8	113	68.1	109	58.9	
No	129	36.2	53	31.9	76	41.1	
Antimetabolite							0.15[e]
Yes	54	15.4	20	12.4	34	18.0	
No	296	84.6	141	87.6	155	82.0	
Used GnRH agonist during treatment							0.01[f]
Yes	58	17.5	38	22.7	20	12.1	
No	274	82.5	129	77.3	145	87.9	
Missing	65		12		53		
Menstrual Status after Cancer Treatment[g]							0.10
Menses present	357	89.9	156	87.1	201	92.2	
Menses absent	40	10.1	23	12.9	17	7.8	

[a] All variables were categorical and were compared using a chi-square test.
[b] Race category "other" includes: American Indian, Alaskan Native, Asian, Native Hawaiian, and Pacific Islander
[c] Relationship category "other" was reserved for women who felt the other listed options did not accurately reflect their relationship status
[d] AJCC: American Joint Committee on Cancer
[e] 10-12% of the data are missing due to incomplete available medical records
[f] 16% of the data are missing due to incomplete available medical records
[g] Menstrual status assessed by participant's response to the questions, "Did your menstrual periods stop during your cancer treatment?" and "For how long did your period stop?" Women who reported their period stopping and never returning are classified as having absent menses.
GnRH = gonadotropin-releasing hormone

Table 2. Unadjusted hazard ratios for analysis of the association between tamoxifen and having a child after cancer diagnosis, 2012-2013.

| | | **Unadjusted** | | |
	Total n	**Women who gave birth to a child after diagnosis (n)**	**HR**	**95% CI**
All breast cancer survivors				
Tamoxifen	170	13	0.29	(0.16, 0.54)
No tamoxifen	196	48	1.00	Referent
Among those who were childless at diagnosis[a]				
Tamoxifen	75	9	0.36	(0.17, 0.76)
No tamoxifen	84	27	1.00	Referent
Among those who have not yet met reproductive goals[b]				
Tamoxifen	106	13	0.32	(0.17, 0.60)
No tamoxifen	131	45	1.00	Referent
Among women who were hormone-receptor positive[c]				
Tamoxifen	170	13	0.39	(0.15, 0.98)
No Tamoxifen	49	7	1.00	Referent
Tamoxifen non-users restricted to those who were hormone-receptor negative[d]				
Tamoxifen	170	13	0.26	(0.13, 0.49)
No Tamoxifen	110	33	1.00	Referent
Adjusted for hormone receptor status				
Tamoxifen	151	8	0.28	(0.11, 0.73)
No Tamoxifen	159	40	1.00	Referent
Among women who had menses after cancer treatment[e]				
Tamoxifen	148	12	0.29	(0.16, 0.55)
No Tamoxifen	182	48	1.00	Referent

HR = hazard ratio; 95% CI = 95% confidence interval
[a]Childless: not having given birth to a child by the time of the interview
[b]Had not yet met reproductive goals: calculated by subtracting the number of children women gave birth to from the total number they reported they desired
[c]Hormone-receptor positive: women who took tamoxifen and women with documented hormone receptor status in medical records were considered to be hormone-receptor positive.
[d]Women with breast cancer who are hormone-receptor negative are typically not candidates for adjuvant tamoxifen treatment

[e]Menstrual status assessed by participant's response to the questions, "Did your menstrual periods stop during your cancer treatment?" and "For how long did your period stop?" Women who reported their period stopping and never returning are classified as having absent menses.

Table 3. Adjusted hazard ratios for analysis of the association between tamoxifen and having a child after cancer diagnosis, 2012-2013.

	Adjusted for alkylating agent, age at diagnosis, and race			
	Total n	**Women who gave birth to a child after diagnosis (n)**	**HR**	**95% CI**
All breast cancer survivors				
Tamoxifen	159	13	0.25	(0.14, 0.47)
No tamoxifen	176	48	1.00	Referent
Among those who were childless at diagnosis[a]				
Tamoxifen	73	9	0.30	(0.13, 0.66)
No tamoxifen	78	27	1.00	Referent
Among those who have not yet met reproductive goals[b]				
Tamoxifen	103	13	0.29	(0.16, 0.55)
No tamoxifen	122	45	1.00	Referent
Among women who were hormone-receptor positive[c]				
Tamoxifen	159	13	0.40	(0.14, 1.15)
No Tamoxifen	49	7	1.00	Referent
Tamoxifen non-users restricted to those who were hormone-receptor negative[d]				
Tamoxifen	159	13	0.24	(0.13, 0.47)
No Tamoxifen	109	33	1.00	Referent
Adjusted for hormone receptor status				
Tamoxifen	150	8	0.20	(0.07, 0.58)
No Tamoxifen	158	40	1.00	Referent
Among women who had menses after cancer treatment[e]				
Tamoxifen	132	7	0.25	(0.13, 0.48)
No Tamoxifen	146	40	1.00	Referent

HR = hazard ratio; 95% CI = 95% confidence interval
[a]Childless: not having given birth to a child by the time of the interview
[b]Had not yet met reproductive goals: calculated by subtracting the number of children women gave birth to from the total number they reported they desired
[c]Hormone-receptor positive: women who took tamoxifen and women with documented hormone receptor status in medical records were considered to be hormone-receptor positive.
[d]Women with breast cancer who are hormone-receptor negative are typically not candidates for

adjuvant tamoxifen treatment
[e]Menstrual status assessed by participant's response to the questions, "Did your menstrual periods stop during your cancer treatment?" and "For how long did your period stop?" Women who reported their period stopping and never returning are classified as having absent menses.

Table 4. Demographic and cancer characteristics of breast cancer survivors who participated in the telephone interview (2012-2013) and came to clinic (2013-2015)

	Total (n = 108)		Tamoxifen (n = 45)		No Tamoxifen (n = 63)		
	n	**%**	**n**	**%**	**n**	**%**	**p-value**[a]
Demographics							
Age at Clinic Visit (years)							0.50
27-36	22	20.4	11	24.4	11	17.5	
37-40	31	28.7	10	22.2	21	33.3	
41-43	29	26.9	14	31.1	15	23.8	
44-47	26	24.1	10	22.2	16	25.4	
Race							0.07
White	54	50.0	24	53.3	30	47.6	
Black	47	43.5	21	46.7	26	41.3	
Other[b]	7	6.5	0		7	11.1	
BMI at Clinic Visit							0.39
Underweight	2	1.9	0		2	3.2	
Normal	37	34.3	18	40.0	19	30.2	
Overweight	34	31.5	15	33.3	19	30.2	
Obese	35	32.4	12	26.7	23	36.5	
Level of education							0.80
High School or less	5	4.6	2	4.4	3	4.8	
Some college	29	26.9	14	31.1	15	23.8	
College graduate	38	35.2	16	35.6	22	34.9	
Some grad school or grad degree	36	33.3	13	28.9	23	36.5	
Relationship status at interview							0.67
Married, Living with a Partner, or in a Committed Relationship	80	74.1	33	73.3	47	74.6	
Single	27	25.0	12	26.7	15	23.8	
Other[c]	1	0.9	0		1	1.6	
Pregnancies, Childbirth, and Reproductive Goals							
Pregnancy history at diagnosis							0.41
Nulligravid	43	39.8	20	44.4	23	36.5	
Gravid	65	60.2	25	55.6	40	63.5	
Childless at Diagnosis							0.42
Childless	55	50.9	25	55.6	30	47.6	
Had at least one biological child by diagnosis	53	49.1	20	44.4	33	52.4	

Had a child after diagnosis							0.04
Yes	19	17.6	4	8.9	15	23.8	
No	89	82.4	41	91.1	48	76.2	
Had fewer kids than desired							0.16
Yes	62	57.9	29	65.9	33	52.4	
No	45	42.1	15	34.1	30	47.6	
Had a period of infertility before cancer diagnosis							0.32
Yes	32	29.6	11	24.4	21	33.3	
No	76	70.4	34	75.6	42	66.7	
Cancer Diagnosis and Treatment							
Age at Diagnosis (years)							0.95
20-24	6	5.6	3	6.7	3	4.8	
25-29	22	20.4	10	22.2	12	19.0	
30-34	60	55.6	24	53.3	36	57.1	
35	20	18.5	8	17.8	12	19.0	
Time from diagnosis to clinic visit (years)							0.48
3-5	14	13.0	8	17.8	6	9.5	
6-7	25	23.1	8	17.8	17	27.0	
8-9	23	21.3	9	20.0	14	22.2	
10 or more	46	42.6	20	44.4	26	41.3	
AJCC Stage[d]							0.58
DCIS	17	16.0	6	13.3	11	18.0	
Stage I	26	24.5	9	20.0	17	27.9	
Stage II	45	42.5	21	46.7	24	39.3	
Stage III	17	16.0	9	20.0	8	13.1	
Stage IV	1	0.9	0		1	1.6	
Surgery							0.74
Less than mastectomy	40	37.4	16	35.6	24	38.7	
Mastectomy or more	67	62.6	29	64.4	38	61.3	
Radiation							0.04
Yes	75	69.4	36	80.0	39	61.9	
No	33	30.6	9	20.0	24	38.1	
Chemotherapy							
Alkylating agent							0.75
Yes	84	78.5	36	80.0	48	77.4	
No	23	21.5	9	20.0	14	22.6	
Topoisomerase Inhibitor							0.84
Yes	75	70.1	32	71.1	43	69.4	
No	32	29.9	13	28.9	19	30.6	

Antimitotic agents							0.69
Yes	69	64.5	30	66.7	39	62.9	
No	38	35.5	15	33.3	23	37.1	
Antimetabolite							0.69
Yes	16	15.0	6	13.3	10	16.1	
No	91	85.0	39	86.7	52	83.9	
Used GnRH agonist during treatment							0.002
Yes	19	17.6	14	31.1	5	7.9	
No	89	82.4	31	68.9	58	92.1	
Menstrual Status after Cancer Treatment[e]							0.86
Menses present	99	91.7	41	91.1	58	92.1	
Menses absent	9	8.3	4	8.9	5	7.9	

[a]Categorical variables were compared using a chi-square test.
[b]Race category "other" includes: American Indian, Alaskan Native, Asian, Native Hawaiian, and Pacific Islander
[c]Relationship category "other" was reserved for women who felt the other listed options did not accurately reflect their relationship status
[d]AJCC: American Joint Committee on Cancer
[e]Menstrual status assessed by participant's response to the questions, "Did your menstrual periods stop during your cancer treatment?" and "For how long did your period stop?" Women who reported their period stopping and never returning are classified as having absent menses.
GnRH = gonadotropin-releasing hormone

Table 5. Estimates for the predicted geometric mean value of anti-Müllerian hormone (AMH) and the predicted mean antral follicle count (AFC) comparing breast cancer survivors who took tamoxifen to survivors who did not take tamoxifen.

	Adjusted for age at clinic visit			**Adjusted for additional variables**[a]		
	Estimate[b]	**95% CI**	**Ratio**[e]	**Estimate**[c]	**95% CI**	**Ratio**[e]
AMH (ng/dL)						
Tamoxifen	0.34	(0.13, 0.90)	1.57	0.33	(0.12, 0.95)	2.47
No Tamoxifen	0.22	(0.09, 0.50)		0.14	(0.05, 0.34)	
AFC (n)						
Tamoxifen	6.7	(4.6, 9.9)	1.18	5.5	(3.5, 8.7)	1.21
No Tamoxifen	5.7	(4.1, 7.9)		4.6	(3.1, 6.8)	

CI = confidence interval

[a]Adjusted for age at clinic visit, chemotherapy use, cancer stage, gonadotropin-releasing hormone (GnRH) agonist use, and race[d]

[b]Estimate for a woman who was 39 years old at the time of the clinic visit.

[c]Adjusted estimate for a white woman who was 39 years old at the time of the clinic visit, received chemotherapy for stage 2 cancer, and did not receive a GnRH agonist.

[d]Race category "other" includes: American Indian, Alaskan Native, Asian, Native Hawaiian, and Pacific Islander.

[e]Estimated ratio comparing estimated values for women who took tamoxifen to estimated values for women who did not take tamoxifen.

Table 6. Estimates for the predicted geometric mean value of anti-Müllerian hormone (AMH) and the predicted mean antral follicle count (AFC) comparing breast cancer survivors who have a history of taking tamoxifen but are not actively taking it to survivors who have never taken tamoxifen.

	Adjusted for age at clinic visit			Adjusted for additional variables[a]		
	Estimate[b]	95% CI	Ratio[e]	Estimate[c]	95% CI	Ratio[e]
AMH (ng/dL)						
Past Tamoxifen	0.39	(0.12, 1.27)	1.74	0.34	(0.10, 1.20)	2.51
Current Tamoxifen	0.30	(0.09, 1.00)	1.32	0.33	(0.10, 1.08)	2.41
No Tamoxifen	0.22	(0.10, 0.53)		0.14	(0.05, 0.35)	
AFC (n)						
Past Tamoxifen	7.6	(4.9, 12.0)	1.31	5.9	(3.5, 9.8)	1.26
Current Tamoxifen	5.6	(3.5, 9.1)	0.96	5.3	(3.2, 8.7)	1.13
No Tamoxifen	5.8	(4.2, 8.1)		4.7	(3.1, 6.9)	

CI = confidence interval

[a]Adjusted for age at clinic visit, chemotherapy use, cancer stage, gonadotropin-releasing hormone (GnRH) agonist use, and race[d]

[b]Estimate for a woman who was 39 years old at the time of the clinic visit.

[c]Adjusted estimate for a white woman who was 39 years old at the time of the clinic visit, received chemotherapy for stage 2 cancer, and did not receive a GnRH agonist.

[d]Race category "other" includes: American Indian, Alaskan Native, Asian, Native Hawaiian, and Pacific Islander.

[e]Estimated ratio comparing estimated values for women in the tamoxifen group (either the past tamoxifen use or the current tamoxifen use) to estimated values for women who have never taken tamoxifen.
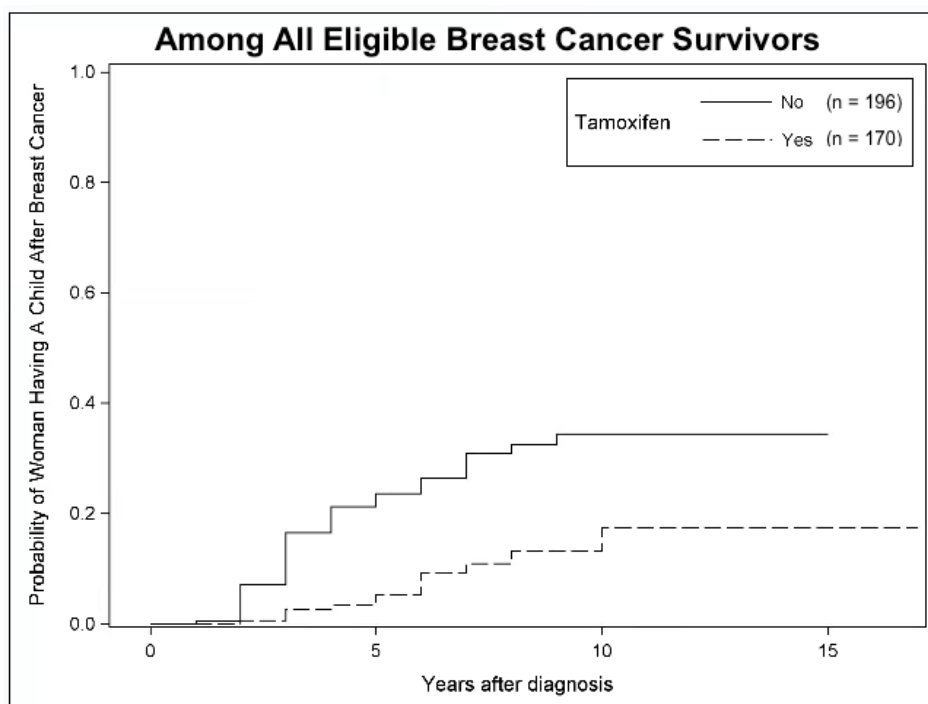
FIGURES

Figure 1. Unadjusted Kaplan-Meier curves of time to first child following breast cancer diagnosis by tamoxifen status (**A,** includes all breast cancer survivors; **B**, restricted to women who were childless at diagnosis; **C**, restricted to women who had not yet met their reproductive goals at the time of diagnosis**; D**, restricted to women who were estrogen/progesterone receptor positive[a]; **E**, tamoxifen group versus women who were hormone-receptor (ER/PR) negative[b]) in a cohort of young breast cancer survivors, censored at time of hysterectomy, bilateral oophorectomy, tubal ligation, or study interview; **F**, excludes women who reported their period stopping during cancer treatment and never returning.

[a]Women who took tamoxifen and women with documented hormone receptor status in medical records were considered to be hormone-receptor positive.
[b]Breast cancer survivors who are estrogen/progesterone receptor negative are generally not candidates for adjuvant tamoxifen.
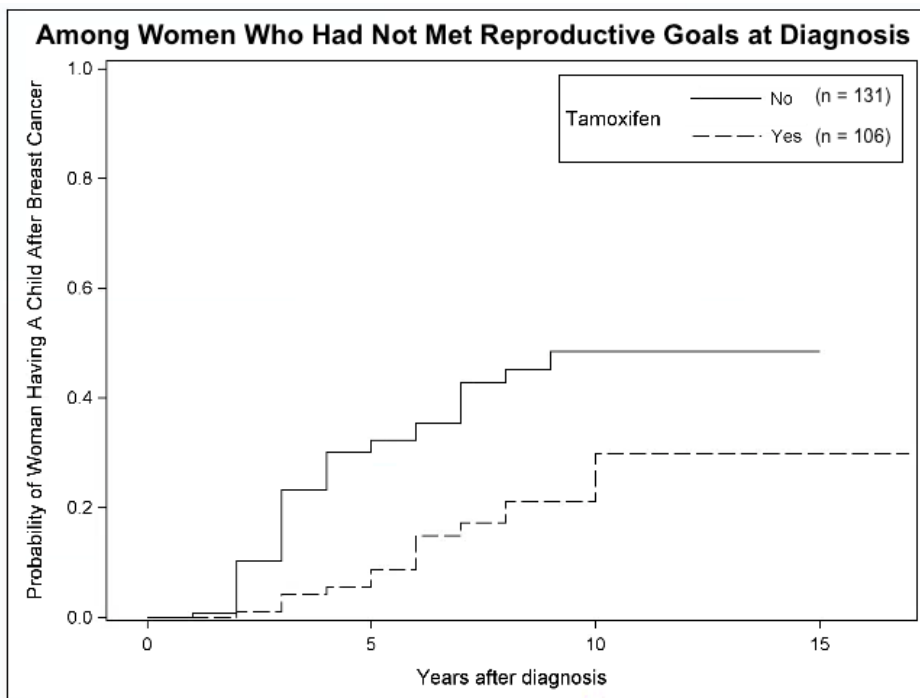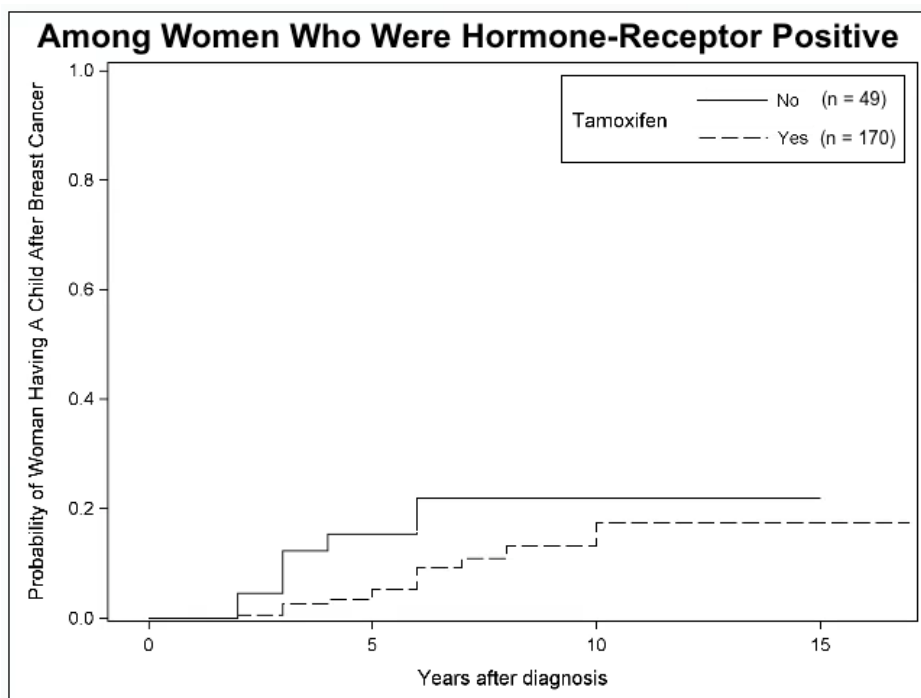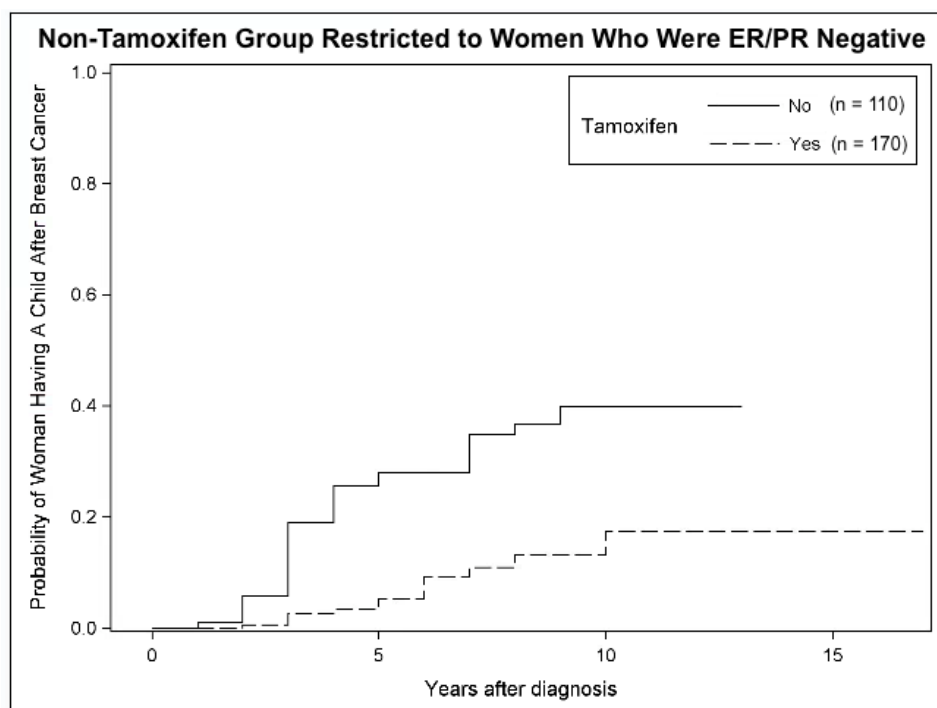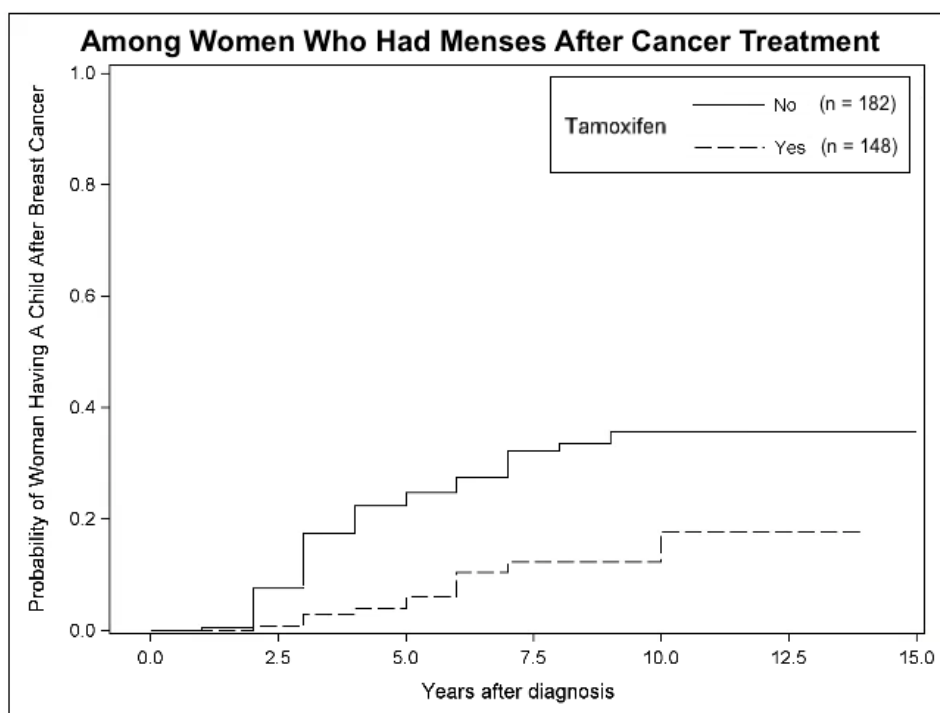
A.

B.

Among Women Who Were Childless at Diagnosis

C.

Among Women Who Had Not Met Reproductive Goals at Diagnosis

D.

E.

F.

Among Women Who Had Menses After Cancer Treatment
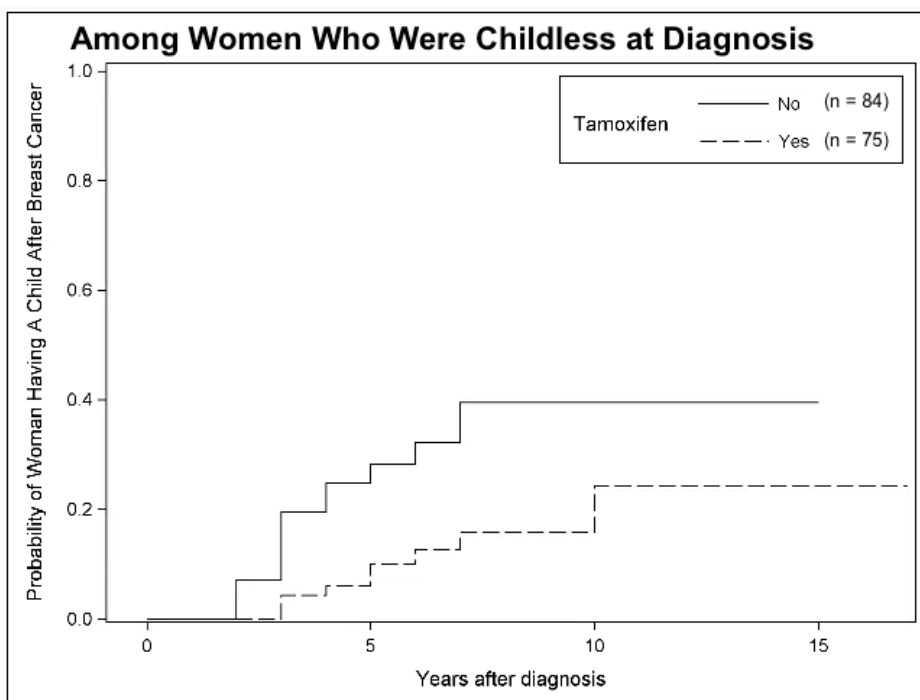
SUPPLEMENTAL MATERIALS

Supplemental Appendix. Additional information on supplemental analysis for time to

first child following breast cancer where time at risk began when the survivor finished

breast cancer treatment or tamoxifen use.

A supplemental analysis was performed to take into account treatment time,

including treatment with tamoxifen. Time at risk began when the survivor finished breast

cancer treatment or tamoxifen use. For women with available medical records, treatment

end date was used. For participants who did not have available medical records, treatment

end date was estimated based on what types of treatment (surgery, chemotherapy,

radiation, hormone) the patient reported receiving. The average length of treatment for

those with available medical records was used to make this estimation, and this time was

added to the diagnosis date of each participant without an end date in the available

medical record information. For participants in the tamoxifen group, treatment end time

was the end of tamoxifen use as documented in the medical records. When medical

records were unavailable or incomplete, treatment end time was calculated based on the

participant's report of length of time they took tamoxifen. Cox proportional hazard

models were used to estimate the hazard ratios (HR) for the association between

tamoxifen and time to having a child after cancer diagnosis among those who were

capable of childbearing with risk time being time off breast cancer treatment.

Supplemental Figure 1. Unadjusted Kaplan-Meier curve of time to first child following breast cancer treatment by tamoxifen status. Time at risk began when the survivor finished breast cancer treatment or tamoxifen use. Women who got pregnant while taking tamoxifen are not included in this analysis.