Impact of tamoxifen therapy on fertility in breast cancer survivors

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Objective: To determine whether tamoxifen use is associated with decreased ovarian reserve and decreased likelihood of having a child after a breast cancer diagnosis, using data from the Furthering Understanding of Cancer, Health, and Survivorship in Adult (FUCHSIA) Women Study.
Design: Population-based cohort study.
Setting: Not applicable.
Patient(s): Three hundred ninety-seven female breast cancer survivors aged 22–45 years whose cancer was diagnosed between ages 20 and 35 years and who were at least 2 years after 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 (antimüllerian hormone [AMH] and antral follicle count [AFC]) after cancer.
Result(s): Women who had ever used tamoxifen were substantially less likely to have a child after the 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 times higher (95% CI, 1.08, 5.65) than women who had never taken tamoxifen. Antral follicle count was also higher in the tamoxifen group compared with the tamoxifen nonusers when adjusted for the same variables (risk ratio 1.21; 95% CI, 0.84, 1.73).
Conclusion(s): Breast cancer survivors who had used tamoxifen were less likely to have a child after breast cancer diagnosis compared with survivors who never used tamoxifen. However, tamoxifen users did not have decreased ovarian reserve compared with the tamoxifen nonusers. (Fertil Steril® 2017;107:243–52. ©2016 by American Society for Reproductive Medicine.)
Key Words: Breast cancer, cancer survivorship, infertility, ovarian reserve, tamoxifen

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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 after chemotherapy and radiation treatment (2).

Between 55% and 70% of women aged 30 to 50 years with a breast cancer diagnosis have a malignancy that is responsive to and stimulated by hormones (3). Since the 1980s, it has been the standard of care to treat hormone-sensitive breast cancer with antiestrogen 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 is thought to be cytostatic rather than cytotoxic (5, 6). When taken daily for the recommended

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5 years, tamoxifen has been shown to statistically 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 with 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 with 5 years of treatment with tamoxifen (RR 0.71 for 10 years compared with 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 epidemiologic or experimental evidence regarding tamoxifen's effect on fertility (9). Tamoxifen is more selective than conventional chemotherapies and thus is assumed to have fewer systemic side effects compared with 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 antimüllerian 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 statistically significantly lower AMH levels compared with 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 currently published studies 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 childbirth and ovarian reserve in breast cancer survivors.

MATERIALS AND METHODS

Study Population

We used data from the Furthering Understanding of Cancer, Health, and Survivorship in Adult (FUCHSIA) Women Study. The FUCHSIA Women 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. The eligibility criteria included female sex; a reportable malignant cancer (20) or ductal carcinoma in situ diagnosed between the ages of 20 and 35; cancer diagnosis between 1990 and 2009; age 22 to 45 at the time of enrollment in the study between 2012 and 2013; and at least 2 years since cancer diagnosis at enrollment. The 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 Georgia Cancer Registry 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 substudy 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 hormone 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 with 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 (J.B.S.). 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). For participants whose AMH was undetectable by the UltraSensitive assay, samples were measured in duplicate using the Ansh Labs picoAMH ELISA 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. SAS 9.4 was used for all statistical analyses (SAS Institute).

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 evaluated from breast cancer diagnosis until the birth of their first child after diagnosis or until they were censored due to tubal ligation, hysterectomy, bilateral oophorectomy, or the end of the follow-up period (i.e., the time of the interview).

Several subanalyses 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 subanalysis was performed that included only women who were childless at diagnosis (75 women in the tamoxifen group and 84 women in the nontamoxifen group). Likewise, a subanalysis that included only women who had not yet met their reproductive goals at the time they were diagnosed with cancer was performed; this analysis included 106 women in the tamoxifen group and 131 women in the nontamoxifen group. Another subanalysis 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 nontamoxifen 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 the Supplemental Appendix for more information).

To analyze the clinical 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 measurements that were below the limit of detection (LOD) were assigned a value of $\mathrm{LOD}/\sqrt{2}$. A negative binomial model was fit for AFC to determine whether the mean total AFC values were lower for women treated with tamoxifen compared with 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 subanalysis was performed that excluded participants who were actively taking tamoxifen at the time of the clinic visit.

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 with the nontamoxifen 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 with the nontamoxifen 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 nontamoxifen group. Five of the six 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 children than desired compared with the nontamoxifen group (55.9% vs. 48.1%, respectively). Women who took tamoxifen were 65% more likely to be childless at the time of interview (odds ratio 1.65; 95% CI, 1.07, 2.55).

Time to First Child after Diagnosis

Thirty-one women (7.8%) reported having a tubal ligation before cancer diagnosis and were not included in our analysis of time to first child after 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 three women censored for a tubal ligation. The time to first child after diagnosis differed by tamoxifen status (Fig. 1), with tamoxifen users consistently taking a longer time to have their first child after diagnosis.

Among breast cancer survivors who had a child after diagnosis, the median time between diagnosis and birth of

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)		
Variable	**n**	**%**	**n**	**%**	**n**	**%**	***P* value[a]**
Demographics							
Age at interview (y)							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	
At least one biological child by diagnosis	237	59.7	104	58.1	133	61.0	
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	
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	
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	
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 (y)							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 (y)							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							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[d]
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[d]
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[d]

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TABLE 1

Continued.

Variable	Total (n = 397) n	Total (n = 397) %	Tamoxifen (n = 179) n	Tamoxifen (n = 179) %	No tamoxifen (n = 218) n	No tamoxifen (n = 218) %	*P* value[a]
Yes	280	78.7	137	82.0	143	75.7	
No	76	21.3	30	18.0	46	24.3	
Topoisomerase Inhibitor							0.97[d]
Yes	236	66.9	111	66.9	125	66.8	
No	117	33.1	55	33.1	62	33.2	
Antimitotic agents							0.08[d]
Yes	222	63.8	113	68.1	109	58.9	
No	129	36.2	53	31.9	76	41.1	
Antimetabolite							0.15[d]
Yes	54	15.4	20	12.4	34	18.0	
No	296	84.6	141	87.6	155	82.0	
GnRH agonist during treatment							0.01[e]
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[f]							0.10
Menses present	357	89.9	156	87.1	201	92.2	
Menses absent	40	10.1	23	12.9	17	7.8	

Note: All data presented as n (%), unless stated otherwise. AJCC = American Joint Committee on Cancer; GnRH = gonadotropin-releasing hormone.
[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] Data are missing due to incomplete available medical records, 10-12%.
[e] Data are missing due to incomplete available medical records, 16%.
[f] 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.

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first child after diagnosis was 5 years for those who took tamoxifen compared with 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 subanalyses, the median time to first child in the tamoxifen and nontamoxifen 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 nonusers was restricted to women who were not candidates for tamoxifen (i.e., ER/PR negative) 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 Fig. 1, available online).

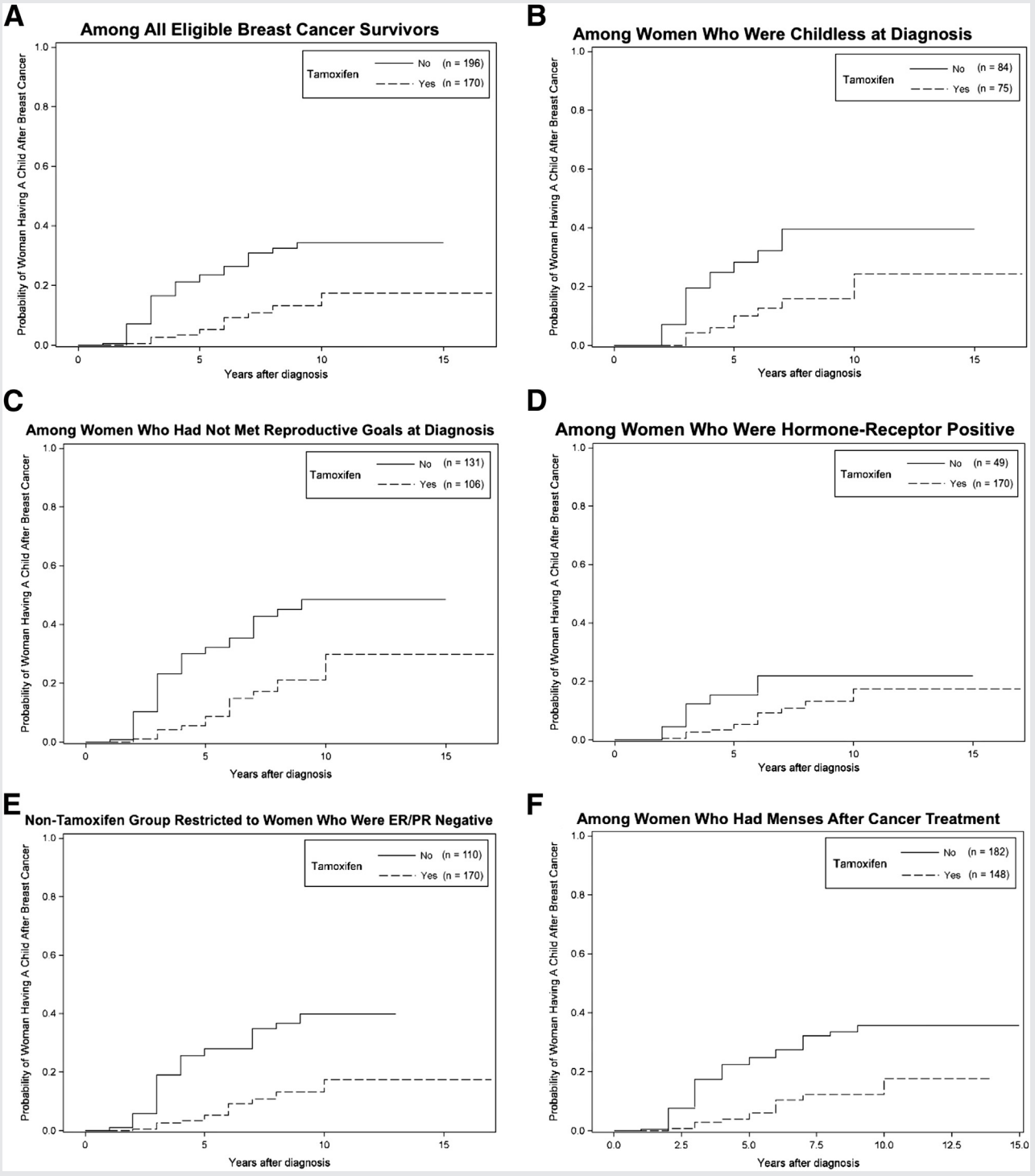
The unadjusted HR for the association between tamoxifen use and having a child after breast cancer diagnosis was 0.29 (95% CI, 0.16, 0.54) (Table 2). This association remained in the subset of women who were childless at the time of diagnosis (HR 0.36; 95% CI, 0.17, 0.76) and in the subset of women who 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 nonusers was restricted to women who were ER/PR negative 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). 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 (Supplemental Table 1, available online). Two women (1.8%) did not have blood collected for AMH assessment 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

FIGURE 1



Unadjusted Kaplan-Meier curves of time to first child after breast cancer diagnosis by tamoxifen status in a cohort of young breast cancer survivors, censored at time of hysterectomy, bilateral oophorectomy, tubal ligation, or study interview. (**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. (Note: Women who took tamoxifen and women with documented hormone receptor status in medical records were considered to be hormone-receptor positive.) (**E**) Tamoxifen group versus women who were hormone-receptor (ER/PR) negative. (Note: Breast cancer survivors who are estrogen/progesterone receptor negative are generally not candidates for adjuvant tamoxifen.) (**F**) Excludes women who reported their period stopping during cancer treatment and never returning.

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TABLE 2

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

	Unadjusted				Adjusted[a]			
Breast cancer survivors	Total, n	Women who gave birth to a child after diagnosis, n	HR	95% CI	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)	159	13	0.25	(0.14, 0.47)
No tamoxifen	196	48	1.00	Referent	176	48	1.00	Referent
Childless at diagnosis[b]								
Tamoxifen	75	9	0.36	(0.17, 0.76)	73	9	0.30	(0.13, 0.66)
No tamoxifen	84	27	1.00	Referent	78	27	1.00	Referent
Not yet met reproductive goals[c]								
Tamoxifen	106	13	0.32	(0.17, 0.60)	103	13	0.29	(0.16, 0.55)
No tamoxifen	131	45	1.00	Referent	122	45	1.00	Referent
Hormone-receptor positive women[d]								
Tamoxifen	170	13	0.39	(0.15, 0.98)	159	13	0.40	(0.14, 1.15)
No tamoxifen	49	7	1.00	Referent	49	7	1.00	Referent
Tamoxifen non-users restricted to those who were hormone-receptor negative[e]								
Tamoxifen	170	13	0.26	(0.13, 0.49)	159	13	0.24	(0.13, 0.47)
No tamoxifen	110	33	1.00	Referent	109	33	1.00	Referent
Adjusted for hormone receptor status								
Tamoxifen	151	8	0.28	(0.11, 0.73)	150	8	0.20	(0.07, 0.58)
No tamoxifen	159	40	1.00	Referent	158	40	1.00	Referent
Menses after cancer treatment[f]								
Tamoxifen	148	12	0.29	(0.16, 0.55)	132	7	0.25	(0.13, 0.48)
No tamoxifen	182	48	1.00	Referent	146	40	1.00	Referent

Note: HR = hazard ratio; 95% CI = 95% confidence interval.
[a] Adjusted for alkylating agent, age at diagnosis, and race.
[b] Childless: not having given birth to a child by the time of the interview.
[c] Fewer children than desired: calculated by subtracting the number of children women gave birth to from the total number they reported they desired.
[d] Hormone-receptor positive: women who took tamoxifen and women with documented hormone receptor status in medical records were considered to be hormone-receptor positive.
[e] Women with breast cancer who are hormone-receptor negative are typically not candidates for adjuvant tamoxifen treatment.
[f] 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.

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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, $P=.80$). The level of AMH was inversely associated with age at clinic visit ($P<.0001$), chemotherapy exposure ($P<.0001$), and cancer stage ($P=.012$), but was not statistically significantly associated with childlessness at diagnosis ($P=.63$), race ($P=.50$), gravidity ($P=.62$), body mass index ($P=.84$), or use of a GnRH agonist during treatment ($P=.48$).

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 times higher (95% CI, 0.67, 3.68) than the estimated geometric mean AMH for women who did not use tamoxifen. Table 3 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 times (95% CI, 1.08, 5.65) that of nonusers. The three most influential confounders of AMH level were age at clinic visit, cancer stage, and exposure to chemotherapy. When women receiving tamoxifen at the time of the clinic visit were excluded, the results did not change (Supplemental Table 2, available online). Additionally, when women with polycystic ovaries on ultrasound were excluded, the association remained strong (ratio of the adjusted estimated geometric mean comparing tamoxifen to no tamoxifen = 2.74; 95% CI, 1.09, 6.85).

The 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 with those who did not (RR 1.18; 95% CI, 0.84, 1.67) (see Table 3). 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 with those who did not (adjusted RR 1.21; 95% CI, 0.84, 1.73). In the subanalysis that excluded women on

TABLE 3

Estimates for the predicted geometric mean value of antimüllerian hormone and the predicted mean antral follicle count 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]		
Clinic variable	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)	

Note: AMH = antimüllerian hormone; AFC = antral follicle count; 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.

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tamoxifen at the time of the clinic visit, the results did not change (see Supplemental Table 2). Additionally, when women with polycystic ovaries 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 after cancer diagnosis compared with 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 after cancer diagnosis and performed many subgroup analyses to account for scenarios that may have led to confounding. For each subanalysis, our conclusions remained unchanged, with hazard ratios for having a child after diagnosis comparing the tamoxifen group with the nontamoxifen group ranging from 0.16 to 0.39. Although the small sample size of women who participated in a clinic visit precluded subanalyses 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 a higher ovarian reserve.

The most obvious possible explanation for our findings that women who take tamoxifen are less likely to have a child after 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 2 months before attempting to conceive (25). However, beyond the guidelines for the 2-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 after breast cancer (26, 27), even for those who are hormone receptor-positive (28), but women are extensively counseled on the benefit of tamoxifen against cancer recurrence and may be hesitant to discontinue or interrupt treatment.

Because the median age at diagnosis for the tamoxifen group in our study was 32 years, 5 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 our present analysis.

There exist other possible explanations for tamoxifen users being less likely to have a child after 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 after 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 nontamoxifen group would result in more women seeking to become pregnant in the nontamoxifen group than would be observed if women were randomized to tamoxifen use. However, when the analysis was limited to comparing women who took tamoxifen with women who were not candidates for tamoxifen (ER/PR negative), 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 after 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 after 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); another study 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). 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. (19) reported that breast cancer survivors using tamoxifen had lower AMH and AFC compared with survivors who were not using tamoxifen. 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 using tamoxifen at the time of the clinic visit. However, when we excluded women who were using 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 with 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, for 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 after cancer diagnosis. Additionally, our study is strengthened by data from clinic visits that allowed us to draw conclusions not only regarding childbearing after diagnosis but also in regards to ovarian reserve and therefore reproductive potential.

Our study has some limitations. We could not 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, to address this issue we defined our tamoxifen group as reporting at least 6 months of use and verified this with medical records.

Our study provides preliminary results for future research on the association between tamoxifen use, reproductive outcomes, and ovarian reserve after breast cancer. 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). Although 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 the ability to meet reproductive goals.

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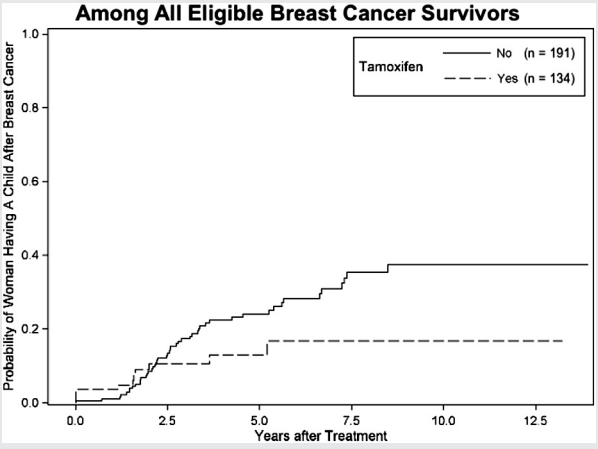
SUPPLEMENTAL APPENDIX

We performed a supplemental analysis for time to first child after breast cancer where the time at risk began when the survivor finished breast cancer treatment or tamoxifen use, which takes 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, the treatment end date was used. For participants who did not have available medical records, the treatment end date was estimated based on what types of treatment (surgery, chemotherapy, radiation, hormone therapy) 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, the 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 the length of time they took tamoxifen. Cox proportional hazard models were used to estimate the hazard ratios for the association between tamoxifen and time to having a child after cancer diagnosis among those who were capable of childbearing, with the risk time being the time off breast cancer treatment.

SUPPLEMENTAL FIGURE 1



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

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SUPPLEMENTAL TABLE 1

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)		
Characteristics	**n**	**%**	**n**	**%**	**n**	**%**	***P* value[a]**
Demographics							
Age at clinic visit (y)							.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							.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							.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							.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 graduate school or graduate degree	36	33.3	13	28.9	23	36.5	
Relationship status at interview							.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							.41
Nulligravid	43	39.8	20	44.4	23	36.5	
Gravid	65	60.2	25	55.6	40	63.5	
Childless at diagnosis							.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							.04
Yes	19	17.6	4	8.9	15	23.8	
No	89	82.4	41	91.1	48	76.2	
Had fewer children than desired							.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							.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 (y)							.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 (y)							.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							.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							.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							.04
Yes	75	69.4	36	80.0	39	61.9	
No	33	30.6	9	20.0	24	38.1	

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SUPPLEMENTAL TABLE 1

Continued.

	Total (n = 108)		Tamoxifen (n = 45)		No tamoxifen (n = 63)		
Characteristics	**n**	**%**	**n**	**%**	**n**	**%**	***P* value**[a]
Chemotherapy							
Alkylating agent							.75
Yes	84	78.5	36	80.0	48	77.4	
No	23	21.5	9	20.0	14	22.6	
Topoisomerase inhibitor							.84
Yes	75	70.1	32	71.1	43	69.4	
No	32	29.9	13	28.9	19	30.6	
Antimitotic agents							.69
Yes	69	64.5	30	66.7	39	62.9	
No	38	35.5	15	33.3	23	37.1	
Antimetabolite							.69
Yes	16	15.0	6	13.3	10	16.1	
No	91	85.0	39	86.7	52	83.9	
GnRH agonist during treatment							.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[d]							.86
Menses present	99	91.7	41	91.1	58	92.1	
Menses absent	9	8.3	4	8.9	5	7.9	

Note: AJCC = American Joint Committee on Cancer; BMI = body mass index; DCIS = ductal carcinoma in situ; GnRH = gonadotropin-releasing hormone.
[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] Menstrual status was assessed by participant's response to these 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.

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SUPPLEMENTAL TABLE 2

Estimates for the predicted geometric mean value of antimüllerian hormone and the predicted mean antral follicle count, comparing breast cancer survivors who have a history of taking tamoxifen but are not actively taking it with the survivors who have never taken tamoxifen.

	Adjusted for age at clinic visit			Adjusted for additional variables[a]		
Tamoxifen use	**Estimate[b]**	**95% CI**	**Ratio[c]**	**Estimate[d]**	**95% CI**	**Ratio[c]**
AMH (ng/dL)						
Past use	0.39	(0.12, 1.27)	1.74	0.34	(0.10, 1.20)	2.51
Current use	0.30	(0.09, 1.00)	1.32	0.33	(0.10, 1.08)	2.41
None	0.22	(0.10, 0.53)		0.14	(0.05, 0.35)	
AFC (n)						
Past use	7.6	(4.9, 12.0)	1.31	5.9	(3.5, 9.8)	1.26
Current use	5.6	(3.5, 9.1)	0.96	5.3	(3.2, 8.7)	1.13
None	5.8	(4.2, 8.1)		4.7	(3.1, 6.9)	

Note: AFC = antral follicle count; AMH = antimüllerian hormone; CI = confidence interval; GnRH = gonadotropin-releasing hormone.

[a] Adjusted for age at clinic visit, chemotherapy use, cancer stage, GnRH agonist use, and race. The race category "other" includes American Indian, Alaskan Native, Asian, Native Hawaiian, and Pacific Islander.

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

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

[d] 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.

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