Original Article

Impact of Fertility Concerns on Endocrine Therapy Decisions in Young Breast Cancer Survivors

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BACKGROUND: The diagnosis and treatment of breast cancer can have profound effects on a young woman's family planning and fertility, particularly among women with hormone receptor–positive breast cancer. **METHODS:** The Young Women's Breast Cancer Study was a multicenter cohort of women aged 40 years or younger and newly diagnosed with breast cancer from 2006 to 2016. Surveys included assessments of fertility concerns, endocrine therapy (ET) preferences, and use. Characteristics were compared between women who reported that fertility concerns affected ET decisions and those who did not. Logistic regression was used to identify factors associated with having an ET decision affected by fertility concerns. **RESULTS:** Of 643 eligible women with hormone receptor–positive, stage I to III breast cancer, one-third (213 of 643) indicated that fertility concerns affected ET decisions. In a multivariable analysis, only parity at diagnosis was significantly associated with fertility concerns affecting ET decisions (odds ratio for nulliparous vs ≥2 children, 6.96; 95% confidence interval, 4.09-11.83; odds ratio for 1 vs ≥2 children, 5.30; 95% confidence interval, 3.03-9.87). Noninitiation/nonpersistence was higher among women with fertility concerns versus those without fertility concerns (40% vs 20%; $P < .0001$). Among women with fertility-related ET concerns, 7% (15 of 213) did not initiate ET, and 33% (70 of 213) were nonpersistent over 5 years of follow-up. Of these women, 66% (56 of 85) reported 1 or more pregnancies or pregnancy attempts; 27% (15 of 56) had resumed ET at the last available follow-up through 5 years. **CONCLUSIONS:** Concern about fertility is a contributor to adjuvant ET decisions among a substantial proportion of young breast cancer survivors. Ensuring family planning is addressed in the setting of ET recommendations should be a priority throughout the cancer care continuum. ***Cancer* 2021;127:2888-2894**. © *2021 American Cancer Society*.

KEYWORDS: adherence, breast cancer, endocrine therapy, fertility concerns, pregnancy.

INTRODUCTION

Adjuvant endocrine therapy (ET) is associated with significant improvements in breast cancer recurrence and mortality in women with hormone receptor–positive breast cancer.[1] For premenopausal women, a minimum of 5 years of treatment is routinely recommended, and additional benefits can be achieved by extending treatment to 10 years, adding gonadotropin-releasing hormone agonists, and, after the achievement of ovarian function suppression, switching to an aromatase inhibitor.[2] Despite advances in adjuvant ET, adherence remains suboptimal, particularly among younger women.[3] Women younger than 40 years at diagnosis are less likely to take ET as indicated in comparison with older women, and in 1 study, they were 50% more likely to discontinue therapy and 40% more likely to be nonadherent than those diagnosed between the ages of 50 and 65 years.[4] Nonadherent behaviors, including forgotten pills, have been reported by more than half of young women on adjuvant ET.[5]

Young women with breast cancer are a vulnerable group facing unique challenges and experiencing disparate outcomes in comparison with older woman, and international consensus guidelines have been established to optimize their management.[6] Fertility and family planning are significant concerns because of the potential of antineoplastic treatment to impair fertility. For many young premenopausal women with hormone receptor–positive breast cancer,

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long-term ET can delay childbearing and expose them to the natural age-related decline in ovarian reserve and fertility.

Thus, fertility concerns and ET decisions are often interrelated. Llarena et al[7] identified fertility concerns as significant predictors of both noninitiation and early discontinuation of tamoxifen: 35% of interviewed patients who did not initiate or stopped tamoxifen early reported that fertility concerns affected their decision. We previously reported that at diagnosis, more than half of women enrolled in a prospective cohort of young breast cancer survivors were concerned about future fertility, and 29% stated that these concerns affected treatment decisions.[8] We update this analysis to report on the prospective effect of fertility concerns on ET-related decision-making and initiation and nonpersistence of ET in a cohort of young women with hormone receptor–positive early breast cancer.

MATERIALS AND METHODS

The Young Women's Breast Cancer Study (YWS; NCT01468246) is a multicenter, prospective cohort that enrolled 1302 young women with newly diagnosed breast cancer between 2006 and 2016 from 13 sites in the United States and Canada. Women enrolled at the Canadian site completed an abbreviated form of the survey and were excluded from the current analysis. Eligibility requirements included an age ≤ 40 years and diagnosis with stage 0 to IV breast cancer within the 6 months before enrollment. Data on tumor stage, subtype, and treatment were gathered through medical record review. Surveys included items regarding sociodemographics, financial comfort,[9,10] medical/treatment history, current medications, fertility concerns,[11] and ET decision-making. After the baseline survey, participants were surveyed every 6 months for the first 3 years after their diagnosis and then annually after that. The current analysis includes data collected through 5 years of follow-up as of February 2019. Survey completion rates at each time point for the first 5 years of follow-up ranged from 85% to 89%. The study protocol was approved by the Dana-Farber/Harvard Cancer Center institutional review board and participating sites. Participants provided signed informed consent before enrollment.

Women with estrogen or progesterone receptor–positive, stage I to III breast cancer were included in the current analysis. The impact of fertility concerns on ET decision-making (Supporting Table 1) was assessed at baseline, 6 months after baseline, and 12 and 24 months after diagnosis. Women who responded that they chose not to take ET or chose/may choose to take less than 5 years of ET because of fertility concerns on any survey corresponding to these time points were classified as having ET decisions affected by fertility concerns. Self-reported current ET use and pregnancies were evaluated semiannually (up to year 3) and then annually through 5 years after the diagnosis. Beginning at 1 year, pregnancy attempts were assessed annually. Women who did not report taking ET before 24 months were classified as noninitiators. Those who initiated ET but did not report taking ET on 1 or more subsequent surveys (eg, treatment interruption or early discontinuation) were classified as nonpersistent. Women who initiated ET and remained persistent until experiencing a breast cancer recurrence or a new primary breast cancer (confirmed by medical record review) were censored at that time.

Statistical Analysis

t tests and χ^2 tests were used to compare characteristics between women who reported that fertility concerns affected ET decisions and those who did not. Logistic regression models were fit to identify factors significantly ($P \leq .05$) associated with having an ET decision affected by fertility concerns; variables in univariable analyses where P was <.20 were included in the final multivariable model. Analyses were conducted with SAS 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

We identified 752 women with estrogen/progesterone receptor–positive breast cancer with at least 1 survey available after the 6-month time point. After the exclusion of patients initially diagnosed with stage 0 breast cancer (n = 71) or stage IV breast cancer (n = 37) and 1 patient for whom data regarding decision-making were unavailable, 643 women were eligible for inclusion in the current analytic cohort (Fig. 1).

Study Population Characteristics

Table 1 lists patient and disease characteristics. The mean age at diagnosis was 36 years (range, 17-40 years), and the median follow-up from diagnosis was 59.8 months (range, 11.7-68.1 months). Eighty-six percent (554 of 643) were non-Hispanic White; 36% (220 of 643) were nulliparous, 17% (104 of 643) had 1 child, and 47% (285 of 643) had 2 or more children before their breast cancer diagnosis. A majority of women (77% [496 of 642]) were treated with neoadjuvant or adjuvant chemotherapy.

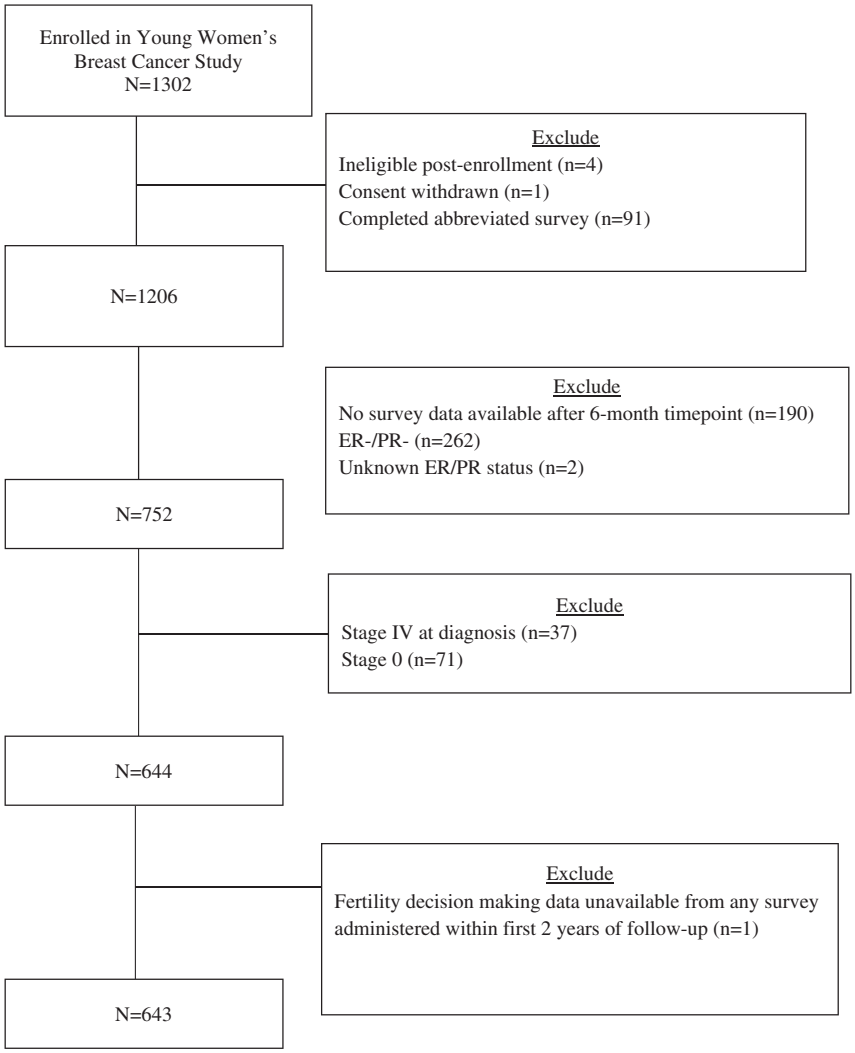

Figure 1. Study flow diagram. ER indicates estrogen receptor; PR, progesterone receptor.

Fertility Concerns and ET Decisions

Within 2 years of their diagnosis, one-third of the study population (213 of 643) indicated that fertility concerns affected their ET decisions. Women who were younger, identified as a race/ethnicity other than White non-Hispanic, were nonmarried, were nulliparous, and had a pretreatment fertility discussion with a provider were more likely to indicate that fertility concerns affected their ET decision (Table 1). In the multivariable analysis (Table 2), only parity at diagnosis remained statistically significant (odds ratio for nulliparous vs ≥2 children, 6.96; 95% confidence interval, 4.09-11.83; odds ratio for 1 child vs ≥2 children, 5.30; 95% confidence interval, 3.03-9.27).

ET initiation/persistence was evaluable among 99% (636 of 643) of those with (210 of 213) and without (426 of 430) fertility concerns (Table 1). Overall, 6% of women (40 of 636) did not initiate ET within 2 years of their diagnosis, and 20% (128 of 636) were nonpersistent and reported discontinuation of ET for at least 1 time point subsequent to initiation. Among women with fertility-related ET concerns, 7% (15 of 213) did not initiate ET, and another 33% (70 of 213) were nonpersistent. A greater proportion of women who reported that fertility concerns affected their ET decisions did not initiate or were nonpersistent with ET in comparison with those who did not report such a consideration (40% vs 20%; $P < .0001$). Approximately one-third of women who were

TABLE 1. Study Population Characteristics

Characteristic	Total (n = 643)	Fertility Concerns Affected ET Decision (n = 213)	Fertility Concerns Did Not Affect ET Decision (n = 430)	*P*
Age at diagnosis, mean (SD), y	36 (3.9)	34.6 (4.1)	36.7 (3.7)	<.0001
Race/ethnicity, No. (%)				.02
White non-Hispanic	554 (86)	174 (82)	380 (88)	
Other race/ethnicity	89 (14)	39 (18)	50 (12)	
Stage, No. (%)				.22
I	263 (41)	95 (45)	168 (39)	
II	282 (44)	92 (43)	190 (44)	
III	98 (15)	26 (12)	72 (17)	
Neo/adjuvant chemotherapy, No. (%)				.06
Yes	496 (77)	155 (73)	341 (79)	
No	146 (23)	58 (27)	88 (21)	
Missing	1		1	
Radiation, No. (%)				.48
Yes	415 (65)	133 (63)	282 (66)	
No	227 (35)	79 (37)	148 (34)	
Missing	1	1		
Married/living as married, No. (%)				<.0001
Yes	507 (79)	147 (69)	360 (84)	
No	136 (21)	66 (31)	70 (16)	
Children before diagnosis, No. (%)				<.0001
No children	220 (36)	121 (60)	99 (24)	
1 child	104 (17)	45 (22)	59 (15)	
≥2 children	285 (47)	37 (18)	248 (61)	
Missing	34	10	24	
Financial comfort, No. (%)				.61
After paying bills enough money for special things	317 (52)	101 (50)	216 (54)	
Enough to pay bills but little money for extra	177 (29)	64 (31)	113 (28)	
Enough to pay bills but because you cut back/ difficulty paying bills	113 (19)	39 (19)	74 (18)	
Missing	36	9	27	
Fertility discussion with doctor before starting therapy, No. (%)				.0002
Yes	477 (79)	175 (88)	302 (75)	
No	125 (21)	24 (12)	101 (25)	
Missing	41	14	27	
Initiation/persistence, No. (%)				<.0001[a]
Did not initiate	40 (6)	15 (7)	25 (6)	
Initiated/nonpersistent	128 (20)	70 (33)	58 (14)	
Initiated/persistent	468 (74)	125 (60)	343 (81)	
Missing	7	3	4	

Abbreviation: ET, endocrine treatment.
[a]The *P* value corresponds to a comparison of noninitiation/nonpersistence and initiation/persistence among 636 evaluable patients.

nonpersistent stopped ET at least temporarily within 2 years of their diagnosis (33% of the concerned [23 of 70] and 34% of those without concerns [20 of 58]).

Among those who reported that fertility concerns affected treatment decisions and did not initiate ET or were nonpersistent, 56% (48 of 85) reported a pregnancy. Of the women who did not report a pregnancy (n = 37), 8 reported at least 1 pregnancy attempt during this time period. Of the women who reported either a pregnancy (n = 48) or a pregnancy attempt (n = 8), 27% (15 of 56) had resumed ET and reported taking ET at their last available follow-up through 5 years.

Among those who reported that fertility concerns did not affect treatment decisions and did not initiate ET or were nonpersistent, 10% (8 of 83) reported a pregnancy. Of the women who did not report a pregnancy (n = 75), 4 reported at least 1 pregnancy attempt during this period. Of the women who reported either a pregnancy (n = 8) or a pregnancy attempt (n = 4), only 1 woman (1 of 12) had resumed ET and reported taking ET at the last available follow-up through 5 years.

DISCUSSION

Our findings support the notion that for many young premenopausal women with hormone receptor–positive breast cancer, fertility concerns and ET decisions are interconnected. These striking findings highlight the

TABLE 2. Univariable and Multivariable Analyses of Factors Associated With the Impact of Fertility on ET Decisions (n = 590)

	Univariable		Multivariable[a]	
Factor	OR (95% CI)	*P*	OR (95% CI)	*P*
Age at diagnosis (y)	0.88 (0.84-0.92)	<.0001	0.95 (0.91-1.01)	.08
Other race/ethnicity (reference = White non-Hispanic)	1.68 (1.05-2.69)	.03	1.28 (0.75-2.16)	.36
Stage (reference = I)				
II	0.84 (0.58-1.22)	.35	1.00 (0.63-1.58)	.99
III	0.70 (0.41-1.18)	.18	0.86 (0.46-1.63)	.65
Neo/adjuvant chemotherapy (reference = none)	0.71 (0.47-1.06)	.09	0.61 (0.36-1.04)	.07
Radiation (reference = none)	0.90 (0.63-1.28)	.55		
Married/living as married (reference = unmarried)	0.42 (0.28-0.63)	<.0001	0.87 (0.54-1.39)	.55
Children before diagnosis (reference = ≥2 children)				
No children	8.76 (5.57-13.76)	<.0001	6.96 (4.09-11.83)	<.0001
1 child	5.61 (3.29-9.59)	<.0001	5.30 (3.03-9.27)	<.0001
Financial comfort (reference = enough money for special things)				
Enough to pay bills but little money for extra	1.20 (0.81-1.78)	.37		
Enough to pay bills but because you cut back/difficulty paying bills	1.07 (0.67-1.70)	.79		
Fertility discussion with doctor before starting therapy (reference = No)	2.29 (1.41-3.72)	.0008	0.99 (0.55-1.76)	.96

Abbreviations: CI, confidence interval; OR, odds ratio.
Women missing data for variables included in the univariable and multivariable models (n = 53) are excluded.
[a]Variables with $P < .20$ in univariable analyses were included in the final multivariable model.

dilemma facing many young women with hormone receptor–positive breast cancer and their loved ones: whether to optimize adjuvant breast cancer treatment or fulfill near-term family planning desires. Among the general population of women with breast cancer, ET nonadherence is driven by multiple factors, including side effects, a perceived lack of efficacy, and financial constraints.[12] Fertility and future childbearing issues, however, are unique to the youngest women with breast cancer, a group at increased risk for nonadherence.[3] In an early cross-sectional study of women diagnosed with breast cancer when they were 40 years old or younger, 29% reported that fertility concerns influenced their treatment decisions.[11] In a prior YWS study, 15% of women reported soon after diagnosis that these concerns specifically affected ET decisions,[8] and this was reported by 13% of women in an ancillary European cohort that used the same survey.[13] Limited to a population for which ET is clearly recommended, our current analysis demonstrates that in extended follow-up, fertility concerns affected the ET decisions of one-third of women with hormone receptor–positive early breast cancer enrolled in the YWS.

Women with children before their cancer treatment show a decreased interest in fertility preservation, take less action to preserve their fertility, and may also be underinformed by their providers regarding available strategies.[14] Thus, it is not unexpected that in the current analysis, nulliparous and monoparous women, compared with multiparous women, reported significantly more fertility concerns affecting their ET decision-making. Disease- and treatment-related factors, however, such as stage and exposure to radiotherapy or chemotherapy, were not significantly associated with these concerns, although there was a nonsignificant trend toward a lower likelihood of having ET decisions affected by fertility concerns among women who received chemotherapy. We previously showed that nulliparity was a significant predictor of reporting at least some degree of concern about fertility when treatment decisions were being made after a diagnosis, with significant associations also identified for younger age, non-White ethnicity, and receiving chemotherapy.[8] Taken together, our findings support the importance of providers ascertaining the priorities of each individual patient around fertility beginning at diagnosis and throughout all phases of survivorship and not relying on prognosis-based assumptions.

Moreover, a substantial proportion of women who expressed ET-related fertility concerns did not initiate, interrupted, or discontinued ET without resumption in the 5 years after their diagnosis. In a prior study including more than 500 women with hormone receptor–positive breast cancer at an age < 45 years, 22% reported a desire for future fertility at diagnosis, with fertility concerns significantly associated with tamoxifen noninitiation and discontinuation.[7] Of women who did not initiate or discontinued tamoxifen, 35% attributed their decision to fertility concerns.[7] In a survey of women younger than 45 years enrolled in the Sister Study, a nonstatistically significant trend toward

nonadherence among women with an interest in future fertility was observed.[14] Restarting ET after a period of interruption may be beneficial; however, women younger than 40 years are the least likely to restart,[16] and this underscores the importance of addressing this issue early. Although the role of fertility and fertility preservation in the successful treatment of young women with breast cancer is widely accepted and clinical practice guidelines support early counseling and implementation of strategies to preserve fertility,[17] additional guidance to support patients and providers when managing fertility and childbearing in survivorship would be beneficial. It is expected that the prospective Pregnancy Outcome and Safety of Interrupting Therapy for Women with Endocrine Responsive Breast Cancer (POSITIVE) trial (NCT02308085) will inform how temporarily stopping ET in young women desiring pregnancy affects disease, fertility, and psychosocial outcomes.

Study strengths include the YWS's prospective design, adequate follow-up, and understudied patient population. We used direct questioning, rather than circumstantial assumptions, to assess the effect of fertility concerns on ET decision-making. We were unable to measure adherence objectively and limited our analysis to noninitiation and any discontinuation (including temporary), both based on self-report and subject to respondent biases, which may overestimate adherence. Because follow-up was limited to 5 years, some women may resume ET at a later time, and this was not captured in the current analysis. Although the majority of YWS participants had reached 5 years of follow-up, some participants did not have complete follow-up data (eg, because of nonresponse or because they enrolled later in the study and had not yet reached either the 4- or 5-year survey time point). Furthermore, the majority of YWS participants (86.2%) identify as White and non-Hispanic, and our population may not reflect all young women with breast cancer.

Nevertheless, our prospectively designed study documents the relationships among fertility concerns, ET use, and pregnancies over time and sheds light on fertility concerns as a unique driver of ET nonadherence in young breast cancer survivors. Fertility concerns are common in the broader adolescent and young adult cancer patient population.[18,19] The evolution of fertility priorities over time is particularly evident among adolescents and young adults, with interest in fertility and pregnancy increasing with age.[18] The importance of re-evaluating fertility-related needs after the completion of active treatment and into survivorship has been similarly acknoweleged.[20] Collectively, these findings should encourage continued efforts to identify strategies to support young survivors and effectively address their family planning needs.

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CONFLICT OF INTEREST DISCLOSURES

Tal Sella reports an honorarium from Roche. Philip D. Poorvu reports peer review of educational materials for Medscape. Jeffrey M. Peppercorn reports employment by and stock in GlaxoSmithKline for his spouse, research funding from Pfizer, and consulting for Athenex and Abbott Laboratories. Ann H. Partridge reports personal fees from UpToDate outside the submitted work. The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Tal Sella: Conceptualization, methodology, visualization, writing–original draft, writing–review and editing, and investigation. **Philip D. Poorvu:** Conceptualization, data curation, methodology, visualization, writing–review and editing, and investigation. **Kathryn J. Ruddy:** Resources, writing–review and editing, and investigation. **Shari I. Gelber:** Data curation, writing–review and editing, and investigation. **Rulla M. Tamimi:** Writing–review and editing and investigation. **Jeffrey M. Peppercorn:** Resources, writing–review and editing, and investigation. **Lidia Schapira:** Resources, writing–review and editing, and investigation. **Virginia F. Borges:** Resources, writing–review and editing, and investigation. **Steven E. Come:** Resources, writing–review and editing, and investigation. **Ann H. Partridge:** Conceptualization, data curation, funding acquisition, methodology, project administration, resources, supervision, writing–original draft, writing–review and editing, and investigation. **Shoshana M. Rosenberg:** Conceptualization, data curation, formal analysis, funding acquisition, methodology, project administration, supervision, visualization, writing–original draft, writing–review and editing, and investigation.

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