



Does Use of Neoadjuvant Chemotherapy Affect the Decision to Pursue Fertility Preservation Options in Young Women with Breast Cancer?

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ABSTRACT

Background. The American Society of Clinical Oncology guidelines recommend early referral to reproductive endocrinology and infertility (REI) specialists for young women diagnosed with breast cancer. Current practice patterns demonstrate an increased utilization of neoadjuvant chemotherapy (NAC). We evaluated premenopausal women with breast cancer after consultation with a Fertility Nurse Specialist (FNS) and determine factors associated with referral to REI specialists.

Methods. This retrospective review included all premenopausal women diagnosed at our institution with stage 0–III unilateral breast cancers between 2009 and 2015 who completed an FNS consultation. Clinicopathologic features and factors associated with referral to REI after FNS consultation were analyzed.

Results. A total of 334 women were identified. Median age was 35 years (interquartile range 32–38). The majority of women were single ($n = 198$, 59.3%) and nulliparous ($n = 239$, 71.6%). REI referrals were common ($n = 237$, 71.0%). The Breast Surgery service was the most frequent referring service ($n = 194$, 58.1%), with significantly more

REI referrals compared to Breast Medicine and Genetics services ($p = 0.002$). Nulliparity was associated with REI referral ($p < 0.0001$). Adjuvant chemotherapy ($p = 0.003$) was associated with pursuing REI referral, whereas NAC ($p < 0.001$) was associated with declining REI referral.

Conclusions. Most women elected to consult with an REI specialist, confirming strong interest in fertility preservation among premenopausal women with breast cancer. However, women receiving NAC more frequently declined referral to REI, suggesting that the need to start NAC may influence decisions regarding fertility preservation. With increasing utilization of NAC, our study supports the need for further counseling and education regarding fertility preservation for women undergoing NAC.

Breast cancer is the most commonly diagnosed malignancy in women of reproductive age.¹ Although prevalence of breast cancer in young women is low, 6.6% of all breast cancers are diagnosed in women 40 years of age or younger.^{2,3} Recent advances in treatment regimens over the past several decades have dramatically improved disease-free and overall survival, prompting providers to focus more attention on optimizing patient quality of life.⁴ As women increasingly delay childbearing for personal and professional reasons, it is likely that many women will be diagnosed with breast cancer before completion of childbearing.^{5,6} These intersecting trends help to explain the heightened awareness and concern regarding fertility after breast cancer treatment.

Breast cancer treatment is associated with infertility.^{7,8} Cytotoxic chemotherapeutic agents induce fibrosis, apoptosis of primordial follicles, and vascular damage, compromising stromal function and depleting ovarian reserve.⁹ In addition to inciting direct toxicity to the ovary and accelerating natural declines in ovarian function, adjuvant therapies can impose temporal delays on child-bearing, further compromising fertility.

Current practice patterns demonstrate a trend toward increasing NAC utilization in women with invasive breast cancer.^{10–12} Use of NAC has historically been limited to treatment of locally advanced disease, but recommendations for NAC in early-stage breast cancer are increasing, especially in the setting of high-risk molecular tumor subtypes.^{13,14} Young women are more likely to have delays in diagnosis and to harbor these aggressive subtypes with higher rates of high-grade, triple negative, and HER2 overexpressing tumors, compared with their older counterparts.^{4,15,16} The benefits of NAC include both prognostic and predictive information as well as potentially minimizing surgical intervention, particularly for women with nodal involvement.¹⁷ Thus, for women of reproductive age, the use of NAC has significant implications for future fertility.^{7,8}

Previous studies have indicated that chemotherapy-induced infertility is associated with negative quality of life as well as increased anxiety and psychological burden.^{18,19} Indeed, significant interest in and concerns regarding fertility have been reported in premenopausal women with breast cancer.^{8,20–23} The American Society of Clinical Oncology (ASCO) has recognized the need for fertility counseling in the setting of a new cancer diagnosis and has implemented recommendations that emphasize the paramount importance of accurate reproductive counseling and timely referral to reproductive endocrinologists.²⁴ Despite these recommendations, studies have consistently demonstrated that women do not receive adequate counseling regarding potential impact on future fertility and options for fertility preservation.^{21,25–28}

In an effort to meet this need, Memorial Sloan Kettering Cancer Center (MSKCC) established the MSKCC Cancer and Fertility Program in 2009 with the goal of educating women about treatment-related fertility risks, as well as fertility preservation and family building options, and facilitating referrals to reproductive endocrinologists and infertility (REI) specialists. This study evaluates the factors associated with referral to REI specialists for women with breast cancer and the effect of NAC on the decision to pursue REI consultation.

METHODS

We performed an Institutional Review Board-approved retrospective review of a prospectively maintained breast cancer database to identify all women with stage 0-III breast cancer between 2009 and 2015 who consulted with a Fertility Nurse Specialist (FNS) in the MSKCC Cancer and Fertility Program. Clinicopathologic features, treatment variables, referring service, and outcome of FNS consultation were collected. FNS consultation outcomes were prospectively recorded as REI consult accepted or declined. Women who accepted REI referral were compared with those who declined REI referral following FNS consultation. Women with bilateral cancer or women who were missing information on REI referral status were excluded.

Continuous characteristics were summarized with the median and interquartile range (IQR), whereas categorical characteristics were summarized with the frequency and percentage. Comparisons between those accepting and declining REI referral, and between those receiving NAC or not, were made with the Wilcoxon rank-sum test for continuous variables, and the Chi square test or Fisher's exact test, as appropriate, for categorical variables. A p value ≤ 0.05 was considered statistically significant. All statistical analyses were conducted in R software version 3.2.5 (R Core Development Team, Vienna, Austria).

MSKCC Cancer and Fertility Program

MSKCC established its Cancer and Fertility Program in 2009 to address the growing need for comprehensive patient education about the impact of cancer diagnosis and treatments on subsequent fertility and family planning. An FNS provides counseling regarding potential reproductive toxicities of proposed cancer treatments as well as opportunities for fertility preservation before initiation of cancer therapy, including facilitating referrals to REI specialists. All premenopausal women who are diagnosed with breast cancer are offered consultation with an FNS before beginning treatment.

RESULTS

Patient Demographics

A total of 334 women who underwent FNS referral were identified. During this time period, 3242 premenopausal women were evaluated at MSKCC with a new diagnosis of breast cancer. Patient demographics are detailed in Table 1. Median age was 35 years (interquartile [IQR] 32–39). Most women were Caucasian ($n = 210$, 62.8%)

TABLE 1 Patient demographic, clinicopathologic, and treatment features

Characteristic	Total (<i>n</i> = 334)
Median age, years (range)	35 (32–39)
Marital status	
Single	198 (59.3%)
Married	136 (40.7%)
Race	
White	210 (62.8%)
Asian	49 (14.7%)
Black	39 (11.7%)
Other	6 (1.8%)
Declined to answer	30 (9.0%)
Insurance type	
Private	296 (88.6%)
Government	31 (9.3%)
Uninsured	7 (2.1%)
Nulligravid	185 (55.4%)
Nulliparous	239 (71.6%)
Previous hormonal exposure	
Oral contraceptives	232 (69.5%)
Fertility treatments	28 (8.4%)
Genetic mutation	
Not tested	88 (26.3%)
No mutation	198 (59.3%)
BRCA1	25 (7.5%)
BRCA2	18 (5.4%)
TP53	3 (0.9%)
Unknown	2 (0.6%)
Family history	
Breast cancer	38 (11.4%)
Ovarian cancer	5 (1.5%)
Tumor characteristics	Total (<i>n</i> = 334)
Median tumor size, cm (IQR)	2.0 (1.2–2.8)
Histology	
IDC	309 (92.5%)
ILC	15 (4.5%)
DCIS	10 (3.0%)
Tumor grade	
I	4 (1.2%)
II	135 (40.4%)
III	177 (53.0%)
Unknown	18 (5.4%)
Receptor profile	
ER positive	257 (76.9%)
HER2 positive	67 (20.1%)
Triple negative	58 (17.4%)
Stage	
0	10 (3.0%)
I	121 (36.2%)

TABLE 1 continued

Tumor characteristics	Total (<i>n</i> = 334)
II	158 (47.3%)
III	45 (13.5%)
Breast cancer treatment	Total (<i>n</i> = 334)
Breast surgery	
Lumpectomy	126 (37.7%)
Mastectomy	208 (62.3%)
Contralateral prophylactic mastectomy	138 (41.3%)
Axillary surgery	
Sentinel lymph node biopsy alone	216 (64.7%)
Axillary lymph node dissection	110 (32.9%)
None	8 (2.4%)
Systemic therapy	
Adjuvant chemotherapy	195 (58.4%)
Neoadjuvant chemotherapy	63 (18.9%)
Endocrine therapy	244 (73.1%)

IQR interquartile range, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *DCIS* ductal carcinoma in situ, *ER* estrogen receptor

and had private insurance (*n* = 296, 88.6%). The majority of women were single (*n* = 198, 59.3%), nulligravid (*n* = 185, 55.4%), and nulliparous (*n* = 239, 71.6%). Previous oral contraceptive use was common (*n* = 232, 69.5%), whereas previous fertility treatment was rare (*n* = 28, 8.4%). Germline mutations were detected in 13.8% (*n* = 46) of women, and family history of a first-degree family member with breast or ovarian cancer was uncommon (*n* = 38, 11.4%; and *n* = 5, 1.5%, respectively).

Tumor Characteristics

The predominant histology was invasive ductal carcinoma (*n* = 309, 92.5%) with a median tumor size of 2.0 cm (IQR 1.2–2.8 cm; Table 1). Stage II was the most common stage at diagnosis (*n* = 158, 47.3%), followed by stage I (*n* = 121, 36.2%), and stage III (*n* = 45, 13.5%). Stage 0 cancers comprised only 3% (*n* = 10) of the entire cohort. The majority of tumors were high grade (*n* = 177, 53.0%), expressed estrogen receptor (ER) (*n* = 257, 76.9%), and did not demonstrate HER2 amplification (*n* = 267, 79.9%). Triple negative tumors comprised 17.4% (*n* = 58) of tumors.

Treatment Characteristics

Table 1 summarizes treatment characteristics. The most common surgical approach was mastectomy (*n* = 208, 62.3%). Of women who underwent mastectomy, 66.3%

($n = 138$) elected to undergo contralateral prophylactic mastectomy for risk reduction. Almost all patients underwent axillary staging ($n = 326$, 97.6%), the majority with sentinel lymph node biopsy alone ($n = 216$, 64.7%). The eight women who did not undergo axillary staging had pure ductal carcinoma in situ. Axillary lymph node dissection (ALND) was performed in 32.9% ($n = 110$) of patients.

The majority of women received systemic therapy. Adjuvant chemotherapy was administered to 195 (58.4%) women, whereas a neoadjuvant approach was less common ($n = 63$, 18.9%). Endocrine therapy was prescribed to 73.1% (244 of 334) of all patients and to 91.1% (234 of 257) of those who were ER positive.

Fertility Nurse Specialist Consults

All women met with an FNS (either in-person or via phone consultation) to discuss fertility concerns and the option to obtain an REI referral. The Breast Surgery Service was the most common source of referral to the FNS team ($n = 194$, 58.1%; Table 2). The majority of FNS consultations were performed over the phone ($n = 268$, 80.2%), whereas the minority ($n = 66$, 19.8%) were performed as office-based consultations. After FNS consultation, 237 (71.0%) women proceeded with an REI referral, and 97 (29.0%) declined REI referral.

Factors Associated with REI Referral

Nulliparity was associated with more frequent acceptance of REI referral ($p < 0.0001$); however, there was no association between age, marital status, gravida status, race, or insurance type with REI referral (Table 2). Referral from the Breast Surgery Service was associated with higher frequency of acceptance of REI referral ($p = 0.002$) as was early-stage disease ($p < 0.001$). Additionally, timing of chemotherapy administration was associated with outcome of FNS consultation; adjuvant chemotherapy was associated with REI referral ($p = 0.003$), whereas NAC was associated with declining REI referral ($p < 0.001$). Of the 195 women who received adjuvant chemotherapy, 151 (77.4%) pursued REI referral compared with 25 (39.7%) of 63 women who received NAC (Table 3). On multivariate analysis, only referring service and receipt of NAC were associated with decision of whether to pursue REI referral or not.

NAC Versus Adjuvant Chemotherapy

Women in our study group receiving chemotherapy received anthracycline-based regimens in the majority of cases ($n = 210$, 81.4% of women receiving chemotherapy). The majority of women were treated before 2015 before

the results of the POEMS (*Prevention of Early Menopause Study*) trial were published. As a result, use of GnRH agonists for fertility preservation was only routinely offered to patients starting in 2015.

To investigate the finding that women who received NAC were more likely to decline REI referral ($p < 0.001$), we performed a subset analysis comparing women who received NAC ($n = 63$) with those who received adjuvant chemotherapy ($n = 195$). The two subsets of women were similar with regard to demographics (Table 3). Although the distribution of tumor histology was similar, tumor molecular profiles differed between groups. Women receiving NAC had more advanced disease, with larger tumor size and a higher proportion of adverse molecular subtypes (ER negative and HER2 positive), compared with those who received adjuvant chemotherapy (all $p < 0.05$). Women receiving NAC also had a higher frequency of clinically node-positive disease (NAC $n = 43$, 68.3% vs. adjuvant chemotherapy $n = 93$, 47.7%; $p = 0.006$) and more frequently received ALND at the time of surgery. The receipt of endocrine therapy was similar between groups.

A total of 97 women who received chemotherapy declined REI consultation ($n = 44$ in the adjuvant chemotherapy group and $n = 38$ in the NAC group) (Table 4). There was no statistical difference in molecular profile, but among women who declined REI consultation, women who received NAC did have more advanced disease compared with those who received adjuvant chemotherapy ($p = 0.03$).

Treatment delays, defined as initiating chemotherapy more than 6 weeks after initial diagnosis in the NAC setting, and more than 12 weeks in the adjuvant setting, were uncommon. In the women undergoing NAC, a total of four (6.3%) women receiving NAC started chemotherapy ≥ 6 weeks after initial diagnosis; of those, three women had pursued an REI referral. Similarly, a total of seven (3.5%) women receiving adjuvant chemotherapy failed to initiate chemotherapy by 12 weeks after surgery; of those, six women pursued an REI referral. Overall, the number of women who had delays in receiving chemotherapy is too small to make any statistical comparisons.

DISCUSSION

More than 70% of consultations with the FNS resulted in an REI referral, confirming previous findings of significant interest in future fertility among premenopausal women with breast cancer. Women who pursued an REI referral tended to be nulliparous, in agreement with existing studies.²¹ We noted an interesting relationship between

TABLE 2 Factors associated with REI referral

Factors	Declined REI referral (<i>n</i> = 97)	Accepted REI referral (<i>n</i> = 237)	<i>p</i> value
Median age, years (IQR)	36 (32.0–39.9)	35 (31.0–39.0)	0.4
Single	57 (58.8%)	141 (59.5%)	> 0.9
Race			0.3
White	55 (56.7%)	155 (65.4%)	
Black	17 (17.5%)	22 (9.3%)	
Asian	14 (14.4%)	35 (14.8%)	
Other	2 (2.1%)	4 (1.7%)	
Declined to answer	9 (9.3%)	21 (8.9%)	
Insurance type			> 0.9
Private	86 (88.6%)	210 (88.6%)	
Government	9 (9.3%)	22 (9.3%)	
Uninsured	2 (2.1%)	5 (2.1%)	
Nulligravid	45 (46.4%)	140 (59.1%)	0.3
Nulliparous	53 (54.6%)	186 (78.5%)	< 0.0001
Referring service			0.002
Breast surgery	43 (44.3%)	151 (63.7%)	
Breast medicine	53 (54.6%)	84 (35.4%)	
Genetics/GYN	1 (1.0%)	2 (0.8%)	
Breast surgery			0.2
Lumpectomy	42 (43.3%)	84 (35.4%)	
Mastectomy	55 (56.7%)	153 (64.6%)	
Contralateral prophylactic mastectomy	39 (40.2%)	99 (41.8%)	0.9
Axillary surgery			0.05
SNLB	54 (55.7%)	162 (68.4%)	
ALND	41 (42.3%)	69 (29.1%)	
None	2 (2.1%)	6 (2.5%)	
Genetic mutations			0.3
Not tested	24 (24.7%)	64 (27.0%)	
Negative testing	58 (60.0%)	140 (59.1%)	
BRCA1	7 (7.2%)	18 (7.6%)	
BRCA2	7 (7.2%)	11 (4.6%)	
TP53	0	3 (1.3%)	
Unknown	1 (1.0%)	1 (0.4%)	
Tumor grade			0.3
I	1 (1.0%)	3 (1.3%)	
II	33 (34.0%)	102 (43.0%)	
III	55 (56.7%)	122 (51.5%)	
Unknown	8 (8.3%)	10 (4.2%)	
Receptor profile			0.053
ER positive	67 (69.1%)	192 (81.0%)	
HER2 positive	23 (23.7%)	44 (18.6%)	0.4
Triple negative	21 (21.6%)	37 (15.6%)	0.4
Node positive	44 (45.4%)	92 (38.8%)	0.3
Stage			< 0.001
0	3 (3.1%)	7 (3.0%)	
I	19 (19.6%)	102 (43.0%)	
II	58 (59.8%)	100 (42.2%)	
III	17 (17.5%)	28 (11.8%)	

TABLE 2 continued

Factors	Declined REI referral (n = 97)	Accepted REI referral (n = 237)	p value
Systemic therapy			
Adjuvant chemotherapy	44 (45.4%)	151 (63.7%)	0.003
Neoadjuvant chemotherapy	38 (39.2%)	25 (10.5%)	< 0.001
Endocrine therapy	64 (66.0%)	180 (75.9%)	0.07
Consultation type			0.3
Clinic	15 (15.5%)	51 (21.5%)	
Phone	82 (84.5%)	186 (78.5%)	

IQR interquartile range, *REI* reproductive endocrinology and infertility, *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection

REI referral and timing of chemotherapy; despite similar demographic characteristics, women who received NAC declined REI referral more frequently compared with those who received adjuvant chemotherapy. This relationship persisted on multivariate analysis, while early stage of disease, which was significantly associated with REI referral, failed to be associated with REI referral on multivariate analysis. This finding suggests that it is the receipt of NAC rather than advanced disease that drives the trend to decline REI referral among premenopausal women who receive NAC.

NAC offers a range of potential benefits, ranging from downstaging the breast and axilla, allowing for breast conservation and potential obviation of ALND, to providing a measure of histologic response to chemotherapeutic agents.^{17,30} Oncologists also can tailor adjuvant therapies according to degree of pathologic response.^{17,30} Despite these advantages, recommendation for NAC is associated with a potential “scare factor” that may indicate increased severity and urgency to a patient.³¹ Indeed, women who received NAC in our study had more advanced disease and higher incidence of unfavorable molecular subtypes (ER negative and HER2 positive subtypes). Internalization of this fear and anxiety could partially explain our study finding that only 40% of patients undergoing NAC sought an REI referral and that receipt of NAC was associated with a decision to decline consultation with an REI specialist. Additionally, NAC has been associated with higher levels of psychological distress, which have been linked to anxiety and depression.³² A study of infertile women demonstrated that patients who screened positive for depression were less likely to initiate fertility treatments, highlighting the complexity of potential factors that enter into the decisional calculus regarding fertility treatment.³³

While the finding that receipt of NAC was associated with less-frequent acceptance of REI referral is novel and significant on its own, it becomes even more important in the context of a recent multicenter study that demonstrated that NAC was an independent negative predictor of

completing ovarian stimulation following REI consultation.³⁴ The less-frequent referral to REI and higher odds of not completing ovarian stimulation makes the NAC setting particularly challenging for women who are interested in fertility preservation.

Although current advances in fertility preservation techniques are associated with favorable outcomes and include a range of options, such as administration of ovarian suppression with gonadotropin-releasing hormone analogs during chemotherapy, ovarian tissue, oocyte, and embryo cryopreservation strategies, potential concerns may lead to clinician and patient reluctance to pursue these options before NAC.^{29,35} These concerns include estradiol level elevations during ovarian stimulation treatment as well as temporal delays in starting NAC because of pursuit of these options. Ovarian stimulation is associated with a tenfold increase in baseline estradiol levels, which could promote mitogenic effects on ER positive tumors, especially in the neoadjuvant setting, in which the tumor remains in situ.³⁶ Although the exposure is limited, the concept of intentionally generated hormonal milieus with elevated levels of estradiol before or during breast cancer treatment is difficult to reconcile and has led to increased interest in alternative strategies, including cryopreservation of ovarian tissue.³⁷ Research leading to refinement of ovarian stimulation cycles to maximize oocyte yield while minimizing serum estradiol levels is ongoing.^{38–44} However, it is reassuring that several studies have reported equivalent rates of recurrence and survival in patients with breast cancer electing to undergo ovarian stimulation compared to those who do not undergo ovarian stimulation.^{30,45–47}

Regarding concerns about treatment delay, traditional protocols require ovarian stimulation to commence during the follicular phase, which can lead to patients waiting 6 weeks to complete a single cycle.⁴³ The introduction of random-start protocols has revolutionized the timing of ovarian stimulation cycles, allowing patients to complete a single cycle within 2 weeks.^{5,48} The time between surgery

TABLE 3 Comparison of patients receiving NAC and those receiving adjuvant chemotherapy

Factor	Adjuvant chemotherapy (<i>n</i> = 195)	NAC (<i>n</i> = 63)	<i>p</i> value
Median age, years (IQR)	35 (31–38)	35 (30.5–38)	0.8
Race			0.11
White	130 (66.7%)	31 (49.2%)	
Black	22 (11.3%)	10 (15.9%)	
Asian	23 (11.8%)	13 (20.6%)	
Other	3 (1.5%)	2 (3.2%)	
Declined to answer	17 (8.7%)	7 (11.1%)	
Insurance type			> 0.9
Private	172 (88.2%)	57 (90.5%)	
Government	18 (9.2%)	5 (7.9%)	
Uninsured	5 (2.6%)	1 (1.6%)	
REI referral	151 (77.4%)	25 (39.7%)	< 0.001
Single	105 (53.8%)	41 (65.1%)	0.2
Nulligravid	108 (55.4%)	29 (46.0%)	0.11
Nulliparous	139 (71.3%)	38 (60.3%)	0.3
Breast surgery			
Lumpectomy	70 (35.9%)	19 (30.2%)	0.5
Mastectomy	125 (64.1%)	44 (69.8%)	
Contralateral prophylactic mastectomy	90 (46.2%)	25 (39.7%)	0.5
Axillary surgery			0.006
SNLB	124 (63.6%)	27 (42.9%)	
ALND	71 (36.4%)	36 (57.1%)	
Histology			0.3
IDC	190 (97.4%)	63 (100%)	
ILC	5 (2.6%)	0	
Genetic testing			0.3
Not tested	51 (26.2%)	16 (25.4%)	
Negative testing	112 (57.4%)	41 (65.1%)	
BRCA1	21 (10.8%)	2 (3.2%)	
BRCA2	10 (5.1%)	3 (4.8%)	
TP53	1 (0.5%)	1 (1.6%)	
Median tumor size, cm (IQR)	2 (1.5–2.6)	3.4 (2.3–4.7)	< 0.001
Node-positive	93 (47.7%)	43 (68.3%)	0.006
Tumor grade			0.11
II	73 (37.4%)	16 (25.4%)	
III	116 (59.5%)	45 (71.4%)	
Unknown	6 (3.1%)	2 (3.2%)	
Receptor profile			0.003
ER positive	144 (73.8%)	39 (61.9%)	
HER2 positive	39 (20.0%)	26 (41.3%)	
Triple negative	44 (22.6%)	14 (22.2%)	
Stage			< 0.001
I	66 (33.8%)	1 (1.6%)	
II	101 (51.8%)	47 (74.6%)	
III	28 (14.4%)	15 (23.8%)	
Endocrine therapy	147 (75.4%)	43 (68.3%)	0.3

NAC neoadjuvant chemotherapy, IQR interquartile range, REI reproductive endocrinology and infertility, SLNB sentinel lymph node biopsy, ALND axillary lymph node dissection, IDC invasive ductal carcinoma, ILC invasive lobular carcinoma, ER estrogen receptor

TABLE 4 Comparison of patients who received chemotherapy and declined REI referral

Factor	Adjuvant chemotherapy (n = 44)	NAC (n = 38)	p value
Tumor grade			> 0.9
II	14 (31.8%)	3 (7.9%)	
III	28 (63.6%)	34 (89.5%)	
Unknown	2 (4.5%)	1 (2.6%)	
Receptor profile			
ER positive	31 (70.4%)	22 (57.9%)	0.3
HER2 positive	6 (13.6%)	14 (38.8%)	0.08
Triple negative	2 (4.5%)	10 (26.3%)	> 0.9
Node positive	22 (50.0%)	18 (47.4%)	> 0.9
Stage			0.03
I	9 (20.5%)	1 (2.6%)	
II	26 (59.1%)	30 (78.9%)	
III	9 (20.5%)	7 (18.4%)	

REI reproductive endocrinology and infertility, NAC neoadjuvant chemotherapy, ER estrogen receptor

and initiation of adjuvant chemotherapy is a preferred time to pursue cryopreservation cycles, as waiting up to 12 weeks to start chemotherapy does not adversely impact survival outcomes.^{49,50} Timing of fertility treatment certainly becomes more complex in the setting of NAC; however, recent studies have suggested that use of ovarian stimulation is not associated with clinically meaningful delays in initiation of NAC or deleterious oncologic outcomes.^{51,52} Similarly, our study demonstrated that REI referral rarely delayed initiation of chemotherapy in both the neoadjuvant and adjuvant settings.

Current recommendations for prolonged endocrine therapy (10 years) also may affect decisions for pursuit of fertility preservation options in young women with ER-positive breast cancer.^{53–55} Although the need for endocrine therapy was not associated with patient acceptance of referral to an REI in our study, it is important to note recent studies have shown that up to 40% of women receiving endocrine therapy for breast cancer are interested in interruption of endocrine therapy to pursue pregnancy.⁵⁶ The POSITIVE (*Pregnancy Outcome and Safety of Interrupting Therapy for women with endocrine responsive breast cancer*) trial is ongoing, and may answer questions regarding oncologic safety of endocrine therapy interruption. In the future, the use of prolonged endocrine therapy without interruption may change REI referral uptake and pursuit of fertility preservation options.

In our study, Breast Surgery was the most common referring service, responsible for 58% of referrals to the FNS, and was associated with uptake of REI consultation. Indeed, along with receipt of NAC, referral to an FNS from the Breast Surgery service was one of only two factors that remained associated with decisions regarding REI consultation. Previous studies from our institution have suggested

that breast surgical oncologists are uniquely positioned to facilitate early referrals to fertility specialists, because they often are the initial point of contact for women with a new breast cancer diagnosis.²¹ Timely referral to REI specialists is of paramount importance, as early referral has been shown to permit multiple cryopreservation cycles without delaying initiation of neoadjuvant or adjuvant chemotherapy.^{49,51}

This study is limited by its single-institution retrospective design, which may compromise its generalizability. Another important limitation is that this study did not capture the outcome of the REI consultations. At a tertiary care cancer center without an REI department, all consultations were performed at different outside institutions; as a result, this retrospective review was unable to identify the rate of uptake of ovarian stimulation or other forms of fertility preservation in the study population. Additionally, our study focuses on decision making and use of REI consultation at time of diagnosis, and thus subsequent pregnancy after breast cancer (including successful pregnancy after pursuing advanced reproductive techniques) is beyond the scope of this study. Additionally, although we were able to capture some differences in demographics, clinicopathologic features, and treatments between women who pursued REI referral and those who declined, the study lacks the granularity to understand patient-level decision making. Additional studies are planned to evaluate trends in uptake of fertility options in women who elect to pursue formal fertility consultation.

Despite these limitations, this study indicates interest in fertility preservation among premenopausal women with breast cancer and suggests that NAC may affect decisions regarding pursuit of fertility preservation options. With increasing utilization of NAC in breast cancer, our study

supports the need for further counseling and education regarding fertility preservation for women undergoing NAC. Future studies evaluating the impact of both FNS education programs and clinician counseling on choice of fertility preservation options are necessary in the NAC setting.

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