ORIGINAL ARTICLE – BREAST ONCOLOGY

Sexual Dysfunction in Survivorship; the Impact of Menopause and Endocrine Therapy

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ABSTRACT

Background. Sexual dysfunction is common for breast cancer survivors. Premenopausal women with breast cancer are increasingly offered ovarian suppression and aromatase inhibitor (AI) therapy. We evaluated the association of menopausal status and treatment modalities on sexual dysfunction.

Methods. We conducted a cross-sectional anonymous Female Sexual Function Index (FSFI) survey of breast cancer survivors between 2000 and 2016. Analysis utilized Kruskal–Wallis test for FSFI scores, Chi square, or Fisher's exact test for categorical data, and regression analysis for associations.

Results. Of 585 respondents, 278 (47.5%) had complete FSFI scores. Of these, 24 (8.6%) were premenopausal and 80 (28.8%) were pre/perimenopausal at survey completion. Median FSFI scores for premenopausal (31.2, interquartile range [IQR] 26.8–33.6) and pre/perimenopausal (29.2, IQR 25.9–32.2) were similar, whereas postmenopausal women (25.9, IQR 21.0–30.3) were significantly lower ($p = 0.0007$ and $p = 0.0002$, respectively). Premenopausal women were less likely to meet criteria for sexual dysfunction (FSFI score ≤ 26.55) than postmenopausal women (21 versus 55%, $p < 0.0001$, univariate analysis [odds ratio (OR) 0.32, 95% confidence interval (CI) 0.18–0.56]). Adjusting for treatment modality did not impact the significance (OR 0.43, 95% [CI] 0.23–0.80) but revealed that AIs independently are associated with sexual dysfunction (OR 2.41,

95% CI 1.32–4.40). The interaction between menopausal status and AIs was not significant ($p = 0.24$).

Conclusions. Our study demonstrates that menopausal status is associated with sexual dysfunction in breast cancer patients and sexual dysfunction in premenopausal women is not impacted by treatment modality outside of aromatase inhibitor therapy. As more premenopausal patients are treated with ovarian suppression, these data may guide clinicians in counseling patients regarding sexual dysfunction expectations.

Breast cancer is the most common noncutaneous cancer in women, with an estimated 266,120 cases of breast cancer diagnosed in the United States in 2018 with roughly 30% of cases presenting in patients < 55 years of age and 10% of cases in patients < 45 years of age. Due to the improved outcomes through modern treatment modalities and multidisciplinary care, there is an estimated 98.7% 5-year survival rate for local and 85.3% 5-year survival rate for regional disease.[1]

While the majority of women with breast cancer are diagnosed postmenopausally, for those who are premenopausal at diagnosis, suppression of ovarian function has increasingly become part of the treatment plan. Premenopausal women transition to postmenopausal via ovarian senescence as a result of chemotherapy or therapeutically intentional ovarian suppression for hormone-positive breast cancers. Side effects of endocrine therapy in pre- and postmenopausal patients can include significant declination in sexual function and arousal, weight gain, vasomotor dysfunction, and overall decreased quality of life.[2–4] Recent updated results from two large trials evaluating ovarian suppression in premenopausal women have demonstrated improvements in breast cancer-free interval

(BCFI) and overall survival (OS), although the absolute reduction in OS with the addition of ovarian suppression to endocrine therapy was small.[5–7] The authors also reported significant detriments in quality of life measures in these patients. Given the significant BCFI and OS advantages, the American Society of Clinical Oncologists (ASCO) guidelines currently recommend expanding the use of ovarian suppression and consideration of extending duration of endocrine therapy.[8]

Sexual dysfunction is a well-described consequence of comprehensive breast cancer care. While sexual dysfunction has been traditionally addressed during survivorship, guidelines suggest consequences of therapy should be considered during the formulation of the patient's care plan. In light of recent ASCO guidelines, additional escalating endocrine therapy may be offered. As a graded clinical benefit corresponds to composite risk of advanced disease, the significant lifestyle modifying effects need to be better delineated and discussed with the patient when planning therapy.[9,10]

Our institution has performed and published previous work in regard to survivorship, sexual function, and overall satisfaction with appearance in breast cancer patients. We previously reported on the use of the female sexual function index (FSFI) and its relationship to body mass index (BMI) in the postoperative setting.[11] We also evaluated the type of surgery performed and its relationship to a patient's FSFI and described additional questions related to intimacy with the Breast Specific Sensuality (BSS) survey.[12]

With the expanding use of ovarian suppression and endocrine therapy in general, we wanted to determine if there was a significant interaction with premenopausal women and sexual dysfunction in our patient population with regards to ovarian suppression and endocrine therapy with the use of both the FSFI and BSS questionnaires.

METHODS

An institutional review board-approved, anonymous, cross-sectional survey was collected from 600 women accessed as a convenience sample during routine cancer surveillance appointments between 2014 and 2016. Eligible patients underwent index breast cancer surgery between 2000 and 2015 at Women and Infants' Hospital of Rhode Island, a Brown University affiliated nonprofit teaching institution. Eligible subjects had to be English-speaking and > 18 years of age. Patients were invited to complete a paper questionnaire labeled "Survivorship Sexual Function Survey." Anonymity was added to the study to improve participation and response accuracy. The implied consent was described in the cover letter, and all surveys were collected via a secured drop box in the clinic or return mail.

Information collected in the survey included demographic data, surgery type, and adjuvant treatment, including radiation, chemotherapy, and hormonal therapy. Sexual activity was only assessed for the 30 days before the survey and was defined as caressing, foreplay, masturbation, or vaginal intercourse. Sexual function was quantified by utilizing the FSFI, a 19-question survey instrument that specifically assessed sexual functioning via six domains, including desire, arousal, lubrication, orgasm, satisfaction, and pain. This tool was developed based on the major categories of female sexual dysfunction as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM). Baser et al. validated the FSFI in cancer survivors, demonstrating its reliability and validity, making it the most commonly used tool for measuring sexual dysfunction in cancer patients.[13] Higher scores correspond with better sexual function, and an overall score of ≤ 26.55 is associated with sexual dysfunction.[14] The reliability of this tool has been reported > 0.9 and validated in other cultures.[13–16]

To detect differences among groups based on menopausal status, the survey includes four options of answering; premenopausal, perimenopausal, postmenopausal, and not sure. We compared all groups individually and also combined the premenopausal and perimenopausal/not sure patients together to ensure those who were not clearly postmenopausal were treated along the premenopausal algorithm.

Survey results were entered in an Excel spreadsheet. Data analysis was performed with the statistical package SAS 9.4 (SAS Institute, Cary, NC). Survey items that were left blank were excluded from the analysis of that particular question or reported as "unknown" for demographic data. Fisher's exact test was used for categorical data. Wilcoxon rank-sum test was used to compare FSFI scores. Multiple logistic regression was used to assess menopausal status, adjuvant treatment, and interactions between these factors in relation to sexual dysfunction (FSFI ≤ 26.55).

RESULTS

Six hundred completed surveys were collected for an estimated response rate of 49%. Fifteen surveys were excluded from the analysis for multiple conflicting entries. Patients who reported no sexual activity within the previous 4 weeks ($n = 285$) were excluded, not meeting criteria to be assessed by FSFI. Patients with incomplete FSFI responses ($n = 22$) also were excluded, for a total of 307 women excluded. In this group of 285 patients with no sexual activity, 4.3% were premenopausal, 20.7% were
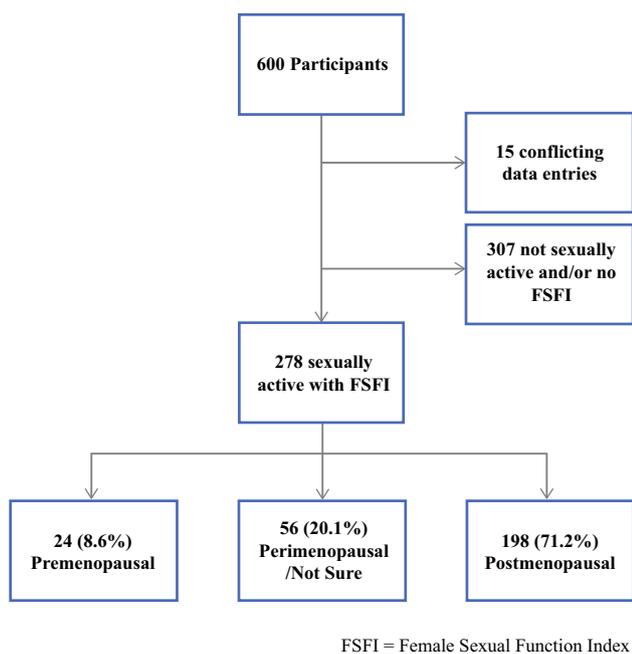
FIG. 1 Participant flow

perimenopausal/not sure, and 75.0% were postmenopausal (Fig. 1). The final group of sexually active patients with complete FSFI scores consisting of 278 individuals.

Of the patients included in the analysis, a majority were postmenopausal (71.2%), < 60 years old (65.8%), non-Hispanic white (92.1%), and treated surgically by lumpectomy (65.5%). At the time of survey response, time interval from surgery was similarly distributed among menopausal status groups (Table 1). Radiation, chemotherapy, and endocrine therapy by menopausal status is presented in Table 1.

Postmenopausal patients had lower median FSFI scores compared with premenopausal patients (Table 2). Premenopausal and perimenopausal patients combined had lower FSFI scores than premenopausal patients but remained significantly higher than postmenopausal women (Table 2). More than half of postmenopausal patients met the criteria for sexual dysfunction (FSFI ≤ 26.55) compared with 20.8% of premenopausal patients ($p = 0.0021$) and 27.5% of pre/perimenopausal patients ($p < 0.0001$).

Within each menopausal status group, sexual dysfunction was most common among patients with a history of aromatase inhibitor use (Fig. 2). Sexual dysfunction differed significantly by endocrine therapy use among pre/perimenopausal women ($p = 0.021$) and postmenopausal women ($p = 0.035$).

The relationships among menopausal status, endocrine therapy, and sexual dysfunction were further evaluated by multiple logistic regression (Table 3). Adjusting for history of radiation therapy or chemotherapy, the odds of sexual

dysfunction remained lower for premenopausal women (aOR = 0.31, $p = 0.0071$, vs. postmenopausal) and higher for aromatase inhibitor users (aOR = 2.40, $p = 0.0043$, vs. no endocrine therapy). The associations were similar when pre- and perimenopausal women were combined. The interaction between menopausal status and endocrine therapy was not significant.

DISCUSSION

Recent publications from the SOFT and TEXT trials demonstrate improved BCFI and OS outcomes in premenopausal women treated with enhanced endocrine therapy, which was more pronounced in patients who had ovarian suppression therapy added to their treatment regimen.[5–7] The greatest absolute gains in BCFI and OS were seen in patients with a high composite risk of distant metastatic disease with decreased treatment effects in intermediate and lower risk patients. With the results of these trials and other published research, there is growing support for escalation of endocrine therapy in premenopausal patients treated with or without chemotherapy.[8,17] As extended endocrine therapy is increasingly employed, a better understanding of its consequences is needed to better guide patients.

The results of this study add to the growing body of literature in regard to sexual function in female breast cancer patients. The data from this study show that menopausal status is a significant factor in regard to sexual dysfunction regardless of therapy. The study also shows that aromatase inhibitors increase odds of sexual dysfunction, regardless of menopausal status. These findings are important for both premenopausal patients who sustain treatment-induced menopause and postmenopausal patients with breast cancer. With multiple follow-up visits that patients attend, providers have the ability to identify sexual dysfunction and intervene. At this institution, interventions include topical medications, individual or group therapy, and referral to sexual health clinics.

In premenopausal women treated for breast cancer, chemotherapy, endocrine therapy, and ovarian suppression will almost invariably induce menopause. This state of menopause may be temporary or permanent and a consequence of therapy or naturally occurring. Menopausal status has a significant association with sexual dysfunction as indicated by the results of this study. Patients reporting a premenopausal status reported significantly higher sexual function scores. Current literature demonstrates the significant incidence of chemotherapy-induced menopause, and correlates to length of induced menopause and decreased quality of life metrics. A series of 101 patients with hormone receptor-positive breast cancer treated with

TABLE 1 Demographic and treatment characteristics by menopausal status

	Menopausal status				
	Premenopausal	Pre/perimenopausal/not sure	Postmenopausal	P value[a]	P value[b]
All participants, n	24	80	198		
Age < 60 years, n (%)	23 (95.8)	74 (93.7)	109 (55.3)	<0.0001	<0.0001
Non-Hispanic white ethnicity, n (%)	19 (79.2)	70 (87.5)	186 (93.9)	0.024	0.087
Surgical modality, n (%)					
Lumpectomy	7 (29.2)	42 (52.5)	140 (70.7)	0.0002	0.013
Mastectomy with reconstruction	5 (20.8)	8 (10.0)	14 (7.1)		
Mastectomy only	12 (50.0)	30 (37.5)	44 (22.2)		
Years sines surgery					
≤ 2	12 (50.0)	36 (45.0)	75 (37.9)	0.13	0.35
2–4	3 (12.5)	19 (23.8)	63 (31.8)		
> 4	9 (37.5)	25 (31.3)	60 (30.3)		
Radiation therapy	13 (54.2)	51 (63,3)	156 (78.8)	0.011	0.015
Chemotherapy	13 (54.2)	32 (40.0)	101 (51.0)	0.83	0.11
Endocrine therapy					
Tamoxifen and Aromatase inhibitor	0 (0.0)	0 (0.0)	2 (1.0)	0.0024	<0.0001
Tamoxifen only	11 (45.8)	38 (47.5)	36 (18.7)		
Aromatase inhibitor only	2 (8.3)	9 (11.3)	76 (39.4)		
Neither	11 (45.8)	33 (41.3)	79 (40.9)		
Ovarian suppression	2 (8. 3)	7 (8.8)	4 (2.0)	0.13	0.016
Fulvestrant therapy	1 (4.2)	1 (1.3)	4 (2.0)	0.44	1.0

Data are N (column %). Responses were missing for age (n = 2), endocrine therapy (n = 5), and ovarian suppression (n = 1)

[a]Premenopausal versus postmenopausal

[b]Pre/perimenopausal/not sure versus postmenopausal

TABLE 2 Sexual function by menopausal status

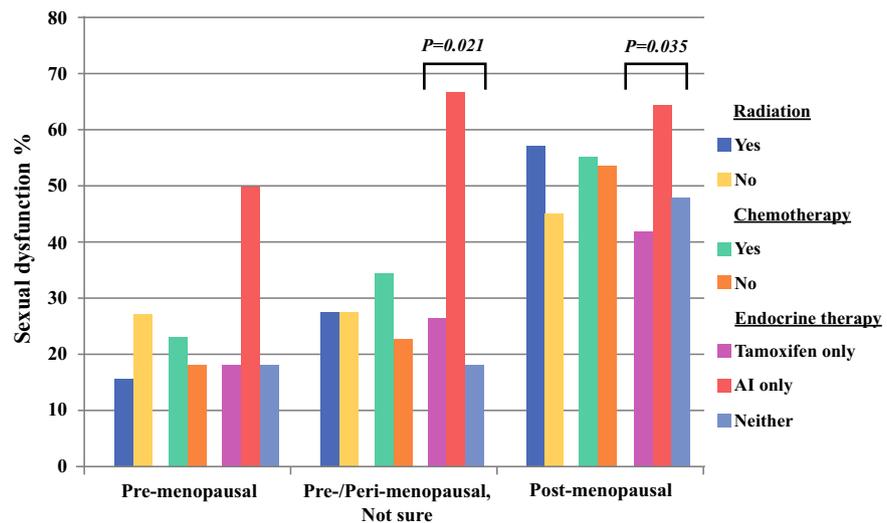|	Menopausal status				
	Premenopausal	Pre/perimenopausal/not sure	Postmenopausal	P value[a]	P value[b]
FSFI score					
Median (IQR)	31.2 (26.3–33.6)	29.2 (25.9–32.2)	25.9 (21.0–30.3)	0.00073	0.00016
Range	19.1–35.7	15.5–36.0	7.2–35.7		
Sexual dysfunction (FSFI < 26.55), n (%)	5 (20.8)	22 (27.5)	108 (54.5)	0.0021	<0.0001

FSFI = Female Sexual Function Index; IQR = Interquartile range (25th, 75th percentiles)

[a]Premenopausal versus postmenopausal

[b]Pre/perimenopausal/not sure versus postmenopausal

neoadjuvant or adjuvant chemotherapy demonstrated that 96% of their patients developed clinically induced amenorrhea (CIA). All patients aged 40 years or younger resumed menstruation after completion of therapy, and no patients aged 50 years or older resumed menstruation. The time to resume menstruation varied with some patients' amenorrhea status lasting up to 3 years.[18] Dohou et al.[19] showed that 13.3% of patients in their study developed complete menopause with no recovery of menstruation. Yoo demonstrated a significant number of patients having long term CIA, which resulted in significant negative changes in quality of life based on The Menopause Specific Quality of Life tool.[20] The results of this study compare favorably with the findings of these researchers. A third of the patients in our study were more than 4 years removed from their index surgical procedure, demonstrating the

FIG. 2 Sexual dysfunction by adjuvant therapy, stratified by menopausal status

Sexual dysfunction = Female Sexual Function Index score $\leq$ 26.55
AI = aromatase inhibitor
Two participants who reported both tamoxifen and aromatase inhibitor use were excluded.

TABLE 3 Multiple logistic regression of menopausal status, adjuvant therapy, and sexual dysfunction

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	
		Premenopausal	Pre/perimenopausal/not sure
Menopausal status (vs. postmenopausal)			
Premenopausal	0.23 (0.08–0.64)	0.31 (0.11–0.89)[a]	–
Pre/perimenopausal/not sure	0.33 (0.19–0.58)	–	0.44 (0.24–0.80)[a]
Endocrine therapy (vs. neither)			
Tamoxifen	0.79 (0.43–1.46)	0.94 (0.49–1.80)[b]	0.94 (0.49–1.80)[b]
Aromatase inhibitor	2.83 (1.58–5.08)	2.40 (1.31–4.38)[b]	2.41 (1.32–4.40)[b]

OR = odds ratio for sexual dysfunction (FSFI < 26.55), 95% CI = 95% confidence interval

All models included 271 patients after excluding those missing endocrine therapy data and two who reported both tamoxifen and aromatase inhibitor use

[a] Adjusted for radiation chemotherapy, tamoxifen, and aromatase inhibito

[b] Adjusted for menopausal status, radiation and chemotherapy

persistence of menopausal status with associated sexual dysfunction as a measure of quality of life. Because menopause has a strong association with sexual dysfunction, treatment plans limiting ovarian senescence may offer patients improvements in sexual function. To this end, the recently published data in the TailorRx trial demonstrated that women < 50 years of age with a genomic score < 16 may be safely treated without chemotherapy with non-significant differences in OS and BCFI at 5–9 years.[21] The expected decrease in chemotherapy and thus chemotherapy induced amenorrhea also may decrease sexual dysfunction.

Endocrine therapies are associated with an increase in side effects to include vasomotor disturbances, weight gain, depression, and sexual dysfunction. The addition of ovarian suppression has been shown to worsen side effects of hot flashes, loss of sexual interest, vaginal dryness, dyspareunia, and sleep disturbances. This results in a significantly lower sexual desire and sexual interest due to the amenorrheic state.[22,23] In a subgroup analysis of 240 patients < 35 years of age enrolled in the SOFT trial, Saha reported that the most pronounced side effects attributed to endocrine therapy were documented at 6 months, including vasomotor symptoms, loss of sexual interest, and difficulties in becoming aroused. This was similar in older cohorts of patients in the same study. Interestingly, nearly 20% of patients younger than 35 years of age stopped endocrine therapy early.[24] Our study showed similar results with younger premenopausal patients having significant negative changes in their reported sexual health, predominantly in those receiving an aromatase inhibitor.

A significant component of breast cancer care is quality of life within survivorship. Ganz has reported in multiple studies a significant proportion of depression, low body image self-esteem, gynecological dysfunction, sexual dysfunction, and overall lower quality of life scores in patients undergoing breast cancer treatment with endocrine therapy.[25,26] Similarly to studies in U.S. women, multiple international studies have demonstrated comparable outcomes, reinforcing that these side effects cross cultural boundaries.[2,4] Studies by Fobair, Kowalcyzk, Takahashi, and Arraras demonstrated a wide range of negative effects on body image, relationship status, anxiety, sexual activity, and sexual function in their patient populations.[3,4,27,28] While variations in surgery performed and adjuvant therapies utilized existed in these studies, they highlight the high prevalence of these issues and the need for continued work in survivorship for breast cancer patients.

This study was performed to look at the associations of adjuvant therapy and menopausal status with the sexual health in breast cancer patients at a single academic institution. Limitations of this study include the survey bias of the study have been previously reported.[29] Given the anonymous nature of the survey, all treatment reporting was based on patient recall and could not be checked against medical records for accuracy. The authors made the assumption of menopausal status at time of treatment based on patient's responses to the questionnaire. As one's cancer diagnosis is the entry point into our center, we were also unable to perform an assessment of sexual function prior to cancer diagnosis. A truly prospective evaluation may provide additional information of change in sexual function and limit recall bias.

This study adds to the growing body of literature that addresses the multifaceted approach to survivorship care demonstrating the significant association of menopausal status and aromatase inhibitor therapy on sexual dysfunction. Both chemotherapy and endocrine therapies have been shown to improve BCFI and OS outcomes in patients. The side effects of these therapies, including sexual dysfunction, should be put into context as it relates to the potential absolute survival gains of intended therapy. In breast oncology care and treatment, a completely informed discussion that encompasses endpoints of not only overall survival and recurrence, but also consequences of therapy and the impact on quality of life and survivorship should be the goal in communication with patients.

DISCLOSURE The authors have indicated they have no potential conflicts of interest to disclose.

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