Sexual Dysfunction in Postmenopausal Women with Breast Cancer on Adjuvant Aromatase Inhibitor Therapy

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Keywords

Aromatase inhibitors · Breast cancer survivors · Sexual dysfunction · Female Sexual Function Index · EORTC QLQ-BR23 · State-Trait Anxiety Inventory questionnaire

Abstract

Introduction: The aim of this study was to investigate whether postmenopausal women with breast cancer (BC) on adjuvant aromatase inhibitor (AI) therapy have a higher prevalence of female sexual dysfunction (FSD). Second, the aim was to determine the quality of life (QoL) and level of anxiety depending on whether or not they are AI users. **Methods:** A prospective cross-sectional study involving 168 patients was performed. Three questionnaires were carried out: sexual functioning was evaluated with the Female Sexual Function Index (FSFI), while the EORTC QLQ-BR23 measures to study QoL in patients with BC and the State-Trait Anxiety Inventory (STAI) questionnaire (trait and status) were used to assess anxiety status in patients under treatment with AIs or not. **Results:** 47.6% (80/168) of the postmenopausal BC survivors were not sexually active (mean time after surgery: 48.6 months) despite a relatively low mean age (56.43 years). Postmenopausal AI-treated women had significantly worse sexual function as measured by the FSFI (23.40 ± 5.26 vs. 30.16 ± 2.24 ; $p = 0.000$). There were significant differences

between both groups in all domains, except orgasm. The QoL score was 37.67 ± 7.38 in AI users versus 39.00 ± 1.44 among nonusers ($p = 0.053$). Patients under endocrine treatment also presented STAI scores significantly higher (25.83 ± 4.99 vs. 19.00 ± 7.12 ; $p = 0.000$). Trait anxiety was high in both groups, but this was not statistically significant. **Conclusions:** We observed a high prevalence of sexual inactivity among BC survivors regardless of AI use. Patients with AI use presented significantly higher prevalence of FSD, worse QoL, and greater anxiety.

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Introduction

In developed countries, 75% of breast cancer (BC) incidents occur in postmenopausal women, with 70% of these cancers being estrogen receptor positive (ER+) [1].

In women with BC-ER+, clinical practice guidelines recommend the use of third-generation aromatase inhibitors (AIs; anastrozole, letrozole, and exemestane) in early-stage postmenopausal women as adjuvant endocrine therapy because they have shown better results in terms of disease-free and overall survival than tamoxifen (TMX), especially in patients at higher risk of recurrence [2]. However, side effects of endocrine therapy in pre- and postmenopausal patients can include significant va-

Table 1. Demographic and clinical variables

Outcome	All patients (n = 168; 100%)	Patients with AIs (n = 144; 85.71%)	Patients without AIs (n = 24; 14.28%)	p value
Age, years	56.23±8.66	56.84±9.27	54.93±0.48	0.08
Menarche, years	12.24±1.62	12.24±1.60	12.25±1.75	0.966
Pretreatment menopause				0.002
Yes	131 (77.98)	107 (61.31)	24 (100)	
No	37 (22.02)	37 (22.02)	0 (0)	
Childbirth	2.33±0.93	2.39±1.01	2±0.00	0.043
Breastfeeding				0.07
Yes	130 (77.38)	114 (79.16)	16 (66.66)	
No	38 (22.61)	30 (20.83)	8 (33.33)	
Duration of breastfeeding, months	6.97±4.87	7.34±4.92	5.14±4.23	0.029
Family history of cancer				0.000
Yes				
Breast	37 (22.02)	37 (22.02)	0 (0)	
Ovary	20 (11.90)	20 (11.90)	0 (0)	
No	111 (66.07)	87 (51.78)	24 (14.28)	
Age at diagnosis of cancer, years	51.49±8.47	52.28±9.20	49.32±0.47	0.092
Survival time from diagnosis, months	48.01±33.43	48.22±35.54	37.32±13.42	0.100
Use of vaginal lubricants ^a	36 (40.90)	31 (43.00)	5 (37.50)	0.235
Use of vaginal moisturizers ^a	13 (14.70)	11 (15.20)	2 (12.50)	0.174

Data are shown as the means ± SD or absolute numbers (%). ^a Only when sexually active.

somotor dysfunction, weight gain, and overall decreased health-related quality of life (QoL) [3].

Anxiety is the most prevalent psychosocial sequela after cancer diagnosis [4]. Anxiety includes trait and state anxiety. High anxiety predicted worse QoL and well-being concurrently and longitudinally [5], and QoL is a key aspect of cancer survivorship.

Female sexual dysfunction (FSD) is a highly complex phenomenon and a well-described consequence of comprehensive BC care [6, 7]. The diagnosis of BC itself, aspects of personality, and previous personal and sexual relationships influence the sexual function of patients with BC [8]. The type of surgery and adjuvant treatment also influence the sexual response of these patients [9, 10]. Thus far, sexual function in AI-treated BC patients has only been studied with generic endocrine or QoL questionnaires that include some items on sexuality, but not with specific sexual function questionnaires. The results obtained, with these limitations, indicate that AI-treated patients report a decrease in sexual interest compared to TMX-treated patients and that AI treatment has negative effects on overall FSD [11]. However, there is a lack of studies focusing on more specific aspects of FSD conducted with specific questionnaires to assess sexual function in AI-treated patients.

Therefore, this study aimed to investigate whether AI-treated patients with postmenopausal BC have a higher prevalence of FSD than those who do not use it. Second, we aimed to determine the QoL and level of anxiety among postmenopausal women survivors with BC depending on their use of AIs.

Materials and Methods

Inclusion Criteria

A prospective cross-sectional study was conducted with 168 postmenopausal women treated for BC. Participants were selected according to the following criteria: postmenopausal (more than 1 year of amenorrhea with FSH levels ≥40 mIU/mL), invasive BC included in our database, aged between 50 and 70 years, BC-ER+ in current treatment with adjuvant endocrine therapy with AIs (study group; at least 12 months) or without adjuvant treatment at that time (ER-, ex-users for more than 5 years, no current need for it; control group), claimed to understand the purpose of the study, and signed informed consent to participate. Patients with stage IV BC, those with a history of psychiatric pathology, including anxiety or depressive syndrome, women with a previous to current diagnosis of FSD, and patients with any other conditions related to sexual response (pelvic floor dysfunction, heart disease, diabetes, arthritis, drug or alcohol abuse, or use of antihypertensive drugs) were excluded.

Methods

A detailed gynecological history was taken in all patients, paying special attention to the treatments received both in a neoadjuvant and adjuvant form as well as the tumor stage and type of surgery performed. The term “sexually active” was used only for heterosexual relationship with penetration. Homosexual relationship and masturbation were not included.

QoL was measured by the EORTC QLQ-BR23 questionnaire [12], which measures more specific aspects of BC. The questions in the questionnaire are based on several multi-item scales and refer to the previous week. Patients completed the EORTC QLQ-BR23 questionnaire, which had been validated for use in Spain [13].

Participants completed the Female Sexual Function Index (FSFI) questionnaire. This questionnaire assesses 6 dimensions of sexual functioning over the previous 4 weeks; a total FSFI score

Table 2. Type of surgery

	All patients (<i>n</i> = 168)	Patients with AIs (<i>n</i> = 144)	Patients without AIs (<i>n</i> = 24)	<i>p</i> value
Breast-conserving therapy + SLNB or ALND	144 (85.7)	125 (86.8)	20 (83.3)	0.442
Mastectomy + SLNB or ALND	24 (14.3)	19 (13.2)	4 (16.7)	

All data are shown as *n* (%). SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

Table 3. Clinical stage of breast cancer

	All patients (<i>n</i> = 168)	Patients with AIs (<i>n</i> = 144)	Patients without AIs (<i>n</i> = 24)	<i>p</i> value
Stage I	101 (60.11)	90 (62.50)	14 (58.33)	0.142
Stage II	53 (31.54)	42 (29.16)	8 (33.33)	
Stage III	14 (8.33)	12 (8.33)	2 (8.33)	

All data are shown as *n* (%).

Table 4. Sexual activity of the women

	Current sexual activity		Total	<i>p</i> value
	no	yes		
No AIs	8 (33.33)	16 (66.66)	24 (100)	0.124
AIs	72 (50.00)	72 (50.00)	144 (100)	
Total	80 (47.60)	88 (52.30)	168 (100)	

All data are shown as *n* (%).

<26.5 is suggestive of FSD [8]. FSFI has been validated for women with cancer [14]. The Spanish FSFI is a valid and reliable instrument for assessing and discriminating FSD among Spanish postmenopausal women [15].

Finally, trait and state anxiety were assessed by the State-Trait Anxiety Inventory (STAI) [16], a questionnaire aimed at assessing the level of anxiety of individuals. More specifically, the STAI measures individuals' predisposition to perceive diverse stimuli as threatening (i.e., trait anxiety). STAI includes 2 subscales, the Trait Anxiety Scale (STAI-T) and the State Anxiety Scale (STAI-S), which contain 20 items for trait and state anxiety. We used a short version of the STAI validated for a Spanish sample [17]. Anxiety was considered low (<30 points), medium (30–44 points), or high (>44 points).

The results were compared according to whether or not the patients were under treatment with AIs.

Statistical Analysis

The data were collected and analyzed with SPSS 23.0 for Windows (version 23.0, SPSS Inc., USA). Clinical and demographic variables of the patients (age, parity, age of menarche, time of disease survival) were compared in the 2 groups of women (with and without AIs). The prevalence of FSD and altered QoL among postmenopausal women with BC were analyzed according to AI use as well as trait anxiety and state anxiety in each of the groups.

Statistical analysis was performed by calculating frequencies and means and standard deviations. Pearson's χ^2 or Fisher's exact test was used for frequency comparison and Student *t* test for mean comparisons. Statistical significance was established at *p* < 0.05.

Results

This study involved 168 women, 144 (85.7%) of whom were undergoing AI treatment (cases), while 24 (14.3%) were without such treatment (controls). Table 1 shows a

series of clinical and demographic variables of the patients. It should be noted that there were no differences between the 2 groups in the percentage of use of vaginal lubricants for sexual intercourse or the rate of use of vaginal moisturizers.

No differences were found between the 2 groups of patients in relation to the type of surgery performed (Table 2), the clinical stage of the tumor (Table 3), or whether they were sexually active at the time of the survey (Table 4).

Quality of Life: EORTC QLQ-BR23

The data collected from this questionnaire are shown in Table 5. The score of patients with adjuvant AI treatment was 37.67 ± 7.38 compared to 39.00 ± 1.44 for those who did not receive treatment (*p* = 0.053); therefore, although this first group seemed to have a worse QoL, it could not be stated categorically, as the statistical significance was at the limit.

Compared to those without treatment, AI-treated patients presented significantly worse body image (5.67 ± 3.27 vs. 9.00 ± 2.50 ; *p* = 0.000); worse sexual function among patients with sexual activity (72 vs. 16 : 3.39 ± 1.53 vs. 4.00 ± 0.1 ; *p* = 0.000); less sexual enjoyment (2.11 ± 1.05 vs. 3.00 ± 0.83 ; *p* = 0.000); more concern about the future (2.39 ± 1.21 vs. 1.67 ± 0.48 ; *p* = 0.005); more concern about hair loss (1.61 ± 1.11 vs. 1.00 ± 0.00 ; *p* = 0.008), and more affectation at the breast level (6.67 ± 3.61 vs. 5.33 ± 1.27 ; *p* = 0.001) (Table 5). Although not significant, AI users also showed greater effects of systemic treatment (13.67 ± 4.695 vs. 12.00 ± 3.00 ; *p* = 0.095) and more symptoms in the arm (4.28 ± 1.86 vs. 4.00 ± 0.83 ; *p* = 0.235).

Table 5. EORTC QLQ-BR23

	All patients (n = 168)	Patients with AIs (n = 144)	Patients without AIs (n = 24)	p value
Total score	38.48±6.9	37.67±7.38	39.00±1.44	0.053
Body image	5.95±3.31	5.67±3.27	9.00±2.50	0.000
Sexual functioning ^a	3.55±1.41	3.39±1.53	4.00±0.00	0.000
Sexual enjoyment ^a	2.32±1.05	2.11±1.05	3.00±0.83	0.000
Concern about the future	2.17±1.07	2.39±1.21	1.67±0.48	0.005
Systemic treatment effects	13.53±4.57	13.67±4.69	12.00±3.00	0.095
Concern about hair loss	1.58±1.10	1.61±1.11	1.00±0.00	0.008
Breast symptoms	6.76±3.52	6.67±3.61	5.33±1.27	0.001
Arm symptoms	4.31±1.86	4.28±1.86	4.00±0.83	0.235

Data are shown as the means ± SD or absolute numbers (%). Bold values indicate statistical significance.
^a Analyzed only in patients with sexual activity (72 in AI group vs. 16 in non-AI group).

Table 6. STAI

	All patients (n = 168)	Patients with AIs (n = 144)	Patients without AIs (n = 24)	p value
State anxiety	24.26±5.76	25.83±4.99	19.00±7.12	0.000
Trait anxiety	26.61±7.20	27.78±7.45	29.33±12.49	0.420

Data are shown as means ± SD. Bold values indicate statistical significance.

Anxiety: STAI Questionnaire

The values obtained in this questionnaire are shown in Table 6. Anxiety was assessed both at baseline (trait anxiety) and for state anxiety (which is produced at specific moments in the lives of patients as a result of a trigger, which, in this case, is BC).

Patients under AIs showed a significantly higher score in the area of state anxiety (25.83 ± 4.9 vs. 19.00 ± 7.12; $p = 0.000$). There were no significant differences between the groups in terms of trait anxiety (29.33 ± 12.40 in non-AI users vs. 27.78 ± 7.45 in AI users; $p = 0.42$).

Sexual Function: FSFI

Of the 168 women participating in the study, only 88 were sexually active, of which 72 (81.8%) were on adjuvant AI treatment, and 16 (18.2%) were off this medication (Table 7). In general, AI-treated patients had significantly ($p = 0.000$) worse sexual function (23.40 ± 5.26) than those who did not take this treatment (30.16 ± 2.24). On average, AI users were within the range of what is considered sexual dysfunction (<26.55), while nonusers were not.

Compared to those not taking AIs, we found that AI-treated patients presented significantly lower sexual desire (2.1 ± 0.92 vs. 4.17 ± 0.83; $p = 0.000$); significantly lower level of arousal (3.90 ± 1.23 vs. 4.76 ± 0.67; $p =$

0.015); significantly less lubrication at the time of sex (4.20 ± 0.61 vs. 5.51 ± 0.53; $p = 0.000$), significantly more pain at penetration (4.88 ± 0.49 vs. 3.60 ± 1.23; $p = 0.001$), and significantly less satisfaction in their sexual relationships (5.40 ± 0.61 vs. 5.91 ± 0.25; $p = 0.005$).

Although not statistically significant ($p = 0.094$), women without AI treatment reached orgasm more easily than those taking AIs (4.75 ± 1.27 vs. 4.20 ± 0.61).

Discussion

Even though most BC patients with partners “are sexually active in the year before surgery” [18], at 48.1 months of average follow-up, approximately half (47.6%) of our patients were sexually inactive. A committee of multidisciplinary specialists reported in 2010 [19] that: “Cancer and its treatment has a significant impact on patient sexual function and satisfaction,” which can be improved by “understanding pre-diagnostic sexual activity, undertaking less aggressive treatment, and using appropriate pharmacological and psychological treatment.” All of this is important because, although we did not ask this question in our study, the high prevalence of sexual inactivity found among our patients could probably be reduced if they were invited to consult about its causes.

Regarding the assessment of QoL, we found a worse QoL in AI users than in nonusers. In the recent (2016) study carried out by de Moraes et al. [20] with 77 patients, they showed, as we do, a low score in the domains of desire, frequency, and sexual satisfaction. However, unlike our study, the scores obtained in the body image section were higher in patients taking AIs. As for the significantly higher state anxiety score among AI patients than among those who were not treated with AIs, we point out that this has not been studied before; however, in the overall BC patients, our data coincide with a study carried

Table 7. FSFI

Domains	All sexually active women (<i>n</i> = 88)	Sexually active women on AI treatment (<i>n</i> = 16; 66.6%)	Sexually active women without AI treatment (<i>n</i> = 72; 50.0%)	<i>p</i> value
Desire	3.83±1.21	2.1±0.92	4.17±0.83	0.000
Arousal	4.67±0.86	3.90±1.23	4.76±0.67	0.015
Lubrication	5.35±0.71	4.20±0.61	5.51±0.53	0.000
Orgasm	4.70±1.24	4.20±0.61	7.75±1.27	0.094
Satisfaction	5.78±0.42	5.40±0.61	5.91±0.25	0.005
Pain ^a	4.65±0.89	4.88±0.49	3.60±1.23	0.001
Total	29.01±4.17	23.40±5.26	30.16±2.24	0.000

Data are shown as means ± SD. Bold values indicate statistical significance. ^a Genito-pelvic pain/penetration disorder.

out in China involving 60 BC women [21]. Here, they determined this higher score as posttraumatic. This means that patients with BC have greater anxiety than the general population since they have suffered from the disease.

Regarding FSD, we have not found any studies that analyzed differences between the 2 populations (with or without AI treatment). Studies have observed a high prevalence of such sexual dysfunctions among users of hormone therapy (AIs or TMX) with respect to the general population without BC.

When comparing continuators (AI treatment adherence) and noncontinuators, Schover et al. [22] found lower scores among the continuators (although not statistically significant) for the total and all FSFI domains (desire, lubrication, orgasm, satisfaction), except for equal proportions of pain in both groups. Among all AI-treated patients, 93% were in the dysfunctional range in FSFI, and 75% were distressed by this problem [22]. As in our sample, only half of the women were sexually active, and almost 80% of that subgroup experienced new sexual problems after starting AIs. Half of the women with sexual problems sought help in trying to resolve them, including 24% of the patients who stopped having sex with their partners after treatment for BC. Thirty-nine percent of sexually active women with a new problem of vaginal dryness consulted a physician, and 18% sought help because of their low desire, which may indicate the severity of these problems.

Although vaginal dryness is debilitating and painful, having cancer, even without vaginal dryness, is also associated with problems in sexual intercourse, such as decreased sexual desire, arousal, orgasm, and intensity [23], which we confirmed in our study. In a recent study based on Internet evaluation, 63% of women reported that their diagnosis of ovarian cancer had negatively influenced their sex life, with a lack of interest in sex as their main complaint [24].

The 2013 study by Baumgart et al. [25], where the aim was to investigate sexual function in postmenopausal AI-treated women with BC versus untreated or TMX controls, found similar results using a cross-sectional study to those found by us.

Recently, Gandhi et al. [26] conducted a survey of 278 BC survivors. No significant differences in the prevalence of sexual dysfunction were observed depending on the surgical modality, even when adjusted for adjuvant therapy. Chemotherapy or radiation was not associated with sexual dysfunction when adjusted for type of surgery. The prevalence of sexual dysfunction was 1.6 times higher for the AI group compared to the nonendocrine therapy group (*p* = 0.01), even when adjusted for other types of treatments. They concluded that the highest rates of sexual dysfunction are seen among BC survivors treated with AIs and that neither surgical modality, chemotherapy, nor radiation were associated with sexual dysfunction [26].

Regarding the treatment to improve such high rates of sexual dysfunction among AI users, although it was not the aim of our work, we comment that different clinical trials are being carried out on the efficacy of both hormonal and nonhormonal, local and systemic treatment, as well as sexual psychotherapies [27]. These discussions and management decisions can be complex but are of paramount importance to the QoL of cancer survivors with vulvovaginal atrophy [28, 29]. However, earlier treatment of vulvovaginal atrophy symptoms, when symptoms are moderate rather than severe, may be associated with greater treatment benefits [30].

Study Strengths and Limitations

In addition to the possible methodological problems with research on sexual functioning and being aware that sexual problems associated with cancer treatment may be undervalued in patient interviews and surveys, a potential

limitation of our study is that of an observational study and the possible response biases when dealing with an intimate subject, such as sexuality, and with more peculiar implications in older patients with a serious pathology who can “blame themselves” for their decrease in sexual activity due to that cause. However, despite being a population with a higher presumed prevalence of these FSDs, this should be homogeneous among all patients, and the finding of a higher prevalence among women under treatment with AIs, and not in nonusers, would support the role of the most marked hypoestrogenism in the genesis or maintenance of FSD.

Another limitation of the study is the low representativeness of the group without AIs (24 controls vs. 144 cases), since most BCs among postmenopausal women are hormone receptor positive and susceptible to treatment with endocrine therapy (especially with AIs).

The last limitation is that the women with AIs were slightly older than those without endocrine treatment (56.84 ± 8.6 vs. 54.93 ± 0.42), although these differences were not statistically significant ($p = 0.08$).

Despite these limitations, our study bridges psychology and cancer research for enhancing supportive cancer care. Finding the same proportion of mutilating surgery (radical mastectomy) in both groups increases the value of the results, since the effect of the surgery was not a bias on the impact of the QoL, possible sexual dysfunctions, or anxiety in the patients of our sample.

Conclusions

Given the relatively high rates of sexual dysfunction and sexual inactivity among postmenopausal BC survivors, especially AIs users (close to 50% in our study), and the possibility that these rates are even higher but underestimated by both the patients themselves and the physician, we believe that the early detection of such dysfunctions through an appropriate clinical interview and/or the use of sexual function questionnaires could be useful to identify patients in need of behavioral (change of lifestyle), pharmacological, or even psychotherapeutic interventions.

Considering the higher anxiety levels of AI patients, they should be actively informed that sexual dysfunction, that has also a relevant social cost [31], will improve after

AI stopping and could be safely and effectively treated with nonhormonal treatments, like ospemifene [32]. While waiting, it is important to suggest trying to empower them telling that they can do something important even during AI use to keep up sexual activity. In order to do that, adequate moisturizer use can improve vaginal dryness, and pelvic floor exercises could maintain adequate vaginal blood flow and trophism, perineal muscular function, and ability to actively relax during intercourse [33].

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Statement of Ethics

The study was conducted according to the guidelines of the Declaration of Helsinki and the National Health Council resolution 196/96 on research involving human subjects. Authorization was obtained from the Hospital Ethics Committee, and the informed consent of all patients involved in this study was obtained before data collection. This qualitative study was approved by the Medical Ethics Committee of the University Hospital of Puerto Real, Cádiz (Spain), in March 2016.

Conflict of Interest Statement

The authors did not report any potential conflicts of interest.

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Author Contributions

The following contributions were made by the authors: D.M.L.L.: project conceptualization; D.M.L.L. and C.A.B.H.: data generation; D.M.L.L. and C.A.B.H. data analysis; D.M.L.L., N.M., and R.S.-B. clinical interpretation; D.M.L.L., N.M., and R.S.-B.: writing – original draft preparation; D.M.L.L., C.A.B.H., M.S.-P., N.M., and R.S.-B.: writing – review and editing. All authors have read and agreed to the published version of the manuscript.

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