Factors associated with worsening sexual function during adjuvant endocrine therapy in a prospective clinic-based cohort of women with early-stage breast cancer

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Abstract
Purpose Sexual function problems are common but under-reported among women receiving adjuvant endocrine therapy for breast cancer. Worsening scores on patient-reported outcomes (PROs) may identify those at risk for sexual function problems during treatment. We performed a secondary analysis of prospectively collected PROs in women receiving adjuvant endocrine therapy to identify factors associated with worsening sexual function.

Methods Women with stage 0–III breast cancer initiating adjuvant endocrine therapy participating in a prospective cohort completed PROs at baseline, 3, 6, 12, 24, 36, 48, and 60 months. Sexual function was evaluated by the MOS-SP measure. Other measures included PROMIS pain interference, fatigue, depression, anxiety, physical function, and sleep disturbance and the Endocrine Symptom Subscale of the FACT-ES. We evaluated associations between score worsening of at least the minimal important difference (MID) in PROMIS T-scores (4 points) and FACT-ES scores (5 points) with score worsening of at least the MID in MOS-SP scores (8 points) using logistic regression.

Results Among 300 participants, 45.7% experienced ≥ 8-point worsening of MOS-SP score at any time point compared to baseline. Worsening endocrine symptoms (OR 1.34, 95% CI 1.22–1.49, \( p < 0.001 \)), worsening physical function (OR 1.09, 95% CI 1.00–1.18, \( p = 0.06 \)), and prior mastectomy (OR 1.45, 95% CI 0.94–2.23, \( p = 0.09 \)) were associated with MOS-SP score worsening by at least the MID.

Conclusion Worsening endocrine symptoms and physical function identified on PROs are associated with worsening sexual function during adjuvant endocrine therapy. Routine assessment of these domains with PROs may identify women at risk for sexual function problems.

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Keywords Patient-reported outcomes · Adjuvant endocrine therapy · Sexual problems · Sexual function · Minimal important difference · Breast cancer
**Introduction**

Sexual function problems are common among women treated for early breast cancer [1–8]. Adjuvant endocrine therapies for hormone receptor-positive (HR+) breast cancer, including aromatase inhibitors (AI), tamoxifen, and ovarian function suppression (OFS), have anti-estrogenic effects, often leading to vaginal dryness, dyspareunia, trouble reaching climax, and loss of libido [9]. Sexual function problems are often distressing for women receiving adjuvant endocrine therapy and negatively affect quality of life (QOL) [5, 6, 10, 11].

Prior studies have identified multiple factors associated with sexual function problems during adjuvant endocrine therapy; however, sexual function problems remain under-reported by patients and under-detected and under-addressed by clinicians [1, 2, 7, 8, 11–27]. Evidence-based interventions can improve sexual function problems during endocrine therapy, and routine assessment to identify women who may benefit from these interventions is an unmet need [28–34]. Patient-reported outcome (PRO) measures can be used to assess symptoms during cancer treatment and can identify sexual function problems during endocrine therapy [26].

We present a secondary analysis from a prospective clinic-based cohort of women receiving adjuvant endocrine therapy for early-stage HR+ breast cancer who completed serial PRO measures over 5 years. Our aim was to identify clinicodemographic variables and patient-reported symptoms associated with the worsening sexual function during adjuvant endocrine therapy.

**Methods**

**Study population**

From March 2012 to December 2016, we recruited women with HR+ stage 0–III breast cancer initiating adjuvant endocrine therapy with tamoxifen or an AI to an IRB-approved prospective observational cohort at Johns Hopkins clinical sites. Potential participants were identified by screening provider schedules. The type of endocrine therapy (tamoxifen or AI) was determined by the treating clinician. Concurrent OFS was permitted in pre-menopausal women. Participants could enroll upon first initiating endocrine therapy or upon switching from one endocrine therapy to another. Written informed consent was obtained.

**Patient-reported outcomes**

Participants completed PROs using the online PatientViewpoint interface at baseline (the time of endocrine therapy initiation) and 3, 6, 12, 24, 36, 48, and 60 months later [35–37]. Participants were followed until the last PRO survey or the last clinic visit prior to the date the database was locked (May 15, 2020), whichever was longer. Sexual function was evaluated by the Medical Outcomes Study Sexual Problems (MOS-SP) measure [38]. Respondents rate the severity of problems in four domains of sexual function (“lack of sexual interest,” “unable to relax and enjoy sex,” “difficulty being aroused,” and “difficulty achieving orgasm”) using a 4-point scale (“not a problem”—1, “little of a problem”—2, “somewhat of a problem”—3, and “very much of a problem”—4). For each item, there is also a “not applicable” response which is recoded as “not a problem.” The MOS-SP total score is calculated by summing the individual items (range 4–16) and rescaling from 0 to 100, with higher scores indicating more sexual function problems [38]. The reported mean MOS-SP score for women with early-stage breast cancer ranges from 20 to 36, with standard deviation (SD) 27–31 [1, 21, 38]. In accordance with prior analyses utilizing a distribution-based method to identify the minimal important difference (MID, i.e., the smallest change in PRO score that patients would perceive as beneficial or harmful and that would affect clinical management) on the MOS-SP, we considered an increase in MOS-SP score of ≥ 8 points to represent clinically significant worsening of sexual function [1, 39, 40]. Participants with baseline MOS-SP scores 0–92 were included in this analysis as participants with baseline scores > 92 could not experience ≥ 8-point worsening.

Participants also completed other PRO measures, including the Patient-Reported Outcomes Measurement Information System (PROMIS) Version 1.0 short forms for pain interference, fatigue, depression, anxiety, physical function, and sleep disturbance, and the Endocrine Symptom Subscale of the Functional Assessment of Cancer Therapy—Endocrine Symptom (FACT-ES) measure [41–45]. PROMIS measures are scored using a T-score metric with higher scores indicating more of the outcome measured. T-scores of 50 (SD 10) represent the mean for PROMIS measures [42]. Using a combination of anchor- and distribution-based methods, the reported MID for PROMIS measures in patients with early-stage cancer is 3–5 points [41–44, 46]. We considered the midpoint of this range (4 points) to be the MID on the PROMIS measures. Scores on the Endocrine Symptom Subscale of the FACT-ES range from 0 to 76 with a mean of 59 (SD 9.7) in women with early-stage breast cancer. Lower scores indicate worse endocrine-related (QOL) and more endocrine symptoms [45]. We considered 0.5 SD (rounded to 5 points) to be the MID for the Endocrine Symptom Subscale of the FACT-ES [39, 40].

**Statistical analysis**

Clinicodemographic characteristics of participants and PRO scores over time are presented descriptively using mean (SD), median (range), and proportions. The frequency and
percentage of participants with worsening by ≥8 points on the MOS-SP relative to baseline were calculated at each time point. To account for repeated measures in each participant over time, we fit a logistic regression model with generalized estimating equations (GEE) to examine changes in the distribution over time.

We used a similar modeling approach to assess how variables measured at baseline and during follow-up were associated with worsening of MOS-SP score by at least 8 points. Non-time-dependent demographic covariates considered for the models included age at enrollment, race (White vs. other), and neighborhood poverty (NP) rate. NP rate, the percentage of persons living in a zip code with a family income under the federal poverty line based on United States 2010 census data, was considered a surrogate for socioeconomic status (SES), with low SES defined as residence in a zip code with NP rate >15% [47]. Non-time-dependent clinical covariates included stage (continuous variable), type of surgery (mastectomy/breast conservation), receipt of chemotherapy (yes/no), receipt of radiation therapy (yes/no), number of self-reported concomitant medications at enrollment, menopausal status at diagnosis (post/pre), and type of endocrine therapy (AI/tamoxifen). Time-dependent covariates included change in PRO scores at all time points up to 60 months in units based on MIDs, defined as worsening of scores on the PROMIS measures in 4-point increments and on the FACT-ES in 5-point increments. The follow-up time point was included as a covariate in all models.

We first evaluated univariate associations of each covariate with worsening of MOS-SP score by ≥8 points. Next, we estimated the model quasi-information criterion (QIC) for each possible combination of the covariates listed above. The model yielding the smallest QIC was selected as the final multivariable model describing the association between clinicodemographic variables and minimally important changes in the PROMIS and Endocrine Symptom Subscale FACT-ES scores up to 5 years with worsening in the MOS-SP score of ≥8 points [48, 49]. Analyses were completed with R version 4.0.0 [50].

**Results**

**Participant characteristics**

Of 321 participants in the overall cohort, 21 were excluded from this secondary analysis due to baseline MOS-SP score >92 (N = 15) or incomplete baseline MOS-SP measure (N = 6). Characteristics of the 300 participants included in this analysis are summarized in Table 1 and were similar to those excluded due to baseline MOS-SP score >92 (Supplementary Table 1). Mean age at enrollment was 62 years and 195 (65%) participants were post-menopausal. Prior to endocrine therapy, 132 (44%) underwent mastectomy, 199 (66%) received radiation, and 84 (28%) received chemotherapy. Thirteen percent of study participants were of low SES. A total of 119 (39.7%) participants initiated tamoxifen only, 15 (5%) initiated tamoxifen plus OFS, 165 (55%) initiated an AI only, and 1 (0.3%) initiated an AI plus OFS. Five participants (1.7%) enrolled upon switching endocrine therapy agents. Median follow-up was 56.1 months.

**Sexual function over time**

In all four MOS-SP domains, at least 30% of participants reported having at least a “little of a problem” at every time point (Fig. 1). Overall, 165 (55%) participants reported ≥1 sexual function problem during study participation (i.e., response other than “not a problem”). A total of 137 (45.7%) participants experienced ≥8-point worsening of MOS-SP score compared to baseline at any time point. The distribution of participants with worsening MOS-SP by ≥8 points relative to baseline through 60 months is shown in Fig. 2. On average, the percentage of participants with worsening sexual function increased over time (p < 0.001). Differences between MOS-SP scores at each time point for participants treated with AI compared to tamoxifen were small (Supplementary Table 2).

**Scores on PRO surveys**

For the overall study population, mean scores at baseline and at each follow-up time point for all measures were within one SD of published population means (Table 2) [1, 21, 38, 42, 45]. The proportions of participants who completed each PRO measure declined over time. Overall, 36% of participants experienced at least a 4-point worsening in physical function score (Fig. 3) and 53% of participants experienced at least a 5-point worsening in endocrine symptom score (Fig. 4) at any time compared to baseline.

**Association of clinicodemographic characteristics and PROs over time with worsening of sexual function**

Univariate and multivariate analyses evaluating the association between clinicodemographic variables and worsening symptoms, as assessed with PROs, with worsening sexual function, as measured by increase in MOS-SP score by ≥8 points, are shown in Table 3. In the univariate analyses, worsening in all symptoms was associated with worsening sexual function. In the final multivariable model, every 5-point worsening in endocrine symptoms (OR 1.34, 95% CI 1.22–1.49, p < 0.001) and every 4-point worsening in physical function (OR 1.08, 95% CI 1.00–1.18 p = 0.06) were associated with worsening sexual function. Participants with
prior mastectomy (OR 1.45, 95% CI 0.94–2.23, \( p = 0.09 \)) were also more likely to experience worsening sexual function. Participants of lower SES were less likely to have an increase in MOS-SP score \( \geq 8 \) (OR 0.51, 95% CI 0.25–1.03, \( p = 0.06 \)).

### Sensitivity analyses

Because of the decline in PRO completion rates over time, we performed a sensitivity analysis comparing participants who completed all measures during the first 24 months to those with at least one missing measure during that timeframe (Supplementary Table 3). Apart from the number of concomitant medications, baseline characteristics were similar between the two groups. Mean baseline scores on the PROMIS fatigue and physical function measures revealed less fatigue (\( p = 0.01 \)) and better physical function (\( p = 0.01 \)) for participants who completed all measures; however, differences in mean scores were smaller than the MID.

Additionally, because the MOS-SP and the Endocrine Symptom Subscale of the FACT-ES questionnaires both contain an item about sexual interest, we recalculated the Endocrine Symptom Subscale FACT-ES score excluding this item and re-estimated the logistic regression model. Excluding this item did not change the result (Supplementary Table 4). Furthermore, since patients who do not tolerate one endocrine therapy agent may experience toxicities limiting tolerance of other endocrine therapy agents [51], we re-estimated our logistic regression model excluding the five patients who enrolled in the study upon switching from one endocrine therapy agent to another. Excluding these 5 patients did not meaningfully change the final model (Supplementary Table 5).

Finally, since it is possible that responses to PROs may differ following cessation or change in endocrine therapy and our analysis included all

### Table 1  Characteristics of study population

| Characteristic                                      | \( N = 300 \) |
|----------------------------------------------------|----------------|
| Mean age in years (SD)                             | 62.4 (11.0)    |
| Post-menopausal—\( N \) (%)                        | 195 (65)       |
| Race—\( N \) (%)                                   |                |
| White                                              | 252 (84)       |
| Black                                              | 30 (10)        |
| Other                                              | 18 (6)         |
| Median number of self-reported concomitant medications at enrollment (range) | 4 (0–29)       |
| Neighborhood poverty rate—\( N \) (%)             |                |
| 0–15%                                              | 258 (86.6)     |
| > 15%                                              | 40 (13.4)      |
| Mean baseline body mass index (SD)                 | 27.5 (6.0)     |
| Stage—\( N \) (%)                                  |                |
| 0                                                  | 28 (9.3)       |
| I                                                  | 180 (60)       |
| II                                                 | 73 (24.3)      |
| III                                                | 19 (6.3)       |
| ER positive—\( N \) (%)                            | 299 (100)      |
| PR positive—\( N \) (%)                            | 264 (88.9)     |
| HER-2 positive—\( N \) (%)                         | 25 (9.2)       |
| Mastectomy—\( N \) (%)                             | 132 (44)       |
| Radiation—\( N \) (%)                              | 199 (66.3)     |
| Chemotherapy—\( N \) (%)                           | 84 (28.2)      |
| Adjuvant endocrine therapy—\( N \) (%)             |                |
| Tamoxifen only                                      | 119 (39.7)     |
| Tamoxifen plus OFS                                 | 15 (5)         |
| Aromatase inhibitor only                           | 165 (55)       |
| Aromatase inhibitor plus OFS                       | 1 (0.3)        |
| Enrolled upon switching type of endocrine therapy—\( N \) (%) | 5 (1.7)        |
| Median duration of follow-up in months (range)     | 56.1 (6.9–87.7) |

*SD standard deviation, ER estrogen receptor, PR progesterone receptor, HER-2 human epidermal growth factor receptor-2, OFS ovarian function suppression*
Fig. 1 Bar plots display responses to the four domains of the MOS-SP at each time point. Respondents rate the severity of problems in each domain using a 4-point scale (“not a problem”—1, “little of a problem”—2, “somewhat of a problem”—3, and “very much of a problem”—4). For each item, there is also a “not applicable” response which is recoded as “not a problem.” Response options are denoted by color according to the legend. The number of responses at each time point is noted under the x-axis at the corresponding time points. There was only 1 study participant who answered “not applicable” to the item “Difficulty in having an orgasm” at the baseline assessment. However, she responded “Very much of a problem” to two other items and “Little of a problem” to the other item at baseline. None of her responses at other time points were “not applicable” nor were any of the responses from the other study participants at any time points.

Fig. 2 Graph displays percentage of participants with worsening MOS-SP scores by 8 points or more relative to baseline through 60 months. The size of the dot is proportional to the number of participants who completed the MOS-SP measure at that time point. Bars represent exact 95% confidence intervals.
submitted PROs regardless of treatment status, we repeated our analysis excluding all PRO responses participants submitted after (1) discontinuing the endocrine therapy initiated at enrollment, (2) the development of locoregional or distant recurrence, or (3) switching from tamoxifen to an AI. Only 52 of 947 (5.5%) of the PROs included in our analysis were submitted after one of these events. After excluding these PROs, the selection algorithm yielded a similar final model with similar effect sizes (Supplementary Table 6).

Discussion

In this prospective cohort of women with early-stage HR+ breast cancer receiving adjuvant endocrine therapy, sexual function problems were common, with 55% of patients reporting at least one sexual function problem and 45.7% experiencing clinically significant worsening sexual function. For every 5-point worsening in Endocrine Symptom Subscale FACT-ES score, participants were 34% more likely to experience a clinically significant worsening in MOS-SP score \( (p < 0.001) \). For every 4-point worsening in PROMIS physical function score, participants were 8% more likely to experience a clinically significant worsening in MOS-SP score \( (p = 0.06) \). Worsening of endocrine symptoms and decline in physical function were common, with 53% of patients experiencing at least a 5-point worsening in Endocrine Symptom Subscale FACT-ES score and 36% experiencing at least a 4-point worsening in PROMIS physical function score. In addition, participants who had undergone a mastectomy were 45% more likely to experience a clinically significant worsening in MOS-SP score \( (p = 0.09) \).

Our findings are consistent with prior studies demonstrating an association between endocrine symptoms and sexual problems during endocrine therapy. Hot flashes and vaginal dryness are among the most common endocrine symptoms patients experience during endocrine therapy [9, 51–53] and these have previously been identified as predictors of sexual health outcomes [1, 13, 20, 21, 23, 25]. Vaginal dryness often leads to dyspareunia, which may affect multiple domains on the MOS-SP, including relaxing and enjoying sex and achieving orgasm [9]. Hot flashes are associated with mood disturbance and sleep disruption, which may lead to sexual function problems [1, 7, 17, 18, 20, 25, 54–56].

A key finding in our study is that worsening physical function was associated with worsening sexual function problems during adjuvant endocrine therapy. Physical function refers to an individual’s ability to execute activities requiring physical capability, including basic activities of daily living and more vigorous activities that require strength, endurance, and/or mobility [57]. Several prior studies have evaluated the association of QOL, as assessed with a multi-dimensional measure that includes a physical

Table 2 Mean scores on patient-reported outcome measures at each study time point

| Measure                        | Baseline | Time point (months) | N | Mean (SD) | N | Mean (SD) | N | Mean (SD) | N | Mean (SD) | N | Mean (SD) | N | Mean (SD) | N | Mean (SD) | N | Mean (SD) |
|-------------------------------|----------|---------------------|---|-----------|---|-----------|---|-----------|---|-----------|---|-----------|---|-----------|---|-----------|
| MOS-SP 300                    | 24 (4.8) | 264                 | 62 | 64.2 (8.9) | 238 | 63.3 (8.3) | 204 | 62.1 (9.1) | 138 | 61.1 (9.8) | 87 | 60.7 (9.3) | 50 | 60.2 (9.0) | 22 | 61.4 (9.2) |
| FACT-ES endocrine Symptom subscale | 300     | 24 (3.1) | 264 | 62.1 (8.8) | 238 | 63.2 (8.1) | 204 | 62.1 (9.0) | 138 | 61.1 (8.8) | 87 | 60.6 (8.4) | 50 | 60.2 (8.1) | 22 | 61.3 (8.1) |
| PROMIS: physical function 299 | 24 (3.8) | 264                 | 62 | 66.2 (8.9) | 238 | 64.3 (8.3) | 204 | 63.1 (9.1) | 138 | 62.1 (9.8) | 87 | 61.6 (9.3) | 50 | 61.2 (9.0) | 22 | 62.4 (9.2) |
| PROMIS: pain interference 300 | 24 (3.1) | 264                 | 62 | 64.2 (8.8) | 238 | 63.3 (8.3) | 204 | 62.1 (9.1) | 138 | 61.1 (9.8) | 87 | 60.6 (8.4) | 50 | 60.2 (8.1) | 22 | 61.3 (8.1) |
| PROMIS: depression 300        | 24 (3.1) | 264                 | 62 | 64.2 (8.8) | 238 | 63.3 (8.3) | 204 | 62.1 (9.1) | 138 | 61.1 (9.8) | 87 | 60.6 (8.4) | 50 | 60.2 (8.1) | 22 | 61.3 (8.1) |
| PROMIS: anxiety 300           | 24 (3.1) | 264                 | 62 | 64.2 (8.8) | 238 | 63.3 (8.3) | 204 | 62.1 (9.1) | 138 | 61.1 (9.8) | 87 | 60.6 (8.4) | 50 | 60.2 (8.1) | 22 | 61.3 (8.1) |
| PROMIS: sleep disturbance 300 | 24 (3.1) | 264                 | 62 | 64.2 (8.8) | 238 | 63.3 (8.3) | 204 | 62.1 (9.1) | 138 | 61.1 (9.8) | 87 | 60.6 (8.4) | 50 | 60.2 (8.1) | 22 | 61.3 (8.1) |
function subscale and sexual function problems in breast cancer survivors. Among these prior studies, some have demonstrated an association between worse scores on the physical function subscales and sexual function problems; however, this association has not been consistently reported \[11, 18, 22, 56\]. In contrast to prior studies, we evaluated physical function using the PROMIS physical function measure, a stand-alone measure validated in the early-stage cancer population, as opposed to evaluating physical function with a subscale of a multi-dimensional QOL measure \[41, 57, 58\].

The mechanism by which impairment in physical function during adjuvant endocrine therapy leads to sexual function problems is not known and cannot be determined based on the responses to the PROMIS physical function measure used in this study. It is possible that physical function limitations are attributable to joint pain during adjuvant endocrine therapy which, in turn, may affect
multiple domains on the MOS-SP, such as sexual interest and ability to relax and enjoy sex [59]. Supporting this hypothesis is the fact that joint pain in the setting of arthritic conditions is associated with sexual function problems [60]. It must be noted that a limitation of our study is that we evaluated pain using the PROMIS pain interference measure, a tool that is not specific to joint pain and that may not be sufficiently sensitive to detect endocrine therapy-associated joint pain, thus limiting our ability to evaluate whether joint pain is associated with worsening physical function during endocrine therapy.

Another possible mechanism by which physical function problems may lead to sexual function problems during endocrine therapy is via physical inactivity. Female breast cancer survivors with poor physical function are more likely to be physically inactive and physical inactivity is associated with sexual function problems [11, 56, 61]. Future studies are needed to evaluate the reasons for declining physical function during adjuvant endocrine therapy and to define the mechanism(s) by which physical function impairment during adjuvant endocrine therapy limit sexual function.

Our study confirmed the previously demonstrated association between prior mastectomy and sexual function problems during adjuvant endocrine therapy [2, 8, 12, 14, 15]. Patients who undergo mastectomy may experience body image concerns that may lead to sexual function problems [8, 12–14, 23, 62].

We found that patients of low SES, defined by residence in a zip code with NP rate > 15%, were less likely to experience worsening sexual function during adjuvant endocrine therapy (p=0.06). The explanation for this finding is unclear and should be interpreted with caution. NP rate is not a precise measure of SES and only a small percentage of our cohort was low SES [47, 63].

Our study, like others, confirmed that sexual function problems are common during endocrine therapy [1–8]. Despite being common and distressing for patients, sexual problems are under-reported and under-treated [2, 24, 26, 27]. Approximately 60% of breast cancer patients experiencing a sexual function problem who feel a need for intervention do not consult a healthcare professional [2]. Common patient-reported barriers to accessing support for sexual problems include embarrassment or discomfort in bringing up sexual concerns [27]. Many patients want their clinicians to initiate these discussions; however, clinicians may be reluctant to do so due to time constraints, lack of knowledge and training, and concerns about causing offense [27, 64].

Multiple evidence-based interventions have been shown to improve sexual function during adjuvant endocrine

| Variable | Univariate analysis | Multivariate analysis |
|----------|---------------------|----------------------|
|          | Odds ratio (95% CI) | p value              |
|          |                     | Adjusted odds ratio (95% CI) | p value |
|**Clinicodemographic characteristics** | | | |
| Age in years | 0.98 (0.96–1.0) | 0.04 |
| Race (White vs. Black or Other) | 0.75 (0.45–1.25) | 0.27 |
| Adjuvant endocrine therapy (AI vs. Tamoxifen) | 1.05 (0.71–1.55) | 0.80 |
| Number of baseline concomitant medications | 1.02 (0.98–1.07) | 0.30 |
| Stage | 1.11 (0.85–1.46) | 0.42 |
| Menopausal status at diagnosis (Post vs. Pre) | 0.90 (0.60–1.34) | 0.60 |
| Mastectomy | 1.67 (1.13–2.46) | 0.01 |
| Radiation | 1.15 (0.76–1.73) | 0.51 |
| Chemotherapy | 1.33 (0.87–2.04) | 0.18 |
| Neighborhood poverty rate (> 15% vs. ≤ 15%) | 0.52 (0.26–1.02) | 0.05 |
|**Patient-reported outcomes** | | | |
| Physical Function (4-point worsening) | 1.09 (1.02–1.18) | 0.02 |
| Endocrine Symptoms (5-point worsening) | 1.43 (1.31–1.57) | <0.001 |
| Pain Interference (4-point worsening) | 1.11 (1.03–1.19) | 0.007 |
| Fatigue (4-point worsening) | 1.15 (1.06–1.24) | 0.002 |
| Depression (4-point worsening) | 1.14 (1.06–1.23) | 0.001 |
| Anxiety (4-point worsening) | 1.12 (1.04–1.2) | 0.003 |
| Sleep disturbance (4-point worsening) | 1.13 (1.05–1.21) | 0.003 |

CI confidence interval, AI aromatase inhibitor
therapy [28–34]. Vaginal moisturizers, tablets, suppositories, gels, oils, topical vitamin D or E, and hyaluronic acid can help alleviate vaginal dryness, and lubricants can be used during sexual activity for dyspareunia associated with vaginal dryness [28–30]. Topical lidocaine can also improve dyspareunia in this population [32]. Local hormonal treatments, including vaginal estrogen or dehydroepiandrostosterone (DHEA), can also be used; however, there is some concern about systemic absorption, and not all patients and clinicians are comfortable with the use of these products [28–30, 34]. Additionally, pelvic floor muscle training can improve sexual function and vaginal dilators can improve dyspareunia [28, 29, 33].

Given the availability of evidence-based interventions to address sexual function problems, routine assessment of sexual function during adjuvant endocrine therapy is critical. Based on the associations we identified, patients who experience worsening endocrine symptoms or worsening physical function are at particular risk for worsening sexual function, as are those who have had a mastectomy. Thus, our findings are actionable in that they support the use of PROs as a part of routine clinical care to monitor sexual function, endocrine symptoms, and physical function in patients receiving adjuvant endocrine therapy. Doing so may help identify patients experiencing sexual problems and also those at particular risk for worsening sexual function. Since the extent of symptoms identified by PROs is greater than that reported by clinicians, PROs may be particularly informative in this setting, as both patients and clinicians may otherwise hesitate to initiate discussions about sexual health [26, 27, 64]. Moreover, beyond identifying symptoms that may not have been identified otherwise, PROs have been shown to enhance communication between patients and providers, to facilitate conversations about symptoms, and to impact management [65–67]. Thus, use of PROs during adjuvant endocrine therapy may not only lead to greater awareness of patients’ sexual function problems, endocrine symptoms, and declining physical function, but it may facilitate communication between patients and providers about these issues and the opportunity to offer evidence-based interventions to alleviate these problems.

A strength of this study is that, unlike many prior studies, we evaluated the association between worsening sexual function and other symptoms prospectively over 5 years. Additional strengths include our real-world population and inclusion of both pre- and post-menopausal women. Furthermore, we used validated measures assessing multiple common symptoms during endocrine therapy and used MIDs to identify clinically meaningful changes in PRO scores. Finally, a strength of our analysis is that we used the QIC model selection approach. This approach is unique to analyses with repeated measures in individual participants using GEE and achieves a favorable fit and correlation structure [68]. It must be noted that this approach is based on the model likelihood and is not value driven and, that, as is the case in our analysis, it can yield a final model that includes variables with $p > 0.05$. Despite this fact, the directionality of the odds ratios in our final multivariable model supports the associations of the selected variables with worsening sexual function problems.

Our study has several limitations. Few participants received OFS, limiting generalizability of our findings to this population that faces high risk of sexual problems [1, 69]. Additionally, our participants were predominantly White and of high SES. Some participants may have been on medications that can affect sexual function, such as selective serotonin reuptake inhibitors; however, we did not collect data on specific concomitant medications. In addition, the proportion of participants who completed each measure declined over time, and participants with complete data during the first 24 months reported slightly less fatigue and better physical function at baseline than those with missing measures, thus it is possible that missing data resulted in an underestimation of the strength of the association of these symptoms with worsening sexual function. Additionally, on the MOS-SP, respondents who are not sexually active indicate “not applicable” and this is recoded as “not a problem,” which may underestimate the prevalence of sexual function problems [1, 38]. However, only one participant responded “not applicable” to one question at baseline, so we do not think this limitation is likely to have impacted our findings. Furthermore, the MOS-SP and the Endocrine Symptom Subscale of the FACT-ES questionnaires both contain an item regarding sexual interest; however, in a sensitivity analysis excluding this item when calculating the Endocrine Symptom Subscale FACT-ES score, our findings remained robust. Finally, given that we evaluated the association of worsening symptoms by at least the MID at any time during endocrine therapy with co-occurring worsening of sexual function, we were not able to demonstrate causality.

In conclusion, in this prospective clinic-based cohort of women with early-stage HR+ breast cancer receiving endocrine therapy, we confirmed that sexual function problems are common. Worsening endocrine symptoms, worsening physical function, and prior mastectomy are associated with worsening sexual function. Routine assessment for endocrine symptoms, physical function, and sexual function problems using PROs may reduce under-detection of sexual function problems and identify patients who can benefit from interventions to alleviate sexual symptoms.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest Karen Lisa Smith has received research support (to institution) from Pfizer. Karen Lisa Smith’s spouse has stock ownership in ABT Labs and Abbvie. Vered Stearns has received research grants (to institution) from Abbvie, Biocept, Pfizer, Puma Biotechnology, and Novartis. Vered Stearns has been on an advisory board for Novartis (10/25/21). Vered Stearns is a Data Safety Monitoring Board member for Immunomedics, Inc. and for AstraZeneca. Vered Stearns has received non-financial support from Foundation Medicine for Study Assays. Claire Snyder has research funding (to institution) from Pfizer and Genentech and has received personal consulting fees from Janssen via Health Outcomes Solutions. Elissa Thorner has received research support (to institution) from Pfizer. The following authors declare that they have no conflicts of interest related to the work presented in this manuscript: Neha Verma, Amanda Blackford, and Jennifer Lehman.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. We obtained approval from the Johns Hopkins (JH) Institutional Review Board (IRB) to conduct this prospective study. All participants signed written informed consent.

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