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Title: Priorities for alleviating menopausal symptoms after cancer

Running title: Symptom priorities in cancer survivors

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ABSTRACT

OBJECTIVE: To determine treatment priorities in women cancer patients attending a dedicated Menopausal Symptoms After Cancer (MSAC) service.

METHODS: Cancer type and stage were abstracted from medical records. Women ranked up to three symptoms as treatment priorities from the list “hot flushes/night sweats”, “mood changes”, “vaginal dryness or soreness”, “sleep disturbances”, “feeling tired or worn out (fatigue)”, “sexual problems and/or pain with intercourse”, “joint pain”, and “something else” with free-text response. For each prioritized symptom, patients completed standardized patient-reported outcome measures to determine symptom severity and impact.

RESULTS: Of 189 patients, most had breast cancer (48.7%, n=92), followed by hematological (25.8%, n=49), gynecological (18.0%, n=34), or colorectal (2.6%, n=5). The highest (first-ranked) treatment priority was vasomotor symptoms (33.9%, n=64), followed by fatigue (18.0%, n=34), vaginal dryness/soreness (9.5%, n=18), and sexual problems/pain with intercourse (9.5%, n=18). Symptoms most often selected in the top three (“prioritized”) were fatigue (57.7%, n=109), vasomotor symptoms (57.1%, n=108), and sleep disturbance (49.2%, n=93). In patients who prioritized vasomotor symptoms, medians on the “Problem”, “Distress” and “Interference” dimensions of the Hot Flash Related Daily Interference Scale were, respectively, 6.0 (IQR 5.0-8.0), 5.5 (IQR 3.0-8.0), and 5.0 (IQR 3.0-7.0), indicating moderate severity. In patients who prioritized fatigue, the median Fatigue Scale score was 28 (IQR: 19 – 36), 37% worse than general population.

CONCLUSIONS: Vasomotor symptoms, fatigue, sexual problems and vaginal dryness/soreness were the leading priorities for treatment. Understanding symptom severity and patient priorities will inform better care for this growing population.

KEYWORDS: Climacteric; insomnia; dyspareunia; genitourinary syndrome of menopause

INTRODUCTION

Early menopause, and more frequent and severe menopausal symptoms, are some of the most common and distressing side effects of treatments for cancer in women including gynecologic, breast, and blood cancers.[1, 2] Oophorectomy, chemotherapy, radiation therapy, and endocrine therapy may all induce menopausal symptoms.[3, 4] As survival rates from cancer are increasing, more women are managing long-term menopausal symptoms.

While it may be difficult to distinguish which symptoms are attributable to menopause and which are due to aging or other comorbidities, several symptoms are consistently associated with menopause.[5] These include vasomotor symptoms (hot flushes and night sweats), sleep disturbances and vaginal dryness.[6-8] Other symptoms, such as reduced libido, pain with sex, mood changes (anxiety and depression), fatigue, and joint pain are also common but it is uncertain whether they are attributable to menopause.[9, 10]

Many women experience multiple, concurrent symptoms.[11, 12] After breast cancer, menopausal symptoms and joint pains have been identified as a major contributor to discontinuation of adjuvant endocrine therapy.[13] Understanding which symptoms patients most wish treated (treatment priorities) is essential to shared decision-making, and patient-centered care. However, healthcare providers only document half of the symptoms patients consider a priority.[14] In the general population of women, participants in the Menopausal Strategies - Finding Lasting Answers to Symptoms and Health (MsFLASH) trial[15] most commonly prioritized vasomotor symptoms, followed by sleep disturbance, difficulty in concentrating, and fatigue. Several studies have reported that menopausal symptoms are more severe in cancer survivors. However, no previous studies have measured menopausal symptom treatment priorities in cancer survivors or whether they relate to symptom severity.

We aimed to determine the priorities of female cancer survivors with menopausal symptoms referred to a tertiary service, and the severity of these symptoms.

METHODS

Study population

The Menopausal Symptoms after Cancer (MSAC) clinic at the Royal Women's Hospital, Victoria, Australia manages female cancer survivors and those at high inherited risk of cancer who are experiencing menopausal symptoms. In a clinical audit undertaken as part of routine care, data were collected from all eligible new and review patients presenting to the clinic between May 2019 and January 2020.

Data collection and measures

Prior to the patient's medical appointment, demographic and medical history information were abstracted from medical files. At the appointment, patients completed a Symptom Priority Form (Appendix 1) and the Rand Short Form Health Survey (SF-12),[16] which measures physical and mental health-related quality of life, with higher scores corresponding to better health status (standardized score range 0-100, mean 50, standard deviation 10). Depending on their treatment priorities, patients completed up to three patient-reported outcome measures (PROMs) measuring severity of menopausal symptoms. Irrespective of treatment priority, all patients were asked to report if they experienced hot flushes and night sweats including frequency of daytime flushes and number of night-time awakenings.

Demographic data and medical history

Age, Indigenous status, marital status, and first language were abstracted from the medical files. Cancer history including cancer type, date of diagnosis, hormone receptors status if

breast cancer, gene mutations, cancer treatment, and time since the most recent treatment were also abstracted. Menopause-related information included gynecological/obstetric history, reproductive stage, cause of menopause (spontaneous or iatrogenic), and any treatments used for menopausal symptoms. As the Stages of Reproductive Ageing Workshop criteria depend on menstrual bleeding history,[17] and thus exclude women with hysterectomy and chemotherapy-related amenorrhea, we used a modification, based on symptom trajectories from Mishra and Kuh, to define reproductive stage.[18] Reproductive stage was defined as "premenopausal" if the patient had regular menstrual periods and no vasomotor symptoms in the twelve months prior to the clinic visit; "perimenopausal" if the patient had irregular menstrual periods and/or was experiencing vasomotor symptoms in the last twelve months; "postmenopausal" if the patient had no menstrual period in the last twelve months; and "cannot determine" if available information from the medical history was insufficient to determine reproductive stage.

Symptom Priority Form

Participants were asked to identify and rank up to three menopausal symptoms they "would most like to get rid of or be free of" from the list: "hot flushes/night sweats", "mood changes", "vaginal dryness or soreness", "sleep disturbances", "feeling tired or worn out (fatigue)", "sexual problems and/or pain with intercourse", "joint pain", and "something else" with free-text response. Information on use of self-management strategies (i.e. over-the-counter medications, psychological therapy/cognitive behavioral therapy, yoga, exercise, hypnosis, lifestyle of behavior changes, or something else specified by the patients) was also collected.

PROMs for menopausal symptoms

Participants were asked to complete PROMs for the three symptoms they ranked as highest priorities (Table 1).

Statistical analysis

Categorical data were summarized using frequencies and proportions. Normally distributed continuous variables were summarized using means and standard deviations. Continuous variables that were not normally distributed were summarized using medians, interquartile ranges (IQRs), and ranges.

Frequencies of hot flushes and of awakenings due to night sweats were compared between those who chose vasomotor symptoms as one of the top three treatment priorities, and those who did not, using t-tests for unequal variance. Associations among potentially related treatment priorities (sleep disturbance and fatigue, hot flushes/night sweats and sleep disturbance, vaginal dryness or soreness and sexual problems) were assessed by comparing frequencies using Fisher's exact test. Median fatigue score was compared between those who did and did not prioritize sleep disturbance using the Wilcoxon rank-sum test. Associations between treatment priority and cancer type (breast cancer versus other type of cancer) were assessed using logistic regression models adjusted for age at visit.

Data were analyzed using Stata (Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC. StataCorp). All hypothesis tests were two-sided, and $p < 0.05$ was considered statistically significant.

RESULTS

Study population characteristics

From May 2019 to January 2020, 189 patients with a history of cancer attending for new appointments at the MSAC clinic completed treatment priority questionnaires. Demographic characteristics and medical history are shown in Table 2. Median age was 49 years (IQR: 41 - 56, range: 18 - 80). Participants had a wide range of cancer diagnoses. The most common cancer type was breast cancer (48.7%, n=92), followed by hematological cancer (25.8%, n=49), gynecological cancer (18.0%, n=34), and colorectal cancer (2.6%, n=5). The median SF-12 physical well-being score was 42.6 (IQR: 35.4 - 51.1, range: 21.1 - 60.8) and mental well-being score was 46.8 (IQR: 36.8 - 54.0, range: 13.7 - 67.5). These are within the range of 40 - 49 conventionally regarded as mildly disabled [16] and below the median standardized general population score in Australia (50, SD = 10).[19] Over three-quarters of patients (76.7%, n=145) reported hot flushes and/or night sweats. The median number of hot flushes per day was 4 (IQR: 1.5 - 5.5, range: 0 - 24) and of awakenings due to night sweats was 2 (IQR: 1 - 3, range: 0 - 8).

Menopausal symptom priorities

The symptoms most often chosen as the highest (first-ranked) treatment priority were hot flushes/night sweats (33.9%, n=64), followed by fatigue (18.0%, n=34), vaginal dryness or soreness (9.5%, n=18), sexual problems and/or pain with intercourse (9.5%, n=18), sleep disturbance (9.0%, n=17), joint pain (7.4%, n=14), and mood changes (5.8%, n=11) (Figure 1). The one woman choosing “something else” as her highest treatment priority specified “weight gain”.

The symptoms most often chosen as one of the top three treatment priorities are summarized in Figure 2. These were fatigue (57.7%, n=109) and hot flushes/night sweats (57.1%, n=108), followed by sleep disturbance (49.2%, n=93), mood changes (31.2%, n=59), vaginal dryness or soreness (25.4%, n=48), sexual problems and/or pain with intercourse (24.8%, n=47), and joint pain (23.8%, n=45). Women choosing "something else" as one of their top three priorities (6.3%, n=11) specified weight gain (n=4), nausea/vomiting (n=2), breast pain (n=1), chills/sinusitis (n=1), mental health (n=1), muscle cramping (n=1), and sensation of prolapsed uterus (n=1).

Those who chose vaginal dryness or soreness as one of the top three treatment priorities ("prioritized" vaginal dryness or soreness) were more likely than those who did not to prioritize sexual problems and/or pain with intercourse (52.1%, n=25 v. 15.5%, n=22, $p<0.001$) . Those who prioritized sleep disturbance were no more likely than those who did not to prioritize fatigue (57.5%, n=54 v. 57.9%, n=55, $p>0.9$). Those who prioritized hot flushes/night sweats were more likely than those who did not to prioritize sleep disturbance (58.7%, n=64 v. 37.5%, n=30, $p=0.005$).

After adjusting for age, women with breast cancer history were more likely to choose hot flushes/night sweats as the first or top 3 treatment priorities (Appendix 2; 50.0%, n=46 vs. 19.6%, n=19, adjusted odds ratio (aOR) 3.0, 95% confidence interval (CI) 1.5-5.9, Wald $p = 0.002$; 71.7%, n=66 vs. 44.3%, n=43, aOR 3.0, 95%CI 1.6-5.9, Wald $p = 0.001$). Cancer type did not otherwise consistently affect priorities, including arthralgia (Appendix 2). Hormone therapy use among women with breast cancer history was lower than among women with history of other cancers (3.3%, n=3 vs. 28.9%, n=28, $p < 0.001$).

Among women who chose hot flushes/night sweats as a top-three treatment priority, the median number of hot flushes per day was 4 (IQR: 2.5-6, range: 0-24) and awakenings due to hot sweats was 2 (IQR: 1-3.5, range: 0-8). Among those who did not prioritize hot flushes/night sweats, the median number of hot flushes was 2 (IQR: 1-4, range 0-10), and awakenings due to night sweats was 1.5 (IQR: 1-2, range 0-6). The difference between groups was significant for both hot flushes (p=0.0007) and night sweats (p=0.03).

Menopausal symptom severity

Severity of menopausal symptoms as measured by PROM instruments among patients who chose the symptom as one of the top three treatment priorities ("prioritized the symptom") are shown in Table 3 .

Among patients who prioritized vasomotor symptoms, medians on the "Problem", "Distress" and "Interference" dimensions of the Hot Flash Related Daily Interference Scale were, respectively, 6.0 (IQR 5.0-8.0), 5.5 (IQR 3.0-8.0), and 5.0 (IQR 3.0-7.0). This corresponds to moderate severity.[20]

In patients who prioritized fatigue, the median Fatigue Scale score was 28 (IQR: 19 – 36), more severe than the general population median of 47 and the median of 42 among non-anemic cancer patients.[21]

Among patients who prioritized sleep disturbances, a few met criteria for severe clinical insomnia (11.4%, n=10), and most had moderately severe clinical insomnia (36.4%, n = 32) or subthreshold insomnia (36.4%, n = 32)[22]. A few had no clinically significant insomnia (12.5%, n=11). Amongst those who prioritized fatigue and thus completed the Fatigue Scale (n=110), the median score did not differ between those who did and did not prioritize sleep disturbance (28 v. 28, p>0.9).

Among patients who prioritized mood changes, median scores were 10 for depression, 8 for anxiety, and 20 for stress, exceeding score thresholds for mild depression, mild anxiety and moderate stress[23]. Eight (14.0%), 12 (21.1%) and five (8.8%) participants exceeded score thresholds for extremely severe depression, anxiety, and stress, respectively.

Among patients who prioritized sexual problems and/or pain with intercourse, most patients were married or in an intimate relationship (87.0%, n=40). Only 56.5% (n=26) were sexually active with a partner. Only one (2.2%) had changed sexual partners in the prior 6 months. Among sexually active patients, median scores for the "Habit", "Pleasure", and "Discomfort" subscales were 4, 16, and 2, corresponding to less frequency of sexual activity than usual, low sexual pleasure and satisfaction, and mild discomfort during penetration.

Among those prioritizing vaginal soreness or dryness, the median score on the "Daily living" scale was 0.2, indicating little impact of vaginal disorders on daily life. The median scores for "Emotional well-being", "Sexual functioning", and "Self-concept and body image" were 1, 2, and 2.6, respectively, indicating that vaginal disorders caused mild impact on emotions and moderate to high impact on sexual function and self-concept[24].

Among the patients who prioritized arthralgia, the median score on the PRAI was 1.8, where a score of 10 represents maximum symptom severity.

DISCUSSION

This is the first study to measure the priorities of women cancer patients for treatment of their menopausal symptoms. Symptom severity was also measured for the three symptoms that patients prioritized for treatment. Compared with population norms, we observed that

hot flushes, fatigue, and sexual problems were rated as more severe than among general population menopausal women.

As expected, vasomotor symptoms (hot flushes and night sweats) were the highest treatment priority. This is consistent with women seeking treatment for menopausal symptoms in the general population (MsFLASH trial)[15]. However, the proportion prioritizing vasomotor symptoms was substantially lower in our study than reported in MsFLASH (highest treatment priority: 33.9% vs. 59.2%, top three treatment priorities: 57.1% vs. 90.7%) as our patients prioritized fatigue and sexual symptoms more highly. Vasomotor symptoms were more common in our population than in the general population[25], and breast cancer patients were more likely to prioritize vasomotor symptoms than women with other cancers. This might be because hormone therapy was contraindicated in these women, or might reflect use of endocrine therapy, which is known to cause vasomotor symptoms [26, 27]. In contrast, the degree to which symptoms were bothersome was similar to that among MsFLASH participants[25], which might reflect the fact that both included women seeking treatment for vasomotor symptoms.

Fatigue was much more commonly prioritized in our population than among MsFLASH participants (highest treatment priority: 18.0% vs 7.2%, top three treatment priorities 57.7% vs. 32.7%)[15], consistent with the high prevalence of fatigue among cancer patients (47% - 61%)[28]. We found no relationship between prioritizing fatigue and prioritizing sleep disturbance. The severity of fatigue reported in our sample was greater than that reported in the general population and was nearly as severe as that among cancer patients in treatment for chemotherapy-related anemia[21]. Taken together, these observations suggest that

although fatigue is not a core symptom of menopause, fatigue related to cancer or its treatment may add to the burden of menopausal symptoms in this population.

Our patients were less sexually active than reports from the general population (55.3% vs. 79.5%) and experienced less sexual pleasure and more discomfort[16, 29]. Our participants also reported worse impact of vaginal disorders on emotional well-being, sexual functioning, and self-concept and body image as compared with the general population[24]. This is consistent with extensive evidence that sexual dysfunction is common in female cancer patients[30]. Prioritizing sexual problems was related to prioritizing vaginal symptoms, suggesting that vaginal dryness plays an important role in sexual problems after cancer. Vaginal estrogen is effective in treating vaginal dryness and is not contraindicated after cancer apart from requiring an individualized approach in breast cancer[31]. For those patients for whom estrogen is contraindicated, effective treatment options for sexual dysfunction include cognitive behavioral therapy and DHEA gel[32].

Although joint pain is a common side effect of aromatase inhibitors and reduces adherence[13, 33, 34], we found that breast cancer patients were no more likely to prioritize joint pain than patients with other cancers. This could reflect the nature of treatment priority – even if joint pain is more common among breast cancer patients than patients with other cancers, breast cancer patients might prioritize their joint pain below other symptoms. Another possibility is that aromatase-inhibitor-related joint pain might not be perceived as a symptom appropriate for referral to MSAC, limiting its importance in this study population. We were also surprised that patients who prioritized joint pain reported low symptom severity, with a median of 1.8 out of a possible 10. We chose the Patient Reported Arthralgia Inventory because it was validated in breast cancer survivors with aromatase inhibitor-related arthralgia[35]. However,

low scores are common[36], and the instrument may be better-suited for measuring changes in severity over time than absolute severity at a single timepoint.

Strengths of this study include its relatively large size and its novelty. Because charts were not always complete, and cancer diagnoses were up to 33 years prior, one limitation is that some clinical data were missing, ranging between 1% for cancer type to 32% for history of radiation therapy. This missingness limited our ability to ascertain cause of menopause, precluding subgroup analyses and prevented model adjustment for potential clinical confounders. Although we had information regarding therapies relevant to menopausal symptoms (e.g. hormone therapy, SSRIs), we did not know the specific indication for these treatments. Hence, some of the SSRI/SNRI may have been prescribed for depression. We defined reproductive stage based on menstrual patterns, which may be affected by contraceptive or surgical history. We were unable to ascertain reproductive stage in around a third of patients.

Conclusion

Patients with breast and other types of cancer who seek treatment for menopausal symptoms prioritized vasomotor symptoms, fatigue, sexual problems and vaginal symptoms. Women prioritized the symptoms that were most severe for them. Hot flushes, fatigue, sexual problems and vaginal symptoms were rated as more severe than among general population of menopausal women. Understanding symptom severity and patient priorities will inform better care for this growing population.

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Table 1. *PROMs for assessment of menopausal symptoms*

Symptom	**PROM**	**Score range/assessments**
Hot flushes and night sweats	Hot Flush Rating Scale (HFRS)[23]	Part 1 measures whether women are partnered and sexually active; Part 2, reasons for inactivity among those who are not active; Part 3, characteristics of sexual life among those who are active: "Problem" score: 1 – 10, higher = worse; "Distress" score: 1 – 10, higher = worse; "Interference" score: 1 – 10, higher = worse; Overall bother (average of the three scores): 1 – 10, higher = worse.
Mood changes	21-item Depression Anxiety Stress Scale (DASS21)[24]	"Depression" score: 0 – 42, higher = worse; "Anxiety" score: 0 – 42, higher = worse; "Stress" score: 0 – 42, higher = worse.
Vaginal dryness or soreness	Day-to-Day Impact of Vaginal Aging Questionnaire (DIVA)[25]	"Daily living" score: 0 – 4, higher = worse; "Emotional well-being" score: 0 – 4, higher = worse; "Sexual functioning" score: 0 – 4, higher = worse; "Self-concept and body image" score: 0 – 4, higher = worse.
Sleep disturbance	Insomnia Severity Index (ISI)[26]	ISI overall score: 0 – 28, higher = worse.
Fatigue	Functional Assessment of Chronic Illness Therapy - fatigue subscale (FACIT-fatigue)[27]	Fatigue overall score: 0 – 52, lower = worse.
Sexual problems	Fallowfield's Sexual Activity Questionnaire (SAQ)[28]	"Pleasure" score: 4 -24, pleasure obtained from sexual activity, higher = less pleasure; "Discomfort" score: 2 - 8, sexual discomfort caused by vaginal dryness and soreness, higher = more discomfort; "Habit" score: 1 - 4, frequency of sexual activity, higher = lower frequency.
Joint pain	Patient-Reported Arthralgia Inventory (PRAI)[29]	PRAI overall score: 0 – 10, higher = worse.

Table 2. *Participant characteristics*

Characteristic	N = 189
Age at visit, median (IQR) [range]	49 (42-56) [18-80]
CALD/LOTE, N (%)	
Yes	132 (69.8%)
No	33 (17.5%)
Cannot be determined	24 (12.7%)
Year since cancer diagnosis, median (IQR) [range]	3 (1-6) [0-33]
Cancer type, N (%)	
Breast cancer	92 (48.7%)
Hematological cancer	49 (25.9%)
Gynecological cancer	34 (18.0%)
Colorectal cancer	5 (2.6%)
Other[a]	7 (3.7%)
Not recorded	2 (1.1%)
Chemotherapy, N (%)	
Yes	94 (49.7%)
No	46 (24.3%)
Not recorded	49 (25.9%)
Radiation therapy, N (%)	
Yes	77 (40.7%)
No	51 (27.0%)
Not recorded	61 (32.3%)
Surgery, N (%)	
Yes	109 (57.7%)
No	45 (23.8%)
Not recorded	35 (18.5%)
Ultimate gynecological surgery, N (%)	
Unilateral salpingo-oophorectomy	8 (4.2%)
Bilateral salpingo-oophorectomy	36 (19.1%)
Hysterectomy	37 (19.6%)
Endocrine therapy, N (%)	
Current endocrine therapy	49 (25.7%)
Ever endocrine therapy	79 (41.4%)
Stem cell transplant/Bone marrow transplant (hematological cancer only), N (%)[b]	
Yes	43 (87.8%)
Yes, allograft	30 (61.2%)
Yes, autograft	4 (8.2%)
Graft type unknown	9 (18.4%)
No	3 (6.1%)
Missing	3 (6.3%)
Current reproductive stage, N (%)	
Premenopause	5 (2.6%)
Perimenopause	26 (13.8%)
Postmenopause	92 (48.7%)

Cannot be determined	66 (34.9%)
Reproductive stage at cancer diagnosis, N (%)	
Premenopause	66 (34.9%)
Perimenopause	11 (5.8%)
Postmenopause	25 (13.2%)
Cannot be determined	87 (46.0%)
Ever hormone therapy, N (%)	
Yes	63 (32.8%)
Estrogen only	17 (9.0%)
Progestogen only	3 (1.6%)
Estrogen plus progestogen	22 (11.6%)
Type not recorded	20 (10.6%)
No	72 (38.1%)
Not recorded	55 (29.1%)
Current hormone therapy, N (%)	
Yes	30 (16.2%)
No	104 (55.0%)
Cannot be determined	55 (29.1%)
Non-hormone therapy, N (%)	
SSRI/SNRI	45 (23.8%)
Clonidine	4 (2.1%)
Gabapentin	30 (15.9%)
Other medical history, N (%)	
Anxiety/Depression	20 (10.6%)
Venous thromboembolism	3 (1.6%)
Diabetes	8 (4.2%)
Genital graft-versus-host disease	11 (5.8%)
Hypertension	16 (8.5%)

CALD/LOTE: Culturally and linguistically diverse/Language other than English; IQR: interquartile range; SNRI: Serotonin and norepinephrine reuptake inhibitor; SSRI: Selective serotonin reuptake inhibitor.

a. Other: one case each of skin, lung, and kidney malignancy, and two each of sarcoma and central nervous system malignancy.

b. Percentages were calculated against the number of patients with a diagnosis of hematological cancer (n = 49).

Table 3. *Scores from patient-reported outcome measure instruments*

	Median (IQR)	Range
Patient-reported outcome measures		
Hot Flush Rating Scale (N=102)		
Problem	6.0 (5.0 – 8.0)	1.0 - 10.0
Distress	5.5 (3.0 – 8.0)	1.0 – 10.0
Interference	5.0 (3.0 – 7.0)	1.0 – 10.0
Overall score	5.3 (3.7 – 7.0)	1.0 – 10.0
Functional Assessment of Chronic Illness Therapy – Fatigue (N=105)		
Overall score	28.0 (19.0 – 36.0)	3.0 – 49.0
Insomnia Severity Index (N=85)		
Overall score	14.0 (10.0 – 18.0)	1.0 – 28.0
Depression Anxiety Stress Scale (N=57)		
Depression	10.0 (4.0 – 20.0)	0 – 42.0
Anxiety	8.0 (4.0 – 16.0)	0 – 34.0
Stress	20.0 (10.0 – 26.0)	0 – 38.0
Fallowfield's Sexual Activity Questionnaire (N=44)		
Habit	4.0 (3.0 – 4.0)	1.0 – 4.0
Pleasure	16.0 (16.0 – 21.0)	7.0 – 24.0
Discomfort	2.0 (2.0 – 8.0)	2.0 – 8.0
Day-to-day Impact of Vaginal Aging (N=45)		
Daily living	0.2 (0 – 1.0)	0 – 3.2
Emotional well-being	1 (0.5 – 2.0)	0 – 4.0
Sexual functioning	2 (1.2 – 3.0)	0 – 4.0
Self-concept and body image	2.6 (1.2 – 3.8)	0 – 4.0
Patient Reported Arthralgia Inventory (N=44)		
Overall score	1.8 (0.9 – 3.3)	0.6 – 8.0

Appendix 1: Symptom priorities form

Do you have hot flushes and/or night sweats?

☐ NO ☐ YES

IF YES: Average number of hot flushes/day: _____ Average number nighttime awakenings: _____

PLEASE WRITE THE NUMBERS 1, 2, 3 next to the TOP THREE symptoms you would most like to get rid of or be free of (that is, RANK your top three):

_____Hot flush/night sweats HFRS

_____Mood changes DASS

_____Vaginal Dryness or Soreness DIVA

_____Sleep Disturbance ISI

_____Feeling Tired or Worn Out (Fatigue) FATIGUE

_____Sexual Problems and/or Pain with Intercourse SAQ

_____Joint Pain PRAI

_____Something else : _____

_____ I have no symptoms, I am here for this reason :_____

Appendix 2: Relationships between symptom priorities and cancer type, adjusted for age.

	Symptom is highest treatment priority				Symptom is in top 3 treatment priorities			
Symptom	Breast cancer N (%)	Other cancer N (%)	Adjusted OR (95% CI)	p	Breast cancer N (%)	Other cancer N (%)	Adjusted OR (95% CI)	p
Hot flushes and night sweats	46 (50.0)	19 (19.6)	3.0 (1.5 - 5.9)	0.002	66 (71.7)	43 (44.3)	3.0 (1.6 - 5.9)	0.001
Mood changes	6 (6.5)	6 (6.2)	1.5 (0.4 - 5.4)	0.5	32 (34.8)	28 (28.9)	1.6 (0.8 - 3.2)	0.15
Vaginal dryness or soreness	5 (5.4)	12 (12.4)	0.3 (0.1 - 1.1)	0.07	19 (20.7)	28 (28.9)	0.5 (0.3 - 1.1)	0.085
Sleep disturbance	9 (9.8)	8 (8.2)	1.6 (0.5 - 4.8)	0.4	55 (59.8)	39 (40.2)	1.9 (1.0 - 3.6)	0.04
Fatigue	11 (12.0)	23 (23.7)	0.5 (0.2 - 1.2)	0.11	56 (60.9)	53 (54.6)	1.3 (0.7 - 2.5)	0.4
Sexual problems	4 (4.4)	13 (13.4)	0.3 (0.1 - 1.2)	0.08	13 (14.1)	33 (34.0)	0.4 (0.2 - 0.9)	0.03
Joint pain	9 (9.8)	5 (5.2)	3.1 (0.9 - 11.2)	0.08	24 (26.1)	21 (21.7)	1.3 (0.6 - 2.7)	0.5

CI: confidence interval; OR: odds ratio

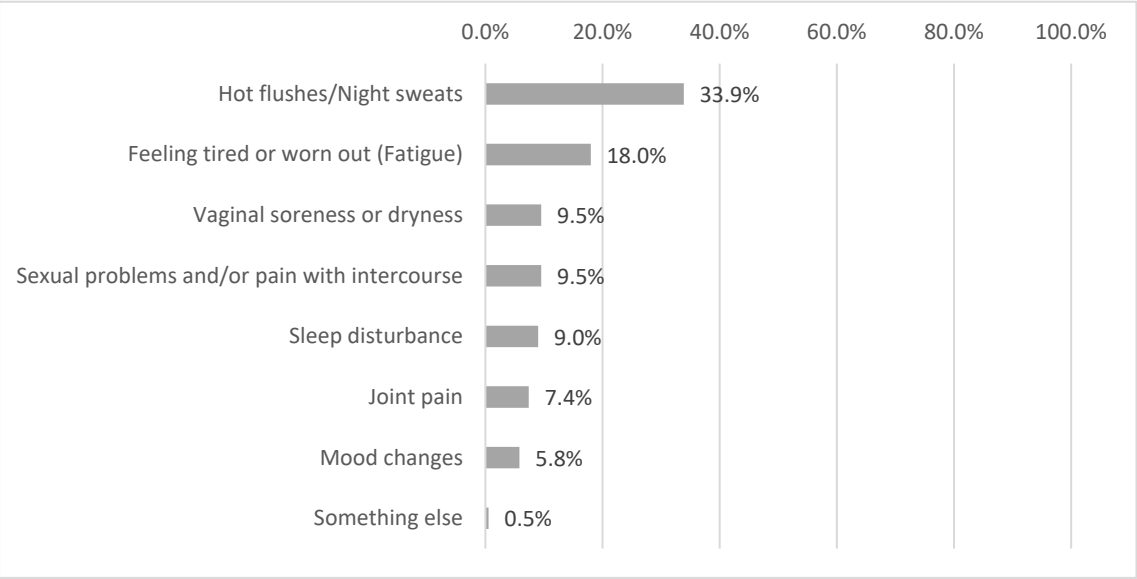

Figure 1. *Symptoms ranked as highest (top-ranked) treatment priority (n=189)*

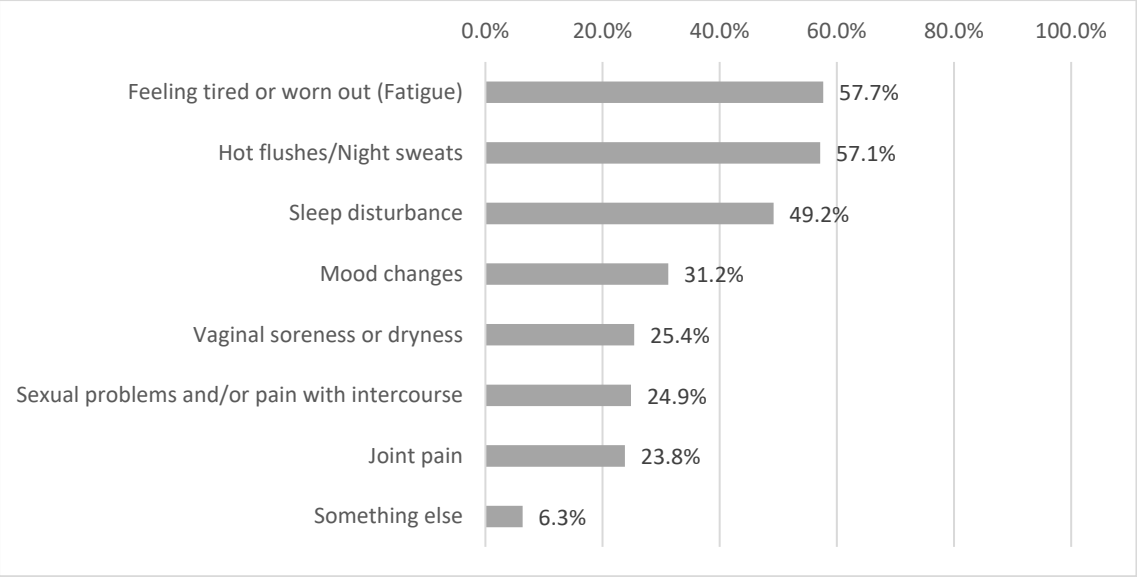

Figure 2. *Symptoms ranked as one of top three treatment priorities (n=189)*