Seminars in Oncology Nursing 39 (2023) 151451

Contents lists available at ScienceDirect

Seminars in Oncology Nursing

journal homepage: https://www.journals.elsevier.com/seminars-in-oncology-nursing

# Prevalence of Psychoneurological Symptoms and Symptom Clusters in Women with Breast Cancer Undergoing Treatment: Influence on Quality of Life

Noelia Durán-Gómez[a], Casimiro F. López-Jurado[a], Marta Nadal-Delgado[b], Jesús Montanero-Fernández[c], Patricia Palomo-López[a], Macarena C. Cáceres[a,*]

[a] PhD, Departamento de Enfermería, Facultad de Medicina y Ciencias de la Salud, Universidad de Extremadura, 06006, Badajoz, Spain
[b] PhD, Hospital Universitario de Badajoz, Asociación Oncológica Extremeña, 06006 Badajoz, Spain
[c] PhD, Departamento de Matemáticas, Facultad de Medicina y Ciencias de la Salud, Universidad de Extremadura, 06006 Badajoz, Spain

ARTICLE INFO

*Key Words:*
breast neoplasm
quality of life
depressive symptoms
anxiety
cognitive dysfunction
fatigue
insomnia
pain

ABSTRACT

*Objectives:* To identify subgroups of psychoneurological symptoms (PNS) and their relationship to different clinical variables in a sample of women with breast cáncer (BC) with different type of treatment, and the possible influence of these on quality of life (QoL), using a factorial principal components analysis.
*Data Sources:* Observational, cross-sectional, non-probability study (2017–2021) at Badajoz University Hospital (Spain). A total of 239 women with BC receiving treatment were included.
*Results:* 68% of women presented fatigue, 30% depressive symptoms, 37.5% anxiety, 45% insomnia, and 36% cognitive impairment. The average score obtained for pain was 28.9. All the symptoms were related between themselves, and within the cluster of PNS. The factorial analysis showed three subgroups of symptoms, which accounted for 73% of variance: state and trait anxiety (PNS-1), cognitive impairment, pain and fatigue (PNS-2), and sleep disorders (PNS-3). The depressive symptoms were explained equally by PNS-1 and PNS-2. Additionally, two dimensions of QoL were found (functional-physical and cognitive-emotional. These dimensions correlated with the three PNS subgroups found. A relationship was found between chemotherapy treatment and PNS-3, and its negative impact on QoL.
*Conclusions:* A specific pattern of grouped symptoms in a psychoneurological cluster with different underlying dimensions has been identified which negatively influences QoL of survivors of BC.
*Implication for Nursing Practice:* It is important to raise awareness among professionals and patients about the existence of a cluster of PNS, the patient's profile, as well as the factors that exacerbate them. This will allow them to be treated more effectively and comprehensively.


## Introduction

It has been shown that cancer and its treatments produce multiple symptoms, which are often concurrent.[1] These symptoms often do not occur in isolation, meaning that one symptom can affect the onset and severity of other symptoms.[2] The appearance of these symptom clusters, compared to only one symptom, seems to worsen patients' outcomes.[3] A symptom cluster has been defined as a group of two or more concurrent symptoms that occur independently of other clusters, which may or may not share a common aetiology.[1,4] Two distinct clusters were identified in women receiving treatment for breast cancer (BC): a psychoneurological cluster (depressed mood, cognitive disturbance, fatigue, insomnia, and pain) and an upper gastrointestinal cluster.[5]

It has been published that several demographic and clinical variables were predictive of greater intensity of symptoms for each cluster, which would serve to identify patients at higher risk of experiencing certain groups of intense symptoms during treatment.[6] Several studies have related the symptom cluster with age, education level, employment situation, comorbidity, disease stage, treatment modality, and trajectory.[7]

Both symptoms individually and in groups are dynamic, affecting women with BC at the time of diagnosis, during treatment, and sometimes post-treatment.[8–10] Specifically, pain, sleep disturbances, fatigue, and depressive symptoms may be more severe during chemotherapy treatment.[11]

* Address correspondence to: Macarena C. Cáceres, Departamento de Enfermería, Universidad de Extremadura, Avda de Elvas s/n, Badajoz, España 06006.
*E-mail address:* mcaceres@unex.es (M.C. Cáceres).

https://doi.org/10.1016/j.soncn.2023.151451

Kim et al showed that some patient subgroups share the unique experience of psychoneurological symptoms (PNS). Furthermore, they found a subgroup of patients with a high depressed mood and cognitive disturbance, related principally to chemotherapy.[12] A recent study published by our group reported that women undergoing chemotherapy treatment do so with objective and subjective cognitive costs; we found that lower scores in perceived cognitive impairment determine a worsening of the regional saturation index ($rSO_2$) and a worse performance in phonological and semantic verbal fluency tasks.[13]

Several theories have previously been published to describe the relationships of factors associated with chemotherapy-related cognitive impairment (CRCI) such as the Theory of Unpleasant Symptoms (TUS)[14] and the Conceptual Model of Chemotherapy-Related Changes in Cognitive Function.[15] It has been proposed that a combination of the two may provide an improved framework for future research. In addition to the association between factors such as age, anemia, fatigue, depression, anxiety, hormone levels, cytokine release, and genetic makeup, these theories describe how patients have reported a significant effect on quality of life (QoL).[16] Several studies have analyzed that PNS can have a significant impact on the QoL of women undergoing treatment.[17,18]

Identification of symptom clusters, as well as individual symptoms, in women with BC, can be beneficial because symptom clusters have a synergic effect on morbidity, mortality, prognosis, and QoL.[3] However, further research is required to determine whether the collective management of the symptoms can be beneficial[6] because the methodology used in the different studies is widely diverse. As Miaskowski et al propose, identification of symptom clusters can be performed using de novo methods to identify one or more symptom clusters, each of which contains two or more symptoms, or a priori methods in which researchers previously specify the symptom cluster of interest, based mainly on empirical evidence of a relationship between the symptoms.[3] Some studies have previously reported the existence of a PNS cluster[2]; we have based our study on this evidence to analyze the possible existence of subgroups of patients with experiences of similar symptoms.

So et al suggest analyzing separately symptom clusters experienced by patients with BC depending on their treatments, using standardized instruments to evaluate the symptoms.[2] We previously described the prevalence of some PNS and their relation with other clinical variables and therapeutic management.[8,13,18] In the present study, we proposed to identify subgroups of PNS and their relationship to different clinical variables in a larger sample of women with BC with different types of treatment, and the possible influence of these on QoL, using a factorial principal component analysis (PCA) as the statistical approach. It is important to be able to identify patients with the greatest risk of experiencing these PNS subgroups. In this way, we could reach a higher level of understanding and interpretation of the clinical status of these women, and so carry out more suitable planning of future intervention strategies.[3,17]

## Materials and Methods

### *Study Population and Setting*

We performed an observational, cross-sectional, nonprobability study between 2017 and 2021 at Badajoz University Hospital (Spain). Women diagnosed with BC who were receiving oncological treatment were included. Exclusion criteria were being a minor; being over 85 years; not being a patient of Badajoz University Hospital; not signing the informed consent; having a neurological or cognitive impairment that would impede carrying out the assessment; having previously received treatment for another type of primary cancer; having a diagnostic record of comorbidity associated with depression, anxiety, and/or cognitive impairment; having linguistic or communicative barriers; having a previously diagnosed psychiatric disorder; and being under psychopharmacological and/or psychotherapeutic treatment.

### *Procedure*

Identification of the cases was carried out by the Medical Oncological Service of Badajoz University Hospital. Inclusion and exclusion criteria were then revised, and the programmed activity for each patient was reviewed with a view to their participation in the study when they attended the hospital for their next appointment. Once the informed consent was signed, a trained researcher conducted the clinical interview, and each participant was given the study questionnaires. All documents were completed face-to-face in the Medical Oncological Service with a researcher. The time taken to complete scales ranged from 20 to 30 minutes. Some patients needed the help of the researcher in charge of passing out the questionnaires.

Permission was obtained from the Ethics in Clinical Investigation Committee of Badajoz (approval date: 05/07/2018). Confidentiality of the information was maintained at all times following current legislation (Spanish Organic Law 3/2018, December 5, on Protection of Personal Data and Guarantee of Digital Rights).

### *Instruments and Measures*

#### *Interview and clinical history*

A clinical interview was used to assess the self-reported sociodemographic data and clinical and psychological variables of the patients. Patients' clinical histories were used to assess characteristics of the tumor, pathological anatomy, and therapeutic management variables.

#### *PNS assessment*

*Mood measures*. The patients were screened for depressive symptoms using the Beck Depression Inventory (BDI)[19] and for anxiety using the State-Trait Anxiety Inventory (STAI).[20]

- The BDI-II, validated to Spanish language,[21] assesses the symptoms of depression in the individual in the previous 2 weeks. The standard cut-off score is 14, and the presence and degree of symptoms of depression can be detected. Scores of 0 to 13 indicate no or minimal depression; scores of 14 to 19 indicate mild depression; scores of 20 to 28 indicate moderate depression; and scores of 29 to 63 indicate severe depression.
- The STAI, validated to Spanish language,[22] includes separate scales of autoevaluation, which measure two concepts of anxiety: state anxiety (S/A) and trait anxiety (T/A). Each of the two STAI scales consists of 20 items: one part of them is written in positive terms, and the other is written in negative terms. Scores of $\leq$21 indicate mild anxiety (percentile 50); scores of 22 to 31 indicate moderate anxiety (percentile 75); and scores of 32 to 60 indicate severe anxiety (percentile 99).

*QoL measurements.* The patients completed the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (3.0)[23] and the QLQ-BR23[24] questionnaires, which had been translated into Spanish and validated for use in Spain.[25]

- EORTC QLQ-C30 is a 30-item questionnaire assessing function and symptoms that affect QoL in people with cancer. It is subdivided into three scales: global health status and QoL (GHS); functional scales relating to physical functioning (PF), role functioning (RF), emotional functioning (EF), cognitive functioning (CF), and social functioning (SF); and symptom scales relating to fatigue (FA), nausea and vomiting (NV), pain (PA), dyspnea (DY), insomnia (SL),

appetite loss (AP), constipation (CO), diarrhea (DI), and financial difficulties (FI). A high score for a functional scale represents a high/healthy level of functioning, a high score for the GHS represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems. In addition, and specifically for the purpose of this study, the PA subscale was used to address pain as a symptom in the sample.

- QLQ-BR23 is a QLQ-C30 supplemental questionnaire created specifically for people with BC. It consists of 23 questions, which are subdivided into two scales: the functional scales, composed of body image (BRBI), sexual functioning (BRSEF), sexual enjoyment (BRSEE), and future perspective (BRFU), and the symptom scales, consisting of the subscales systemic therapy side effects (BRST), breast symptoms (BRBS), arm symptoms (BRAS), and upset by hair loss (BRHL). The scoring approach for QLQ-BR23 is identical in principle to that for the function and symptom scales/single items of QLQ-C30.

*Sleep complaints and disturbances measurements*. Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI),[26] and insomnia was assessed using the Insomnia Severity Index (ISI)[27] validated for use in Spain.[28]

- The PSQI was designed to measure a 1-month interval. It includes 19 self-rated questions that generate seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Component scores (range 0 to 3) are summed to provide a global sleep quality score (range 0 to 21); a score >5 indicates poor sleep quality. For the present study, we used a previously published and validated Spanish version of the PSQI.
- The ISI is a brief self-report instrument measuring the patient's perception of their insomnia. It is a reliable and valid instrument to quantify the perception of insomnia and its severity. The ISI comprises seven items assessing: (1) the severity of sleep onset (initial), (2) sleep maintenance (middle), (3) early morning awakening (terminal) problems, (4) satisfaction with current sleep pattern, (5) interference with daily functioning, (6) noticeability of impairment attributed to the sleep problem, and (7) level of distress caused by the sleep problem. Each item is rated on a $0 \pm 4$ scale, and the total score ranges from 0 to 28. A higher score suggests more severe insomnia. The total score is interpreted as follows: absence of insomnia (0 to 7), sub-threshold insomnia (8 to 14), moderate insomnia (15 to 21), and severe insomnia (22 to 28).[29]

To evaluate fatigue, we used the Fatigue Symptom Inventory (FSI).[30] It is a 14-item self-report measure designed to assess fatigue severity, fatigue frequency, perceived interference associated with fatigue, and the daily pattern of fatigue. Severity is measured with separate 11-point items that assess most, least, and average fatigue in the past week and fatigue "right now" (ítems 1 to 4). Each of these is scored as an individual item. Frequency is measured as the number of days (from 0 to 7 days) in the past week that respondents felt fatigued and the amount of each day on average respondents felt fatigued (ítems 12 and 13). Each of these is scored as an individual item. Perceived interference is measured with separate 11-point items that assess the degree to which fatigue in the past week interfered with the general level of activity, ability to bathe and dress, normal work activity, ability to concentrate, relations with others, enjoyment of life, and mood (ítems 5 to 11). These seven items are averaged to obtain an interference scale score. A score of ≥3 on the average fatigue severity item or a mean score of ≥3 on those items assessing fatigue severity in the past week is the recommended cut-off for discriminating cases of clinically meaningful fatigue from non-cases.[31]

Finally, for the subjective neuropsychological assessment, we used the Functional Assessment of Cancer Treatment, Cognitive Scale [FACT-Cog], version 3. The subjective assessment, consisting of self-report measures of cognitive complaints,[32] contains 37 items grouped into four subscales: Perceived Cognitive Impairments (PCI), Impact on Quality of Life, Comments from Others, and Perceived Cognitive Abilities on which mental sharpness, attention and concentration, memory, verbal fluency, functional interference, deficits observed by others, change of previous functioning, and impact on QoL of the patient were evaluated. Each item was rated based on the experience of the previous week, on a scale of 5, from never/not at all (0) to several times a day/a lot (4). For version 3 of FACT-Cog, the developers of the scale recommend the use of one of the four subscales, the PCI score, as the preferred result, and that which is most cited in the literature. Recently, the cut-off points for PCI have been described to classify CRCI: the 18-point PCI (cut-off point <54) and the complete 20-item PCI (cut-off point <60) were examined. Both PCI-18 and PCI-20 showed a good discriminatory capacity for classification of CRCI.[33] In the present study PCI-18 was used.

*Therapeutic management*

To evaluate the effect of the number of chemotherapy cycles, we decided to categorize the variable into ≤ 3, and ≥ 4 cycles based on the standard treatment regimen of six initial cycles after diagnosis.

*Statistical Analysis*

The statistical analysis was carried out using the SPSS 27 and jamovi 2.2.5 programs. The sociodemographic and clinical characteristics of the women studied, together with the results of the different questionnaires on the symptoms assessed, were analyzed initially from a descriptive point of view.

For the PNS group, a factorial PCA was performed with varimax rotation. The aim was to determine possible factors or underlying dimensions. The same technique was applied to a group of functional scales of QLQ-C30. The degree of consistency of the different factors was quantified by Cronbach $\alpha$ coefficients. The relations between the PNS factors detected, the QLQ-C30 factors, and the QLC-B23-Body image scale of QoL were analyzed by Pearson r coefficient.

The relations between the six variables outlined above and the clinical variables (tumor stage, adjuvant therapy, estrogen receptors, progesterone receptors, chemotherapy treatment, number of chemotherapy cycles, current situation, surgery, Ki67) were analyzed by multivariant variance (MANOVA, Pillay test), one for each clinical variable considered. This joint technical analysis was used with the aim of controlling probability of Type I error. Only in significant ($P < .05$) or close to significant cases was a detailed analysis made of the influence of the clinical variable on each dimension by one-way ANOVA. Again, only for significant cases, separate analyses were made of the influence on each of the variables involved in the dimension using Student, Mann-Whitney, one-way ANOVA, and Kruskal-Wallis tests.

## Results

Two hundred thirty-nine women participated in the present study. A description of the sociodemographic and clinical variables is given in Table 1. The average time since diagnosis of BC was $23.59 \pm 43.37$ months (median = 5, IQR = 17).

*Therapeutic Management*

The most representative therapeutic combinations are shown in Table 2.

In the chemotherapy group, the average number of cycles in our sample was $6.02 \pm 7.91$. We established a cut-off point at ≥4 cycles, which gave the following result: 59% (n = 141) of patients had received <4 cycles, and 41% (n = 98) had received ≥4 cycles. The

**TABLE 1**
Sociodemographic and Clinical Characteristics of the Patients Included in the Study (Mean Age ± Standard Deviation).

| Variable | Categories | N (%)/Mean ± SD |
|---|---|---|
| Age | | 53.21 ± 10.85 |
| Marital status | Married | 172 (72) |
| | Single | 25 (10.5) |
| | Divorced | 19 (8) |
| | Widowed | 23 (9.6) |
| Education level | No studies | 20 (8.4) |
| | Elementary school | 66 (27.6) |
| | Middle school | 31 (13) |
| | High school | 57 (23.8) |
| | Higher education | 65 (27.2) |
| Employment situation | Currently in employment | 25 (10.5) |
| | Temporary sick leave | 105 (43.9) |
| | Permanent sick leave | 19 (7.9) |
| | Unemployed | 50 (20.9) |
| | Retired | 40 (16.7) |
| Tumor staging | 0 | 10 (4.2) |
| | I | 69 (28.9) |
| | II | 87 (36.4) |
| | III | 43 (18) |
| | IV | 30 (12.6) |
| Grade | 1 | 40 (16.7) |
| | 2 | 76 (31.8) |
| | 3 | 123 (51.5) |
| Molecular subtype | Luminal A/ Luminal B *HER2* negative−like | 124 (51.9) |
| | Luminal B *HER2* positive−like/ HER2-type | 91 (38.1) |
| | Triple negative | 24 (10) |
| Current situation | Initial treatment | 173 (72.4) |
| | Relapse | 43 (18) |
| | Checkups | 23 (9.6) |
| Therapy | Neoadjuvant | 43 (18) |
| | Adjuvant | 196 (82) |
| Menopause | Natural | 100 (41.8) |
| | Drug-induced menopause | 69 (28.9) |
| | Intervention-induced menopause | 14 (5.9) |
| | Reproductive stage | 56 (23.4) |
| Treatment | Surgery | 193 (80.8) |
| | Chemotherapy | 204 (85.4) |
| | Radiotherapy | 105 (43.9) |
| | Hormonotherapy | 84 (35.1) |
| | Immunotherapy | 52 (21.8) |
| Surgical treatment | Conservative surgery | 126 (52.7) |
| | Uni- or bilateral mastectomy | 64 (26.8) |
| | Without surgical treatment | 49 (20.5) |
| Chemotherapy cycles | <4 | 141 (59) |
| | ≥4 | 98 (41) |

patients in this group were, therefore, treated with regimens of standard-dose polychemotherapy, and the majority of them (58.6%; n = 140) received a combination of two or three cytotoxic agents such as doxorubicin (anthracycline agent), cyclophosphamide (alkylating agent), and docetaxel (taxane).

**TABLE 2**
Therapeutic Combinations in the Sample.

| | n | % |
|---|---|---|
| Surgery and chemotherapy | 44 | 18.4 |
| Surgery, chemotherapy, radiotherapy, and hormonotherapy | 34 | 14.2 |
| Chemotherapy | 33 | 13.8 |
| Surgery, chemotherapy, and radiotherapy | 26 | 10.9 |
| Surgery, chemotherapy, radiotherapy, hormonotherapy, and immunotherapy | 12 | 5.1 |
| Surgery | 8 | 3.3 |
| Other combinations | 82 | 34.3 |

*Psychoneurological Symptoms*

Regarding mood, the average scores for anxiety were 18.71 ± 12.39 for S/A and 22.21 ± 9.59 for T/A. The percentages of S/A symptoms classified by level were 62.3% (n = 149) for mild anxiety, 20.5% (n = 49) for moderate anxiety, and 17.2% (n = 41) for severe anxiety. The percentage of patients with mild, moderate, or severe T/A was 59.4% (n = 142), 25.1% (n = 60), and 15.5% (n = 37), respectively.

Almost 30% (n = 71) of the women had clinically relevant depressive symptoms (cut-off point ≥14). The average of the scores from the BDI questionnaire was 10.82 ± 7.94. The levels of depression of the sample were no or minimal depression at 70.3% (n = 168), mild depression at 18.4% (n = 44), moderate depression at 7.9% (n = 19), and severe depression at 3.3% (n = 8).

Considering the sleep quality, the results of the PSQI showed a mean score of 8.48 ± 4.81. The 34.3% (n = 82) of the sample had good sleep quality, qualifying as good sleepers compared to almost two-thirds of the sample, 65.7% (n = 157), who had poor sleep quality, thus being poor sleepers.

The study of sleep disorders, concerning insomnia, determined a mean score for the sample of 7.90 ± 6.20, establishing a prevalence of insomnia in 107 of the patients (cut-off point ≥8), which corresponds to a percentage of around 45% of the sample (44.8%). In the different ISI categories, we found the following distribution: 55.2% (n = 132) had no insomnia, 29.7% (n = 71) showed subclinical insomnia, 12.1% showed moderate clinical insomnia (n = 29), and 2.9% showed severe clinical insomnia of the patients (n = 7).

About fatigue, the mean scores obtained in the three dimensions of fatigue were (1) severity: 9.17 ± 7.69, representing maximum, minimum, and average fatigue in the last week, as well as current fatigue; (2) frequency: 6.10 ± 5.27, indicating the number of days in the last week that patients felt fatigued, as well as the part of the day they felt fatigued on average; and (3) interference: 16.12 ± 17.16, which reflects the degree to which fatigue in the last week was considered to interfere with general activity level, ability to bathe and dress, normal work activity, ability to concentrate, relationships with others, enjoyment of life, and mood.

Taking into consideration the cut-off point for clinically significant fatigue (≥3 points), we found that 69% of the sample (n = 165) had scores compatible with clinically significant fatigue, indicating a high prevalence. Patients above this cut-off reported significantly greater fatigue interference, more days of fatigue on average, and fatigue in a greater proportion of each day in the last week.

Subjective neuropsychological assessment (cognitive impairment) revealed that 36.8% (n = 88) of the sample had PCI (cut-off points <54). The average score on the PCI subscales of the FACT-Cog is 53.39 ± 13.19.

*Quality of Life*

The scores for the different scales of QoL corresponding to the EORTC QLQ-C30 and EORTC QLQ-BR23 are shown in Table 3. A high score for a functional scale represents a high/healthy level of functioning, a high score for the GHS represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems. In this sense, scores were high on most QoL dimensions except for GHS and EF.

The QLQ-BR23 module assessed BC-specific symptoms, treatment-related side effects, and QoL domains affected by both disease and treatment. From a functional point of view, BRFU was the most affected scale.

Regarding symptomology, BRST and BRHL were the symptoms that most negatively affected patients' QoL.

**TABLE 3**
Values (Mean ± Standard Deviation) of the Functional and Symptoms Scales of EORTC QLQ-C30 and EORTC QLQ-BR23.

| EORTC QLQ-C30 | N = 239<br>mean ± SD |
|---|---|
| Global health status | 63.09 ± 24.57 |
| **Functional scales** | |
| Physical functioning | 78.50 ± 22.27 |
| Role functioning | 76.36 ± 28.87 |
| Emotional functioning | 73.04 ± 23.42 |
| Cognitive functioning | 78.45 ± 29.68 |
| Social functioning | 75.66 ± 26.58 |
| **Symptom scales/items** | |
| Fatigue | 31.84 ± 27.24 |
| Nausea and vomiting | 7.55 ± 16.89 |
| Pain | 29.34 ± 29.84 |
| Dyspnea | 10.72 ± 24.45 |
| Insomnia | 35.26 ± 35.72 |
| Appetite loss | 13.10 ± 24.74 |
| Constipation | 21.60 ± 30.75 |
| Diarrhea | 10.44 ± 21.96 |
| Financial difficulties | 17.04 ± 28.17 |
| **EORTC QLQ-BR23** | **Mean ± SD** |
| **Functional scales** | |
| Body image | 78.06 ± 25.62 |
| Sexual functioning | 71.40 ± 33.18 |
| Sexual enjoyment | 69.74 ± 38.90 |
| Future perspective | 54.65 ± 34.26 |
| **Symptom scales/items** | |
| Systemic therapy side effects | 27.24 ± 20.41 |
| Breast symptoms | 18.18 ± 20.79 |
| Arm symptoms | 17.86 ± 22.64 |
| Upset by hair loss | 20.54 ± 35.27 |

EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-BR23, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire. Breast Cancer scale; SD, standard deviation.

*Symptom Clusters*

A PCA was applied to the PNS-assessed group in the cluster associated with underlying factors or dimensions. The heatmap in Fig. 1 shows the correlations between the PNS. We observe a strong consistency in these, with all the correlations being high ($P < .001$ in all cases).

We also observe, however, that the PCI scores correlate negatively with the rest of the scales; that is, they score in the opposite direction. If this is inverted (PCI-reversed), we obtain a positive correlation. In this case, the Cronbach $\alpha$ value on the PNS scale is 0.768.

According to the PCA, we can account for 73.4% of the total variance through three dimensions that make up three subgroups of symptoms (PNS-1, PNS-2, and PNS-3). The first dimension clearly groups together the ST and SA scales; the second, PA, FA, and PCI; the third, SL and sleep quality. The depressive symptoms scale is explained in equal parts by PNS-1 and PNS-2. This three-dimensional cluster is illustrated in Fig. 2 in which PCI is inverted. The PNS-1 dimension has a value of $\alpha = 0.790$ (including depressive symptoms), PNS-2 (also including depressive symptoms and with PCI inverted) has a value of $\alpha = 0.663$, and PNS-3, $\alpha = 0.842$. A similar procedure was followed with the six scales on the functional level of QLQ-C30. Once again, the heatmap in Fig. 3 shows a strong consistency, with $P < .001$ in all cases and $\alpha = 0.808$.

The PCA distinguishes two dimensions (QLQ-C30-1, QLQ-C30-2) that account for 64.9% of the variance. The dimension or factor QLQ-C30-1 groups the scales GHSS, PF, and RF; the dimension QL-C30-2 groups EF and CF; and the SF scale is explained jointly by both factors.

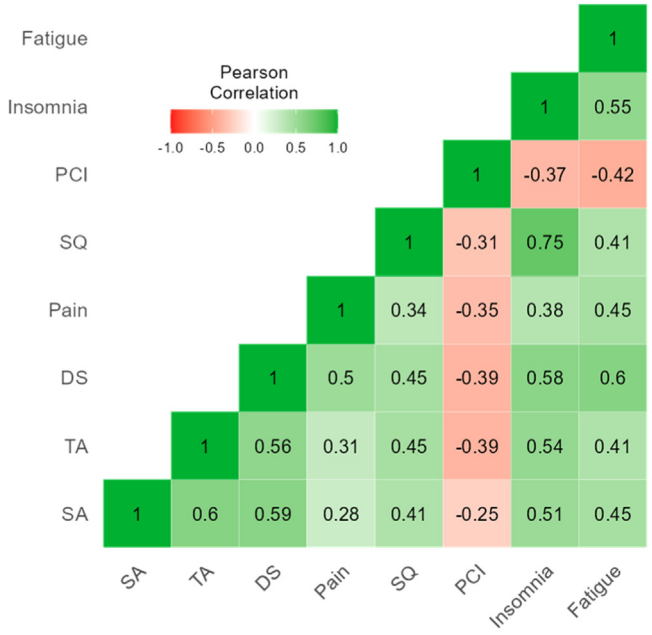


**FIG. 1.** Correlations between PNS. PCI, perceived cognitive impairment; SQ, sleep quality; DS, depressive symptoms; TA, trait anxiety; SA, state anxiety.

This two-dimensional grouping is shown in Fig. 4. The QLQ-C30-1 dimension has a value of $\alpha = 0.767$ (including SF), and QLQ-C30-2 has a value of $\alpha = 0.700$ (including SF).

*Correlations between PNS and Functional Scales QLQ-C30 and BR23*

The relations between PNS, QLQ-C30, and QlQ-BR23 were analyzed (only the BRBI functional scale, a correlating sample of this module). Table 4 shows the significant correlations (Pearson r).

Noteworthy is the correlation between PNS-2 and QLQ-C30-1, which is maximum, and is illustrated as an example in Fig. 5 through a scatterplot. It is appreciated that the higher the PNS-2 score (ie, the worse the evaluation in PCI, fatigue, and pain), the lower the average score in QLQ-C30-1 (ie, the worse the evaluation of GHSS, PF, and RF). Something very similar occurs between PNS-1 (ST and SA) and QLQ-C30-2 (EF and CF). The PNS and QLQ-C30 factors correlate with BRBI as expected.

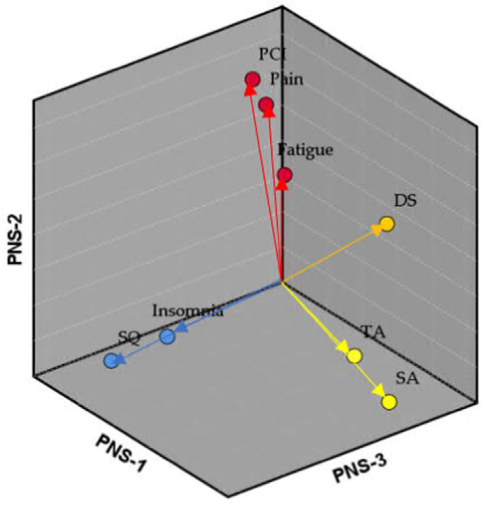


**FIG. 2.** Three-dimensional PNS cluster. DS, depressive symptoms; PCI, perceived cognitive impairment; SA, state anxiety; SQ, sleep quality; TA, Trait Anxiety.

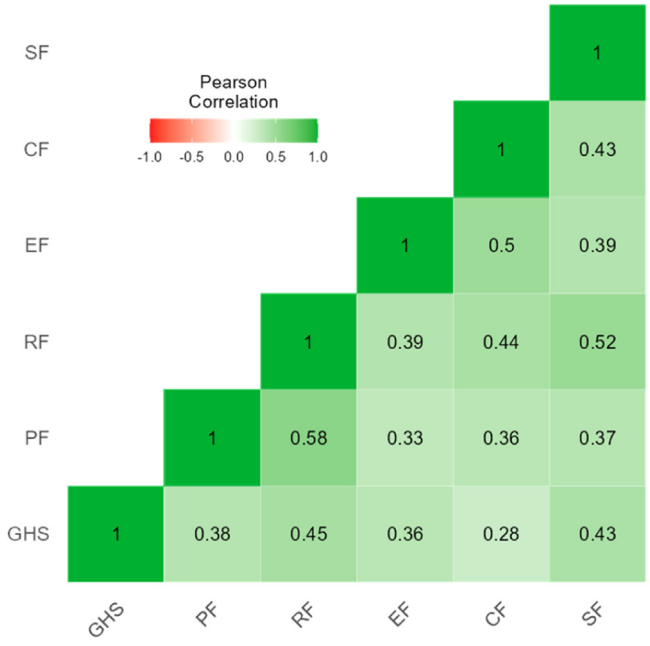


**FIG. 3.** Correlations between the QLQ-C30 functional scales. SF, social functioning; CF, cognitive functioning; EF, emotional functioning; RF, role functioning; PF, physical functioning; GHS, general health status.

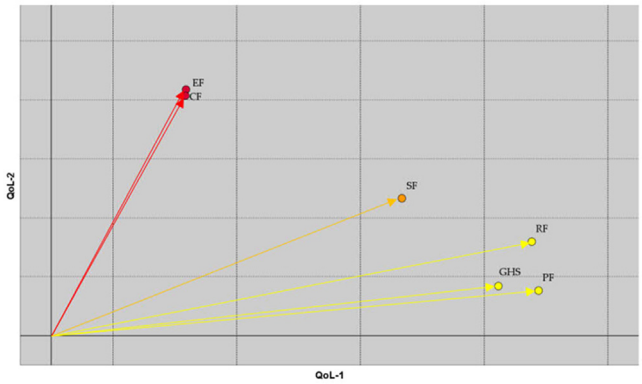


**FIG. 4.** Two-dimensional grouping of QLQ-C30 functional scales. CF, cognitive functioning; EF, emotional functioning; GHS, global health status; PF, physical functioning; RF, role functioning; SF, social functioning; QLQ-C30-1, Quality of Life Questionnaire-dimension 1; QLQ-C30-2, Quality of Life Questionnaire-dimension 2.

The six variables that relate to PNS and to functional QoL in BC (PNS-1, PN2-2, PNS-3, QLQ-C30-1, QLQ-C30-2, and BRBI) were considered jointly. For each of the clinical variables considered, a MANOVA test was applied to detect significant associations with the symptoms, summarized in these six dimensions. The result was $P = .552$ for the stage of illness, $P = .569$ for adjuvant treatment, $P = .386$ for estrogen receptors, $P = .195$ for progesterone receptors, $P = .005$ for chemotherapy treatment, $P < .001$ for number of chemotherapy cycles (up to 3 or $\geq 4$), $P = .091$ for the current situation, $P = .602$ for treatment with surgery, and $P = .105$ for Ki67. Consequently, a significant influence was detected both in chemotherapy treatment and in the number of cycles received in the PNS cluster. A result close to significance was also found for the current situation variable. These three results are analyzed in more detail.

**TABLE 4**
Correlations between Symptoms, QLQ-C30 Dimensions, and the Body image Functional Scale of QLQ-BR23.

| | PNS-1 | PNS-2 | PNS-3 | QLQ-C30-1 | QLQ-C30-2 |
|---|---|---|---|---|---|
| QLQ-C30-1 | −0.248*** | −0.497*** | −0.159* | | |
| QLQ-C30-2 | −0.492*** | −0.306*** | −0.136* | | |
| Body image | −0.367*** | −0.282*** | −0.200** | 0.354*** | 0.307*** |

*$P < .05$; **$P < .01$; ***$P < .001$, according to the Pearson correlation test.
PNS, psychoneurological symptoms; QLQ-C30-1, Quality of Life Questionnaire-dimension 1; QLQ-C30-2, Quality of Life Questionnaire-dimension 2.

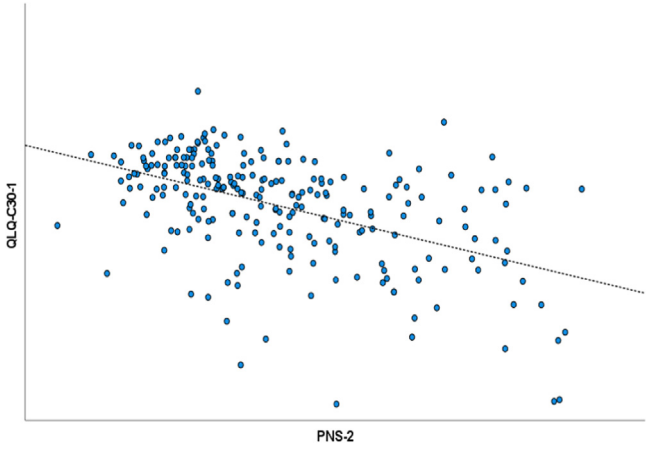


**FIG. 5.** Correlation between PNS-2 and QLQ-C30-1 dimension. PNS, psychoneurological symptoms; QLQ-C30-1, Quality of Life Questionnaire-dimension 1.

Concerning chemotherapy treatment, the separate one-way ANOVA analysis of each of the seven dimensions that summarize the symptoms gave the following results: $P = .558$ for PNS-1; $P = .546$ for PNS-2; $P = .003$ for PNS-3; $P = .166$ for QLQ-C30-1; $P = .498$ for QLQ-C30-2, and $P = .004$ for BRBI. These data demonstrate the significant relation between chemotherapy treatment and PNS-3 and its negative impact on QoL in BRBI; this relation is illustrated in the box diagram in Fig. 6.

Table 5 displays a more detailed analysis (mean ± SD) of each of the variables involved in the PNS-3 factor together with BRBI. The results of the comparisons from the t-test and Mann-Whitney test are included.

For the number of chemotherapy cycles variable, the detailed analysis gave the following results: $P = .463$ for PNS-1, $P = .002$ for PNS-2, $P = .183$ for PNS-3, $P = .021$ for QLQ-C30-1, $P = .112$ for QLQ-C30-2, and $P < .001$ for BRBI. This shows that the higher the number of chemotherapy cycles received, the higher is the score in PNS-2 (ie, the worse the evaluation in PCI, FA, and PA) and the lower is the average score in QLQ-C30-1 (the worse the evaluation of GHS, PF, and RF) and on the functional scale BRBI. The relation with PNS-2, QLQ-C30-1, and BRBI can be seen in the box diagram in Fig. 7.

Table 6 presents a more detailed analysis (mean ± SD) of each of the variables involved in the PNS-2 and QLQ-C30-1 factors together with BRBI.

Last, for the variable current situation, the results of the detailed analysis were $P = .775$ for PNS-1, $P = .432$ for PNS-2, $P = .026$ for PNS-3, $P = .340$ for QLQ-C30-1, $P = .756$ for QLQ-C30-2, and $P = .047$ for BRBI. These results determine a higher score in PNS-3 (worse evaluation in sleep quality and insomnia), in patients in checkup situations, and a lower average score in BRBI in the patients of this same group compared to patients during relapse or initial treatment. The relation with PNS-3 and BRBI is illustrated in the box diagram in Fig. 8.

Table 7 presents the detailed analysis (mean ± SD) of each of the variables involved in the PNS-3 factors together with BRBI. In this case, one-way ANOVA and the Kruskal-Wallis test were applied.

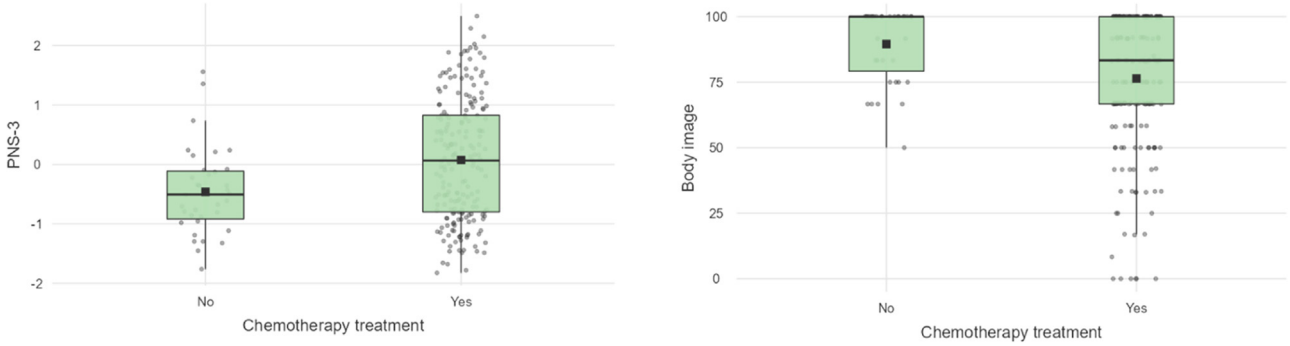


**FIG. 6.** Relationship between PNS-3, body image, and chemotherapy treatment. PNS, psychoneurological symptoms.

## Discussion

### *Prevalence of Symptoms*

Regarding the prevalence of PNS symptoms in women with BC undergoing treatment, we observed that many of the patients had fatigue (68%), depressive symptoms (30%), anxiety (37.5%), insomnia (45%), cognitive impairment (36.3%), and pain (average of 28.9 on the symptom scale).

In the literature consulted, the prevalence of fatigue in BC oscillates between 20% and 30%,[34] although some studies have reported 66%,[5] which is more in agreement with our findings. The data on depressive symptoms and anxiety are consistent with studies that determined that the prevalence of depressive symptoms is between 25% and 66%,[7,35] and anxiety, between 33% and 60%.[36,37] The prevalence of insomnia is higher in our sample with respect to recent methodological similar studies,[38] although other studies report even higher percentages (51.9%).[39] In previous studies, rates of self-informed cognitive impairment ranged between 37% and 71%.[40] Variation in the prevalence of symptoms depends on factors such as the type of instruments used, the size and characteristics of the sample, and the moment when data collection is made.

### *Symptom Clusters*

The existence of PNS clusters in women with BC has been previously established, but the symptoms in the cluster vary among different publications.[2] In our study, although all the PNS are related among themselves, the factorial analysis performed shows three subgroups of symptoms within the cluster, which were accounted for with 73.4% of the variance: state anxiety and trait anxiety (PNS-1), cognitive impairment, pain, and fatigue (PNS-2), and sleep disorders (PNS-3 [sleep quality and insomnia]). Depression is explained in equal parts by PNS-1 and PNS-2. These results support the following hypothesis: symptom clusters are made up of stable groups, are relatively independent of other groups, and can reveal specific underlying dimensions of the symptoms. The relations between the symptoms in a cluster must be stronger than the relations between the symptoms in the different groups. This idea was proposed by Kim et al,[1] although it was not statistically verified as it has been in our study.

In the systematic review conducted by So et al,[2] it was found that the symptom clusters most commonly reported by patients undergoing active oncological treatment were pain-fatigue-sleep disorders and the cluster composed of anxiety-depression-worry-sadness-nervousness-irritability, sub-groups that were also found in our study although in different dimensions. It has been demonstrated that pain is a significant factor both in fatigue and in insomnia, which might explain why in our cluster it is factorially associated with dimension PNS-2 together with fatigue and cognitive impairment, although it could well belong to PNS-3 according to the literature.[41] Cognitive impairment, which is a very significant symptom in BC patients undergoing treatment with chemotherapy, was analyzed by Sanford et al,[11] who performed a prospective study of sleep, fatigue, depression, anxiety, and cognitive impairment in BC patients. In this work, we find a similarity with ours in the dimensions PNS-1, -2, and -3. Those authors found a worse functional state, and QoL had a higher score on the symptoms scale.

Similarly, those studies that include longitudinal evaluations of symptoms report that psychological symptoms, in particular anxiety and depression, were present before, during, and/or after treatment.[42,43] It has been previously suggested that anxiety and depression coexist with pain, fatigue, and sleep disorder and that the seriousness of each group of symptoms is exacerbated by the appearance of other symptoms.[44] This coexistence has been confirmed in our study. The co-occurrence of groups or sub-groups of symptoms could be potentially caused by alterations in certain molecular pathways associated with the two mentioned groups, such as dysregulation of functioning of the hypothalamic-pituitary-adrenal axis, altered neurotransmission of serotonin, or increased production of proinflammatory cytokines.[45,46] In fact, a previous review also revealed that proinflammatory cytokines and immunity markers might be related with symptom clusters associated with cancer treatment.[47] It is likely that the symptoms in these groups are caused by the common biological pathways previously mentioned, in such a way that alterations in these pathways could lead to concurrent expression of both groups of symptoms. This pattern of shared pathways could explain why these two groups of systems frequently coexist. What does seem to be clear is that fatigue, pain (PNS-2), and insomnia (PNS-3) can have direct and indirect effects on psychological symptoms (PNS-2), which is in agreement with recent findings.[17]

It is important to note that there is wide variability in the results from the different studies due to differences in designs (transversal, longitudinal), the instruments used for measuring symptoms, the types of statistical analysis, the stage of the illness when studied, types of treatment, patients' cultures, etc., all of which make comparisons difficult. It is clear, however, that a group of PNS symptoms exists that has an important effect on QoL.

**TABLE 5**
Relation between PNS-3, Body Image, and Chemotherapy Treatment.

| | No Chemotherapy (N = 35) | Chemotherapy (N = 201) | t-test | M-W test |
|---|---|---|---|---|
| Insomnia | 5.63 ± 4.72 | 8.21 ± 6.33 | *P* = .022 | *P* = .038 |
| Sleep quality | 6.53 ± 3.56 | 8.79 ± 4.92 | *P* = .010 | *P* = .019 |
| Body image | 89.42 ± 14.20 | 76.40 ± 26.22 | *P* = .004 | *P* = .006 |

PNS, psychoneurological symptoms; M-W test, Mann-Whitney test.

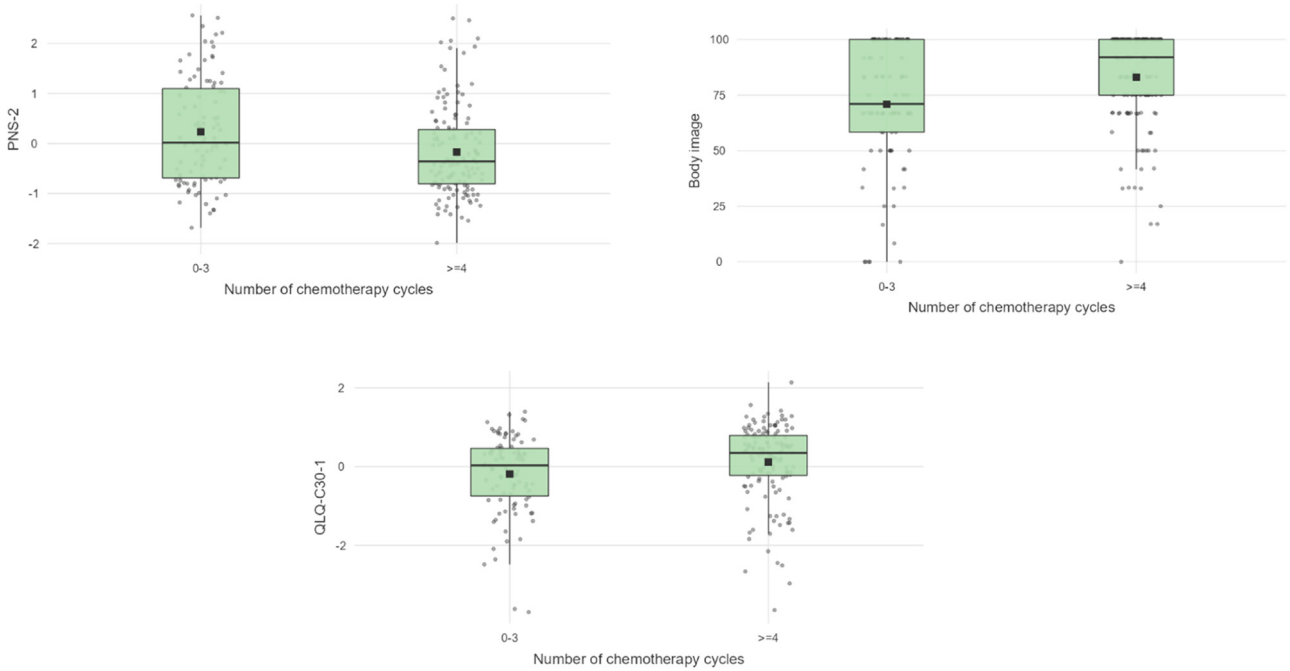


**FIG. 7.** Relationship between PNS-2, body image, QLQ-C30-1, and number of CT cycles. PNS, psychoneurological symptoms; QLQ-C30-1, Quality of Life Questionnaire-dimension 1.

**TABLE 6**
Relation between PNS-2, QLQ-C30-1, Body Image, and Number of Chemotherapy Cycles.

| | 0–3 Chemotherapy cycles (n = 98) | ≥4 Chemotherapy cycles (n = 141) | t-test | M-W test |
|---|---|---|---|---|
| Pain | 25.3 ± 26.85 | 34.22 ± 31.82 | *P* = .023 | *P* = .033 |
| Fatigue | 13.34 ± 15.92 | 19.83 ± 17.80 | *P* = .004 | *P* = .002 |
| Perceived cognitive impairment | 54.82 ± 11.73 | 52.10 ± 13.46 | *P* = .103 | *P* = .194 |
| Depressive symptoms | 10.06 ± 7.45 | 12.01 ± 8.36 | *P* = .063 | *P* = .078 |
| Global health status | 66.091 ± 23.64 | 58.51 ± 24.80 | *P* = .019 | *P* = .012 |
| Physical functioning | 80.98 ± 22.85 | 75.29 ± 19.73 | *P* = .050 | *P* = .003 |
| Role functioning | 77.23 ± 28.46 | 75.35 ± 29.10 | *P* = .626 | *P* = .518 |
| Social functioning | 75.90 ± 26.64 | 76.77 ± 25.18 | *P* = .802 | *P* = .984 |
| Body image | 83.00 ± 21.92 | 70.85 ± 28.17 | P < .001 | *P* < .001 |

PNS, psychoneurological symptoms; QLQ-C30-1, Quality of Life Questionnaire-dimension 1; M-W test, Mann-Whitney test.

*QoL*

In the QoL analysis, our patients presented lower scores than those found in the nononcological population both on the GHS, with similar scores to those found by other authors,[48,49] and on the EF scale, also similar to the results from other studies.[50,51] On the functional scales, EF showed the highest negative repercussion, in agreement with the results obtained in emotional symptomatology in our sample. The worst results on the symptoms scales were insomnia, fatigue, and pain, which coincided with other studies,[50,51] and constipation, which is also in agreement with a recent study.[52] In the specific module QLQ-BR23, the patients obtained a score of 53.81 on

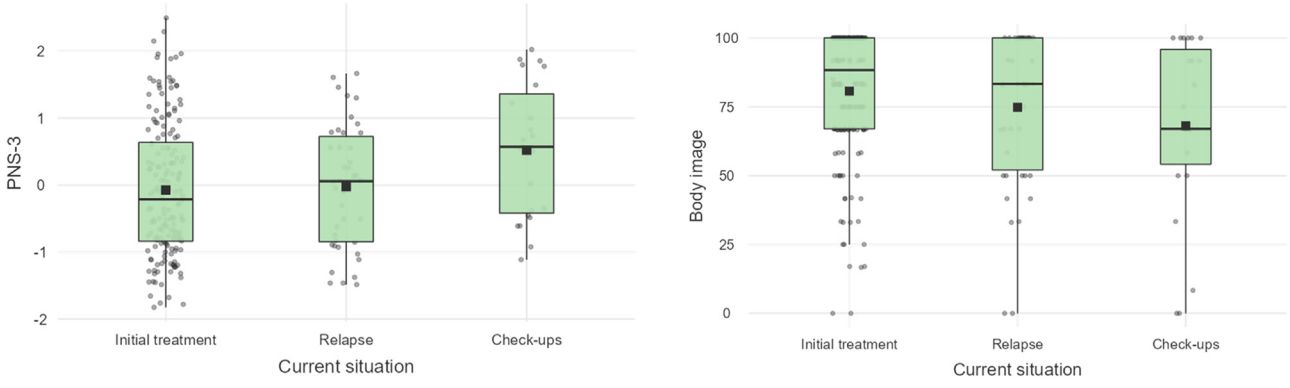


**FIG. 8.** Relation between PNS-3, body image, and current situation. PNS, psychoneurological symptoms.

**TABLE 7**
Relation between PNS-3, Body Image, and Current Situation.

| | Initial (N = 173) | Relapse (n = 43) | Checkups (n = 23) | ANOVA | KW test |
|---|---|---|---|---|---|
| Insomnia | 7.442 ± 6.07 | 8.19 ± 6.66 | 9.96 ± 5.63 | *P* = .169 | *P* = .118 |
| Sleep quality | 7.99 ± 4.59 | 8.69 ± 5.10 | 11.26 ± 4.99 | *P* = .008 | *P* = .015 |
| Body Image | 80.70 ± 23.26 | 74.81 ± 27.40 | 68.13 ± 32.23 | *P* = .047 | *P* = .088 |

PNS, psychoneurological symptoms; KW test, Kruskal-Wallis test.

the future perspective scale, which was a similar figure to those reported in recent publications, this scale being the most affected.[50,51]

A factorial analysis was also performed with the different dimensions of the questionnaires on QoL, and two dimensions were found: a mainly physical functional dimension (FF and RF) and a cognitive-emotional one (EF and CF). These dimensions correlate with the three PNS sub-groups found, which corroborates the fact that there exists in our BC patients a functional condition both on a physical and a cognitive-emotional level. We can therefore state that QoL is worse in BC patients with higher degrees of symptoms than in those with lower degrees of symptoms, which is in line with the results from the scientific literature, and with the view that these concurrent symptoms are the cause of reduced QoL and functional state in BC patients.[17,53]

*Relation between Symptoms and QoL*

In the research on symptom clusters carried out by Dong et al,[54] the authors found three symptom sub-groups similar to our dimensions. Group PNS-1, which they named the emotional group, was a stronger predictor of general QoL than the other groups. The fatigue-pain group was a stronger predictor of general health (GHS scale) than the other groups. PNS-2, which they named cognitive, and fatigue-pain predicted physical functioning (PF scale), role functioning (RF scale), and social functioning (SF scale). These results coincide with those obtained in our study, given that the correlation found between PNS-2 and QLQ-C30-1 was maximum: the higher the score in PNS-2 (ie, the worse the evaluation of pain, fatigue, and cognitive impairment), the lower the average score in QLQ-C30-1 (ie, the worse the evaluation of PF and RF). Something very similar occurred between PNS-1 (ST and SA) and QLQ-C30-2 (EF and CF) whose correlation is maximum, although there is also a correlation with QLQ-C30-1. In contrast to Dong et al,[54] although the emotional sub-group PNS-1 is an important predictor, in our case the PNS-2 is a stronger predictor of general QoL than the other sub-groups or dimensions.

Each isolated symptom influences the deterioration of patients' QoL, but when we view the symptoms as a group, their impact is even more significant. All the symptoms that form part of the PNS group and the functional scales of QoL are correlated between themselves. Our study focuses on a group of patients with simultaneous risk of eight PNS while undergoing cancer treatment that have serious repercussions on QoL. It has been previously reported that patients with high symptomatic intensity experienced the most serious limitations in functional performance in all types of daily activities.[12] Similarly, Miaskowski et al[55] reported that patients in the subgroup of high intensity of symptoms had lower scores for QoL and that the sub-group of all the patients with low intensity had better results for QoL and functional state.

*Relation between Symptoms and Clinical-Type Variables*

Finally, we propose to determine the relationship between different clinical variables and the symptom sub-groups in,tending to find predictors of these sub-groups. A relation was found between chemotherapy and the PNS-3 group (specifically, insomnia and sleep quality), as well as with body image. Moreover, a relationship was established between the number of chemotherapy cycles and the PNS-2 group of symptoms (ie, with pain, fatigue, and cognitive impairment). Chemotherapy has been shown to present adverse effects, but in addition, patients experience multiple concurrent physical, emotional, and cognitive symptoms related to the treatment and/or the illness itself, negatively affecting QoL in our sample in the same way as that described by other authors.[43,56]

Chemotherapy as a method of treatment has been described as a predictor of PNS intensity.[6,7] It has been established as a significant predictor of PNS clusters of a somatic nature (ie, pain, fatigue, and sleep disorders) over time, and the application of chemotherapy cycles in the month previous to the detection of the symptoms can predict more intense somatic symptoms, including pain, fatigue, and sleep disorders.[57] Our analysis, both on separate symptoms and on clusters, enabled us to determine that treatment and number of chemotherapy cycles are predictors both in PNS-3 (sleep quality and insomnia) and in PNS-2 (pain, fatigue, and cognitive impairment, the latter being in the analysis of the cluster, as in PNS-1).

Concerning PNS-3 and PNS-2, it has been demonstrated that regardless of the symptoms analyzed, sleep disorders, pain, cognitive impairment, and fatigue are present in women diagnosed with BC undergoing treatment with chemotherapy. Trudel-Fitzgerald et al,[58] on the evolution of symptoms in the 18 months following administration of chemotherapy, found that the patients who did not receive chemotherapy had significantly lower scores than the chemotherapy patients, lower levels of fatigue, compared to the other treatment groups, and lower levels of pain.

For PNS-1 (state anxiety and trait anxiety), in the separate analysis, no relation with clinical variables was observed, although there was a relation in the group analysis, and so this dimension of a more psychologically emotional nature, when it appears grouped with other symptoms, contributes to the cluster, worsening the symptoms. There is, therefore, a clear worsening of PNS-2 and PNS-3 when PNS-2 intervenes in the cluster. The anxiety symptoms in their two dimensions are also linked to chemotherapy treatment, additionally correlated with the number of cycles received, although as stated before, in the group analysis of the cluster. Regarding depressive symptomatology, it has already been pointed out that factorially this was explained both by PNS-1 and PNS-2.

From the data analyzed, we observe that treatment for BC, though efficient, generates a series of secondary effects that can negatively affect QoL of patients.[11]

Analysis of the current situation shows that patients receiving checkups had higher scores in PSQI; that is, they presented worse sleep quality than patients beginning treatment, and an association was found between the current checkup situation and clinical insomnia. We found little evidence of this occurrence, which may be explained by the relation with time since diagnosis, time since the commencement of chemotherapy and/or other treatments, and uncertainty and fear caused by the possible reappearance of the illness at each checkup. In this sense, Desai et al[59] found a greater prevalence of insomnia depending on the time passed. Therefore, women who had been diagnosed with BC between 2 and 5 years previously were significantly more likely to report insomnia than those with diagnoses of 2 years or less.

Among the limitations related to the design is the impossibility of inferior causal mechanisms. A longitudinal follow-up study could have allowed us to determine the influence of different factors on

PNS and QoL at different times of the disease. However, our efforts were focused on recruiting as many BC patients as possible. In addition, objective tests could have been included to determine the level of cognitive impairment in a complementary way to the subjective tests. The strengths of our research must also be highlighted. This study has made it possible to describe and analyze the characteristics of different groups of generalizable symptoms. Likewise, consistency has been found between the groups of symptoms identified and the data published in the literature, being able to identify different symptom profiles in women with BC undergoing treatment.

## Conclusion

The present study has identified a specific pattern of grouped symptoms in a PNS cluster with different underlying dimensions that negatively influence the QoL of survivors of BC. Through a factorial analysis of data, three dimensions were observed: dimension 1, which corresponds to psychoemotional symptoms (state of anxiety and anxiety trait); dimension 2, which corresponds to symptoms of pain, fatigue, and cognitive impairment; and dimension 3, which corresponds to symptoms related to sleep disturbance. This cluster and its grouped dimensions are concurrent during the active process of oncological treatment and make up an indissoluble unit with disturbing repercussions on emotional, physical cognitive, and social functioning. Chemotherapy as a treatment method has been described as a predictor of the intensity of the cluster of PNS. We conclude that QoL is lower in patients with BC with higher levels of symptoms and that these concurrent symptoms are the cause of reduced QoL and functional state.

Implications for Practice

It is important to raise awareness among professionals and patients about the existence of a cluster of PNS, the patient's profile, as well as the factors that exacerbate them. This will allow them to be treated more effectively and comprehensively.

## ROR (Research Organization Registry)

https://ror.org/0174shg90

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Duran reports financial support, equipment, drugs, or supplies, travel, and writing assistance were provided by Extremadura Government.

## Funding

Supported by grant No. IB18101 (Support to the Research Projects in the R&D&I Public Centers in Comunidad Autónoma de Extremadura). Consejería de Economía e Infraestructuras. Junta de Extremadura (Spain), and the European Regional Development Fund.

## Acknowledgments

To all patients and professionals involved in the study. Without the contribution of all of them, it would not have been possible. We thank the Oncology Unit of the Badajoz University Hospital and Asociación Oncológica Extremeña for their collaboration in carrying out this study.

## References

1. Kim HJ, McGuire DB, Tulman L, Barsevick AM. Symptom clusters: concept analysis and clinical implications for cancer nursing. *Cancer Nurs*. 2005;28(4):270–282.
2. So WKW, Law BMH, Ng MSN, et al. Symptom clusters experienced by breast cancer patients at various treatment stages: a systematic review. *Cancer Med*. 2021;10(8):2531–2565. https://doi.org/10.1002/cam4.3794.
3. Miaskowski C, Barsevick A, Berger A, et al. Advancing symptom science through symptom cluster research: expert panel proceedings and recommendations. *J Natl Cancer Inst*. 2017;109(4):1–9. https://doi.org/10.1093/jnci/djw253.
4. Dodd MJ, Miaskowski C, Paul SM. Symptom clusters and their effect on the functional status of patients with cancer. *Oncol Nurs Forum*. 2001;28.
5. Kim HJ, Barsevick AM, Tulman L, McDermott PA. Treatment-related symptom clusters in breast cancer: a secondary analysis. *J Pain Symptom Manage*. 2008;36(5):468–479. https://doi.org/10.1016/j.jpainsymman.2007.11.011.
6. Kim HJ, Barsevick AM, Tulman L. Predictors of the intensity of symptoms in a cluster in patients with breast cancer. *J Nurs Scholarsh*. 2009;41(2):158–165. https://doi.org/10.1111/j.1547-5069.2009.01267.x.
7. Lee L, Ross A, Griffith K, Jensen RE, Wallen GR. Symptom clusters in breast cancer survivors: a latent class profile analysis. *Oncol Nurs Forum*. 2020;47(1):89–100. https://doi.org/10.1188/20.ONF.89-100.
8. Cáceres M, Pérez-Civantos D, Guerrero-Martín J, Delgado M, Jurado C, Durán-Gómez N. Depressive symptoms and quality of life associated with the use of monoclonal antibodies in breast cancer treatment. *Oncol Nurs Forum*. 2021;48(5):535–545. https://doi.org/10.1188/21.onf.535-545.
9. Kim JH, Paik HJ, Jung YJ, et al. A prospective longitudinal study about change of sleep, anxiety, depression, and quality of life in each step of breast cancer patients. *Oncol*. 2019;97(4):245–253. https://doi.org/10.1159/000500724.
10. Bjerkeset E, Röhrl K, Schou-Bredal I. Symptom cluster of pain, fatigue, and psychological distress in breast cancer survivors: prevalence and characteristics. *Breast Cancer Res Treat*. 2020;180(1):63–71. https://doi.org/10.1007/s10549-020-05522-8.
11. Sanford SD, Beaumont JL, Butt Z, Sweet JJ, Cella D, Wagner LI. Prospective longitudinal evaluation of a symptom cluster in breast cancer. *J Pain Symptom Manage*. 2014;47(4):721–730. https://doi.org/10.1016/j.jpainsymman.2013.05.010.
12. Kim HJ, Barsevick AM, Beck SL, Dudley W. Clinical subgroups of a psychoneurologic symptom cluster in women receiving treatment for breast cancer: a secondary analysis. *Oncol Nurs Forum*. 2012;39(1). https://doi.org/10.1188/12.ONF.E20-E30.
13. Durán-Gómez N, López-Jurado CF, Nadal-Delgado M, Pérez-Civantos D GMJ, C M. Chemotherapy-related cognitive impairment in patients with breast cancer based on functional assessment and NIRS analysis. *J Clin Med*. 2022;11:2363. https://doi.org/10.3390/jcm11092363.
14. Lenz ER, Suppe F, Gift AG, Pugh LC, Miligan RA. Collaborative development of middle-range nursing theories: toward a theory of unpleasant symptoms. *Adv Nurs Sci*. 1995;17(3):1–13.
15. Hess LM, Insel KC. Chemotherapy-related change in cognitive function: a conceptual model. *Oncology Nursing Forum*. 2007;34.
16. Myers JS. Comparison of the theory of Unpleasant Symptoms. *Oncol Nurs Forum*. 2009;36(1):E1–E10.
17. Nho JH, Kim SR, Park MH, Kweon SS. Symptom clusters and quality of life in breast cancer survivors after cancer treatment in a tertiary hospital in Korea. *Eur J Cancer Care (Engl)*. 2018;27(6):1–9. https://doi.org/10.1111/ecc.12919.
18. Cáceres MC, Nadal-Delgado M, López-Jurado C, Pérez-Civantos D, Guerrero-Martín J, Durán-Gómez N. Factors related to anxiety, depressive symptoms and quality of life in breast cancer. *Int J Environ Res Public Health*. 2022;19(6). https://doi.org/10.3390/ijerph19063547.
19. Beck AT, Steer RA, Brown G. Beck Depression Inventory−II (BDI-II). *APA PsycTests*. 1996. https://doi.org/10.1037/t00742-000.
20. Spielberger CD, Gorsuch RL, Lushene RE. *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press; 1970.
21. Sanz J, Perdigón AL, Vázquez C. Spanish adaptation of the Beck Depression Inventory-II (BDI-II): 3. Psychometric features in patients with psychological disorders. *Clin Salud*. 2003;14(3):249–280.
22. Buela-Casal G, Guillén-Riquelme A, Seisdedos Cubero N. State Trait Anxiety Inventory (STAI): Psychometric Analysis and Functioning in a Sample of Drug Addicts and controls, 8th ed. Madrid: TEA ediciones; 2011.
23. Aaronson N, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365–376. https://doi.org/10.1093/jnci/85.5.365.
24. Sprangers MA, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. *J Clin Oncol*. 1996;14(10):2756–2768. https://doi.org/10.1200/JCO.1996.14.10.2756.
25. Arraras JI, Arias F, Tejedor M, et al. The EORTC QLQ-C30 (version 3.0) Quality of Life Questionnaire: validation study for Spain with head and neck cancer patients. *Psychooncology*. 2002;11(3):249–256. https://doi.org/10.1002/pon.555.
26. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ, Buysse DJ, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28:193–213.
27. Morin CM. *Insomnia: Psychological Assessment and Management*. New York, NY: Guilford Press; 1993.
28. Sierra JC, Guillén Serrano V, Santos Iglesias P. Insomnia Severity Index: algunos indicadores acerca de su fiabilidad y validez en una muestra de personas mayores. *Rev Neurol*. 2008;47(11):566. https://doi.org/10.33588/rn.4711.2008221.
29. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep*. 2011;34(5):601–608. https://doi.org/10.1093/sleep/34.5.601.
30. Hann DM, Denniston MM, Baker F. Measurement of fatigue in cancer patients: further validation of the Fatigue Symptom Inventory. *Qual Life Res*. 2000;9(7):847–854. https://doi.org/10.1023/A:1008900413113.

31. Donovan KA, Jacobsen PB, Small BJ, Munster PN, Andrykowski MA. Identifying clinically meaningful fatigue with the Fatigue Symptom Inventory. *J Pain Symptom Manage*. 2008;36(5):480–487. https://doi.org/10.1016/j.jpainsymman.2007.11.013.
32. Wagner LI, Sweet J, Butt Z, Lai J, Cella D. Measuring patient self-reported cognitive function: development of the functional assessment of cancer therapy-cognitive function instrument. *J Support Oncol*. 2009;7(6):W32–W39.
33. Van Dyk K, Crespi CM, Petersen L, Ganz PA. Identifying cancer-related cognitive impairment using the FACT-Cog perceived cognitive impairment. *JNCI Cancer Spectr*. 2020;4(1):2019–2021. https://doi.org/10.1093/jncics/pkz099.
34. Ruiz-Casado A, Álvarez-Bustos A, de Pedro CG, Méndez-Otero M, Romero-Elías M. Cancer-related fatigue in breast cancer survivors: a review. *Clin Breast Cancer*. 2021;21(1):10–25. https://doi.org/10.1016/j.clbc.2020.07.011.
35. Okati-Aliabad H, Ansari-Moghadam A, Mohammadi M, Kargar S, Shahraki-Sanavi F. The prevalence of anxiety and depression and its association with coping strategies, supportive care needs, and social support among women with breast cancer. *Support Care Cancer*. 2021. https://doi.org/10.1007/s00520-021-06477-2. 0123456789.
36. Civilotti C, Botto R, Maran DA, De Leonardis B, Bianciotto B, Stanizzo MR. Anxiety and depression in women newly diagnosed with breast cancer and waiting for surgery: Prevalence and associations with socio-demographic variables. *Med*. 2021;57(5). https://doi.org/10.3390/medicina57050454.
37. Zainal NZ, Ng CG, Wong A, Andrew B, Mohd Taib NA, Low SY. Prevalence of depression, trait anxiety, and social support during the diagnostic phases of breast cancer. *J Taibah Univ Med Sci*. 2021;16(4):497–503. https://doi.org/10.1016/j.jtumed.2021.01.013.
38. Haque R, Hsu JW, Avila C, Olmstead R, Carroll JE, Irwin MR. Insomnia and susceptibility to depressive symptoms and fatigue in diverse breast cancer survivors. *J Women's Heal*. 2021;30(11):1604–1615. https://doi.org/10.1089/jwh.2019.8135.
39. Liou KT, Ahles TA, Garland SN, et al. The relationship between insomnia and cognitive impairment in breast cancer survivors. *JNCI Cancer Spectr*. 2019;3(3):1–8. https://doi.org/10.1093/jncics/pkz041.
40. Janelsins MC, Heckler CE, Peppone LJ, et al. Cognitive complaints in survivors of breast cancer after chemotherapy compared with age-matched controls: an analysis from a nationwide, multicenter, prospective longitudinal study. *J Clin Oncol*. 2017;35(5):506–514. https://doi.org/10.1200/JCO.2016.68.5826.
41. Beck SL, Schwartz AL. Unrelieved pain contributes to fatigue and insomnia. *Oncology Nursing Society's 25th Congress*. San Antonio, TX27, ; 2000350–351.
42. Chow S, Wan BA, Pidduck W, et al. Symptom clusters in patients with breast cancer receiving radiation therapy. *Eur J Oncol Nurs*. 2019;42(July):14–20. https://doi.org/10.1016/j.ejon.2019.07.004.
43. Li H, Sereika SM, Marsland AL, Conley YP, Bender CM. Symptom clusters in women with breast cancer during the first 18 months of adjuvant therapy. *J Pain Symptom Manage*. 2020;59(2):233–241. https://doi.org/10.1016/j.jpainsymman.2019.10.002.
44. Fiorentino L, Rissling M, Liu L, Ancoli-Israel S. The symptom cluster of sleep, fatigue and depressive symptoms in breast cancer patients: severity of the problem and treatment options. *Drug Discov Today Dis Model*. 2011;8(4):167–173.
45. Clevenger SS, Malhotra D, Dang J, Vanle B, IsHak WW. The role of selective serotonin reuptake inhibitors in preventing relapse of major depressive disorder. *Ther Adv Psychopharmacol*. 2018;8(1):49–58.
46. Kwekkeboom KL, Tostrud L, Costanzo E, et al. The role of inflammation in the pain, fatigue, and sleep disturbance symptom cluster in advanced cancer. *J Pain Symptom Manage*. 2018;55(5):1286–1295.
47. Kelly DL, Dickinson K, Hsiao CP, et al. Biological basis for the clustering of symptoms. *Semin Oncol Nurs*. 2016;32(4):351–360.
48. Villar RR, Fernández SP, Garea CC, Pillado MTS, Barreiro VB, Martín CG. Quality of life and anxiety in women with breast cancer before and after treatment. *Rev Lat Am Enfermagem*. 2017;25:e2958. https://doi.org/10.1590/1518-8345.2258.2958.
49. Montagnese C, Porciello G, Vitale S, et al. Quality of life in women diagnosed with breast cancer after a 12-month treatment of lifestyle modifications. *Nutrients*. 2020;13(1):136.
50. Konieczny M, Cipora E, Sygit K, Fal A. Quality of life of women with breast cancer and socio-demographic factors. *Asian Pacific J Cancer Prev*. 2020;21(1):185.
51. Mejía-Rojas ME, Contreras-Rengifo A, Hernández-Carrillo M. Calidad de vida en mujeres con cáncer de mama sometidas a quimioterapia en Cali, Colombia. *Biomédica*. 2020;40(2):349–361.
52. Montagnese C, Porciello G, Vitale S, et al. Quality of life in women diagnosed with breast cancer after a 12-month treatment of lifestyle modifications. *Nutrients*. 2021;13(1):1–15. https://doi.org/10.3390/nu13010136.
53. Dodd MJ, Cho MH, Cooper BA, Miaskowski C. The effect of symptom clusters on functional status and quality of life in women with breast cancer. *Eur J Oncol Nurs*. 2010;14(2):101–110.
54. Dong ST, Costa DSJ, Butow PN, et al. Symptom clusters in advanced cancer patients: an empirical comparison of statistical methods and the impact on quality of life. *J Pain Symptom Manage*. 2016;51(1):88–98.
55. Miaskowski C, Cooper BA, Paul SM, et al. Subgroups of patients with cancer with different symptom experiences and quality-of-life outcomes: a cluster analysis. *Oncol Nurs Forum*. 2006;33.
56. Starkweather A, Kelly DL, Thacker L, Wright ML, Jackson-Cook CK, Lyon DE. Relationships among psychoneurological symptoms and levels of C-reactive protein over 2 years in women with early-stage breast cancer. *Support Care Cancer*. 2017;25(1):167–176.
57. Thomas BC, Waller A, Malhi RL, et al. A longitudinal analysis of symptom clusters in cancer patients and their sociodemographic predictors. *J Pain Symptom Manage*. 2014;47(3):566–578. https://doi.org/10.1016/j.jpainsymman.2013.04.007.
58. Trudel-Fitzgerald C, Savard J, Ivers H. Evolution of cancer-related symptoms over an 18-month period. *J Pain Symptom Manage*. 2013;45(6):1007–1018.
59. Desai K, Mao JJ, Su I, et al. Prevalence and risk factors for insomnia among breast cancer patients on aromatase inhibitors. *Support Care Cancer*. 2013;21(1):43–51.