The Breast 23 (2014) 697–709

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Review

# Impact of breast cancer treatments on sleep disturbances – A systematic review

Ana Rute Costa [a, b], Filipa Fontes [a, b], Susana Pereira [b, c], Marta Gonçalves [a, b, d], Ana Azevedo [a, b], Nuno Lunet [a, b, *]

[a] Department of Clinical Epidemiology, Predictive Medicine and Public Health, University of Porto Medical School, Porto, Portugal
[b] EPIUnit – Institute of Public Health of the University of Porto (ISPUP), Porto, Portugal
[c] Department of Neurology, Portuguese Oncology Institute, Porto, Portugal
[d] Department of Psychiatry and Sleep Medicine Center, CUF Porto Hospital, Porto, Portugal

ARTICLE INFO

*Article history:*
Received 14 April 2014
Received in revised form
6 August 2014
Accepted 10 September 2014
Available online 11 October 2014

*Keywords:*
Breast neoplasms
Antineoplastic protocols
Sleep
Systematic review

ABSTRACT

Sleep disturbances are highly prevalent in women with breast cancer; side effects of cancer treatment may worsen pre-existing sleep problems and have been pointed to as important determinants of their incidence. Therefore, we aimed to assess the association between different types of breast cancer treatment and sleep disturbances, through a systematic review. Medline (using PubMed), CINAHL Plus with full text, PsycINFO and Cochrane Central Register of Controlled Trials (Central) were searched from inception to January 2014. Studies that evaluated samples of women with breast cancer, assessed sleep disturbances with standardized sleep-specific measures, and provided data for different cancer treatments were eligible. A total of 12 studies met the inclusion criteria. Three studies evaluated insomnia, five studies assessed sleep quality, two provide data on general sleep disturbances and two analysed specific sleep parameters. Women submitted to chemotherapy, or radiotherapy, tended to report higher levels of sleep disturbances. More heterogeneous findings were observed regarding the effect of surgical treatment and hormonal therapy. However, a sound assessment of the impact of these treatments was hampered by differences across studies regarding the outcomes assessed, reporting bias and the fact that most studies did not control for the effect of potential confounders. The present review highlights the potential relation between breast cancer treatments and sleep disturbances, particularly of chemotherapy, though more robust evidence is needed for a proper understanding of these associations.



## Introduction

In the last decades, the trends towards earlier detection of breast cancer and use of more effective treatments have resulted in higher incidence and improved survival, along with lower mortality rates [1–3]. Currently, breast cancer is one of the most frequent, with an estimated 1.7 million new cases diagnosed in 2012, corresponding to 25% of all cancers among women [4]. It is also a major contributor to the overall number of disability-adjusted life-years (DALYs) lost due to oncological diseases. In countries with a very high human development index, the years of life lived with disability account for over one-third of the age-adjusted DALYs due to breast cancer [5], which highlights the importance of a comprehensive assessment of its burden.

Sleep disorders are defined as a specific diagnostic of a wide range of problems characterized by the symptoms of insomnia, excessive day sleepiness and/or abnormal movements, behaviours, or sensations [6]. However, different terms related to sleep disorders have been used in the literature, namely sleep disturbances, insomnia, impaired sleep, sleep patterns and sleep-wake disturbances. Since most of the studies in this topic include the evaluation of sleep disorders, global sleep quality or other sleep characteristics, sleep disturbances have been previously used to name all sleep-related outcomes [7].

* Corresponding author. Departamento de Epidemiologia Clínica, Medicina Preditiva e Saúde Pública, Faculdade de Medicina da Universidade do Porto, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal. Tel.: +351 225 513 652; fax: +351 222 513 653.
*E-mail address:* nlunet@med.up.pt (N. Lunet).

http://dx.doi.org/10.1016/j.breast.2014.09.003
0960-9776/

Breast cancer patients often complain of sleep problems; it is estimated that the prevalence of poor sleep in breast cancer patients range from 20 to 70% [8], depending on the study design and method of assessment. The proportion of sleep disturbances in this population is higher than the observed in healthy adults [9,10], and in other oncological patients [11]. These findings are particularly relevant since sleep disturbances have a negative impact on the physiological and psychological functions, including immune function [12], cognitive impairment [13], depression [14] and fatigue [15], being likewise a strong predictor of different measures of quality of life in this population [16].

The aetiology of sleep disturbances in breast cancer patients is multi-factorial; in fact, demographic, environmental and lifestyle factors, psychological disturbances and comorbid medical disorders have been pointed to as main factors contributing for its occurrence [8,17,18]. Cancer-related treatments, and their wide range of side effects, are other important feature frequently associated with the occurrence of sleep disturbances [19,20]. In addition, breast cancer diagnosis and associated treatments, may also contribute for worsening pre-existing sleep problems [21].

Therefore, we aimed to assess the relation between different types of breast cancer treatment and sleep disturbances, through a systematic review of the published evidence.

## Methods

We searched Medline (using PubMed), CINAHL Plus with full text, PsycINFO and Cochrane Central Register of Controlled Trials (Central), from inception to January 2014, with the following search expression: (sleep* OR insomnia OR circadian rhythm OR parasomnia OR hypersomnia OR awakening OR somnolence OR drowsiness OR wakefulness) AND breast cancer. Searches in CINAHL Plus with full text were expanded to also include related words.

Observational and experimental studies addressing the effect of breast cancer treatments (*i.e.*, surgical treatment, chemotherapy, radiotherapy and hormonal therapy) on sleep disturbances were eligible. There were no language restrictions.

The exclusion criteria were the following: 1) studies not involving humans (*in vitro* or research conducted in animals); 2) case reports, qualitative research studies, non-systematic reviews or reviews not addressing the impact of breast cancer treatments on sleep disturbances, guidelines, conference or meeting abstracts and theses; 3) studies not involving women with breast cancer; 4) studies addressing the role of sleep disturbances as a risk factor for breast cancer; 5) studies not providing data on sleep disturbances evaluated with standardized sleep-specific measures, such as sleep questionnaires with established psychometric properties of validity and reliability, sleep diary, actigraphy or polysomnography; 6) studies not presenting quantitative data on sleep measures for different breast cancer treatments.

In addition, we excluded all studies that only evaluated circadian phase markers, including melatonin and core body temperature, as well as cortisol and other endocrine hormones. This is because there is insufficient evidence to recommend circadian phase markers for routine clinical evaluation of circadian rhythm sleep disorders, as some of these biomarkers are strongly affected by many other factors that may mask the underlying circadian signals [22–24].

After the identification of potentially relevant references of original studies and the exclusion of multiple reports of the same article, we performed an initial screening of the reference list based on their titles and abstracts. Further, we conducted a detail assessment of the full texts and extracted data from those that met the selection criteria. The reference lists of the studies selected for inclusion in the systematic review were also screened, following the same criteria, to identify other potentially eligible reports.

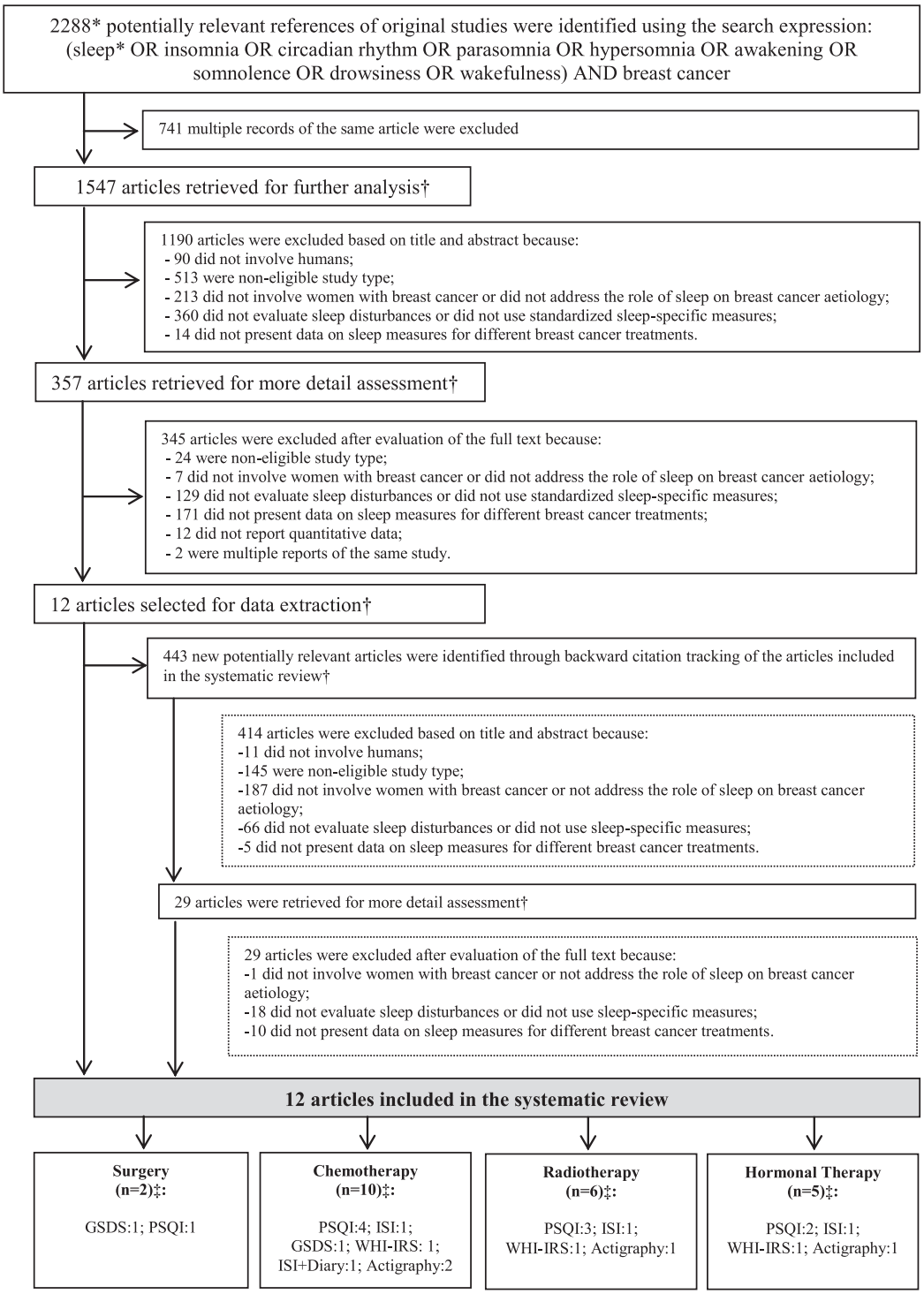
From each paper selected for the systematic review, we collected data regarding the country where the study was conducted, the type of study (clinical trial, cohort, case–control, cross-sectional), sample characteristics (sample size, age, cancer stage, time since diagnosis), instruments used to assess sleep disturbances, estimates of the association between breast cancer treatments and sleep characteristics, or the necessary information to compute them, and strategies used to control confounding, whenever applicable. When multiple reports from the same study were identified, we extracted data from the report providing the most detailed and/or valid estimates of the effects of cancer treatments on sleep. Regarding prospective studies with evaluations at different moments after baseline, only the results corresponding to the longest follow-up were extracted.

The screening of the reference lists, selection of papers for the review and data extraction, were accomplished independently by two researchers (ARC, FF), following predefined criteria. Discrepancies in the assessment performed by the two reviewers were resolved by consensus or involving a third researcher (NL). A detailed flowchart of the systematic review is presented as Fig. 1.

Due to the heterogeneity of the methods used for the assessment of sleep disturbances, and options for presentation of results, it was not possible to perform a quantitative synthesis of the main findings. Therefore, the impact of different breast cancer treatments on sleep was analysed taking into account the direction and statistical significance of the associations observed when comparing each treatment with a reference group (other treatment or absence of that specific type of treatment). The results were classified as “lower levels of sleep disturbances” when the breast cancer treatments being assessed were negatively associated with the occurrence of sleep disturbances, or “higher level of sleep disturbances” when a positive relation was observed. Additionally, the results were classified in relation to the corresponding *P*-values and categorized as follows: $<0.050$ (statistically significant); $\geq 0.050$ and $<0.100$ (close to statistical significance); $\geq 0.100$ (not statistically significant). Whenever necessary, additional comparisons between treatments were computed by the authors of the present systematic review, using the chi-square test for categorical variables, or the *t*-test for continuous variables. When the studies evaluated several sleep-related outcomes, only one result, corresponding to the strongest and/or statistically significant relation between treatment and sleep disturbances, was considered.

## Results

Twelve studies were included in the systematic review [13,16,25–34], which are described in detail in Appendix 1. Most of these investigations were conducted in North America (10 in the United States [16,25–28,30–34] and one in Canada [13]) and one was from Denmark [29]. The reports were published between 1998 and 2013, but mostly since 2011 (58% of the studies). The median sample size was 101, ranging between 32 and 3002. Nearly all analyses of the effects of cancer treatment on sleep were cross-sectional, and longitudinal data was retrieved from one study [27]. The patients' age ranged between 26 and 89 years, and most studies included only non-metastatic breast cancer patients; only two reports included metastatic breast cancer patients [27,30]. In most studies, data were collected after surgery or after completion of chemotherapy and/or radiotherapy, with the exception of two cohort studies, one with a baseline assessment prior to surgery and with monthly assessments for six months following surgery [27],




ISI, insomnia severity index; GSDS, general sleep disturbance scale; PSQI, Pittsburgh sleep quality index; WHI-IRS, women's health initiative – insomnia rating scale.
*Medline (using PubMed) = 1257; CINAHL Plus with full text = 557; PsycINFO = 257; Cochrane Central Register of Controlled Trials (Central) = 217.
†The screening of the reference lists, selection of papers for the review and data extraction, were accomplished independently by two researchers (ARC, FF), following predefined criteria. Discrepancies in the assessment performed by the two reviewers were resolved by consensus or involving a third researcher (NL).
‡Total number of studies is higher than 12 because some reports provided data of more than one type of treatment.

**Fig. 1.** Systematic review flowchart.

**Table 1**
Assessment of risk of bias or confounding of the studies included in the systematic review.

| Studies included in the systematic review | Assessment of sleep disturbances before treatment | Control of confounding[a] | Absence of reporting bias[b] |
|---|---|---|---|
| Caplette-Gingras, 2013 [13] | ● | ● | ● |
| Desai, 2013 [25] | ● | ● | ● |
| Starkweather, 2013 [26] | ● | ● | ● |
| Van Onselen, 2013 [27] | ● | ● | ● |
| Bower, 2011 [28] | ● | ● | ● |
| Colagiuri, 2011 [29] | ● | ● | ● |
| Rand, 2011 [16] | ● | ● | ● |
| Palesh, 2008 [30] | ● | ● | ● |
| Bardwell, 2008 [31] | ● | ● | ● |
| Fortner, 2002 [32] | ● | ● | ● |
| Stein, 2000 [33] | ● | ● | ● |
| Berger, 1998 [34] | ● | ● | ● |

● Low risk of bias or confounding ● High risk of bias or confounding.
[a] Control of confounding was considered absent when studies only provided crude estimates or data to compute them, regarding the relation between treatments and sleep disturbances.
[b] Quantitative data regarding the impact of breast cancer treatments on sleep disturbances is presented only when results are statistically significant.

and another that evaluated sleep parameters only during chemotherapy treatments [34]. Furthermore, the full range of the treatments received by the patients in each of the groups being compared is not described in most studies.

A summary of the methodological characteristics potentially associated with bias or confounding is presented in Table 1. Regarding the timing of assessment of sleep, only one study stated the evaluation of the participants before surgical treatment [27]. The estimates available from six studies did not control for the effect of potential confounders [13,25,26,31,32,34]. In four studies, the impact of breast cancer treatments on sleep disturbances were not fully reported because the results were not statistically significant [16,27,32,33].

Concerning the evaluation of sleep disturbances, six different sleep-specific instruments were used (Table 2), including five types of subjective assessment [mostly based on the Pittsburgh Sleep Quality Index (PSQI)], and one type of objective measurement of sleep (wrist actigraphy). Insomnia was evaluated in three studies included in this systematic review [13,25,31]. Five studies evaluated sleep quality [16,28,29,32,33], two assessed general sleep disturbances [26,27] and two provided data on specific sleep parameters [30,34].

The association between breast cancer treatments and sleep disturbances is summarized in Fig. 2.

### *Surgical treatment*

The effect of different surgical treatments on sleep was evaluated in two studies [26,29] (Fig. 2A). Mastectomy and lumpectomy were associated with lower levels of disturbances when compared to no surgical treatment (in this case, women were only submitted to breast biopsy) [26], though not statistically significant. Inconsistent findings were observed regarding the effect of mastectomy when compared with lumpectomy [26,29].

### *Chemotherapy*

Overall, a tendency for higher levels of sleep disturbance was observed in women submitted to chemotherapy [27,28,30,31], although the opposite was observed in three studies (not statistically significant in two) [25,27,29]. When compared with radiotherapy, chemotherapy was also associated with higher levels of sleep disturbances [31,33]. Regarding the comparison between different types of chemotherapy, doxorubicin [34] and FEC [fluorouracil (5-FU) + epirubicin + cyclophosphamide] regimens may have higher prevalence of sleep disturbances [13]. Women treated with taxane agents had lower prevalence of sleep disturbance than those treated with chemotherapy without taxane agents [13,25] (Fig. 2B).

### *Radiotherapy*

Breast cancer patients submitted to radiotherapy tended to report higher levels of sleep disturbances than those not submitted to this type of treatment [25,29–31]. However, as previously mentioned, when radiotherapy was compared with chemotherapy, lower levels of sleep disturbances were observed [31,33] (Fig. 2C).

### *Hormonal therapy*

As shown in Fig. 2D, two studies showed that women submitted to hormonal therapy were more prone to report sleep disturbances than those not receiving this type of treatment [29,30]. Although one study found higher levels of sleep disturbances in women treated with tamoxifen [31], two other studies reported lower levels in those women [16,25]. In addition, women taking anastrozole presented higher prevalence of insomnia, when compared with women taking letrozole or exemestane, although these associations were not statistically significant [25].

## Discussion

This systematic review provides an overview of the best available evidence on the association between different breast cancer treatments and sleep disturbances.

Despite the inconsistent results, women submitted to chemotherapy, as well as radiotherapy, tended to report higher levels of sleep disturbances. Less consistent results were observed regarding the impact of surgical treatments and hormonal therapy. However, the achievement of most robust findings was hampered by the heterogeneity of sleep-related outcomes and their assessment, the partial description of all treatments received by the patients, the absence of control for confounding observed in most of the studies, and the presence of reporting bias.

Breast cancer treatments have several associated side effects, which may contribute to impaired sleep in these patients. The cumulative effect of toxic agents on body functions, the physical impact of distressing symptoms (including nausea, vomiting, diarrhoea, urinary frequency or skin reactions related with radiotherapy), changes in body image and hospitalization, as well as other comorbid-related conditions (*e.g.*: pain, fatigue, depression, anxiety, stress), are frequently reported as the main cause or aggravating factor for sleep disturbances in this population [17,18,41]. Another potential risk factor for sleep disturbances among breast cancer patients is the high proportion of vasomotor symptomatology, namely hot flashes and night sweats, as a side effect of chemotherapy-induced ovarian disruption or hormonal therapy following chemotherapy [42]. Additionally, surgical procedures are associated with functional impairment, producing pain and inflammatory responses that can impair sleep and anaesthetics

**Table 2**
Description of the methods used for assessment of sleep disturbances in the studies included in the systematic review.

| Studies included in the systematic review | Methods used for the assessment of sleep disturbances | | | | | | Sleep disturbances included in the analysis |
|---|---|---|---|---|---|---|---|
| | PSQI [35] | GSDS [36] | ISI [37] | WHI-IRS [38] | Daily Sleep Diary [39] | Actigraphy [40] | |
| Caplette–Gingras, 2013 [13] | | | ✓ | | ✓ | | **Insomnia:** sleep-onset latency, and/or wake after sleep onset, of at least 30 min occurred at least 3 times per week (assessed by daily sleep diary); OR subjective complaints of sleep difficulties, as defined by (a) a score of 3 (much) or 4 (extremely) on the dissatisfaction item of the ISI and (b) a total ISI score ≥15. |
| Desai, 2013 [25] | | | ✓ | | | | **Insomnia:** total ISI score ≥15. |
| Starkweather, 2013 [26] | | ✓ | | | | | **Sleep disturbance:** higher total GSDS score. |
| Van Onselen, 2013 [27] | | ✓ | | | | | **Sleep disturbance:** higher total GSDS score; **Daytime sleepiness:** higher GSDS daytime sleepiness subscale score. |
| Bower, 2011 [28] | ✓ | | | | | | **Sleep disturbance:** higher PSQI total score. |
| Colagiuri, 2011 [29] | ✓ | | | | | | **Sleep difficulty:** total PSQI score ≥5. |
| Rand, 2011 [16] | ✓ | | | | | | **Sleep disturbance:** higher total PSQI score. |
| Palesh, 2008 [30] | | | | | | ✓ | **Duration of time in bed**: time between entry into bed and wake-up time; **Sleep latency:** latency to sleep onset from entry into bed; **Sleep efficiency:** ratio of time asleep to time in bed; **Wake after sleep onset**: total duration of wake after sleep onset; **Mean Number of Wake Episodes:** mean number of nocturnal wake episodes; **Average Wake Episode Period:** average length of nocturnal wake episodes. |
| Bardwell, 2008 [31] | | | | ✓ | | | **Insomnia:** total WHI-IRS score ≥9. |
| Fortner, 2002 [32] | ✓ | | | | | | **Sleep latency:** higher PSQI sleep latency subscale score; **Sleep disturbance:** higher PSQI sleep disturbance subscale score. |
| Stein, 2000 [33] | ✓ | | | | | | **Poor sleep quality:** higher PSQI score *(modified version of PSQI).* |
| Berger, 1998 [34] | | | | | | ✓ | **Mesor**: average value of activity movements over a specific length of time; **Amplitude:** extent of a rhythmic change or range of activity and rest values over a specified length of time; **Mesor plus amplitude:** overall mean activity and rhythmic fluctuations over the 24-h period approximately 48 h after treatment; **Awakenings at night:** number of awakenings per night. |

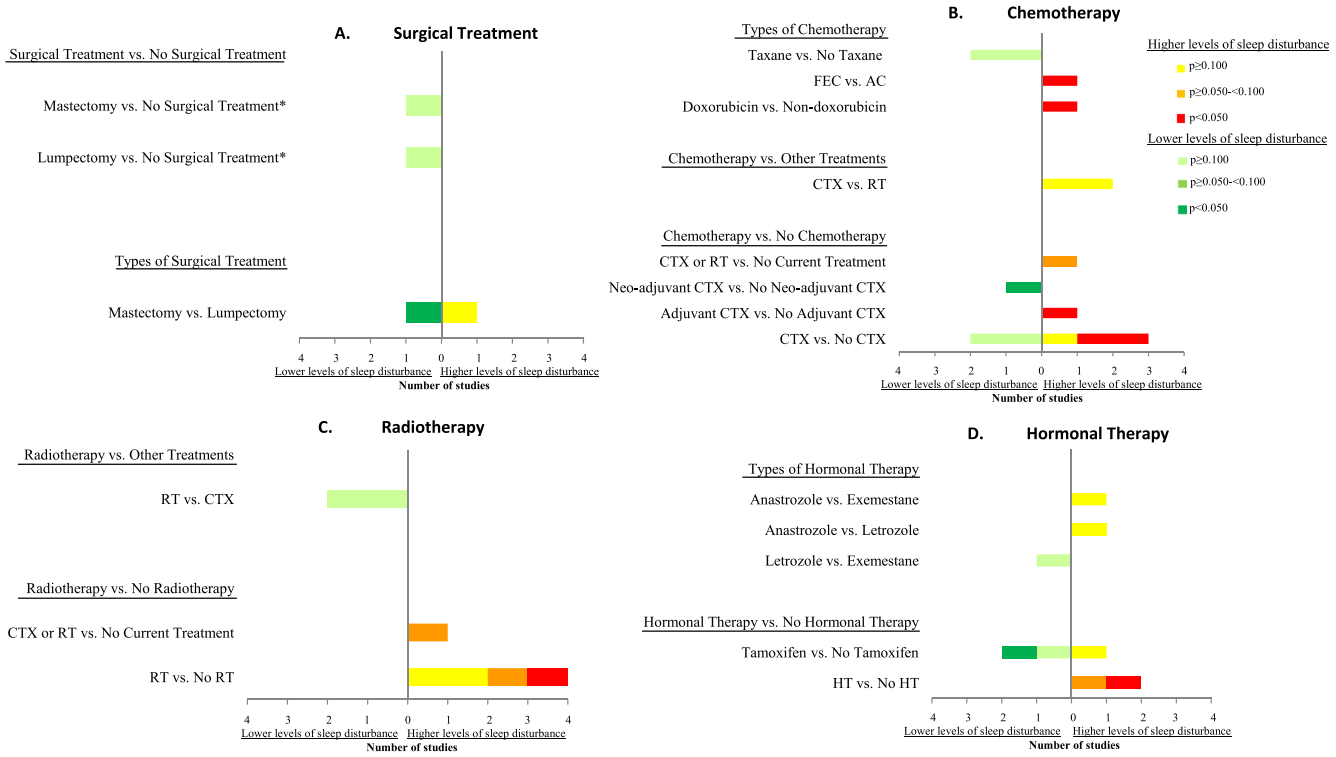
ISI, insomnia severity index; GSDS, general sleep disturbance scale; PSQI, Pittsburgh sleep quality index; WHI-IRS, women's health initiative – insomnia rating scale.

may adversely affect sleep quality and waking for prolonged periods [43]. Although we could expect higher levels of sleep disturbances among women undergoing mastectomy than those receiving breast conserving surgery, this was not confirmed in our study.

For a better understanding of the relation between breast cancer treatment and sleep disturbances, more prospective studies with baseline evaluations before treatment are needed. In fact, previous studies have shown that women with breast cancer frequently report higher levels of sleep disturbances prior to treatment [15,44,45], whereas for some patients the onset of insomnia followed the breast cancer diagnosis and others reported that cancer either caused or aggravated their sleep difficulties [21]. In the only prospective study included in our systematic review that evaluated sleep disturbances prior to treatments, it was possible to observe a slight increase followed by a decrease in sleep disturbances, although the scores remained above the clinically meaningful cut-off for sleep disturbances [27]. The trajectory of disruptive symptoms during treatments also seems to be particularly influenced by pre-treatment symptoms [46].

Despite the increasing interest observed in the last few years regarding the impact of breast cancer and their treatments on sleep disturbances, the assessment of these outcomes also needs to be improved. In fact, several studies were excluded because they did not evaluate sleep with standardized sleep-specific measures. Similar findings were observed in a previous systematic review regarding the methodological approaches of sleep disturbances and quality of life in adults with cancer: of the 40 studies included only four used a multi-item sleep specific instrument [7]. According to the recommendations for a standard research assessment of sleep or insomnia symptoms, in epidemiological studies, these characteristics should be evaluated with global sleep and insomnia measures (namely PSQI and Insomnia Severity Index), sleep diary, actigraphy or polysomnography [47]. Thus, we opted to only include those studies using these types of sleep measures, aiming to guarantee the quality of sleep assessment. None of the studies included evaluated sleep disorders with polysomnography, which is the gold standard for the assessment of sleep disorders, possibly reflecting the costs and efforts that this measure implies. Additionally, even when different studies used the same instrument, distinct sleep-related outcomes were provided in the reports; this hindered the comparison of the impact of breast cancer treatments by type of sleep disturbance.

Although no formal assessment of selection bias could be accomplished due to the heterogeneity of data presented in each study, a total of 12 reports were excluded because they did not present any quantitative estimates regarding the association between breast cancer treatment and sleep disturbances [48–59]. With the exception of one study that reported that women taking tamoxifen had poorer sleep quality than those not submitted to this treatment [58], all of the other studies did not report the direction




AC, doxorubicin + cyclophosphamide; CTX, chemotherapy; FEC, fluorouracil (5-FU) + epirubicin + cyclophosphamide; HT, hormonal therapy; RT, radiotherapy.
* Original study compared mastectomy and lumpectomy with breast biopsy.

**Fig. 2.** Association between breast cancer treatments and sleep disturbances, namely surgical treatment (A), chemotherapy (B), radiotherapy (C) and hormonal therapy (D).

of the results. Also, some of the reports included in this systematic analysis underreported results without statistical significance, which may have overestimated our assessment of the impact of breast cancer treatments on sleep disturbances. Three of the 12 studies included in our review reported data on several sleep-related outcomes, and we opted to include in the figures summarizing evidence only those corresponding to the strongest and/or statistically significant relation between treatment and sleep disturbances; although this strategy for data synthesis may also have contributed to overestimating the relation between treatments and these side effects, it is more sensitive for the detection of potentially deleterious effects of treatments.

Another important issue refers to the fact that the associations between breast cancer treatments and sleep disturbance may be misestimates due to the lack of control for potential confounding; in fact, only six of the studies included in the systematic review presented adjusted estimates. Of the wide range of potential confounders, for instance, cancer stage, age and menopausal status appear to be crucial variables. Indeed, treatments options are dependent of cancer stage and related features (*e.g.* tumour size) [60,61], and prevalence of sleep disturbances has been associated with this factor [21]. Age is also taken into account when deciding breast cancer treatments [62], and changes in sleep patterns and higher prevalence of sleep disorders were observed with increasing age [63]. Additionally, menopausal status may determine the type of breast cancer treatments, particularly hormonal therapy [64,65], and postmenopausal women were more likely to present impaired sleep than pre-menopausal [29,66]. Socio-economic factors [67,68] and presence of other co-morbidities [41,62] may also need to be considered in data analysis as potential confounders.

This systematic review highlights the need for improvements in methodological procedures in future studies, particularly the achievement of a consensual definition of sleep disturbances, use of adequate tools for sleep evaluation, longitudinal analysis of sleep disturbances, with evaluations preformed prior to treatments, as well as control for the effect of possible confounders. Our results do not exclude the hypothesis that breast cancer treatments, particularly chemotherapy, are associated with sleep disturbances, but more robust evidence is needed for a proper understanding of the effects of treatment regimens on this outcome with potential impact in the patients' quality of life.

## Conflict of interest statement

The authors have no conflicts of interest to disclose.

## Financial support

The authors have no financial support to disclose.

## Ethical approval

This article is a systematic review of the literature, and therefore no ethical approval was required.

## Appendix 1. Detail description of the studies addressing the association between breast cancer treatments and sleep disturbances.

| 1st author, Year of publication (REF) | Study description | Subjects characteristics | Association between breast cancer treatments and sleep disturbances | | |
|---|---|---|---|---|---|
| | | | Treatment comparison | Main results | Control of confounding |
| Caplette-Gingras, 2013 [13] | Country: Canada<br>Period of data collection: 2005–2007<br>Type of study: Cross-sectional<br>Aim: "To evaluate the relationship between insomnia and objective ( … ) and subjective ( … ) measures of cognitive functioning"<br>Study population: Women treated for a first diagnosis of Stage-1 through Stage-3 BCA combining surgery, CTX, and RT in the past 4 months and having received HT for a minimum of 5 week<br>Sample size: $n = 63$<br>"Insomnia ": $n = 47$ vs. "Good sleepers": $n = 16$ | Age (yr), Range: 30–60<br>Cancer stage, $n$ (%): Stage I: 14 (22.2), Stage II: 29 (46.0), Stage III: 20 (31.7)<br>Treatments, $n$ (%):<br>*CTX regimen:* FEC: 3 (4.8), FEC + Taxane: 18 (28.6), AC: 24 (38.1), AC + Taxane: 18 (28.6) | FEC vs. AC[b] (with or without taxane)<br>Taxane vs. No taxane[b] (FEC or AC) | Insomnia: 90.5% vs. 66.7%, $p = 0.041$[a]<br>Insomnia: 69.4% vs. 81.5%, $p = 0.277$[a] | –<br>– |
| Desai, 2013 [25] | Country: USA<br>Period of data collection: 2008–2009<br>Type of study: Cross-sectional<br>Aim: "To understand the prevalence and risk factors for insomnia in postmenopausal BCA patients receiving AIs"<br>Study population: Postmenopausal women with stage 0–III BCA receiving a third generation AI, who had completed CTX or RT at least 1 month prior to enrolment<br>Sample size: $n = 413$<br>"Clinical insomnia": $n = 77$ vs. "No clinical insomnia": $n = 336$ | Age (yr), Mean: 61.7, Range: 33–88<br>Cancer stage, $n$ (%): Stage I: 167 (40.4), Stage II: 195 (47.2), Stage III: 51 (12.4)<br>Time since diagnosis, $n$ (%): <2 yr: 132 (32.0), 2–5 yr: 132 (32.0), 5–10 yr: 102 (24.7), ≥10 yr: 47 (11.4)<br>Treatments, $n$ (%):<br>*CTX:*None: 158 (38.3), CTX but no Taxane: 105 (25.4), CTX including Taxane: 150 (36.3);<br>*RT:* 288 (69.7);<br>*Prior Tamoxifen:* 140 (33.9),<br>*Current HT:* Letrozole: 86 (20.8), Anastrazole: 278 (67.3), Exemestane: 49 (11.9) | CTX (with or without taxane) vs. No CTX<br>CTX + taxane vs. CTX wihout taxane<br>RT vs. No RT<br>Prior tamoxifen vs. No prior tamoxifen<br>Anastrozole (Arimidex) vs. Letrozole (Femara)<br>Anastrozole (Arimidex) vs. Exemestane (Aromasin)<br>Letrozole (Femara) vs. Exemestane (Aromasin) | Insomnia: 17.6% vs. 20.3%, $p = 0.509$[a]<br>Insomnia: 17.3% vs. 18.1%, $p = 0.875$[a]<br>Insomnia: 19.8% vs. 16.0%, $p = 0.363$<br>Insomnia: 17.1% vs. 19.4%, $p = 0.575$<br>Insomnia: 20.9% vs. 14.0%, $p = 0.155$[a]<br>Insomnia: 20.9% vs. 14.3%, $p = 0.287$[a]<br>Insomnia: 14.0% vs. 14.3%, $p = 0.957$[a] | –<br>–<br>–<br>–<br>–<br>–<br>– |
| Starkweather, 2013 [26] | Country: USA<br>Period of data collection: 2003–2006<br>Type of study: Cross-sectional<br>Aim: "To examine the relationships among pro- and anti-inflammatory biomarkers and | Age (yr), Mean (SD): 47.7 (7.7), Range: 27–63<br>Cancer stage: Stage I–Stage III<br>Time since diagnosis:<br>Treatments, $n$ (%):<br>Mastectomy: 21 (65.6), Lumpectomy: 7 (21.9), Breast biopsy: 4 (12.5) | Mastectomy vs. Lumpectomy<br>Mastectomy vs. No surgical treatment[c]<br>Lumpectomy vs. No surgical treatment[c] | Sleep disturbance: Mean (SD): 45.6 (21.1) vs. 38.1 (10.6), $p = 0.38$<br>Sleep disturbance: Mean (SD): 45.6 (21.1) vs. 52.8 (16.3), $p = 0.527$[a]<br>Sleep disturbance: | –<br>–<br>– |

(*continued on next page*)

(*continued*)

| 1st author, Year of publication (REF) | Study description | Subjects characteristics | Association between breast cancer treatments and sleep disturbances | | |
|---|---|---|---|---|---|
| | | | Treatment comparison | Main results | Control of confounding |
| | the presence of pain and other symptoms (anxiety, depression, fatigue, and sleep disorder) prior to induction of CTX"<br>Study population: Women with early-stage BCA at 1 month following fine needle biopsy or breast tumour resection (lumpectomy or mastectomy) but prior to induction of CTX<br>Sample size: $n$=32 | | | Mean (SD): 38.1 (10.6) vs. 52.8 (16.3), $p = 0.100$[a] | |
| Van Onselen, 2013 [27] | Country: USA<br>Type of study: Cohort<br>Aim: "To evaluate how sleep disturbance and daytime sleepiness changed from before to 6 months following surgery and whether certain characteristics predicted initial levels and/or the trajectories of these parameters"<br>Study population: Women who underwent unilateral BCA surgery were enrolled prior to surgery and evaluated monthly for 6 months<br>Sample size: $n = 396$ | Age (yr), Mean (SD): 54.9 (11.6)<br>Cancer stage, $n$ (%): Stage 0: 73 (18.3), Stage I:151 (37.9), Stage IIA, IIB: 141 (35.4), Stage IIIA, IIIB, IIIC, IV:33 (8.3)<br>Treatments, $n$ (%): Breast-conserving: 318 (79.9), Mastectomy: 80 (20.1), Sentinel node biopsy: 328 (82.4), Axillary lymph node dissection: 149 (37.4), Breast reconstruction at the time of surgery: 86 (21.6), Neo-adjuvant CTX: 79 (19.8), Adjuvant CTX: 133 (33.6), Adjuvant RT: 224 (56.6) | Neo-adjuvant CTX vs. No neo-adjuvant CTX | Daytime sleepiness: Coefficient (SE) from Linear Model[d]: - 0.178 (0.069), $p < 0.05$[f]; Coefficient (SE) from Quadratic Model[e]: 0.019 (0.011), $p$ = NS | Hierarchical linear models adjusted for education, employment status, fear of future diagnostic test, and adjuvant CTX |
| | | | Adjuvant CTX vs. No-adjuvant CTX | Sleep disturbance: Coefficient (SE) from Linear Model[d]: 3.277 (0.874), $p < 0.001$[f]; Coefficient (SE) from Quadratic Model[e]: −0.421 (0.144), $p < 0.010$ | Hierarchical linear models adjusted for education and depression symptoms |
| | | | | Daytime sleepiness Coefficient(SE) from Linear Model[d]: 0.266 (0.056), $p < 0.001$; Coefficient (SE) from Quadratic Model[e]: −0.036 (0.009), $p < 0.001$ | Hierarchical linear models adjusted for education, employment status, fear of future diagnostic test, and neo-adjuvant CTX |
| Bower, 2011 [28] | Country: USA<br>Type of study: Cross-sectional<br>Aim: "To characterize the prevalence and comorbidity of fatigue, depressive symptoms, and sleep disturbance (…); to determine the contribution of treatment-related factors to behavioural symptoms and inflammation (…) and to test the hypothesis that inflammatory processes would contribute to these symptoms"<br>Study population: Women who completed | Age (yr), Mean: 51.2, Range: 32–66<br>Cancer stage: Stage 0 – Stage IIIA<br>Time since diagnosis (months), Mean: 6.7, Range: 1.7–12.5<br>Treatments, $n$ (%): *No CTX* (n = 53, 51.5%) – Surgery only: 14 (13.6), Surgery + RT: 39 (37.9); *CTX* (n = 50, 48.5%) – Surgery + CTX: 9 (8.7), Surgery + RT + CTX: 41 (39.8) | CTX vs. No CTX | Sleep disturbance: Mean (SD): 8.98 (3.62) vs. 7.19 (4.02), $p = 0.01$ | *P*-values from analysis of covariance controlling for age, time since treatment completion, and RT |

| | | | | | |
|---|---|---|---|---|---|
| | primary cancer treatment (surgery, RT, and/or CTX) within the past 3 months and not yet started ET<br>Sample size: $n = 103$ | | | | |
| Colagiuri, 2011 [29] | Country: DNK<br>Period of data collection: 2001–2004<br>Type of study: Cross-sectional analysis<br>Aim: To investigate "the prevalence and predictors of clinically significant sleep difficulty in women with primary BCA"<br>Study population: Women included in a nationwide cohort of Danish women treated for primary BCA completed questionnaires three to four months post-surgery<br>Sample size: $n = 3002$ "No Sleep Difficulty" (PSQI$\leq$5):$n = 1264$ vs. "Sleep Difficulty" (PSQI$\geq$5): $n = 1738$ | Age (yr), Mean: 54.4, Range: 26–70<br>Tumour grade, *n* (%): 1: 720 (23.8), 2: 1094 (36.2), 3: 636 (21.1), Nonductal: 570 (18.9)<br>Treatments, *n* (%):<br>*Type of surgery:*<br>Mastectomy: 1607 (53.5), Lumpectomy: 1395 (46.5);<br>*CTX*: 1335 (44.5);<br>*HT:* 1117 (37.2);<br>*RT:* 1300 (43.3) | Lumpectomy vs. Mastectomy<br><br>No CTX vs. CTX<br><br><br><br><br>Previous RT vs. No RT<br><br>HT vs. No HT | Sleep difficulty:<br>59.7% vs. 56.6%, $p = 0.14$<br>Adjusted OR: 1.22, $p = 0.015$<br>Sleep difficulty:<br>59.1% vs. 56.4%, $p = 0.15$<br>*Premenopausal women*:<br>Adjusted OR: 1.29, $p = 0.16$<br>*Menopausal women:* NS<br>Sleep difficulty:<br>59.8% vs. 56.4%, $p = 0.06$<br>Sleep difficulty:<br>60.2% vs. 56.6%, $p = 0.06$ | Multivariate analysis including age, marital status, ethnicity, education, personal income, household wealth, municipality size, children psychiatric history, comorbidity, BMI, menopausal status, alcohol/week, cigarettes/day, physical activity, physical functioning, depression and anxiety<br>–<br>– |
| Rand, 2011 [16] | Country: USA<br>Type of study: Cross-sectional analysis<br>Aim: "To evaluate the relationships among measures of hot flushes, perceived hot flush interference, sleep disturbance, and (…) QL"<br>Study population: BCA survivors due to receive AI as initial adjuvant HT or following adjuvant tamoxifen and completed adjuvant CTX if indicated<br>Sample size: $n = 395$ | Age (yr), Mean (SD): 59.3(8.7), Range: 35-89<br>Cancer stage: Stage 0–Stage III<br>Treatments: *Time since first surgery for BCA*, Mean (SD): 16.4 months (20.4) | Prior tamoxifen vs. No prior tamoxifen | Sleep disturbance: $\beta = -0.22$, $p < 0.05$ | Structured equation modelling, including age at surgery, SSRI use, alcohol use, CTX, ever smoked, BMI, hot flash severity and frequency, perceived interference, sleep disturbance, perceived health status, anxiety symptoms, depressive symptoms |
| Bardwell, 2008 [31] | Country: USA<br>Type of study: Cross-sectional analysis<br>Aim: To assess the "relative importance of a wide range of risk factors for insomnia" in women in history of BCA | Age (yr), Mean: 53, Range: 28-74<br>Cancer stage, *n* (%): Stage I: 1033 (39.0), Stage II: 1488 (56.2), Stage IIIA: 125 (4.7)<br>Time since diagnosis, *n* (%): <1 yr: 615 (23.2), 1–1.9 yr: 836 (31.6), | CTX (with or without RT) vs. No CTX[g]<br>RT (with or without CTX) vs. No RT[g]<br>CTX vs. RT[g]<br><br>Tamoxifen (ever) vs. No tamoxifen (never)[h] | Insomnia: 40.0% vs. 38.6%, $p = 0.651$[a]<br>Insomnia: 39.4% vs. 39.0%, $p = 0.834$[a]<br>Insomnia: 39.0% vs. 38.4%, $p = 0.828$[a]<br>Insomnia: 39.9% vs. 37.9%, $p = 0.307$[a] | –<br>–<br>–<br>– |

(*continued on next page*)

(*continued*)

| 1st author, Year of publication (REF) | Study description | Subjects characteristics | Association between breast cancer treatments and sleep disturbances | | |
|---|---|---|---|---|---|
| | | | Treatment comparison | Main results | Control of confounding |
| | Study population: Women ≤4 years post-treatment for Stage I (≥1 cm)–IIIA BCA<br>Sample size: $n = 2646$<br>"Insomnia": $n = 1039$ vs. "No insomnia": $n = 1607$ | 2–2.9 yr: 654 (24.7), 3–4 yr: 541 (20.4)<br>Treatments, *n* (%): *Surgery + RT*: 518 (19.6); *Surgery + CTX*: 720 (27.2); *Surgery + CTX + RT:* 1113 (42.1); *Surgery only:* 295 (11.1); *Tamoxifen:* Current: 1589 (60.1), Former: 191 (7.2), Never: 866 (32.7) | | | |
| Palesh, 2008 [30] | Country: USA<br>Period of data collection:<br>Type of study: Cross-sectional<br>Aim: " To determine the relationship between hypothalamic pituitary axis (HPA) dysregulation, vagal functioning, and sleep problems in women with metastatic BCA"<br>Study population: Women with metastatic BCA or recurrent BCA<br>Sample size: $n = 99$ | Age (yr), Mean (SD): 54.7 (9.6), Range: 36–80<br>Cancer stage: Metastatic or recurrent BCA<br>Treatments, *n* (%): *CTX*: 80 (86), *RT*: 75 (81.5), *HT*: 61 (65.6) | CTX vs. No CTX | Total time in bed: rho = −0.29, $p = 0.006$; $\beta = -0.38$, $p = 0.001$[f]<br>Latency: rho = −0.14, $p \geq 0.05$; $\beta = -0.30$, $p = 0.02$<br>Sleep efficiency: rho = −0.12, $p \geq 0.05$<br>WASO: rho = 0.04, $p \geq 0.05$<br>Mean number of wake episodes: rho = 0, $p \geq 0.05$<br>Average wake episode period: rho = 0.09, $p \geq 0.05$ | Hierarchical regression adjusted for CTX, pain, depression<br>Hierarchical regression for CTX, RT and perceived stress<br>–<br>–<br>–<br>– |
| | | | RT vs. No RT | Total time in bed: rho = −0.08, $p \geq 0.05$<br>Latency: rho = 0.21, $p < 0.05$[f]<br>Sleep efficiency: rho = −0.14, $p \geq 0.05$<br>WASO: rho = 0.10, $p \geq 0.05$<br>Mean number of wake episodes: rho = 0.13, $p \geq 0.05$<br>Average wake episode period: rho = 0.09, $p \geq 0.05$ | –<br>–<br>–<br>–<br>–<br>– |
| | | | HT vs. No HT | Total time in bed: rho = 0.16, p≥0.05<br>Latency: rho = 0.20, $p \geq 0.05$<br>Sleep efficiency: rho = −0.19, $p \geq 0.05$<br>WASO: rho = 0.24, $p = 0.03$[f]<br>Mean number of wake episodes: rho = 0.23, $p = 0.03$<br>Average wake episode period: rho = 0.12, $p \geq 0.05$ | –<br>–<br>–<br>–<br>–<br>– |
| Fortner, 2002 [32] | Country: USA<br>Period of data collection:<br>Type of study: | Age (yr), Mean (SD): 51.3 (11.7)<br>Treatments: Receiving | CTX or RT vs. No current treatment | Sleep disturbance: Mean (SD):1.52 (0.64) vs. 1.24 (0.58), $p < 0.06$ (NS)[f] | – |

| | | | | | |
|---|---|---|---|---|---|
| | Cross-sectional<br>Aim: To "describe sleep in a heterogeneous sample of breast cancer patients (…) and examined the relation between sleep disturbance and health-related QL"<br>Study population: Breast cancer patients presenting to an outpatient oncology clinic (19 pre-cancer treatment, 29 receiving cancer treatment, 23 post-cancer treatment)<br>Sample size: $n = 72$ | CTX or RT: 41% | | Sleep latency:<br>Mean (SD): 1.31 (1.04) vs. 0.93 (0.84), $p < 0.10$ (NS) | – |
| Stein, 2000 [33] | Country: USA<br>Type of study: Cross-sectional analysis<br>Aim: "To (…) document the prevalence and severity of hot flashes (…) during treatment for BCA; [to] identify medical, demographic, and treatment correlates of hot flashes during BCA treatment; and [to] determine the impact of the hot flashes on (…) QL"<br>Study population: Postmenopausal women with BCA evaluated during CTX or RT<br>Sample size: $n = 70$ | Age (yr), Range: 39-81<br>Cancer stage, *n* (%): Stage I: 29 (41.4), Stage II: 34 (48.6), Stage III: 7(10.0)<br>Treatments, *n* (%): *Type of Surgery:* Mastectomy: 24 (34.3), Lumpectomy: 43 (61.4), Breast Biopsy: 3 (4.3); *CTX:* 28 (40); *RT*: 42(60); *Tamoxifen*: 6 (8.6) | CTX vs. RT | Sleep Quality: $\beta = -0.11$, $p \geq 0.10$ | Multivariate analysis including education |
| Berger, 1998 [34] | Country: USA<br>Type of study: Cohort<br>Aim: To describe "patterns of fatigue and of activity and rest and the relationship between these variables"<br>Study population: Newly diagnosed women with stage I or II BCA during the first three adjuvant | Age (yr), Mean (SD): 49.5 (8.64), Range: 33–69<br>Cancer stage, *n*: Stage I: 32, Stage II: 40<br>Lymph node status: Positive: 33, Negative: 39<br>Treatments, *n* (%): *Type of Surgery:* Breast conservation: 34, Modified radical mastectomy with reconstruction: 10, Modified radical mastectomy without reconstruction: 28; | Doxorubicin vs. Non-doxorubicin | Mesor:<br>Mean (SD): 101.87 (15.48) vs. 113.73 (13.90), $p = 0.024$<br>Amplitude:<br>Mean (SD):85.86 (19.39) vs. 95.09 (13.90), $p = 0.125$<br>Mesor plus amplitude:<br>Mean (SD): 183.18 (45.46) vs. 209.66 (53.76), $p = 0.002$[f]<br>Awakenings at night:<br>Mean (SD): 21.77 (14.10) | –<br>–<br>–<br>– |

(*continued on next page*)

(*continued*)

| 1st author, Year of publication (REF) | Study description | Subjects characteristics | Association between breast cancer treatments and sleep disturbances | | |
|---|---|---|---|---|---|
| | | | Treatment comparison | Main results | Control of confounding |
| | chemotherapy cycles.<br>Sample size: $n = 72$ | *CTX adjuvant regimen:*<br>CMF:26, AC:20, CAF:26;<br>Doxorubicin: 46;<br>Non-doxorubicin:26 | | vs. 22.13 (11.00),<br>$p = 0.935$ | |

AC, doxorubicin + cyclophosphamide; AI, aromatase inhibitors; BCA, breast cancer; BMI, body mass index; CAF, cyclophosphamide, doxorubicin, and fluorouracil; CMF, cyclophosphamide, methotrexate, and fluorouracil; CTX, chemotherapy; DNK, Denmark; ET, endocrine therapy; FEC, fluorouracil (5-FU) + epirubicin + cyclophosphamide; HT, hormonal therapy; NS, not statistically significant; OR, odds ratio; PSQI, Pittsburgh sleep quality index; QL, quality of life; RT, radiotherapy; SD, standard deviation; SE, standard error; SSRI, selective serotonin reuptake inhibitor; USA, United States of America; WASO, wake after sleep onset; yr, years.

[a] *P*-values computed by the authors of the present systematic review.

[b] Article included data concerning the impact on sleep disturbances of FEC (without taxane), FEC + Taxane, AC (without taxane), AC + Taxane.

[c] Original study compared mastectomy and lumpectomy with breast biopsy.

[d] Linear model assumes that the patients' sleep parameter levels changed at a constant rate.

[e] Quadratic model assumes that the patients' sleep parameter levels accelerate or decelerate over time. Receipt of adjuvant CTX was associated with a gradual increase in sleep disturbance and daytime sleepiness that peaked at the third month and then decreased from three to six months following surgery.

[f] Result represented in Fig. 2.

[g] Article also included data concerning the impact on sleep disturbances of surgery + RT, surgery + CTX, surgery + CTX + RT and surgery only.

[h] Article also included data concerning the impact on sleep disturbances of current, former or never use of tamoxifen.

## References


[1] Amaro J, Severo M, Vilela S, Fonseca S, Fontes F, La Vecchia C, et al. Patterns of breast cancer mortality trends in Europe. Breast 2013;22(3):244–53.

[2] Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 2005;353(17):1784–92.

[3] De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5 – a population-based study. Lancet Oncol 2014;15(1):23–34.

[4] Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer incidence and mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr [accessed on 22.01.14].

[5] Soerjomataram I, Lortet-Tieulent J, Parkin DM, Ferlay J, Mathers C, Forman D, et al. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. Lancet 2012;380(9856):1840–50.

[6] American Academy of Sleep Medicine. The international classification of sleep disorders: diagnostic and coding manual. 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2005.

[7] Berger AM, Sankaranarayanan J, Wanatabe-Galloway S. Current methodological approaches to the study of sleep disturbances and quality of life in adults with cancer: a systematic review. Psychooncology 2007;16(5):401–20.

[8] Fiorentino L, Ancoli-Israel S. Insomnia and its treatment in women with breast cancer. Sleep Med Rev 2006;10(6):419–29.

[9] Carpenter JS, Elam JL, Ridner SH, Carney PH, Cherry GJ, Cucullu HL. Sleep, fatigue, and depressive symptoms in breast cancer survivors and matched healthy women experiencing hot flashes. Oncol Nurs Forum 2004;31(3):591–8.

[10] Carlson LE, Campbell TS, Garland SN, Grossman P. Associations among salivary cortisol, melatonin, catecholamines, sleep quality and stress in women with breast cancer and healthy controls. J Behav Med 2007;30(1):45–58.

[11] Savard J, Villa J, Ivers H, Simard S, Morin CM. Prevalence, natural course, and risk factors of insomnia comorbid with cancer over a 2-month period. J Clin Oncol 2009;27(31):5233–9.

[12] Savard J, Miller SM, Mills M, O'Leary A, Harding H, Douglas SD, et al. Association between subjective sleep quality and depression on immunocompetence in low-income women at risk for cervical cancer. Psychosom Med 1999;61(4):496–507.

[13] Caplette-Gingras A, Savard J, Savard MH, Ivers H. Is insomnia associated with cognitive impairments in breast cancer patients? Behav Sleep Med 2013;11(4):239–57.

[14] Hsiao F, Chang K, Kuo W, Huang C, Liu Y, Lai Y, et al. A longitudinal study of cortisol responses, sleep problems, and psychological well-being as the predictors of changes in depressive symptoms among breast cancer survivors. Psychoneuroendocrinology 2013;38(3):356–66.

[15] Berger AM, Farr LA, Kuhn BR, Fischer P, Agrawal S. Values of sleep/wake, activity/rest, circadian rhythms, and fatigue prior to adjuvant breast cancer chemotherapy. J Pain Symptom Manage 2007;33(4):398–409.

[16] Rand KL, Otte JL, Flockhart D, Hayes D, Storniolo AM, Stearns V, et al. Modeling hot flushes and quality of life in breast cancer survivors. Climacteric 2011;14(1):171–80.

[17] Lee K, Cho M, Miaskowski C, Dodd M. Impaired sleep and rhythms in persons with cancer. Sleep Med Rev 2004;8:199–212.

[18] Vena C, Parker K, Cunningham M, Clark J, McMillan S. Sleep-wake disturbances in people with cancer part I: an overview of sleep, sleep regulation, and effects of disease and treatment. Oncol Nurs Forum 2004;31(4):735–46.

[19] Kotronoulas G, Wengstrom Y, Kearney N. A critical review of women's sleep-wake patterns in the context of neo-/adjuvant chemotherapy for early-stage breast cancer. Breast 2012;21(2):128–41.

[20] Knobf MT, Sun Y. A longitudinal study of symptoms and self-care activities in women treated with primary radiotherapy for breast cancer. Cancer Nurs 2005;28(3):210–8.

[21] Savard J, Simard S, Blanchet J, Ivers H, Morin CM. Prevalence, clinical characteristics, and risk factors for insomnia in the context of breast cancer. Sleep 2001;24(5):583–90.

[22] Morgenthaler TI, Lee-Chiong T, Alessi C, Friedman L, Aurora R, Boehlecke B, et al. Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders. An American Academy of Sleep Medicine report. Sleep 2007;30(11):1145–59.

[23] Sack RL, Auckley D, Auger RR, Carskadon MA, Wright KP Jr, Vitiello MV, et al. Circadian rhythm sleep disorders: part I, basic principles, shift work and jet lag disorders. An American Academy of Sleep Medicine review. Sleep 2007;30(11):1460–83.

[24] Bjorvatn B, Pallesen S. A practical approach to circadian rhythm sleep disorders. Sleep Med Rev 2009;13(1):47–60.

[25] Desai K, Mao JJ, Su I, Demichele A, Li Q, Xie SX, et al. Prevalence and risk factors for insomnia among breast cancer patients on aromatase inhibitors. Support Care Cancer 2013;21(1):43–51.

[26] Starkweather AR, Lyon DE, Schubert CM. Pain and inflammation in women with early-stage breast cancer prior to induction of chemotherapy. Biol Res Nurs 2013;15(2):234–41.

[27] Van Onselen C, Paul SM, Lee K, Dunn L, Aouizerat BE, West C, et al. Trajectories of sleep disturbance and daytime sleepiness in women before and after surgery for breast cancer. J Pain Symptom Manage 2013;45(2):244–60.

[28] Bower JE, Ganz PA, Irwin MR, Kwan L, Breen EC, Cole SW. Inflammation and behavioral symptoms after breast cancer treatment: do fatigue, depression, and sleep disturbance share a common underlying mechanism? J Clin Oncol 2011;29(26):3517–22.
[29] Colagiuri B, Christensen S, Jensen AB, Price MA, Butow PN, Zachariae R. Prevalence and predictors of sleep difficulty in a national cohort of women with primary breast cancer three to four months postsurgery. J Pain Symptom Manage 2011;42(5):710–20.
[30] Palesh O, Zeitzer JM, Conrad A, Giese-Davis J, Mustian KM, Popek V, et al. Vagal regulation, cortisol, and sleep disruption in women with metastatic breast cancer. J Clin Sleep Med 2008;4(5):441–9.
[31] Bardwell WA, Profant J, Casden DR, Dimsdale JE, Ancoli-Israel S, Natarajan L, et al. The relative importance of specific risk factors for insomnia in women treated for early-stage breast cancer. Psychooncology 2008;17(1):9–18.
[32] Fortner BV, Stepanski EJ, Wang SC, Kasprowicz S, Durrence HH. Sleep and quality of life in breast cancer patients. J Pain Symptom Manage 2002;24(5):471–80.
[33] Stein KD, Jacobsen PB, Hann DM, Greenberg H, Lyman G. Impact of hot flashes on quality of life among postmenopausal women being treated for breast cancer. J Pain Symptom Manage 2000;19(6):436–45.
[34] Berger AM. Patterns of fatigue and activity and rest during adjuvant breast cancer chemotherapy. Oncol Nurs Forum 1998;25(1):51–62.
[35] Buysse DJ, Reynolds 3rd CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28(2):193–213.
[36] Lee KA. Self-reported sleep disturbances in employed women. Sleep 1992;15:493–8.
[37] Bastien CH, Vallières A, Morin CM. Validation of the insomnia severity index as an outcome measure for insomnia research. Sleep Med 2001;2(4):297–307.
[38] Levine DW, Dailey ME, Rockhill B, Tipping D, Naughton MJ, Shumaker SA. Validation of the women's health initiative insomnia rating scale in a multicenter controlled clinical trial. Psychosom Med 2005;67(1):98–104.
[39] Morin CM. Insomnia: psychological assessment and management. New York: Guildford Press; 1993.
[40] Morgenthaler T, Alessi C, Friedman L, Owens J, Kapur V, Boehlecke B, et al. Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. Sleep 2007;30(4):519–29.
[41] Kim HJ, McDermott PA, Barsevick AM. Comparison of groups with different patterns of symptom cluster intensity across the breast cancer treatment trajectory. Cancer Nurs 2014;37(2):88–96.
[42] Savard M, Savard J, Quesnel C, Ivers H. The influence of breast cancer treatment on the occurrence of hot flashes. J Pain Symptom Manage 2009;37(4):687–97.
[43] Berger AM, Parker KP, Young-McCaughan S, Mallory GA, Barsevick AM, Beck SL, et al. Sleep/wake disturbances in people with cancer and their caregivers: state of the science. Oncol Nurs Forum 2005;32(6):E98–126.
[44] Ancoli-Israel S, Liu L, Marler MR, Parker BA, Jones V, Sadler GR, et al. Fatigue, sleep, and circadian rhythms prior to chemotherapy for breast cancer. Support Care Cancer 2006;14(3):201–9.
[45] Denieffe S, Cowman S, Gooney M. Symptoms, clusters and quality of life prior to surgery for breast cancer. J Clin Nurs 2014;23(17-18):2491–502.
[46] Liu L, Rissling M, Neikrug A, Fiorentino L, Natarajan L, Faierman M, et al. Fatigue and circadian activity rhythms in breast cancer patients before and after chemotherapy: a controlled study. Fatigue 2013;1(1–2):12–26.
[47] Buysse DJ, Ancoli-Israel S, Edinger JD, Lichstein KL, Morin CM. Recommendations for a standard research assessment of insomnia. Sleep 2006;29(9):1155–73.
[48] Liu L, Fiorentino L, Rissling M, Natarajan L, Parker BA, Dimsdale JE, et al. Decreased health-related quality of life in women with breast cancer is associated with poor sleep. Behav Sleep Med 2013;11(3):189–206.
[49] Dhruva A, Paul SM, Cooper BA, Lee K, West C, Aouizerat BE, et al. A longitudinal study of measures of objective and subjective sleep disturbance in patients with breast cancer before, during, and after radiation therapy. J Pain Symptom Manage 2012;44(2):215–28.
[50] Liu L, Mills PJ, Rissling M, Fiorentino L, Natarajan L, Dimsdale JE, et al. Fatigue and sleep quality are associated with changes in inflammatory markers in breast cancer patients undergoing chemotherapy. Brain Behav Immun 2012;26(5):706–13.
[51] Liu L, Rissling M, Natarajan L, Fiorentino L, Mills PJ, Dimsdale JE, et al. The longitudinal relationship between fatigue and sleep in breast cancer patients undergoing chemotherapy. Sleep 2012;35(2):237–45.
[52] Taylor TR, Huntley ED, Makambi K, Sween J, Adams-Campbell LL, Frederick W, et al. Understanding sleep disturbances in African-American breast cancer survivors: a pilot study. Psychooncology 2012;21(8):896–902.
[53] Mosher CE, Duhamel KN. An examination of distress, sleep, and fatigue in metastatic breast cancer patients. Psychooncology 2012;21(1):100–7.
[54] Rumble ME, Keefe FJ, Edinger JD, Affleck G, Marcom PK, Shaw HS. Contribution of cancer symptoms, dysfunctional sleep related thoughts, and sleep inhibitory behaviors to the insomnia process in breast cancer survivors: a daily process analysis. Sleep 2010;33(11):1501–9.
[55] 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):101–10.
[56] Savard J, Liu L, Natarajan L, Rissling MB, Neikrug AB, He F, et al. Breast cancer patients have progressively impaired sleep-wake activity rhythms during chemotherapy. Sleep 2009;32(9):1155–60.
[57] Aldridge-Gerry A, Zeitzer JM, Palesh OG, Jo B, Nouriani B, Neri E, et al. Psychosocial correlates of sleep quality and architecture in women with metastatic breast cancer. Sleep Med 2013;14(11):1178–86.
[58] Alvarez J, Meyer FL, Granoff DL, Lundy A. The effect of EEG biofeedback on reducing postcancer cognitive impairment. Integr Cancer Ther 2013;12(6):475–87.
[59] Rissling MB, Liu L, Natarajan L, He F, Ancoli-Israel S. Relationship of menopausal status and climacteric symptoms to sleep in women undergoing chemotherapy. Support Care Cancer 2011;19(8):1107–15.
[60] Martin MA, Meyricke R, O'Neill T, Roberts S. Mastectomy or breast conserving surgery? Factors affecting type of surgical treatment for breast cancer–a classification tree approach. BMC Cancer 2006;6:98.
[61] Kurian A, Lichtensztajn D, Keegan T, Leung R, Shema S, Hershman D, et al. Patterns and predictors of breast cancer chemotherapy use in Kaiser Permanente Northern California, 2004–2007. Breast Cancer Res Treat 2013;137(1):247–60.
[62] Yancik R, Wesley M, Ries L, Havlik R, Edwards B, Yates J. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA 2001;285(7):885–92.
[63] Wolkove N, Elkholy O, Baltzan M, Palayew M. Sleep and aging: 1. Sleep disorders commonly found in older people. CMAJ 2007;176(9):1299–304.
[64] De Vos FY, van Laarhoven HW, Laven JS, Themmen AA, Beex LV, Sweep CG, et al. Menopausal status and adjuvant hormonal therapy for breast cancer patients: a practical guideline. Crit Rev Oncol Hematol 2012;84(2):252–60.
[65] Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thürlimann B, Senn HJ, et al. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007 Ann Oncol 2007;18(7):1133–44.
[66] Berger AM, Treat Marunda HA, Agrawal S. Influence of menopausal status on sleep and hot flashes throughout breast cancer adjuvant chemotherapy. J Obstet Gynecol Neonatal Nurs 2009;38(3):353–66.
[67] Bradley CJ, Given CW, Roberts C. Race, socioeconomic status, and breast cancer treatment and survival. J Natl Cancer Inst 2002;94(7):490–6.
[68] Anders M, Breckenkamp J, Blettner M, Schlehofer B, Berg-Beckhoff G. Association between socioeconomic factors and sleep quality in an urban population-based sample in Germany. Eur J Public Health 2013 Nov 26 [Epub ahead of print].