View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Repositório Comum

The Breast 33 (2017) 125–131

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Neuropathic pain after breast cancer treatment and its impact on sleep quality one year after cancer diagnosis

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

[a] ISPUP – EPIUnit, Universidade do Porto, Porto, Portugal
[b] Centro de Medicina do Sono – Hospital CUF Porto, Porto, Portugal
[c] Instituto Português de Oncologia do Porto, Porto, Portugal
[d] Departamento de Ciências da Saúde Pública e Forenses e Educação Médica, Faculdade de Medicina, Universidade do Porto, Porto, Portugal

ARTICLE INFO

Article history:
Received 20 February 2017
Received in revised form
24 March 2017
Accepted 26 March 2017
Available online 4 April 2017

Keywords:
Breast neoplasm
Neuropathic pain
Quality of life
Sleep

ABSTRACT

Objectives: Data regarding the impact of breast cancer treatment-related neuropathic pain (NP) on sleep quality are scarce. Therefore, we aimed to assess the impact of breast cancer treatment-related NP on patients' sleep quality, during the first year after cancer diagnosis.
Materials and methods: A total of 501 breast cancer patients were followed prospectively. Incident NP was identified through systematic evaluations after treatments and one year after enrolment. NP severity was quantified using the Brief Pain Inventory severity subscale and sleep quality was evaluated through the Pittsburgh Sleep Quality Index (PSQI), at baseline and after one year. Adjusted regression coefficients (β) and 95% confidence intervals (95%CI) were used to quantify the relation between NP and the variation in the PSQI z-scores.
Results: The occurrence of NP was associated with a deterioration in sleep quality during the first year of follow-up, more pronounced among those with good sleep quality (PSQI≤5) than those with poor sleep quality at baseline (PSQI>5) (β = 0.44, 95%CI: 0.11 to 0.77 versus β = 0.33, 95%CI: 0.08 to 0.59). These differences were accentuated when only the cases of NP with greater severity were considered (β = 0.86, 95%CI: 0.37 to 1.35 versus β = 0.31, 95%CI: −0.08 to 0.64). Within the PSQI components, daytime dysfunction and sleep duration were the most impaired by NP.
Conclusion: Our findings highlight the importance of the promotion of sleep hygiene among breast cancer patients diagnosed with NP, especially among those with good sleep quality before treatments.
© 2017 Elsevier Ltd. All rights reserved.

1. Introduction

Neuropathic pain is defined, by the International Association for the Study of Pain (IASP), as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" [1]. Among breast cancer patients, it may occur due to: (a) cancer, when resulting from the compression or infiltration of the central or peripheral nervous system [2]; (b) comorbid conditions, such as diabetic neuropathy or postherpetic neuralgia; (c) cancer treatment, as a consequence of intraoperative damage to nervous system structures [3] or following radiotherapy and chemotherapy [4]. The increase in the number of women diagnosed at earlier stages of disease and surviving for longer periods [5] highlights the importance of understanding the burden of cancer treatment-related neuropathic pain and the assessment of its impact on patient-reported outcomes, including health-related quality of life (HRQOL) and specific dimensions of this broad construct.

Sleep disturbances have been shown to be an important contributor to poor HRQOL [6,7] and are estimated to affect up to two thirds of breast cancer patients [6,8–10]. In addition to factors that increase the susceptibility to develop sleep disturbances and to those that contribute to their maintenance over time, side effects of breast cancer treatments are described to act as precipitating factors that may prompt their development among breast cancer patients [11]. Previous studies have shown that pain following cancer treatments was associated with poorer sleep quality in breast cancer patients [12–14]. However, data regarding the specific impact of breast cancer treatment-related neuropathic pain on sleep quality are scarce, and did not take into account the sleep

* Corresponding author: Departamento de Ciências da Saúde Pública e Forenses e Educação Médica, Faculdade de Medicina, Universidade do Porto, Al. Prof Hernâni Monteiro, 4200-319 Porto, Portugal.
E-mail address: nlunet@med.up.pt (N. Lunet).

http://dx.doi.org/10.1016/j.breast.2017.03.013
0960-9776/© 2017 Elsevier Ltd. All rights reserved.

quality of the patients prior to treatments. In fact, in a high proportion of women, sleep disturbances are already present before treatment onset [15,16], whereas in others, sleep problems begin months after cancer diagnosis [17], which emphasizes the need to take into consideration baseline sleep quality status when assessing the impact of neuropathic pain on this outcome.

Studies providing a comprehensive characterization of the impact of cancer treatment-related neuropathic pain on patient reports of sleep quality will contribute to a better characterization of the burden associated with breast cancer treatments and may contribute to the development of strategies to minimize the impact of this condition, during treatment and in the long-term. We previously followed a cohort of breast cancer patients during one year after cancer diagnosis showing that neuropathic pain was the most frequent neurological complication during this period [18]. Now, we aimed to assess the impact of breast cancer treatment-related neuropathic pain on patients' sleep quality, in the same cohort of women evaluated before treatment and followed during one year after cancer diagnosis.

2. Methods

This is a prospective cohort study with a one year follow-up (Fig. 1). The study protocol has been described in detail elsewhere [19]. Briefly, we consecutively selected women with newly diagnosed breast cancer, admitted to the Breast Clinic of the Portuguese Institute of Oncology of Porto, Portugal, proposed for surgery, either as primary treatment or after neoadjuvant chemotherapy, and not having received any treatment for breast cancer before. We excluded those treated with chemotherapy and/or radiotherapy in the chest or axillary areas for other primary cancers and those with a high probability of cognitive impairment (scores less than 17, or less than 16 for women over 65 years old, in the Montreal Cognitive Assessment [20]). From those who underwent a baseline evaluation before treatment (N = 506), a total of 503 were followed during one year (one patient died and two patients abandoned the study).

Sociodemographic data were collected at baseline using a structured questionnaire applied by trained interviewers. Cancer stage was retrieved from clinical records after surgery and classified according to the American Joint Committee on Cancer seventh edition cancer staging manual [21]. Data on breast cancer treatments were obtained from the re-evaluation of clinical records one year after enrolment.

Patients with incident cancer treatment-related neuropathic pain were identified during systematic neurological evaluations performed after surgery, after chemotherapy (when applicable) and one year after enrolment, or through referral by any member of the clinical team (Fig. 1). Patients were considered to have neuropathic pain when it was present in the previous 24 h, in the breast, chest wall, axilla, or medial upper arm on the affected side, donor region of breast reconstruction, or in the hands/feet (secondary to chemotherapy-induced peripheral neuropathy). The grading system adopted by the IASP was used to classify neuropathic pain as "possible", when pain distribution is neuroanatomically plausible and history is suggestive of relevant lesions or diseases affecting the somatosensory system, "probable", when, in addition, the neurological examination confirms the presence of negative or positive sensory signs, confined to the innervation territory of the injury nervous structure, or a lesion or disease of the somatosensory system is confirmed by diagnostic tests (*e.g.*, neurophysiological tests), or "definite", when both the previous criteria are satisfied [22]. In the present study, neuropathic pain was diagnosed using only clinical history and clinical evaluation without complementary exams. Pain sensation was assessed with a wood cocktail-stick and light touch sensation by a piece of cotton wool, as recommend by the IASP [22].

The severity subscale of the Brief Pain Inventory was used to quantify pain severity in the previous 24 h [23]; it consists of a mean score of four questions measuring the "worst", "least", "average" and "current" pain (range: 0 to 10, with 0 corresponding to "no pain" and 10 to "pain as bad as you can imagine") [23]. The pharmacologic management of neuropathic pain was assessed through patients' self-report as well as data collected from clinical files, regarding drugs prescribed to be taken on a daily basis.

The Hospital Anxiety and Depression Scale (HADS) was used to evaluate anxiety and depression at baseline [24]. HADS consists of 14 items, with two 7-item subscales assessing anxiety and depression in the previous week (range: 0 to 21 for each subscale);

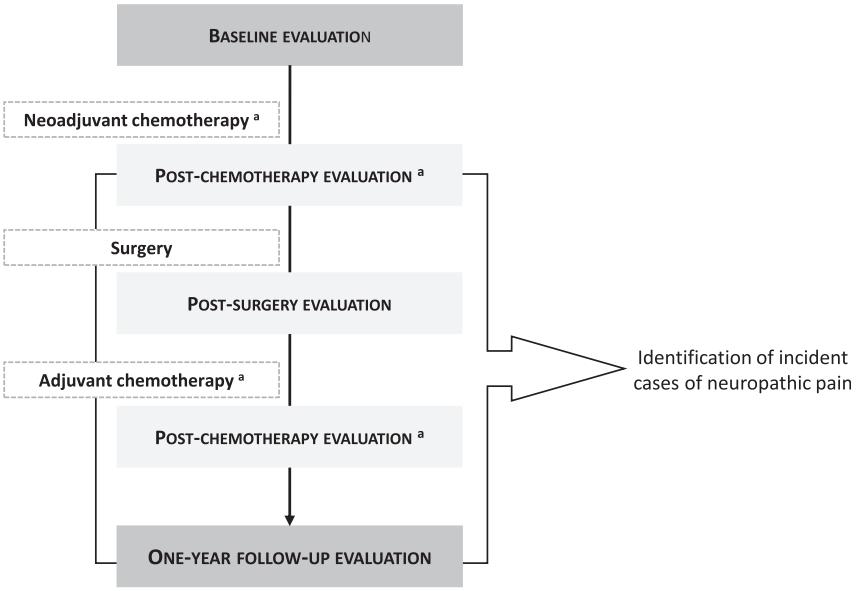

Fig. 1. Study design and timing of baseline and follow-up evaluations. [a] 34 (11.4%) patients performed neoadjuvant chemotherapy and 263 (88.6%) performed adjuvant chemotherapy.

a score greater than or equal to 11 for each of them was considered to be indicative of clinically significant anxiety and/or depression, as applicable [24].

The Pittsburgh Sleep Quality Index (PSQI) was used to evaluate sleep quality at baseline and at one year [25]. The PSQI includes 19 items measuring seven components, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction. All of the components (range: 0 to 3) are summed to provide a global score designed to measured sleep quality over the past month (range: 0 to 21); a score greater than five indicates poor sleep quality [25].

2.1. Statistical analysis

A total of 501 participants were included in the present study, after exclusion of those with missing information on sleep quality (N = 1) and anxiety or depression (N = 1).

Sample characteristics are presented as counts and proportions for categorical variables, and medians and percentiles 25 (P25) and 75 (P75) for quantitative variables. For analysis, age was categorized, using the mean of the distribution among all participants as the cutoff (≤55 years and >55 years), education was categorized as four years or less (primary education), five to nine years (lower secondary school) and 10 years or more (upper secondary and post-secondary education), and cancer stage was categorized as cancer stage 0 (Ductal carcinoma *in situ*) and I, II, and III and IV.

The Mann-Whitney *U* test was used to compare the variation of the PSQI score during the first year after breast cancer diagnosis, according to the occurrence of neuropathic pain. The improvement and deterioration in sleep quality were defined as a decrease or an increase of at least one point in the PSQI score, respectively.

Regression coefficients (β) and the corresponding 95% confidence intervals (95%CI) were used to quantify the association between incident neuropathic pain and the variation in the PSQI global z-score, during the first year after breast cancer diagnosis. Results were stratified by the sleep quality status of the patients at baseline and adjusted for potential confounders. Confounders were selected among those known to be associated with both the exposure and the outcome, but influenced by neither, according to previous studies or expert knowledge, as described in the footnotes of the corresponding table or figure. Similar models were fitted for change in each of the PSQI components between baseline and the one year follow-up evaluation. All analyses were stratified according to sleep quality at baseline (PSQI ≤5 versus PSQI >5, corresponding to good and poor sleep quality, respectively).

Statistical analysis was conducted using STATA®, version 11.2 (StataCorp, College Station, TX, USA).

2.2. Ethics

The study was approved by the Ethics Committee of the Portuguese Institute of Oncology of Porto (Ref. CES 406/011) and by the Portuguese Data Protection Authority (Ref. 9469/2012). All participants provided written informed consent.

3. Results

The sociodemographic and clinical characteristics of the patients are presented in Table 1. Half of the women had less than 55 years of age and almost half had less than four years of education. Less than 10% were diagnosed with ductal carcinoma *in situ* and around two thirds with cancer stage I or II. Nearly half were submitted to breast-conserving surgery. At baseline, 8.2% and 37.9% of the participants had an HADS score indicative of clinical significant depression and anxiety, respectively, and a total of 60.3% had poor sleep quality, according to the PSQI.

Table 1
Sociodemographic and clinical characteristics of the patients (N = 501).

	N (%)
Age at baseline (years)	
≤55	265 (52.9)
>55	236 (47.1)
Education at baseline (years)	
≤4	215 (42.9)
5–9	142 (28.3)
≥10	144 (28.7)
Anxiety at baseline[a]	190 (37.9)
Depression at baseline[b]	41 (8.2)
Poor sleep quality at baseline[c]	302 (60.3)
Cancer stage	
0 (DCIS)	34 (6.8)
I	234 (46.7)
II	155 (30.9)
III	75 (15.0)
IV	3 (0.6)
Breast surgery	
None/Breast-conserving[d]	250 (49.9)
Mastectomy	251 (50.1)
Axillary surgery[e]	
None/SLNB	329 (65.7)
ALND	172 (34.3)
Chemotherapy[f]	297 (59.3)
Radiotherapy (internal and/or external)	369 (73.6)

ALND, Axillary lymph node dissection; DCIS, Ductal carcinoma *in situ*; SLNB, Sentinel lymph node biopsy.

[a] Defined as a score ≥11 in the anxiety subscale of the Hospital Anxiety and Depression Scale.

[b] Defined as a score ≥11 in the depression subscale of the Hospital Anxiety and Depression Scale.

[c] Defined as a score >5 in the Pittsburgh Sleep Quality Index.

[d] Patients who had both mastectomy and breast-conserving surgery are reported as mastectomy; one patient only performed axillary surgery.

[e] Patients who had both ALND and SLNB are reported as ALND.

[f] Concomitant 5-fluorouracil, epirubicin and cyclophosphamide, followed by docetaxel (N = 176); concomitant doxorubicin and cyclophosphamide (N = 60); concomitant doxorubicin and cyclophosphamide, followed by docetaxel (N = 32); concomitant 5-fluorouracil, epirubicin and cyclophosphamide (N = 24); concomitant cyclophosphamide and docetaxel (N = 2); concomitant 5-fluorouracil, cyclophosphamide and methotrexate (N = 1); concomitant carboplatin and docetaxel (N = 1); concomitant doxorubicin and cyclophosphamide, followed by paclitaxel (N = 1).

During the first year of follow-up, a total of 156 patients were diagnosed with neuropathic pain a median time (P25; P75) of 62.5 (35.5; 229.5) days after the baseline evaluation and 308.0 (131.0; 331.5) days before the one year follow-up. All cases were classified as "probable" according to the IASP grading system. The median scores (P25; P75) for pain severity and for worst pain intensity in the last 24 h, at the moment of diagnosis, was 2.5 (1.5; 3.8) and 4 (3; 5), respectively. A total of 55 patients (35.3%) underwent pharmacological treatment for neuropathic pain until the one year follow-up evaluation; the most frequent prescriptions were gabapentin (81.8%) and pregabalin (32.7%). The prescription of treatment for NP occurred more frequent in those with poor sleep quality than in those with good sleep quality at baseline (14.8% and 5.0%, respectively). A total of 3.2% of the patients had symptoms in the hands/feet, corresponding to patients with chemotherapy-induced peripheral neuropathic pain.

The PSQI score variation during the first year after breast cancer diagnosis, according to the occurrence of neuropathic pain and sleep quality at baseline, is depicted in Fig. 2. Among patients with good sleep quality at baseline, there was a deterioration in sleep quality, significantly higher in those with neuropathic pain during the first year of follow-up [median variation (P25; P75): 2 (0; 4)

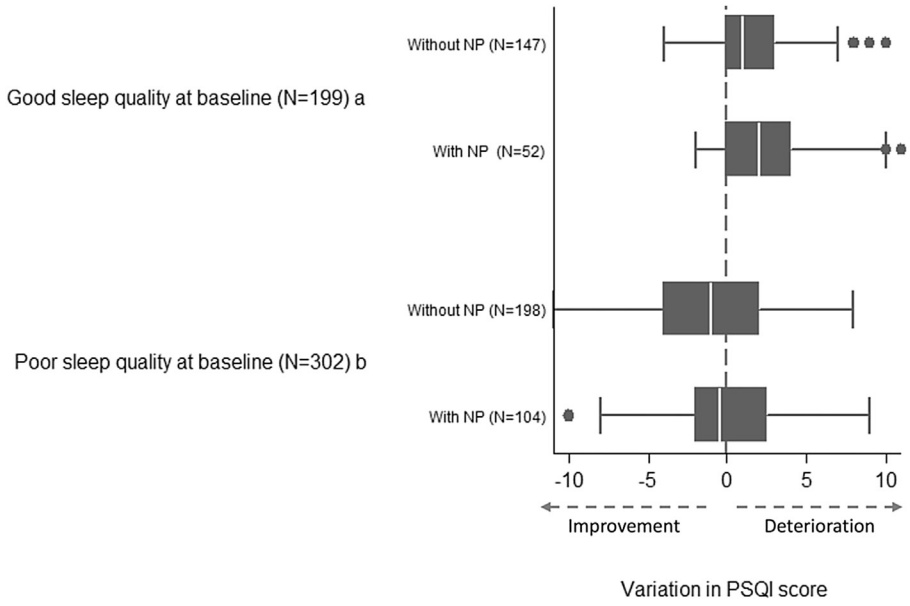

Fig. 2. Variation of the Pittsburgh Sleep Quality Index (PSQI) score during the first year after breast cancer diagnosis, according to the occurrence of neuropathic pain (NP) and sleep quality at baseline. NP, Neuropathic pain; PSQI, Pittsburgh Sleep Quality Index. [a] Defined as a score ≤5 in the PSQI. [b] Defined as a score >5 in the PSQI.

versus 1 (0; 3); p = 0.036]. Among patients with poor sleep quality at baseline, there was an improvement in sleep quality until the one year follow-up evaluation, significantly lower in those with neuropathic pain during the first year of follow-up [median variation (P25; P75): −0.5 (−2; 2.5) versus −1 (−4; 2); p = 0.030].

In the multivariable analysis, when considering all participants, the occurrence of neuropathic pain was associated with a deterioration in sleep quality during the first year of follow-up (variation in the PSQI global z-score: β = 0.32, 95%CI: 0.12 to 0.52) (Table 2). However, this worsening was more pronounced among those with good sleep quality than in those with poor sleep quality at baseline (β = 0.44, 95%CI: 0.11 to 0.77 versus β = 0.33, 95%CI: 0.08 to 0.59). These differences were accentuated when only neuropathic pain with greater severity at the moment of its diagnosis was considered (β = 0.86, 95%CI: 0.37 to 1.35 versus β = 0.31, 95%CI: −0.08 to 0.64).

When considering each of the PSQI components, among those with good sleep quality at baseline, the incidence of neuropathic pain was associated with a tendency for a deterioration in all components during the follow-up, statistically significant only for daytime dysfunction (β = 0.52, 95%CI: 0.18 to 0.86) (Fig. 3A). However, there was also a statistically significant lower sleep duration (β = 0.70, 95%CI: 0.20 to 1.21) and more frequent use of sleep medication (β = 0.58, 95%CI: 0.06 to 1.09) when greater neuropathic pain severity at the moment of its diagnosis was analyzed (Fig. 3B).

Among those with poor sleep quality, the tendency for a deterioration in each PSQI component was less consistent but there was a statistically significant lower sleep duration (β = 0.36, 95%CI: 0.10 to 0.62) and higher daytime dysfunction (β = 0.32, 95%CI: 0.07 to 0.58) among those with incident neuropathic pain (Fig. 3A).

4. Discussion

Our study provides a comprehensive characterization of the impact of treatment-related neuropathic pain on patients' sleep quality, one year after breast cancer diagnosis. The occurrence of neuropathic pain was associated with deterioration in global sleep quality, more pronounced among those with good sleep quality prior to cancer treatments, with a greatest impact in daytime dysfunction and sleep duration.

Table 2
Regression coefficients (β) and the corresponding 95% confidence intervals (95%CI) for the relation between incident neuropathic pain (NP) and the variation of the Pittsburgh Sleep Quality Index (PSQI) global z-score in the first year after breast cancer diagnosis[a], according to sleep quality at baseline.

	All participants		Good sleep quality at baseline[b]		Poor sleep quality at baseline[c]	
	Crude β (95%CI)	Adjusted β (95%CI)[d]	Crude β (95%CI)	Adjusted β (95%CI)[d]	Crude β (95%CI)	Adjusted β (95%CI)[d]
NP incidence						
Without NP	0 (ref.)	0 (ref.)	0 (ref.)	0 (ref.)	0 (ref.)	0 (ref.)
With NP	0.22 (0.03 to 0.41)	0.32 (0.12 to 0.52)	0.29 (−0.02 to 0.61)	0.44 (0.11 to 0.77)	0.30 (0.06 to 0.54)	0.33 (0.08 to 0.59)
Severity of NP[e]						
Without NP	0 (ref.)	0 (ref.)	0 (ref.)	0 (ref.)	0 (ref.)	0 (ref.)
Severity ≤ than median	0.22 (−0.02 to 0.46)	0.28 (0.04 to 0.53)	0.11 (−0.26 to 0.48)	0.21 (−0.18 to 0.59)	0.31 (0.00 to 0.62)	0.31 (−0.02 to 0.63)
Severity > than median	0.19 (−0.07 to 0.45)	0.33 (0.05 to 0.60)	0.64 (0.14 to 1.14)	0.86 (0.37 to 1.35)	0.24 (−0.06 to 0.55)	0.31 (−0.08 to 0.64)

PSQI, Pittsburgh Sleep Quality Index; 95%CI, 95% Confidence intervals.
[a] Scores higher than zero correspond to a worsening of sleep quality during the follow-up.
[b] Defined as a score ≤5 in the PSQI.
[c] Defined as a score >5 in the PSQI.
[d] Adjusted for age, education, cancer stage, anxiety and depression at baseline, breast and axillary surgery, chemotherapy and radiotherapy.
[e] Assessed through the severity subscale of the Brief Pain Inventory. The median value of pain severity in those diagnosed with NP (2.5 out of 10) was used as cut-off.

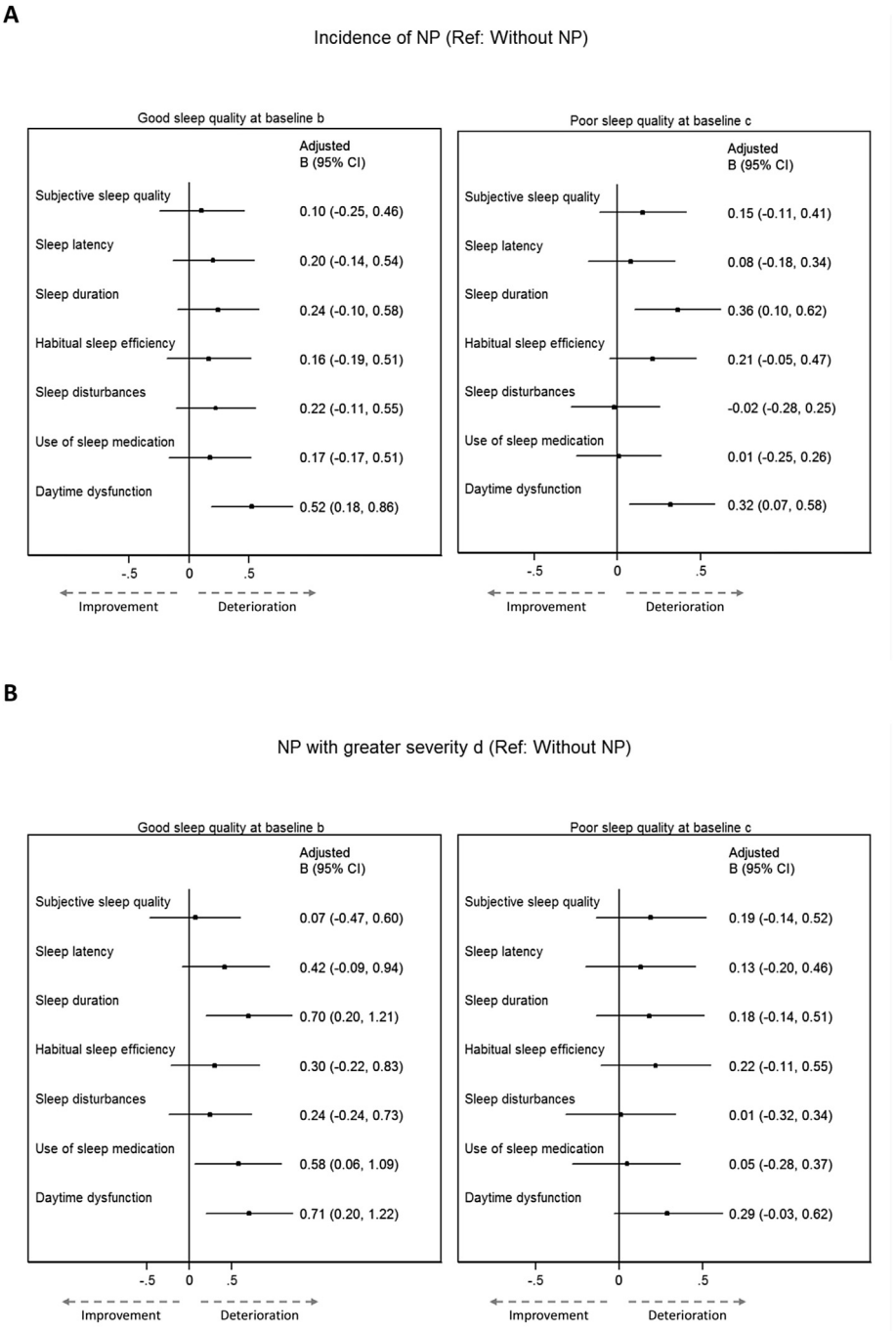

Fig. 3. Regression coefficients (β) and the corresponding 95% confidence intervals (95%CI) for the relation between incidence of neuropathic pain (NP) (**A**) or incidence of NP with greater severity (**B**) and the variation of the Pittsburgh Sleep Quality Index (PSQI) components z-scores in the first year after breast cancer diagnosis [a], according to sleep quality at baseline. NP, neuropathic pain; PSQI, Pittsburgh Sleep Quality Index; 95%CI, 95% confidence intervals. [a] Scores higher than zero correspond to a deterioration in each of the PSQI components during the follow-up, *e.g.* worse subjective sleep quality, greater sleep latency, less sleep duration, less habitual sleep efficiency, greater sleep disturbance, greater use of sleep medication and greater daytime dysfunction, as applicable. All values were adjusted for age, education, cancer stage, anxiety and depression at baseline, breast and axillary surgery, chemotherapy and radiotherapy. [b] Defined as a score ≤5 in the PSQI. [c] Defined as a score >5 in the PSQI. [d] Severity assessed through the severity subscale of the Brief Pain Inventory. The median value of pain severity in those diagnosed with NP (2.5 out of 10) was used as cut-off.

Few previous studies have addressed the relation between treatment-related neuropathic pain and sleep quality of breast cancer patients [26,27]. In a study from Israel, assessing the relationship between symptom clusters and chemotherapy-induced neuropathic pain in a sample of 40 patients treated with paclitaxel, the authors found that the "high cluster group" included patients who reported both high levels of pain with neuropathic pain characteristics and sleep disturbances [26]. A study from Spain assessing patients for a median time of 18 months after cancer diagnosis, found that the pharmacological treatment of neuropathic pain was associated with an improvement in sleep quality eight weeks later [27]. In both studies, the identification of

neuropathic pain was based on a screening instrument, estimated to fail to detect 10% to 20% of the patients with clinically diagnosed neuropathic pain [22,28] and in the study from Spain only approximately 20% of the patients included had breast cancer and only 30% of the neuropathic pain was treatment-related, which did not allow for direct comparisons with our results.

The interrelationship between neuropathic pain and sleep is complex and far from being completely explained [29]. Experimental studies have shown a development of hyperalgesia and a decrease of pain threshold with sleep deprivation [30,31], in accordance with the growing number of epidemiological studies showing that in addition to neuropathic pain impairing sleep, poor sleep quality may also exacerbate neuropathic pain, and the two symptoms may coexist in breast cancer patients as part of a symptom cluster that could also include fatigue and psychiatric disorders, namely anxiety and depression [29]. In our study, the fact that the percentage of patients with neuropathic pain diagnosed among those with good and poor sleep quality at baseline was approximately the same argues in favor of neuropathic pain impairing sleep rather than the inverse relation.

Among the PSQI components, neuropathic pain was more strongly associated with the daytime dysfunction and sleep duration specific components. This is consistent with previous studies using objective sleep measures that showed that patients suffering from different pain disorders presented lower sleep efficiency and increased wakefulness [32]. In fact, sleepiness and the decrease of slow wave sleep are frequently reported as a side-effect of the most commonly used drugs in neuropathic pain treatment [32] and could, at least in part, explain these findings. In our study, gabapentin and pregabalin were the most frequently used drugs to treat neuropathic pain, which is in accordance with the recommendations for neuropathic pain pharmacological management of the European Federation of Neurological Societies Task Force [33]. However, this may have contributed to attenuate the effect of this neurological condition on global sleep quality, mostly among those with poor sleep quality at baseline, who were more frequently treated, as both drugs have consistently demonstrated efficacy in reducing sleep disturbances associated with neuropathic pain [34,35]. The use of complementary therapies for pain relief (*e.g.* acupuncture) may have also contributed to lessen the effect of neuropathic pain on sleep quality, but these exposures were not evaluated in our study.

The major methodological strengths of our study are the prospective design, with a systematic evaluation of sleep quality prior to treatments, the nearly complete follow-up of patients and the use of the IASP grading system to classify neuropathic pain. Still, some limitations need to be addressed. First, the assessment of a cohort with a large number of participants precluded the use of objective measures of sleep, obtained through polysomnography or actigraphy. Nevertheless, the individuals' perception about sleep has demonstrated to be an important determinant of quality of life [6,7] and thus should be analyzed in addition to objective measures, and the PSQI is one of the recommended instruments for the assessment of sleep or insomnia symptoms [36]. Secondly, we evaluated essentially women in early stages of disease who underwent surgery, which limits the generalization of our results to patients with more advanced stages. Third, future studies may include information regarding other potential confounders of the relation between neuropathic pain and poor sleep quality, including preexisting conditions such as back pain or fibromyalgia, that were not evaluated in the present study. Finally, the use of sleep medication, expectedly more frequent among those with poor sleep quality at baseline, may have played a role as a regulator of pain, decreasing neuropathic pain severity. Also, during the follow-up period, sleep medication prescription may have been more intensive among women diagnosed with neuropathic pain, as a response to a deleterious effect of this condition on sleep. Both of the situations may had contributed to the underestimation of the association found in our analysis. Unfortunately, although we have self-reported data regarding the frequency of sleep medication use, evaluated using the PSQI, a finer characterization of these treatments was not available, precluding a better understanding of these relations.

In conclusion, we provide evidence of the relation between cancer treatment-related neuropathic pain and the decrease of perceived sleep quality during the first year of follow-up, mainly among those with good sleep quality at baseline. Our findings highlight the importance of the promotion of sleep hygiene in those diagnosed with neuropathic pain, and bring attention to those with higher sleep quality prior to treatments as the target population for this intervention. Additional research is needed to elucidate the dynamic interrelationship nature among neuropathic pain and sleep quality, within those recently treated for breast cancer and in survivors.

Acknowledgments

This study was funded by FEDER through the Operational Programme Competitiveness and Internationalization (POCI-01-0145-FEDER-016867) and national funding from the Foundation for Science and Technology – FCT (Portuguese Ministry of Science, Technology and Higher Education) (PTDC/DTP-EPI/7283/2014) under the Unidade de Investigação em Epidemiologia - Instituto de Saúde Pública da Universidade do Porto (EPIUnit) (POCI-01-0145-FEDER-006862; Ref.UID/DTP/04750/2013); the PhD Grant SFRH/BD/92630/2013 (Filipa Fontes) co-funded by the FCT and the POPH/FSE Program. Data management activities were supported by the Chair on Pain Medicine of the Faculty of Medicine, University of Porto and by the Grünenthal Foundation – Portugal.

Conflict of interests

None declared.

References

[1] Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 2008;70:1630–5.
[2] Khasraw M, Posner JB. Neurological complications of systemic cancer. Lancet Neurol 2010;9:1214–27.
[3] Jung BF, Ahrendt GM, Oaklander AL, Dworkin RH. Neuropathic pain following breast cancer surgery: proposed classification and research update. Pain 2003;104:1–13.
[4] Jung BF, Herrmann D, Griggs J, Oaklander AL, Dworkin RH. Neuropathic pain associated with non-surgical treatment of breast cancer. Pain 2005;118:10–4.
[5] Sant M, Chirlaque Lopez MD, Agresti R, Sanchez Perez MJ, Holleczek B, Bielska-Lasota M, et al. Survival of women with cancers of breast and genital organs in Europe 1999-2007: results of the EUROCARE-5 study. Eur J Cancer 2015;51:2191–205.
[6] Fortner BV, Stepanski EJ, Wang SC, Kasprowicz S, Durrence HH. Sleep and quality of life in breast cancer patients. J Pain Symptom Manag 2002;24:471–80.
[7] 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;11:189–206.
[8] Otte JL, Carpenter JS, Russell KM, Bigatti S, Champion VL. Prevalence, severity, and correlates of sleep-wake disturbances in long-term breast cancer survivors. J Pain Symptom Manag 2010;39:535–47.
[9] 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;21:43–51.
[10] 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;17:9–18.
[11] Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. J Clin Oncol 2001;19:895–908.

[12] Belfer I, Schreiber KL, Shaffer JR, Shnol H, Blaney K, Morando A, et al. Persistent postmastectomy pain in breast cancer survivors: analysis of clinical, demographic, and psychosocial factors. J Pain 2013;14:1185–95.
[13] Palesh OG, Collie K, Batiuchok D, Tilston J, Koopman C, Perlis ML, et al. A longitudinal study of depression, pain, and stress as predictors of sleep disturbance among women with metastatic breast cancer. Biol Psychol 2007;75:37–44.
[14] Jensen MP, Chang HY, Lai YH, Syrjala KL, Fann JR, Gralow JR. Pain in long-term breast cancer survivors: frequency, severity, and impact. Pain Med 2010;11:1099–106.
[15] Denieffe S, Cowman S, Gooney M. Symptoms, clusters and quality of life prior to surgery for breast cancer. J Clin Nurs 2014;23:2491–502.
[16] 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;27:5233–9.
[17] 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;24:583–90.
[18] Pereira S, Fontes F, Sonin T, Dias T, Fragoso M, Castro-Lopes JM, et al. Neurological complications of breast cancer: a prospective cohort study. Breast 2015;24:582–7.
[19] Pereira S, Fontes F, Sonin T, Dias T, Fragoso M, Castro-Lopes J, et al. Neurological complications of breast cancer: study protocol of a prospective cohort study. BMJ Open 2014;4:e006301.
[20] Freitas S, Simoes MR, Alves L, Santana I. Montreal cognitive assessment (MoCA): normative study for the Portuguese population. J Clin Exp Neuropsychol 2011;33:989–96.
[21] Edge S, Byrd D, Comptom C, Fritz A, Greene F. In: AJCC cancer staging manual. seventh ed. New York: Springer; 2010.
[22] Haanpaa M, Attal N, Backonja M, Baron R, Bennett M, Bouhassira D, et al. NeuPSIG guidelines on neuropathic pain assessment. Pain 2011;152:14–27.
[23] Cleeland CS, Ryan KM. Pain assessment: global use of the Brief pain inventory. Ann Acad Med Singap 1994;23:129–38.
[24] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.
[25] 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;28:193–213.
[26] Golan-Vered Y, Pud D. Chemotherapy-induced neuropathic pain and its relation to cluster symptoms in breast cancer patients treated with paclitaxel. Pain Pract 2013;13:46–52.
[27] Manas A, Monroy JL, Ramos AA, Cano C, Lopez-Gomez V, Masramon X, et al. Prevalence of neuropathic pain in radiotherapy oncology units. Int J Radiat Oncol Biol Phys 2011;81:511–20.
[28] Cruccu G, Sommer C, Anand P, Attal N, Baron R, Garcia-Larrea L, et al. EFNS guidelines on neuropathic pain assessment: revised 2009. Eur J Neurol 2010;17:1010–8.
[29] Argoff CE. The coexistence of neuropathic pain, sleep, and psychiatric disorders: a novel treatment approach. Clin J Pain 2007;23:15–22.
[30] Schuh-Hofer S, Wodarski R, Pfau DB, Caspani O, Magerl W, Kennedy JD, et al. One night of total sleep deprivation promotes a state of generalized hyperalgesia: a surrogate pain model to study the relationship of insomnia and pain. Pain 2013;154:1613–21.
[31] Tiede W, Magerl W, Baumgartner U, Durrer B, Ehlert U, Treede RD. Sleep restriction attenuates amplitudes and attentional modulation of pain-related evoked potentials, but augments pain ratings in healthy volunteers. Pain 2010;148:36–42.
[32] Onen SH, Onen F, Courpron P, Dubray C. How pain and analgesics disturb sleep. Clin J Pain 2005;21:422–31.
[33] Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol 2010;17:1113–e1188.
[34] Ogawa S, Arakawa A, Hayakawa K, Yoshiyama T. Pregabalin for neuropathic pain: why benefits could Be expected for multiple pain conditions. Clin Drug Investig 2016;36:877–88.
[35] Moore RA, Wiffen PJ, Derry S, Toelle T, Rice AS. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev 2014;27. Cd007938.
[36] Buysse DJ, Ancoli-Israel S, Edinger JD, Lichstein KL, Morin CM. Recommendations for a standard research assessment of insomnia. Sleep 2006;29:1155–73.