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Original article

A prospective study on the neurological complications of breast cancer and its treatment: Updated analysis three years after cancer diagnosis

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ABSTRACT

Objectives: To quantify the prevalence of neurological complications among breast cancer patients at one and three years after diagnosis, and to identify factors associated with neuropathic pain (NP) and chemotherapy-induced peripheral neuropathy (CIPN).
Material and methods: Prospective cohort study including 475 patients with newly diagnosed breast cancer, recruited among those proposed for surgical treatment (Portuguese Institute of Oncology, Porto). Patients underwent a neurological evaluation and had their cognitive function assesses with the Montreal Cognitive Assessment, before treatment and at one and three years after enrollment. We estimated the prevalence of each neurological complication, and odds ratios (OR), adjusted for socio-demographic and clinical characteristics, to identify factors associated with NP and CIPN.
Results: More than half of the patients [54.7%, 95% confidence interval (95%CI): 50.2–59.2] presented at least one neurological complication, at one or at three years after cancer diagnosis. Between the first and the third year of follow-up, there was an increase in the prevalence of NP (from 21.1% to 23.6%), cognitive impairment (from 7.2% to 8.2%), cerebrovascular disease (from 0.6% to 1.5%) and brain metastasis (from 0.0% to 0.6%). The prevalence of CIPN decreased from 14.1% to 12.6%. Axillary lymph node dissection was associated with NP at one year (OR = 2.75, 95%CI: 1.34–5.63) and chemotherapy with NP at three years (OR = 2.10, 95%CI: 1.20–3.67). Taxane-based chemotherapy was strongly associated with prevalence of CIPN at one and three years.
Conclusion: Neurological complications are frequent even three years after cancer diagnosis and NP remained the major contributor to the burden of these conditions among survivors.

Introduction

Breast cancer is the most frequent cancer among women, estimated to have accounted for approximately one quarter of all cases of cancer diagnosed in 2012 [1]. Access to early diagnosis through mammography screening and effective treatments [2] makes breast cancer one of those with a better prognosis. The 5-year net survival is now greater than 80% in most developed countries [3], and this translates into a high number of women living for longer periods with possible sequelae of breast cancer and its treatment, emphasizing the relevance of a comprehensive study of the burden of cancer among survivors.

Neurological complications, either direct, namely metastatic disease, or due to indirect mechanisms, including vascular disorders, paraneoplastic syndromes or side-effects of treatments, may be a frequent source of morbidity among breast cancer patients [4,5]. We previously followed a cohort of breast cancer patients during the first year after diagnosis, and showed that nearly half of the women treated for breast cancer had at least one neuro-oncological complication and one quarter developed at least two during this period; the most frequent were neuropathic pain (NP) and chemotherapy-induced peripheral neuropathy (CIPN) [6].

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The progression of cancer itself and the subsequent exposure to additional treatments, the late and/or cumulative effects of some options of cancer management, but also the possibility of recovering from some of the neuro-oncological complications over time, bring attention to the importance of a comprehensive assessment of the prevalence of these conditions in the long term. Therefore, we updated the follow-up of this cohort up to three years after diagnosis, aiming to quantify the prevalence of neurological complications among breast cancer patients, and to identify factors associated with NP and CIPN.

Material and methods

We conducted a prospective study with newly diagnosed breast cancer women, followed for three years. The study protocol has been described in detail elsewhere [7].

Patients and setting

Patients proposed for surgery were consecutively recruited in 2012, among those admitted to the Breast Clinic of the Portuguese Institute of Oncology of Porto, Portugal. We excluded women that had received any treatment for breast cancer before, those previously treated with chemotherapy and/or radiotherapy in the chest and/or axillary areas for other primary cancers, and those considered less likely to be able to cooperate due to cognitive impairment [score lower than 17, or lower than 16 for women over 65 years, in the Montreal Cognitive Assessment (MoCA) [8,9]].

The cohort included 506 patients with incident breast cancer, from whom 31 were lost to follow-up until the three-year of follow-up (11 patients died, 10 abandoned the study, six could not be contacted, two were transferred to another hospital and two were considered unable to cooperate by the neurologist). Therefore, a total of 475 (93.9%) completed the three-year follow-up evaluation with a median [percentile 25-percentile 75 (P25-P75)] time of follow-up of 1095 (1073–1126) days and were included in the present analysis. The patients lost to follow-up were not significantly different (participants vs. lost to follow-up) regarding age (median: 54.7 vs. 58.1 years, $p = 0.130$), education [median: 6 vs. 4 schooling years (4–6), $p = 0.081$] and cancer stage (stage 0/I: 53.9% vs. 48.4%, $p = 0.581$).

Data collection

All participants underwent a neurological evaluation at baseline (before any treatment) and at one and three years after enrollment.

Complementary exams (e.g.: computed tomography, magnetic resonance imaging, nerve conducting studies) were requested whenever indicated, according to the usual practice of the hospital. In all evaluations, socio-demographic data were collected using a structured questionnaire and clinical records were reviewed for cancer stage, breast cancer treatments and the presence of recurrence. Cancer stage was classified according to the American Joint Committee on Cancer staging manual [10].

Prevalence of neurological complications

Neurological complications affecting the patients at one and three years after cancer diagnosis were recorded; this included conditions identified *de novo* in any of these follow-up evaluations or diagnosed before, but still present at the follow-up evaluation.

CIPN was defined as peripheral neuropathy occurring after chemotherapy. Among subjects with peripheral neuropathy at baseline, CIPN was considered present only if there was a worsening of the preexisting neuropathy. The severity of CIPN was quantified using the Total Neuropathy Score, clinical version (TNSc) (range: 0 to 28) [11] and the Common Terminology Criteria for Adverse Events, V.4.0 (CTCAE) (range: 1 to 5) [12]. In both scales, higher scores represent greater severity.

NP was considered probable, according to the International Association for the Study of Pain (IASP) [13], if pain distribution was neuroanatomically plausible and history was suggestive of relevant lesions or diseases affecting the somatosensory system, plus negative or positive sensory signs in neurological examination, confined to the innervation territory of the injured nervous structure. Pain sensation and light touch sensation were assessed using a wood cocktail stick and a piece of cotton wool, respectively, as recommended by the IASP [13]. We considered NP secondary to breast cancer treatments as prevalent in each of the evaluations if it was present in the last 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 CIPN). In order to quantify pain severity, the severity subscale of the Brief Pain Inventory Short Form was used [14]; it consists of a mean score of four questions measuring the worst, least, average and current pain in the past 24 h (range: 0 to 10, with 0 = “no pain” and 10 = “pain as bad as you can imagine”).

Among patients submitted to mastectomy, phantom breast syndrome was defined as the presence of the sensation that the removed breast is still present [15]. When in addition, patients described a sensation of pain in the removed breast, phantom breast pain was considered present [15] and the CTCAE was used to grade phantom pain (range: 1 to 5) [12].

Cognitive impairment was considered present when the patients' MoCA score (range: 0 to 30) was at least 2.0 standard deviations below age- and education-adjusted cut-offs for possible cognitive impairment [8].

Statistical analysis

Patients' characteristics were presented as counts and proportions for all categorical variables, and median and P25-P75 for quantitative variables.

Prevalence estimates and corresponding 95% confidence intervals (95%CI) were estimated for each of the neurological complications at one and three years after cancer diagnosis. The McNemar's test was used to compare the proportion of patients with each complication at one and three years.

Adjusted odds ratios (OR) and 95%CI were computed using logistic regression, to quantify the relation between sociodemographic and clinical characteristics of the patients and the presence of NP and CIPN at one and three years after cancer diagnosis.

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

Results

Patients' characteristics

At baseline, half of the women had less than 55 years of age and more than two thirds had less than 10 years of education. A total of 6.5% were diagnosed with non-invasive breast cancer (ductal carcinoma in situ) and the remaining with invasive breast cancer stage I (47.4%), II (30.7%), III (14.7%) or IV (0.6%).

The breast cancer treatments performed during the first year after diagnosis are presented in Table 1. Nearly half of the patients were submitted to mastectomy and just over one third to axillary lymph node dissection (ALND). Most of the participants underwent adjuvant treatment. Docetaxel-based regimens were used by more than two thirds of women receiving chemotherapy.

Table 1
Breast cancer treatments performed during the first year after diagnosis (N = 475).

	N (%)
Breast surgery[a]	
Mastectomy	220 (46.3)
Mastectomy + breast-reconstruction	15 (3.2)
Breast-conserving	239 (50.3)
Axillary surgery[b]	
Lymph node dissection	162 (34.1)
Sentinel lymph node biopsy	299 (62.9)
Chemotherapy	288 (60.6)
Timing[c]	
Neoadjuvant	32 (11.1)
Adjuvant	256 (88.9)
Drugs[c]	
Doxorubicin + cyclophosphamide	59 (20.5)
Doxorubicin + cyclophosphamide + docetaxel	30 (10.4)
Doxorubicin + cyclophosphamide + paclitaxel	1 (0.4)
Cyclophosphamide + docetaxel	2 (0.7)
Carboplatin + docetaxel	1 (0.4)
5-FU + epirubicin + cyclophosphamide	23 (8.0)
5-FU + epirubicin + cyclophosphamide + docetaxel	171 (59.4)
5-FU + cyclophosphamide + methotrexate	1 (0.4)
Radiotherapy (chest, axillary and/or supraclavicular)	350 (73.7)
Brachytherapy	91 (19.2)
Endocrine therapy[d]	400 (84.2)
Immunotherapy[d]	63 (13.3)

5-FU, 5-Fluorouracil.
[a] Patients who had both mastectomy and breast-conserving surgery are reported as mastectomy. Does not sum 100.0% because one patient only performed axillary surgery.
[b] Patients who had both lymph node dissection and sentinel lymph node biopsy are reported as lymph node dissection. Does not sum 100.0% because 14 patients only performed breast surgery.
[c] Only computed among those who performed chemotherapy.
[d] All patients began this treatment during the first year of follow-up and remained under treatment after the one-year follow-up evaluation.

Between the first and the third year of follow-up, less than 2% of the patients underwent each of the following treatments: ALND, metastasectomy, radiotherapy or chemotherapy (Table 2).

Prevalence of neurological complications at one and three years of follow-up

Just over 40% of breast cancer patients had at least one cancer-related neurological complication, at one (42.7%, 95%CI: 38.4–47.2) and three years of follow-up (41.7%, 95%CI: 37.3–46.2). More than half of the participants (54.7%, 95%CI: 50.2–59.2) presented at least one neurological complication, either at one- or at three-year follow-up evaluation.

Table 2
Cancer treatments performed after the first year after diagnosis (N = 475).

	N (%)
Breast surgery	
Breast-reconstruction	26 (5.5)
Axillary surgery	
Lymph node dissection	1 (0.2)
Hepatic metastasectomy	1 (0.2)
Cerebral metastasectomy	1 (0.2)
Chemotherapy	9 (1.9)[a]
Drugs[b]	
Capecitabine	3 (33.3)
Docetaxel	2 (22.2)
Paclitaxel	5 (55.6)
Vinorelbine	1 (11.1)
Rituximab + cyclophosphamide + doxorubicin + vincristine	1 (11.1)[c]
Radiotherapy (chest, axillary, supraclavicular, bone and/or cerebral)	7 (1.5)

[a] Only one of these patients was not submitted to chemotherapy during the first year of follow-up.
[b] Only computed among those who performed chemotherapy. Does not sum 100.0% because some patients were submitted to more than one scheme after the first year after diagnosis.
[c] Patient submitted to chemotherapy due to a second primary cancer.

As depicted in Fig. 1, between the first and the third year after breast cancer diagnosis, there was a non-statistically significant increase in the prevalence of NP, from 21.1% to 23.6% ($p = 0.225$), and a significant decrease in the proportion of women with phantom breast syndrome, from 17.1% to 10.7% ($p < 0.001$). The prevalence of cognitive impairment varied from 7.2% to 8.2% ($p = 0.466$), though 55.9% and 28.2% of those with cognitive impairment at one and three years, respectively, already presented this condition prior to treatment. The variation in the prevalence of cerebrovascular disease (from 0.6% to 1.5%; $p = 0.125$) and CIPN (from 14.1% to 12.6%; $p = 0.127$) was not statistically significant. Brain metastasis were identified in three patients (0.6%, 95%CI: 0.1–1.9) at the three-year evaluation.

The association between different characteristics of the patients and the presence of NP at one and three years after cancer diagnosis are reported in Table 3. At one year, older patients were less likely to present NP and those with cancer stage III/IV and those who underwent ALND presented higher odds of NP. At three years after cancer diagnosis only the patients submitted to chemotherapy had higher odds of NP. Those with NP at one year after cancer diagnosis had eight fold higher odds of NP at three years (OR = 8.20, 95%CI: 4.84–13.9, adjusted for all variables presented in Table 3).

The association between different characteristics of the patients and the presence of CIPN at one and three years after cancer diagnosis are reported in Table 4. Cancer stage III/IV and taxane-based chemotherapy were associated with a higher odds of CIPN, both at one and three years. Patients undergoing chemotherapy between the first and the third year had higher odds of CIPN at the three-year follow-up than those treated with chemotherapy only during the first year (OR = 11.7, 95%CI: 2.16–63.89, adjusted for all variables presented in Table 4).

Fig. 2 depicts the number of patients with the most common neurological complications, according to their presence at one and three years of follow-up. More than three quarters of the women with CIPN and more than half of those with NP remained affected by these conditions three years after cancer diagnosis. A total of 66.7% of the patients presenting cognitive impairment and 49.1% of those with NP at the three-year follow-up were not prevalent cases at the one-year evaluation.

Pain severity scores among patients with NP are presented in Fig. 3. Among those with NP in both moments there was a significant increase in the median score (2.4 vs. 3.2, $p < 0.005$). NP was less severe among women presenting this condition at the one-year evaluation only, than those with NP at the three-year follow-up only (median score: 1.2 vs. 2.5, $p < 0.001$).

Among those with CIPN in both moments, there was a significant decrease in the median score of TNSc (5.0 vs. 4.0, $p = 0.006$). CIPN had greater severity among women presenting this condition at the three-year evaluation only, than those with CIPN at the one-year follow-up only (median score: 10.0 vs. 1.5, $p < 0.005$) (Fig. 4).

According to the CTCAE, in patients with CIPN at both moments of follow-up, almost all presented peripheral sensory neuropathy grade 1 or 2 (100.0% at the one- and 98.1% at the three-year follow-up); motor symptoms (grade 1 to 3) were much less frequent (7.6% at the one- and 15.1% at the three-year follow-up). Among women with CIPN at only the one-year or at the three-year follow-up evaluation, the prevalence of sensory neuropathy (grade 1 to 3) was 92.9% and 100.0%, respectively, and the proportion of patients with motor neuropathy (grade 1) was 7.1% and 57.1%, respectively.

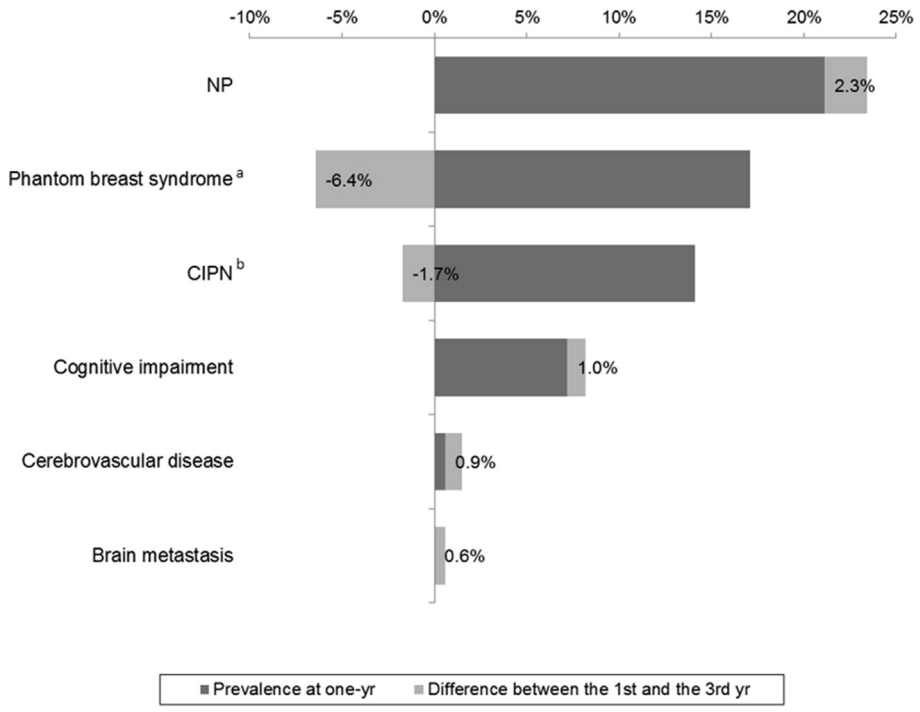

Fig. 1. Prevalence of neurological complications at one and three years after diagnosis ($N = 475$). CIPN, Chemotherapy-induced peripheral neuropathy; NP, Neuropathic pain. [a]A total of 29.6% and 29.4% of the patients with phantom breast syndrome at one and three years, respectively, experienced painful sensations and were classified as cases of phantom breast pain grade 1, according to the Common Terminology Criteria for Adverse Events, V.4.0. The prevalence of phantom breast syndrome among women who underwent mastectomy without reconstruction was 36.4% (95%CI: 30.3–42.9) at one year and 26.3% (95%CI: 20.6–32.9) at three years ($p < 0.001$). [b]Among the patients undergoing chemotherapy, the prevalence of CIPN was 23.3% (95%CI: 18.7–28.5) and 20.5% (95%CI: 16.2–25.5) at one and three years ($p = 0.074$), respectively.

Table 3
Association between sociodemographic and clinical characteristics of the patients and NP at one and three years after cancer diagnosis (N = 475).

	Neuropathic pain at one year		Neuropathic pain at three years	
	Patients with NP [N (%)]	Adjusted OR (95%CI)	Patients with NP [N (%)]	Adjusted OR (95%CI)
Age (years)				
≤55	61 (25.3)	1 (ref.)	64 (26.6)	1 (ref.)
>55	39 (16.7)	0.59 (0.38–0.93)	48 (20.5)	0.71 (0.47–1.09)
Education (years)				
≤4	40 (20.0)	1 (ref.)	51 (25.5)	1 (ref.)
5–9	29 (21.5)	0.86 (0.48–1.53)[c]	28 (20.7)	0.62 (0.35–1.08)[c]
≥10	31 (22.1)	0.87 (0.49–1.55)[c]	33 (25.6)	0.71 (0.41–1.24)[c]
Cancer stage at baseline				
0/I	40 (15.6)	1 (ref.)	53 (20.7)	1 (ref.)
II	29 (19.9)	1.30 (0.76–2.22)[d]	36 (24.7)	1.27 (0.78–2.07)[d]
III/IV	31 (42.5)	3.83 (2.13–6.86)[d]	23 (31.5)	1.75 (0.97–3.16)[d]
Breast surgery[a] (N = 474)				
Breast-conserving	39 (16.3)	1 (ref.)	53 (22.2)	1 (ref.)
Mastectomy	61 (26.0)	1.33 (0.82–2.17)[e]	59 (25.1)	1.01 (0.64–1.60)[e]
Axillary surgery[b] (N = 461)				
SLNB	44 (14.7)	1 (ref.)	58 (19.5)	1 (ref.)
ALND	56 (34.6)	2.75 (1.34–5.63)[e]	49 (30.1)	1.59 (0.82–3.07)[e]
Chemotherapy				
No	26 (13.9)	1 (ref.)	30 (16.1)	1 (ref.)
Yes	74 (25.7)	1.47 (0.80–2.70)[e]	82 (28.4)	2.10 (1.20–3.67)[e]
Radiotherapy				
No	24 (19.2)	1 (ref.)	24 (19.4)	1 (ref.)
Yes	76 (21.7)	0.72 (0.32–1.59)[f]	88 (25.1)	1.24 (0.58–2.65)[f]
Brachytherapy				
No	89 (23.2)	1 (ref.)	91 (23.7)	1 (ref.)
Yes	11 (12.1)	0.53 (0.24–1.15)[f]	21 (32.1)	0.93 (0.48–1.82)[f]

ALND, Axillary lymph node dissection; NP, Neuropathic pain; SLNB, Sentinel lymph node biopsy.
[a] Patients who had both mastectomy and breast-conserving surgery are reported as mastectomy; N < 475 because one patient only performed axillary surgery.
[b] Patients who had both ALND and SLNB are reported as ALND; N < 475 because 14 patients only performed breast surgery.
[c] Adjusted for age.
[d] Adjusted for age and education.
[e] Adjusted for age, education and cancer stage.
[f] Adjusted for age, education, cancer stage, breast and axillary surgery.

Table 4
Association between sociodemographic and clinical characteristics of the patients and CIPN at one and three years after cancer diagnosis, among those who performed chemotherapy until the first (N = 288) and until the third year of follow-up (N = 289).

	CIPN at one year		CIPN at three years	
	Patients with CIPN [N (%)]	Adjusted OR (95%CI)	Patients with CIPN [N (%)]	Adjusted OR (95%CI)
Age (years)				
≤55	39 (22.7)	1 (ref.)	33 (19.2)	1 (ref.)
>55	28 (24.1)	1.09 (0.62–1.89)	27 (23.1)	1.26 (0.71–2.24)
Education (years)				
≤4	22 (22.0)	1 (ref.)	21 (20.8)	1 (ref.)
5-9	21 (21.0)	0.99 (0.49–2.02)[a]	17 (17.0)	0.87 (0.41–1.83)[a]
≥10	24 (27.3)	1.41 (0.69–2.85)[a]	22 (25.0)	1.42 (0.69–2.93)[a]
Cancer stage at baseline				
0/I	12 (13.2)	1 (ref.)	13 (14.1)	1 (ref.)
II	29 (22.8)	2.01 (0.96–4.22)[b]	22 (17.3)	1.34 (0.63–2.86)[b]
III/IV	26 (37.1)	4.12 (1.87–9.06)[b]	25 (35.7)	3.73 (1.70–8.14)[b]
5-FU-based chemotherapy				
No 5-FU	15 (16.1)	(ref.)	16 (17.0)	(ref.)
5-FU	52 (26.7)	1.99 (1.00–4.00)[c]	44 (22.6)	1.65 (0.83–3.30)[c]
Taxane-based chemotherapy				
No taxane	1 (1.20)	1 (ref.)	2 (2.5)	1 (ref.)
Taxane	66 (32.2)	34.59 (4.57–261.96)[c]	58 (27.9)	14.76 (3.31–65.79)[c]

CIPN, Chemotherapy-induced peripheral neuropathy; 5-FU, 5-Fluorouracil.
[a] Adjusted for age.
[b] Adjusted for age and education.
[c] Adjusted for age, education and cancer stage.

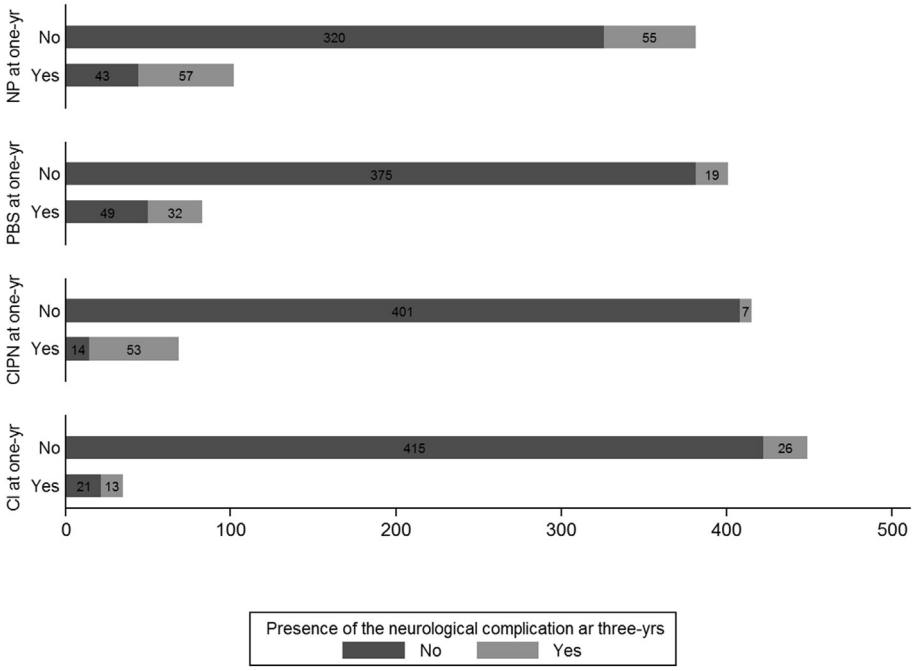

Fig. 2. Variation of the number of patients with the most common neurological complications, according to its presence at one-year after diagnosis. CI, Cognitive impairment; CIPN, Chemotherapy-induced peripheral neuropathy; NP, Neuropathic pain; PBS, Phantom breast syndrome.

Discussion

Three years after a diagnosis of breast cancer, more than 40% of the patients presented at least one oncological-related neurological complication, largely due to conditions that were not observed one year after cancer diagnosis. During this period, there was an increase in the prevalence of NP, cognitive impairment, cerebrovascular disease and brain metastasis and a decrease in the proportion of patients with phantom breast syndrome and CIPN, though differences were not statistically significant except for phantom breast syndrome and brain metastasis. ALND was associated with NP at one year and chemotherapy with NP at three years. Taxane-based chemotherapy was strongly associated with prevalence of CIPN at one and three years.

NP was the most frequent treatment-related complication, both one and three years after cancer diagnosis. Two recent studies addressing the frequency of NP in breast cancer patients reported prevalence estimates close to those observed in our study [16,17]; in a prospective study of women who underwent surgery for primary breast cancer, Bruce et al. reported a prevalence of 24% of predominantly NP at nine months, according to the Self-Administered Leeds Assessment of Neuropathic Symptoms and

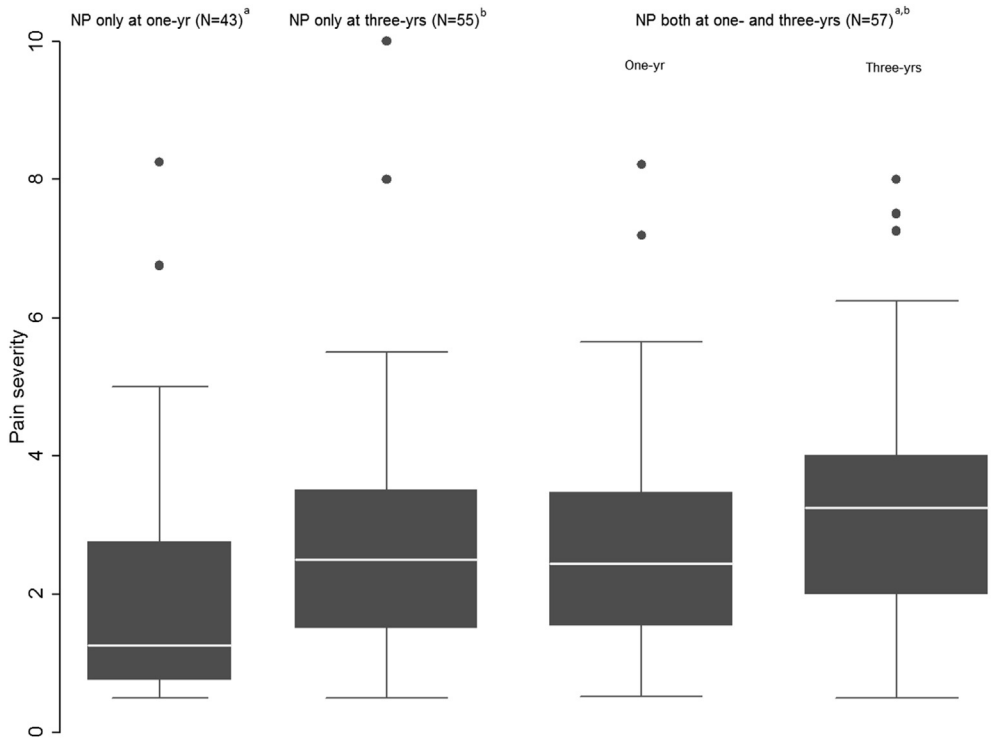

Fig. 3. Pain Severity at one- and three-years after cancer diagnosis, among those with NP, according to the moment of evaluation. NP, Neuropathic pain. [a]Patients with prevalent NP at one-year after cancer diagnosis had its severity assessed at the diagnosis of NP (within the first year of follow-up) and six-months after (if NP was still present); for these patients, we selected the score obtained at the evaluation closest to the one-year follow-up. [b]Patients with prevalent NP at the three-year follow-up evaluation had its severity evaluated at that moment.

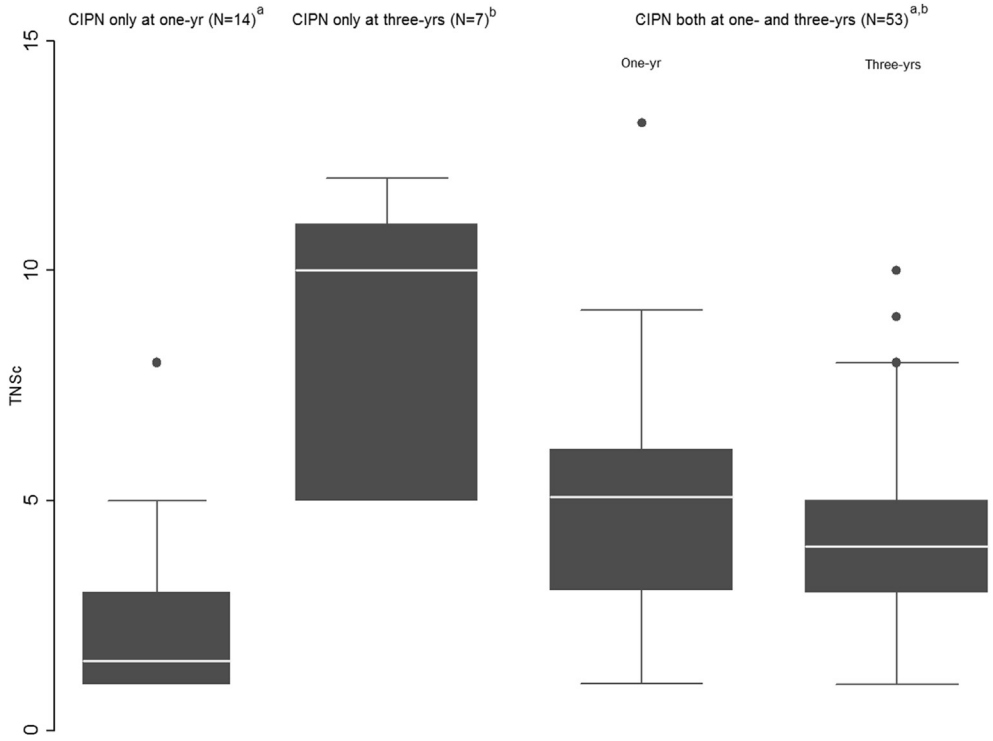

Fig. 4. Total neuropathy score at one- and three-years after cancer diagnosis, among those with CIPN, according to the moment of evaluation. CIPN, Chemotherapy-induced peripheral neuropahy; TNSc, Total Neuropathy score (clinical version). [a]Patients with prevalent CIPN at one-year after cancer diagnosis had its severity assessed at the diagnosis of CIPN (within the first year of follow-up) and six-months after (if CIPN was still present); for these patients, we selected the score obtained at the evaluation closest to the one-year follow-up. [b]Patients with prevalent CIPN at the three-year follow-up evaluation had its severity evaluated at that moment.

Signs (S-LANSS) or the Neuropathic pain questionnaire (DN4) [16]. In a retrospective study including women treated between two to six years before, Bredal et al. described the presence of symptoms and signs of NP in 26% of the participants, according to the S-LANSS [17].

Even though NP is a frequently recognized complication of surgical and adjuvant treatments for breast cancer [15,18], there is scarce information regarding how it evolves in the long term in the same patients. The fact that signs and symptoms that characterize NP occur as a dynamic spectrum that is unstable over time [19,20] could, at least in part, explain our findings of an increase in its prevalence during follow-up. Among breast cancer patients, damage of the intercostobrachial nerve, which can occur with ALND, has been considered the most common source of NP [15] and patients submitted to chemotherapy may develop NP secondary to CIPN [18]; our results are in agreement with these findings.

Our study yielded a prevalence of phantom breast syndrome similar to those found by previous authors reporting that between 15% and 45% of those submitted to mastectomy were diagnosed with this complication [21–23]. Recently, Medina et al., reported a decrease in the prevalence from 45% at six weeks to 18% at two years after surgery [21], which is a accordance to our findings of a decrease over time.

Despite direct comparisons being difficult due to the heterogeneous chemotherapeutic schemes performed by patients and the lack of uniformity in CIPN assessment methods, our observations of a decrease in the prevalence of CIPN between the first and the third year after diagnosis are consistent with previous studies [24,25]. A systematic review assessing the prevalence of CIPN over time yielded prevalence estimates of 60.8% in the first month after chemotherapy, 60.0% at three months and 30.0% at six months or more [25]. In a more recent study, Eckhoff et al. reported a CIPN prevalence of 16.2% and 13.6% among breast cancer survivors who underwent docetaxel based-regimens, 1–1.5 years and 2.0–3.2 years after treatment, respectively [24]. The low number of patients with CIPN diagnosis at only three years reflects the scarce number of women re-submitted to chemotherapy due to cancer recurrence and its higher severity when compared to those diagnosed at one-year may reflect the use of more neurotoxic drugs [26]. Also, our finding of a higher odds of CIPN in those who underwent taxane-based chemotherapy is in accordance with previous reports suggesting that both docetaxel and paclitaxel could be an important source of peripheral neuropathy among those undergoing chemotherapy for breast cancer [18,26].

Cognitive impairment has been studied among breast cancer patients, especially in those submitted to chemotherapy [27–29]. Results from cross-sectional studies suggest a decrease in cognitive function after chemotherapy but prospective designs show an improvement in cognition over time after treatment [27–29]. However, the former did not take into account the baseline cognitive status of patients and the latter may be explained by learning effects due to evaluations using the same instrument at different moments. In our study, the long period between the one- and the three-year follow-up evaluations contributes to overcome learning effects and may explain the contrast with previous results.

Cerebrovascular disease and brain metastasis have been found in less than 2% of the participants in our study. The latter has been describes as the most common direct form of nervous system involvement by cancer, estimated to affect around 5% of breast cancer patients, up to five years after diagnosis [30]; the shorter follow-up of our cohort and the fact that those not proposed for surgery were excluded, are probably contributing to our observed prevalence.

Our study contributes to a comprehensive characterization of the burden of neurological conditions of breast cancer in the long term. Its major methodological strengths are the prospective design with a systematic evaluation of all patients before treatment, one year and three years after breast cancer diagnosis, the nearly complete follow-up of the patients and the use of standardized instruments to evaluate cognitive function, and to quantify CIPN and NP severity. However, some limitations need to be addressed. We excluded those not submitted to surgical treatment, which may limit the generalization to patients with more advanced disease, where direct complications of breast cancer are expected to be more frequent. Finally, most of the neurological complications had only clinical diagnosis, which limits the accuracy of the information regarding these disorders. However, our results are expected to reflect findings in usual clinical practice, since all patients were treated according to the usual practice of a major oncological hospital.

In conclusion, our study shows that neurological complications are frequent even three years after cancer diagnosis and highlights the role of NP as a major contributor to the burden of these conditions among survivors.

Ethical approval

The study was approved by the Ethics Committee of the Portuguese Institute of Oncology of Porto (Ref. CES 406/011 and Ref. 99/014).

Conflict of interest statement

None declared.

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