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What makes surgical nerve injury painful? A 4-year to 9-year follow-up of patients with intercostobrachial nerve resection in women treated for breast cancer

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Abstract

Nerve injury during breast cancer surgery can cause neuropathic pain (NP). It is not known why some, but not all, patients develop chronic postsurgical neuropathic pain (CPSNP) after the same nerve injury. In this study, we examined 251 breast cancer survivors with surgeon-verified intercostobrachial nerve resection to identify factors that associate with CPSNP. The patients were recruited from a previous study of 1000 women treated for breast cancer in 2006 to 2010. This enabled us to analyze preoperative factors that associate with future CPSNP. The patients were re-examined in 2014 to 2016 to diagnose CPSNP using the revised NP diagnostic criteria. Preoperative assessments were pain in the area to be operated on, any chronic pain condition, depressive symptoms, anxiety, sleep, and experimental cold pain sensitivity using the cold pressor test (CPT). Follow-up assessments were CPT, psychological factors, sleep, any chronic pain, and basic laboratory tests. One hundred thirty-seven (55%) patients with intercostobrachial nerve resection fulfilled CPSNP diagnostic criteria after 4 to 9 years. Of them, 30 patients (22%) had moderate to severe pain in self-reports and 86 (63%) presented moderate to severe evoked pain at examination. Preoperative pain in the surgical area, other chronic pains, and breast-conserving surgery were associated with future CPSNP. Other chronic pains, increased psychological burden, and insomnia, both before surgery and at the follow-up, were associated with CPSNP. Preoperative CPT did not associate with future CPSNP. Patients with established CPSNP showed increased pain sensitivity in CPT and higher levels of inflammatory markers, suggesting that central sensitization and inflammation may associate with the maintenance of CPSNP.

Keywords: Neuropathic pain, Intercostobrachial nerve, Breast cancer, Cold pressor tolerance, Central sensitization, Anxiety, Depression

1. Introduction

The reported pooled prevalence estimates of chronic postsurgical neuropathic pain (CPSNP) after breast cancer surgery are 14% to 31% in all patients and 33% to 58% in those reporting persistent postsurgical pain (PPSP).[16,17] The intercostobrachial nerve (ICBN) is frequently resected in breast cancer surgery, leading to sensory abnormalities.[44] However, the evidence is conflicting about how the ICBN is handled and subsequent pain.[2,3,14,32,44]

Neuropathic pain (NP) is defined as pain caused by a lesion or a disease of the somatosensory nervous system.[12] In the revised criteria for the diagnosis of NP, surgeon-verified nerve injury is one of the confirmatory tests for definite NP, in addition to sensory abnormalities and pain in the corresponding area.[12]

Multiple mechanisms encompassing both the peripheral and central nervous systems have been identified in the pathophysiology of NP,[9] but these do not explain why some patients, but not all, develop NP despite the same etiology.[9,20,25] This also applies to ICBN resection and CPSNP.[20]

Previous prospective studies analyzing the association of preoperative patient-related factors and CPSNP have shown that pain, opioid use, poorer neuropsychological function, female sex, and anxiety associate with future CPSNP.[4,11,25,26,32]

In other types of NP, predictive factors are more difficult to assess because the onset of nerve injury is not as well-defined as in CPSNP. However, other NP conditions provide cross-sectional information of neuropathic patients with or without pain. In diabetes, the role of inflammation is of significant interest in both polyneuropathy and NP.[34] Interestingly, different inflammatory profiles have been reported in painful vs nonpainful diabetic polyneuropathy.[10,45] To our knowledge, there are no studies on the role of inflammation in painful

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vs nonpainful traumatic nerve injury. However, higher cytokine levels in the cerebrospinal fluid have been measured in patients with traumatic NP compared with healthy controls.[7]

Lipid profiles differ in HIV patients with or without neuropathy.[33] However, their role has not been clarified in painful vs nonpainful neuropathy. Elevated plasma glucose levels have been reported to associate with daily chronic pain,[31] but not with painful compared with nonpainful diabetic polyneuropathy.[34]

No study has assessed the role of general pain sensitivity, measured with the cold pressor test (CPT) before surgery, to predict development of CPSNP. However, patients with established CPSNP have been reported to be more pain sensitive in the CPT compared with those who do not have NP after similar nerve transection.[42]

To study factors that may differentiate patients with or without CPSNP after ICBN resection, we used the data from a previous study of 1000 patients treated for breast cancer[21] and invited those having a surgeon-defined ICBN resection for a new examination 4 to 9 years after surgery to confirm whether the patients had the diagnosis of definite CPSNP or not. To study group differences, we repeated the preoperative assessments of pain sensitivity and tolerance using CPT, presence of any chronic pain, distress, and self-reported sleep disturbances. In addition, we measured inflammatory biomarkers, glucose, and lipid levels in plasma at the follow-up.

2. Patients and methods

2.1. Original cohort: preoperative and treatment-related variables

The patients in the current study were recruited from a previous original cohort of 1000 women operated on for unilateral breast cancer during 2006 to 2010 at the Helsinki University Hospital. The patient selection and study procedures of this original cohort have previously been described in detail.[21] In brief, women scheduled for surgery of nonmetastasized unilateral breast cancer without neoadjuvant treatment or immediate breast reconstruction were invited. The preoperative and follow-up visit assessments are listed in **Table 1**.

Experimental heat pain sensitivity was analyzed with a 16 × 16-mm thermode (TSA-II NeuroSensory Analyzer; Medoc Ltd, Ramat Yishai, Israel). In the heat pain test, the patients reported their pain intensity with a Numerical Rating Scale (NRS 0-10) after a 5-second stimulation with 43°C and 48°C. Cold pain sensitivity and tolerance were assessed using the CPT. Patients immersed their contralateral (to the side to be operated on) hand into circulating cold water (+2-4°C) bath (JULABO USA Inc, Allentown, PA) up to the wrist for the maximum time tolerated but no longer than 90 seconds (referred to as cold pain tolerance). During the CPT, patients reported pain intensity every 15 seconds and at the end of CPT on an NRS 0 to 10 (referred to as cold pain sensitivity).

The surgical procedure was either mastectomy or breast-conserving surgery (BCS) with sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND). Clinically node-negative patients with radiologically unifocal tumors not exceeding 30 mm in size underwent SLNB. Generally, all patients with tumor-positive sentinel nodes underwent completion ALND. Patients with large (>30 mm) or multifocal tumors in breast imaging, as well as clinically node-positive patients, underwent direct ALND of Berg levels I and II. Level III was also dissected if clinically suspicious nodes were present. Surgery was performed or directly supervised by experienced breast surgeons. The operating surgeon documented whether ICBN was preserved, totally or partially resected, or not visualized during surgery.

Anesthesia was standardized with remifentanil, propofol, and rocuronium. Postoperatively, the patients were given acetaminophen 1 g every 8 hours, and they were titrated pain-free with intravenous oxycodone, first by the research nurse at the postanesthesia care unit (PACU) and then with patient-controlled analgesia on the ward.[21] Data on pain intensity before oxycodone titration and consumption of oxycodone during the 2-hour period at the PACU were collected. Data concerning oncological treatments, reoperation, and breast reconstructions were collected.

2.2. Current cohort: patients with injury of the intercostobrachial nerve

To address the question of why some patients but not all develop CPSNP after similar nerve injury, we, in this study, included patients with a surgeon-verified, total, or partial ICBN resection. In the original cohort of 1000 patients, 440 patients underwent either total or partial ICBN resection. Forty-one patients (9.3%) had died, and 38 patients (8.6%) had reached 75 years of age at the time of recruitment and were therefore not invited. Eight patients (1.8%) were excluded for other reasons (eg, no breast cancer at final histology). Thus, 353 patients (353/440, 80.2%) were eligible for the follow-up visit. The research nurse contacted these patients through telephone to ask about their willingness to participate in the study. Of the 353 patients, 37 (10.5%) could not be reached and 65 patients (18.4%) declined. Thus, 251 patients (251/440, 57%) participated. The participants (N = 251) and eligible nonparticipants (N = 102) did not differ in terms of preoperative and treatment-related variables (see supplementary Table 1, supplemental digital content, available at http://links.lww.com/PAIN/A661, which demonstrates comparison of participants and eligible nonparticipants). **Figure 1** illustrates the complete patient flow.

The study was approved by the Coordinating Ethics Board of the Helsinki and Uusimaa Hospital District and registered in ClinicalTrials.gov (NCT02487524). All patients gave informed written consent.

2.3. Follow-up visit—clinical examination and grading criteria for definite neuropathic pain due to injury of intercostobrachial nerve

The 251 patients with surgeon-verified injury to the ICBN underwent a thorough sensory examination of the upper body at the follow-up. Sensory examination consisted of testing tactile sensation by a cotton tuft, static allodynia by finger compression, dynamic allodynia by a painter's brush, pinprick sensation by a sharp wooden cocktail stick, and cold and warm sensation by a metal roller. The affected side was compared with the contralateral side and the surrounding skin. The examination consisted of the following sensory modalities: hypoesthesia (diminished sensitivity), hyperesthesia (heightened sensitivity), dysesthesia (unpleasant sensation), and allodynia (pain evoked by normally painless stimuli). If evoked pain was observed during examination, the patients were asked to rate the pain intensity (NRS 0-10). The examining neurologist was blinded to the ICBN status of the patients during the sensory evaluation. To identify pain in the surgical area, we used the pain intensity rating 1 or higher (NRS 0-10) in at least one of the following 2 measures: Brief Pain Inventory (BPI) for the worst pain during past week or evoked pain in the clinical sensory examination. The patient located the pain to a body map drawing and the examining neurologist located the sensory findings to a similar body map drawing of the upper body.

Table 1

Assessments at preoperative and follow-up visits.

	Preoperative	Follow-up 4–9 y after operation
Demographics	Age, BMI	Age, BMI, marital status, education, smoking, alcohol consumption, and use of medication (self-report)
Pain and sensory changes in the operative area		
Neuropathic pain diagnosis	N/A	According to revised diagnostic grading criteria (Finnerup et al., 2016)
Clinical sensory examination of the upper body	N/A	Static mechanical allodynia, light touch, dynamic touch, pinprick, and thermal sensation
Pain intensity in the operative area	0-10 NRS, worst pain past week	0-10 NRS, worst pain past week
Evoked pain in the operative area	N/A	0-10 NRS, at clinical examination
Other pain		
Other chronic pain conditions	Yes/No	Pain in the following locations (yes/no): back, joints, neck, head, and other
Intensity of other pain	0-10 NRS, worst pain past week	0-10 NRS, worst pain past week
Mood and sleep		
Depressive symptoms	BDI II	BDI II, HADS-D
Anxiety	STAI state and trait	HADS-A
Insomnia	Not at all/at least once a wk/every night	ISI
Pain catastrophizing	N/A	PCS
Experimental pain		
Heat pain	Heat pain at 43°C and 48°C	N/A
Cold pain	CPT	CPT
Blood samples	N/A	GHb-A1c, lipids, 25-hydroxyvitamin-D, hs-CRP, and ORM

BDI II, Beck's Depression Inventory II; BMI, body mass index; CPT, cold pressor test; GHb-A1c, glycated hemoglobin A1c; HADS-A, Hospital Anxiety and Depression Scale–Anxiety; HADS-D, Hospital Anxiety and Depression Scale–Depression; hs-CRP, high-sensitivity C-reactive protein; ISI, insomnia severity index; N/A, not assessed; NRS, numerical rating scale; ORM, orosomucoid; PCS, pain catastrophizing scale; STAI, State-Trait Anxiety Inventory.

We used the revised stepwise grading criteria for NP[12] to identify patients with CPSNP. The steps include A) a history of relevant neurological lesion and neuroanatomically plausible pain distribution, B) that the pain associates with sensory signs in the same neuroanatomical distribution, and C) that a diagnostic test confirms the lesion in the somatosensory nervous system. According to the recent revision of the grading system, a surgeon's report of nerve resection is equivalent to a diagnostic test in the case of postsurgical neuropathic pain.[12]

All patients in this study had a history of breast cancer surgery and ICBN resection. The region of interest was the innervation area of the ICBN: axilla, medial upper arm, flank of chest, and lateral breast.[2] Patients were classified as "unlikely CPSNP" if no pain was present or the localization of pain was not neuroanatomically plausible for the surgical area (criterion A not met). Patients with pain in the surgical area without sensory abnormality in the corresponding region were classified as possible CPSNP (criterion B not met). The patients with either self-reported or evoked pain in the surgical area with at least one sensory abnormality in the corresponding region were classified as definite CPSNP if these findings occurred in the area of ICBN innervation[2] (criteria A, B, and C fulfilled). If the patients had pain and sensory abnormalities in the surgical area, but outside the ICBN innervation (eg, medial breast), they were classified as probable CPSNP (criterion C not met).

We excluded the possible CPSNP (N = 32) and probable CPSNP (N = 15) groups from the analyses to avoid possible bias caused by uncertain NP diagnosis (**Fig. 1**). In the final analysis we had only patients with definite CPSNP (CPSNP group) or unlikely CPSNP (non-CPSNP group). Two patients from each group were excluded because of ongoing cancer treatments. We analyzed differences in these 2 groups to understand what makes a similar nerve injury painful or not. Thus, we had a nested case–control design including patients having had a previous ICBN resection with or without current CPSNP.

2.4. Demographic factors, questionnaires, and cold pressor test

Demographic factors preoperatively and at the follow-up visit are presented in **Table 1**. Preoperatively, the question of insomnia was included after the study had started, and therefore, data are missing from 33 patients. For pain intensity, we considered NRS ≥4/10 as moderate to severe pain. At the follow-up visit, BPI for other pains was included after the start of the study, and therefore, data are missing from 26/251 (10%) patients. The patients reported other chronic pains with an open question and a pain drawing. Based on these, other pains at the follow-up were categorized as follows: headaches, pain in the joints, back, neck, or other area.

For the psychological and sleep questionnaire outcomes, we used cutoff values for clinically relevant outcomes to report the proportion of patients with clinically significant symptoms. These were used as follows: ≥10 for at least mild and ≥19 for at least moderate depressive symptoms in the Beck's Depression Inventory II (BDI II)[5,29]; 8 to 10 for borderline and ≥11 for clinically significant anxiety/depression in HADS[6,29]; ≥40 for clinically significant anxiety in STAI[39]; ≥8 for mild to severe insomnia in ISI[30]; and ≥30 for clinically significant catastrophizing in PCS.[40] Cronbach's alphas for these are reported in the supplementary Table 2 (available at http://links.lww.com/PAIN/A661).

The fasting blood samples for glucose level, lipids, vitamin D, and inflammatory markers (high-sensitivity CRP [hs-CRP]; orosomucoid [ORM]) were drawn at the follow-up and analyzed according to the standard laboratory protocol (HUSLAB, Helsinki, Finland). The CPT was performed similarly preoperatively and at the follow-up, by the same research nurse, protocol, and equipment.

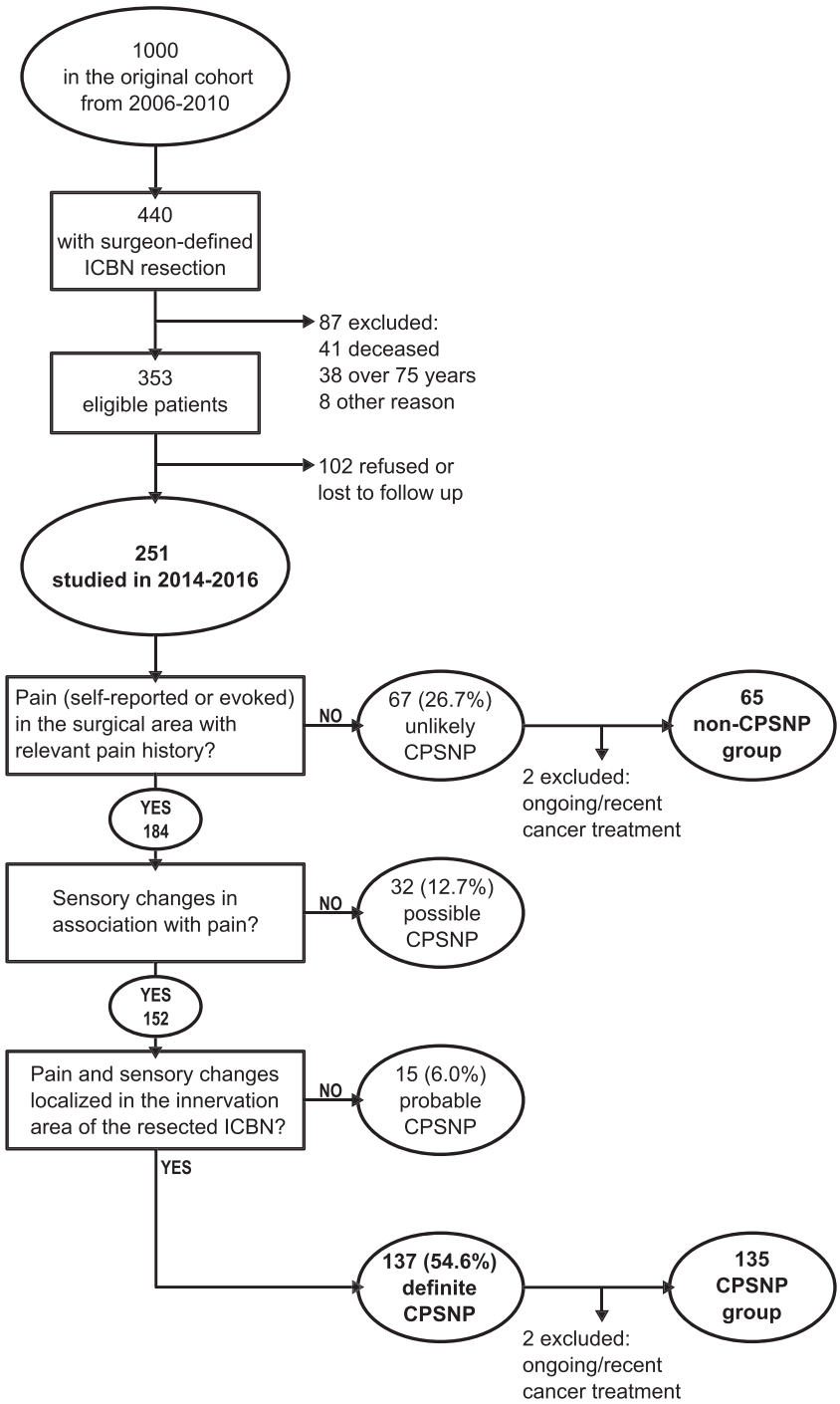

Figure 1. Patient selection and clinical grading for chronic postsurgical neuropathic pain. Surgical area refers to the breast, axilla, upper side of the chest, and medial arm in the operated side. The area of ICBN resection refers to the lateral side of the breast, axilla, upper side of the chest, and medial arm in the operated side. CPSNP, chronic postsurgical neuropathic pain; ICBN, intercostobrachial nerve.

2.5. Statistical analysis

We used Student *t* test for normally distributed continuous variables in pairwise comparisons and repeated measures. Mann–Whitney *U* test and χ^2-tests were used for non-normally distributed and categorical variables, respectively. Spearman's rho (r_s) was used for correlations and Cronbach's alpha for reliability assessments.

To predict CPSNP with preoperative and breast cancer treatment–related clinical variables, the variables reaching $P < 0.05$ in the bivariate analysis were entered as predictors in a logistic regression analysis using the forward stepwise method. In addition, we tested the model with the backward stepwise method to control for multicollinearity. We combined the type of breast surgery and radiotherapy as a single categorical variable for the regression analysis because nearly all patients with BCS receive radiotherapy. Continuous variables were not categorized for this analysis. To detect the effect of possible multicollinearity, we tested entering the susceptible variables (BDI II, STAI state, and trait) one by one and in different combinations.

To assess the role of preoperative thermal pain sensitivity in predicting future CPSNP, we conducted a logistic regression analysis. Preoperatively measured variables for age, body mass index (BMI), chronic pain (yes/no), depression (yes/no, cutoff ≥19 in BDI II), and anxiety (yes/no, cutoff ≥40 in STAI state) were entered as covariates to control for possible confounding.

To analyze the cold pain sensitivity and tolerance in established CPSNP 4 to 9 years after breast cancer surgery, we conducted a Cox-regression analysis. We used (1) time to withdrawal and (2) time to NRS 10 during CPT as the time to event. Data were right-censored if the participant endured the CPT the maximum of 90 seconds or if NRS values did not reach 10 during CPT. Variables measured at the research visit 4 to 9 years after surgery, including age, BMI, other pain of at least moderate intensity (yes/no), depression (yes/no, cutoff ≥19 in BDI II), and anxiety (yes/no, cutoff ≥11 in HADS-A), were added as covariates to control for possible confounding. We performed an interaction analysis for inflammatory markers (hs-CRP and ORM) and CPSNP on CPT parameters using cross-product terms in Cox models. Inflammatory markers were inserted into the model as continuous variables.

Two-tailed $P \leq 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS 22.0 version for Windows (SPSS Inc, Chicago, IL).

3. Results

3.1. Clinical grading of chronic postsurgical neuropathic pain and patients with definite chronic postsurgical neuropathic pain

Figure 1 shows the distribution of patients to unlikely, possible, probable, and definite CPSNP groups. In definite CPSNP patients (135), evoked pain at examination presented in 114 (84%) patients and was mostly static allodynia (99%). Pain intensity was moderate to severe in 30 of 135 (22%) BPI reports.

3.2. Factors associating with established chronic postsurgical neuropathic pain: patients with and without chronic postsurgical neuropathic pain 4 to 9 years after surgery

The intergroup comparisons of demographic factors, other pains, psychological factors and sleep questionnaires, and laboratory parameters are shown in **Table 2**. The groups were homogenous in terms of age, time from surgery, and other demographic factors. Body mass index was significantly higher in CPSNP patients compared with non-CPSNP patients (**Table 2**).

The CPSNP patients had significantly more other pain conditions than non-CPSNP patients (**Table 2**), particularly joint, back, and neck pains. The CPSNP patients had more other pains and reported higher intensities for other chronic pains: moderate to severe pain was reported by 52/118 (44%, 17 missing values) of CPSNP patients compared with 12/60 (20%, 5 missing values) by non-CPSNP patients ($P = 0.003$).

Only a few patients in either group reported current use of NP medications (ie, tricyclics, serotonin–norepinephrine reuptake inhibitors, and gabapentinoids), whereas the use of other pain medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) was more prevalent among CPSNP patients compared with non-CPSNP patients (**Table 2**).

The CPSNP group reported significantly more symptoms in all questionnaires related to psychological factors and sleep (**Table 2**). A total of 60/131 (45%, 4 missing values) of the CPSNP patients reported at least mild depressive symptoms in BDI II compared with 14/65 (22%) of non-CPSNP patients ($P = 0.001$). A total of 33/134 (25%, one missing value) of CPSNP patients compared with 7/65 (11%) of non-CPSNP patients showed borderline or clinically significant levels of anxiety ($P = 0.025$). A total of 67/132 (51%, 3 missing values) CPSNP patients and 20/65 (31%) non-CPSNP patients suffered from at least mild insomnia ($P = 0.008$).

The CPSNP patients had significantly higher levels of hs-CRP and ORM (**Table 2**). There were no differences between the groups in other biochemical parameters (**Table 2**). The levels of hs-CRP correlated positively with BMI in both groups: r_s 0.374 and $P < 0.001$ in CPSNP group; r_s 0.344 and $P = 0.005$ in non-CPSNP group. Orosomucoid and BMI showed a weaker positive correlation: r_s 0.175 and $P = 0.045$ in CPSNP group; r_s 0.239 and $P = 0.055$ in non-CPSNP group.

3.3. Preoperative and treatment-related factors associating with future chronic postsurgical neuropathic pain

Table 3 depicts the intergroup comparison of factors related to cancer and its treatment. In both groups, most patients (CPSNP: 124/135, 92%; non-CPSNP: 57/65, 88%) had undergone axillary clearance. Partial resections of ICBN were more frequent than total resections. The CPSNP patients had undergone BCS and received radiotherapy more frequently than the non-CPSNP patients. There was no difference between the groups regarding administration of chemotherapy or hormonal therapy (**Table 3**).

Preoperatively, future CPSNP patients showed higher BMI, reported more pain in the surgical area and elsewhere, had more depressive symptoms and anxiety, and reported insomnia more frequently than future non-CPSNP patients (**Table 4**). In addition, CPSNP patients presented with higher immediate postoperative pain intensity ratings and higher oxycodone consumption at the PACU. In multivariate analysis, preoperative pain in the surgical area, the presence of chronic pain conditions, and BCS as the type of breast surgery were associated with increased risk of CPSNP (**Table 4**). The effect of the type of breast surgery remained significant even after controlling for radiotherapy. The results remained unaltered despite the method of stepwise logistic regression used. Similarly, entering variables susceptible for multicollinearity (BDI II, STAI state and trait) one by one or in different combinations did not affect the outcome. No significant differences in cancer type, number of metastatic lymph nodes, nerve resection type, reoperations, or late reconstructions were detected (**Table 3**).

3.4. General pain sensitivity and chronic postsurgical neuropathic pain: preoperative and postoperative cold pressor test and preoperative heat pain assessment

Compared with non-CPSNP patients, CPSNP patients presented with a significantly lower cold pain tolerance and higher cold pain sensitivity postoperatively, but not preoperatively (**Table 5**). Both patient groups showed a significant increase of withdrawal times (CPSNP: mean difference 14.2 seconds, $P < 0.001$; non-CPSNP: mean difference 15.6 seconds, $P < 0.001$), although no significant mean differences were detected between groups ($P = 0.716$). Preoperative heat pain (48°C) intensity predicted CPSNP, although the association remained non-significant after multivariate adjustment (**Table 6**).

A Cox-regression analysis of the postoperative CPT (**Table 7**) showed that patients with CPSNP aborted the CPT significantly earlier than non-CPSNP patients (**Fig. 2**). The association remained unaltered after multivariate adjustment. Patients in the

Table 2

Patient demographics and clinical features 4–9 years after breast cancer surgery.

	CPSNP (n = 135)	Non-CPSNP (N = 65)	*P*
Demographics			
Age, mean (SD), y	60.4 (8.01)	61.4 (8.89)	0.45*
Time from index surgery, mean (SD), mo	77.9 (13.31)	77.7 (13.35)	0.93*
BMI, mean (SD), kg/m^2	26.2 (3.90)	24.1 (3.95)	**<0.001***
Marital status, no. (%)			0.96†
Married or cohabiting	76 (56.3)	38 (58.5)	
Single	22 (16.3)	10 (15.4)	
Divorced or widowed	37 (27.4)	17 (26.2)	
Educational level, number (%)			0.78†
Low	18 (13.3)	9 (13.8)	
Moderate	33 (24.4)	13 (20.0)	
High	84 (62.2)	43 (66.2)	
Smoking, number (%)			0.82†
Never smoked	66 (48.9)	30 (46.2)	
Smoker	24 (17.8)	14 (21.5)	
Ex-smoker	45 (33.3)	21 (32.3)	
Alcohol consumption, number (%)§			0.56†
Abstinent	20 (14.8)	13 (20.0)	
<6 doses per week	84 (62.2)	36 (55.4)	
≥6 doses per week	30 (22.2)	16 (24.6)	
Other pain conditions			
Worst other pain past week, median (IQR), 0-10 NRS‖	3 (1-5)	0 (0-2)	**<0.001‡**
Joint pain, number (%)	82 (60.7)	21 (32.3)	**<0.001†**
Back pain, number (%)	42 (31.1)	11 (16.9)	**0.033†**
Neck pain, number (%)	47 (34.8)	5 (7.7)	**<0.001†**
Headache, number (%)	15 (11.1)	2 (3.1)	0.056†
Other pain, number (%)	67 (49.6)	15 (23.1)	**<0.001†**
Overlapping pain conditions, number (%)			**<0.001†**
No other pain	15 (11.1)	33 (50.8)	
1 or 2 other pain conditions	80 (59.3)	27 (41.5)	
3 or more other pain conditions	40 (29.6)	5 (7.7)	
Current use of pain medication			
Tricyclic antidepressant, gabapentinoids, or SNRI, number (%)	6 (4.4)	3 (4.6)	0.96†
NSAID, acetaminophen, or mild opioid, number (%)	25 (18.5)	3 (4.6)	**0.008†**
Mood and sleep			
BDI II, median (IQR)	9 (5-14)	5 (2-9)	**<0.001‡**
HADS-A, median (IQR)	5 (3-7)	3 (1-5)	**<0.001‡**
HADS-D, median (IQR)	3 (1-6)	1 (0-3)	**0.001‡**
PCS, median (IQR)	6 (1-13)	1 (0-8)	**<0.001‡**
ISI, median (IQR)	8 (4-12)	4 (2-9)	**0.001‡**
Laboratory parameters¶			
GHb-A1C, mean (SD), % (4.0-6.0)	5.6 (0.4)	5.5 (0.3)	0.36*
Cholesterol (total), mean (SD), mmol/l (<5.0)	5.5 (1.1)	5.6 (0.9)	0.47*
LDL, mean (SD), mmol/L (<3.0)	3.3 (0.9)	3.4 (0.8)	0.69*
HDL, mean (SD), mmol/L (>1.20)	2.01 (0.55)	2.03 (0.53)	0.75*
Triglyserides, mean (SD), mmol/L (<1.70)	1.13 (0.46)	1.20 (0.57)	0.37*
hs-CRP, median (IQR), mg/L (0.05-3.00)	0.99 (0.37-2.42)	0.53 (0.27-1.14)	**0.005‡**
ORM, mean (SD), mg/L (500-1200)	852 (237)	781 (178)	**0.019***
25-Hydroxyvitamin-D, mean (SD), nmol/L (>50)	76 (25)	82 (22)	0.094*

* Student *t* test.
† Chi-square test.
‡ Mann–Whitney *U* test.
§ One answer is missing from the NP group. One dose corresponds to 12 g of pure alcohol.
‖ Seventeen values are missing from the NP group and 5 from the non-NP group.
¶ The normative values are shown in parenthesis.
P values < 0.05 are shown in bold. BDI II, Beck's Depression Inventory II; BMI, body mass index; CPSNP, chronic postsurgical neuropathic pain; GHb-A1C, glycated hemoglobin A1C; HADS-A, Hospital Anxiety and Depression Scale–Anxiety; HADS-D, Hospital Anxiety and Depression Scale–Depression; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; ISI, insomnia severity index; LDL, low-density lipoprotein; NSAID, nonsteroidal anti-inflammatory drug; ORM, orosomucoid (alpha-1-acid glycoprotein); PCS, pain catastrophizing scale; SNRI, serotonin–norepinephrine reuptake inhibitors.

Table 3

Characteristics of breast cancer and its treatment.

	CPSNP (n = 135)	Non-CPSNP (N = 65)	*P*
Histology, number (%)			0.27*
Ductal	94 (69.6)	40 (61.5)	
Lobular	27 (20.0)	13 (20.0)	
Other	14 (10.4)	12 (18.5)	
Gradus, number (%)			0.40*
I	27 (20.0)	14 (21.5)	
II	61 (45.2)	23 (35.4)	
III	47 (34.8)	28 (43.1)	
Size of the tumor, median (IQR), mm	18 (13-25)	18 (14-25)	0.96†
No. of lymph nodes evacuated, mean (SD)	20.8 (10.35)	20.8 (9.42)	0.98‡
No. of metastatic lymph nodes, median (IQR)	1 (1-4)	1 (1-2)	0.066†
Breast surgery type, number (%)			**<0.001***
Mastectomy	69 (51.1)	50 (76.9)	
BCS	66 (48.9)	15 (23.1)	
Axillary surgery type, number (%)			0.35*
SLNB	11 (8.1)	8 (12.3)	
ALND	124 (91.9)	57 (87.7)	
Type of ICBN resection, number (%)			0.093*
Partial	88 (65.2)	50 (76.9)	
Total	47 (34.8)	15 (23.1)	
Reoperation, number (%)	17 (12.6)	10 (15.4)	0.59*
Late reconstruction, number (%)	45 (33.3)	25 (38.5)	0.48*
Chemotherapy, number (%)	120 (88.9)	56 (86.2)	0.58*
Radiotherapy, number (%)	102 (75.6)	38 (58.5)	**0.013***
Endocrine therapy, number (%)	116 (85.9)	54 (83.1)	0.60*
Tamoxifen, number (%)	92 (68.1)	42 (64.6)	0.62*
Aromatase inhibitor, number (%)	90 (66.7)	47 (72.3)	0.42*

* Chi-square test.
† Mann–Whitney *U* test.
‡ Student *t* test.
P values < 0.05 are shown in bold. ALND, axillary lymph node dissection; BCS, breast-conserving surgery; CPSNP, chronic postsurgical neuropathic pain; ICBN, intercostobrachial nerve; IQR, interquartile range; SLNB, sentinel lymph node biopsy.

CPSNP group were also more likely to score NRS 10 during CPT compared with non-CPSNP patients (**Fig. 2**).

There was a significant association for cold pain tolerance and hs-CRP (HR = 1.06, CI: 1.02-1.10, $P = 0.005$) but not for ORM ($P = 0.201$). There was no significant interaction between CPSNP and hs-CRP ($P = 0.831$) or ORM ($P = 0.201$) on cold pressor tolerance.

4. Discussion

4.1. Main findings

Of the 440/1000 patients with surgeon-verified ICBN resection, 251/440 (57%) were examined 4 to 9 years after index breast cancer surgery. Fifty-five percent of these patients (137/251) fulfilled the diagnostic criteria for definite CPSNP. Twenty-two percent (30/137) of them reported moderate to severe pain in self-report (BPI), and 63% (86/137) had moderate to severe evoked pain at clinical examination. Compared with the non-CPSNP patients, CPSNP patients had more depressive symptoms, anxiety, pain catastrophizing, impaired sleep, and other pains. They also had higher levels of inflammatory markers and increased sensitivity in the CPT, suggesting a possible role of central sensitization. Preoperatively, CPSNP patients showed more psychological distress, insomnia, and more pain both in the surgical area and in other locations than the non-CPSNP patients.

4.2. Prevalence of chronic postsurgical neuropathic pain after breast cancer surgery

The prevalence of NP after breast cancer surgery ranges from 33% to 58% in those patients who have PPSP,[17] depending on when and how the diagnosis of NP is made. The diagnosis is usually based on validated questionnaires in cross-sectional studies. So far, few prospective assessments with clinical examination have been conducted with follow-ups to 1 year.[17,32] Our study is the first, to our knowledge, to use the revised NP grading criteria, combining a thorough clinical sensory examination with surgeons' report of nerve injury to reach the diagnostic level of "definite" CPSNP. Extensive sensory examination of multiple modalities, especially reports of evoked pain, allowed identification of CPSNP patients who might have been unnoticed in previous studies. In addition, our study had a 4-year to 9-year follow-up to provide further evidence of CPSNP being a long-lasting consequence of nerve injury. This is in line with a previous study that showed pain and sensory disturbances to be a marked problem after breast cancer surgery during a follow-up of 5 to 7 years. In that study, PPSP was reported by over a third of the patients.[27]

Table 4

Logistic regression model of the associations of preoperative and treatment-related factors with CPSNP after ICBN resection.

	Bivariate analysis			Stepwise logistic regression analysis		
	CPSNP (n = 135)	Non-CPSNP (n = 65)	*P*	B	OR (95% CI)	*P*
BMI at the time of surgery, mean (SD), kg/m^2	25.4 (3.90)	23.8 (3.64)	0.006*			
Type of breast operation and radiotherapy, number (%)			0.002†			
BCS with radiotherapy§	64 (47.4)	15 (23.1)			1 [reference]	
Mastectomy without radiotherapy	31 (23.0)	27 (41.5)		−1.79	0.17 (0.06-0.44)	<0.001
Mastectomy with radiotherapy	37 (28.1)	23 (35.4)		−1.41	0.24 (0.09-0.65)	0.005
Worst pain in the surgical area past week preoperatively, median (IQR), 0-10 NRS	2 (1-3)	0 (0-1)	<0.001‡	0.83	2.29 (1.55-3.39)	<0.001
Worst other pain past week preoperatively, median (IQR), 0-10 NRS	2 (1-4)	0 (0-3)	<0.001‡			
Presence of any chronic pain condition preoperatively, number (%)	40 (29.6)	4 (6.2)	<0.001†	1.64	5.16 (1.53-17.34)	0.008
Pain in the surgical area upon arrival to PACU, median (IQR), 0-10 NRS‖	3 (0-5)	0 (0-4)	0.015†			
Oxycodone consumption at PACU, mg/kg	0.18 (0.10)	0.14 (0.10)	0.010*			
BDI II preoperatively, median (IQR)¶	9 (4-13)	5 (2-9)	0.002‡			
STAI state preoperatively, mean (SD)#	41.1 (10.41)	37.8 (11.74)	0.041*			
STAI trait preoperatively, mean (SD)**	37.9 (9.39)	34.7 (10.70)	0.034*			
Insomnia preoperatively, number (%)††			0.027‡			
Not at all	50 (37.0)	37 (56.9)				
At least once a week	40 (29.6)	16 (24.6)				
Every night	24 (17.8)	5 (7.7)				

Nagelkerke pseudo-R^2 was 0.364. Hosmer and Lemeshow Test for the model suggests a good fit to data as $P = 0.423$ (>0.05). Preoperative and treatment-related variables with $P < 0.05$ in the bivariate analysis were included in the logistic regression analysis. Thirty-six patients (28 from the NP group and 8 from the non-NP group) had missing values in some of the variables. Only cases with complete sets of data were included in the analysis. The missing values were not imputed. Preoperative insomnia was the source of most missing values in the regression analysis. The outcome of the analysis remained unaltered whether or not preoperative insomnia was included.

* Student *t* test.

† Chi-squared test.

‡ Mann–Whitney *U* test.

§ Two patients from the NP group had undergone BCS without radiotherapy and were excluded from the analysis.

‖ Value missing from one non-NP patient.

¶ Value missing from one NP patient.

Values missing from one NP and one non-NP patient.

** Values missing from 2 NP patients.

†† Values missing from 21 (15.6%) NP and 7 (10.8%) non-NP patients.

BCS, breast-conserving surgery; BDI II, Beck's Depression Inventory II; BMI, body mass index; CI, confidence interval; CPSNP, chronic postsurgical neuropathic pain; IQR, interquartile range; OR, odds ratio; PACU, postanesthesia care unit; STAI, State-Trait Anxiety Inventory.

4.3. Type of surgery and chronic postsurgical neuropathic pain

Axillary lymph node dissection has emerged as an important risk factor for PPSP in multiple studies.[3,15,27,28] In this cohort, ALND was significantly more frequent than SLNB in both groups because ICBN resection is typically performed in ALND but not in SLNB. However, this study demonstrates that CPSNP may also occur in SLNB patients with ICBN resection. The small number of SLNB patients in our cohort does not allow for multivariate analyses of type of axillary surgery. The type of ICBN resection, partial or total, did not associate with a higher risk of having NP agreeing with previous studies.[14]

Breast-conserving surgery was associated with a higher prevalence of CPSNP than mastectomy in multivariate analysis, even after controlling for radiotherapy. Previous studies have also reported high incidence of PPSP after BCS, especially in the ipsilateral arm,[3,41] which may indicate a role for ICBN lesions in the subsequent pain. The association between the type of breast surgery and CPSNP is multifactorial. The access and visualization of the axilla is usually better in mastectomy than in BCS. Mastectomy and BCS patients differ in terms of breast cancer characteristics–mastectomy patients have, on average, larger tumors and more metastatic lymph nodes in the axilla. However, these factors did not differ between CPSNP and non-CPSNP groups (**Table 3**).

4.4. Preoperative factors associating with future chronic postsurgical neuropathic pain

Preoperatively, future CPSNP patients presented more pain, anxiety, and depressive symptoms than non-CPSNP patients. Preoperative pain in the surgical area and other chronic pains have previously been shown to predispose to PPSP.[15,28,36,37] Similarly, we found other chronic pain and preoperative pain in the surgical area to predispose to CPSNP. Chronic pain patients often have significant symptom overlap, which makes assessment of depressive symptoms challenging.[22] Therefore, the intergroup differences in BDI II scores in our cohort may partly reflect the chronic pain load in the patients who developed CPSNP. Moreover, depressive symptoms and anxiety did not present as statistically significant in the multivariate analysis for the prediction of CPSNP, and the impact of preoperative pain and other chronic pains seems to override their effect in our model.

Table 5

General pain sensitivity: preoperative and postoperative cold pressor test and preoperative heat pain test.

	CPSNP	Non-CPSNP	*P*
Preoperative measurements			
Heat pain intensity at 43°C, median (IQR), 0-10 NRS	0 (0-1)	0 (0-0)	0.14*
Heat pain intensity at 48°C, median (IQR), 0-10 NRS	3 (2-5)	3 (1-4)	**0.020***
CPT withdrawal time†, median (IQR), s	38 (21-89)	51 (27-90)	0.12*
CPT pain intensity at withdrawal†, median (IQR), 0-10 NRS	9 (8-9)	9 (8-9)	0.89*
Postoperative measurements after 4-9 y			
CPT withdrawal time, median (IQR), s	65 (33-90)	90 (44-90)	**0.019***
CPT pain intensity at withdrawal, median (IQR), 0-10 NRS	9 (8-10)	8 (6-9)	**0.003***

* Mann–Whitney *U* test.
† Ten values are missing from the CPSNP and 3 from the non-CPSNP group.
P values < 0.05 are shown in bold. CPSNP, chronic postsurgical neuropathic pain; CPT, cold pressor test; IQR, interquartile range.

4.5. Chronic pain load

Chronic postsurgical neuropathic pain patients seem to accumulate pain conditions. They had significantly more multisite pains than non-CPSNP patients. This suggests that inherent patient-related risk factors play a role in both the development and maintenance of CPSNP. Interestingly, increased anxiety, pain catastrophizing, depressive symptoms, and impaired quality of sleep in the CPSNP patients may reflect a similar biopsychosocial profile previously reported in patients with chronic and overlapping pain conditions.[24]

4.6. Lipids, glucose, and inflammatory markers

Lipid profiles and glucose levels did not differ between CPSNP and non-CPSNP patients. A similar finding was reported in patients having painful or nonpainful diabetic polyneuropathies.[34] The CPSNP patients showed higher levels in inflammatory markers (hs-CRP and ORM) compared with non-CPSNP patients. In addition, higher levels of hs-CRP, but not ORM, associated with increased cold pain tolerance in CPT, but with no interaction with CPSNP. Subclinical inflammation with high hs-CRP levels has previously been associated with lower pain tolerance in CPT.[1,35]

Orosomucoid is an acute-phase protein with various immunomodulatory functions, and it has been associated with neuroinflammation.[13,18] To our knowledge, it has not been studied in NP patients before. Further studies are needed to assess its role in the pathogenesis of NP.

Our results suggest a role for low-grade inflammation in the maintenance of CPSNP, in line with previous evidence for other NP conditions.[8,10,38] A recent study also showed that NP patients have increased levels of proinflammatory cytokines in the cerebrospinal fluid compared with healthy individuals.[7] Interestingly, neuroinflammation has also been associated with depression, anxiety, and impaired sleep,[43] which all associated with CPSNP in our cohort.

4.7. Cold pain sensitivity and tolerance

Sensitization and chronic inflammation have been suggested as possible mechanisms in NP. The CPT was assessed preoperatively and re-assessed 4 to 9 years later. To our knowledge, there are no other studies to show consistent CPT results preoperatively and several years after surgery. Previously, a good test–retest reliability of the CPT was shown within a 2-week interval.[23] In this study, years after the initial CPT, patients tolerated the cold water significantly longer (**Table 5**). We were unable to identify an explanation for this. The follow-up period was several years, and the patients had received oncological treatments, which may have affected the cold pressor tolerance. Nearly 90% of the patients in both CPSNP and non-CPSNP groups had received chemotherapy.

Sensitivity to preoperative CPT was not associated with CPSNP at 4 to 9 years postoperatively. However, postoperatively, the CPSNP patients were significantly more sensitive and less tolerant in the CPT than the non-CPSNP patients. A previous cross-sectional study on CPT and PPSP suggested that other chronic pains might override the effect of PPSP on CPT.[19] Our results, however, showed that CPSNP patients were more sensitive in the CPT, even after multivariate adjustment of confounding factors including other pains. In line with this, a small previous study showed that patients having NP after ulnar or median nerve transection had decreased pain tolerance and increased pain sensitivity in CPT, compared with non-NP patients.[42] These results together with ours may suggest a role for central sensitization in NP.

4.8. Strengths and limitations of the study

Strengths of this study are the relatively large and homogenous patient cohort, with a long follow-up, with rich clinical data and

Table 6

Logistic regression analysis of preoperative experimental pain measures to predict CPSNP after ICBN resection.

	Unadjusted model			Fully adjusted model*		
	B	OR (95% CI)	*P*	B	OR (95% CI)	*P*
Cold pain (n = 187)						
Withdrawal time, s	−0.01	0.99 (0.98-1.00)	0.15	−0.01	0.99 (0.98-1.00)	0.27
Pain intensity at withdrawal, 0-10 NRS	0.04	1.04 (0.89-1.21)	0.63	0.01	1.00 (0.85-1.19)	0.97
Heat pain (n = 199)						
Pain intensity at 43°C, 0-10 NRS	0.21	1.24 (0.92-1.67)	0.16	0.15	1.16 (0.85-1.60)	0.35
Pain intensity at 48°C, 0-10 NRS	0.15	1.16 (1.01-1.33)	**0.03**	0.10	1.10 (0.96-1.28)	0.18

Hosmer and Lemeshow Test: cold pain model $P = 0.714$; heat pain model $P = 0.272$ (>0.05).
* Models are adjusted for the following preoperative variables: age, BMI, chronic pain (no/yes), depression (yes/no, cutoff ≥19 in BDI II), and anxiety (yes/no, cutoff ≥40 in STAI state). *P* values < 0.05 are shown in bold. B, unstandardized regression weight, BMI, body mass index; BDI II, Beck's Depression Inventory II; CI, confidence interval; CPSNP, chronic postsurgical neuropathic pain; ICBN, intercostobrachial nerve; NRS, numeric rating scale; OR, odds ratio; STAI, State-Trait Anxiety Inventory.

Table 7

Cox-regression analysis of cold pressor test in CPSNP and non-CPSNP patients.

	HR	95% CI	*P*
Cold pressor tolerance			
Unadjusted model			
CPSNP (yes)	1.70	1.10-2.61	**0.016**
Fully adjusted* model			
CPSNP (yes)	1.59	1.01-2.51	**0.047**
Age (y)	0.99	0.97-1.01	0.268
BMI (kg/m^2)	0.99	0.94-1.04	0.653
Other pain (yes)	1.18	0.79-1.78	0.419
Anxiety (yes)	0.94	0.86-1.03	0.190
Depression (yes)	1.04	0.99-1.07	0.064
Maximum pain intensity NRS = 10			
Unadjusted model			
CPSNP (yes)	2.09	1.13-3.89	**0.019**
Fully adjusted* model			
CPSNP (yes)	2.12	1.11-4.07	**0.023**
Age (y)	0.97	0.94-0.99	**0.020**
BMI (kg/m^2)	0.95	0.89-1.02	0.188
Other pain (yes)	0.89	0.50-1.58	0.689
Anxiety (yes)	0.93	0.82-1.05	0.234
Depression (yes)	1.05	0.99-1.11	0.090

* Adjusted for age, BMI, other pain of at least moderate intensity (yes/no), depression (yes/no, cutoff ≥19 in BDI II), and anxiety (yes/no, cutoff ≥11 in HADS-A). *P* values < 0.05 are shown in bold.
BDI II, Beck's Depression Inventory II; BMI, body mass index; CI, confidence interval; CPSNP, chronic postsurgical neuropathic pain; HADS-A, Hospital Anxiety-Depression Scale-Anxiety; HR, hazard ratio.

new insights into factors predisposing to and associating with CPSNP. All patients were clinically examined and classified according to latest NP grading criteria. The study provides new support for the role of central sensitization in CPSNP as shown with decreased CPT tolerance in the CPSNP patients.

A limitation of this study is that all patients had been treated for cancer and the results can therefore not be directly translated to other traumatic nerve injuries. Second, some of the variables were only cross-sectional, and no conclusions regarding causal relationship can be drawn, eg, regarding the possible role of preoperative inflammation. Third, the data of chronic and other pains were collected more thoroughly at the research visit 4 to 9 years from surgery than preoperatively. Although this does not allow for direct comparison between the time points, we can demonstrate a clear difference between CPSNP and non-CPSNP groups at both time points. Fourth, due to the long and varying follow-up period, we cannot exclude the possibility that some of the non-CPSNP could have fulfilled the NP diagnostic criteria at some point during the follow-up. However, the time span from the index operation did not differ significantly between the CPSNP and non-CPSNP groups.

5. Conclusions

The CPSNP and non-CPSNP patient groups differed preoperatively in terms of other chronic pain, sleep, and psychological factors. The CPSNP patients showed enhanced pain sensitivity and decreased pain tolerance in CPT only after they had developed NP, suggesting central sensitization. In addition to the mounting load of chronic pain, systemic inflammation may also have contributed to this. Our results suggest that several, possibly interlinked, patient-related risk factors may play a significant role in the development and maintenance of chronic NP after ICBN resection. These factors should be considered when attempting to improve prevention and management of CPSNP.

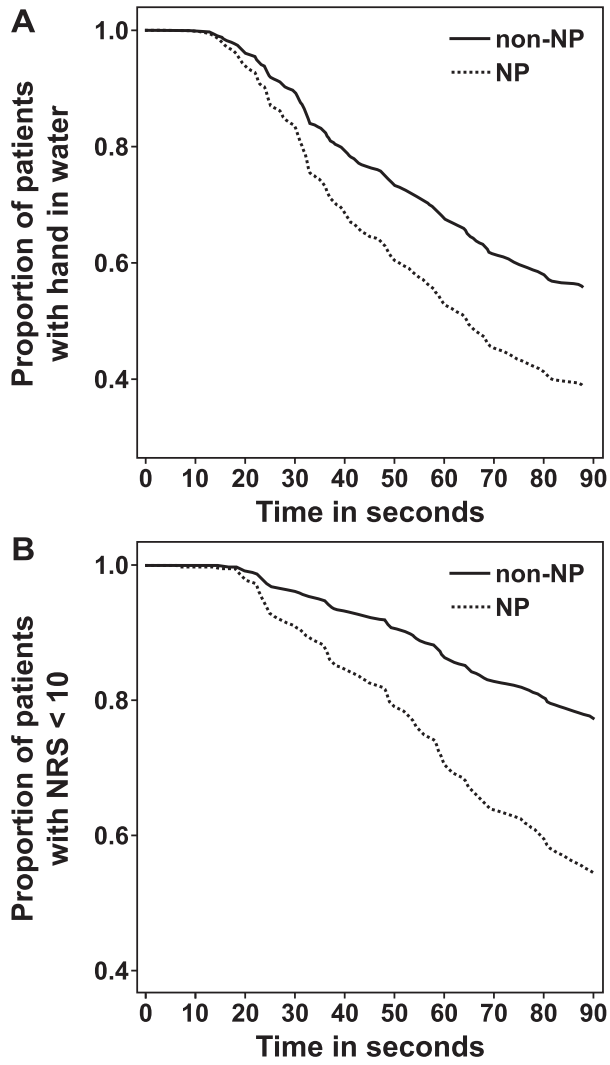

Figure 2. Cox-regression analysis. Survival curves for cold pain tolerance (A) and sensitivity (B). CPSNP, chronic postsurgical neuropathic pain; NRS, Numeric Rating Scale.

Conflict of interest statement

T. Meretoja has received a grant from Cancer Foundation Finland sr. The remaining authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A661.

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