TITLE PAGE

Biopsychosocial risk factors for pain and pain-related disability one year after surgery for breast cancer

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Mrs. Lore Dams: defining the study concept and design, recruitment of participants, acquisition, analysis and interpretation of data, drafting the manuscript for important intellectual content, manuscript writing, approval of the final version to be published

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ABSTRACT

Purpose: Knowledge regarding risk factors for pain in the long term after surgery for breast cancer may be of great value in preventing this prevalent and debilitating side effect. Despite the biopsychosocial nature of pain, the predictive value of both pre- and postoperative biopsychosocial functioning for long-term pain intensity and pain-related disability has not yet been studied.

Methods: One hundred sixty-six women planned for unilateral breast cancer surgery were included in this prospective cohort study. Pre- and postoperative outcomes related to pain, psychosocial and somatosensory functioning (questionnaires and quantitative sensory testing) were evaluated as risk factors for pain intensity (Visual Analog Scale) and pain-related disability (Pain Disability Index) one year after surgery for breast cancer. Both bivariable and stepwise linear regression analyses were performed.

Results: The most consistent biopsychosocial risk factors were symptoms related to altered central somatosensory functioning (Central Sensitization Inventory), psychological symptoms and social support (psychological symptoms and support subscale of McGill Quality of Life Questionnaire). Results also showed that a pre- and postoperative disturbed functioning of the somatosensory nervous system in the surgical area could provide additional information regarding pain intensity or pain-related disability in the long term after surgery for breast cancer.

Conclusion*:* This study revealed several biopsychosocial characteristics that might be used to identify women more vulnerable to have pain and pain-related disability in the long term after surgery for breast cancer, allowing for more effective pain management and prevention.

Keywords: prospective cohort study, breast cancer surgery, persistent pain, risk factors, biopsychosocial model

INTRODUCTION

Persistent pain is one of the most common and profound sequelae after treatment for breast cancer. More than one year after breast cancer surgery, about 31% of women still experience pain.[1] Given that breast cancer is the most common cancer among women worldwide[2], and improvements in diagnosis and treatments have resulted in a five-year survival rate of 80-85%[3], an increasing number of women have to deal with this debilitating side effect.

The biopsychosocial model considers pain as a result of the dynamic interaction among biological, psychological and social factors. In addition, the impact of pain on a person's biopsychosocial functioning is equally important. Pain may affect biological and psychosocial functioning and can therefore seriously impair someone's quality of life.[4] Ferreira et al. (2015) investigated pain-related disability in breast cancer survivors who reported persistent pain and concluded that pain has a negative impact on mood, normal work and sleep.[5]

Given the disabling impact of persistent pain, it is necessary to identify its risk factors in order to provide a basis for prevention. Breast cancer patients with a perioperative predisposition for persistent pain may be identified by these factors. Various patient- and breast cancer treatment-related risk factors for the development of persistent pain, such as higher age, obesity, surgery with axillary lymph node dissection or treatment with chemotherapy have already been extensively described.[6, 7] In addition, literature has shown that psychological factors, including preoperative anxiety[8, 9], psychological distress[10] and the inability to identify and express emotions (alexithymia)[11] are also risk factors for persistent pain after surgery for breast cancer.

A few studies also highlighted the importance of considering the functioning of the somatosensory nervous system in the development of persistent pain after surgery for breast cancer.[12, 13] Quantitative sensory testing (QST) can be used to evaluate the functioning of the somatosensory system by quantifying how individuals experience (non-)nociceptive stimuli (mechanical, pressure or thermal stimuli) in the area of the surgery (local somatosensory functioning) and/or at more distant locations (central somatosensory functioning).[14] Besides evaluating extra segmental sensitivity at remote body regions, central somatosensory functioning can also be evaluated using a conditioned pain modulation and/or temporal summation protocol. These QST methods explore the physiological phenomena of diffuse noxious inhibitory control and wind-up of repeated nociceptive input and may provide more information on someone's endogenous inhibitory and facilitatory pain modulatory mechanisms.[15]

In a population of breast cancer, only one study evaluated the predictive value of preoperative somatosensory functioning for persistent pain one year after surgery for breast cancer.[12] Increased wind-up of pain was found to be a significant risk factor, remote pressure pain sensitivity however was not related with pain in the long term after breast cancer surgery.[12] To our knowledge, the predictive value of local (pain) sensitivity to mechanical or thermal stimuli or of conditioned pain modulation for persistent pain after surgery for breast cancer has not yet been investigated.

In addition to QST, questionnaires evaluating self-reported signs and symptoms that may indicate a lesion or disease of the peripheral somatosensory nervous system[16] or assessing self-reported symptoms that may be related to altered central somatosensory functioning[17], can also provide more information about the functioning of the somatosensory system. However, the perioperative presence of these symptoms in relation to persistent pain following surgery for breast cancer has yet to be explored.

Next to identifying preoperative risk factors for persistent pain, postoperative factors may also be relevant given that surgery for breast cancer has a significant impact on both biological and psychosocial functioning.[18, 19] To date, no study has evaluated the predictive value of both immediately postoperative somatosensory and psychosocial functioning for pain one year after surgery for breast cancer.

Therefore, the aim of this prospective cohort study was to investigate the predictive value of pre- and postoperative somatosensory and psychosocial functioning for pain and pain-related disability one year after surgery for breast cancer. The findings of the study may help in the early identification of patients who are at risk for developing persistent pain and pain-related disability after surgery for breast cancer.

METHODS

Participants

This prospective cohort study was conducted from November 2017 to February 2021 at the Department of Physical Medicine and Rehabilitation of the University Hospitals of Leuven campus Gasthuisberg (Belgium). The present study was part of a larger randomized controlled trial examining the effectiveness of pain neuroscience education on pain, physical, emotional and work-related functioning after breast cancer surgery (EduCan trial, NCT03351075).[20] The study was approved by the Ethical Committee of the University Hospitals of Leuven (s60702). All participants were consecutively recruited at the Multidisciplinary Breast Centre (MBC) of the University Hospitals of Leuven campus Gasthuisberg (Belgium). Inclusion criteria were (1) diagnosis with histologically confirmed invasive or non-invasive primary breast cancer, (2) scheduled for one of the following surgeries: mastectomy including either a sentinel node biopsy or axillary lymph node dissection (with or without breast reconstruction) or breast conserving surgery including axillary lymph node dissection, (3) female, (4) aged 18 years or older, (5) comprehended the Dutch language (reading, listening, writing and speaking). Patients with active metastases were excluded. All included patients provided written informed consent.

Outcome variables

The dependent variables of interest were pain intensity and pain-related disability twelve months after surgery. Pain intensity was evaluated using a Visual Analog Scale (VAS).[21] The VAS has been found to have good psychometric properties to evaluate pain in women diagnosed with breast cancer.[22] Pain-related disability was evaluated using the Pain Disability Index (PDI).[23] The PDI-Dutch language version has been found to be internally consistent and test-retest reliable in patients with musculoskeletal pain.[24]

The independent variables were perioperative pain-related outcomes (pain intensity and pain-related disability), somatosensory functioning and psychosocial functioning. Somatosensory functioning was evaluated using two questionnaires and a comprehensive QST evaluation. Table 1 provides an overview of the included variables and their evaluation methods.

Study procedure

Participants were evaluated one week before and after surgery, as well as twelve months after surgery. During a face-to-face consultation, the assessor (L.D. or E.v.D.G.) evaluated pain intensity as well as pain-related disability (by guiding the participant through the questionnaire while they were completing it on their own) and assessed somatosensory functioning with the Douleur Neuropathique en 4 questions questionnaire (DN4) and a comprehensive QST evaluation. The other variables were evaluated through questionnaires completed in written

form by the participant themselves. Demographic and treatment-related variables (age, BMI, type of surgery, tumor size and lymph node stage, type of (neo)-adjuvant treatments) were collected through the electronic patient medical file.

Statistical analysis

First, patient characteristics were analyzed using descriptive statistics. Mean, standard deviation, median and interquartile range were given for continuous variables and numbers and percentages for ordinal variables. A log transformation was applied to the data of QST methods evaluating mechanical detection, mechanical pain and pressure pain sensitivity.

Second, the associations between pain intensity and pain-related disability one year after surgery for breast cancer (dependent variables) and perioperative pain intensity, pain-related disability, somatosensory and psychosocial functioning (independent variables) were explored using bivariable analyses (Spearman correlation coefficient, rs). The correlation coefficients were interpreted as follows: <0.3 weak, 0.3-0.5 moderate, 0.5-0.7 good and >0.7 very good.[25]

Third, a stepwise linear regression analysis was performed to evaluate the contribution of the independent variables that were significantly correlated to one of the two dependent variables in the bivariable analysis. Following assumptions of linear regression analysis were tested for the regression models: linearity (linear relationship between independent and dependent variables), homoscedasticity (variance of the residuals consistent at each level of the independent variable), multicollinearity (variance inflation factor below 5, tolerance above 0.2), normality (normal distribution of residuals) and independence of errors (autocorrelation between residuals). A total of four stepwise regression analyses were performed: two with pain intensity and two with pain-related disability as the dependent variable, with each model separately examining the pre- and postoperative independent variables. All statistical analyses were performed with IBM SPSS Statistics 27 software. P-values of less than 0.05 were regarded as statistically significant.

Please insert Table 1 here

RESULTS

A total of 166 women were included. Patient and tumor characteristics are presented in Table 2. Mean (SD) score for pain intensity (VAS) one year after surgery was 23.6 (21.6) with a minimum score of 0 and a maximum score of 84. Mean (SD) score for pain-related disability (PDI) was 9.7 (13.2) with a minimum score of 0 and a maximum score of 53.

Please insert Table 2 here

Risk factors for higher pain intensity one year after surgery for breast cancer

According to the **bivariable analyses** (Table 3), both pre- (T0) and postoperative (T1) higher pain intensity (T0 rs=0.305; p<0.001, T1 rs=0.263; p<0.001), higher pain-related disability (T0 rs=0.242; p=0.002, T1 rs=0.168; p=0.032) and more symptoms related to altered central somatosensory functioning (T0 rs=0.315; p<0.001, T1 rs=0.304; p<0.001) were significantly associated with higher pain intensity one year after surgery for breast cancer. However, strength of associations was weak to moderate. Increased intensity of aftersensations in the pectoral area following repeated pinprick stimulation demonstrated a trend toward a significant association with pain intensity (aftersensations: T0 rs=0.142; p=0.070, T1 rs=0.141; p=0.077). Only preoperatively, increased mechanical pain sensitivity at the inner upper arm was significantly though weakly associated with higher pain intensity (local mechanical pain sensitivity: T0 rs=-0.264; p=0.001). All variables that evaluated psychosocial functioning showed a significant but weak association with pain intensity one year after surgery for breast cancer, both pre- and postoperatively.

Table 4 gives an overview of the results of the stepwise regression analyses for pain intensity one year after surgery for breast cancer. All tested assumptions for linear regression analysis were met. Preoperative symptoms related to altered central somatosensory functioning, feeling of support and mechanical pain sensitivity at the inner upper arm were found to be significant contributors to pain one year after surgery (R^2=0.207). Postoperatively, psychological symptoms and symptoms related to altered central somatosensory functioning appeared to play a role in long-term pain following breast cancer surgery (R^2=0.150).

Risk factors for higher pain-related disability one year after surgery for breast cancer

According to the **bivariable analyses** (Table 3), both pre- and postoperative higher pain intensity (T0 rs=0.276; p<0.001, T1 rs=0.248; p=0.001), higher pain-related disability (T0 rs=0.378; p<0.001, T1 rs=0.244; p=0.002), more symptoms related to altered central somatosensory functioning (T0 rs=0.394; p<0.001, T1 0.424; p<0.001) were significantly associated with higher pain-related disability one year after surgery for breast cancer. The strength of the associations ranged from weak to moderate. Mechanical pain sensitivity at the

inner upper arm was only associated with pain-related disability one year after surgery when assessed before surgery (local mechanical pain sensitivity: T0 rs=-0.278; p<0.001). More postoperative symptoms associated with a lesion or disease of the peripheral somatosensory nervous system (DN4: T1 rs=0.207; p=0.010) and increased intensity of aftersensations in the pectoral area following repeated pinprick stimulation (aftersensations: T1 rs=0.218; p=0.006), were significantly but weakly associated with higher pain-related disability one year after surgery for breast cancer.

Table 5 gives an overview of the results of the **stepwise regression analyses** for pain-related disability one year after surgery for breast cancer. All tested assumptions for linear regression analysis were met. Preoperative symptoms related to altered central somatosensory functioning and psychological symptoms were found to be significant risk factors (R^2=0.194). Regarding postoperative risk factors, stepwise regression analysis revealed that symptoms related to altered central somatosensory functioning, feeling of support and symptoms related to a lesion or disease of the peripheral somatosensory nervous system accounted for 26% of the variance in score on the PDI (R^2=0.263).

Please insert Table 3 here

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DISCUSSION

The aim of this prospective cohort study was to investigate the predictive value of pre- and postoperative outcomes related to pain, somatosensory and psychosocial functioning for pain intensity and pain-related disability one year after surgery for breast cancer. An increased number of **symptoms related to altered central somatosensory functioning** was found to be a risk factor for higher pain intensity and pain-related disability one year after surgery for breast cancer, both pre- and postoperatively. **Preoperative increased mechanical pain sensitivity at the affected side's inner upper arm** seems to provide information about pain intensity in the long term, whereas **postoperative symptoms related to a lesion or disease of the peripheral somatosensory nervous system** tend to give information about long-term pain-related disability. All variables related to psychosocial functioning were significantly associated with pain and pain-related disability based on bivariable analyses, but especially **pre- and postoperative feelings of support** tend to be relevant for pain and pain-related disability in the long term. According to the present study, the majority of pre- and postoperative QST results, as well as pain-related catastrophizing, do not appear to have a significant predictive value for pain intensity or pain-related disability one year after breast cancer surgery.

Given that mood and cognitions can have a strong influence on the experience of pain and its persistence[30], as well as evidence of a relationship between preoperative psychological functioning and pain in the long term after surgery for breast cancer[8-10], the present study expected these factors to be risk factors for pain over time. However, **preoperative pain-related catastrophizing and psychological symptoms related to depressive feelings, worrying, and anxiety** were not found as risk factors for higher pain intensity in the long term after breast cancer surgery. This finding is in line with the study of Schreiber et al. (2021), which investigated the predictive value of outcomes related to pain, sleep, somatosensory and psychological functioning for pain intensity and pain-related disability one year after surgery for breast cancer.[12] Regarding pain-related disability, the study of Schreiber et al. (2021) did find that greater pain catastrophizing and negative affect were independently predictive of pain-related disability. The present study's stepwise regression analyses confirmed the predictive value of preoperative psychological symptoms for pain-related disability, but not of pain-related catastrophizing. A possible explanation might be that pre- and postoperative pain intensity and pain-related disability in our study sample were rather limited, making pain-related questionnaires less relevant. Consequently the contribution of the pain-related psychological variable (pain-related catastrophizing) in the stepwise regression models may have been overshadowed by general psychological factors, known to be associated with pain catastrophizing (such as depression and anxiety).[31] Indeed, the present study found that more general, non-pain-related pre- and postoperative psychological functioning (e.g. psychological symptoms related to depressive feelings, worrying, and anxiety), were predictive of pain-related disability and pain intensity, one year after surgery for breast cancer. Besides psychological risk factors, the present study was able to identify a number of other important risk factors whose influence had not yet been evaluated, or had only been evaluated to a limited extent, in previous studies in a breast cancer population.

First, a higher score on the **Central Sensitization Inventory** (CSI) was identified pre- and postoperatively as a significant risk factor for both pain intensity and pain-related disability one year after surgery for breast cancer. To the best of our knowledge, this questionnaire has not been previously included in any prospective study investigating risk factors for long-term pain following surgery for breast cancer. The CSI is described as a tool for the evaluation of symptoms that can be related to an altered central somatosensory functioning.[17] This altered functioning of the central somatosensory nervous system can be seen as an augmentation of responsiveness of central neurons to somatosensory input, which may result in increased sensitivity for (non-)painful physical or non-physical stimuli such as light, sound or chemical substances.[32] By means of questions evaluating the occurrence of hypersensitivity for senses unrelated to the musculoskeletal system, the CSI score may give indirect information about

(abnormal) functioning of the central somatosensory system. However, literature in various musculoskeletal pain populations describes a weak association between QST methods intended to evaluate central somatosensory functioning and CSI results.[33-36] On the other hand, literature indicates strong associations between CSI results and various questionnaires evaluating psychological functioning such as anxiety, distress, depression, somatization as well as an individual's personality (e.g. individuals perceiving environmental stimuli more readily as threatening show higher CSI scores).[33, 35-38] In light of the present study findings, it may be argued that a higher perioperative CSI score may be indicative of the presence of elements that may neurophysiologically influence the experience of pain and its' persistence (e.g. distress), and/or may impact pain-related behavior, rather than the presence of perioperative altered central somatosensory functioning at neurophysiological level.

Second, results of the present study showed that **feeling supported before and after surgery** for breast cancer was a significant protective factor for pain and pain-related disability in the long term. To our knowledge, two studies in a breast cancer population have looked at the predictive value of social support for pain more than a year following surgery, but the results were inconclusive.[39, 40] To the best of our knowledge, no previous study has evaluated the predictive influence of social support on pain-related disability in the long term after surgery for breast cancer. Some hypotheses may be drawn about the mechanism of social support's protective effect. On the one hand, women who feel supported may receive more practical support, reducing the (physical) load on the arm-shoulder area.[41] On the other hand, higher levels of social support would be related to more adaptive pain coping strategies in non-oncological populations with persistent pain, which may explain why social support is a protective factor for pain intensity and in particular pain-related disability.[42]

Third, stepwise regression analysis revealed that pre- and postoperative disturbed **local somatosensory functioning** (i.e. intercostobrachial and intercostal nerve innervation areas) could provide additional information regarding vulnerability to increased pain intensity and pain-related disability in the long term after surgery for breast cancer. Preoperative increased mechanical pain sensitivity (evaluated with QST) as well as postoperative symptoms related to a lesion or disease of the peripheral somatosensory nervous system (evaluated with the DN4 questionnaire) were found to be significant risk factors for long-term pain intensity and pain-related disability, respectively. The study of Andersen et al. (2017) already stated that both local and central somatosensory functioning may play a role in the presence of persistent pain after surgery for breast cancer.[43] Despite promising literature on the value of QST methods evaluating pain modulatory pathways (e.g. temporal summation and conditioned pain

modulation) for predicting persistent postsurgical pain, none of these QST methods were shown to have a predictive value for pain after surgery for breast cancer.[44]

Nevertheless, some **limitations** of the present study need to be acknowledged. First, this study was an exploratory analysis as part of a larger randomized controlled trial and no sample size calculation was performed for the present research question. Second, there was not accounted for adjuvant breast cancer treatments (e.g. radiotherapy, systemic therapy) despite that these could play a substantial role in whether or not women present with pain or pain-related disability one year after breast cancer surgery. Third, despite that the regression analyses revealed multiple significant risk factors, the percentages of explained variances in pain intensity and pain-related disability were not large (unadjusted R^2). This suggests that there may be other important perioperative risk factors that were not included in the models. Nonetheless, several **strengths** of this study can be discussed. First, different assumptions for linear regression analysis were tested and confirmed. Second, both pain intensity and pain-related disability were included as independent variables. Evaluation tools that are highly recommended for assessing these aspects in a breast cancer population were used.[22] Third, the inclusion of a comprehensive and reliable QST protocol to evaluate somatosensory functioning.[45]

To our knowledge, this is the first study evaluating pre-and postoperative biopsychosocial risk factors for pain and pain-related disability one year after breast cancer surgery. The most consistent risk factors were symptoms related to altered central somatosensory functioning evaluated (CSI), psychological symptoms and social support. Results also showed that pre- and postoperative disturbed local somatosensory functioning can provide additional information regarding pain intensity or pain-related disability in the long term. These risk factors may aid in screening breast cancer patients at risk of developing pain and pain-related disability in the long term after breast cancer surgery, which is crucial for improving patient-centered care both in research as in clinical practice.

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Table 1. *Overview of variables related to pain, somatosensory and psychosocial functioning and their evaluation method*

Variable	Instrument	Description	Scoring	Interpretation
Pain-related outcomes				
Pain intensity	Visual Analog Scale [21, 22]	Global average pain intensity over the past week	**Response** Written **Scale** Horizontal 100-mm line with 2 endpoints; "no pain" and "worst pain possible" **Outcome** Absolute value **Min-Max** 0-100	Higher score = higher pain intensity
Pain-related disability	Pain Disability Index [23, 24]	Degree pain interferes with normal role functioning on 7 life domains: 1) family/home responsibilities, 2) recreation, 3) social activity, 4) occupation, 5) sexual behavior, 6) self-care, 7) life-support activity	**Response** Written **Scale** 11-point Likert scale from 0 (no disability) to 10 (total disability) **Outcome** Sum 7 item scores **Min-Max** 0-70	Higher score = higher self-perceived pain-related disability
Somatosensory functioning				
Symptoms and signs of a lesion or disease of the peripheral somatosensory nervous system	Douleur Neuropathique en 4 questions questionnaire[16]	Part 1 interview 7 items related to pain quality (sensory + pain descriptors) evaluated over the past week Part 2 physical examination: 3 items **Test location**: intercostobrachial + intercostal nerve innervation area	**Response** Verbal by saying 'yes' or 'no' **Scale** Dichotomous yes (1) - no (0) scale **Outcome** Sum 10 item scores **Min-Max** 0-10	Higher score = more disturbance in peripheral somatosensory functioning
Symptoms related to altered central somatosensory functioning	Central Sensitization Inventory[17]	25 items about symptoms related to altered central somatosensory processing	**Response** Written **Scale** 5-point Likert scale from 0 (never) to 4 (always) **Outcome** Sum 25 item scores **Min-Max** 0-100	Higher score = greater symptomatology associated with altered central somatosensory functioning
Local mechanical detection – pain sensitivity	Von Frey monofilaments (Optihair2-Set, Marstock, Germany,0.25-512 mN)	Method of limits[26] Detection**:** series of ascending and descending stimulus intensities are given and the stimulus intensity that is first/last identified is recorded Pain: series of ascending and descending stimulus intensities are given and the stimulus intensity that is first/last identified as painful (not unbearable) is recorded **Rate** Skin contact of 2s on-2s off **Test location** inner upper arm AS*	**Response** Verbal by saying 'yes' **Outcome** Geometric mean of ascending and descending stimulation (i.d. the first and last detected stimulus) (mN)[26] **Min-Max** 0.25mN-512mN	Higher score = decrease in local mechanical detection-pain sensitivity
Remote pressure pain sensitivity	Digital algometer (Wagner FDX, Greenwich CT, USA) rubber tip 1 cm²	Method of limits: amount of pressure by which the perception of pressure turns for the first time into a painful (not unbearable) sensation[26] **Rate** 0.1 kgf/s **Test location** quadriceps NAS*	**Response** Verbal by saying 'stop' **Outcome** Arithmetic mean 2 trials (kgf) **Min-Max** 0 kgf/s-12kgf/s	Higher score = decrease in remote pressure pain sensitivity
Local thermal detection – pain sensitivity	Computer-controlled Thermode system TSA II (Medoc, Israel) 3×3 cm thermode	Method of limits[26] Detection**:** temperature when a change from a thermoneutral state to a distinct warm (WDT) or cold (CDT) sensation is experienced Pain: temperature when a change from a thermoneutral state to a painful (not unbearable) warm (HPT) or cold (CPT) sensation is experienced **Test location** Inner upper arm AS*	**Response** Pushing computer-controlled button **Outcome** Arithmetic mean 3 trials (°C) for each thermal threshold (WDT, CDT, HPT, CPT) **Rate** 1°C/s **Min-Max** 0°C-50°C	WDT, HPT: Higher score = decrease in local thermal detection-pain sensitivity CDT, CPT: lower score = decrease in local thermal detection-pain sensitivity

Wind-up Aftersensations	Von Frey monofilament (Optihair2-Set, Marstock, Germany, 256 mN)	Pain rating after single pinprick stimulation, after 30s of repeated pinprick stimulation and 15s after final stimulation[26] **Rate** 1/s **Test location** pectoral region AS*	**Response** Verbal **Outcome** Wind-up = pain rating after 30s stimulation minus pain rating single stimulation (NRS) Aftersensations = pain rating 15s after final stimulation (NRS) **Min-Max** 0-10	Higher score = greater degree of temporal summation
Conditioned pain modulation	Thermode system Q-sense (Medoc, Israel) two 3×3 cm thermodes	Parallel heat design[27] ** 1. Test stimulus (45s): Individually determined test stimulus (temperature Pain4) applied alone. Pain rating at 10s, 20s, 30s and 40s of stimulation. 2. Break (120s) 3. Conditioning stimulus (temperature Pain4 + 0.5°C) (65s) + test stimulus in parallel (45s). Pain rating at 10s, 20s, 30s and 40s of stimulation. **Rate** 1°C/s **Test location** Test stimulus lower arm AS, conditioning stimulus lower arm NAS*	**Response** Verbal **Outcome** Arithmetic mean differences in NRS conditioning + test stimulus and NRS test stimulus without conditioning for 4 10s-long epochs (NRS) **Min-Max** -10-10	Negative values indicate efficient conditioned pain modulation
Psychosocial functioning				
Pain-related catastrophizing	Pain Catastrophizing Scale[28]	13 pain-related thoughts or feelings are described, and participants are asked if they have experienced them while in pain	**Response** Written **Scale** 5-point Likert scale from 0 (not at all) to 4 (all the time) **Outcome** Sum 13 item scores **Min-Max** 0-52	Higher score = more severe catastrophic thoughts about pain
Psychological symptoms, existential well-being and support	McGill Quality of Life Questionnaire[29]	Overall quality of life over the past two days. Following subscales are related to psychosocial functioning and included in the present study: psychological symptoms (4 items relating to depressive feelings, worrying, and anxiety), existential well-being (6 items), support (2 items)	**Response** Written **Scale** 11-point Likert scale from 0 to 10 with opposite anchors at the end **Outcome** Arithmetic mean item scores per subscale **Min-Max** 0-10	Higher score = better psychosocial functioning

AS: affected side, CDT: cold detection threshold, CPT: cold pain threshold, HPT: heat pain threshold, kgf: kilogram-force, mN: millinewton, NAS: non-affected side, NRS: numerical rating scale, s: seconds, WDT: warmth detection threshold
* See Appendix I for a detailed description of the test locations of the QST protocol.
**See Appendix I for a detailed description of the complete CPM protocol.

Table 2

Table 2. *Patient and tumor characteristics. Numbers (%) are given unless specified otherwise (n=166)*

Age (years), mean (SD) median (IQR)	55.9 (11.1) 55.1 (13.7)
BMI (kg/m²), mean (SD) median (IQR)	25.6 (5.2) 24.5 (6.4)
Surgery at dominant side	77 (47%)
Type of surgery	
Breast conserving surgery + ALND	13 (8%)
Mastectomy + SLNB	75 (45%)
Mastectomy + ALND	78 (47%)
Tumor size (histopathological staging)	
pTis	12 (7%)
pT0	14 (8%)
pT1	52 (31%)
pT2	64 (39%)
pT3	22 (13%)
pT4	2 (1%)
Lymph node stage (histopathological staging)	
pNx	1 (1%)
pN0	82 (50%)
pN1	59 (39%)
pN2	15 (9%)
pN3	9 (5%)
Radiotherapy	127 (76.5%)
Breast	12 (7%)
Thorax	104 (63%, n=165)
MSP	116 (70%, n=165)
Axilla	12 (7%, n=165)
Chemotherapy	104 (63%)
Neo-adjuvant	44 (26.5%)
Anthracyclines	67 (40%)
Taxane-based	105 (63%)
Hormonal therapy (ongoing)	126 (76%)
Tamoxifen	25 (15%)
Aromatase inhibitors	101 (61%)
Target therapy (ongoing)	23 (25%)

ALND: axillary lymph node dissection, BMI: body mass index, MSP: median subclavian and parasternal lymph node areas, SLNB: sentinel lymph node biopsy.

Table 3

Table 3. *Bivariable associations between pre- (T0) en postoperative (T1) pain-related outcomes, somatosensory and psychosocial functioning, and pain intensity and pain-related disability one year after surgery for breast cancer (n=166)*

	n		Mean (SD)		Median (IQR)		Correlation coefficient (p value)			
							Pain intensity (VAS)		**Pain-related disability (PDI)**	
	T0	T1	T0	T1	T0	T1	T0	T1	T0	T1
Pain-related outcomes										
Pain intensity (VAS 0-100)	164	166	13.8 (18.7)	30.3 (21.3)	5.5 (20.0)	27.5 (33.0)	0.305 (0.000) **	0.263 (0.001) **	0.276 (0.000) **	0.248 (0.001) **
Pain-related disability (PDI 0-70)	165	164	4.6 (8.6)	21.0 (15.6)	0.0 (6.0)	19.4 (27.0)	0.242 (0.002) **	0.168 (0.032) *	0.378 (0.000) **	0.244 (0.002) **
Somatosensory functioning										
Signs- symptoms lesion-disease peripheral somatosensory nervous system (DN4 0-10)	-	153	-	3.9 (1.9)	-	4.0 (2.0)	-	0.092 (0.258)	-	0.207 (0.010) *
Symptoms related to altered central somatosensory functioning (CSI 0-100)	164	164	29.8 (10.9)	30.6 (12.5)	30.0 (16.0)	31.0 (15.0)	0.315 (0.000) **	0.304 (0.000) **	0.394 (0.000) **	0.424 (0.000) **
Local mechanical detection+	164	165	0.5 (0.7)	0.8 (0.9)	0.4 (1.0)	0.7 (1.4)	0.132 (0.094)	0.069 (0.383)	0.007 (0.930)	-0.035 (0.659)
Local mechanical pain sensitivity+	164	165	2.5 (0.3)	2.4 (0.3)	2.6 (0.4)	2.6 (0.4)	-0.264 (0.001) **	0.029 (0.708)	-0.278 (0.000) **	-0.023 (0.767)
Remote pressure pain sensitivity+	161	163	0.4 (0.2)	0.5 (0.2)	0.5 (0.3)	0.5 (0.3)	0.111 (0.161)	0.050 (0.523)	0.093 (0.241)	0.057 (0.468)
Local thermal detection warmth (°C)	163	165	36.3 (2.5)	39.5 (5.5)	35.7 (2.0)	37.2 (7.6)	-0.011 (0.894)	0.072 (0.359)	-0.101 (0.200)	-0.010 (0.897)
Local thermal detection cold (°C)	163	165	29.3 (2.7)	23.9 (9.6)	29.9 (1.7)	28.0 (6.3)	-0.077 (0.328)	-0.074 (0.344)	0.003 (0.968)	-0.023 (0.772)
Local thermal pain sensitivity warmth (°C)	163	165	42.5 (3.5)	44.8 (4.0)	42.8 (6.3)	45.4 (6.5)	-0.037 (0.636)	0.033 (0.674)	-0.082 (0.296)	0.054 (0.487)
Local thermal pain sensitivity cold (°C)	163	165	17.4 (9.2)	13.8 (10.8)	21.1 (15.8)	15.1 (24.6)	0.058 (0.461)	-0.037 (0.639)	0.023 (0.769)	-0.048 (0.544)
Wind-up (NRS)	164	163	2.3 (1.8)	2.4 (2.0)	2.0 (2.0)	2.0 (3.0)	0.069 (0.380)	0.046 (0.565	0.092 (0.241)	0.006 (0.941)
Aftersensations (NRS)	164	160	0.6 (1.3)	1.1 (1.8)	0.0 (1.0	0.0 (2.0)	0.142 (0.070)	0.141 (0.077)	0.130 (0.096)	0.218 (0.006) **
Conditioned pain modulation (NRS)	164	165	-0.4 (1.1)	-0.4 (1.2)	-0.5 (1.6)	-0.5 (1.2)	0.075 (0.340)	0.021 (0.793)	-0.039 (0.621)	-0.031 (0.695)
Psychosocial functioning										
Pain-related catastrophizing (PCS 0-52)	161	163	9.5 (8.6)	8.7 (8.1)	8.0 (13.0)	7.0 (13.0)	0.203 (0.010) **	0.250 (0.001) **	0.169 (0.032) *	0.264 (0.001) **
Psychological symptoms (MQOL 0-10)	164	163	5.4 (2.4)	7.1 (2.3)	5.5 (3.75)	7.5 (3.5)	-0.321 (0.000) **	-0.317 (0.000) **	-0.303 (0.000) **	-0.333 (0.000) **
Existential well-being (MQOL 0-10)	161	163	6.5 (1.6)	6.6 (1.7)	6.7 (2.3)	6.7 (2.3)	-0.240 (0.002) **	-0.249 (0.001) **	-0.250 (0.001) **	-0.275 (0.000) **
Support (MQOL 0-10)	162	163	8.3 (1.5)	8.2 (1.6)	8.5 (2.0)	8.5 (2.0)	-0.275 (0.000) **	-0.148 (0.060)	-0.188 (0.017) *	-0.204 (0.009) **

+log-transformed values, ** Correlation significant at the 0.01 level, * Correlation significant at the 0.05 level, independent variables included in the stepwise regression models

CSI: Central Sensitization Inventory, DN4: Douleur Neuropathique en 4 Questions, MQOL: McGill Quality of Life questionnaire, NRS: Numerical Rating Scale, PCS: Pain Catastrophizing Scale, PDI: Pain Disability Index, T0: assessment one week before surgery, T1: assessment one week after surgery, VAS: Visual Analog Scale.

Table 4

Table 4. *Stepwise linear regression analysis for perioperative biopsychosocial functioning and pain intensity one year after surgery for breast cancer*

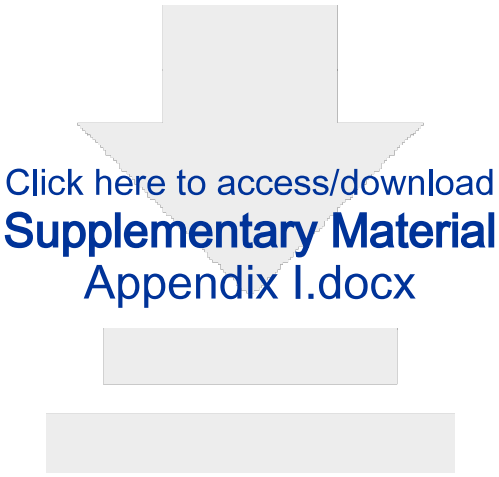
Model	R	Unadjusted R^2	P value	Risk factors
Preoperative risk factors pain intensity				
1	0.343	0.118	<0.001	Symptoms related to altered central somatosensory functioning
2	0.410	0.168	<0.001	Symptoms related to altered central somatosensory functioning and support
3	0.455	0.207	<0.001	Symptoms related to altered central somatosensory functioning, support and local mechanical pain sensitivity
Postoperative risk factors pain intensity				
1	0.335	0.113	<0.001	Psychological symptoms
2	0.388	0.150	<0.001	Psychological symptoms and symptoms related to altered central somatosensory functioning

Table 5

Table 5. *Stepwise linear regression analysis for perioperative biopsychosocial functioning and pain-related disability one year after surgery for breast cancer*

Model	R	Unadjusted R^2	P value	Risk factors
Preoperative risk factors pain-related disability				
1	0.402	0.162	<0.001	Symptoms related to altered central somatosensory functioning
2	0.440	0.194	<0.001	Symptoms related to altered central somatosensory functioning and psychological symptoms
Postoperative risk factors pain-related disability				
1	0.416	0.173	<0.001	Symptoms related to altered central somatosensory functioning
2	0.492	0.242	<0.001	Symptoms related to altered central somatosensory functioning and support
3	0.513	0.263	<0.001	Symptoms related to altered central somatosensory functioning, support and symptoms lesion-disease peripheral somatosensory nervous system

Appendix I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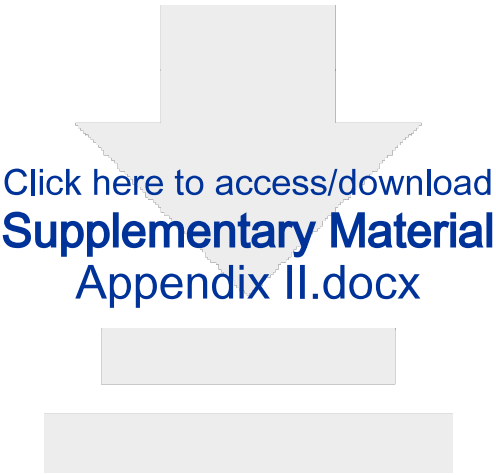
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