Cross-Sectional Study

Unraveling Self-Reported Signs of Central Sensitization in Breast Cancer Survivors with Upper Limb Pain: Prevalence Rate and Contributing Factors

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Background: Hypersensitivity of the central nervous system to environmental and chemical stimuli is a clinical feature of central sensitization mechanisms that can be assessed with the central sensitization inventory (CSI).

Objective: The aim was to determine prevalence rate of this feature and explore the treatment-, patient-, pain-, and psychosocial-related variables associated with the degree of self-reported signs of central sensitization, assessed with the CSI (0-100), in breast cancer survivors at long-term.

Study Design: Cross-sectional study.

Setting: University Hospitals, Leuven, Belgium.

Methods: One hundred and forty-six women with persistent pain, more than one year after breast cancer surgery, were included. The following factors were analyzed by bivariable and multivariable analysis: 1) treatment-related variables (type of surgery, levels of lymph node dissected, radiotherapy, chemotherapy, hormone therapy, and trastuzumab); 2) patient's related variables (age and body mass index); 3) pain-related variables (pain intensity, pain quality, primary hyperalgesia, and index of widespread pain); and 4) psychosocial variables (the degree of pain catastrophizing and vigilance and awareness to pain). The dependent variable was degree of central sensitization measured with the CSI. Additionally, a stepwise regression was performed.

Results: Fifty-five (38%) patients reported signs of central sensitization measured with the CSI (i.e., > 40/100). From multivariable analysis, it appears that more severe pain quality and higher levels of pain catastrophizing contribute to a higher degree of central sensitization. The stepwise regression revealed that up to 24% of variance of the CSI can be explained by these factors.

Limitations: A selection bias may be present since patients were all recruited from a larger cohort participating in clinical trials on the effectiveness of physical therapy after breast cancer treatment.

Conclusion: Signs of central sensitization cannot be neglected in breast cancer survivors at long term. More severe pain quality and pain catastrophizing contribute to higher levels of central sensitization in this population.

Key words: Breast neoplasm, pain, central sensitization mechanisms, central sensitization inventory

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Advances in medicine and technology have led to earlier detection and better treatment options for breast cancer, resulting in higher survival rates. Besides fatigue, pain is the most frequently reported side effect of breast cancer treatment. Despite the effectiveness of physical therapy modalities, such as specific exercises, passive mobilizations, stretching, myofascial therapy, and general exercises (1-4), prevalence rates of upper limb pain are still high (between 12-82% up to one year after surgery and between 9-72% later on) (5-8). Better understanding of a patient's pain complaint, especially at long-term, is needed to improve these pain management strategies.

In the early stage of breast cancer treatment, nociceptive and/or neuropathic pain caused by surgery, radiotherapy, and/or chemotherapy, is present in most cases (7,9). However, in a later stage, when these local effects of the different breast cancer treatment modalities should have been healed, this primary cause of pain may be overshadowed by sensitization of the central nervous system in a subgroup of breast cancer survivors (9-13). Previous studies have indeed found that central sensitization mechanisms may contribute to persistent upper limb pain in breast cancer survivors (10-12,14). These studies found signs of local and widespread pain hypersensitivity, enhanced temporal summation, deficits in endogenous pain inhibition and more intense painful aftersensations in breast cancer patients with persistent pain, all typical central sensitization mechanisms (10-12,14).

These central mechanisms are translated in typical clinical features, such as pain disproportional to the extent of injury or pathology and widespread pain and hyperalgesia (9,15,16). Another typical clinical feature of central sensitization is altered sensitivity to environmental stimuli such as light, cold/heat, food, stress, and chemical stimuli (odors and medication). The central sensitization inventory (CSI) is proposed for assessment of these symptoms of hypersensitivity of the central nervous system (17). To our knowledge, this questionnaire has not yet been applied in breast cancer survivors. Therefore, the first aim of this study is to explore the level of self-reported hypersensitivity of the central nervous system, assessed with the CSI, in a group of breast cancer survivors with persistent pain (i.e., more than one year after breast cancer surgery).

Additionally, more insight is needed in the factors contributing to this self-reported hypersensitivity of the central nervous system. First, certain treatment modalities have already been described as risk factors for persistent pain after breast cancer treatment (18-20). Therefore, the contribution of treatment-related variables, such as type of surgery and adjuvant treatment modalities (radiotherapy, chemotherapy, trastuzumab), and different types of hormone therapy to higher levels of central sensitization, has to be evaluated. Second, as described above, different clinical pain features, such as widespread pain, hyperalgesia, and disproportional pain, have been associated with central sensitization pain (9,15,16). Therefore, the contributing value of certain pain variables, such as pain intensity, pain quality, and primary and secondary hyperalgesia, has to be explored. Third, since previous studies also showed that psychosocial factors can mediate central sensitization mechanisms in breast cancer survivors, the contributing value of vigilance and awareness to pain and pain catastrophizing to hypersensitivity of the central nervous system has to be investigated (14,21,22). Therefore, the second aim is to explore the possible contribution of specific categories of variables to this self-reported central sensitization symptoms in breast cancer survivors with upper limb pain at long-term.

Methods

The approval for this trial was obtained by the local ethics committee of the University Hospitals of Leuven (s 54570). The study is reported following the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) statement (23).

Patients

Patients were recruited from a cohort of breast cancer patients participating in clinical trials on the effectiveness of physical therapy after breast cancer treatment at the Multidisciplinary Breast Centre of the University Hospitals Leuven between October 2012 and March 2015. All patients had (1) pain at the upper limb region during the week before the assessment (visual analog scale (VAS) for pain intensity > 0); (2) unilateral primary breast cancer; and (3) breast cancer surgery at least one year ago. Patients were excluded if they had current episodes of cancer or metastasis.

Procedure

Assessment of all patients was performed at least one year after surgery by 3 physical therapists. The dependent variable of interest was self-reported signs of central hypersensitivity assessed with the CSI. The CSI is a screening instrument to help identify patients presenting symptoms that may be indicative for central

sensitization mechanisms. The CSI has a high degree of test-retest reliability and internal consistency (Pearson's r = 0.82; Cronbach's alpha = 0.88) (17). Part A of the CSI measures 25 symptoms with each item score from 0 to 4. The total score on the CSI ranges between 0 and 100, with higher scores indicating increased symptom frequency/severity. Part B asks whether subjects have previously been diagnosed with 7 specific conditions indicative for central sensitization mechanisms (i.e., fibromyalgia, chronic fatigue syndrome, temporomandibular joint disorder, irritable bowel syndrome, migraine or tension headaches, multiple chemical sensitivities, and restless leg syndrome) or 3 central sensitization-related disorders (i.e., depression, anxiety or panic attacks, and neck injury). A cut-off score of 40 out of 100 produces good sensitivity (81%) and specificity (75%) (24,25). Recently, CSI severity levels were established: subclinical = 0-29; mild = 30-39; moderate = 40-49; severe = 50 to 59; and extreme = 60-100 (26).

Treatment-, patient-, pain- and psychosocial-related variables are investigated as contributing factors. An overview of the measurement methods of the pain-related and psychosocial variables is given in Table 1 (33,37-39).

Statistical Analysis

For the patient characteristics, mean and standard deviation are given for continuous variables and numbers and percentages for ordinal variables.

First, the number of patients with self-reported signs of central sensitization (cut-off of 40/100) and the degree of central sensitization in breast cancer survivors is described.

Second, the association between the different contribution factors (treatment-, patient-, pain- and psychosocial-related factors) and CSI was explored with bi-variable analyses (Pearson correlation coefficient for continuous variables and independent t-test or ANOVA for nominal variables) because data were normally distributed. Arbitrary guidelines for interpretation of the correlations are formulated by Evans (27). A correlation coefficient between 0 and 0.19 indicate a very weak correlation, between 0.20-0.39 weak, between 0.40-0.59 moderate, between 0.60-0.79 strong, and between 0.80-1.00 very strong. Third, general linear models were used to perform multivariable analyses.

Additionally, a stepwise regression analysis was performed with CSI as dependent variable and statistical significant predictive variables from the multivariable analyses. Statistical analyses were performed us-

Table 1. *Overview of the pain-related and psychosocial variables and their measurement method.*

Outcome parameter	Measurement methods
Pain-related factors	
Pain intensity (0-100)	Maximum score on the Visual Analog Scale (0-100) during the past week for pain at the upper limb region (i.e., shoulder-neck region, arm, axilla, trunk side and breast region)
Pain Quality	The McGill pain questionnaire was used to assess Pain Quality. First, the outcome 'total number of words chosen (NWC-total)' was counted. Second, the 'total pain rating index (PRI-total)', based on the numerical value of each word was determined (32).
Primary hyperalgesia (kg/cm^2)	Mean of the pressure pain thresholds at different locations at the operated side are measured by a digital Wagner FPX™ algometer. Points of measurement were defined by palpation for tender points at the region of M upper trapezius (between the C7 spinous process and the acromion), M Supraspinatus (above the spine of the scapula), M Infraspinatus (muscle belly under the spine of the scapula), M Pectoralis Major (under the clavicle), M Pectoralis Minor (between the caudal edge of the 4th rib and the inferomedial aspect of the coracoid process) and the M Serratus Anterior (below the axilla, on the muscle belly which branches to the ribs). Pressure was applied with a constant rate of 1 kg/second by a 1 cm^2 probe. The subject was asked to say 'stop' when the sensation of pressure first changed to pain (36).
Index of widespread hyperalgesia	Ratio between the mean pressure pain thresholds at the operated side (primary hyperalgesia) and the pressure pain threshold of the quadriceps muscle at the non-operated side.
Psychosocial-related factors	
Pain catastrophizing (0-52)	The Pain Catastrophizing Scale (PCS) is a 13-item questionnaire that examines the rumination, magnification, and helplessness patients have about their perceived ability to manage their pain. A total PCS score of 30 or more represents a clinically relevant level of catastrophizing (37).
Pain vigilance and awareness (0-82)	The Pain Vigilance and Awareness Questionnaire (PVAQ) is a 16-item questionnaire. Higher scores indicate a higher degree of vigilance and awareness to pain (38).

ing Statistical Package for the Social Sciences software (SPSS for Windows, version 23.0). Statistical significance was taken as $P < 0.05$.

Results

In total, 146 women with pain after breast cancer treatment were included. Mean (standard deviation (SD)) age was 56.8 (9.9) years and median time after surgery was 1 year (range 1 to 14.6) years. All patients' characteristics are given in Table 2.

Table 2. *Patient characteristics. Numbers (%) are given unless specified otherwise (n = 146).*

Mean (SD) age (years)	56.8 (9.9)
Mean (SD) BMI (kg/m²)	25.9 (5.0)
Median time after surgery (range) (years)	1.0 (1.0 to 14.6)
Type of breast surgery:	
Mastectomy	81 (56%)
Breast Conserving	65 (44%)
Type of axillary surgery	
Sentinel lymph node biopsy	47 (32%)
Axillary lymph node dissection	99 (68%)
Surgery at dominant side	61 (42%)
Level of lymph nodes removed:	
I	47 (32%)
I-II	51 (35%)
I-III	48 (33%)
Tumor size:	
pTis	9 (6%)
pT1	52 (36%)
pT2	69 (47%)
pT3	16 (11%)
Lymph node stage:	
pN0	77 (53%)
pN1	60 (41%)
pN2	3 (2%)
pN3	6 (4%)
Radiotherapy	133 (91%)
Hormone therapy:	
No	28 (19%)
Tamoxifen	73 (50%)
Aromatase Inhibitors	45 (31%)
Chemotherapy	70 (48%)
Trastuzumab	29 (20%)

SD = Standard Deviation; BMI = Body Mass Index

Mean (SD) score on the CSI was 37 (14) with a minimum score of 8 and maximum score of 86. In Part A of the CSI, 55 (38%) patients reached the cut-off score of 40. Half of patients are situated around this cut-off score with 36 (25%) patients with a score between 40 and 49 and 42 (29%) patients with a score between 30 and 39. Only 9 (6%) patients had extreme signs of central sensitization with a score above 60. Sixty-seven (46%) patients did not have a condition indicative for central sensitization or a central sensitization-related disorder questioned in Part B of the CSI. Seventy-nine (54%) patients were diagnosed with at least one of these conditions, with migraine or tension headaches the most frequent (n = 33, 25% of patients) (Table 3 and Fig. 1).

Table 4 gives an overview of the bi-variable analysis for the contributing factors to signs of central sensitization in breast cancer survivors at long-term. First, no treatment-related variables were found to be significantly associated with the CSI. However, for type of breast surgery, a trend towards significance ($P = 0.066$) was found. The mastectomy procedure was associated with higher levels of central sensitization. Second, no patient-related variables were found to be associated. Third, all pain-related variables were

Table 3. *Results for the CSI (n = 146).*

PART A	
Central Sensitization Inventory (0-100) (Mean (SD))	37 (14)
Number of patients with signs of central sensitization (CSI > 40)	55 (38%)
PART B	
None	67 (46%)
Fibromyalgia	4 (3%)
Chronic Fatigue Syndrome	6 (3%)
Temporomandibular Joint Disorder	3 (2%)
Irritable Bowel Syndrome	21 (14%)
Migraine or Tension Headaches	33 (25%)
Multiple Chemical Sensitivities	10 (7%)
Restless Leg Syndrome	6 (3%)
Depression	22 (15%)
Anxiety or Panic Attacks	11 (7%)
Neck Injury	27 (18%)

SD = Standard Deviation; CSI = Central Sensitization Inventory

found to be significantly associated with the CSI, except for the index of widespread pain. The highest correlations were found for pain intensity (r = 0.353, $P < 0.001$), 'total number of words' and 'total pain rating index' on the McGill pain quality questionnaire (r = 0.381, $P < 0.001$ and r = 0.496, $P < 0.001$, respectively). These results indicate the higher the pain intensity and scores on the McGill, the higher the level of central sensitization. A weak negative significant correlation between primary hyperalgesia (r = -0.302, $P < 0.001$) and the CSI was found. Primary hyperalgesia is represented by the mean pressure pain thresholds at the operated side so this result indicates the lower the pressure pain thresholds the higher the level of central sensitization. For the psychosocial variables, a weak significant correlation was found for vigilance and awareness to pain (r = 0.262, $P < 0.001$) and a moderate significant correlation for pain catastrophizing (r = 0.477, $P < 0.001$).

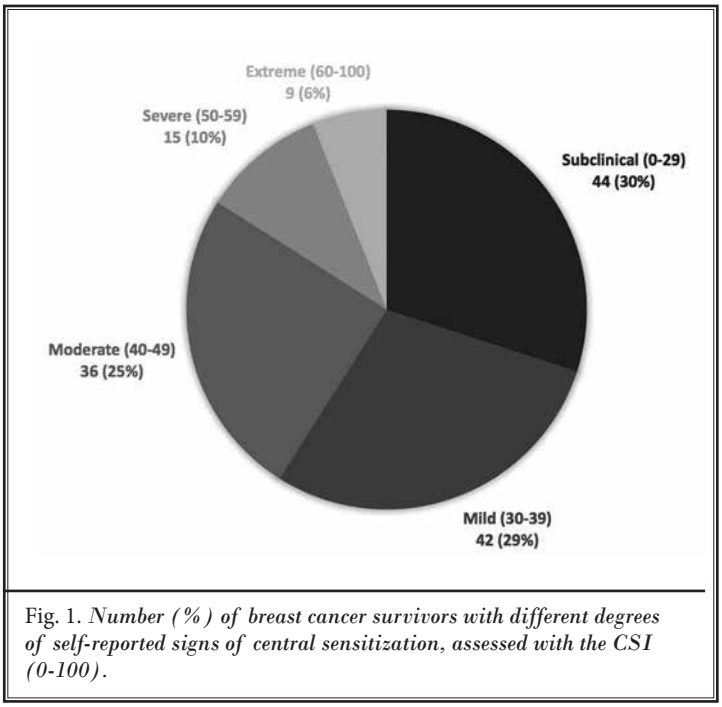

Fig. 1. *Number (%) of breast cancer survivors with different degrees of self-reported signs of central sensitization, assessed with the CSI (0-100).*

Table 4. *Associations between the treatment-, patient-, pain- and psychosocial related variables and signs of central sensitization (CSI) after breast cancer treatment is determined with bi-variable analyses.*

Treatment-related variables	Mean Change (SD)	*P* value (ANOVA)
Surgery at dominant side		
No (58%)	-0.96 (2.44)	0.696
Yes (42%)[a]	0.0	
Type of breast surgery		
Mastectomy (56%)	+4.43 (2.39)	0.066
Breast Conserving (44%)[a]	0.0	
Type of axillary surgery		
Sentinel lymph node biopsy (32%)	-1.76 (2.57)	0.494
Axillary lymph node dissection (68%)[a]	0.0	
Radiotherapy		
No (9%)	-3.05 (4.22)	0.470
Yes (91%)a	0.0	
Chemotherapy		
No (52%)	-2.95 (2.40)	0.220
Yes (48%)[a]	0.0	
Trastuzumab		
No (80%)	-0.32 (3.02)	0.914
Yes (20%)[a]	0.0	
Hormone therapy		
No (19%)	-2.34 (3.50)	0.504
Tamoxifen (50%)	+0.62 (2.76)	0.822
Aromatase Inhibitors (31%)[a]	0.0	

Table 4 (cont.). *Associations between the treatment-, patient-, pain- and psychosocial related variables and signs of central sensitization (CSI) after breast cancer treatment determined with bi-variable analyses.*

Patient-related variables	Mean (SD)	r	*P* value
Age (years)	56.8 (9.9)	-0.020	0.814
Body Mass Index (kg/cm^2)	25.9 (5.0)	0.058	0.489
Pain-related variables	**Mean (SD)**	**r**	***P* value**
Pain intensity (VAS 0-100)	46 (23)	0.353	< 0.001
Pain Quality			
Total number of words (0-20)	8.3 (6.4)	0.381	< 0.001
Total pain rating index (0-63)	11.6 (9.3)	0.496	< 0.001
Primary hyperalgesia (kg/cm^2)	2.7 (1.3)	-0.302	< 0.001
Index of Widespread Hyperalgesia	0.52 (0.19)	-0.140	0.091
Psychosocial-related variables	**Mean (SD)**	**r**	***P* value**
Pain catastrophizing (PCS 0-52)	12 (10)	0.477	< 0.001
Pain vigilance and awareness (0-80 PVAQ)	38 (15)	0.262	0.001

VAS = Visual Analog Scale; CSI = Central Sensitization Inventory; PCS = Pain Catastrophizing Scale; PVAQ = Pain Vigilance and Awareness Questionnaire; r = Pearson correlation; SD = Standard deviation. [a]This parameter is set at zero because it is redundant

In the multivariable analysis (Table 5), 'total pain rating index' on the McGill questionnaire and degree of pain catastrophizing remained positively associated with the CSI, meaning higher scores on these factors indicate higher levels of central sensitization. However, the estimated changes (B) were all relatively small.

From the stepwise regression analysis, it appears that the 'total pain rating index' on the McGill alone (model 1) explains about 24% of the variance of the CSI. The 'total pain rating index' in combination with the pain catastrophizing scale explains up to 33% of the variance in the level of central sensitization in breast cancer survivors at long-term.

Discussion

In a cohort of 146 breast cancer survivors with pain more than one year after breast cancer surgery, 55 (38%) patients reported signs of hypersensitivity of the central nervous system. No treatment- and patient-related factors were found to be associated with the degree of self-reported signs of central sensitization. Even though almost all pain- and psychosocial-related factors were significantly associated with the CSI in the bi-variable analyses, only pain quality and pain catastrophizing remained significantly associated in the multivariable analysis. The stepwise regression revealed that up to 33% of variance in the CSI can be explained by those 2 factors.

For decades, the awareness of the contribution of central sensitization mechanisms to persistent pain in the breast cancer populations has increased (10,12,14). The CSI is developed to assess one of the clinical features of central sensitization, namely symptoms of hypersensitivity of the central nervous system (24,25). The results of the present study indeed confirm presence of these mechanism in a relatively large number of breast cancer survivors with pain more than one year after surgery.

Many studies indicate higher risk of persistent pain after breast cancer treatment when more extensive surgery, radiotherapy and chemotherapy are applied (19,28-30). Therefore, it was hypothesized that more extensive treatment would also increase the risk of central sensitization mechanisms. The results of the present study only confirm this to a limited extent since only in the bi-variable analysis, the mastectomy procedure was found to be associated with higher scores on the CSI and this result was only of borderline significance. The most important contributing factors to hypersensitivity of the central nervous system, assessed with the CSI appear to be pain-related factors. Higher pain intensity, more severe pain quality and higher degree of primary hyperalgesia are related to higher scores on the CSI. For widespread pain, no meaningful results were found. Only pain quality remained significantly associated in the multivariable analysis. More specific, a higher total pain rating index on the McGill pain quality questionnaire was found to be contributing to the higher CSI score. The pain rating index reflects the intensity of the different pain descriptors of the McGill pain questionnaire. In each of the 20 groups of words, the descriptors that qualify pain appear in increasing order of intensity (31-33). Higher pain rating index indicates thus more

Table 5. *Associations between the treatment-, patient- and pain-related variables and signs of central sensitization (CSI) after breast cancer treatment determined with multivariable analyses.*

Treatment-related variables	**B**	**95% CI**	***P* value**
Operation at dominant side			
No (57%)	-2.46	-6.90 to 1.98	0.274
Yes (43%)[a]	0.0		
Type of surgery			
Mastectomy (58%)	+3.94	-1.01 to 8.88	0.118
Breast Conserving (42%)[a]	0.0		
Type of axillary surgery			
Sentinel lymph node biopsy (34%)	+2.50	-3.26 to 8.26	0.392
Axillary lymph node dissection (66%)[a]	0.0		
Radiotherapy			
No (11%)	-4.40	-13.46 to 4.67	0.339
Yes (89%)[a]	0.0		
Chemotherapy			
No (50%)	-1.21	-5.94 to 3.53	0.615
Yes (50%)[a]	0.0		
Trastuzumab			
No (29%)	+0.19	-5.59 to 5.96	0.949
Yes (71%)[a]	0.0		
Hormone therapy			
No (21%)	+2.02	-4.40 to 8.43	0.535
Tamoxifen (48%)	-0.90	-5.52 to 5.34	0.974
Aromatase Inhibitors (31%)[a]	0.0		
Patient-related variables	**B**	**95% CI**	***P* value**
Age (years)b	+0.02	-0.22 to 0.26	0.860
Body Mass Index (kg/cm2)b	-0.11	-0.55 to 0.32	0.608
Pain-related variables	**B**	**95% CI**	***P* value**
Pain intensity (VAS 0-100)[b]	+0.06	-0.05 to 0.17	0.285
Pain Quality			
Total number of words (0-20)[b]	-0.54	-1.31 to 0.22	0.163
Total pain rating index (0-63)[b]	+0.76	0.21 to 1.30	0.007
Primary Hyperalgesia (kg/cm^2)[b]	-1.26	-3.18 to 0.66	0.196
Index of widespread hyperalgesia	-6.60	-19.51 to 6.31	0.314
Psychosocial-related variables	**B**	**95% CI**	***P* value**
Pain catastrophizing (PCS 0-52)[b]	+0.43	0.17 to 0.69	0.001
Pain vigilance and awareness (PVAQ 0-80)[b]	+0.03	-0.14 to 0.19	0.741

VAS = Visual Analogue Scale; PCS = Pain Catastrophizing Scale; PVAQ = Pain Vigilance and Awareness Questionnaire CI = Confidence Interval; B = estimated change (and 95% confidence interval) of the outcome compared with the change in the reference category (= 0), thus a negative value refers to a stronger decrease as compared to the reference category; [a]This parameter is set zero because it is redundant; [b]An increase of the predictive variable with one unit is associated with a change of B (95% CI) of the dependent variable

severe pain. Additionally, the total score of the pain rating index has been found to explain up to 24% of variance in the CSI. Since patients in this cohort were at least one year after surgery, it is expected that the local effects of the different treatment modalities for breast cancer should have been healed at this stage.

These high scores for pain quality may therefore be disproportionate to the present extent of injury or nociceptive input (9). Presence of disproportionate pain is another typical clinical feature of central sensitization mechanisms and is for example also included, besides the CSI, in the clinical algorithm for the differentiation between pain mechanisms in cancer patients developed by Nijs et al (9). Further research has to confirm these findings.

From the bi-variable and multivariable analysis as well it appears that the contribution of psychosocial factors, in particular pain catastrophizing, to hypersensitivity of the central nervous system may not be underestimated in breast cancer survivors. This has been found by other studies in other populations as well (34,35). In breast cancer patients themselves, Edwards et al (14) and Schreiber et al (21) reported the contribution of psychosocial factors to persistent pain, enhanced temporal summation, deficits in endogenous pain inhibition and more intense painful aftersensations which are all signs of central sensitization,.

Interpreting the results of the present study, following considerations should be made. First, almost half of the cohort reported diagnosis of a condition indicative for central sensitization or a central sensitization-related disorder in part B of the CSI. These disorders are all characterized by presence of central sensitization mechanisms. Consequently, it is difficult to conclude to which extent these disorders on the one hand and the pain that resulted from the breast cancer treatment on the other hand explain the higher scores on the CSI in breast cancer survivors. Second, a cut-off score of 40/100 was found to have good sensitivity and specificity in a group of patients with various central sensitization syndromes. The results of the present study indicate that more than half of the cohort (54%) of breast cancer patients with persistent pain is situated either 10 point below or above this proposed cut-off score. The specificity and sensitivity of this cut-off score in this population should therefore be further investigated. Ad last, the validity of the CSI for the assessment of central sensitization mechanisms in breast cancer survivors has not yet been investigated. The present study showed only meaningful associations between pain quality, a self-reported subjective evaluation of a patient's pain complaint, and psychosocial factors. No associations were found in the multivariable analysis with more objective evaluation methods of pain such as algometry and the visual analog scale (VAS). Therefore, the question arises if the CSI is a valid instrument to assess central sensitization pain or does it measures a different construct like distress?

Strengths and Limitations

The present study has several strengths. First, a relatively large cohort was analyzed making multivariable analysis possible. A possible limitation of the study may be the heterogeneity in the cohort. Patients followed different rehabilitation programs after surgery, which were not considered. Second, a selection bias may be present since patients were all recruited from a larger cohort participating in clinical trials on the effectiveness of physical therapy after breast cancer treatment.

Clinical Recommendations

In clinical practice, we recommend using the CSI as screening tool for the presence of central sensitization mechanisms in breast cancer survivors, in particular the clinical feature of hypersensitivity of central nervous system. Since the cut-off score of 40/100 is not yet validated in the (breast) cancer population, it may be more useful and clinically relevant to consider the degree of the hypersensitivity instead of the cut-off. When scoring high on the CSI, a biopsychosocial treatment approach that takes into account factors, such as pain catastrophizing, may be warranted. Second, as for part B of the CSI, it may be interesting for the health care provider to also take into account previous diagnoses of certain disorders associated with central sensitization mechanisms when evaluating the patient's pain complaint. Third, hypersensitivity of the central nervous system is not the only clinical feature of central sensitization mechanisms. The guidelines for the identification of the predominant pain mechanisms in cancer pain published by Nijs et al (9) can be used to get an overall picture of the patient's pain complaint and contribution of the different pain mechanisms.

Further Research

Further research should explore the validity of the CSI, and in particular the cut-off score of 40, in the (breast) cancer population. As postulated in the recent article of the developers of the CSI, the CSI may be useful for identifying patients who are at risk for having central sensitization mechanisms contributing to their pain complaint. Since the complexity of central sensitization more research is needed to explore other contributing factors.

Conclusion

This is the first study to explore self-reported symptoms of hypersensitivity of the central nervous system in breast cancer survivors with pain after finishing treatment. Up to 38% of these patients showed signs of hypersensitivity of the central nervous system, assessed with the CSI. The results indicate that these symptoms cannot be neglected and that in particular more severe pain quality and pain catastrophizing contribute to higher levels of central sensitization in breast cancer survivors.

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