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Acknowledgements

We thank Elies Clabau and Roxane Van Hemelrijck for measuring the patients. We thank all patients who took part in this study. This study was funded by the agency for Innovation by Science and Technology (Applied Biomedical Research) (IWT 110703).

Ethical approval statement

This study was approved by the Ethical Committee of the University Hospitals Leuven (ref number: s54579). All participants gave written informed consent before data collection began.

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Abstract

Purpose: The aim of this study was to explore the treatment, patient, and impairment-related risk factors associated with upper limb dysfunctions in breast cancer survivors.

Methods: A cross-sectional study was performed in 274 women treated for breast cancer. The following risk factors were analysed 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) and finally impairment-related variables such as pain (intensity, quality and pressure hypersensitivity, signs of central sensitisation, the degree of pain catastrophizing and vigilance and awareness to pain), active ROM and upper limb strength were investigated. The dependent variable was upper limb function measured with the Disability of Arm, Shoulder and Hand (DASH) questionnaire. Additionally, a stepwise regression was performed.

Results: An impaired upper limb function was noted in 170 (62%) of patients. Mean time after surgery was 1.5 (1.6) years. From multivariable analysis, it appears that in particular certain pain characteristics such as pain intensity, pain quality, signs of central sensitization and pain catastrophizing are contributing to upper limb dysfunctions after breast cancer treatment at long term. Additionally, higher age, shoulder ROM and handgrip strength are possible contributing factors. The stepwise regression analysis revealed that central sensitization mechanisms alone can explain about 40% of the variance in upper limb function**.**

Conclusions: At long term, especially pain and central sensitisation mechanisms contribute to upper limb function in breast cancer survivors.

Key words: breast neoplasms, physical functioning, pain, physical therapy modalities

Introduction

Breast cancer is the most common cancer in women with 464.000 new cases diagnosed in Europe in 2012, representing 29% of the overall cancer burden.[1] Advances in medicine and technology has led to earlier detection and better treatment options for breast cancer, resulting in higher survival rates. While survivorship has increased, upper limb dysfunctions and disabilities have become a significant complication following breast cancer treatment.[2,3] Common upper limb dysfunctions include difficulties lifting and carrying objects, combing hair, reaching overhead to put an item on a shelf, and pushing and pulling objects such as a vacuum cleaner.[2] These dysfunctions lead to limitations in activities of daily life and eventually a reduced quality of life. At long term, i.e. more than one your after surgery, upper limb dysfunctions developed in the early stage of breast cancer treatment should have been resolved.[4] However, limitations in activities of daily life are reported in 9-57% of breast cancer survivors one year after surgery.[3,5]

Several risk factors for upper limb dysfunctions after breast cancer have been described in the literature.[5,6] First, *treatment-related variables* such as type of surgery and applied adjuvant treatment modalities have been identified as risk factors.[5-10] Women whose treatment includes mastectomy, axillary lymph node dissection and/or radiation therapy have an increased risk of developing more upper limb problems compared to women who have had breast conserving surgery, sentinel lymph node dissection, and no or less aggressive radiation therapy.[5-10] Second, *patient-related variables* such as increased Body Mass Index and higher age have been associated with upper limb dysfunctions as well.[11] Third, *impairment-related variables* such as a decreased active range of motion (ROM) and loss of muscle strength have already been described as contributing variables to upper limb dysfunctions.[5,12,13]

To date, the contribution of pain to upper limb dysfunctions in breast cancer survivors has not yet been investigated. In the first place, the contribution of different dimensions of pain (e.g. pain intensity and pain quality) is not known. Second, the awareness on the presence of altered pain processing and sensitisation of the central nervous system in breast cancer patients has increased but its contribution to upper limb dysfunctions has not yet been investigated.[14-16] Further, the awareness on the influence of psychosocial factors to recovery of upper limb function has increased resulting in a more biopsychosocial approach.[14,17] However, it has not been investigated either if certain pain-related psychosocial factors such as pain catastrophizing and vigilance and awareness to pain are associated with upper limb function in breast cancer patients. Further, the studies that already focused on disease- or treatment related variables studied the contribution of different variables separately and at rather short term.[6,9,10,18] However, since survival rates are increasing, long-term outcome parameters become more important.[1]

Therefore, the aim of this study was to explore the contribution of breast cancer treatment-related, patient-related and impairment-related factors such as shoulder ROM, strength and several pain dimensions to upper limb dysfunctions in breast cancer survivors at long term (i.e. more than one year after surgery).

Methods

The approval for this trial was obtained by the local ethics committee of the xx. The study is reported following the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) statement [19,20].

Participants

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 xx between October 2012 and March 2015. Data from the 1 year follow measurement of 3 clinical trials and baseline measurement of one other trial was merged for this cross-sectional study. Assessments were performed by three physical therapists. All participants had (1) unilateral primary breast cancer and (2) 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. The outcome parameter of interest was upper limb function questioned with the Disability of Arm, Shoulder and Hand questionnaire (DASH). The DASH consists of a 30-items, self-report questionnaire. Item responses range from 1 (no difficulty/no effort) to 5 (unable). Total scores range from 0-100, a higher score indicates greater disability. The reliability and validity has been found to be good. An impaired upper limb function has been defined as a score of 15 or more. Scores between 16-40 indicate a problem with upper limb function that is still tolerable, whereas scores above 40 indicate that these patients are unable to work. Reliability and validity of the DASH has found to be good. The minimal detectable change is 8-15 points.[21]

First, patients' characteristics and *treatment- related variables* such as type of surgery (mastectomy versus breast conserving surgery/ axillary lymph node dissection versus sentinel node biopsy), surgery at dominant side (yes/no), levels of axillary lymph node

dissected (level I (i.e. below the lower edge of the minor pectoral muscle) versus I-II (i.e. including the level underneath the minor pectoral muscle) vs I-III (i.e. including the level above the minor pectoral muscle)), pathological tumour (pT) and lymph node stage (pN), radiotherapy (yes/no), chemotherapy (yes/no), hormone therapy (no versus tamoxifen versus aromatase inhibitors) and trastuzumab (yes/no) were collected from the patient's medical file and analysed as contributing variables.

Second, patient's age, Body Mass Index (BMI) and hand dominance were evaluated as *patient- related contributing variables* for upper limb dysfunctions.

Third, *impairment-related variables* such as pain (intensity, quality and local pressure hypersensitivity), active ROM and upper limb strength at the operated side are investigated as contributing factors. Additionally, the contributing value of pain-related variables such as signs of central sensitisation and psychosocial factors (the degree of pain catastrophizing and vigilance and awareness to pain) was investigated. An overview of the measurement methods of the impairment-related variables is given in Table 1.

Table 1: Overview of the impairment-related predictive variables and their measurement method

Outcome parameter	**Measurement methods**
Active forward flexion and abduction ROM (°)	ROM measured with a Dr. Rippstein Plurimeter-V gravity reference analogue inclinometer.[22,23] The inclinometer was velcro taped perpendicular to the humeral shaft, just below the tuberositas deltoidea. The subject was instructed to perform glenohumeral abduction in the coronal plane and glenohumeral forward flexion in the frontal plane with full elbow extension, neutral wrist flexion/extension and with the thumb leading to ensure vertical alignment of the inclinometer. The rater corrected the patient for compensations (Figure 1).
Handgrip strength (kg)	Handgrip strength measured with the Jamar Handheld dynamometer.[24] Patient is sitting with shoulder adducted and neutrally rotated, elbow flexed to 90 degrees, forearm and wrist in neutral position. The average of 2 measurements was used for analysis (Figure 2).
Pain intensity (0-100)	Maximum score on the Visual Analogue 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.[25]

Pressure Hypersensitivity (kg/cm^2)	Pressure pain threshold were evaluated by a digital Wagner FPX™ algometer. The mean of the pressure pain thresholds of upper limb muscles (upper trapezius, supraspinatus, infraspinatus, serratus anterior, pectoralis major and pectoralis minor muscle) at the operated side was calculated. The assessor placed the algometer on the examination point and pressed against the device in a vertical direction while increasing the force at a constant rate of 1 kg/second. The subject was asked to say 'stop' when the sensation of pressure first changed to pain. After examining all muscles, the subjects had to rest during 5 minutes. After the resting period, the procedure was repeated. The mean value of the 2 measurements was calculated and used for the analysis.[26]
Signs of Central sensitisation (0-100)	The Central Sensitization Inventory (CSI) is a 25-item questionnaire on hypersensitivity to senses unrelated to the musculoskeletal system. A score of >40 on the CSI indicates presence of central sensitization mechanisms.[27,28]
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 represents clinically relevant level of catastrophizing.[29]
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.[30]

ROM =range of motion

Statistical Analysis

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

First, the association between the predictors and upper limb function 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.[31] 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.

Second, general linear models were used to perform **multivariable analyses**.

Additionally, a **stepwise regression analysis** was performed with upper limb function as dependent variable and statistical significant predictive variables from the multivariable analyses. Statistical analyses were performed using Statistical Package for the Social Sciences software (SPSS for Windows, version 23.0). Statistical significance was taken as $p < 0.05$.

Results

In total 274 women treated for breast cancer were included. Mean age was 57.2 years (10.9) and mean time after surgery was 1.5 (1.6) years.

Mean score for upper limb function on the DASH was 23 (18) with a minimum score of 0 and maximum score of 77. An impaired upper limb function (>15 on DASH) was reported in 170 (62%) of patients. Fifty-two patients (19%) had a score above 40, indicating that these patients are even unable to work. All characteristics are given in Table 2.

Table 2: Patients characteristics. Numbers (%) are given unless specified otherwise. (n=274)

Mean (SD) age (years)	57.2 (10.9)
Mean (SD) BMI (kg/m²)	25.3 (4.9)
Mean time after surgery (SD) (years)	1.5 (1.6)
Type of breast surgery:	
Mastectomy	160 (58%)
Breast Conserving	114 (42%)
Type of axillary surgery	
Sentinel lymph node biopsy	92 (34%)
Axillary lymph node dissection	182 (66%)
Surgery at dominant side	119 (43%)
Level of lymph nodes removed:	
I	92 (34%)
I-II	91 (33%)
I-III	91 (33%)
Tumour size:	
pTis	22 (8%)

pT1	107 (39%)
pT2	117 (43%)
pT3	28 (10%)
Lymph node stage:	
pN0	151 (55%)
pN1	102 (37%)
pN2	11 (4%)
pN3	10 (4%)
Radiotherapy	244 (89%)
Hormone therapy:	
No	57 (21%)
Tamoxifen	131 (48%)
Aromatase Inhibitors	86 (31%)
Chemotherapy	136 (50%)
Trastuzumab	52 (19%)
Upper limb function (0-100) (Mean (SD))	23 (18)
Patients with impaired upper limb function	170 (62%)
Pain intensity (0-100) (Mean (SD))	25 (28)
Patients with pain during the past week (i.e. VAS > 0)	147 (53%)

Table 3 gives an overview of the **bi-variable analysis** for prediction of upper limb dysfunctions in breast cancer survivors. First, *treatment-related variables* significantly associated with decreased upper limb function were axillary surgery and hormone therapy. The sentinel lymph node biopsy was associated with a decrease of 5.6 on the DASH

compared to axillary lymph node dissection (p=0.013). Tamoxifen and no hormone therapy were associated with a decrease of 5.5 (p=0.025) and 5.1 (p=0.091) on the DASH, respectively, compared to aromatase inhibitors.

Regarding *patient-related variables,* higher age and Body Mass Index were significantly associated with worse upper limb function. However, the correlation coefficients were very weak (r=0.191 for age and r=0.131 for Body Mass Index, p=0.002 and p=0.030, respectively).

Finally, all *impairment-related variables* were significantly associated with upper limb function. Both active forward flexion and abduction ROM and handgrip strength were negatively correlated with upper limb function, indicating a higher ROM and better strength is associated with lower scores on the DASH (i.e. better upper limb function). All pain characteristics were positively correlated with upper limb function. The highest correlation was found for signs of central sensitisation (CSI) with a correlation coefficients of 0.615 (see Table 3). These correlations indicate that higher pain intensity, higher 'total number of words chosen' and 'total pain rating index' on the McGill Pain Questionnaire, higher pressure hypersensitivity, more signs of central sensitization, catastrophizing and vigilance and awareness to pain is associated with higher levels of upper limb dysfunctions. (Table 3.)

In the **multivariable analysis,** a more complex predictive model was used compared to the bivariable analysis, resulting in no significant association between treatment-related and patient-related variables with upper limb function (Table 4). (Table 4). For the *impairment-related variables*, active abduction ROM, handgrip strength, pain intensity, 'total pain rating index', signs of central sensitization and pain catastrophizing remained significantly associated with upper limb function. However, the estimated changes (B) were all relatively small.

From the **stepwise regression analysis** (Table 5), it appears that the CSI alone (model 1) explains about 40% of the variance in upper limb function. The CSI in combination with the

total Pain Rating Index (McGill), active abduction range of motion, PCS, handgrip strength and pain intensity explain up to 63% of the variance in upper limb function in breast cancer survivors.

Table 3. Associations between the predictors and upper limb function (DASH) after breast cancer treatment determined with bi-variable analyses

Treatment-related variables	*Mean Change (SD)*	P value (ANOVA)	
Surgery at dominant side			
No (57%)	- 0.530 (2.155)	0.806	
Yes (43%)[a]	0.0		
Type of breast surgery			
Mastectomy (58%)	+ 3.072 (2.159)	0.156	
Breast Conserving (42%)[a]	0.0		
Type of axillary surgery			
Sentinel lymph node biopsy (34%)	- 5.583 (2.237)	**0.013**	
Axillary lymph node dissection (66%)[a]	0.0		
Radiotherapy			
No (11%)	- 6.199 (3.400)	*0.069*	
Yes (89%)[a]	0.0		
Chemotherapy			
No (50%)	+ 0.165 (2.137)	0.938	
Yes (50%)[a]	0.0		
Trastuzumab			
No (29%)	- 1.290 (2.723)	0.636	
Yes (71%)[a]	0.0		
Hormone therapy			
No (21%)	-5.083 (2.995)	0.091	
Tamoxifen (48%)	-5.493 (2.434)	**0.025**	
Aromatase Inhibitors (31%)[a]	0.0		
Patient-related variables	***Mean (SD)***	***r***	**P value**
Age (years)	57.2 (10.9)	0.191	**0.002**
Body Mass Index (kg/cm^2)	25.3 (4.9)	0.131	**0.030**
Impairment-related variables	***Mean (SD)***	***r***	**P value**
Active forward flexion ROM (°)	148 (18)	-0.338	**<0.001**
Active abduction ROM (°)	140 (24)	-0.363	**<0.001**
Handgrip strength (kg)	24 (6)	-0.307	**<0.001**
Pain intensity (VAS 0-100)	25 (28)	0.475	**<0.001**

Pain Quality			
Total number of words (0-20)	6.7 (6.0)	0.507	**<0.001**
Total pain rating index (0-63)	9.1 (8.7)	0.596	**<0.001**
Pressure Hypersensitivity (kg/cm^2)	2.83 (1.28)	0.267	**<0.001**
Central sensitisation (CSI 0-100)	33 (15)	0.615	**<0.001**
Pain catastrophizing (PCS 0-52)	10 (10)	0.533	**<0.001**
Pain vigilance and awareness (0-80 PVAQ)	35 (15)	0.285	**<0.001**

ROM=Range of Motion; VAS=Visual Analogue Scale; CSI=Central Sensitisation Inventory; PCS=Pain Catastrophizing Scale; PVAQ=Pain Vigilance and Awareness Questionnaire; *r* Pearson correlation; *SD* Standard deviation. [a]This parameter is set zero because it is redundant

Table 4. Associations between the predictors and upper limb function (DASH) after breast cancer treatment determined with multivariable analyses

Treatment-related variables	B	95% CI	P value
Operation at dominant side			
No (57%)	+ 2.143	-22.933 to 27.220	0.866
Yes (43%)[a]	0.0		
Type of surgery			
Mastectomy (58%)	-2.185	-24.990 to 20.620	0.850
Breast Conserving (42%)a	0.0		
Type of axillary surgery			
Sentinel lymph node biopsy (34%)	-5.212	-30.637 to 20.214	0.686
Axillary lymph node dissection (66%)[a]	0.0		
Radiotherapy			
No (11%)	+5.212	-30.637 to 20.620	0.850
Yes (89%)[a]	0.0		
Chemotherapy			
No (50%)	+18.208	-25.314 to 61.729	0.410
Yes (50%)[a]	0.0		
Trastuzumab			
No (29%)	-7.506	-31.153 to 16.141	0.532
Yes (71%)[a]	0.0		
Hormone therapy			
No (21%)	+9.625	-14.143 to 33.394	0.425
Tamoxifen (48%)	-14.505	-43.634 to 14.625	0.327
Aromatase Inhibitors (31%)[a]	0.0		
Patient-related variables	*B*	*95% CI*	P value
Age (years)[b]	0.160	-0.010 to 0.330	0.065
Body Mass Index (kg/cm^2)[b]	-0.063	-0.386 to 0.261	0.701
Impairment-related variables	*B*	*95% CI*	P value
Active forward flexion ROM (°)[b]	-0.041	-0.181 to 0.099	0.562
Active abduction ROM (°)[b]	-0.133	-0.232 to -0.034	**0.009**
Handgrip strength (kg)[b]	-0.310	-0.582 to -0.038	**0.025**
Pain intensity (VAS 0-100)[b]	+0.088	0.027 to 0.148	**0.005**
Pain Quality			
Total number of words (0-20)[b]	-0.337	-0.933 to 0.260	0.267
Total pain rating index (0-63)[b]	+0.674	0.232 to 1.116	**0.003**

Pressure Hypersensitivity (kg/cm^2)[b]	-0.218	-1.408 to 0.973	0.719
Central sensitisation (CSI 0-100)[b]	+0.387	0.257 to 0.516	**<0.001**
Pain catastrophizing (PCS 0-52)[b]	+0.392	0.186 to 0.598	**<0.001**
Pain vigilance and awareness (PVAQ 0-80)[b]	-0.011	-0.141 to 0.120	0.872

ROM=Range of Motion; VAS=Visual Analogue Scale; CSI=Central Sensitisation Inventory; 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

Table 5: Stepwise linear regression. Dependent variable: Upper limb function (DASH)

Model	R	R^2	Sig	Predictors
1	0.625	0.391	<0.001	CSI
2	0.707	0.501	<0.001	CSI, Total Pain Rating Index (McGill)
3	0.759	0.575	<0.001	CSI, Total Pain Rating Index (McGill), Active abduction ROM
4	0.778	0.605	<0.001	CSI, Total Pain Rating Index (McGill), Active abduction ROM, PCS
5	0.790	0.624	<0.001	CSI, Total Pain Rating Index (McGill), Active abduction ROM, PCS, Handgrip strength
6	0.795	0.633	<0.001	CSI, Total Pain Rating Index (McGill), Active abduction ROM, PCS, Handgrip strength, VAS

DASH=Disability of Arm, Shoulder and Hand Questionnaire; CSI=Central Sensitization Inventory; ROM=Range Of Motion; PCS=Pain Catastrophizing Scale; VAS=Visual Analogue Scale for pain

Discussion

Since survival rates after treatment for breast cancer are increasing, more attention for long term functioning after the treatment is needed.[1] Therefore, the aim of this study was to investigate factors associated with upper limb function in breast cancer survivors at long term (i.e. more than one year after surgery). Mean time after surgery was 1.5 (1.6) years. The results from the multivariable analyses revealed that treatment-related variables are not associated with upper limb function at this stage post-treatment for breast cancer. Multivariable analysis showed that in particular impairment-related variables are significantly associated with upper limb function. Besides shoulder ROM and handgrip strength, certain pain characteristics such as pain intensity, pain quality, signs of central sensitization and pain catastrophizing were identified as possible risk factors for upper limb dysfunctions (i.e. DASH > 15) more than 1.5 years after breast cancer surgery. Remarkably, the stepwise regression analysis revealed that signs of central sensitization were the main predictor of upper limb function and that certain pain characteristics were important contributors as well.

The prevalence rate of upper limb dysfunctions in this cohort was found to be 62%. Other studies reported prevalence rates of impaired upper limb function between 9 and 57% more than one year after surgery.[3,5] Participants in the present study were even more than 1.5 years after surgery, indicating that natural history of upper limb function is not favourable and possibly worsens over time. Additionally, 65% of these patients with upper limb dysfunctions reported upper limb pain (i.e. VAS > 0). These results indicate that long term follow-up of upper limb function and pain is necessary.

In accordance with other studies, axillary lymph node dissection and aromatase inhibitors were found as contributing factors for upper limb function in the bi-variable analysis.[5,32] Surprisingly, in the multivariable analysis no *treatment-related variables* were associated with upper limb function at long term in breast cancer survivors. However, previous studies all

agree that more invasive surgery is associated with more dysfunctions and difficulties in performing activities of daily living.[5] Possibly, due to the complexity and heterogeneity of the (combinations of) treatment modalities (i.e. types of surgery and adjuvant radiotherapy, chemotherapy, hormone therapy and trastuzumab) in the present study no clear associations may have been detected. Namely, treatment of breast cancer is individualized and different treatment modalities are combined depending on the stage and type of cancer. Additionally, this is the first study that investigated treatment-related variables as risk factor for upper limb function at long-term after surgery. Possibly, complications of different treatment modalities (e.g. wound healing, fibrosis, scar tissue formation, …) that influenced upper limb function at short term might have resolved after a certain time. At long term, other risk factors for upper limb dysfunctions may be more prominent. In line with other studies, *patient-related risk variables* revealed in the present study were higher Body Mass Index and higher age.[5,11] However, they were only significantly associated with upper limb function in the bi-variable analysis.

From the results of the present study it appears that especially *impairment-related variables* are associated with upper limb function of breast cancer survivors at long term. First, active shoulder range of motion (in particular abduction) and handgrip strength are predictors for upper limb function. These results have also been found in previous studies at shorter term.[12,13] Second, pain intensity itself and certain pain-related characteristics are associated with upper limb function at long term. A positive moderate correlation between pain intensity and DASH scores was found. The fact that not all patients with upper limb dysfunctions reported pain may have weakened the correlation. This may also explain why the estimated change (B) was rather small. An increase in pain intensity with 1 point is associated with an increase of only 0.088 points on the DASH, which is below the clinically relevant decrease of 15 points on the DASH.[21] For the outcome parameter ‘pain quality’, both ‘total number of words chosen’ and ‘total pain rating index’ were moderately associated with DASH scores in the bi-variable analyses. Indicating the more pain descriptors and the higher numerical value

of each descriptor, the higher score on the DASH. In the multivariable analysis, only 'total pain rating index' remained a risk factors. This suggest that the more severe the pain is described, the worse the upper limb function. Three more pain characteristics were found as risk factors for upper limb function in breast cancer survivors at long term: signs of central sensitisation and psychosocial factors such as pain catastrophizing and vigilance and awareness to pain. Likewise, the stepwise regression analyses confirmed that central sensitisation and pain catastrophizing contribute to upper limb dysfunction to a relatively large extent. Central sensitization mechanisms alone explain about 40% of the variance in upper limb function, which is considerably large percentage. As discussed above, local effects of breast cancer treatment (wounds, seroma, scar formation, fibrosis) modalities should have been healed such a long time after surgery.[4] These primary causes of pain and upper limb dysfunctions may be overshadowed by sensitisation of the central nervous system at this stage. The awareness on the contribution of the central nervous system to persistent pain complaints has increased. Sensitization of the central nerve system may contribute to persistent pain and widespread pain sensations after cancer treatment.[16] Typical features of central sensitization are persistent widespread pain and secondary hyperalgesia[16] (i.e. increased pain sensitivity also at non-symptomatic sites), enhanced temporal summation of pain[33,34] (i.e. wind-up) and impaired descending inhibitory pain mechanisms.[33] Additionally, previous studies also showed that psychosocial factors are important predictors for persistent upper limb dysfunctions as well.[33,35,36] This is the first study that indicates that in persistent upper limb dysfunctions developed after breast cancer, central mechanisms and psychosocial factors may be important as well.

Clinical implications

The described risk factors associated with upper limb dysfunctions at long term are all modifiable. First, upper limb impairments such as ROM and strength deficits should be treated with physical therapy modalities in the early postoperative stage. [37] Additionally, these impairments should be monitored over time to prevent upper limb dysfunctions and

consequent difficulties in performing activities of daily living and participation at long term. Second, pain and psychosocial factors should be monitored as well. More specific, deterioration of a patient's pain complaint after finishing all treatments should be monitored because it appears that especially central sensitisation mechanisms contribute to upper limb dysfunction at long term. Chronic conditions where central sensitisation mechanisms are involved, are much more complicated and more difficult to treat so prevention of increased central sensitivity is necessary in the early postoperative stage.[6] Additionally, psychosocial factors should be taken into account. A multidisciplinary approach may be warranted including therapy strategies such as graded activity, pain neuroscience education, cognitive-behavioral therapy, etc.[14,38]

Further research

To our knowledge, this is the first study including a relatively large cohort that focused on upper limb function as outcome parameter in breast cancer survivors at long term. Results indicated that central sensitisation mechanisms among others may contribute to persistent upper limb problems in breast cancer survivors. More research is needed to explore the contribution of other pain mechanisms (e.g. neuropathic pain and nociceptive pain) and factors (e.g. kinesiophobia, cognitions, etc.) contributing to chronic pain and dysfunctions in breast cancer survivors. Additionally, strategies to prevent deterioration of upper limb function should be developed.

Strengths and limitations

The present study has several strengths. First, a relatively large cohort was analysed. Second, due to the large sample size an extensive multi-variable analysis was possible including a wide range of possible risk factors. A possible limitation of the study may be the heterogeneity in the studied population. Participants followed different rehabilitation programs after surgery which were not considered. The influence of the whether or not received interventions for treatment and/or prevention of upper limb impairments and

dysfunctions has not been taken into account. Second, a selection bias may 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

Treatment-related and patient-related variables are less important contributing variables for upper limb function at long term after surgery. Remarkably, especially *impairment-related* variables appear to be associated with upper limb function at long term. Certain pain characteristics such as pain intensity, pain quality, pain catastrophizing and, in particular signs of central sensitization contribute to upper limb function in breast cancer survivors at long term.

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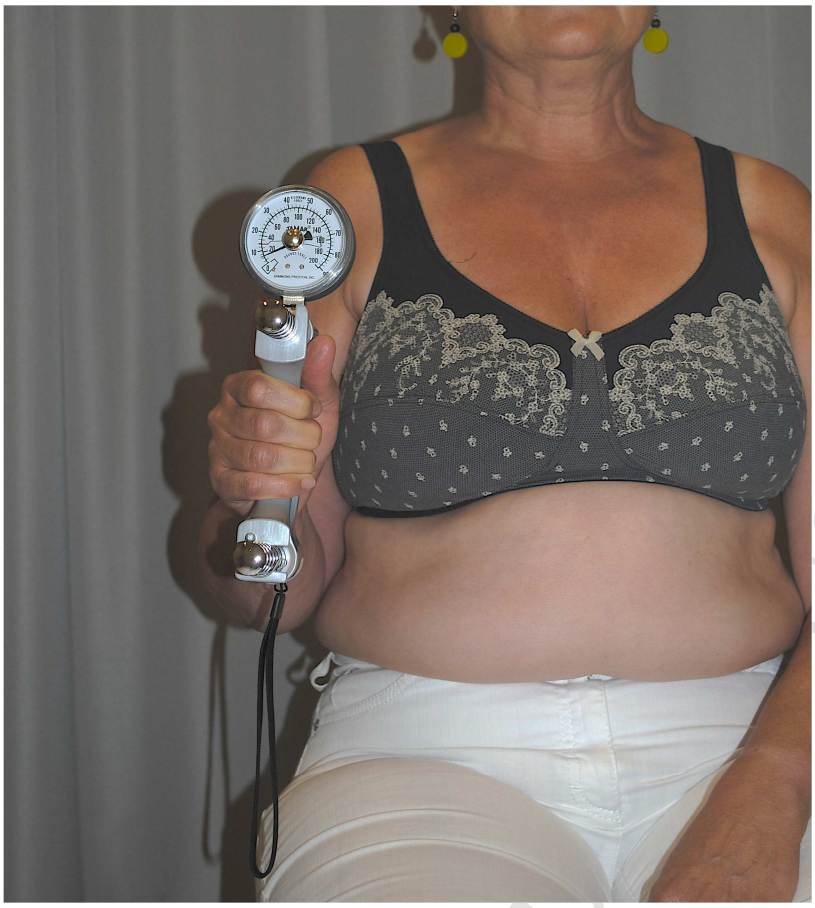
Figure 1: Measurement of shoulder range of motion with an inclinometer

Figure 2: Measurement of handgrip strength with a handheld dynamometer



Highlights

- More than one year after breast cancer surgery, upper limb dysfunctions are common problems
- Besides decreased shoulder range of motion and strength, pain contributes to these problems
- Pain intensity, pain quality and signs of central sensitisation are contributing factors
- Psychosocial factors such as pain catastrophizing may not be underestimated as well