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Peer-reviewed author version

De Groef, An; Van der Gucht, Elien; Dams, Lore; Evenepoel, Margaux; Teppers, Lien; Toppet-Hoegars, Julie & DE BAETS, Liesbet (2020) The association between upper limb function and variables at the different domains of the international classification of functioning, disability and health in women after breast cancer surgery: a systematic review. In: Disability and rehabilitation, 44(8), p. 1176-1189.

DOI: 10.1080/09638288.2020.1800835
Handle: http://hdl.handle.net/1942/32776

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The association between upper limb function and variables at the different domains of the International Classification of Functioning, Disability and Health in women after breast cancer surgery: a systematic review

Purpose: To investigate the variables per International Classification of Functioning, Disability and Health (ICF)-domain that are associated with upper limb (UL) function in women after breast cancer surgery.

Materials and Methods: PubMed and Web of Science were searched until 7 January 2020. Eligibility criteria were: prospective investigation of an association between one or more variables of the ICF model and UL function in women after breast cancer surgery. PRISMA guidelines were used to conduct and report the systematic review. The Quality In Prognosis Studies tool (QUIPS) was used to evaluate risk of bias.

Results: Twelve studies were included (2244 participants). Risk of bias of the included studies was low to moderate. Variables at the ICF-function level that were systematically associated with decreased UL function across multiple included papers were: increased UL pain, decreased shoulder range of motion, decreased handgrip strength and a higher number of comorbidities. Results on the association between UL function and variables at other ICF-domains were conflicting.

Conclusion: UL function was associated with certain variables at the ICF-function level. Variability in disease stages, treatment and measurement methods

might explain inconsistent associations with other variables. Only limited studies investigated associations between UL function and psychosocial factors.

Keywords: breast cancer; dysfunction; association; upper extremity; upper limb

Introduction

Breast cancer (BC) is the most common type of cancer diagnosed in women. More specifically, it covers more than 33% of all cancers in women worldwide [1]. The different treatment modalities for BC, including axillary and breast surgery, radiotherapy, chemotherapy, hormone therapy and immunotherapy, can have a wide range of somatic sequelae at the breast, the shoulder region and/or the entire upper limb (UL). Commonly reported morbidities are arm lymphedema [2], UL numbness [3, 4] and axillary web syndrome (cording) [5], with reported prevalences of 20%, up to 78% and up to 86%, respectively [5, 6, 7]. Furthermore, shoulder range of motion (ROM) deficits are frequently described after BC surgery and radiotherapy, with reported prevalence rates from 0% to 84%, depending on the axillary surgical management [3, 4, 8, 9]. Apart from reduced mobility, also UL muscle weakness is seen in women following BC surgery (prevalence from 20% to 50%) [4, 10, 11]. At last, (persistent) UL pain is prevalent after BC treatment [12, 13, 14, 15, 16], with reported prevalences ranging from 27% to 79% after finishing primary treatments.

The awareness on the presence of the impairements in BC survivors as described above has increased over the past decades. However, the impact of these impairments may be of larger concern than the impairments themselves, as they may lead to disabilities

on all different domains of a person's functioning [17]. As described by the International Classification of Functioning, Disability and Health, these domains consist of body functions, activities (functioning at level of the individual) and participation (functioning as a member of society), as well as interactions with environmental and personal (including psychological) factors [17].

Decreased UL function, i.e. experiencing difficulties in performing activities of daily living with the UL, is indeed very common following breast cancer treatment, with a prevalence rate of 60% at one year after surgery [4, 18, 19]. A decreased UL function has a negative influence on the quality of life, the ability to particpate in society and the perceived wellbeing of BC survivors [20, 21]. Therefore, re-acquiring optimal UL function is one of the primordial goals of post-surgical physical therapy.

Currently applied rehabilitation programmes in women following BC surgery show rather disappointing results regarding the restoration of UL function [22, 23]. To improve future management programmes, it is therefore important to have knowledge on the factors underlying the development and chronification of UL dysfunction in women following BC treatment.

First, as described above, different functional impairments at the level of the body are potential contributors to a decreased UL function after BC surgery. However, factors on other ICF domains should be considered as well, including activity – and participation related factors and other personal and external factors. Research in non-cancer populations for example, identified self-efficacy and expectations of recovery, together with being unemployed, as predictors of UL function [24].

To our knowledge, a comprehensive overview of the currently known variables associated with UL function after BC surgery is not available. Therefore, this review aims

to systematically describe the available knowledge on the factors (classified per domain of the ICF) related to UL function in women following BC surgery.

Methods

This review was designed according to the PRISMA criteria for systematic reviews [25] and protocol details were registered in the international prospective register of systematic reviews (PROSPERO, ID 137042, definitive registration number not received yet).

A literature search was conducted using the electronic databases 'PubMed' and 'Web of Science' until January, 7th, 2020 , using a combination of search terms for 'breast cancer', 'upper limb' and 'dysfunction' (Supplemental online material 1).

Studies were eligible if (1) the relation between a variable located at one of the domains of the ICF model *(including function-related variables, personal variables, external variables, and treatment-related variables)* and UL function in women after breast cancer surgery was assessed, (2) the statistical method used was regression analysis with perceived UL function as dependent variable, (3) the manuscript was peer-reviewed, available in full text, and written in English. Reasons for exclusion were: (1) previous treatment(s) for cancer(s) in the upper extremity, (2) studies concerning men, (3) retrospective studies, case studies, and/or (systematic) reviews, (4) studies using a self-constructed questionnaire to measure UL function as outcome, and (5) studies without ethical approval and informed consent. If eligible criteria were not clear, authors were contacted directly, with up to three attempts before exclusion.

The study selection was performed in two phases. After removing duplicates, two researchers (xx and xx) first independently screened the titles and abstracts for inclusion. Afterwards, full texts of these papers and from those which the title and abstract did not provide enough information, were read by the same reviewers for the final paper

selection. If both reviewers disagreed regarding eligibility, the article was discussed with a third reviewer (xx) to achieve consensus. Furthermore, the reference lists were screened for relevant papers that were missed based on the systematic database search.

The risk of bias (RoB) of each included study was assessed by two researchers independently (xx and xx) using the Quality In Prognosis Studies (QUIPS) tool [26, 27]. Although specifically developed to study risk of bias in prognostic research, the tool was also used when cross-sectional correlational studies were selected for inclusion, given that most items are relevant for those studies as well. The QUIPS tool uses six important domains that should be critically appraised when evaluating validity and bias in studies of prognostic factors: 1) study participation, 2) study attrition, 3) prognostic factor measurement, 4) outcome measurement, 5) study confounding, 6) statistical analysis and reporting. Based on the ratings of the included items, a conclusive judgment of the RoB within each domain is made and expressed on a three-grade scale (high, moderate or low RoB).

The overall RoB rating was determined based on the mean scores of the six domains per study, with score 2 for high, 1 for moderate and 0 for low RoB. Mean scores from 0 to 0.65, from 0.66 to 1.32 and from 1.33 to 2 were considered low, moderate and high RoB respectively. The Quality In Prognosis Studies tool is recommended to assess RoB by the Cochrane Prognosis Methods Group for prognosis studies [28].

Data extraction from the included studies was performed by one researcher (xx) and cross-checked by another researcher (xx). The authors retained the study population and number of participants, participant characteristics including stage and treatments, research setting, time after surgery, the dependent (i.e. measure of UL function) and independent variables (i.e. variables at different domains of the ICF, see further) from the regression analyses, and the results including a measure of association and level of

significance. Results of multivariable regression analyses were extracted; variables that were not significant in the multivariable model were not reported (Table 1).

The independent variables that could possibly be associated to UL function were categorized into four domains based on the ICF (World Health Organization, 2013).

No meta-analysis could be performed due to study-heterogeneity in investigated independent variables. Therefore, a best-evidence synthesis was performed.

Results

The conducted database search resulted in 3495 articles. Seven articles were additionally screened based on expert opinion and by checking the reference lists of the selected papers. The full texts of 27 papers were read and the corresponding author of one manuscript was contacted for more information. Eventually, 12 papers were retained for inclusion in this systematic review based on the eligibility criteria. The paper selection process is visualized in figure 1.

[Insert figure 1 here]

Eleven papers had a cross-sectional design with a mean time after surgery of less than 1 year [29, 30], between 1 and 2 years after surgery [19, 31, 32, 33] or more than 2 years after surgery [34, 35, 36, 37]. One study did not report time after surgery [38]. One study followed a cohort of women longitudinally from 6 to 18 months post-operatively [39].

In all but one study, the (Quick)DASH was used as patient reported outcome measure of UL function. In one study [33], the Pennsylvania Shoulder Score was administered next to the DASH. One study used the SPADI as dependent outcome [35].

No consistent set of independent variables was evaluated across the different studies. The association between UL function and factors at *function* level of the ICF

(n=3) [33, 34, 38]; between UL function and a combination of *function* and *personal* factors (n=1) [37]; between UL function and a combination of *function* and *treatment* factors (n=1) [31]; between UL function and a combination of *personal* and *treatment* factors (n=2) [32, 35]; between UL function and a combination of *function*, *personal* and *treatment* factors (n=2) [19, 36]; between UL function and a combination of *personal*, *external* and *treatment* factors (n=1) [29]; between UL function and a combination of *personal*, *function*, *external* and *treatment* factors (n=2) [30, 39] was studied in the included papers. As such, function factors were assessed in 9 studies, treatment factors in 8 studies, personal factors in 6 studies and external factors in 3 studies.

Results of the factors significantly associated with UL function are described per study in table 1. In table 2, a summary of the different assessed independent variables with and without association with UL function is presented, per ICF category.

[insert table 1 and 2 here]

Significant predictors of UL function that were consistent across multiple studies and not contradicted by other included studies, were all factors on *function* level: UL pain quality as assessed by the McGill pain questionnaire [19, 34], shoulder abduction ROM [19, 36, 37], number of comorbidities [34, 37] and hand(grip) strength [19, 37].

Signs and symptoms of central sensitization [19] and UL numbness [31] (*function* level), post-operative infection [29] (*treatment* level) and pain catastrophizing [19] (*external* level) were also identified predictors of UL function. However, their predictive value was only shown in one study, although not contradicted in other studies. Additionally, Hayes et al found that presence of more than one physical symptom was associated with decreased UL function [39] (*function* level).

The results on the influencing role of *function* factors "UL pain intensity"[19, 31, 36, 38], "lymphedema"[30, 31, 34, 36, 37, 39] and "shoulder girdle/upper extremity strength"[33, 37, 38]; the *treatment* factors "type of adjuvant therapy"[19, 29, 30, 32, 35, 36, 39] and "time since surgery"[29, 31, 35]; and the *personal* factors "BMI"[19, 29, 30, 32, 39] and "income"[30, 32, 37, 39] on UL function were contradictory between different studies.

The factors not significantly associated with UL function, as found by multiple studies, were: "shoulder flexion and rotation ROM" [19, 36, 37] on *function* level; "affected side" [19, 30, 35, 39], "type of surgery" [19, 29, 30, 35, 36, 39] and "disease stage" [29, 30, 35, 36] on *treatment* level; "age" [19, 30, 32, 35, 36, 37, 39], "race/ethnicity" [35, 37], "occupation" [30, 36, 37] and "education level" [29, 30] on *personal* level; and "childcare responsibilities" [30, 39] and "partner status" [29, 30, 32, 39] on *external* level.

The factors not significantly associated with UL function, as found in only one study, were: "passive shoulder ROM" [33], "menopausal status" [37], "fine motor skills" [37], "tactile sensitivity" [37], "vibration perception threshold" [37] and "local pressure hypersensitivity" [19] on *function* level; "treatment-related complications" [39] and "reconstructive surgery" [32] on *treatment* level; "health literacy" [32], "pain vigilance and awareness" [19], "performance and activity status" [37], "diabetes mellitus" [32], "prior shoulder complaints" [32] and "physical activity level" [39] on *personal* level; and "insurance rate" [30] on *external* level.

In table 3, the QUIPS RoB results are shown. Five studies had a low RoB whilst seven a moderate RoB. Mainly on the item "3. Prognostic factor measurement", risk factors were identified in the studies with a moderate overall RoB.

[insert table 3 here]

Discussion

The aim of this review was to get an overview of the variables per domain of the ICF model associated with UL function in women after breast cancer surgery. The variables that were systematically associated with decreased UL function across multiple included papers were increased UL pain, decreased shoulder ROM, decreased handgrip strength and a higher number of comorbidities; all at function level of the ICF. Treatment-related, personal and external factors appeared to have less influence on UL function. However, external factors were generally understudied.

UL pain intensity and quality [19, 31, 34, 38] were the first factors identified by multiple studies and contradicted only by one study [36]. Together with fatigue, pain is one of the most prevalent and persistent problems reported by breast cancer survivors [16]. Several studies have confirmed the impact of pain on a person's functioning after breast cancer. This review highlights the impact on UL function in particular. Pain may impair UL function in different ways. Motor function of UL muscles may be inhibited by pain [40, 41, 42] and/or pain may influence a person's behavior and result in pain-related fear and avoidance of certain activities [43]. Moreover, one might try to get control over pain and catastrophize about the experienced pain. This is supported by the results of this review since pain catastrophizing was associated with decreased UL in one study [19], which took a high number of potential contributors to UL function into account. However, pain is a complex phenomenon and other dimensions besides pain intensity and pain quality should be investigated as contributors to UL function, such as the dominant pain type. Symptoms of central sensitization as assessed by the Central Sensitisation Inventory were in one study associated with UL function [19]. Second, in particular abduction shoulder ROM was identified as associated factor, while forward flexion and rotation

ROM were not. Possibly, hypertonic pectoral muscles and soft tissue restrictions in the pectoral region, often seen after surgery and/or radiotherapy for breast cancer, explain the impaired abduction movement [22, 44, 45]. Decreased soft-tissue flexibility at the pectoral region is indeed described in literature [44, 46]. Third, our results confirm that handgrip strength is an important measure of function in BC patients as already indicated by Cantarereo-Villanueva et al [47]. For other factors at the different domains of the ICF model, evidence is inconsistent.

No less than 8 out of 12 studies investigated the association between treatment-related factors and UL function. Remarkably, no clear associations were identified between applied medical treatments and the subsequent UL function. Clear associations may not have been detected due to complexity and heterogeneity of the (combinations of) treatment modalities for breast cancer. With breast cancer treatment becoming more personalized, different treatment modalities are combined depending on the stage and type of cancer. In particular for the topic of this review, different surgical approaches and radiotherapy modalities may affect UL function in different ways. Patient and treatment characteristics of the included studies are indeed highly variable and heterogeneous (table 1). Assis et al was e.g. the only study including women with bilateral surgery [31] and two studies did not exclude women with a history of shoulder pathologies [31, 32]. Another explanation may be the variable time after surgery the included studies took place. Time after surgery ranged from 6 months up to 6 years after surgery. Questions may raise to which extent treatment-related variables are relevant and attributable to UL function at these time points post-surgery.

Next to the discussion of the specific study-results, some general issues related to this type of research in this specific population should be addressed. First, the breast cancer population becomes more heterogeneous given the wide range of treatment options and consequent side effects, possibly affecting a person's functioning. To increase the power/value of studies investigating associations with UL function, it is important to adequately recruit the specific population of interest. Second, it is important to acknowledge that the result of a regression analysis is dependent on the number and type of different independent factors included in the model. This is illustrated in the present review by the fact that the few significant associations for treatment-related factors were found by those studies not including independent factors at *function level*. This raises the question how many and which combination of independent factors should be considered in these studies, taking into account sufficient statistical power for proper regression analyses. In this review, no less than 41 independent factors were investigated. Future research should consider available results and select the most relevant factors reflecting all domains of a person's functioning on the ICF model. Third, all studies, except one[39] had a cross-sectional design. Indepth understanding of determinants of UL function in BC patients requires more robust longitudinal studies with a baseline (i.e. at time of diagnosis) assessment and sufficient follow-up assessments. Most included cross-sectional studies took place more than one year after breast cancer surgery. Again, relevance of certain cancer- and treatment-related factors at this stage should be questioned. Other factors at other domains of the ICF model, e.g. personal psychological factors and environmental/social factors such as work and family status, may be more interesting to investigate at this stage. Additionally, no study identified potential mediators and moderators of the relation between certain variables and UL function at different time points after surgery, which certainly is a limitation.

Apart from potential methodological limitations in the included studies, there might also have been a limitation to the search used for this systematic review. Although a systematic search was performed in multiple databases and experts were contacted, it is possible that relevant studies were not included in this review.

Clinical implications

The identified associated factors, i.e. UL pain, decreased handgrip strength and shoulder (abduction) ROM are modifiable factors. This means that the assessment of these factors is essential in the clinical examination of women following breast cancer surgery, and that adequate physical therapy modalities, adapted according to the impairment identified in the clinical examination, are warranted. Such treatments might include specific exercises and mobilizations, which target from the early phase after breast cancer surgery the different identified impairments. This way, impairments and consequent decreased UL function might be prevented or appropriately treated [22, 23, 48].

Future research

Research in non-cancer populations highlights the importance of psychosocial predictors for (chronic) pain and disability [24, 49]. This review indicates that in (breast) cancer populations, these associations between personal (psychological) and external factors and UL function are not yet properly investigated. Given the complex context of cancer diagnosis and treatment, evaluation of all domains of the ICF model is even more important in this population. Next to negative psychological predictors such as anxiety, depression, stress and avoidance behavior, possible positive traits including optimism, resilience, self-efficacy and positive expectations should be considered. Longitudinal study designs exploring predictors, moderators and mediators are warranted.

Conclusion

Factors significantly associated with UL function, reported by multiple studies and not contradicted by others are: UL pain, active (abduction) shoulder ROM, handgrip strength and number of comorbidities, all at *function level* of the ICF model. Given that UL dysfunctions are one of the main sequelae after breast cancer treatment, it is meaningful to get a better understanding of the factors contributing to UL function in order to improve prevention and treatment strategies.

Acknowledgements: Support statement: ADG is a post-doctoral research fellow of the FWO-Flanders.

Declaration of interest: The authors report no conflicts of interest

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Figure 1. Flowchart visualizing the selection process

Table 1. Table 1: Overview of the data extracted from the included studies

Table 2. Summary of variables with or without association with upper limb function per category of the International Classification of Functioning, Disability and Health. Author (year) and assessment method of the variables with and without association with upper limb function are listed.

Table 3. Risk of bias according to the QUIPS tool.

Table 1: Overview of the data extracted from the included studies

Article	Study population	Treatment	Dependent variable (UL function)	Independent variables (assessment method) per category of the ICF model	Analyses	Results (significantly associated factors from multivariable analysis)
CROSS-SECTIONAL						
Assis et al 2013 Reference Center of Women's Health (Brazil), 2005-2009	n=81 - BC stage: NR - Mean (SD) age: 52.9 (10.12) y - Mean time since surgery: 1.79 y Inclusion: - Female patients - 1-5 y after surgery Exclusion: - Bilateral BC - Patients with	Surgery: BCS: 63% ME: 37% SNB: 18.5% ALND: 81.5% Adjuvant treatment: chemotherapy: 16%, radiotherapy: 10%, chemotherapy and radiotherapy: 67%, hormone therapy or without	DASH	Function: - UL pain (interview) - Shoulder ROM (interview) - Lymphedema (interview) - UL numbness (interview) Treatment: (medical record) - Time since surgery	Stepwise multivariable linear regression	- UL Pain (explained 34.7% of variance, $p<0.05$)[1] - Length of time since surgery ($p<0.05$)[1] - Limitation in active shoulder ROM ($p=0.05$)[1] - Lymphedema ($p=0.05$)[1] - UL numbness ($p<0.05$)[1]

	functional impairment (motor or sensory) arising from sequelae of diseases or trauma to the UL prior to surgery	adjuvant treatment: 7%				→ 53.5 % of variance in UL dysfunctions is explained by pain > length of time since surgery > limitation in ROM > lymphedema > numbness
Chrischilles et al 2019 University of Texas Southwestern Medical Center; University of Kansas Medical Center; University of Wisconsin Carbone Cancer Center; University of Nebraska Medical Center; University of	n=833 - BC stage: 16% stage 0, 45% stage I, 28% stage II, 9% stage III - Age: 27.9% <50y, 30.7% 50-59y, 28.7% 60-69y, 12.7% >70y - Mean (SD) time since diagnosis: 22 (5.4) months <u>Inclusion:</u> - Female patients	<u>Surgery:</u> Unilat ME: 17% Bilat ME: 27% BCS: 56% SNB: 60.6% ALND: 30.5% No axillary surgery: 8.9% <u>Adjuvant treatment</u>: radiotherapy: 65% chemotherapy: 46%	QuickDASH	<u>Personal</u> (self-reported): - Age - Income - BMI at diagnosis - Health literacy - Prior rotator cuff/frozen shoulder - Prior shoulder arthritis - Prior diabetes <u>Treatment:</u> (self-reported)	Multivariable logistic regression (Least squares means) (QuickDASH 0 vs >0)	- combination of surgery/radiotherapy: patients treated with post-mastectomy radiation (accompanied by chemotherapy in over 90% of cases) experienced the greatest (9 points) disability compared with the reference category, i.e. unilateral mastectomy without radiation (accompanied by chemotherapy in 33%)

Minnesota; Medical College of Wisconsin; and Marshfield Clinic Research Foundation (USA), 2013-2014	- Ductal carcinoma in situ or invasive stage I-III BC Exclusion: - Previously diagnosed with BC - Deceased at time of selection sample	hormone therapy: 65%		- Combination of surgery and radiotherapy - Axillary surgery - Reconstruction - Hormone therapy		
Dawes et al 2008 McGill University Health Centre, Montreal (Canada), 1992-2002 (sub-study of an epidemiologic study)	n=50 - BC stage: NR - Mean (SD) age: 61 (11.8) y - Mean (SD) time since diagnosis: 3.6 (3.1) y Inclusion: women who had undergone surgery for unilateral	Surgery: ME (partial, segmental, total, modified, radical) lumpectomy) Complementary treatment: radiotherapy,	DASH	Function: - UL pain (Short Form McGill pain questionnaire) - Arm volume (water displacement, bioelectrical impedance, tape measurement)	Path analyses (regression coefficients)	Significant paths between UL dysfunction and: - number of comorbidities ($r=4.76$, $p<0.05$) - UL pain ($r=0.73$, $p< 0.05$)

	stage I or II BC Exclusion: not reported	chemotherapy, ALND, SNB *(Numbers NR)*		- Number of symptoms of lymphedema (self-developed questionnaire) - Number of comorbidities		
De Groef et al 2017 Multidisciplinary Breast Centre of the University Hospital Leuven (Belgium), 2012-2015	n=274 - BC stage: 0-III - Mean (SD) age: 57.2 (10.9) y - Mean (SD) time after surgery: 1.5 (1.6) y Inclusion: - unilateral primary BC - surgery took place at least one y ago Exclusion: - Current cancer or metastasis	Surgery: BCS: 42% ME: 58% SNB: 34% ALND: 66% Adjuvant treatment: radiotherapy: 89% chemotherapy: 50% hormone therapy: 79% trastuzumab: 19%	DASH	Function: - UL pain intensity (VAS) - UL pain quality (McGill pain questionnaire) - Local pressure hypersensitivity (pressure pain thresholds) - Active shoulder forward flexion and abduction ROM (inclinometer), - Handgrip strength (handheld dynamometer) - Self-reported signs of central sensitization (CSI)	1) multivariable regression analysis 2) stepwise regression analysis	1) Multivariable regression analysis: - active abduction ROM (B=-0.133, 95%CI (-0.232 to -0.034), handgrip strength (B=-0.310, 95%CI (-0.582 to -0.038), pain intensity (B= +0.088, 95%CI (0.027 to 0.148), 'total pain rating index' for pain quality (B=+0.674, 0.232 to 1.116), CSI (B= +0.387, 95%CI (0.257 to 0.516) and PCS (B=+0.392, 95%CI (0.186 to 0.598) 2) stepwise regression analysis

				<u>Personal:</u> - Age - BMI - Pain catastrophizing (PCS) - Pain vigilance and awareness (PVAQ) <u>Treatment:</u> (medical record) - Type surgery (ME/BCS and SNB/ALND) - Surgery at dominant side - Adjuvant treatment (radiotherapy,		CSI, 'total pain rating index' for pain quality, active abduction ROM and PCS explain 80% of variance in DASH

				chemotherapy, trastuzumab, hormone therapy)		
de Souza Cunha et al 2019 Hospital Universitário Polydoro Ernani de São Thiago, Florianópolis, Santa Catarina (Brazil), August 2016 - April 2017	n=62 - BC stage: NR - Mean (SD) age: 51 (8.18) y - Mean (SD) time since diagnosis: NR <u>Inclusion:</u> - age 30-65 y - adjuvant therapies (chemotherapy and/or radiotherapy) finished in prior 3 months - working population (before diagnosis) <u>Exclusion</u> - psychiatric/psychology disease	<u>Surgery:</u> ME: 43 (69.4%) ALND: 45 (72.6%) SNB: 13 (21.0%) <u>Adjuvant treatment:</u> chemotherapy: 48 (77.40%) radiotherapy: 43 (69.40%) hormone therapy: 48 (77.40%)	DASH	<u>Function:</u> - Pain in upper quadrant at affected side (VAS) - Weakness in arms (self-reported 0-100) - Stiffness in shoulder (self-reported 0-100)	Multivariable linear regression	- pain in upper quadrant at affected side (B=0.8; p=0.001) 64% of variance in the DASH-scores is explained by pain in upper quadrant at affected side

	- rheumatological/chronic musculoskeletal disease - cancer recurrence - palliative care					
Hack et al 2010 Cancer clinics in Montreal, Surrey, Winnipeg and Fredericton (Canada), *dates not reported*	n=316 - BC stage: 39.2% stage I, 44.3% stage II, 16.5% stage III - Mean (SD) age: 54.3 (11.0) y - Mean time since surgery: 253.9 days <u>Inclusion:</u> - Women (>18y) - stage I-III unilateral breast cancer with BCS or ME - Time since surgery 6-12 months <u>Exclusion:</u>	<u>Surgery:</u> BCS: 74.7% ME: 25.3% SNB: 22.2% ALND: 78.0% <u>Adjuvant treatments:</u> radiotherapy: 94.6% chemotherapy: 70.3%	DASH	<u>Personal:</u> - BMI - Education level <u>External:</u> - Partner status <u>Treatment:</u> (medical record) - SNB/ALND - ME/BCS - Number of axillary nodes dissected - Disease stage - Post-operative	Multivariable regression analyses	- BMI (p=0.026) - Post-op infections (p=0.036)

	- Metastatic, bilateral, in-situ and/or recurrent BC			infection - Radiotherapy to the axilla - Time since surgery		
Harrington et al 2013 The BCS group was recruited through physicians who had knowledge of the Get REAL and HEEL Breast Cancer Research Program eligibility criteria at the University of North Carolina-Chapel Hill (UNC-CH), *dates not specified*	n=24 - BC stage: 0-III (*numbers NR)* - Mean (SD) age: 50.8 (9.5) y - Mean time since surgery: NR <u>Inclusion:</u> - Finished surgery, radiotherapy and chemotherapy ≤ 6 months before inclusion - Female 25-75 y - No recent history (6 months before diagnosis of BC) of rehabilitation for UL, thoracic or cervical condition - No known neuromuscular dysfunctions or taking	<u>Surgery</u>: BCS: 33% ME: 67% <u>Adjuvant treatments:</u> radiotherapy: 88% chemotherapy: 79%	1) DASH 2) PSS	<u>Function:</u> - Shoulder active ROM (inclinometer) - Shoulder passive ROM (inclinometer) - Shoulder girdle strength (hand-held dynamometer)	Forward stepwise multivariable regression analyses	1) <u>DASH</u> - Active ROM accounted for 40% variance, r=−0.63, p = 0.001 2) <u>PSS</u> - Shoulder girdle strength accounted for 20% variance, r=0.45, p=0.02

	medications that may have an influence on neuromuscular performance					
Hayes et al 2005 Brisbane, Queensland (Australia), 2002	n=258 - BC stage: stage I 26.5%, stage II 31.4%, stage III 32.2% - Mean (SD) age: 53 (10) y - Time after surgery: 6 months <u>Inclusion:</u> - Women with unilateral BC - Aged $\leq$ 75 y - Within 100 km of Brisbane	<u>Surgery:</u> BCS: 72.2% ME: 27.8% ALND: 86.8% SNB: 13.4% <u>Adjuvant treatment:</u> radiotherapy: 71% chemotherapy: 44% hormone therapy: 42%	DASH	*All self-reported* <u>Function:</u> - Diagnosis of lymphedema <u>Personal:</u> - Age - BMI - Income - Occupation - Level of education <u>External:</u> - Marital status - Number and age of children	Multivariable linear regression model	- Income ($p<0.001$)

				- Level of health insurance <u>Treatment:</u> - Surgery at dominant side - Surgery radiotherapy, chemotherapy, hormone therapy - Number of lymph nodes removed		
Kramer et al 2019 Breast clinic at Groote Schuur Hospital, Cape Town (South Africa), 2015-2017	n=349 Tumor grade: 1-3 Mean age (SD): 60.05 (10.32) y Mean time since surgery (SD): 6.52 (2.43) y	<u>Surgery</u> - BCS: 64 (18.3%) - ME: 256 (73.4%) (missing type of breast surgery: 29 (8.3%) - SNB: 46 (13.2%)	SPADI *with 0 = 'no pain/no disability', 1–30 = 'mild pain/mild disability',*	<u>Personal</u> - Race (Black, Caucasian, Mixed ancestry) - Age <u>Treatment</u> - Surgery at right side	Multivariable ordinal logistic regression with covariates with a p value < 0.2 in the bivariable analysis selected for consideration in the multivariable model.	- no chemotherapy: OR=0.37 95%CI (0-18-0.77), p<0.01

	Inclusion criteria: - unilateral BC - Women 18 y of age and older - ≥ 1 y post-surgery Exclusion criteria - Reconstructive surgery - Current or previous history of shoulder complex trauma, surgery, pathology or dysfunction - Current or previous history of cervical neuropathy	- ALND: 273 (78.2%) (missing type of axillary surgery: 30 (8.6%)) Adjuvant treatment chemotherapy: 254 (72.8%) radiotherapy: 221 (63.3%) hormonal therapy: 246 (70.5%)	*31–50 = 'moderate pain/moderate disability' and > 50 = 'severe pain/severe disability'*	- Tumor grade (1-3) - Number of lymph nodes dissected - No chemotherapy - No hormonal therapy - Date of surgery - Radiotherapy - Type of breast surgery (BCS/ME) - Type of axillary surgery (SNB/ALND)		
Marazzi et al 2019 *Setting not reported*, 2016	n=111 - BC stage: 8% stage 0, 56.7% stage 1, 18.9% stage II, 15.4% stage III, 1% stage IV	Surgery: BCS: 93% ME: 6% excisional biopsy: 1% ALND: 40%	DASH	Function: - Lymphedema (circumference measurement) - Active shoulder ROM (goniometer)	Cox linear regression analyses	- Active shoulder ROM abduction ($p<0.0001$)

	- Mean (range) age: 60 (41-85) y - Mean (range) time since radiotherapy: 34 (6-66) months <u>Inclusion:</u> - Women after BC surgery - Adjuvant radiotherapy with or without chemotherapy and/or hormone treatment - Absence of moderate/severe arthrosis history and/or rheumatologic diseases - At least 6 months follow-up from the end of radiotherapy - Absence of locoregional or distant relapse	SNB: 59% no axillary surgery: 1% <u>Adjuvant Treatment:</u> radiotherapy: 100% chemotherapy: 3%		- Pain (VAS) <u>Personal:</u> - Age - Occupation <u>Treatment:</u> (medical record) - Stage of BC at diagnosis - Type of surgery on breast and axilla - Radiotherapy (doses and volumes), chemotherapy and/or hormonal therapy		
Smoot et al 2010	n=144	<u>Surgery:</u> BCS: 57%	DASH	<u>Function:</u> - Lymphedema	Multivariable linear regression	- Past diagnosis of lymphoedema

National Lymphedema Network website, San Francisco Bay area hospitals, San Francisco Bay area breast cancer or lymphedema support groups, and breast cancer conferences, *dates not reported*.	- BC stage: 0-III - Mean (SD) age: 56.33 (9.44) y - Mean (SD) time since diagnosis: 6.17 (5.35) y <u>Inclusion:</u> - Unilateral BC - With/without lymphedema - Completed BC treatment 6 months prior to assessment - Read, speak, and understand English <u>Exclusion:</u> - Bilateral BC - Current UL infection - Lymphangitis - Pre-existing lymphedema	ME: 43% ALND: 75% SNB: 25% <u>Adjuvant treatment:</u> radiotherapy: 74% chemotherapy: 70%		(diagnosis based on circumference and bioimpedance) - UL strength (handheld dynamometer) - Grip strength (full grip – hand dynamometer, key grip pinch gauge, pinch grip - microfet2) - Fine motor skills (Purdue Pegboard & Finger Tapper Test) - shoulder ROM (goniometer) - Tactile sensitivity (monofilaments) - Vibration perception threshold		(p<.0.001) - Grip strength (p<0.001) - Shoulder abduction ROM (p=0.003) - Number of comorbidities (p<0.001). 46.3 % of the variance in the DASH-scores is explained by these four variables.

	- Pre-existing neuromuscular or musculoskeletal conditions of the UL - Recurrence of BC			(biothesiometer) - Menopausal status <u>Personal:</u> (demographic questionnaire) - Comorbidities - Age - Ethnicity - Performance and activity status - Income - Occupation		
LONGITUDINAL						
Hayes et al 2008 Institute of Health and Biomedical Innovation, School of Public Health; and School of Physical and	n=246 Stage: 26.6% stage I, 31.8% stage II, 30.6% stage III, 11.5% stage unavailable Mean (SD) age: 55 (10) y Time since surgery: NR	<u>Surgery:</u> - BCS: 72.5% - ME: 27.5% - SNB: 13.3% - ALND: 86.7% <u>Adjuvant treatment</u>	*18 months after surgery* DASH (dichotomized as worse than most *versus*	*Every three months between 6 and 18 months after surgery* <u>Function</u>	Multivariable logistic regression analysis	Factors associated with having poorer upper body function at 18 months: - Having lymphedema at 6 and 18 months post surgery/diagnosis (OR=1.9; 95% CI (0.8 to 4.6); P=0.15);

Chemical Sciences, Queensland University of Technology, Kelvin Grove, Queensland (Australia), 2002	Inclusion criteria: - unilateral BC within the previous 6 months (diagnosed in 2002) - Aged < 75 y - residing within a 100-km radius of Brisbane, Queensland	NR	better than most (< 7 versus 7+ based on the median score))	- Presence of lymphedema (Bioimpedance spectroscopy) Personal: - Age - Income - BMI - Complication Symptoms (including stiffness, pain, tingling, weakness, poor range of movement, numbness, and stiffness of the treated side of least mild severity) Physical activity levels External: - Marital status - Children in care		Adjusted for baseline upper body function: OR=1.5; 95% CI (0.5 to 4.7); P=0.53 - lower income (OR=0.19; 95%CI 0.07 to 0.51);p=0.01 - having +1 symptoms at 6 months post diagnosis (OR=4.15; 95%CI (1.75 to 9.8); p<0.01)

				Treatment: - Side of treatment - Type of surgery (ME/BCS) - Extent of lymph node excision - Adjuvant treatment (radiotherapy, chemotherapy)		

[1]No specific p-values for multiple regression mentioned

UL=Upper Limb; ICF= International Classification of Functioning, Disability and Health; (Quick)DASH=Disability of Arm, Shoulder and Hand Questionaire, scored 0 (no disability) -100 (most severe disability); y=Year; BCS=Breast Conserving Surgery; ME=Mastectomy; ALND=Axillary Lymph Node Dissection; SNB=Sentinel Node Biopsy; SD=Standard Deviation; BC=Breast Cancer; BMI=Body Mass Index; VAS=Visual Analogue Scale; ROM=Range of Motion; CSI=Central Sensitisation Inventory; PCS=Pain Catastrophizing Scale; PVAQ=Pain Vigilance Awareness Scale; PSS= Pennsylvania Shoulder Score, scored 0 (most severe disability) – 100 (no disability); SPADI=Shoulder Pain and Disability Inde, scored 0 (no disability) – 130 (most severe disability); NR=Not Reported

Table 2. Summary of variables with or without association with upper limb function per category of the International Classification of Functioning, Disability and Health. Author (year) and assessment method of the variables with and without association with upper limb function are listed.

	Associated factors	Factors without association
Assessed independent factors	**FUNCTION**	
Upper limb pain intensity	Assis 2013 - Interview De Groef 2017 – VAS de Souza Counha 2019 - VAS	Marazzi 2019 – VAS
Upper limb pain quality	Dawes 2008 – McGill pain Questionnaire De Groef 2017 - McGill pain Questionnaire	
Shoulder active range of motion	Assis 2013 - Interview De Groef 2017 – Abduction - Inclinometer Harrington 2013 – Inclinometer (Outcome DASH) Marazzi 2019 – abduction - Goniometer Smoot 2010 – abduction – Goniometer	De Groef 2017 – Forward flexion – Inclinometer Harrington 2013 – Inclinometer (Outcome PSS) Marazzi 2019 – forward flexion and rotations - Goniometer Smoot 2010 – forward flexion and rotations – Goniometer de Souza Cunha 2019 (self-reported)
Shoulder passive range of motion		Harrington 2013 – Inclinometer (outcome DASH and PSS)
Lymphedema/arm swelling	Assis 2013 - Interview Smoot 2010 – past diagnosis – self-reported Hayes 2008 - BIS	Dawes 2008 - Number of symptoms of lymphedema - self-developed questionnaire and water displacement, bioelectrical Impedance, tape measurement Hayes 2005 – presence of lymphoedema - self-reported Marazzi 2019 – circumference measurement
Numbness	Assis 2013 - Interview	

Comorbidities	Dawes 2008 – number of co-morbidities - ND Smoot 2010 – self-reported	
Local pressure hypersensitivity		De Groef 2017 - pressure pain thresholds with algometer
Shoulder girdle/upper limb strength	Harrington 2013 - Hand-held dynamometer (Outcome PSS)	Harrington 2013 - Hand-held Dynamometer (Outcome DASH) Smoot 2010 - shoulder abduction, elbow flexion and wrist flexion- handheld Dynamometer de Souza Cunha 2019 (self-reported)
Handgrip strength	De Groef 2017 - handheld Dynamometer Smoot 2010 - full handgrip with hand dynamometer/key grip with pinch gauge/pinch grip with microfet2	
Fine motor skills		Smoot 2010 - Purdue Pegboard & Finger Tapper Test
Tactile sensitivity		Smoot 2010 – monofilaments
Vibration perception threshold		Smoot 2010 - Biothesiometer
Signs of central sensitization	De Groef 2017 – Central Sensitization Inventory	
Menopausal status		Smoot 2010 - self-reported
> 1 Symptom ((include stiffness, pain, tingling, weakness, poor range of movement, numbness, and stiffness of the treated side of least mild severity)	Hayes 2008 – Self-reported	
	TREATMENT	
Time since surgery	Assis 2013 – Medical record	Hack 2010 – medical record Kramer 2019 – medical record
Disease stage		Hack 2010 – BC stage/number of lymph nodes dissected - medical record Hayes 2005 – Number of lymph nodes dissected – self-reported

		Marazzi 2019 – BC stage – medical record Kramer 2019 – Tumour grade/number of lymph nodes dissected - medical record
Post-operative infection	Hack 2010 – medical record	
Type of surgery (SNB/ALND and ME/BCS)		De Groef 2017 - medical record Hack 2010 – medical record Hayes 2005 – self-reported Marazzi 2019 – medical record Hayes 2008 — self-report Kramer 2019 – medical record
Surgery on dominant side		De Groef 2017 - medical record Hayes 2005 – self-reported Hayes 2008 – self-report
Surgery at right side		Kramer 2019 – medical record
Adjuvant treatment	Kramer 2019– no chemotherapy – medical record Chrischilles 2019 – combination surgery and radiotherapy – self-reported	Chrischilles – axillary surgery/reconstruction/hormone therapy - self-reported De Groef 2017 – radiotherapy/chemotherapy/trastuzumab/hormone therapy - medical record Hack 2010 – radiotherapy to axilla - medical record Hayes 2005 – radiotherapy/chemotherapy/hormone therapy - self-reported Hayes 2008 – chemotherapy/radiotherapy – self-report Marazzi 2019 – radiotherapy/chemotherapy/endocrinal therapy - medical record Kramer 2019 – chemotherapy/no hormone therapy/radiotherapy - medical record
Reconstructive surgery		Chrischilles 2019 – self-reported
Treatment-related complications		Hayes 2008 – self-reported
	PERSONAL	
Age		Chrischilles 2019 - self-reported

		De Groef 2017 – self-reported
		Hayes 2005 – self-reported
		Marazzi 2019 – self-reported
		Smoot 2010 - self-reported
		Hayes 2008 – self-reported
		Kramer 2019 – self-reported
Race/ethnicity		Smoot 2010 – self-reported
		Kramer 2019 – self-reported
Occupation		Hayes 2005 – self-reported
		Marazzi 2019 – self-reported
		Smoot 2010 - self-reported
Education level		Hack 2010 – self-reported)
		Hayes 2005 – self-reported
Income	Hayes 2005 – self-reported	Smoot 2010 - self-reported
	Hayes 2008 – self-reported	Chrischilles 2019 - self-reported
BMI	Hack 2010 – clinical assessment	Chrischilles 2019 - self-reported
		De Groef 2017 – clinical assessment
		Hayes 2005 – self-reported
		Hayes 2008 – self-reported
Health literacy		Chrischilles 2019 – self-reported
Performance and activity status		Smoot 2010 - self-reported
Physical activity level		Hayes 2008 – self-report
Prior diabetes		Chrischilles 2019 – self-reported
Prior shoulder complaints		Chrischilles 2019 – self-reported
Pain catastrophizing	De Groef 2017 – Pain Catastrophizing Scale	

Pain vigilance and awareness		De Groef 2017 – Pain vigilance and awareness Questionnaire
	EXTERNAL	
Partner status		Chrischilles 2019 – self-reported Hack 2010 – self-reported Hayes 2005 – self-reported Hayes 2008 – self-reported
Insurance state		Hayes 2005 – self-reported
Childcare responsibilities		Hayes 2005 – self-reported Hayes 2008 – self-reported

VAS: Visual Analogue Scale; ND=not defined; BC=Breast Cancer; DASH=Disability of Arm, Shoulder and Hand questionnaire; PSS=Pennsylvania Shoulder Score; BIS=Bioimpedance Score

Table 3. Risk of bias according to the QUIPS tool.

	1. Study Participation	2. Study Attrition	3. Prognostic Factor Measurement	4. Outcome Measurement	5. Study Confounding	6. Statistical Analysis and Reporting	Overall risk
Assis et al, 2013	Low risk	Low risk	High risk	Low risk	High risk	Moderate risk	Moderate
Chrischilles et al, 2019	Low risk	Low risk	High risk	Low risk	Moderate risk	Low risk	Low
Dawes et al, 2008	Moderate risk	Moderate risk	Moderate risk	Low risk	Moderate risk	Low risk	Moderate
De Groef et al, 2017	Moderate risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low
de Souza Cunha et al, 2019	Moderate risk	Moderate risk	High risk	Low risk	Moderate risk	Low risk	Moderate
Hack et al, 2010	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low
Harrington et al., 2013	Moderate risk	Moderate risk	Moderate risk	Low risk	Moderate risk	Moderate risk	Moderate
Hayes et al., 2005	Moderate risk	Moderate risk	High risk	Low risk	Low risk	Moderate risk	Moderate
Hayes et al., 2008	Moderate risk	Moderate risk	High risk	Low risk	Low risk	Moderate risk	Moderate
Kramer et al, 2019	Low risk	Moderate risk	Low risk	Low risk	Moderate risk	Moderate risk	Low
Marazzi et al, 2019	Moderate risk	Moderate risk	Low risk	Low risk	Moderate risk	Moderate risk	Moderate
Smoot et al., 2010	Moderate risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low

QUIPS tool: Quality In Prognosis Studies tool