Manuscript Title

Prevalence of upper-body symptoms following breast cancer and its relationship with upper-body function and lymphoedema

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Abstract

This investigation describes the prevalence of upper-body symptoms in a population-based sample of women with breast cancer (BC) and examines their relationships with upper-body function (UBF) and lymphoedema, as two clinically important sequelae. Australian women (n=287) with unilateral BC were assessed at three-monthly intervals, from six to 18 months post-surgery (PS). Participants reported the presence and intensity of upper-body symptoms on the treated side. Objective and self-reported UBF and lymphoedema (bioimpedance spectroscopy) were also assessed. Approximately 50% of women reported at least one moderate-to-extreme symptom at 6- and at 18-months PS. There was a significant relationship between symptoms and function ($p<0.01$), whereby perceived and objective function declined with increasing number of symptoms present. Those with lymphoedema were more likely to report multiple symptoms and presence of symptoms at baseline increased risk of lymphoedema (ORs>1.3, $p=0.02$). Although, presence of symptoms explained only 5.5% of the variation in the odds of lymphoedema. Upper-body symptoms are common and persistent following breast cancer and are associated with clinical ramifications, including reduced UBF and increased risk of developing lymphoedema. However, using the presence of symptoms as a diagnostic indicator of lymphoedema is limited.

Keywords

Breast cancer, upper-body symptoms, arm function, lymphoedema

Introduction

The extent of arm morbidity, including the presence of upper-body symptoms, following treatment for breast cancer was a major driving force in the quest for identifying less invasive treatment strategies that could reduce morbidity without adversely influencing survival (1). There is now an established and growing literature base demonstrating that morbidity following treatment is reduced among those who undertake less invasive treatment options, such as sentinel node biopsy versus axillary dissection, breast-conserving surgery versus mastectomy, and/or radiation to the axilla only versus chest wall in addition to axilla (2-7). However, it is difficult to distil from this literature how common the presence of symptoms are for the wider breast cancer community, because these studies typically deal with specific clinical cohorts, and for some, cancer stage may dictate more invasive treatment. Further, many assess only a subset of the known symptoms reported by women with breast cancer (e.g., weakness, stiffness and tingling are rarely assessed) and it is plausible that we're yet to fully understand the full spectrum of possible symptoms women experience.

Upper-body morbidity, as defined by presence of specific symptoms (such as pain and/or oedema), and dysfunction (as assessed by strength and/or flexibility), has been associated with restrictions in daily activities and reduced quality of life (8-11). This work provides direct evidence demonstrating the importance of managing symptoms with respect to optimising quality of life. However, the clinical consequences of upper-body symptoms on upper-body function (UBF) and lymphoedema are less understood. Of particular interest is whether presence of symptoms can be used to predict who will develop lymphoedema and/or whether specific symptoms can be used as diagnostic criteria.

The purpose of this work therefore is to describe the presence of upper-body symptoms between six- and 18-months following breast cancer surgery in a prospective, longitudinal study involving a population-based sample. A major objective is to explore the relationships between upper-body symptoms, and UBF and lymphoedema.

Materials and Methods

Patient group

This work represents a planned component of the *Pulling Through Study*, which was designed to track the physical and psychosocial recovery of a cohort of Australian women between six- and 18-months following breast cancer (12). Eligibility criteria included a first diagnosis of invasive, unilateral breast cancer, age of 74 years or younger and place of residence within a 100 kilometre radius of Brisbane, Queensland. A unilateral diagnosis allowed for the untreated side to serve as a 'control' for certain outcomes, such as lymphoedema, while the residence criterion facilitated logistics of collection of objective outcomes. Excluding women 75 years and older minimised the potential impact that other age-related co-morbidities may have on study findings.

Following ethical approval, population-based sampling was undertaken through the Queensland Cancer Registry. It takes up to three months for patient records to arrive at the Registry, therefore recruitment procedures commenced at approximately four-months post-surgery (PS). Registry recruitment processes dictate the need for doctor consent before potential participants can be approached and was obtained from doctors of 417 (out of 511) women. Participant consent was then received from 71% (n=294) of these women, with seven withdrawing consent or unable to be contacted before baseline assessment. Hence, 287 women participated in baseline measures (six-months PS). Of these, the majority (75%) participated in all components (clinical and questionnaire assessment) of data collection, while the remainder participated on a 'questionnaire-only' basis (that is, objective lymphoedema data are not available for these women).

Data collection

Participation in the study involved five data collection sessions, commencing at six-months PS and every three months thereafter. The self-administered questionnaire was used to collect information on a range of patient, treatment and behavioural characteristics, including age, income, number and ages of children, body mass index (BMI), place of residence, marital status, side of dominance, physical activity levels, and type of surgery and adjuvant therapy undertaken. Disease characteristics were collected from medical records at

the Cancer Registry. Our clinical assessment protocol (described elsewhere [8]) was used to objectively quantify aspects of UBF and evidence of lymphoedema.

Upper-body symptoms and self-reported upper-body function

Information pertaining to presence and severity of upper-body symptoms was assessed using the Functional Assessment of Cancer Therapy-Breast (FACTB+4) questionnaire (13), specifically the arm subscale. The FACTB+4 arm subscale asks women to rate the severity of pain, range of movement (ROM), numbness, stiffness and swelling on the treated side during the past seven days, by reporting how 'true' on a 5-point Likert-like scale of 'not at all' through to 'very much', are statements regarding each symptom: for example. 'one or both of my arms are swollen or tender', 'I have poor range of arm movement on this [treated] side'. The score from each of the these items is summed to form the FACTB+4 arm subscale (14), with final scores ranging between 0 to 20 (higher scores reflect lower number and/or severity of arm symptoms). In addition to calculating the arm subscale, each item was assessed separately to determine the proportion of women who reported 'somewhat' to 'very much' for individual symptoms, as this was a priori defined as the measure by which to identify clinically relevant symptoms.

The Disability of the Arm, Shoulder and Hand (DASH) questionnaire was administered as a measure of self-reported UBF. The DASH (15) comprises 30 items and collects information about the level of difficulty experienced when performing specific tasks, the extent to which any upper-body problem interferes with normal activities, and the severity of specific upper-body symptoms (pain, tingling, weakness and stiffness). Final scores range from 0 to 100, where 0 reflects no disability (good function) and 100 reflects extensive disability (poor function).

In addition to using the DASH to assess UBF, the tingling and weakness symptom items were considered separately to calculate the proportion of women reporting these symptoms as moderate to extreme (a priori defined as clinically important). These two symptoms are not captured by the FACTB+4 arm subscale.

Objective measures of upper-body function and lymphoedema

Clinical assessments of UBF were conducted for strength and endurance using an incremental exercise protocol, with each stage lasting one minute in duration and increments made by increasing speed of movement and weight held (0.5kg increments, with the first one-minute stage commencing with no weight held). The movement combined a traditional 'upright row' and 'shoulder press', but the specific ROM was individualised for each participant and each arm. To advance levels, the participant must have maintained correct form, ROM and speed for the entire one-minute stage. Weight (kilograms) held during the last successfully completed stage, assessed separately for each arm, was recorded. More details including comparison of this technique with assessment of strength and endurance using an isokinetic dynamometer are reported elsewhere (16).

Lymphoedema status was evaluated objectively using bioimpedance spectroscopy (BIS) (12). The impedance of the extracellular fluid for each limb was assessed using a SEAC SFB7 monitor (SEAC Australia, Impedimed), and the ratio of impedance values, comparing the treated and untreated sides, was then calculated. A participant was classified as having lymphoedema when the impedance ratio was more than three standard deviations above normative data, taking into account side of dominance (17, 18).

Statistical methods

Distributions of the FACTB+4 arm subscale scores were approximately Normal, hence means and standard deviations were used to summarise data at each time point. A change in three units of the arm subscale score was a priori defined as clinically important [1]. Percentages were used to describe the prevalence of upper-body symptoms at each testing phase. Unadjusted relationships between the FACTB+4 arm subscale and objective and self-reported UBF were assessed using Pearson correlations, while analysis of variance was used to determine the statistical significance of the unadjusted, cross-sectional relationships between upper-body symptoms and UBF at six months. The latter included an interaction

term to consider the effect of lymphoedema status on the overall relationship. Tukey's tests were used for post-hoc pairwise comparisons.

The independent predictive relationships of upper-body symptoms and UBF at six-months PS with development of lymphoedema between nine- and 18-months PS were explored using logistic regression. Symptoms and function were separately added to a model that included all those characteristics found to be statistically or clinically predictive of lymphoedema in prior work (12).

Results

Study participants were, on average, aged 54 years (standard deviation, SD 10 years); approximately 74% were diagnosed with infiltrating ductal carcinoma; 74% received complete local excision; and 87% had one or more lymph nodes dissected, with a median of 12 (range: 1-47) nodes examined and 0 (range: 0-39) positive nodes. Adjuvant therapy was common, as approximately 70%, 40% and 60% of women received radiation therapy, chemotherapy and hormone therapy, respectively. The demographic and clinical characteristics of the sample were generally representative of the target sample (n=511) and representative of the wider breast cancer community, with more detailed results presented elsewhere (12).

Presence of upper-body symptoms

Scores derived from the FACTB+4 arm subscale, which included items relating to pain, ROM, numbness, swelling and stiffness, were stable over time (mean±SD = 16.2±3.8 at six-months PS; 17.0±3.6 at 18-months PS; Table 1). Those with lymphoedema had lower arm subscale scores at each phase when compared to those without lymphoedema; however, the differences were neither statistically, nor clinically, significant (data not shown).

When considering results from individual items, taken from the DASH and FACTB+4, almost 50% of women reported at least one moderate to extreme upper-body symptom at six-months PS (Table 1) and 51% of these women continued to report symptoms at 18-months PS. While at all testing phases, numbness and swelling were the most common symptoms

(reported by 19-29% and 13-23%, respectively), confidence intervals for the majority of symptoms overlapped. Of those reporting symptoms, between 57-82% reported these symptoms as moderate, with the remainder reporting symptoms as severe or extreme. In general, the proportion of women reporting symptoms declined over time, and these results were statistically significant for numbness and swelling ($p<0.05$) but only clinical relevant for numbness. At 18-months PS, 33% of women reported one or more symptoms.

With the exception of stiffness, those with lymphoedema were between 1.6-3.4 times more likely to report specific moderate to extreme symptoms at six-months PS (Figure 1) and the differences in proportions were statistically significant ($p<0.05$) for tingling (3.4-fold increase) and weakness (2.3-fold increase). By 18-months PS, the differences in proportions reporting weakness, stiffness and poor ROM between those with and without lymphoedema were minimal (Figure 2). Those with lymphoedema were, however, more likely to report tingling, swelling ($p<0.05$) and numbness. The proportions of women reporting the presence of any one symptom, irrespective of lymphoedema status, were the same at six-months PS, but multiple symptoms (2+) were 1.7 times more common among those with lymphoedema ($p<0.05$) (data not shown). By 18-months PS, having lymphoedema doubled the likelihood of reporting one or more symptoms ($p<0.05$).

Relationships between upper-body symptoms and upper-body function

Higher FACTB+4 arm subscale scores (indicating reduced number and/or intensity of arm symptoms) had a modest association with better objectively-measured UBF (depending on lymphoedema status $r=0.2$-0.3, $p<0.01$) and was moderately associated with higher perceived function ($r=-0.6$, $p<0.01$; lower DASH scores = better function). The presence of symptoms (0, 1, 2 or 3+ symptoms) was inversely associated with UBF (Table 2). Specifically, at six-months PS, having multiple symptoms was associated with lower objective and perceived UBF ($p<0.01$). These associations remained the same irrespective of lymphoedema status ($p=0.67$ for objective UBF and $p=0.72$ for subjective UBF).

Relationship between incidence of lymphoedema and upper-body symptoms and upper-body function at 6 months PS

Table 3 presents the unadjusted and adjusted predictive relationships between upper-body symptoms and UBF at six-months PS and incidence of lymphoedema between 9 and 18 months PS, as assessed separately in 4 different models (one model each for upper-body symptoms, FACTB+4 arm subscale, objective UBF and self-report UBF). Odds of lymphoedema increased two-fold, with the presence of one or more symptoms at six-months PS ($p<0.05$). For every one unit increase in the arm subscale score (indicating fewer and/or less severe symptoms), every one unit increase in objective UBF and every one unit decrease in self-report UBF (whereby lower scores indicate improved function) there was a 6%, 20% and 1% reduction in the odds of lymphoedema, respectively, although these associations were not supported statistically.

The inclusion of upper-body symptoms, arm subscale score, objective UBF or self-reported UBF into a model that takes into account other important predictive personal, treatment and behavioural characteristics (which together explain 25.5% of the total variance), contributed an additional 5.5%, 1.5%, 0% and 9.5% of the total variance explained, respectively. Both multiple symptoms ($p=0.02$) and the FACTB+4 arm subscale ($p=0.09$) at six-months PS were independently associated with lymphoedema status at nine- to 18-months PS. Similarly, poorer self-reported UBF at baseline was associated with greater odds of later having lymphoedema ($p=0.04$), whereas objective UBF was not.

Discussion

Upper-body morbidity is common following treatment for breast cancer despite advances in treatment methods that have led to less invasive surgical techniques, such as sentinel node biopsy, and more refined, targeted radiation methods. One in two women report moderate to extreme pain, tingling, weakness, stiffness, poor ROM, swelling and/or numbness at six-months PS, and 51% of these women report at least one of these arm complaints 12-months later. Further, the majority of those reporting moderate-extreme symptoms (56-68% across time points) report the presence of multiple symptoms.

Experiencing upper-body symptoms is associated with both objectively measured and self-reported UBF. Additionally, the presence of multiple symptoms six months following breast cancer surgery is associated with subsequent development of lymphoedema, although no particular symptom is diagnostic.

By using the percentage of women reporting specific symptoms, symptoms could be ranked from the most common through to the least common, for all women, as well as for those with and without lymphoedema. When this is done, numbness and swelling are the most common symptoms and poor ROM is the least common, irrespective of lymphoedema status and time of measurement. While others report poor ROM (11), pain (9) or tightness (19) as being among the most common, the number and type of symptoms assessed differed between studies. Further, it is important to highlight that confidence intervals around the percentages reported in our work are wide, and it is likely that this is the case in other studies, although typically not reported. Consequently, it seems more appropriate to highlight that symptoms are common and varied, rather than focusing on which symptom is the most or least common and whether the presence of any one specific symptom is an indicator of lymphoedema status.

Using instruments such as the FACTB+4 arm subscale or the BR 23 subscale of the European Organisation for Research and Treatment of Cancer quality of life questionnaire (20), which fail to capture the broad spectrum of possible symptoms, may also fail to capture the full extent of morbidity caused by upper-body symptoms following breast cancer and how morbidity changes over time. In this study, despite there being fewer women reporting moderate to extreme symptoms at 18-months as compared to six-months PS, there was no change observed in the arm subscale score over this time frame. Also, there was no difference in mean arm subscale scores (and the variance around the mean) for those with lymphoedema compared to those without lymphoedema, but by looking at individual symptoms, it was clear that the presence of multiple symptoms is more common in those with lymphoedema.

We also explored the unadjusted relationship between upper-body symptoms and UBF and found an inverse, linear relationship with self-reported function. Upper-body symptoms were also associated with objective UBF, but results suggested that multiple symptoms, as opposed to any one symptom, were required before declines in objective UBF were observed. Although findings require further investigation, it seems plausible that measurement of symptoms in the clinical setting could be used to educate women that the presence of symptoms may be more likely to influence perceived function than actual function and to help identify women who may benefit from physical/exercise therapy to optimise objective UBF.

The results from this work raise questions as to whether the presence of upper-body symptoms or reduced UBF can be used as diagnostic criteria for lymphoedema, as currently occurs in clinical practice. While this work demonstrates that the presence of symptoms and/or reduced perceived UBF are risk factors for developing lymphoedema, these characteristics in addition to the 11 other clinically and/or statistically important personal, treatment and behavioural characteristics explain no more than 35% of the variation between those who do and do not develop lymphoedema. Therefore, while presence of symptoms and/or reduced UBF are of clinical relevance, caution should be applied when using this information in the diagnosis of lymphoedema. Lymphoedema is considered the most feared breast cancer complication and its treatment is costly and time-consuming (21), highlighting the importance of minimising misdiagnosis.

This work could be criticised for presenting results of individual items taken from a psychometric questionnaire and for including ‘swelling’ as a symptom when lymphoedema was objectively assessed. It is important to note that participants responded to the symptom questions by completing the psychometric questionnaires (FACTB+4 and DASH) in their validated format. We then described the response from each item separately, and in doing so, have been able to extract more information about reported symptoms than otherwise would have been available from the subscale score alone. With respect to including swelling as one of the symptoms assessed, all analyses considering symptoms grouped (as 0, 1, 2, 3+) were

replicated with swelling removed and results remained unchanged (data not shown). This was anticipated, as previous work (22) demonstrated that approximately 40% of those with lymphoedema (according to BIS) do not report swelling and 40% of those without lymphoedema (according to BIS) report swelling.

Conclusion

This was a longitudinal study, using a population-based, representative sample of women with breast cancer, with results representing current estimates of upper-body morbidity between six- and 18-months PS. It is evident that upper-body morbidity following breast cancer treatment is common and persists into longer-term survivorship. Further, the results demonstrate that presence of symptoms has clinical ramifications with respect to UBF and development of lymphoedema. Consequently, these results provide support for the assessment and management of symptoms to be integrated within standard care of women with breast cancer, with a focus on minimising burden and optimising function. However, caution is necessary in applying presence of symptoms as a diagnostic indicator of lymphoedema.

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Table 1 Mean arm subscale scores and percentages of women experiencing specific upper-body symptoms at six-, nine-, 12-, 15- and 18-months post-surgery[a]

	Months post-surgery									
	6		9		12		15		18	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
FACTB+4 arm subscale	285	16.2 (3.8)	277	16.5 (3.8)	277	16.8 (3.5)	270	17.0* (3.3)	271	17.0* (3.6)
Upper-body symptoms[b]	**n**[c]	**%**	**n**[c]	**%**	**n**[c]	**%**	**n**[c]	**%**	**n**[c]	**%**
Tingling	40	13.7	38	14.1	28	10.5	30	11.4	31	12.0
Weakness	54	18.6	50	17.9	41	14.9	38	14.2	37	13.7
Pain	41	14.3	43	15.6	34	12.3	33	12.3	28	10.4
Poor ROM	29	10.1	31	11.2	27	9.8	25	9.2	28	10.0
Numbness	86	29.2	68	24.1	62	22.1[d]	55	19.5[d]	52	18.6[d]
Stiffness	42	13.9	37	12.9	30	10.4	25	9.1	30	10.8
Swelling	67	22.8	55	20.0	52	19.0	37	13.5[d]	40	15.1[d]
Number of symptoms										
0	148	52.8	163	58.6[d]	164	59.2[d]	173	63.7[d]	181	66.9[d]
1	59	20.1	37	13.2	50	18.0	40	15.2	36	13.0
2	25	8.6	31	11.3	23	8.4	21	7.7	19	6.9
3+	55	18.5	48	17.0	40	14.3	37	13.4	36	13.1

[a] Results presented have been appropriately weighted (< 50 years:1.0; ≥ 50 years:1.3) for oversampling of younger women.
[b] Symptoms: tingling and weakness as "moderate to extreme" (taken from DASH questionnaire); pain, poor range of movement (ROM), numbness, stiffness and swelling defined as "somewhat to very much" (items comprise the FACTB+4 arm subscale range 0 to 20).
[c] Number of women with symptoms at each time point.
[d] Statistically significant difference ($p<0.05$) from 6 months post-surgery, as determined by post-hoc Tukey's *post-hoc* test when the overall p-value was $p<0.05$; for number of symptoms, statistically significant difference ($p<0.05$) relates to women reporting 1+ symptoms compared to 0 symptoms.
Abbreviations: ROM, Range of movement; FACTB+4, Functional Assessment of Cancer Therapy, Breast questionnaire; SD, standard deviation.

Table 2 Relationships between concurrent upper-body symptoms and upper-body function at six-months following breast cancer surgery[a]

	n	Upper-body symptoms[b] at six-months post-surgery Mean (95% CI)				Overall p-value
		0	1 month	2 months	More than 3months	
Upper-body function						
Objective (UBSE; kg)	212	0.8 (0.7, 0.9)	0.9 (0.8, 1.1)	0.6 (0.4, 0.8)	0.5 (0.4, 0.6)[c]	<0.01
Self-reported (DASH)	258	7.1 (6.0, 8.2)	11.4 (9.0, 13.8)[c]	22.4 (17.5, 27.3)[c]	31.9 (27.9, 35.9)[c]	<0.01

[a] Results presented have been appropriately weighted (< 50 years:1.0; ≥ 50 years:1.3) for over sampling of younger women.
[b] Symptoms: tingling and weakness as "moderate to extreme" (taken from DASH questionnaire); pain, poor range, numbness, stiffness and swelling defined as "somewhat to very much" (taken from the FACTB+4 questionnaire).
[c] Statistically significant difference p<0.05 when compared with score for 0 symptoms, as determined by Tukey's *post-hoc* test.
Abbreviations: UBSE, upper-body strength and endurance; DASH, Disability of the Arm, Shoulder and Hand questionnaire (0-100 scale, lower score = better function); CI, Confidence Interval.

Table 3 Relationships between upper-body symptoms and upper-body function at baseline and lymphoedema incidence (n=55) between 9 and 18 months post-surgery[a]

		Odds of Lymphoedema 9 to 18 months post-surgery				
		Crude Results		Adjusted Results[b]		
	n	OR (95% CI)	p-value	OR (95% CI)	p-value	R^2
Symptoms[c] at 6 months post-surgery						
0	92	1.00 ref	0.05	1.0 ref	0.02	0.31
1	37	1.92 (0.90, 4.08)		2.41 (1.03, 5.65)		
2	17	1.54 (0.55, 4.31)		1.37 (0.39, 4.87)		
3+	35	2.82 (1.33, 5.99)		4.07 (1.53, 10.80)		
FACTB+4 arm subscale	181	0.94 (0.88, 1.01)	0.08	0.92 (0.84, 1.01)	0.09	0.27
Objective UBF (UBSE)	177	0.83 (0.44, 1.56)	0.56	0.78 (0.36, 1.71)	0.54	0.25
Self-reported UBF (DASH)	162	1.01 (0.99, 1.03)	0.38	1.03 (1.00, 1.06)	0.04	0.35

[a] Results presented have been appropriately weighted (< 50 years, 1.0; ≥ 50 years, 1.3) for oversampling of younger women.
[b] Models adjusted for baseline age, treatment on dominant side, income, marital status, children, BMI, type of surgery, extent of lymph node dissection, radiation, chemotherapy and physical activity.
[c] Symptoms: tingling and weakness as “moderate to extreme” (taken from DASH questionnaire); pain, poor range of movement (ROM), numbness, stiffness and swelling defined as “somewhat to very much” (items comprise the FACTB+4 arm subscale range 0 to 20).
Abbreviations: FACTB+4, Functional Assessment of Cancer Therapy Breast questionnaire, arm subscale; UBSE, upper body strength and endurance; DASH, Disability of the Arm, Shoulder and Hand questionnaire (0-100 scale, lower score = better function); OR, Odds ratio; UBF, Upper-body function.

Figure 1 Proportions (95% CI) of women with (Yes) or without (No) lymphoedema, reporting moderate to extreme upper-body symptoms at 6 months post-surgery[a]

Figure 2 Proportions (95% CI) of women ever (Yes) or never (No) having lymphoedema, reporting moderate to extreme upper-body symptoms at 18 months post-surgery[a]