Comparison of methods to diagnose lymphoedema among breast cancer survivors: 6-month follow-up

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Key words: breast cancer, lymphoedema, measurement, prevalence, risk factors

Summary

One of the more problematic and dreaded complications of breast cancer is lymphoedema. Our objective was to determine the prevalence of lymphoedema 6-months following breast cancer treatment and to examine potential risk factors among a population-based sample of women residing in South-East Queensland ($n = 176$). Women were defined as having lymphoedema if the difference between the sum of arm circumferences (SOAC) of the treated and untreated sides was >5 cm (prevalence = 11.9%) or $>10\%$ (prevalence = 0.6%), their multi-frequency bioelectrical impedance (MFBIA) score was ≥ 3 standard deviations above the reference impedance score (prevalence = 11.4%), or they reported 'yes' when asked if arm swelling had been present in the previous 6 months (prevalence = 27.8%). Of those with lymphoedema defined by MFBIA, only 35% were detected using the SOAC method (difference $>$ 5 cm), while 65% were identified via the self-report method (i.e., respective sensitivities). Specificities for SOAC (difference $>$ 5 cm) and self-report were 88.5% and 76.9%, respectively. When examining associations between presence of lymphoedema and a range of characteristics, findings also varied depending on the method used to assess lymphoedema. Nevertheless, one of the more novel and significant findings was that being treated on the non-dominant, compared to dominant, side was associated with an 80% increased risk of having lymphoedema (MFBIA). Our work raises questions about the use of circumferences as the choice of measurement for lymphoedema in both research and clinical settings, and assesses MFBIA as a potential alternative.

Introduction

Following breast cancer treatment women may experience significant and enduring problems relating to physical function, some of which specifically involve upper-body function. Arguably one of the more problematic and most dreaded upper-body complications following breast cancer treatment is lymphoedema [1]. Lymphoedema is a condition in which fluid and protein accumulate in the extravascular, interstitial spaces [2], and is associated with feelings of discomfort and heaviness, functional limitations, disfigurement, psychological distress and an elevated risk of recurrent infection [3, 4].

Reported prevalence of lymphoedema in women treated for breast cancer varies, ranging between 5 and 30% [1], and a paucity of prevalence data for Australian women exists. Furthermore, little is known about the aetiology of lymphoedema or effective prevention methods, as there is inconsistent evidence regarding possible relationships with axillary dissection, radiation, presence of axillary metastases, body mass index, use of tamoxifen, tumour size, age, presence of pre-existing health conditions and risk of lymphoedema [5].

Differences in lymphoedema measurement techniques, definitions of what constitutes lymphoedema and timing of assessments contribute to the variations in prevalence reported and to the disagreement within the literature regarding potential risk factors. Techniques currently used to assess lymphoedema include circumferences, perometry, tonometry, ultrasound, water displacement and multifrequency bioelectrical impedance (MFBIA). However, even with the use of some of these measures, there is little agreement in the specific methodologies used and what constitutes appropriate criteria for diagnosis of lymphoedema.

The purpose of this investigation was to determine the prevalence of lymphoedema 6-months following breast cancer treatment, among a population-based sample of women residing in South-East Queensland, Australia. We also sought to compare the prevalence of lymphoedema as determined by two objective measures and a subjective self-report measure, and to determine any differences in patient, treatment and behavioural characteristics between those with and those without lymphoedema.

Methods

Subject group

Following ethical approval, 511 women diagnosed with unilateral breast cancer within the previous 6 months, aged 75 years or younger, and residing within 100 km radius of Brisbane, Queensland, were randomly selected from the Queensland Cancer Registry to participate in the study. The recruitment protocol required doctor consent prior to contacting eligible participants and was obtained for 417 women (81.6%). Of these, informed consent was obtained for 71.0% ($n = 294$). This study forms part of a larger investigation designed to assess the physical and psychosocial recovery of women following breast cancer treatment, with some of the women agreeing to participate in the study on a 'questionnaire only' basis (26%). Therefore, 218 women participated in the clinical component, and among these, data analysis is complete for 176 women.

Testing protocol

At 6-months post-breast cancer surgery, the presence of lymphoedema was assessed using MFBIA, the difference in sum of arm circumferences (SOAC) and self-report.

Multifrequency bioelectrical impedance
The use of MFBIA as a measurement tool for the presence of lymphoedema has been previously well-described [6, 7]. Briefly, two measurement electrodes were placed at either end of a 40 cm long segment of the limb with current drive electrodes placed approximately 10 cm distally. Identical electrode positions were used on both arms. MFBIA measurement on each arm was performed using a SEAC SFB3 multiple frequency bioimpedance monitor (SEAC Australia), and the impedance of the extracellular fluid for each limb calculated using the manufacturer's software. The ratio of these values comparing the treated and untreated sides of these women with unilateral breast cancer (unaffected arm:affected arm) was calculated. A patient was classified as having lymphoedema when the impedance ratio was more than 3 standard deviations above normative data, with the normative data taking into account the significant effect of limb dominance [8].

Difference between sum of arm circumferences (SOAC)
Circumferences were measured at the hand (at the 1st and 5th metacarpal), wrist (using the distal edge of the styloid process of the ulna and radius) and then every 10 cm along the arm. The sum of these circumferences was calculated and the difference between the treated and untreated sides was assessed. Two definitions currently being used within clinical practice to identify lymphoedema cases were applied, namely when the difference between the treated and untreated sides was greater than 5 cm or more than 10%.

Self-report
Women were asked to answer 'yes' or 'no' to the question, 'Since the diagnosis of your breast cancer have you experienced arm swelling?' with a 'yes' response being used to indicate the presence of lymphoedema.

Pathological and treatment data were collected as was age, side of dominance, place of residence, educational level, marital status and yearly income. Information also was collected on certain behavioural characteristics including whether participants had flight travel, experienced trauma to the treated side, used their treated side as much as the untreated side, had injections in the treated side, or had blood pressure readings taken from the treated side, during the previous 6 months.

Statistical methodology
The prevalence of lymphoedema was calculated using the various definitions for diagnosis of lymphoedema. Specificity and sensitivity of the SOAC and self-report measures were assessed against the MFBIA method. Finally, logistic regression was used to examine the associations between presence of lymphoedema and treatment and patient characteristics, with a two-tailed $p < 0.05$ taken as evidence of statistical significance. Statistical procedures were performed using the statistical package SPSS 10.0 for Windows.

Results

Demographic and disease characteristics were similar for the women in this study and those in the target sample (Table 1). The prevalence of lymphoedema ranged between 0.6 and 27.8%, depending on the definition used to classify lymphoedema cases (Table 2). The highest prevalence was obtained with the self-report of arm swelling and the lowest for a difference in SOAC > 10%. Both MFBIA and difference in SOAC > 5 cm gave similar prevalences between 11–12%, however used together, only 3.4% of women were diagnosed with lymphoedema. Using MFBIA as the reference method for identifying the presence of lymphoedema, the sensitivity and specificity of the other measures were assessed (Table 3). Nearly two-thirds of lymphoedema cases detected by MFBIA were found using the self-report method, while the difference in SOAC > 5 cm method was capable of identifying only 35% of these. When the difference in SOAC > 10% method was used, nearly all subjects with lymphoedema based on MFBIA went undetected. While the sensitivity of SOAC > 10% was the lowest, it showed the highest specificity at 100%. Specificity using the self-report measure was lowest with approximately 25% of those without lymphoedema based on MFBIA being classified as a positive case.

Women with lymphoedema were more likely to be treated on their nondominant side and more likely to

Table 1. Demographics of target sample and study group

N	Target sample	Study participants
	511	176
Age (years), mean (sd)	54 (10)	54 (10)
Place of residence		
North Brisbane	29.2%	30.7%
South Brisbane	21.4%	22.7%
West Brisbane	18.0%	19.9%
East Brisbane	17.3%	17.6%
Sunshine and Gold Coasts	14.1%	9.1%
Most extensive surgery		
Complete local excision	72.2	73.9
Mastectomy	27.8	26.1
Largest tumour size (mm), median (range)	14 (0.3–230)	14 (50–140)
Lymph node dissection		
Yes	86.3%	87.5%
No	13.7%	12.5%
Number of nodes examined, median (range)	12 (1–47)	12 (1–47)
Number of positive nodes, median (range)	0 (0–39)	0 (0–39)
Overall histological grade		
1	24.3%	26.7%
2	35.7%	31.3%
3	32.2%	32.4%
Unavailable	7.8%	9.6%
Histological type		
infiltrating ductal/NOS carcinoma	78.2%	73.9%
tubular/cribrioform carcinoma	3.9%	5.1%
medullary/mucinous/colloid adenocarcinoma	0.8%	0.6%
infiltrating lobular/ductal	13.6%	15.9%
other mixed type	3.5%	4.6%
Oestrogen (ER)/Progesterone (PR) Status		
ER+/PR+	33.5%	30.7%
ER-/PR-	11.2%	10.8%
Other	8.8%	9.7%
Unavailable or missing data	46.5%	48.8%

have had blood pressure readings taken on their treated side ($p < 0.05$) when compared to those without lymphoedema (Table 4). There was a trend across all measures of lymphoedema indicating a relationship between lower education level and higher risk of being diagnosed with lymphoedema; however, these results did not reach statistical significance. Additional characteristics including treatment, lymph node removal, income, marital status and various behaviours were also compared between those with and those without lymphoedema, with no significant differences found.

Table 2. Prevalence of lymphoedema as defined by various criteria

Method	N	Prevalence
MFBIA[a]	20	11.4%
Difference in SOAC > 5 cm[b]	21	11.9%
Difference in SOAC > 10%[c]	3	0.6%
Either MFBIA or difference in SOAC > 5 cm[b]	35	19.9%
Both MFBIA and difference in SOAC > 5 cm[b]	6	3.4%
Self-report	49	27.8%

[a] MFBIA, multi-frequency bioelectrical impedance.
[b] SOAC > 5 cm, sum of arm circumferences greater than 5 cm.
[c] SOAC > 10%, sum of arm circumferences greater than 10%.

Table 3. Sensitivity and specificity of lymphoedema measures against multi-frequency bioelectrical impedance

	Sensitivity	Specificity
Difference in SOAC > 5 cm[a]	35.0%	88.5%
Difference in SOAC > 10%[b]	5.0%	100.0%
Self-report	65.0%	76.9%

[a] SOAC > 5 cm, sum of arm circumferences greater than 5 cm.
[b] SOAC > 10%, sum of arm circumferences greater than 10%.

Discussion

Depending on the definition used to diagnose lymphoedema, prevalence ranged between 0.6 and 27.8%, with MFBIA and SOAC > 5 cm measurement techniques yielding similar estimates of point prevalence between 11–12%. Since the self-report measure assesses period prevalence over the past 6 months, while the other measures assess evidence of lymphoedema at one particular time point, it is not surprising that the self-report measure yielded the highest prevalence at 27.8%.

The large range in prevalence found with these various methods within the same study group highlights the importance of determining a method that is accurate, reliable, timely, cost-effective and suitable for clinical practice and research. The use of circumferences is arguably the most popular method for the assessment of lymphoedema. However, the technique is associated with several limitations, including poor repeatability and variations in the specific measurement methods and formulae used. MFBIA accurately and reliably measures extracellular fluid [9], has been successfully used in the estimation of unilateral lymphoedema and has resulted in a four-fold increase in sensitivity over the more common anthropometric methods such as circumferences [8]. We therefore used the MFBIA technique as the ‘reference standard’ against which other measures were compared. The sensitivity analysis demonstrated that the difference in SOAC > 5 cm method was capable of identifying only 35% of cases when compared against the MFBIA method, that is, approximately two-thirds of lymphoedema cases went

Table 4. Relationships (odds ratio (OR) and 95% confidence interval (CI)) between treatment and patient characteristics and presence of lymphoedema (as defined by 3 methods) in a sample of women with unilateral breast cancer, 75 years or younger, residing within 100 km of Brisbane

		MFBIA[a]		Difference in SOAC > 5 cm[b]		Self-report	
		OR	95% CI	OR	95% CI	OR	95% CI
age[c]		1.0	(1.0, 1.1)	1.0	(1.0, 1.1)	1.0	(1.0, 1.0)
Treated on dominate side[d,k]	yes	0.2	(0.1, 0.7)*	1.9	(0.7, 4.8)	0.8	(0.4, 1.5)
Chemotherapy[d,l]	yes	0.7	(0.2, 2.3)	0.4	(0.1, 1.3)	1.2	(0.6, 2.4)
Radiotherapy[d,l]	yes	0.5	(0.2, 1.5)	1.0	(0.4, 2.9)	1.8	(0.8, 4.1)
Hormone therapy[d,l]	yes	1.5	(0.6, 3.9)	1.9	(0.7, 5.0)	1.3	(0.7, 2.6)
Lymph node removal[l]	none	1.0		1.0		1.0	
	< 10	0.4	(0.1, 3.0)	0.2	(0.0, 2.2)	0.2	(0.1, 1.2)
	10–19	0.3	(0.1, 1.5)	0.2	(0.0, 1.2)	0.4	(0.1, 1.2)
	20 +	0.7	(0.2, 2.9)	0.8	(0.2, 3.0)	0.9	(0.3, 2.5)
Education level[l]	high	1.0		1.0		1.0	
	moderate	4.8	(0.6, 41.6)	0.8	(0.2, 3.8)	1.3	(0.5, 3.3)
	low	10.1	(1.2, 85.1)	2.5	(0.6, 10.0)	1.6	(0.6, 4.0)
Marital status[l]	Married or living as married	1.0		1.0		1.0	
	single, widowed, divorced	0.8	(0.3, 2.3)	0.6	(0.2, 2.0)	1.1	(0.5, 2.3)
Yearly income[l]	$52,000 +	1.0		1.0		1.0	
	$26,000–$51,999	2.7	(0.8, 9.4)	0.2	(0.0, 1.2)	0.7	(0.3, 1.8)
	$0–25,999	0.5	(0.1, 2.7)	0.6	(0.2, 2.4)	1.2	(0.5, 3.0)
Flight[e,d]	yes	1.4	(0.5, 4.1)	2.5	(0.9, 6.6)	1.4	(0.7, 3.0)
Trauma[f,d,l]	yes	1.8	(0.5, 7.3)	2.8	(0.8, 9.9)	2.5	(0.9, 6.9)
Use arm[g,d,l]	yes	1.5	(0.5, 4.2)	1.5	(0.5, 4.4)	0.7	(0.4, 1.5)
Sunburn[h,d,l]	yes	2.3	(0.5, 9.8)	3.6	(0.8, 15.7)	1.1	(0.3, 3.7)
Injection[i,d,l]	yes	0.7	(0.1, 5.7)	0.0	(0.0, 0.0)	0.2	(0.0, 2.0)
Blood pressure[j,d,l]	yes	1.1	(0.2, 5.4)	3.4	(1.0, 11.1)*	1.5	(0.5, 4.4)

[a] MFBIA, multi-frequency bioelectric impedance.
[b] SOAC > 5 cm, sum of arm circumferences greater than 5 cm.
[c] Relative odds of lymphoedema for each additional year of age (i.e., relative odds to preceding year).
[d] Referent category (odds ratio = 1) being 'no'.
[e–j] [e] Flight, 'In the past 6 months, have you had flight travel?'; [f] trauma, 'In the past 6 months, have you experienced trauma or injury to the operated side?'; [g] use arm, 'In the past 6 months, have you used your operated side as much as the unoperated side?'; [h] sunburn, 'In the past 6 months, have you had sunburn on the operated side?'; [i] injection, 'In the past 6 months, have you had an injection in the operated arm?'; [j] blood pressure, In the past 6 months, have you had blood pressure readings taken on your operated arm?
[k] Adjusted for age
[l] Adjusted for age and treated side with respect to side of dominance
* Statistical significance of the odds ratio < 0.05

undetected. Sensitivity was even lower for the other circumference method (difference in SOAC > 10%), with more than 9 out of 10 women with lymphoedema going undetected. Interestingly, a basic self-report method proved to be more sensitive (nearly two-thirds of 'true' lymphoedema cases were identified) than the time-consuming circumference methods. In contrast, the self-report measure had the lowest specificity, with approximately 25% of those not having lymphoedema at the clinical exam being classified as a positive case. However, this could be explained by the self-report measure covering a 6-month period as compared with MFBIA measuring a single point in time.

The sensitivity and specificity calculated for the circumference measures and the self-report measure demonstrate that an unacceptable percentage of potentially 'true' positives will go undetected, while an inappropriate percentage of potentially 'true' negatives will be classified as having lymphoedema, respectively. This raises concerns given the widespread use of circumferences and self-report in clinical practice, particularly since it is believed that early detection of lymphoedema results in more effective treatment. Current treatment options are potentially costly and timeconsuming, so it is also necessary to minimise inappropriate diagnosis of lymphoedema. However, since specificity was greater than 75% while sensitivity ranged between 5 and 65%, it is clear that sensitivity of these techniques is the greater concern in terms of room for improvement as well as provision of treatment to those in need.

Although we consider the use of MFBIA as the more accurate method for determining the presence of lym-

phoedema, the limitations behind its use should also be considered. The criteria applied for defining lymphoedema cases include when the impedance score is greater than 3 standard deviations above normative data [8]. While this ensures individual variation is taken into account and minimises the risk of false-positive cases, it is also plausible that the prevalence of lymphoedema is underestimated and a proportion of true positives go undetected. Obtaining pre-surgery impedance scores should overcome this limitation and further strengthen the use of this technique. Although MFBIA is more costly than other methods for diagnosing lymphoedema as specific equipment and software are required, the use of single-frequency BIA has been shown to be a suitable alternative [10] and overcomes this limitation to a large degree. It therefore seems plausible that BIA could be readily integrated into pre- and post-surgery clinical workups, and as such, provide a useful measure of lymphoedema for women with either unilateral or bilateral breast cancer.

Logistic regression was used to examine the associations between presence of lymphoedema and a range of characteristics. As was seen with the prevalence data, odds ratios varied depending on the definition of lymphoedema used. Nevertheless, some significant findings emerged from these analyses. Being treated on the non-dominant side was associated with an 80% increased risk of having lymphoedema (MFBIA) compared with being treated on the dominant side. One plausible explanation for this could be that it is more difficult for a woman to 'protect' (avoid using or moving) her treated side when the treated side is also the dominant side, and that the required or habitual use of the dominant side provides a protective function in relation to lymphoedema. Although not statistically significant at the predefined level, the odds of having lymphoedema (MFBIA) increased as education level decreased and were 10-fold higher among those with a low education level (maximum level of education completed grade 12) compared with those with tertiary degrees ($p < 0.07$, MFBIA). The findings in relation to being treated on the dominant side as well as education levels are novel and, to our knowledge, have not been reported elsewhere. The most common finding from previous work is that the extent of axillary dissection and axillary radiation increase lymphoedema risk [4, 11–14]. In contrast, no significant differences were found in this study for these treatment characteristics, regardless of the definition of lymphoedema used.

Women following breast cancer treatment are commonly advised that certain activities or behaviours, such as flight travel, having blood pressure measured or injections on the treated side, experiencing trauma or sunburn to the treated side or overusing the treated side, may increase risk of developing lymphoedema. The origin of these theories is unknown and, to date, we are unaware of any evidence that supports or refutes these claims. A novel aspect of this study was to compare the rates of lymphoedema among those who follow these recommendations compared with those who do not. Having blood pressure measured on the affected side was associated with a 3.4-fold increase in prevalence of lymphoedema when lymphoedema was assessed using the SOAC > 5 cm method. No other significant relationships were found between the other behavioural characteristics and presence of lymphoedema. Since the aetiology of lymphoedema remains relatively poorly understood, it is not surprising that advice given to women regarding prevention is cautionary in nature, e.g. minimise flight travel, avoid 'over-using' the treated side, etc. However, unless this advice has some theoretical basis, it seems unreasonable to expect or even encourage women to adjust their behaviour, particularly when this may create other adverse effects, physically or emotionally. These results provide limited evidence in support of the current advice given to women following breast cancer treatment regarding blood pressure measurement, but neither refute nor support other behavioural related advice.

Conclusion

These are preliminary findings, represent cross-sectional relationships between lymphoedema and a variety of characteristics, and statistical power was limited. Continued research is required utilising greater subject numbers before we can better understand the key risk factors for lymphoedema. Nevertheless, this study includes a representative sample and therefore the conclusions derived from this work are likely generalisable to the wider population of women with unilateral breast cancer, aged 75 years or less and residing within 100 km of Brisbane. Clinical characteristics are provided to assist in determining whether the findings are potentially relevant to women in other geographic areas. Perhaps most importantly, these results highlight that the method used to measure and diagnose lymphoedema significantly influences prevalence estimates as well as the identification of potential risk factors. This work also raises questions about the use of circumferences as the choice of measurement for lymphoedema in both research and clinical settings.

Acknowledgements

This work was funded in part by a research grant from the National Breast Cancer Foundation.

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