Lymphology 41 (2008) 18-28

LYMPHEDEMA SECONDARY TO BREAST CANCER: HOW CHOICE OF MEASURE INFLUENCES DIAGNOSIS, PREVALENCE, AND IDENTIFIABLE RISK FACTORS

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ABSTRACT

Research on secondary lymphedema primarily uses indirect methods for diagnosis. This paper compares prevalence and cumulative burden following breast cancer surgery, as well as personal, treatment, and behavioral characteristics associated with lymphedema, using different assessment techniques. Lymphedema status was assessed at three-monthly intervals between six- and 18-months post-surgery in a population-based sample of Australian women with recently diagnosed, unilateral, invasive breast cancer, using three methods: bioimpedance spectroscopy (BIS), difference between sum of arm circumferences (SOAC) and self-report. Depending on the method, point prevalence ranged between 8 to 28%, with 1 in 5 to 2 in 5 women experiencing lymphedema at some point in time. Of those with lymphedema defined by BIS, almost 40%-60% went undetected, and 40%-12% were misclassified as having lymphedema, based on self-report and SOAC, respectively. The choice of measure also had significant implications for identified risk factors. Over 10 characteristics were associated with lymphedema, however only one, experiencing other upper-body symptoms at baseline, influenced odds of lymphedema across all three methods. These findings highlight that secondary lymphedema poses a significant public health problem. Utilizing the most accurate and reliable method for assessment is crucial to advance our understanding of preventive and treatment strategies.

Keywords: bioimpedance spectroscopy, breast cancer, lymphedema, measurement, prevalence, risk factors

The high incidence of breast cancer in conjunction with favorable prognosis makes quality of life among survivors an important issue (1). Although advances in breast cancer treatment have reduced treatment-related side effects, women continue to experience significant and enduring problems, some of which specifically influence upper-body strength and flexibility. Between 16-43% of breast cancer patients experience heaviness, tightness, numbness, stiffness, lymphedema (swelling), pain, or reduced strength and range of motion on the treated side (2-4). Of these, lymphedema is arguably considered the most problematic and dreaded complication (5).

Lymphedema occurs when fluid and protein accumulate in the extravascular, interstitial spaces (6) and is associated with feelings of discomfort and heaviness, functional limitations, disfigurement, psychological distress, body image concerns and an elevated risk of recurrent infection (7,8). Lymphedema following breast cancer usually occurs in the upper limb and/or trunk

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of the treated side. Reported prevalence of lymphedema among women with breast cancer varies, ranging between 2-83% (5,9,10), but is generally believed to be around 30%. Lymphedema may develop at any time following breast cancer treatment, within 6 months to 10 years (4,11), leaving a "shadow" of apprehension over many women.

Having radiation therapy, more extensive surgery and axillary node dissection, obesity, wound infection and advanced tumor stage are considered characteristics that adversely influence risk of lymphedema (12), despite inconsistent relationships reported in the literature for these and other risk factors (13). Differences in lymphedema measurement techniques, definitions of what constitutes lymphedema and timing of lymphedema assessments contribute to variations in findings. Furthermore, most lymphedema research employs indirect methods for assessing lymphedema status, including arm circumferences, water displacement or perometry, although a more direct measure of extracellular fluid (and therefore lymphedema) has been available for more than a decade (14). It was therefore the purpose of this investigation to explore the impact of different assessment techniques on the prevalence and cumulative burden between 6 to 18-months following surgery and the personal, treatment and behavioral characteristics associated with lymphedema development, in a population-based sample of women with breast cancer.

METHODS

Subject Group

The Queensland Cancer Registry, which records clinical details of all those diagnosed with cancer in Queensland, was used to recruit women with unilateral breast cancer, aged 75 years or younger, residing within 100 km radius of Brisbane, Australia. To allow for comparisons between younger and older women, we over-sampled women aged <50 years. Following ethical approval, 511 women were randomly selected for this longitudinal investigation, known as the "Pulling Through Study." Prior to contacting these women, doctor consent was required and obtained for 81.6% of the sample (n=417), and of these, 287 women (69%) provided informed consent. The Pulling Through Study was designed to track and assess the physical and psychosocial recovery of women following breast cancer treatment, and lymphedema assessment comprised one of the measures. Participation involved a clinical assessment and/or completion of a self-administered questionnaire. While all women participated in the self-report component of the study, only 74% of participants were able to complete the clinical assessment.

Testing Protocol

Lymphedema status was assessed using bioimpedance spectroscopy (BIS, also known as multifrequency bioelectrical impedance), sum of arm circumferences (SOAC) and self-report, at 3 monthly intervals between 6- and 18-months post-surgery. The methods of lymphedema status were specifically chosen as BIS represents a direct, objective measure of extracellular fluid, while the latter two methods (SOAC and self-report) represent the most common diagnostic tools used in clinical practice as well as being commonly used methods in research. Baseline (as a consequence of the method of recruitment, six-months post-surgery was the earliest point at which data could be collected) lymphedema status by BIS and SOAC was available for 211 women (97% of those who participated in the clinical component of the study). Of these, complete data (for each of the 5 testing phases) were available for BIS on 158 women (75%) and for SOAC on 164 women (78%). Baseline self-reported arm swelling was available for 287 women; of these, data were complete for 265 women (92%; 22 surveys were not returned across the testing phases). Staff involved with data collection

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procedures were all trained in the same manner, by the same senior researcher.

Bioimpedance Spectroscopy

BIS measurements were performed (SEAC SFB3, Impedimed) and the impedance of the extracellular fluid for each arm was calculated. The ratio of the impedance for the treated and untreated sides was then calculated, and values outside normal range (i.e., more than 3 standard deviations from the normative mean, with side of dominance taken into account) were considered diagnostic for lymphedema. Others have described these methods in more detail (15,16).

Sum of Arm Circumferences

Circumferences were measured at the hand (at the 1st and 5th metacarpal), wrist (the distal edge of the styloid process) and then every 10 cm along each arm. The sum of these circumferences was calculated and the difference between arms was assessed (treated minus untreated side). When the difference of the sums was greater than 5 cm, women were classified as having lymphedema. This particular definition for this technique was chosen as it is commonly used within clinical practice and research settings.

Self-Report

Using a self-administered questionnaire, women were asked to answer "yes" or "no" to the question "since the diagnosis of your breast cancer (at baseline)/in the past three months (at 9-, 12-, 15- and 18-months post-surgery), have you experienced arm swelling?" At 18-months post-surgery, women also were asked specifically whether they had been clinically diagnosed with lymphedema since their breast cancer diagnosis.

Risk Factor Assessment

An audit of pathology reports was performed to collect information relating to type of surgery and number of lymph nodes removed. Other treatment-related, patient and behavioral characteristics were assessed at three-monthly intervals by way of self-administered questionnaires. Patient characteristics included age, yearly income, number and ages of children, weight and height, marital status, and side of dominance in relation to treatment. Treatment-related characteristics included details of adjuvant treatment including chemotherapy, radiation therapy and hormone therapy; number and timing of complications; and presence and intensity of symptoms including pain, tingling, weakness, poor range of movement, numbness and stiffness of the treated side. Behavioral characteristics included stress and ability to cope with stress, physical activity levels, smoking history, advice regarding recovery, and from whom.

Statistical Methods

Point prevalence was calculated for each definition of lymphedema/arm swelling, at each of the five testing phases. Cumulative burden (CB) was the term used to describe the proportion of the sample that experienced lymphedema at any stage between 6- and 18-months post-surgery. Spearman correlations were computed between BIS and SOAC measures at each of the five testings phases. Specificity and sensitivity of the SOAC and self-reported measures were assessed against the BIS method. Bivariate statistics described unadjusted relationships between cumulative burden and each characteristic measured at baseline (covering the first 6 months following surgery). Characteristics that were theoretically (known from literature), statistically ($p<0.05$) or clinically (defined as odds ratio (OR) ≤ 0.67 or ≥ 1.5) important were incorporated into four separate logistic regression models, under the headings of patient, treatment, treatment-related complications or behavioral factors. Those

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TABLE 1
Prevalence and Cumulative Burden* of Lymphedema at Each Study Phase According to Three Methods of Assessment, Including BIS[a], SOAC[b] and Self-Report[c]

Testing phases	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
Point prevalence[d]	%	%	%	%	%
BIS[a]	10.7	11.3	8.0	13.9	14.9
SOAC[b]	11.2	10.6	10.9	7.6	12.0
Self-reported swelling[c]	28.3	20.9	20.1	20.1	18.8
Cumulative burden[e]					
BIS[a]	10.7	16.9	22.7	31.2	33.6
SOAC[b]	11.2	15.4	19.1	20.1	21.6
Self-reported swelling[c]	28.3	35.6	40.2	43.0	44.9
Self-reported diagnosis with lymphedema					19.4

*Results presented have been appropriately weighted (<50 years: 1.0; ≥50 years: 1.3) for oversampling of younger women, [a]BIS, Bioimpedance spectroscopy, [b]SOAC, sum of arm circumferences, [c]Self-report of arm swelling, [d]Point prevalence: number of women with lymphedema (or self-reported arm swelling) at that phase/all participants with relevant measurement, [e]Cumulative burden: number of women ever having lymphedema (or self-reported arm swelling) at that phase or previously/all participants with relevant measurement.

characteristics that retained theoretical, statistical or clinical importance (for any of the outcome variables) were incorporated into a combined multivariable model to further consider independent relationships with each outcome. This model, which included the same characteristics for each outcome (BIS, SOAC, self-report), then was refined to retain only those characteristics that showed statistical (two-tailed $p<0.05$) or clinical (OR ≤ 0.67 or ≥ 1.5) significance, as well as age. Reducing the comprehensive model to the most parsimonious model for each outcome did not influence the significance of the relationships observed and therefore only the results from the parsimonious model are presented. Results are expressed as OR with 95% confidence intervals (CI). Statistical procedures were performed using the packages SPSS version 13 for Windows, and all analyses were corrected for the over-sampling of younger women using the statistical software, SUDAAN (weights of 1.0 for those <50 years and 1.3 for those 50-74 years were applied).

RESULTS

Participants in this study were aged 54±10 years on average. Approximately 74% had infiltrating ductal carcinoma, 16% had infiltrating lobular carcinoma and the balance had other or mixed histological types. Twenty-six percent were treated with mastectomy and 87% had lymph node dissection, with a median of 12 (range 1-47) nodes examined and 0 (range 0-39) positive nodes. The majority (approximately 70%) received radiation therapy, while 40% received chemotherapy and/or hormone therapy.

Prevalence, Cumulative Burden and Duration of Lymphedema

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TABLE 2
Duration of Lymphedema According to 3 Methods of Assessment Including BIS[a], SOAC[b] and Self-Report[c]

	None	Duration			Unknown lymphedema status[d]
		Intermittent (1 phase)	Long-term (<1 phase)	Unknown duration	
BIS[a] (n)	128	36	24	2	97
% of women with known status	67.4%	19.0%	12.6%	1.1%	-
% of women with lymphedema of classifiable duration	-	60.0%	40.0%	-	-
SOAC[b] (n)	154	16	22	3	92
% of women with known status	79.0%	8.2%	11.3%	1.5%	-
% of women with lymphedema of classifiable duration	-	42.1%	57.9%	-	-
Self-report[c] (n)	162	45	80	0	0
% of women with known status	56.5%	15.7%	27.9%	0.0%	-
% of women with lymphedema of classifiable duration	-	36.0%	64.0%	-	-

[a]BIS, Bioimpedance spectroscopy, [b]SOAC, sum of arm circumferences, [c]Self-report of arm swelling, [d]If a participant missed at least 3/5 observations, she was classified as unknown lymphedema status (if showed no evidence of lymphedema), or having lymphedema of unknown duration (if had lymphedema once).

The prevalence of lymphedema at any point in time ranged between 8 and 28% *(Table 1)*, depending on the definition to classify lymphedema cases as well as the timing of the measurement. Both the BIS and SOAC methods gave similar prevalence estimates at most testing phases, despite including different women (demonstrated in later analyses). Self-reported arm swelling produced consistently higher prevalence when compared with the objective measures. Similarly, cumulative burden *(Table 1)* was substantially higher when based on personal perceptions of arm swelling. However, when participants were asked to self-report clinical diagnosis of lymphedema, cumulative burden was lower than for all other measures, at 19.4%. According to the BIS method, 33.6% of the sample experienced clinically significant fluid increase at a minimum of one visit during the study period. Long-term lymphedema, being measurable evidence of the condition for more than 3 months, was experienced by 40% of the sample according to the BIS method and 60% of the sample according to the other measurement methods *(Table 2)*.

Correlations, Sensitivity and Specificity

Correlations were performed on BIS and SOAC measures at each testing phase for all women, women treated on their dominant side, women treated on their non-dominant side and women with or without lymphedema, to assess the relationships between the two measures. Low to moderate associations were found ($r=0.3$-0.5, $p<0.05$) at each of the testing phases for all groups assessed, with the exception of women with lymphedema.

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TABLE 3
Sensitivity and Specificity of Lymphedema Measures Against Bioimpedance Spectroscopy

	Sensitivity % (95% CL)	Specificity % (95% CL)
All participants		
SOAC[a]	42.1 (29.3, 54.9)	88.3 (82.7, 93.9)
Self-report[b]	61.3 (49.2, 73.4)	58.6 (50.1, 67.1)
Participants treated on dominant side		
SOAC[a]	72.7 (54.1, 91.3)	80.6 (71.1, 90.1)
Self-report[b]	45.5 (24.7, 66.3)	58.2 (46.4, 70.0)
Participants treated on non-dominant side		
SOAC[a]	22.9 (9.0, 36.8)[b]	96.7 (92.3, 101.2)
Self-report[b]	70.0 (55.8, 84.2)	59.0 (46.7, 71.4)

[a]SOAC, sum of arm circumferences, [b]Self-report of arm swelling

In this group, associations were not consistent, being low (r=0.1, p>0.05) at 12 months post-treatment but moderate (r=0.6, p<0.05) at 9 and 15 months post-surgery.

Using BIS as the reference method for lymphedema diagnosis, the sensitivity and specificity of the other measures were assessed *(Table 3)*. Over 60% of cases detected by BIS were found using the self-report method, while the SOAC method identified only 40% of cases (that is, approximately 3/5 of lymphedema cases went undetected). The sensitivity of the SOAC measure improved substantially to 73% when used for women treated on their dominant side, but was low for women treated on their non-dominant side, with approximately 8 out of 10 women with lymphedema going undetected. Specificity of the SOAC method was relatively high in all sub-groups (80-97%). In contrast, self-reported arm swelling showed poor specificity (58-59%), with approximately 40% of those not having lymphedema at the clinical exam being classified as a positive case.

Risk Factors

Results of logistic regression models identifying potential risk factors for lymphedema diagnosed by each assessment mode are presented in *Table 4*. Upper-body symptoms at baseline was the only characteristic to be positively associated with lymphedema status regardless of defining criteria, but the odds ratio was highest for diagnosis by BIS. Older age, being single, divorced or widowed, having more extensive surgery or lymph node removal, a sedentary lifestyle, as well as experiencing treatment-related complications or symptoms were each associated with increased odds of lymphedema defined by BIS (higher than 1.5-fold increased odds). Other positive associations included radiation treatment (with self-reported arm swelling) and body mass index (with SOAC-defined lymphedema). Being treated on the dominant side was positively associated with lymphedema based on SOAC, however it was negatively associated when defined by the BIS and self-report methods.

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TABLE 4
Significant* Relationships (Odds Ratio and 95% Confidence Interval#) Between Patient, Treatment and Behavioral Characteristics and Lymphedemaa, as Defined by Three Different Measurement Techniques

Characteristics	BIS[b]			SOAC[c]			Self-report[d]		
	n	OR#	95% CI#	n	OR#	95% CI#	n	OR#	95% CI#
Age									
< 50 years	63	1.0	referent	64	1.0	referent	94	1.0	referent
≥ 50 years	127	2.0	(0.8, 4.9)	131	1.2	(0.5, 2.9)	193	1.1	(0.6, 1.9)
Income									
> $52,000/year	73	1.0	referent						
≤ $52,000/year	117	0.5	(0.2, 1.0)**						
Marital status									
Married/significant relationship	131	1.0	referent						
Other[e]	59	1.5	(0.7, 3.2)						
Children in care									
none and never	29	1.0	referent						
aged >14 years[f]	123	0.6	(0.2, 1.7)						
aged ≤ 14 years	38	0.2	(<0.1, 0.7)**						
Body mass index (kg/m^2)									
healthy or underweight				77	1.0	referent			
overweight, obese or unknown				118	2.3	(0.9, 6.0)			
Side of treatment									
non-dominant side	101	1.0	referent	99	1.0	referent	144	1.0	referent
dominant side	89	0.5	(0.2, 0.9)**	96	4.7	(2.0,11.2)**	143	0.6	(0.4, 1.0)
Most extensive surgery									
CLE[g]	142	1.0	referent				207	1.0	referent
mastectomy	48	2.2	(0.9, 5.5)				80	2.0	(1.0, 4.1)
Extent of lymph node excision									
none	24	1.0	referent	27	1.0	referent			
1-19	145	0.9	(0.2, 3.1)	144	7.4	(0.7,74.9)			
≥20	21	1.6	(0.5, 5.3)	24	11.1	(1.2, 100.9)**			
Radiation treatment									
no	87	1.0	referent						
yes	200	3.2	(1.5, 6.6)**						
Chemotherapy treatment									
no				113	1.0	referent			
yes				82	0.6	(0.2, 1.3)			
Baseline complications[h]									
0	51	1.0	referent						
≥1	139	1.9	(0.8, 4.6)						
Baseline symptoms[i]									
0	104	1.0	referent	109	1.0	referent	155	1.0	referent
≥1	86	3.1	(1.5, 6.4)**	86	2.0	(0.9, 4.4)	132	2.3	(1.4, 3.8)**
Physical activity levels[j]									
sufficient	90	1.0	referent						
insufficient	74	1.7	(0.8, 3.6)						
sedentary	26	2.3	(0.8, 6.6)						

*Significant refers to statistical (** p < 0.05) or clinical importance as defined by OR≥1.5 or <0.67 (however, age was retained in all models), # OR, Odds ratios, and CI, confidence intervals have been appropriately weighted (<50 years: 1.0; >50 years: 1.3) for oversampling of younger women, [a]cumulative burden of lymphedema between 6-18 months post-surgery; [b]BIS, Bioimpedance spectroscopy; [c]SOAC, sum of arm circumferences; [d]Self-report of arm swelling; [e]other includes single, divorced or widowed; [f]children in care are aged older than 14 years or their ages are unknown; [g]complete local excision, [h]complications include wound infection, other infections, skin or tissue reaction, seromas and hematomas; [i]symptoms include stiffness, pain, tingling, weakness, poor range of movement and numbness of the treated side and were at least of mild severity; [j]categorized according to Australian national recommendations (i.e., ≥150 minutes per week represents sufficient activity levels; 1-150 minutes per week represents insufficient activity levels).

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DISCUSSION

The method used to diagnose lymphedema has significant implications for prevalence, cumulative burden and identifiable risk factors. Depending on the definition used, prevalence at any point in time throughout the medium-term recovery ranged from 8 to 28%, while cumulative burden ranged between 1 in 5 to 2 in 5 women having experienced lymphedema. Since the self-report measure assesses period prevalence, that is, over a 3-month period, and the other measures assess evidence of lymphedema at one particular point in time, it is not surprising that the self-report measure yielded the highest prevalence and cumulative burden. Nevertheless, the large variations in these estimates highlight the importance of determining standard diagnostic criteria. Until this occurs, determining the true extent of lymphedema will remain problematic.

Each lymphedema status method currently applied in research has limitations (17). Measures such as water displacement, circumferences and perometry, irrespective of whether the raw data are converted into arm volume, assess limb size change rather than fluid change and these changes may not always be causally related to lymphedema. The size of a limb may change for reasons other than extracellular fluid accumulation (e.g., change in body composition as a consequence of change in diet and/or physical activity levels), and density of lymphedema can be variable. Additionally, these methods are time-consuming and variations in the specific method and formula used are common, with these variations influencing results reported (18). For example, use of circumferences as the diagnostic tool for lymphedema could assess one to seven sites and apply a diagnostic definition of greater than 10%, 200 ml or 5 cm between the arm sums or 2 cm at any site, when comparing the treated and untreated sides. Ultrasound and tonometry have been found to be insensitive in detecting low-grade, clinically-assessed lymphedema (17), while minimally invasive, some consider lymphoscintigraphy costly and time-consuming (17). The technique of lymphangiography may result in clogging of lymphatic channels, thereby potentially exacerbating lymphedema. Furthermore, in the absence of pre-treatment measures, as is the case in this study, all techniques are limited, particularly in identifying lymphedema development among bilateral breast cancer patients.

The application of BIS to lymphedema research is assisting in advancing the field. BIS is based on measuring impedance in the body to the flow of an electric current, which is frequency dependent, and allows for estimation of total and extracellular body water (19). Since the conductive properties of individual limbs will be directly related to the limb's water content, an increase in extracellular fluid, as occurs in lymphedema, can be directly assessed (20, 21). While other factors such as abnormally high intakes of fat, alcohol or caffeine, or injury omation can influence fluid changes, appropriate data collection protocols can determine the likelihood ofse factors influencing results. Consequently, the BIS method has been shown to be a direct, accurate and reliable measure for lymphedema diagnosis (16), and is more sensitive to change than other objective measures (22). As such, BIS is our reference standard, against which we compared the other measures.

A low-to-moderate association (R=0.3-0.5) was identified between the BIS and SOAC measurements in our sample of breast cancer patients, irrespective of whether treatment occurred on the dominant or non-dominant side and irrespective of the measurement timing during the 18-month recovery period. While these results reflect a low-to-moderate relationship between arm size and amount of extracellular fluid, they also suggest there are differences in what the two techniques actually measure. Furthermore, and of some concern, the association

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between the two techniques showed the greatest variation over the medium-term when applied specifically to women with lymphedema (r=0.1-0.6). The sensitivity and specificity analyses also indicate that the two measures assess different physiological parameters. The sensitivity analysis showed that 60% of women with lymphedema defined by BIS went undetected when the SOAC method was used for diagnosis, which was further reduced among women treated on their non-dominant side (8 out of 10 women with lymphedema went undetected). Interestingly, a basic self-report method proved more sensitive than the time-consuming circumference method. In contrast, the SOAC method had relatively high specificity, with only 5-20% of women not having lymphedema being incorrectly classified. The low specificity of the self-report method could be explained by its 3- to 6-month timeframe compared with the BIS method assessing a single point in time, but could also reflect over-reporting based on personal perception. According to the BIS method, 60% of women experiencing lymphedema have transitory symptoms as compared to 40% when using the self-report or SOAC methods. This also may reflect BIS being more sensitive to change than the other measures.

This study also clearly shows how the measurement technique used to define lymphedema influences the identifiable risk factors, as well as the direction of the relationship. When the BIS method was used, 10 characteristics were associated with lymphedema, compared with 5 or fewer using the SOAC or self-report methods. Two characteristics, specifically experiencing treatment-related symptoms at baseline and being treated on the dominant side, were common across the three methods; however, being treated on the dominant side was associated with reduced odds when diagnosis was determined by BIS or self-report and increased odds when determined by the SOAC method. Having a higher BMI was identified as increasing odds of lymphedema only when the SOAC method was used. Both the dominant side and higher BMI are associated with larger arms and consequently larger sum of arm circumferences, therefore, a 5+cm difference in or between arms might be "easier" to detect. This raises concern regarding use of the SOAC method for a significant proportion of breast cancer patients, since approximately 50% are treated on the dominant side and breast cancer is more common among overweight or obese women. Further, radiation was associated with increased odds of having lymphedema only when the self-report method was used. It is plausible that arm symptoms associated with radiation, such as heaviness, burning, itching, could be confused with developing lymphedema.

When the BIS measure was used, some novel findings also were identified. In particular, treatment on the dominant side, child care responsibilities, levels of physical activity and the more manual occupations associated with having lower yearly income point towards a protective influence of an active lifestyle. This has important recovery-related implications because remaining active during and following breast cancer treatment has also been associated with improvements in other physical and psychosocial aspects of quality of life (23) as well as potential survival benefits (24). Further, common prevention guidelines available from various sources, including national breast cancer and lymphedema associations or hospital information flyers, are more likely to advocate protection of the treated side, which in turn may inadvertently lead to reduced use. For example, "avoid holding heavy objects on your treated side, avoid holding your handbag on your treated side, avoid injury, etc." Clearly, more research is needed before "evidence-based guidelines" can be developed. It may be more appropriate for prevention guidelines to encourage use of the treated side in a progressive, controlled fashion.

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These findings are derived from a population-based study which, due to slightly lower participation rates among women with more advanced disease and aggressive treatment, may underestimate the true rates of lymphedema present in the breast cancer population. A significant strength of this work was the ability to compare prevalence, cumulative burden and identified risk factors when lymphedema status was measured on the same group using three different methods. In doing so, the results challenge our current understanding regarding lymphedema following breast cancer, in particular the relationship between specific personal, treatment and behavioral characteristics and lymphedema. Since this is the first time lymphedema has been diagnosed using the BIS method in a longitudinal study, further replication is warranted. Perhaps most importantly, these findings highlight the need to establish consensus on lymphedema diagnosis (method and criteria). Anecdotally, circumference methods are the most popular for diagnosing lymphedema in clinical practice. This is supported by the cumulative burden data showing that self-report of a clinical diagnosis of lymphedema over the medium term was 20%, which approximates that calculated with the SOAC method. However, our sensitivity analyses raise concern for the potential to under-diagnose lymphedema using this technique, particularly when research is emerging that early diagnosis may result in more effective treatment (25).

ACKNOWLEDGMENTS

The authors acknowledge Sheree Harrison for study implementation, Elizabeth Winkler for statistical analysis, the National Breast Cancer Foundation (NBCF) for funding the "Pulling Through Study," Johnson and Johnson for contributions to NBCF to fund Dr Hayes' fellowship, and the women and clinicians who made this research possible.

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