

LYMPHEDEMA FOLLOWING BREAST CANCER TREATMENT, INCLUDING SENTINEL LYMPH NODE BIOPSY

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ABSTRACT

To compare the occurrence, signs, and symptoms of lymphedema (LE) the arms of women after axillary lymph node dissection (ALND), sentinel lymph node biopsy (SLNB), combined SLNB and ALND (Both), or neither as part of breast cancer diagnosis and treatment, a concurrent descriptive-comparative cross-sectional four-group design with retrospective chart review was carried out. In a convenience sample of 102 women treated for breast cancer and receiving follow-up care at a midwestern United States cancer center, sequential circumferential measurements at five selected anatomical sites along both arms and hands were used to determine the presence of LE (≥ 2 cm differences between sites). Participants self-reported LE-related signs and symptoms by interview and completion of the Lymphedema and Breast Cancer Questionnaire (LBCQ). Retrospective chart review was carried out to verify lymph node-related diagnostic and treatment procedures. Based on node group, LE occurred as follows: 43.3% (29 of 67) of women who underwent ALND alone; 22.2% (2 of 9) of those who underwent SLNB alone; 25.0% (3 of 12) of those with combined SLNB and ALND; and 22.2% (2 of 9) with neither SLNB nor ALND. LE-related symptoms were reported by women who underwent ALND

alone, SLND alone, combined SLNB and ALND, and neither. Among the node groups, three symptoms were more common: larger arm size, firmness/tightness in past year, and numbness in past year. We conclude that circumferential measurements of the upper arm and forearm may be critical for distinguishing LE from no LE. Overall, the proportion of women who experienced LE-related signs and symptoms was higher among women who underwent ALND versus SLNB. However, numbness and tenderness frequently were reported by those undergoing ALND, SLNB or both; and by women without LE. It is possible that some frequently occurring symptoms, such as numbness and tenderness, may be related to breast cancer surgery and not LE. Findings from this study can assist health professionals in educating women with breast cancer about LE risk factors, as well as early detection and management of LE by using the LBCQ and sequential circumferential arm measurements to evaluate limb changes subjectively and objectively concurrent with each breast cancer survivor's follow-up care.

Breast cancer remains the most frequently occurring carcinoma in women in the United States. The American Cancer Society (ACS) (1) estimates that more than 200,000 American women are diagnosed with breast cancer annually. Among the 2 million

breast cancer survivors in the US (1), approximately 20 to 40% of these women will develop some degree of lymphedema (LE) during their lifetimes (2,3). LE is a morbid complication resulting from breast cancer treatment modalities, including surgery and radiation therapy (4-6). The impact of LE on quality of life among breast cancer survivors encompasses functional status, occupational roles, psychosocial and financial aspects, and lifestyle changes (2,6-11).

Surgical treatment modalities for breast cancer, including radical mastectomy and total or partial mastectomy with axillary lymph node dissection (ALND), remain the major contributing factors for the development of secondary LE (5,6,12). ALND has been the standard of care in the management of all women with invasive carcinoma of the breast. LE and related signs and symptoms following ALND have led to the demand for sentinel lymph node biopsy (SLNB) in breast cancer patients. SLNB is a procedure used to stage disease accurately by assessing lymph node involvement without clearing the axilla, while potentially decreasing the risk for LE and related signs and symptoms. To date, limited evaluation has been carried out to determine whether SLNB does reduce the risk for LE and related signs and symptoms, as compared to ALND, and if so, by how much. The purpose of this study was to examine the occurrence of LE and related signs and symptoms among breast cancer survivors who underwent ALND as a part of their cancer treatment, in comparison with those who underwent SLNB alone, both ALND and SLNB, or neither. The research questions were: (1) What is the frequency of LE as defined by the criterion of ≥ 2 cm circumferential difference at one of five selected anatomical points in arms of women undergoing ALND, SLNB, combined SLNB and ALND, or neither? (2) What is the symptom experience of these women when analyzed by node group (ALND, SLNB, combined SLNB and ALND, or neither)?

BACKGROUND

Definition of Lymphedema

LE is both an acute and chronic condition characterized by persistent accumulation of protein-rich fluid in the affected area due to an interruption or obstruction of the lymphatic vessels (2,10,13,14). The severity of LE is measured by a grading system with three levels based on objective criteria (15). In Grade I, pitting occurs upon application of pressure and edema reverses with limb elevation. In Grade II, edema becomes more pronounced, harder, and no longer pits under pressure. During Grade III, swelling worsens and skin changes occur. These skin changes can include severe thickening with huge skin folds. Areas affected by LE in breast cancer survivors include the hand, arm, breast, and trunk (4,16). LE in the ipsilateral arm is the most common location of swelling, exerting the greatest impact on women's lives after breast cancer (4).

Incidence of Lymphedema

As many as 20% to 40% of women treated for breast cancer will experience LE in their lifetime (2,4,6,7). The reported incidence of LE in women treated with surgery and radiation for breast cancer ranges from 6 to 89% (2,3,17-20). The wide variation in reported LE incidence is due, in part, to 1) difficulties in measurement and 2) problems with diagnosis. The incidence of LE following mastectomy with ALND has been reported to be 20% to 40% (18). As an alternative to ALND, SLNB has been performed with the intention of decreasing the incidence of LE and related signs and symptoms while obtaining accurate staging information. Few studies address the incidence and prevalence of LE and related signs and symptoms following SLNB. Overall, women with breast cancer who underwent SLNB have not been assessed for sufficient time to determine LE incidence, since LE may occur up to 30 years after treatment (5,21).

Measurement of Lymphedema

Currently, the commonly accepted objective diagnostic criterion for LE relies upon findings of ≥ 2 cm difference in arm circumference as compared to the non-affected limb (4,22). Sequential circumferential arm and hand measurement has been the method used most frequently to quantify LE (16). Measurement protocols may require single measurement (at one anatomic site) or measurements every 2, 4, or 6 cm. Desired maximal variance between repeated measurements of circumferences is suggested at < 0.2 cm (23), a challenging standard to meet in the clinical setting.

Diagnosis of Lymphedema

Subjective assessment of LE plays an important role in early detection, diagnosis, and management. Patients are generally the first to notice a change in status associated with LE (16). They may experience changes in fit of jewelry or clothing; changes in skin (appearing either shiny or tight, having fewer creases, and feeling stiff or taut); and changes in range of motion of the elbow, wrist, or fingers (12,24-26). The sensation of increased interstitial pressure generally precedes a measurable increase in size (27). The amount of interstitial fluid may increase 50-100% before edema is noticeable clinically (27). Even in the presence of a 40% to 50% increase in interstitial fluid (a hardly-clinically-detectable 150 ml increase), arm edema exists. Some health care providers advocate that the subjective presence of LE symptoms should warrant early interventions (25). Some further suggest that subjective assessment, including sensation of heaviness, pain, and difficulty in limb movement, should be an index for assessing the effectiveness of LE treatment (28).

Impact of Lymphedema

The impact of LE on breast cancer survivors is multidimensional, encompassing

functional abilities; occupational roles; psychosocial, cognitive and financial aspects; and lifestyle changes (2,6,8-11,15,29). Many patients with breast cancer LE experience degrees of functional impairment that impede satisfactory daily life (17,30,31). The heaviness and bulkiness of the affected arm may prevent women from wearing their usual clothing, completing household chores, or carrying out their occupational roles (8,10,24).

LE of the arm in survivors of breast cancer results in extensive psychosocial distress. Altered body image in breast cancer survivors with LE differs from those without LE in that the visible appearance of disfigurement of the affected arm cannot be disguised (8,10,32). This visibility of the altered body image may produce social anxiety and serves as a constant reminder of the cancer experience (10). The presence of psychological disorders, such as anxiety and depression, has been reported in both qualitative and quantitative studies (2,6,8-11, 15,33). The impact of LE on interpersonal and family relationships may lead to increased stress and decreased self-esteem (8,9,31,34).

Changes in lifestyle are dramatic and extensive for women with LE, including wearing compression garments daily and purposefully avoiding certain daily activities. The scheduling of time-consuming and costly LE treatment is also an important issue. The standard treatment programs require 4 to 6 weeks of intensive treatment and a lifetime of wearing compression garments or sleeves that are costly (12). In addition, third-party payers in the United States often do not reimburse long-term treatment regimes.

Axillary Lymph Node Dissection

Although surgical options for breast cancer have improved remarkably over the past few decades from radical mastectomy to breast conservation surgery, treatment alternatives for ALND have not changed as rapidly. The status of axillary lymph nodes is

still considered the single most important predictor of breast cancer survival (5,35). The presence of regional metastasis in patients with breast cancer decreases 5-year survival by approximately 28% to 40% (1,36,37).

ALND remains the standard approach for the surgical management of all women with invasive breast cancer (6,36,38,39). ALND refers to the complete removal of 10-30 axillary lymph nodes with the goals of obtaining information key to diagnosis, staging disease, recommending therapy for control of local disease, and determining prognosis (5,26,40,41). Routine performance of ALND has been considered to expose a large number of breast cancer survivors, particularly those with node-negative disease, to potentially unnecessary complications and an increased risk for LE and related signs and symptoms (26,38,39). In addition to symptoms such as discomfort, numbness, and pain, LE remains the major morbidity resulting from ALND (42) and the most feared outcome of breast cancer treatment, other than recurrence (43). Further, even as treatment evolves and procedures thought to reduce risk of post-treatment complications such as LE are developed, the lifetime risk of LE among the 2 million breast cancer survivors living today continues.

Sentinel Lymph Node Biopsy

In the search for a new approach that is expected to potentially decrease the incidence of LE and related signs and symptoms, SLNB has been performed as an alternative to ALND over the last decade as part of diagnosis, staging, and treatment for breast cancer (36,44-47). SLNB is a less invasive approach to diagnosing lymph node metastases in cancer by mapping the lymphatic route of tumor cells to the first draining lymph node(s). A sentinel lymph node is defined as the first lymph node(s) most likely to drain the primary tumor in a regional lymphatic basin, and thus the first site of metastasis (36,45-47).

In a seminal study, SLNB was introduced by Giuliano and colleagues (48) as a technique of lymphatic mapping using vital blue dye in 174 women with breast cancer. Sentinel nodes were identified in 114 out of the 174 (65.5%) women and accurately predicted the axillary node status in 109 out of the 114 (95.6%) women. Since then, different methods have been used in SLNB, including gamma probe-guided and/or dye-guided methods with or without lymphoscintigraphy (45,46). The sensitivity of identifying sentinel lymph nodes using the above methods was reported from 82 to 98% in two studies (45,46). Experience of the surgeon with the method plays an important role in assuring the sensitivity for identifying sentinel lymph nodes (36,45,46). SLNB generally requires less invasive surgery and, if successful, allows accurate staging and avoids unnecessary ALND (5,26,38-40). Theoretically, SLNB is thought to minimize morbidity associated with complete lymph node dissection, such as pain, numbness, and prolonged hospital stay, as well as acute and chronic LE. Baron et al (49) evaluated prevalence, severity, and level of distress of 18 sensations following SLNB and ALND (N = 283). The researchers concluded that sensations were less prevalent, less severe, and less distressing following SLNB compared with ALND at 3-15 days, 3 months, and 6 months after breast cancer surgery. However, limited research has been undertaken to determine the incidence of LE and related signs and symptoms following SLNB. Furthermore, since LE may occur from weeks to many years following treatment, breast cancer survivors who underwent SLNB have not been followed long enough to document fully LE incidence and prevalence (5). Further, it is important to note current breast cancer treatment protocols require further nodal dissection for node-positive disease.

THEORETICAL FRAMEWORK

This multidisciplinary research team's examination of lymphedema is guided by a

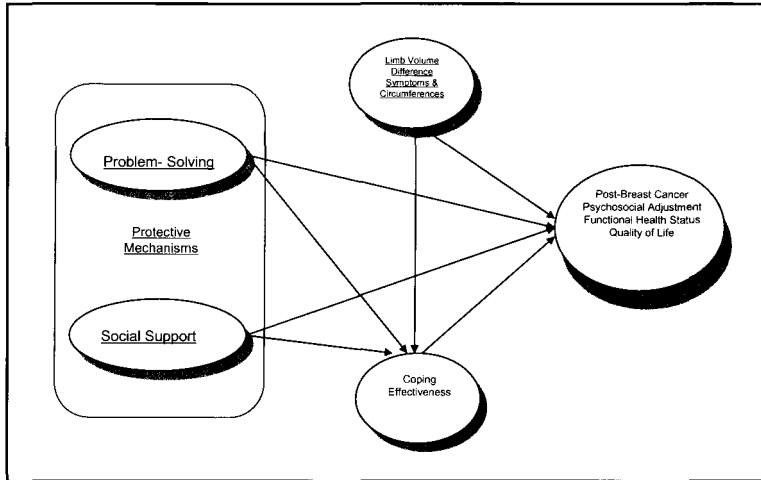


Fig. 1. Theoretical framework of post-breast cancer lymphedema including objective (limb volume differences) and subjective (self-reported symptoms) assessment components. Modified from Armer et al (7).

biobehavioral model of cancer, stress, and disease progression proposed by Anderson, Kiecolt-Glaser, and Glaser (50), and supported by emerging models of stress and coping (51). It has been shown that stressors can substantially affect a person's psychological and physiological well-being (52). Moreover, in the last 15 years there has been growing empirical evidence that psychosocial factors play key roles in adaptive responses to stress [see Zeidner and Endler, 1996 (53)]. In particular, individual characteristics such as problem-solving and environmental systems such as social support can be protective mechanisms that reduce the risk due to potentially adverse events like life crises and transitions (51,54).

Based on these foundations, we developed a framework to guide the present study of LE (7). First, we conceptualize problem-solving and social support as potential protective mechanisms that could reduce the progression of lymphedema (Fig. 1, left). In this study, individual characteristics include the modality of breast cancer treatment, including nodal status, as well as pre-breast cancer treatment patterns of problem-solving and social support. We conceptualize lymphedema as consisting of both objective

and subjective indicators, specifically limb volume difference (LVD), associated signs and symptoms, and coping effectiveness, respectively (Fig. 1, center). Likewise, because very little is known about coping with lymphedema, we examine coping through measurement of lymphedema coping efficacy. Objective (e.g., circumferential measurement) and subjective (e.g., symptom evaluation) assessments describe different dimensions of lymphedema which may help to further our understanding of not only the physical aspects of lymphedema, but also the cognitive and affective components associated with coping with this disease. Finally, Fig. 1, right depicts multiple dimensions of post-breast cancer psychosocial adjustment, specifically psychosocial distress, quality of life, and adjustment to chronic illness, as well as functional health status.

Therefore, based on this framework (and specifically focusing on Fig. 1, center), the purpose of the study reported here was to examine these two research aims: First, to compare the occurrence of lymphedema (LE) as defined by the criterion of ≥ 2 cm circumferential difference at one of five selected anatomical points in arms of women undergoing axillary lymph node dissection

(ALND), sentinel lymph node biopsy (SLNB), combined SLNB and ALND (Both), or neither as part of breast cancer diagnosis and treatment; Second, to compare signs and symptoms and LE occurrence among breast cancer patients who underwent ALND, SLNB, Both, or neither as part of breast cancer diagnosis and treatment.

METHODS

Design

This primary analysis of data is from research that combined concurrent and retrospective methods and a descriptive-comparative, cross-sectional four-group design to examine the occurrence of LE and related signs and symptoms among breast cancer survivors followed at a midwestern United States cancer center. Anthropometric measurements, interviews, and retrospective chart review were used to collect additional data from participants who belonged to one of four groups: those who underwent ALND alone, those who underwent SLNB alone, those who underwent combined SLNB and ALND, and those who had no axillary lymph node surgery.

Sample and Setting

A convenience sample of 102 cancer center patients was recruited during routine follow-up for breast cancer treatment. Over 70% of 140 eligible clinic patients from a midwestern United States cancer center who were invited to participate over a 3½-month period did so. Eligibility for enrollment in the study included history of breast cancer (Stage 0 to IV); prior history of surgical treatment with/without radiation therapy, and with/without chemotherapy; age 18 years old or older; ability to read and understand English; and ability to give informed consent.

Instrumentation

Sequential circumferential limb measure-

ment. For this study, sequential circumferential arm and hand measurements were used to determine the presence of LE at 5 anatomical sites. Following a review of the literature on circumferential measurement, a sequential circumferential measurement protocol was developed using the frequently reported and clinically valid approach of 5 measurement points along the limb: hand proximal to the metacarpals; wrist (smallest circumference); fullest area of the mid-forearm (distance from elbow noted); elbow; fullest part of the upper arm (distance from elbow noted). Arm length from axillary fold to tip of extended middle finger was also recorded. A special non-stretch weighted Gulick tape measure (Country Technology, Inc., Gays Mill, WI) marked in increments of 0.1 centimeters was used to obtain the measurement. Circumferential measurements were recorded on a data form created for this study.

Research data collectors (research nurses and graduate nursing research assistants) were trained by the first author/principal investigator and PT research associate in sequential circumferential limb measurements. Circumferences were measured on both the ipsilateral and contralateral limbs at the identified anatomical sites, with placement of measurements confirmed by distance in cm above the styloid process and above/below the antecubital crease. Three measurements were carried out at one time at each of the 5 sites on both limbs and averaged.

Callaway et al (23) suggest no greater than 0.2 cm variability is desirable for limb circumference measurement, although this is a standard which may be difficult to meet in the clinical setting where multiple clinicians may be carrying out limb assessments in a fast-paced environment. Test and re-test measurements were performed on 3 volunteer breast cancer patients with lymphedema in 1 limb. Variance in circumferential measurements was reviewed and steps in the measurement protocol were clarified, such as placement of the edge of the tape measure, and appropriate tension. Consistency across

raters was compared on these 3 volunteers three months later to assess drift on the part of the measurers.

The presence of LE was confirmed in study participants if measurements met the criterion of ≥ 2 cm difference between circumferences at any of the 5 sites (22), regardless of side of breast cancer surgery. The quality of measurements made by research nurses and graduate nursing research assistants has been monitored on a regular basis. Each data collector makes repeat circumferential measurements on the same subject so that variability within and between measurers can be estimated. The estimated standard deviation of measurements within measurers has consistently been in the 0.25 cm - 0.35 cm range. The estimated standard deviation of the between-measurers effect has been in the 0.10 cm - 0.20 cm range (Armer, unpublished data).

Signs and Symptoms

A survey tool, Lymphedema and Breast Cancer Questionnaire (LBCQ), was developed and piloted by the first author and research team for this study to assess the experience of LE symptoms (29). The LBCQ consisted of 58 items. The first 30 items were questions concerning subjective symptoms related to LE. Of these, a series of 19 symptom items was used to elicit data on symptoms experienced in the affected arm, breast, or chest (1) now, or (2) during the past year. The remaining 28 items were questions to elicit demographic/treatment history information and LE management. Prior to the study, face and expert validity were established by multidisciplinary researchers, clinicians, and patients (i.e. oncology advanced practice nurses, surgical oncologist, physical therapist, oncology social worker, bio-statistician, and breast cancer survivors). Reading level and format were reviewed by expert patient educators; sixth grade reading level was attained in the final tool. The instrument was piloted with 8 breast cancer

survivors with and without LE, leading to minor changes in ordering of items.

Reliability of the LBCQ has been evaluated using Kuder-Richardson-20 and the test-retest method. Kuder-Richardson-20 reveals an acceptable measure of internal consistency ($r = .785$) for all 19 items. Test-retest reliability was evaluated using a sample of healthy women without breast cancer or LE ($n = 35$) with a 2-hour test-retest interval. Findings reveal a high degree of reliability ($r = .98$) (29).

Procedure

Following approval by the Health Sciences Center Institutional Review Board, recruitment and data collection were completed over a 3-month period (June-August 1999). Participants were referred by health care providers. The researchers explained the purpose, risks, and benefits of the study to survivors of breast cancer meeting the study criteria. Informed consent was obtained. Upon agreeing to participate, women were asked to complete the LBCQ. The researchers measured arm circumferences on each woman. At a later date, medical records were reviewed to determine treatment history: node group status (ALND, SLNB, both, or neither), surgery, chemotherapy, and radiation.

Data Analysis

Data were coded, double-entered into a text file, tested for accuracy, and corrected. Hard copies of data were stored in locked filing cabinets and electronic data files were stored in a password-protected computer available only to the research team. Data were analyzed by a biostatistician using SAS 8.0 (SAS Institute, Cary, NC). Descriptive statistics were utilized to analyze demographic data, occurrence of LE, and presence of LE-related signs and symptoms. Shapiro-Wilk test was used to test for normality of the data distribution. Fisher's Exact test was used to

TABLE 1
Sample Characteristics

Sample	Overall (N=100)	ALND (n=67)	SLNB (n=9)	SLNB and ALND (n=12)	No SLNB or ALND (n=9)	With Lymphedema (n=36)	No Lymphedema (n=64)
Mean Age							
(yrs ± SD)	58.7±12.8	57.3±12.2	56.8±15.3	57.8±9.3	70.1±15.7	57.5±12.2	59.4±13.1
(Range)	(31-88)	(33-88)	(39-79)	(46-70)	(31-85)	(56)	(61)
(Median)	(59)	(56)	(61)	(56.5)	(74)		
Mean time since surgery:							
(mos ± SD)	28.1±39.1	33.3±45.1	9.0±3.9	9.0±11.0	22.6±17.8	29.0±53.3	27.7±29.7
(Range)	(2-294)	(2-294)	(4-14)	(3-41)	(2-60)	(3-294)	(2-142)
(Median)	(18)	(21.5)	(8.5)	(5)	(21)	(17)	(19)

determine if there existed a significant difference in LE occurrence and symptom experience by node group. Signed rank test was used to determine whether the mean absolute difference in arm circumference for women with LE was different from 2 cm. Wilcoxon Rank Sum tests were performed to determine if mean absolute difference in arm circumference differed among node treatment groups at each anatomical site. Chi-square tests were employed to explore possible relationships between occurrence of LE and categorical independent variables regarding LE-related signs and symptoms. Fisher's Exact test was also performed for selected independent variables regarding LE-related signs and symptoms, to ensure the validity of Chi-square testing. Data are presented as either means ± standard deviations (SD) or percentages ± 95% exact confidence intervals (CI) unless indicated otherwise. Level of significance was set at 0.05, with adjustment to 0.01 for multiple comparisons

RESULTS

Sample

Two women were excluded from the analysis due to extreme outliers in the circumferential measurements: one had a history of primary LE and bilateral mastectomy and the other had a history of morbid obesity with a recent 150 lb weight loss which may have affected the accuracy of limb volume estimates. Thus, the overall sample for lymphedema occurrence, regardless of node group, consisted of 100 predominantly-Caucasian (95%) women with breast cancer. The sample was normally distributed in terms of age (58.7 ± 12.8 years; range = 31-88 years; $p = 0.5$). The typical participant in the study was 59 years old with 12 years of education.

Medical records were available for review of node treatment for 97 of the women. Of the 97 with node treatment information, 67 (69%) had ALND, 9 (9.3%) underwent SLNB alone, 12 (12.4%) underwent SLNB in combination with ALND, and 9 (9.3%) had neither. Of the combined SLNB and ALND group, some participants may have undergone these procedures at the same time and others may have had a delayed ALND. Overall, the mean time since surgery was

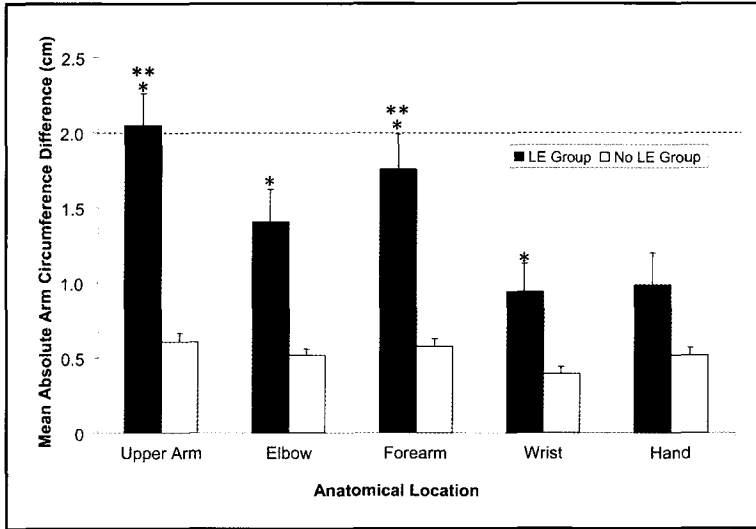


Fig. 2. The absolute mean difference (\pm SE) in circumference at each of the five anatomical locations along the arm and hand for breast cancer survivors with Lymphedema (LE) (grey bars) and without LE (white bars), regardless of node group. The dotted line indicates the diagnostic criterion for LE (≥ 2 cm difference). * Indicates differences between LE and no LE at four of the anatomical sites ($p \leq 0.0016$). ** Indicates that the mean absolute difference at two anatomical sites was not different from 2 cm.

28.1 \pm 39.1 months (median = 20.4 months). Time-since-surgery for these participants ranged from 2 months to 294 months (24.5 years). Table 1 provides more detailed demographic information about the sample.

Lymphedema Occurrence

A preliminary analysis was reported previously regarding the overall sample prevalence of LE and LE-related symptom experience with no attention to lymph node-related surgical procedures (SLNB versus ALND) (17); for the earlier analysis, *self-report* data regarding treatment was used to describe the sample characteristics. For this analysis by treatment group, treatment data were verified through a retrospective chart review; where self-report and medical chart data differed, the *medical record* data were accepted for this analysis. Of the 67 women who underwent ALND only, 43.3% (29 of 67; CI 31.2, 56.0%) had measurable LE (≥ 2 cm), the highest occurrence of any group. Among the women who underwent SLNB only, 22.2%

(2 of 9; CI 2.8, 60.0%) had limb differences ≥ 2 cm, thus meeting the diagnostic criteria for LE. Similarly, among the women with combined SLNB and ALND, 25% (3 of 12; CI 5.5, 57.2%) had measurable LE. Furthermore, 22.2% (2 of 9; CI 2.8, 60.0%) of women who received neither SLNB nor ALND during their breast cancer treatment had measurable LE. No statistically significant difference in LE occurrence existed based on node group ($p = 0.37$). Mean body weight for women with LE was higher (79.1 \pm 15.4 kg; median = 80.0) than for women without LE (74.5 \pm 16.8 kg; median = 72.7) at the time of the study; however, this difference was not statistically significant ($p = 0.10$). Furthermore, no significant relationship was found between adjuvant radiation and LE occurrence among women undergoing breast cancer treatment ($p = 0.11$).

Figure 2 shows the mean absolute difference (\pm SE) in circumference at each of the five anatomical locations along the arm and hand for breast cancer survivors with LE and without LE, regardless of node group

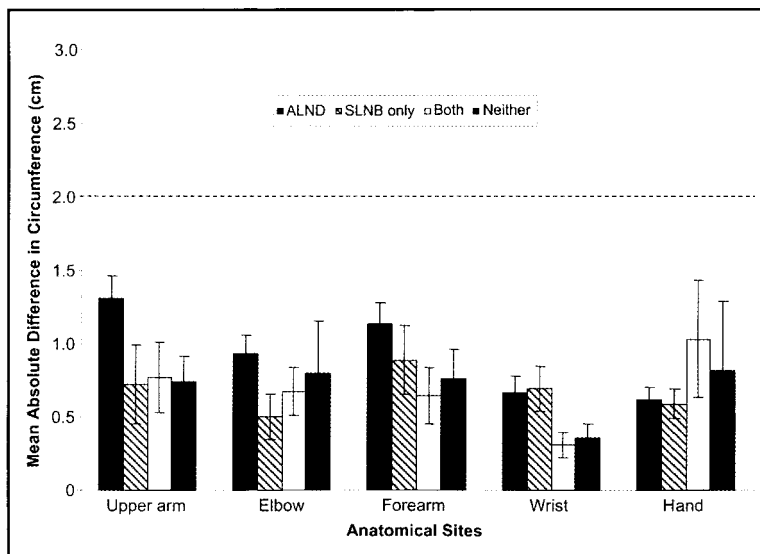


Fig. 3. The absolute mean difference (\pm SE) in circumference for each node treatment group at each of the five anatomical locations along the arm and hand for breast cancer survivors. The dotted line indicates the diagnostic criterion for LE (≥ 2 cm difference).

(range 0.0 to 5.9 cm). The mean absolute differences were greater for women with LE than for women without LE at four of the five locations: upper arm ($p < 0.0001$), elbow ($p = 0.0016$), forearm ($p < 0.0001$), and wrist ($p = 0.0009$). The mean absolute difference for the hand was not different between women with LE and without LE ($p = 0.20$). The only anatomical location at which the overall mean absolute difference in arm circumference was ≥ 2 cm was the upper arm. For women with LE, however, both the upper arm and the forearm were not different from 2.0 cm ($p = 0.98$ and 0.27 , respectively).

Figure 3 shows mean absolute difference (\pm SE) in circumference at the five anatomical locations along the arm and hand for each node group. Mean absolute differences were not different among the node groups at the upper arm ($p = 0.18$), elbow ($p = 0.70$), forearm ($p = 0.63$), wrist ($p = 0.16$) or hand ($p = 0.40$). The range of mean absolute differences between hands for women in the SLNB group was 0.0 to 1.0 cm while it was much more variable for the no node (0.0-4.4 cm) and both (0.0-5.3) groups.

Lymphedema-Related Signs and Symptoms

As reported in the preliminary analysis which did not consider treatment group (17), ten subjectively-reported signs and symptoms were found to occur more often ($p \geq 0.01$) in the women with LE compared to the women without LE. These signs and symptoms were: arm size larger; neck size larger; sleeve fits tighter; sleeve cuff fits tighter; swelling now; swelling in past year; swelling with pitting now; firmness/tightness now; firmness/tightness in past year; and heaviness now (Table 2) (17).

LE-related symptoms occurred in women who underwent ALND alone, SLNB alone, combined SLNB and ALND, and neither. Those who underwent SLNB alone or neither generally reported fewer symptoms than those who underwent ALND alone. Eight symptoms occurred more often ($p \geq 0.05$): larger arm size (ALND); tighter sleeve fit (ALND); tighter sleeve cuff fit (ALND); swelling during past year (ALND, both); firmness/tightness now (ALND, both); firmness/tightness in past year (ALND, both);

TABLE 2
Percent Distribution of Selected Lymphedema (LE)-Related Signs and Symptoms in Participants with ≥ 2 cm Mean Circumferential Limb Differences Versus Those with < 2 cm (n=100)

Signs and symptoms	LE (≥ 2 cm) (n=36) %	No LE (< 2 cm) (n=64) %
Arm size larger**	57	14
Neck size larger**	11	0
Shoulder size larger*	17	3
Sleeve fits tighter**	43	16
Sleeve cuff fits tighter**	46	13
Swelling now**	57	22
Swelling in past year**	59	30
Swelling with pitting now**	24	5
Swelling with pitting in past year*	32	12
Firmness/tightness now**	58	26
Firmness/tightness in past year**	66	32
Heaviness now**	41	13
Heaviness in past year*	41	18
Numbness now	54	56
Numbness in past year	50	60
Tenderness now	56	40
Tenderness in past year	50	46
Aching in past year*	51	26
Breast swelling now*	28	11

LE versus no LE: * $p \leq 0.05$; ** $p \leq 0.01$; Modified from Armer & Whitman, 2002 (17).

numbness now (ALND, SLNB, both) and numbness in past year (ALND, SLNB, both). The highest percentages were reported generally by the ALND and combined ALND and SLNB groups (Table 3). Among the node groups, three symptoms were experienced more commonly ($p \leq 0.01$): larger arm size (ALND), firmness/tightness in past year (ALND, both), and numbness in past year (ALND, SLNB, both). Tenderness now and tenderness in the past year were frequently

occurring symptoms, but their occurrence did not differ in all four node groups ($p > 0.05$; see Table 3).

DISCUSSION

Lymphedema Occurrence

The key finding in this study was that the occurrence of LE ranged from 22% to 43% depending upon the node group treatment

TABLE 3
Percent Distribution of Selected Lymphedema (LE)-Related Signs and Symptoms in Those Who Underwent ALND, SLNB, Combined SLNB and ALND, and Neither (n = 97)

Signs and symptoms	ALND (n = 67) %	SLNB (n=9) %	Both (n=12) %	Neither (n=9) %
Arm size larger**	41	0	17	0
Change in sleeve fit*	36	0	8	0
Change in cuff fit*	35	0	8	0
Swelling in past year*	45	25	60	0
Firmness/tightness now*	45	0	36	11
Firmness/tightness in past year**	55	0	40	0
Numbness now*	60	43	67	11
Numbness in past year**	62	50	67	0
Tenderness now	48	50	50	22
Tenderness in past year	49	38	60	33

ALND versus SLNB versus Both versus Neither: * $p \leq 0.05$; ** $p \leq 0.01$

(ALND alone, SLNB alone, ALND combined with SLNB, and neither). Taken collectively, these findings are in keeping with LE prevalence reported by another researcher (18). Although LE occurrence in the ALND group was not statistically different from the other three node groups in this relatively small sample, women with ALND only had the highest LE occurrence numerically (43.3%) of any of the four groups—a clinically important finding. In contrast, LE occurrence was 40 to 50% lower when women received neither SLNB nor ALND, underwent SLNB alone, or underwent SLNB in combination with ALND as part of their breast cancer treatment.

One interpretation of these ALND findings might suggest that those who underwent axillary dissection only at this time may have had more extensive disease. The ALND group also reported the longest time since treatment: occurrence of LE may

be higher if the other group participants were to be assessed at more years post-treatment. Since the ALND alone group was the group the furthest out following treatment, and we know LE risk continues throughout the lifetime, it is expected LE prevalence would be highest in this group. Even in light of this interpretation, these data suggest that in order to reduce the risk of post-breast cancer lymphedema, ALND alone should be avoided when appropriate clinically.

While LE prevalence was not statistically significantly different among the node groups, the important finding here was that LE did occur, albeit at a level not statistically different, even following SLNB only and in the absence of other nodal manipulation. SLNB has been thought to have the potential to achieve a substantial reduction in LE. One of the relatively few reported studies conducted to examine the occurrence of LE following SLNB revealed no increase in the

circumference of the arm on the side affected by breast cancer compared with the arm on the non-affected side (N=70), using 2 anatomical sites (26).

In contrast, we found that 22.2% of the SNLB group developed LE as determined by one or more of five circumferential measurements ≥ 2 cm. One possible explanation for the more frequent occurrence of LE after SLNB at our institution when compared with Schrenk and colleagues (26) is that treatment of the sample accrued here included the training years of surgeons who perform SLNB. Future studies may reveal a lower LE occurrence due to refinement of surgical technique. Differences in findings may also relate to protocol differences in measuring circumferences.

Nonetheless, although LE occurrence in our SLNB group was not statistically smaller than the other three node groups, women with SLNB, the combination of ALND and SLNB, and neither did have the lowest proportion of LE occurrence. These data suggest that SLNB alone or in combination with ALND is preferable to ALND alone when deemed clinically appropriate. In our small sample, participation may have been higher among women with some signs and symptoms of post-treatment limb swelling. Replication of this research with a larger sample size is necessary to confirm these results.

Perhaps most surprising was the relative frequency of LE in those women who had no surgical manipulation of their lymph nodes whatsoever (22.2%). It is not known why these women developed LE. Characteristics of the "neither" group were further explored in order to assess possible risk factors for the group members who developed LE. Members of this group tended to be somewhat older (median age 5 years older than the group median and all but two were over age 65) and to have undergone surgery fairly recently (within the past 2-3 years) compared to the ALND group. Members of this group had partial mastectomies and frequently had multiple co-morbidities. Interestingly, the two

"neither" group members who had measurable LE had centrally-located pathological stage T1 tumors (≤ 2 cm) with no clinically palpable adenopathy, were clinical stage I, underwent partial mastectomies without radiation, were on Tamoxifen only, and had no recorded infections or other post-operative complications. In addition, there were two members of this group who experienced delayed wound healing, but they did not have measurable LE at the time of the study.

Clearly, the occurrence of LE involves a complex constellation of factors that contributes to risk for the individual. Radiation to the axilla and/or breast has been discussed in the literature as a major contributor to LE occurrence and may serve as one possible explanation for LE prevalence findings (42,55). The results of our study, however, demonstrated no significant relationship between adjuvant radiation and LE occurrence. Indeed, the two participants in the "neither" group who had measurable LE had not received radiation therapy. Weight at time of post-treatment limb measurement also did not have a significant relationship to presence of LE, although published clinical care guidelines suggest maintenance of optimal weight (56,57).

Although the range of absolute differences between arm circumferences varied widely at all five anatomical sites, it is important to note that when examining the data collectively, the upper arm and the forearm were the only anatomical sites found to have mean absolute differences between limbs not different from 2 cm. This finding has important clinical implications in that it suggests observation of the hand, wrist, or elbow would not be sufficient for a preliminary diagnosis of LE by a physician or nurse during a routine clinic visit. Rather, objective circumferential measurement at the upper arm and forearm would be, on average, most likely to reveal LE, and thus are absolutely necessary for accurate LE assessment. That said, the more frequent sequential circumferential measurements, for example at every 4 cm or,

minimally, at 5 matched anatomic points, are preferable for assessment of limb changes.

In this sample of relatively small numbers of women who underwent SLNB alone, combined ALND and SLNB, and neither, mean absolute differences in circumferences did not vary among the node treatment groups. When examined qualitatively, however, our data do suggest a trend (*Fig. 2*). For example, the upper arm and forearm appear to be the anatomical locations most affected by swelling in the ALND group, while the hand may be the area most affected in women who have undergone both ALND and SLNB. Additional research with a larger sample is necessary to further delineate patterns of swelling based upon nodal treatment.

Lymphedema-Related Signs and Symptoms

Participants with LE experienced a variety of signs and symptoms such as larger neck and arm size, sleeve and sleeve cuff fit tighter, swelling, firmness/tightness, and heaviness. Successful management of the signs and symptoms relies on accurate assessment and prompt identification. Future research studies should focus on further refining a reliable and valid clinical instrument to assess LE-related signs and symptoms and management interventions.

Interestingly, more than 40% of women *without* ≥ 2 cm differences (*Table 2*) also reported the symptoms of tenderness and numbness now and in the past year. Some symptoms experienced may be related to breast cancer treatment procedures in the absence of LE. For example, Baron et al (49) found that tenderness, soreness, tightness, and numbness were severe and distressing symptoms that occurred in women who underwent ALND and SLNB (N = 283). Our data support the work by Baron and colleagues (49) in that tenderness now and in the past year occurred frequently in all women treated for breast cancer regardless of node treatment, and numbness now and in the last year occurred in all but the “neither”

group (*Table 3*). These data suggest that some symptoms experienced may be related to the surgery alone and not LE. Nonetheless, additional research is needed to develop and test interventions to minimize symptoms experienced not only by breast cancer survivors with LE, but also by breast cancer survivors without LE.

The published literature on SLNB suggests that SLNB is associated with fewer signs and symptoms than ALND. For example, less numbness and pain have been reported by women undergoing SLNB in comparison with women undergoing ALND (26). Similarly, Swenson and colleagues (58) also found significantly less pain in patients with SLNB than patients with ALND at one and six months post-breast cancer surgery. Our study reinforces these findings (*Table 3*) in that overall LE-related signs and symptoms were reported less often in women following SLNB only compared to ALND. This was particularly dramatic in that no women with SNLB experienced the symptoms of arm size larger, change in sleeve or cuff fit, firmness/tightness now, or firmness/tightness in the past year. Likewise, no women in the “neither” group reported symptoms of arm size larger, change in sleeve or cuff fit, swelling in the past year, firmness/tightness in the past year, or numbness in the past year.

Nonetheless, in our study, 50% of women following SNLB reported numbness in the past year, and 43% of these women reported numbness now. In general, post-treatment symptoms are attributed to the surgical and/or radiation interventions. In this study, based on the structure of the LBCQ items, the numbness may have occurred in any one (or more) of three locations: the arm, breast, or chest wall. Perhaps this reported numbness was located on the breast or chest wall, rather than in the arm, a finding not surprising following SLNB. Specification of location and duration of the symptom for comparison with time-since-surgery would be helpful data for future analysis. Further research is necessary to examine this issue.

Another possible explanation for these findings of reported symptoms at < 2 cm circumferential differences is that the time period during which only subjective signs and symptoms can be detected may be a latent stage of LE. Once post-breast cancer LE becomes established, LE has a tendency to become more severe with time (3). Successful management of LE and related signs and symptoms is dependent upon early detection and intervention. Longitudinal studies that prospectively examine the self-reported signs and symptoms in combination with precise limb volume measurements will assist in determining if subjective signs and symptoms are accurate predictors of latent stage LE. Future researchers should design a model to predict LE occurrence in terms of LE-related signs and symptoms so as to promote early detection and management of LE.

Members of the SLNB and “neither” group reported fewer symptoms of swelling and firmness/tightness. The “neither” group experienced less numbness than the other three groups. If these findings hold up in future prospective longitudinal research with a larger sample and more rigorous methodology, we may better understand factors associated with higher risk of LE, since the SLNB and “neither” groups are two groups with no axillary dissection.

Strengths and Limitations

From a historical perspective, these data were collected at an important window of time, from women who had undergone ALND before SLNB was widely available, from women treated during the time SLNB was being undertaken on an experimental basis, and from women treated as SLNB has become standard of care at many institutions. These findings may not, however, be representative of the future risks for LE among those with breast cancer treated with newer modalities.

In addition to the sequential circumferential arm and hand measurement

and self-reported LE-related symptoms, the study would have been strengthened by inclusion of more accurate and precise limb volume measurements such as volumetrics (water displacement) and infra-red perometry. Further, a longitudinal design with arm volume measurements with a pre-operative baseline would provide a more appropriate comparison for limb changes than a single cross-sectional “snap-shot” comparing 2 limbs of unknown symmetry at only one point in time. The current commonly-used criterion of ≥ 2 cm differences between limbs (22) assumes symmetry prior to cancer treatment and provides no basis for comparison for those cancer survivors with bilateral mastectomies and no adjustment for naturally-occurring limb differences due to limb dominance or activities of daily living. Finally, geographic limitations of the sample and the smaller sample size of breast cancer patients who underwent SLNB (alone and in combination) restrict the generalizability of the study findings.

While the size of the sub-sample treatment groups is recognized as a limitation of the study, that limitation has been statistically accommodated with the setting of a conservative level of significance, so that we can be relatively sure that we are not committing a type I error and establishing valid tests with small sample sizes. As noted, in carrying out the reported analysis, “level of significance was set at 0.05, with adjustment to 0.01 for multiple comparisons.” Thus, we may argue that in the cases of the significant differences we found *even with* small sample sizes (and relatively low power), then the differences are *more likely* to be clinically meaningful. We would suggest this is indeed the case with the findings of statistical significance in differences in reported symptoms among treatment groups. On the other hand, in those cases where we found *no* statistically significant differences to reject the null hypothesis (as in comparison of LE prevalence across the treatment groups), with the small sample size we have relatively small power to detect

differences that may exist. In other words, just because we failed to reject the null hypothesis of no difference does *not mean* that no (clinically meaningful) difference exists. Indeed, we would argue that this is the case. With findings of higher differences of LE occurrence in the ALND group, this may be a *clinically important* finding, even though *not statistically significant*.

Implications for Practice

Findings from this study can assist nurses, physicians, and others caring for women before, during, and after breast cancer treatment. Patient and family education prior to and following breast cancer treatment is necessary to help reduce risk of LE. Health professionals must be knowledgeable about different treatment options and their impact on the risk of LE development. With this knowledge, providers will be better able to explain LE risk accurately. It is important that patients understand LE-related risk factors, as well as signs and symptoms for which to monitor and report to the health care team.

During routine follow-up appointments providers should assess subjective as well as objective signs and symptoms of LE. With further refinement, the LBCQ may be clinically useful for assessment of subjective signs and symptoms. Bilateral sequential circumferential or limb volume measurements are essential to evaluate objective limb changes. Based on our findings, sequential circumferential arm measurements should include multiple anatomical sites along the arm, as well as take into consideration neck and shoulder size. At the very minimum, upper arm and forearm circumferences should be taken.

SUMMARY

This study examined the occurrence of post-breast cancer LE and the relationship between and among the presence of

measurable LE and signs and symptoms in four groups of breast cancer survivors: those who underwent ALND, SLNB, both, or neither. These data suggest that state-of-the-art surgical approaches, such as SLNB and breast conservation surgery with adjuvant radiation, may hold great promise for reducing LE occurrence and related signs and symptoms. They do not, however, fully protect women from the risk of post-breast cancer LE nor from experiencing distressing subjective signs and symptoms.

SLNB is a relatively new procedure and outcomes are still under investigation. This study provides a starting point for examining outcomes of SLNB and SLNB combined with traditional diagnostic procedures and treatments. In the foreseeable future, ALND, SLNB, and the combination will continue to be in the medical “toolbox” for successful treatment of breast cancer, providing further support for continued research in this area. Further, as noted earlier, even as treatment evolves and procedures (such as SLNB) thought to reduce risk of post-treatment complications such as LE are developed, the lifetime risk of LE among the 2 million breast cancer survivors living today continues.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of present and former members of the Lymphedema Research team: Michael C. Perry, MD; Richard Madsen, PhD; Marge Whitman, AOCN, MS(N); Karen Wingert, DPT, RN, MA; Donna A. Williams, PhD; Deidre Wipke-Tevis, PhD, RN; Davina Porock, PhD; Ashley Sherman, MS; Deanna Schoenherr, RN, MS(N); Cynthia Woodcock, RN, MS(N); David Ota, MD; Kevin Lin, MD; and Steven Standiford, MD.

Analyses of a portion of these data were presented previously:

1) Armer, JM, Williams, DA, Wipke-Tevis, DD, Zagar, E, Wainstock, J and Whitman, M (2000, September). Sentinel Lymph Node Biopsy and Post Breast Cancer

Treatment Lymphedema (preliminary analysis). Research poster presented at the 5th National Lymphedema Network Biennial Conference. Ft. Lauderdale, FL.

2) Armer, JM, Fu, MR, Williams, DA, Wipke-Tevis, DD, Porock, D, Wainstock, JM, Zagar, E, Jacobs, LK (2003, May 3). Lymphedema following Breast Cancer Treatment, Including Sentinel Lymph Node Biopsy (primary analysis). Research paper presented at Late-breaking Research Session, Oncology Nursing Society Congress. Denver, CO.

3) Armer, JM, Thiadens, SJK. (2003, September 3). Lymphedema following Breast Cancer Treatment, Among Women In Four Surgical Treatment Groups. Research paper presented at International Society of Lymphology XIX International Congress of Lymphology (September 1-6, 2003). Freiburg, Germany.

This research was funded in part by: MU Research Council, Meredith Baxter Products, Sigma Theta Tau Alpha Iota chapter, and MU Sinclair School of Nursing.

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