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Risk Factors Associated with Breast Lymphedema Following Breast Surgery

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Abstract

Introduction—The development of breast lymphedema (BLE) following breast/axillary surgery is poorly characterized. We prospectively evaluated clinical and surgical factors associated with development of BLE.

Methods—Patients undergoing unilateral breast-conserving surgery were prospectively enrolled preoperatively and followed for development of BLE. To augment the number of patients with BLE for evaluation of risk factors, postoperative patients identified in the clinic with signs and symptoms of BLE were also enrolled. Logistic regression with Firth's penalized likelihood bias-reduction method was used for univariate and multivariate analysis.

Results—Of 144 women, 124 of them were enrolled preoperatively (38 of whom developed BLE) and 20 women with BLE were enrolled postoperatively. Any type of axillary surgery was the strongest factor associated with BLE (odds ratio 134, 95% CI: 18 to >1000). All 58 BLE events occurred in women with axillary surgery as compared to none of the 46 patients without axillary surgery ($p<0.0001$). Among 98 women who underwent axillary surgery, BLE did not occur more often after ALND versus SLN biopsy ($p=0.38$) and was not associated with total number of nodes removed ($p=0.52$). In multivariate analysis, factors associated with the development of BLE in the axillary surgery subgroup included baseline BMI ($p=0.004$), incision location ($p=0.009$), and prior surgical biopsy ($p=0.01$).

Conclusions—Risk of BLE is primarily related to performance of any axillary surgery but not extent of axillary surgery or number of lymph nodes removed. Other factors associated with BLE were increased BMI, incision location, and prior surgical excisional biopsy.

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Keywords

breast lymphedema; breast cancer; lymphedema; risk factors

BACKGROUND

Breast cancer-related lymphedema is a well-known sequela of surgery and adjuvant therapy for the treatment of breast cancer. The majority of patients and physicians, when thinking about lymphedema related to breast cancer treatment, consider lymphedema of the arm; [1] however, breast cancer patients can develop lymphedema in other regions including the chest wall and the breast. [2–4] Breast lymphedema (BLE) has not received as much attention by physicians and patients and has been understudied as it has been more challenging to quantify. Patients who undergo any breast surgery, in particular, those undergoing breast-conservation surgery for breast cancer, are at a theoretically increased risk of developing BLE due to the surgical incision and tissue dissection with potential disruption of lymphatic drainage of the breast.

BLE is characterized by diffuse skin edema and erythema as well as self-reported symptoms including breast heaviness, redness and swelling. [4] In a prospective study evaluating the incidence of BLE, our group demonstrated that 31% of women undergoing breast surgery develop BLE.

In this paper, we further evaluate the clinical and surgical risk factors associated with the development of BLE following breast surgery. Since, anecdotally, early BLE intervention may render the natural history of BLE more benign and less degrading to QOL, we believe that there may be value in identifying variables that enhance our ability to accurately risk-stratify patients with regard to the development of BLE.

METHODS

A prospective clinical study enrolled women undergoing unilateral non-mastectomy breast surgery to study the post-operative complication of breast lymphedema. Women were enrolled from the breast surgical practice from September 2006 to February 2009. The study population, methods, and inter-rater agreement for the BLE diagnosis were previously described in detail. [4] Briefly, patients were evaluated preoperatively and at 1, 3, 6, and 12 months following surgery for the development of BLE. Each patient was evaluated for the development of BLE at each follow-up visit based on a graded physical examination that focused on clinical signs of edema and erythema performed by one of two registered nurses on the study team; interobserver reproducibility between the nurse assessments and surgeon and lymphedema physicians has been previously reported. [4] A patient was classified as having BLE if: 1) a clinical impression of BLE was present at 2 or more visits beyond one month after surgery, or 2) a clinical impression of BLE was present at one visit greater than one month after surgery with either moderate or severe edema or erythema. Risk factor data were collected prospectively and entered into a study database.

To increase the number of women with BLE available for assessment, 20 additional patients were enrolled who had BLE that was identified postoperatively. These patients met the same criteria as patients enrolled preoperatively, and their risk factor data were collected retrospectively from medical records using the same definitions as for the prospective cohort.

Statistical Methods

Univariate associations between potential risk factors and the development of BLE were examined using logistic regression to estimate profile-likelihood p-values, odds ratios and 95% profile-likelihood confidence intervals. The Firth penalized likelihood bias-reduction method was utilized due to sparse data, including complete data separation for some categorical variables. [5] For ordinal variables such as TNM stage and bra cup size, the reported p-value is for a linear trend across categories. Logistic regression was also used to perform multivariate analysis. P-values<0.05 were considered statistically significant. Analysis was performed using SAS (Version 9.2, SAS Institute Inc.) and the logistf package for R (Version 2.15). [6]

RESULTS

A total of 144 women who underwent breast surgery were included in the study. These included 124 women enrolled preoperatively (38 of whom developed BLE during follow-up) and 20 women with BLE enrolled during their postoperative course. Overall, 58 women with BLE and 86 without BLE were available for evaluation of risk factors. Baseline and surgical characteristics are summarized in Table 1. The median length of post-surgical follow-up for BLE was 11 months (range 3–68 months).

Impact of Axillary Surgery

Of the 144 patients, 98 underwent axillary surgery [79 sentinel lymph node biopsy (SLNB), 19 axillary lymph node dissection (ALND)] and 46 did not [32 excisional biopsy, 14 wide local excision (WLE) only]. All 58 of the BLE events were observed in patients with axillary surgery (45 WLE+SLNB, 13 WLE+ALND), and 0/46 (95% CI: 0–7.7%) of patients without axillary surgery developed BLE. Since none of the 46 patients without an axillary procedure developed BLE, axillary surgery was by far the most influential risk factor (OR 134, 95% CI: 18 to >1000, p<0.0001). This remained true with only slight attenuation (adjusted OR 118, 95% CI: 14 to >1000, p<0.0001) after adjusting for age, BMI, total specimen volume, scar length, incision location, smoking, and prior surgical biopsy. Due to these findings, we felt that it was most relevant to evaluate additional risk factors for BLE in the subgroup of patients who had any type of axillary surgery.

Risk Factors in the Axillary Surgery Subgroup

Patient, cancer, and surgery characteristics are summarized by outcome group with univariate odds ratios in Table 2 for patients who underwent an axillary procedure (SLNB and/or ALND). Among patients with BLE, 22% had an ALND as compared to 15% among those without BLE; this corresponds to an odds ratio of 1.58 for ALND versus SLNB, which was not statistically significant (p=0.38). Similarly, the number of nodes removed was

similar in those who did and did not develop BLE with a median of 3 nodes in each group and a non-significant odds ratio for the number of nodes (OR 0.98 per 1 node increase, p=0.52).

The variables BMI (p=0.02), bra cup size (p=0.04), and breast radius (p=0.049) were each significantly associated with BLE in univariate analysis. The mean BMI was 31 in patients with BLE as compared to 28 in those without BLE, and the odds ratio was 1.56 per one unit increase in BMI. Examined as BMI categories, the odds of BLE were 2–3 fold higher in patients classified as obese (BMI 30–34) or morbidly obese (BMI≥35) relative to those with BMI<25. Only 7 women with a bra cup size > D were included in the study, but all 7 developed BLE (odds ratio 9.0 relative to bra cup size A). Similarly, the mean breast radius was larger in those who developed BLE versus not (8.4cm versus 7.6cm, respectively) for an odds ratio of 1.23 per one cm increase. Only six women had a surgical biopsy for diagnosis in the operated breast and all 6 developed BLE (odds ratio 10.0 relative to needle biopsy, p=0.04).

The most common incision location was the upper outer quadrant (55/98=56%). Overall, location of the breast surgical incision was significant (p=0.03) with UOQ, LIQ, and central locations each demonstrating increased odds relative to LOQ, which had the lowest risk of BLE. UIQ showed a non-significant increase in odds (OR 1.7) relative to LOQ. The orientation of a scar (radial, antiradial, or circumareolar) was not associated with BLE. There was no difference in BLE rates by surgeon performing the procedure.

Length of scar was slightly longer (median 4.8cm) in women who developed BLE as compared to those who did not develop BLE (4.1cm); however, this difference did not reach statistical significance (p=0.21). Similarly, volume of tissue resected was slightly higher in patients who developed BLE (median 49.5cm^3) than in those who did not develop BLE (45.4cm^3) but was not significantly different (p=0.26). Tumor size and TNM stage were not associated with BLE. Four patients with N3 disease developed BLE, resulting in an odds ratio of 5 for this category relative to N0 invasive cancer, but the result was not significant with this small number of patients.

Two patients had congestive heart failure and both developed BLE, while three of four patients with prior midline sternotomy developed BLE and both patients with insulin-dependent diabetes developed BLE. There was no difference in use of antihypertensive medications between the two groups (40% in each group, p=0.97). Of the patients that developed BLE, 24% (14 patients) were on diuretic medications compared to 15% (6 patients) in the group without BLE (p=0.29).

Ninety-eight percent of patients received adjuvant radiation, 40% received adjuvant chemotherapy and 71% received adjuvant endocrine therapy. Seven patients (7%) underwent neoadjuvant chemotherapy. None of these variables was significantly associated with BLE; however, since almost all patients received adjuvant RT, our ability to evaluate this potential risk factor was limited.

Multivariate Analysis

BMI, breast radius, and bra cup size were moderately correlated (r=0.40 to 0.66) with each other, and although each was significant by univariate analysis for association with BLE, they were no longer significant when included together in a multivariate model, thus suggesting some degree of multicollinearity. BMI was the strongest univariate predictor and was therefore the one retained for the multivariate model.

The final multivariate model (Table 3) included the variables BMI, prior surgical biopsy, and incision location, each of which was significant at the 0.05 level in both univariate and multivariate analysis. Additionally, we included the extent of axillary surgery (ALND vs SLNB) to confirm that this variable remained non-significant after adjustment for potential confounding variables (p=0.84). The c-statistic for this model as a measure of its ability to discriminate between those with and without BLE was 0.78.

In a sensitivity analysis, we excluded the 20 patients with BLE who were enrolled postoperatively with symptomatic BLE, as they may represent a different patient population than the preoperative enrolees. The multivariate analysis results were very similar when only the preoperative enrolees (n=38 with BLE and n=40 without BLE) were included; specifically, BMI and prior surgical biopsy remained significant, as did the comparison between central and LOQ incision location. The effects for UOQ and LIQ incision locations were each somewhat attenuated and no longer significant in this subset; however, the odds ratios continued to demonstrate clinically important effects sizes at 3.0 and 5.8 versus LOQ, respectively. Again, the extent of axillary surgery was non-significant but actually demonstrated slightly lower odds for ALND versus SLNB in this subset (OR 0.66).

DISCUSSION

In this study, we demonstrate that axillary surgery is the primary risk factor associated with BLE after lumpectomy and axillary staging surgery. However, other contributing risk factors include BMI, surgical excisional biopsy for diagnosis, and location of the surgical incision, which were each significantly associated with the development of BLE in univariate and multivariate analysis.

BLE usually presents in the first few months after breast surgery. Signs of BLE include diffuse skin edema and erythema. [2–4] Symptoms of BLE include breast heaviness, redness and swelling. The overall symptom-associated distress is low; however in a low proportion of cases BLE can develop into a chronic distressing condition. [4] Recognizing BLE and differentiating it from breast cellulitis is important to avoid unnecessary use of antibiotics and to initiate early lymphedema treatment to improve lymphatic drainage of the breast. [7] Risk of infection and impaired wound healing is markedly increased in lymphedematous tissues. [8,9]

An understanding of the clinical and surgical risk factors associated with BLE may enable surgeons to mitigate BLE incidence and severity by identifying patients at increased risk for BLE and providing proactive education and treatment. Of the three risk factors identified in our study, using percutaneous biopsy to diagnose breast lesions is already widely

recommended for many other reasons. [10] Percutaneous biopsy allows the tumor excision and nodal surgery to be performed at the first operation; in contrast, a diagnostic surgical biopsy followed by an oncologic procedure requires at least two operations. [11] When lumpectomy is performed with a known cancer diagnosis, it facilitates a higher rate of negative margins. [11] Additionally, this study suggests that BLE increases with use of surgical excisional biopsy for diagnosis. The American Society of Breast Surgeons has advocated for use of percutaneous biopsy for diagnosis [12] and considers this a quality measure for breast surgery.

For women with higher BMI and/or with larger breast size, appreciable weight loss prior to cancer surgery is not feasible. However, for women identified to be at increased risk for BLE based on high BMI, patient counseling regarding potential risk of BLE can be considered to allow for the early identification of BLE and the timely initiation of therapy. Body weight and increased BMI are established risk factors for development of arm lymphedema [13] and a previous study has also shown that risk of BLE is increased in obese patients. [14] In the present study, each of the variables BMI, breast radius, and bra cup size was univariately significant, but they were generally not significant if included together in a multivariate model, and thus only BMI was retained in our final multivariate model. However, with a larger sample size and particularly a larger number of women in the category of bra cup size > D, which showed a univariate odds ratio of 9.0, we may have been able to elucidate a role for breast size separate from BMI.

In the majority of cases, incision location is impacted by tumor location and is not a risk factor that can be easily adjusted. This study similar to two previous studies showed that location of tumor in the upper outer quadrant predisposes to BLE[14,15], however we also found that central location and lower inner quadrant also predispose to BLE. A possible explanation is that incisions in the central and upper outer quadrant are more disruptive to the main breast lymphatics thus reflected in the increased BLE rates seen. Our finding contrasts with that of one other study where tumor location did not influence the prevalence of BLE.[3]

In our study group, the largest risk factor associated with the development of BLE was axillary surgery. None of our patients without axillary surgery developed BLE suggesting that the risk of BLE in patients undergoing a breast only operation is small. Therefore, we limited the analysis of additional risk factors to women undergoing axillary surgery as the most relevant subgroup. It is noteworthy that the extent of axillary surgery, including SLNB versus ALND and the absolute number of axillary nodes resected, were not associated with BLE. This is in contrast to arm lymphedema where the extent of the axillary surgery has been shown to impact risk. [13] Our findings are consistent with those in the report by Goffman et al who performed a retrospective study of arm and breast lymphedema and found that the number of nodes resected was significant for development of arm lymphedema, but not for BLE. [16] These findings support a theory that SLNB disrupts the primary lymphatic drainage of the breast and therefore BLE risk is similar between SLNB and ALND, SLNB does not necessarily disrupt the primary lymphatic drainage of the arm. However, other studies have reported that BLE rates are higher after ALND than axillary sampling. [2,3]

Limitations of this study include the lack of an objective measurement criteria for BLE. By requiring clinical signs of BLE at more than 1 time point by one of two nurse specialists we believe that provided a reliable definition of BLE. Further work is underway evaluating skin thickness on ultrasound and bioimpedance to be able to better define BLE in the future. Additionally we were unable to evaluate the impact of radiation as a risk factor as the vast majority (98%) of our patients received adjuvant radiation. In a prior study, BLE rates in women undergoing WLE and ALND varied with radiation use, with BLE rates of 5% in non-radiated patients and 21% in patients that received adjuvant radiation. [17] Our data collection only included information on recent surgical breast biopsies that were part of the episode of care for this study; data on remote prior breast biopsies could have shed further light on their role in the development of breast lymphedema. Additionally, although this is the largest study of its kind to evaluate risk factors of BLE, the modest sample size was insufficient to evaluate uncommon risk factors such as smoking and diabetes.

In conclusion, axillary surgery is the strongest risk factor associated with the development of BLE after breast surgery. However, the extent of axillary surgery (ALND versus SLNB) and the number of lymph nodes removed were not significantly associated with BLE. Increased BMI, incision location of UOQ, Central, or LIQ, and prior surgical biopsy were significantly associated with BLE.

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Table 1

Baseline patient and surgical characteristics of subjects (n =144).

	n=144
Age, mean (range)	59 (36–85)
BMI, mean (range)	29 (17–48)
BMI category, n (%)	
<25	32 (22.2)
25–29	58 (40.3)
30–34	27 (18.8)
≥35	27 (18.8)
Current smoker, n (%)	7 (4.9)
Bra cup size, n (%)	
A	9 (6.3)
B	43 (30.1)
C	60 (42.0)
D	22 (15.4)
>D	9 (6.3)
Recent prior biopsy	
None	6 (4.2)
Needle	130 (90.3)
Surgical	8 (5.6)
Operation, n (%)	
Excisional biopsy only	32 (22.2)
WLE only	14 (9.7)
WLE+SLNB	79 (54.9)
WLE+ALND	19 (13.2)
Location scar, n (%)	
UOQ	74 (51.4)
LOQ	16 (11.1)
LIQ	11 (7.6)
UIQ	11 (7.6)
Central	32 (22.2)
Number of nodes removed[*], median (range)	3 (1–38)
Tumor stage[**], n (%)	
Tis	25 (22.3)

	n=144
T1	72 (64.3)
T2	14 (12.5)
T3	1 (0.9)
Tumor size[***] **(cm)**, median (range)	1.3 (0.02–8.4)
Node stage[***], n (%)	
N0	61 (70.1)
N1	18 (20.7)
N2	4 (4.6)
N3	4 (4.6)

[*] Including only those with an axillary procedure (n=98).

[**] Including only those with cancer (n=112).

[***] Including only those with invasive cancer (T1-T3) (n=87).

Table 2

Baseline patient and surgical characteristics by outcome with univariate odds ratios and tests of association in the subgroup with axillary surgery (n = 98).

	BLE n=58	No BLE n=40	Odds ratio* (95% CI)	p-value†
Age, mean (range)	61.2 (44–83)	61.3 (43–85)	1.00 (0.82, 1.20)	0.97
BMI, mean (range)	30.9 (21–48)	28.0 (20–42)	1.56 (1.08, 2.36)	0.02
BMI category, n (%)				0.049
<25	10 (17.2%)	11 (27.5%)	Reference	
25–29	19 (32.8%)	17 (42.5%)	1.22 (0.42, 3.55)	
30–34	15 (25.9%)	7 (17.5%)	2.26 (0.69, 7.86)	
≥35	14 (24.1%)	5 (12.5%)	2.89 (0.82, 11.13)	
Current smoker, n (%)				0.26
Yes	5 (8.6%)	1 (2.5%)	2.71 (0.51, 27.16)	
Bra cup size, n (%)				0.04
A	2 (3.4%)	1 (2.5%)	Reference	
B	15 (25.9%)	15 (37.5%)	0.60 (0.05, 5.05)	
C	24 (41.4%)	19 (47.5%)	0.75 (0.07, 6.15)	
D	10 (17.2%)	5 (12.5%)	1.15 (0.09, 11.05)	
>D	7 (12.1%)	0	9.00 (0.36, 1509)	
Breast radius (cm), mean (range)	8.4 (3.5–14)	7.6 (5–11.4)	1.23 (1.00, 1.53)	0.049
Dominant hand, n (%)				0.88
Affected side	31 (53.4%)	22 (55.0%)	0.94 (0.42, 2.10)	
Recent biopsy type, n (%)				0.04
Needle only	52 (89.7%)	40 (100%)	Reference	
Surgical	6 (10.3%)	0	10.02 (1.13, 1322)	
Tumor size ** **(cm)**, median (range)	1.3 (0.1–4.3)	1.4 (0.4–3.5)	0.84 (0.48, 1.48)	0.54
Tumor stage, n (%)				0.45
Tis	4 (6.9%)	7 (17.5%)	Reference	
T1	46 (79.3%)	26 (65.0%)	2.92 (0.85, 11.20)	
T2	7 (12.1%)	7 (17.5%)	1.67 (0.36, 8.27)	
T3	1 (1.7%)	0	N/A	
Volume resected (cm^3), median (range)	49.5 (2.1–259.9)	45.4 (8.8–217.9)	1.08 (0.94, 1.26)	0.26
(Volume resected)/(breast radius) ratio, median (range)	6.2 (0.2–59.9)	6.3 (1.2–26.6)	1.10 (0.85, 1.42)	0.43
Axillary Operation, n (%)				0.38
SLNB	45 (77.6%)	34 (85.0%)	Reference	
ALND	13 (22.4%)	6 (15.0%)	1.58 (0.58, 4.69)	
Number of nodes removed, median (range)	3 (1–20)	3 (1–38)	0.98 (0.93, 1.04)	0.52
Any positive nodes **, n (%)				
Yes	15 (25.9%)	11 (27.5%)	0.77 (0.31, 1.95)	0.84

	BLE n=58	No BLE n=40	Odds ratio* (95% CI)	p-value†
Node stage**, n (%)				0.54
N0	39 (72.2%)	22 (66.7%)	Reference	
N1	8 (14.8%)	10 (30.3%)	0.46 (0.16, 1.34)	
N2	3 (5.6%)	1 (3.0%)	1.33 (0.15, 12.02)	
N3	4 (7.4%)	0	5.12 (0.19, 139.94)	
Length of scar (cm), median (range)	4.8 (2–15.5)	4.1 (2–12)	1.11 (0.95, 1.33)	0.21
Incision location, n (%)				0.03
LOQ	3 (5.2%)	10 (25.0%)	Reference	
UOQ	35 (60.3%)	20 (50.0%)	5.20 (1.49, 22.57)	
UIQ	2 (3.4%)	4 (10.0%)	1.67 (0.21, 12.25)	
LIQ	8 (13.8%)	2 (5.0%)	10.20 (1.79, 79.99)	
Central	10 (17.2%)	4 (10.0%)	7.00 (1.47, 41.08)	
Orientation of scar, n (%)				0.48
Radial	22 (37.9%)	20 (50%)	Reference	
Antiradial	29 (50%)	17 (42.5%)	1.54 (0.66, 3.60)	
Circumareolar	7 (12.1%)	3 (7.5%)	1.95 (0.50, 8.96)	

* Odds ratios are reported per 5 unit change for the variables age, BMI, and volume resected to breast radius ratio; per 1 unit change for the variables breast radius, invasive tumor size, number of lymph nodes removed, and length of scar; and per 20 unit change for the total specimen volume.

† P-value is for a test of linear trend in the case of ordinal variables (e.g., BMI category, bra cup size, stage).

** Including only those with invasive cancer (T1–T3).

Table 3

Multivariate risk factor model among the subgroup with axillary surgery (n=98).

	Odds Ratio	95% CI	p-value
BMI, per 5 unit increase	1.81	(1.19, 2.95)	0.004
Surgical biopsy vs needle only*	17.71	(1.54, >1000)	0.02
Incision location			0.01
LOQ	Reference		
UOQ	4.67	(1.26, 21.69)	
UIQ	1.31	(0.11, 11.61)	
LIQ	11.49	(1.81, 99.78)	
Central	9.40	(1.80, 62.30)	
Axillary operation			0.84
SLNB	Reference		
ALND	1.13	(0.35, 3.89)	

* Surgical biopsy versus needle biopsy only refers to the recent history of diagnostic work-up preceding the wide local excision included in this study.