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THE EFFECTS OF SYMPTOMATIC SEROMA ON LYMPHEDEMA SYMPTOMS FOLLOWING BREAST CANCER TREATMENT

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ABSTRACT

It has been speculated that symptomatic seroma, or seroma requiring needle aspiration, is one of the risk factors for lymphedema symptoms following breast cancer treatment. These symptoms exert tremendous impact on patients' quality of life and include arm swelling, chest/breast swelling, heaviness, tightness, firmness, pain, numbness, stiffness, or impaired limb mobility. Our aim was to explore if symptomatic seroma affects lymphedema symptoms following breast cancer treatment. Data were collected from 130 patients using a Demographic and Medical Information interview tool, Lymphedema and Breast Cancer Questionnaire, and review of medical record. Arm swelling was verified by Sequential Circumferential Arm Measurements and Bioelectrical Impedance Spectroscopy. Data analysis included descriptive statistics, Chi-squared tests, regression, exploratory factor analysis and exploratory structural equation modeling. Thirty-five patients (27%) developed symptomatic seroma. Locations of seroma included axilla, breast, and upper chest. Significantly, more women with seroma experienced more lymphedema symptoms. A well-fit exploratory structural equation model [$X^2(79)=92.15$, $p=0.148$; CFI=0.97; TLI=0.96] revealed a significant unique effect of seroma on lymphedema symptoms of arm swelling, chest/breast swelling, tenderness, and blistering ($\beta=0.48$, $p<0.01$). Patients who developed symptomatic seroma had 7.78 and 10.64 times the odds of developing arm swelling and chest/breast swelling versus those who did not, respectively ($p<0.001$). Symptomatic seroma is associated with increased risk of developing lymphedema symptoms following breast cancer treatment. Patients who develop symptomatic seroma should be considered at higher risk for lymphedema symptoms and receive lymphedema risk reduction interventions.

Keywords: seroma, symptomatic seroma, lymphedema symptoms, lymphedema, breast cancer

Seroma, an accumulation of serous fluid, is the most common wound healing complication following breast cancer surgery (1). Seroma formation can occur in any space adjacent to the surgical area immediately or weeks or months after mastectomy or lumpectomy (2,3) and the incidence of seroma varies from 15 to 80% depending on the definition of seroma or assessment methods (4,5). There is no consistent definition of seroma. Many studies documented seroma only when it was large enough to cause discomfort to the patient and required needle

aspiration (1). A few studies have demonstrated that seromas were detectable using ultrasound technique even though no apparent clinical presentations were observed by physical examination (3). The incidence of seroma in these studies increased to more than 80% (2,3). In an early study by Jeffrey and colleagues (6), ultrasound was used to examine 81 women who had local excision of breast cancer with axillary lymph node dissection. They found that 92% of patients developed seromas detectable by axillary ultrasonography over the first 2 weeks following the surgery, and 42% of those required at least one needle aspiration. In clinical practice, a seroma is very often defined as an accumulation of serous fluid when at least one needle aspiration is required; or when multiple needle aspirations are needed; or when more than 5-20 ml fluid is obtained by needle aspiration (7-9).

The etiology of seroma formation remains inconclusive (3,10). Some studies suggest that seromas consist of lymphatic fluid drained from intramammary lymphatics to the axillary, supraclavicular, and internal mammary nodal basins (4). Other studies suggest that seromas have an inflammatory origin (1) and possibly develop from acute inflammatory exudates and response to surgical trauma and the acute phase of wound healing (5). In a study by McCaul and colleagues (11), an analysis of the components of the drained serous fluid following surgery for primary breast cancer revealed seroma fluid consisting of lymphatic fluid but the components of the lymphatic fluid were similar to inflammatory exudate. McCaul and colleagues (11) also found that a variety of white cells were present in seroma in which granulocytes and monocytes exceeded the number of lymphocytes. They concluded that the serous accumulation was the exudative fluid from the inflammatory reaction. Wu and colleagues (12) have postulated that a seroma is a physiological response to surgical trauma, which induces angiogenesis due to the increased vascular endothelium growth factor and decreased endostatin in the seroma fluid (2).

Risk for Seroma Formation

It is difficult to predict and identify who will develop postoperative seroma (3,8,13). Several studies have identified patients' personal risk factors for post-surgical seroma as age (1,11,13), body weight (14,15), and hypertension (11,16). Findings from existing research on risk factors related to tumor and surgery include tumor size (17), modified radical mastectomy, number of lymph nodes removed (10), presence of malignant nodes in the axilla (1,3), early removal of drains (13,18), and use of electrocautery (19). Other related factors include skin flap necrosis, delayed wound healing, infection, early shoulder mobilization, previous surgical biopsy, and use of heparin (1-3). Many risk factors are directly related to tumor status and cancer treatment and may be largely unavoidable for patients treated for breast cancer.

Lymphedema Symptoms

Lymphedema remains a major global health problem affecting thousands of breast cancer survivors (20-23). Lymphedema following breast cancer treatment is characterized by an accumulation of lymph fluid in the interstitial spaces of the affected limb and areas, leading to abnormal swelling and multiple symptoms (23,24).

Recent research has revealed lymphedema symptoms elicit tremendous distress in breast cancer survivors and impact their quality of life (24,25) and it is essential to consider lymphedema symptoms as an important patient-centered clinical outcome. Lymphedema symptoms include arm swelling, chest/breast swelling, heaviness, tightness, firmness, pain, numbness, stiffness, or impaired limb mobility (26,27). Longitudinal research on the relationship between limb volume change (LVC) by the infra-red perometer and lymphedema symptoms has

demonstrated that increased number of reported symptoms is significantly associated with increased LVC (21,27). On average, breast cancer survivors reported 4.2 symptoms for survivors with <5.0% LVC, 5.5 symptoms for 5.0-9.9% LVC, 7.0 symptoms for 10.0-14.9% LVC, and 12.5 symptoms for >15% LVC, respectively ($p<0.001$) (21).

Seroma and Lymphedema Symptoms

Seroma and lymphedema can occur immediately after surgery or during radiation or chemotherapy, and may evolve over subsequent years (9,22,23). It has been speculated that seroma is one of the risk factors for lymphedema symptoms following breast cancer treatment (28-30). The accumulation of serous fluid has been assumed to cause tissue inflammation and subsequent soft-tissue fibrosis that triggers lymphedema (29,30). Repeated seroma aspirations often cause infection which is the predictive risk factor for developing lymphedema following breast cancer treatment (31-33). Clinical practice indicates that reduction of seroma formation may reduce the likelihood of developing lymphedema in some patients (10,28,29). The purpose of the study was to determine whether symptomatic seroma following breast cancer treatment affects patients' lymphedema symptoms.

METHODS

This was a cross-sectional study of 130 breast cancer survivors who underwent treatment for breast cancer at New York University (NYU) Cancer Center. Symptomatic seroma was defined as clinically apparent fluid collection in the axilla, or under the skin flaps, or in any space adjacent to the surgical area that required at least one needle aspiration. Data were collected using a Demographic and Medical Information interview instrument, the Lymphedema and Breast Cancer Questionnaire for symptoms, and review of medical records. Arm swelling was verified by Sequential Circumferential Arm Measurements and Bioelectrical Impedance Spectroscopy (BIS). Patients were divided into two groups: those who developed seroma and those who did not. When examining the two groups, we compared patient demographic and clinical characteristics, such as age, body mass index (BMI) prior to surgery, number of lymph nodes removed, surgical procedure (mastectomy or lumpectomy), and type of adjuvant therapy (chemotherapy or radiation, or both).

Data Collection Procedure

This study was approved by the Institutional Review Board of NYU Langone Medical Center and the NYU Cancer Center. After the institutional review board approved the study, patients were invited to participate in the study. The study invitation was distributed to potential patients by surgeons, oncologists and nurses who cared for the patients. Women who completed surgical treatment as well as chemotherapy or radiation or both for breast cancer within prior three years were eligible for the study. Women were excluded from the study if they had bilateral breast disease, recurrent cancer, artificial limb or knee or hip, and kidney or heart failure. Two hundred and seven women were responded to the study invitation. Of the 207 patients screened 152 (73.4%) were eligible for the study and 130 (85.57%) of those eligible consented to participate and completed data collection. No incentives and compensations were offered for participation in the study. Difficult in finding or funding transportation was the main reason for those who declined the study, followed by financial concerns due to days off from work. All data collections were completed in person by the first author and two research assistants. Medical records were reviewed to verify the presence of aspirated seroma and treatment variables. Data was collected from July 2008 to February 2009.

Instruments

Demographic and Medical Information: We used a structured interview tool to gather demographic and medical information regarding breast cancer diagnosis, stage of disease, cancer location, type of adjuvant therapy, weight and height prior to surgery, and treatment complications.

Seroma Status: First, an open-ended interview was conducted with each participant responding to two questions: (1) Did you develop a pocket of fluid under your arm or around the surgical area after breast surgery (or radiation, or chemotherapy)? (2) If yes, did your surgeon or nurse use a needle to aspirate fluid from the pocket of fluid? To ensure the reliability of the data, a review of medical records was conducted with each participant. Patients who were categorized as patients who did have symptomatic seroma were those who responded "YES" to the two questions and were further verified by reviewing medical records.

Lymphedema and Breast Cancer Questionnaire is a reliable and valid instrument to assess lymphedema symptoms, including arm swelling, chest/breast swelling, heaviness, firmness/tightness, numbness, tenderness, pain/aching, stiffness, impaired limb mobility, seroma formation, and arm weakness (34). Participants respond with "yes" or "no" answers regarding whether a symptom is currently present (today or within the past month). Scores for total symptom experienced are calculated for the frequency of the total number of current present symptoms as a continuous variable with absolute zero of the absence of symptoms.

Sequential Circumferential Arm Measurements were used to verify reported arm swelling. A measurement protocol established by Armer and colleagues (35,36) were applied on both the ipsilateral and contralateral limbs at the following points: hand proximal to metacarpals, wrist, fullest part of the mid-forearm below elbow, elbow, and fullest part of the upper arm above elbow. Arm swelling was confirmed if there was 2 cm circumferential difference or more between the affected and nonaffected arm at any of the 5 points at the time of the measurement (35,36).

Bioelectrical Impedance Spectroscopy (BIS): The Imp XCA®, a FDA approved device, was used to verify arm swelling by measuring extracellular fluid volume. The Imp XCA® (Impedimed, Brisbane, Australia) use a single frequency below 30 kHz to measure impedance and resistance of the extracellular fluid. The device uses the impedance ratio values between the unaffected and affected limb to determine arm lymphedema. Ratio means of 1.139 for at-risk dominant arms and 1.066 for at-risk non-dominant arms are indicators of arm lymphedema. The Imp XCA® uses the impedance ratio values to calculate a Lymphedema Index [L-Dex]. The L-Dex scale ranges from -10 to +10, which is equivalent to the impedance ratio from 0.935 to 1.139 for at-risk dominant arms and 0.862 to 1.066 for at-risk non-dominant arms, respectively. Each one standard unit in L-Dex is equivalent to the impedance ratio of 0.03. A patient is determined to have arm lymphedema or arm swelling if the patient's L-Dex exceeds the normal value of +10, i.e., exceed impedance ratio means of 1.139 for at-risk dominant arms and 1.066 for at-risk non-dominant arms, respectively (37). Procedures for Imp XCA® recommended by the industry were followed.

Statistical Analysis

The data were double entered and checked for accuracy. Data were analyzed using the freely-available, open-source *R* program (38) and the Mplus modeling software (39). Alpha level was set at 0.05 (p-values ≤ 0.05) and 95% confidence

TABLE 1
Demographic Characteristics (n=130)

Variable	Seroma (n=35)		No Seroma (n=95)		Total		
	n	%	n	%	n	%	p
Education							0.23
High school	6	17.1	8	8.4	14	10.8	
Partial college	7	20.0	15	15.8	22	16.9	
College graduate	11	31.4	29	30.5	40	30.8	
Graduate degree	11	31.4	43	45.3	54	41.5	
Married							0.34
No	12	34.3	43	45.3	55	42.3	
Yes	23	65.7	52	54.7	75	57.7	
Employed							0.46
No	12	34.3	31	32.6	43	33.1	
Yes	23	65.7	64	67.4	87	66.9	
Race							0.59
White	25	71.4	70	73.7	95	73.1	
Non-White	10	28.6	25	26.3	35	26.9	

All associations between demographics and seroma were tested using the Pearson Chi-Squared test.

intervals (CI) were calculated for all estimates. The sample of 130 participants provided 85% statistical power to detect a difference based on a two-sided test of zero difference in numbers of lymphedema symptoms. Bivariate logistic regression and Chi-Squared tests for contingency tables were applied to evaluate significant associations with symptomatic seroma. The *R* program (38) was used for descriptive statistics, bivariate tests, and to fit generalized linear models. *R* is a system for computation, data analysis, and visualization that is developed by a core team and thousands of other contributors around the world. Exploratory factor analysis (EFA) and exploratory structural equation modeling (ESEM) (40) were used to identify latent variables underlying lymphedema symptoms and determine the effects of seroma and other factors on those latent variables. These analyses were conducted with the Mplus modeling software (39) using the oblique geomin rotation of factors and the robust weight least squares estimator. Exploratory structural equation modeling is less restrictive than traditional structural equation modeling because it allows small cross-loadings in the measurement model. This is an advantage when the measurement of constructs of interest is less well developed. ESEM also allows researchers to regress the underlying factors on other variables, which was needed in this study to examine how symptomatic seroma and other factors were related to lymphedema symptoms.

RESULTS

Among the 130 women who participated in the study, 35 (27%) developed clinically apparent symptomatic seromas, that is, seromas requiring at least one needle aspiration. Locations of seroma formation were axilla, breast, and upper chest. Age ranged from 28 to 75 years (M=54.3, SD=9.9). The majority were married (57.7%) and employed (66.9%). The sample was composed by women of different ethnic backgrounds and the majority were white women (n=95, 73.1%). There were 6 Hispanics (4.6%), 12 African Americans (9.2%), and 17 Asians (13.1%). Sixty women (46%) were overweight (BMI≥25) prior to surgery. We used Chi-

TABLE 2
Clinical Characteristics (n=130)

Variable	Seroma (n=35)		No Seroma (n=95)		Total		
	n	%	n	%	n	%	p
Number of lymph nodes removed							0.39
≤12	18	51.4	57	60.0	75	57.7	
>12	17	48.6	38	40.0	55	42.3	
Mastectomy	17	48.6	38	40.0	55	42.3	0.50
Lumpectomy	18	51.4	57	60.0	75	57.7	0.84
Radiotherapy	15	42.9	68	71.6	83	63.8	0.01*
Chemotherapy	16	45.7	65	64.4	81	62.3	0.05*

All associations between clinical characteristics and seroma were tested using the Pearson Chi-Squared test, *denoting: p<0.05.

Squared tests to determine the differences between the groups of women who had symptomatic seroma and those who did not in terms of demographic variables. There was no significant difference in demographics between the two groups (*Table 1*).

All participants (n=130) had surgical removal of the tumor and removal of lymph nodes. Participants were post-breast cancer surgery from 9 to 36 months with a mean of 29 months. Participants also completed radiation or chemotherapy or both. Fifty-five (42%) women had mastectomy, and 75 (58%) had lumpectomy. The majority of the women received radiation (n=83, 64%) or chemotherapy (n=81, 62%), and 59 (45%) had both chemotherapy and radiation. We compared treatment modalities between the two groups of women who had seroma and who did not. There was a statistically significant difference between the two groups concerning radiation and chemotherapy. More women without seroma had radiation and chemotherapy. Type of surgery and removal of lymph nodes were not significantly different between the group of women who developed seroma and who did not (*Table 2*). We used bivariate logistic regression to consider whether the variables age, BMI prior to surgery, and number of lymph nodes removed predicted symptomatic seroma formation. There were no significant associations of seroma with age and number of lymph nodes removed. BMI prior to surgery had a marginally significant association with seroma (OR=1.06, p=0.07).

Between the women who had seroma and who did not, there were significant differences (p<0.05) for symptoms of arm swelling, chest/breast swelling, tenderness, increased arm temperature, firmness/ tightness, numbness, and stiffness (*Table 3*). The women who reported arm swelling were confirmed to have measurable arm swelling by *Sequential Circumferential Tape Measure*, i.e., >2cm with range from 3cm to 8 cm and by *Bioelectrical Impedance Spectroscopy*, i.e., >+10 L-Dex with range from +11.7 to +124.5 L-Dex. Estimated odds for the women who had seroma of developing arm swelling were 7.78 times more than those who did not (p<0.001), while estimated odds for chest/breast swelling were 10.64 times more than those who did not (p<0.001) (*Table 3*).

To evaluate the effects of seroma and other factors on lymphedema symptoms (e.g., number of lymph nodes removed and radiation) we first used exploratory factor analysis to identify factors underlying lymphedema symptoms. One-, two-, three-, and four-factor models were considered, and the two-factor model was the simplest model with good fit to the data [$X^2(34)=46.56$, p=0.074; CFI=0.97; TLI=0.96]. Next, an exploratory structural equation model (40) estimated the effects of seroma, radiation, chemotherapy, BMI prior to surgery, and

TABLE 3
Distribution of Lymphedema Symptoms According to the Presence of Seroma (n=130)

Symptom	Seroma (n=35)	No Seroma (n=95)	Odds Ratio	p
Arm swelling	74.3%	26.7%	7.78	<0.001*
Chest/breast swelling	57.1%	10.9%	10.64	<0.001*
Tenderness	80.0%	49.5%	4.04	0.002*
Stiffness	57.1%	31.7%	2.85	0.008*
Numbness	62.9%	36.6%	2.90	0.007*
Firmness/tightness	54.3%	33.7%	2.32	0.031*
Increased arm temperature	20.0%	5.9%	3.91	0.015*
Local arm redness	28.6%	14.9%	2.28	0.071
Blistering	8.6%	4.0%	2.26	0.287
Heaviness	31.4%	21.8%	1.64	0.251
Pain	48.6%	39.6%	1.44	0.354

Each association between seroma and a lymphedema symptom was tested using the Pearson Chi-Squared tests; *denoting: $p<0.05$.

number of lymph nodes removed on two lymphedema symptom factors. This model fit the data well [$X^2(79)=92.15$, $p=0.148$; CFI=0.97; TLI=0.96]. Factors were interpreted based on symptoms with loadings of at least 0.45 in absolute value. The first symptom factor was defined by heaviness, firmness, stiffness, increased arm temperature, local arm redness, and pain (*Table 4*). Together, seroma, radiation, chemotherapy, BMI prior to surgery, and number of lymph nodes removed accounted for 22% of the variance in the first symptom factor ($R^2=0.23$), but only seroma (ß=0.31, $p<0.05$) and number of lymph nodes removed (ß=0.25, $p<0.05$) had significant unique effects on the first symptom factor. The second symptom factor was defined by arm swelling, chest/breast swelling, tenderness, and blistering. Seroma, radiation, chemotherapy, and number of lymph nodes removed accounted for 30% of the variance in the second symptom factor ($R^2=0.30$), but only seroma had a significant unique effect (ß=0.48, $p<0.01$).

To evaluate the effect of seroma and other factors on the total number of lymphedema symptoms experienced, we fit a binomial generalized linear model with the proportion of symptoms experienced regressed on seroma, chemotherapy, radiation, number of lymph nodes removed, and being overweight prior to surgery (BMI $\geq$25). Both the number of lymph nodes removed (B=0.0195, $p<0.01$) and seroma (B=1.0663, $p<0.01$) were associated with increased number of lymphedema symptoms experienced. Averaging over other factors in the model, patients with seroma were expected to experience an average of 5.3 symptoms while an average of 2.7 symptoms for patients without seroma.

DISCUSSION

Clinical experience has revealed that a seroma can be distressing because it causes discomfort to patients, requires multiple needle aspirations or drain placements, leads to prolonged wound healing, increases risk of necrosis of the skin flap and infection (10,41). In our study, we found that significantly more patients who developed symptomatic seroma experienced more lymphedema symptoms of arm swelling, chest/breast swelling, tenderness, increased arm temperature, firmness/tightness, numbness, and stiffness. Patients who developed seroma

TABLE 4
Factor Loadings for Lymphedema Symptoms (n=130)

Symptom	Factor One	Factor Two
Arm swelling	0.461	0.545
Chest/breast swelling	0.187	0.864
Tenderness	0.434	0.454
Stiffness	0.518	0.348
Numbness	0.371	0.123
Firmness/tightness	0.553	0.087
Increased arm temperature	0.985	-0.004
Local arm redness	0.521	0.402
Blistering	-0.280	0.924
Heaviness	0.891	-0.278
Pain	0.702	0.036

Factors loadings were estimated within the exploratory structural equation model and were rotated to simple structure using the geomin method.

had 7.78 and 10.64 times the odds of developing arm swelling and chest/breast swelling versus those who did not, respectively. In addition, even when controlling for confounding factors such as number of lymph nodes removed and BMI prior to surgery, we found that patients with seroma were expected to have an average of 5.3 symptoms, while patients without seroma only have 2.7 symptoms. This finding further supported our hypothesis that patients who developed symptomatic seroma had higher risk for lymphedema symptoms.

Needle aspiration of symptomatic seroma is usually used to alleviate symptoms from seroma such as fullness and discomfort. Interestingly, we found unique effects of seroma on the two lymphedema symptom factors. The first symptom factor was defined by increased arm temperature, local arm redness, heaviness, pain, stiffness, and firmness. Half of the symptoms (increased arm temperature, local arm redness, and pain) in the first symptom factor are common symptoms for inflammation-infection. The second symptom factor was defined by arm swelling, chest/breast swelling, tenderness, and blistering. Swelling can be considered symptom resulting from fluid accumulation. The association between seroma and the two lymphedema symptom factors does raise the question about whether or not strategies focusing on inflammation-infection and fluid accumulation would help patients to decrease the risk of seroma and subsequent development of lymphedema symptoms. Chaturvedi and colleagues (42) found no occurrence of seroma requiring needle aspiration by applying axillary compression immediately following operation and continued the compression for a week after the drain was removed. Further research is needed to explore novel strategies to decrease seroma formation, such as strategies to prevent excessive fluid build-up using compression bra, swell spot, or behaviors to promote fluid drainage after surgery.

Our study is not without its limitations. For example, it is impossible to determine real incidence of seroma in this study since we only counted those who had at least one needle aspiration. It is possible some patients developed seromas that were not clinically apparent and did not need needle aspiration. Limitations also include lack of data on volume of tissue removed, aspiration frequency, interval between repeated aspiration and amount of aspiration which

could be possible risk factors for lymphedema symptoms.

Although seroma usually occurs immediately or a few weeks after surgery, it should be noted that seroma can also occur during radiation (9). Since only two patients developed seroma during radiation, our study was not able to assess the effect of radiation on seroma. To delineate the effect of radiation on seroma, future study should investigate the occurrence of seroma during radiation.

CONCLUSIONS

Symptomatic seroma is associated with increased risk of developing lymphedema symptoms. Therefore, we recommend for clinical practice that patients who develop symptomatic seroma be considered at increased risk for lymphedema symptoms and that lymphedema symptoms should be assessed over the course of treatment and subsequent follow-up care. To reduce the risk of lymphedema symptoms, patients with symptomatic seroma should receive focused education on behavioral interventions to promote lymph drainage and prevent inflammation-infection.

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