A Contemporary, Population-Based Study of Lymphedema Risk Factors in Older Breast Cancer Women

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ABSTRACT

BACKGROUND: We studied potential risk factors for lymphedema in a contemporary population of older breast cancer patients.

METHODS: Telephone surveys were conducted among women (65-89 years) identified from Medicare claims as having initial breast cancer surgery in 2003. Lymphedema was classified by self-report. Surgery and pathology information was obtained from Medicare claims and the state cancer registries.

RESULTS: Of 1,338 patients treated by 707 surgeons, 24% underwent sentinel lymph node biopsy (SLNB) and 57% axillary lymph node dissection (ALND). At a median of 48 months postoperatively, 193 (14.4%) had lymphedema. Lymphedema developed in 7% of the 319 patients who underwent SLNB and 21% of the 759 patients who underwent ALND. When controlling for patient age, tumor size, type of breast cancer, type of breast and axillary surgery, receipt of radiation, chemotherapy, and hormonal therapy, and surgeon case volume, the independent predictors of lymphedema were the removal of more than five lymph nodes (OR 4.68-5.61, 95% CI: 1.36-19.74 for 6-15 nodes; OR 10.50, 95% CI 2.88-38.32 for > 15 nodes) and the presence of lymph node metastases (OR 1.98, 95% CI 1.21-3.24).

CONCLUSIONS: Four years postoperatively, 14% of a contemporary, population-based cohort of elderly breast cancer survivors have self-reported lymphedema. In this group of predominately community-based surgeons, the number of lymph nodes removed is more predictive of lymphedema rather than whether SLNB or ALND was performed. As more women with breast cancer undergo only SLNB, it is essential that they still be counseled on their risk for lymphedema.

SYNOPSIS

In this contemporary, population-based cohort of 1,338 older breast cancer survivors, the overall incidence of self-reported lymphedema at 48 months was 14.4%. Risk factors for lymphedema were the removal of more than five lymph nodes and the presence of lymph node metastases.

INTRODUCTION

Lymphedema, arm/hand swelling, is an important source of treatment-related morbidity among breast cancer survivors. It causes physical discomfort and disability as well as a cosmetic deformity which can result in psychosocial issues (anxiety, depression, and emotional distress) that further adversely affect activities of daily living and quality of life.[1, 2] Minimizing treatment-related morbidity in breast cancer survivors is important.[3]

Despite the well-known morbidity of this chronic problem, a better understanding of lymphedema risk factors is important to moving this field ahead. Two well-established risk factors for lymphedema are the extent of axillary lymph node dissection (ALND) and the combined treatment of axillary radiation and ALND.[1, 4] The relative contribution of several other factors to the development of lymphedema needs to be better studied. These factors include patient age, extent of disease, type of breast and axillary surgery, and various treatment modalities (modern radiotherapy, chemotherapy and hormonal therapy).[5-11] Furthermore, since axillary surgery results in the iatrogenic disruption and damage of lymphatic channels, it is likely that surgeon technique plays a role in the development of lymphedema. To our knowledge, no studies have been performed to evaluate the role of surgeon technique in the development of lymphedema after breast cancer surgery.

The current literature has two main limitations. First, there is a paucity of population-based studies.[3] Almost all studies are retrospective, largely single-institutional with small numbers of patients. In addition, these studies are difficult to compare as patient populations were diverse, surgery and radiation treatments differed, and duration of follow-up varied. There is no standard definition or measurement of lymphedema or standard time interval to assess for its development. Finally, these studies have the potential for substantial selection bias of both patients and surgeons. Therefore, these

study results may not be applicable to the at-large population of breast cancer patients who are operated on mostly by community surgeons who perform relatively few breast cancer operations annually.[12, 13]

The second limitation is that much of the literature relates to older surgical techniques. Most of the previous studies were performed 20-30 years ago, when more radical breast and axillary surgeries were performed and axillary radiation therapy was more frequently utilized. Now, we have improved techniques. The combined treatment of ALND and axillary radiation has not been routinely recommended since around the late 1980s.[14] Current guidelines recommend less extensive axillary dissections (levels I and II only in most situations) and the avoidance of circumferential stripping of the axillary vein and removal/splitting of the pectoralis minor muscle.[2, 14] More women are candidates for less invasive breast and axillary surgery: breast-conserving surgery (BCS, lumpectomy followed by breast radiation) and sentinel lymph node biopsy (SLNB).[15] SLNB has been probably the biggest technical advance in decreasing lymphedema and other arm morbidities.[16-18]

Given these limitation factors, we evaluated potential risk factors for lymphedema in a population-based cohort of older women undergoing breast cancer surgery by a large number of different surgeons in the contemporary era. We hypothesized that the extent of axillary surgery alone (number of lymph nodes removed; ALND vs. SLNB) would continue to be the strongest predictor of lymphedema, while surgeon case volume, as a surrogate for surgeon technique, might be associated with lymphedema development. Since radiation treatment is now confined to the breast and chest wall in the majority of cases, we believed it unlikely that radiation therapy would remain a significant risk factor for lymphedema. Finally, in this older cohort of women, we hypothesized that patient age, extent of disease, extent of breast surgery, and receipt of

other treatments (chemotherapy and hormonal therapy) would not be independent predictors of lymphedema development.

METHODS

Study Cohort

The study sample consists of a population-based cohort of women with breast cancer who are participating in an ongoing National Cancer Institute-sponsored survey study examining breast cancer outcomes (all-cause and breast cancer specific mortality, recurrence, functional status, quality of life). The cohort consists of community-dwelling women between the ages of 65 and 89 who reside in four geographically and diverse states (California, Florida, Illinois and New York) and were initially identified from Medicare claims as having had an incident breast cancer surgery during the period of March to October of 2003, using our validated claims-based algorithm.[19] The Medicare program funds most inpatient and outpatient services for more than 97% of U.S. residents 65 years or older. All women were enrolled for all of 2003 in non-health maintenance organization Medicare Parts A and B and had an associated Medicare surgeon claim. Women confirmed that their 2003 operation was for an incident breast cancer and not for a local recurrence of an earlier incident breast cancer that might have occurred prior to them being eligible for Medicare. Women were ineligible for the study if they were deceased, had an ICD-9 diagnosis code of dementia, had a long-term care facility stay of 100 days or more in 2003, or were residing in a long-term care facility at the time of the first interview.

Potential participants were contacted initially by mail in September 2005. Using an *opt-out* recruitment strategy, women who agreed to be contacted or who did not return a response letter were contacted by telephone and subsequent telephone surveys were performed using procedures approved by the Centers for Medicare and Medicaid

Services (CMS) and by our institutional review board. The number of telephone call attempts averaged 7 for completed interview and 9 for non-completed interviews. Messages that did not violate patient confidentiality were left on answering machines. The initial survey, which was fielded between November 2005 and June 2006, yielded 3,083 completed interviews. The median time from surgery to the first interview date was 33 months. The estimated participation rate, among those eligible for the study, was 70%. The second survey was completed in October 2006, with a participation rate of 93% among eligible participants. The third survey, at a median time of 48 months after surgery, was completed by 2,670 women in October 2007, with a participation rate of 92% among eligible participants.

In addition to survey participation, subjects gave informed consent for the use of their Medicare claims and state tumor registry information, both of which were routinely collected in these four states. We used the Standard Analytical Files (SAF) that contains Medicare payments for health care services which were created for research purposes. The Inpatient SAF contains inpatient hospital claims; the Outpatient SAF contains claims for outpatient facilities; the 100% Carrier SAF contains claims for physician services, and the denominator file, which contains information on beneficiary enrollment and zip code of residence. All four state tumor registries are members of the North American Association of Central Cancer Registries (NAACCR), which is a professional organization that develops and promotes uniform data standards for registries in Canada and the United States.[20] The tumor registries contain information on demographics, extent of disease, and initial treatment for cancer.

For this study, the cohort consists of 1,338 women who reside in either California or Illinois, have completed all three waves of the survey, and have available tumor registry information. The 1,745 women residing in New York and Florida were not included in this study as tumor registry information was not available for these women.

Response rates for women residing in New York were slightly lower than the response rates for women residing in the other three states.

Patient and Tumor Characteristics

The patient's age was determined from the Medicare entitlement files as of January 1, 2003.[19] Patient's race (white, African American, native Hawaiian or other Pacific Islander, Asian, American Indian/Alaska Native, or other) was determined from survey response. Tumor characteristics (size and grade of the primary tumor, tumor stage, axillary lymph node status, number of lymph nodes removed) were determined from the state tumor registry data. Per established staging guidelines, if no lymph nodes were removed, patients were categorized as having a negative nodal status.

Treatment Characteristics

Type of breast surgery (BCS or mastectomy) and type of axillary surgery (SLNB, ALND, or no axillary surgery) were determined by Medicare claims. Patients who underwent SLNB alone were classified as SLNB. Patients who underwent ALND were classified as ALND, whether or not they underwent SLNB prior to ALND. Patients who underwent SLNB followed by ALND during the same operation could not be specifically determined as these patients' claims were for ALND only. Receipt of radiation therapy, chemotherapy, and/or hormonal therapy was determined by survey response.

Determination of Surgeon Case Volume

Medicare claims were used to determine annual Medicare surgeon case volume of breast cancer surgery cases, as previously described by our group.[13] Volume for each surgeon was based on Medicare claims for all breast cancer cases treated in each state, not solely for cohort subjects.

Outcomes

Survey items related to lymphedema were asked in all three waves. Four screening items to assess arm functioning related to lymphedema, pain, or tenderness in

the arm or hand, and range of motion in the arm, hand, or fingers on the side of surgery were adapted from previously published work.[21, 22] Women were classified as having self-reported lymphedema if they answered "yes" to either question: 1.) "Since your breast cancer surgery, has a doctor ever told you that you have lymphedema or arm edema?" or 2.) "Since your breast cancer surgery, have you had hand or arm swelling on the side of your breast cancer surgery that you have not had on the other side?" If women were classified as having self-reported lymphedema by a previous survey wave, they were not re-asked these two questions on subsequent survey waves. If women were not previously classified as having self-reported lymphedema, they were asked these two questions on subsequent survey waves.

Statistical Analysis

The primary outcome was the development of self-reported lymphedema, as defined above. Univariate testing for significant differences in the development of self-reported lymphedema according to baseline characteristics and hypothesized risk factors (extent of axillary surgery and surgeon case volume) was performed (Table 1). Differences in the distribution of characteristics were analyzed by the Pearson chi-square test or Fisher's exact test. The differences between the medians of continuous variables were tested by the Mann-Whitney *U*-test.

The association between the development of self-reported lymphedema and various factors, with the simultaneous adjustment of these factors, was assessed with a multiple logistic regression model (Table 2). The independent variables entered into the model included hypothesized risk factors (type of axillary surgery, number of lymph nodes examined, surgeon case volume), variables for which univariate associations were significant at the 0.05 level (tumor size, type of breast cancer [DCIS vs. invasive cancer], lymph node status, type of breast surgery, receipt of chemotherapy), and factors that have been observed as predictors of lymphedema by other studies even

though they were not significant on univariate analysis (patient age, radiation therapy, hormonal therapy). Two additional variables, patient race and tumor grade, are reported in Table 1 but were not included in the model since both of these variables were not hypothesized as risk factors for lymphedema development, have not been found to be predictors of lymphedema by other studies, and were not significant on univariate analyses. Three possible interactions of interest identified *a priori* (receipt of radiation therapy and extent of axillary surgery, receipt of radiation therapy and extent of breast surgery, and extent of breast surgery and extent of axillary surgery) were also tested in the model. Point estimates from the model are reported as odds ratios (OR) along with the corresponding 95% confidence interval (CI) for each odds ratio. Data analyses were conducted using SAS statistical software (Version 8.2, SAS Institute; Cary, NC).

RESULTS

The 1,338 women were operated on by 707 different surgeons. Of these women, 799 (60%) resided in California and were operated on by 415 different surgeons while 539 women resided in Illinois and were operated on by 292 different surgeons. The majority of women had early stage disease (17% DCIS, 54% Stage I, 26% Stage II), while only 3% had Stage III or IV disease. At 48 months after surgery, 14.4% of women had lymphedema by self-report.

As shown in Table 1, on univariate analysis, women who developed self-reported lymphedema were more likely to have more extensive disease (larger tumors, lymph node metastases, higher tumor stage), undergone more extensive surgery (mastectomy vs. lumpectomy; ALND vs. SLNB, more lymph nodes removed), and received chemotherapy than did patients who did not develop lymphedema. Age, race, tumor grade, receipt of radiation or hormonal therapy, and surgeon case volume were not associated with the development of self-reported lymphedema.

Independent predictors of lymphedema

In the multivariate logistic regression model, when simultaneously adjusting for patient age, tumor size, type of cancer (DCIS or invasive), type of breast surgery, type of axillary surgery, receipt of radiation, chemotherapy, and hormonal therapy, and surgeon case volume, the independent predictors of lymphedema were the removal of more than five lymph nodes and the presence of lymph node metastases (Table 2).

In the model, if no lymph nodes were removed, the baseline risk for lymphedema was 4.7%. Compared to the removal of no lymph nodes, the removal of 1-5 lymph nodes was not associated with a significant increased risk of self-reported lymphedema. The removal of 6-15 lymph nodes and 16 or more lymph nodes was associated with a 5-fold and 10-fold increased odds of developing lymphedema, respectively. The three possible interactions of interest identified *a priori* were tested in the multivariate model. There was no interaction detected between receipt of radiation therapy and extent of axillary surgery, receipt of radiation therapy and extent of breast surgery, and extent of breast surgery and extent of axillary surgery.

Traditional analyses assessing one potential confounder (patient age, tumor size, DCIS vs. invasive cancer, type of breast surgery, type of axillary surgery, radiation therapy, chemotherapy, hormonal therapy, and surgeon case volume) at a time as it might affect the base model including the two independent predictors (number of lymph nodes removed and nodal status) were also performed. Compared with the base model, adding one variable at a time to the base model resulted in no change to the base model with stable odds ratios for number of lymph nodes removed and nodal status regardless of covariate adjustment (results not shown). This analysis confirmed the findings of the simultaneously adjusted model shown in Table 2.

Relationship between type of axillary surgery performed, number of lymph nodes removed, nodal status, and risk of lymphedema

The number of lymph nodes removed, regardless of axillary procedure performed, was highly variable. One-fifth of the cohort did not undergo any axillary surgery; 5.7% of these women developed lymphedema. Patients who had no reported axillary surgery had 0 – 15 lymph nodes evaluated. Among the 319 (24%) patients who underwent SLNB, a median of 2 lymph nodes (range: 0 – 29) were evaluated; 7% developed lymphedema. Among the 759 (57%) patients who underwent ALND, a median of 8 lymph nodes (range: 0 – 44) were evaluated; 21% developed lymphedema.

In the logistic regression analysis (Table 2), there was no interaction present between the number of lymph nodes examined and nodal status. As expected, there was a strong correlation between these two variables; nodal positivity was dependent on the number of lymph nodes examined. If the nodal status was negative, the baseline risk of lymphedema was 10.9%.

Of the 759 women who underwent ALND, 80% underwent ALND at the time of their breast operation and 20% underwent SLNB followed by a completion ALND at a second operation. Self-reported lymphedema at 4 years was no different between these two groups; lymphedema developed in 23% of the immediate ALND group and 22% of the delayed ALND group ($P = 0.86$).

Relationship between type of breast cancer and risk of lymphedema

Women with DCIS represented 17% of the cohort. Of these women, 31% had lymph nodes removed. Compared to women with invasive breast cancer, women with DCIS had a lower overall risk of developing lymphedema (6.0% vs. 16.4%). However, adjusting for the number of lymph nodes removed as part of their surgical treatment and lymph node status, women with DCIS had the same risk of developing lymphedema as invasive cancer patients (Table 2). Moreover, while there was substantial correlation between DCIS status and the number of lymph nodes removed for the lymphedema outcome, there was no interaction between these two variables. Thus, beyond the two

important predictors (number of lymph nodes removed and lymph node status), lymphedema risk is not affected by the type of breast cancer (DCIS versus invasive cancer).

DISCUSSION

In this contemporary, population-based cohort of over 1,300 older breast cancer survivors treated by a relatively unbiased group of over 700 predominantly community-based surgeons, the overall incidence of self-reported lymphedema at 48 months was 14.4%, which is consistent with previous recent reports.[4, 23] After adjusting for tumor size, surgeon case volume, and various treatment modalities, the only independent predictors of lymphedema in this population-based cohort of older breast cancer women were the removal of an increasing number of lymph nodes and the presence of lymph node metastases. The extent of axillary surgery (specifically the removal of more than five lymph nodes), regardless of whether SLNB or ALND was performed, was the most important predictor of lymphedema. These results are consistent with both older and more recent studies demonstrating that as the number of lymph nodes excised increases, especially after the removal of 10 or more lymph nodes, the incidence of lymphedema increases in an approximately linear fashion.[5-9] These findings can be explained by the iatrogenic disruption and damage of lymphatic channels with more extensive axillary surgery.

Of note, though, is our finding that the removal of only 6-10 lymph nodes is associated with a substantial risk of lymphedema (OR 4.68, 95% CI 1.36-16.08). Furthermore, we found no association between lymphedema and the removal of up to five lymph nodes (OR 2.11, 95% CI 0.65-6.78). One other study with 240 women reported that no patient with fewer than five nodes removed developed either clinical or self-reported concerns for arm swelling.[11] Further studies with larger numbers are

needed to confirm that the removal of up to five lymph nodes is not associated with an increased risk of lymphedema. If confirmed, this finding will be an important consideration when performing SLNB. We advocate that a sufficient number of lymph nodes need to be removed to accurately determine nodal status. However, among women who undergo SLNB and are found to have a positive/metastatic sentinel lymph node, the metastatic sentinel lymph node is identified in the first three sentinel nodes in 97%-100% of patients.[24-26] For patients who undergo SLNB alone, the increased morbidity of removing more than five sentinel lymph nodes may need to be weighed against the possible additional information gained (if a positive node is identified after the fourth or higher sentinel node) that may alter treatment for a small number of patients.

One could postulate that women undergoing more than one axillary operation (SLNB at initial operation then subsequent completion ALND at a second operation) would be at higher risk for lymphedema due to the scarring from the initial operation and additional disruption of lymphatics as a result of a reoperation. In our study, self-reported lymphedema at 4 years was no different between women undergoing ALND at the initial operation and women undergoing completion ALND at a second operation ($P = 0.86$). These findings support those recently published by the American College of Surgeons Oncology Group who evaluated 1,003 participants in their Z0010 and Z0011 trials; there was no difference in lymphedema at any time point up to 1 year between those undergoing immediate ALND versus those undergoing a delayed ALND.[27]

Whether the location of the sentinel lymph nodes in the axilla plays a role in the development of lymphedema has not been addressed. Arm lymphatics are generally described around or just below the axillary vein. A “high” sentinel lymph node may be located in this general area and theoretically removal of “high” sentinel lymph nodes may increase the risk of lymphedema due to disruption of these arm lymphatics. Since our study is retrospective and the location of the sentinel lymph nodes in the axilla is not

known, we cannot examine this possible association between sentinel lymph node location and development of lymphedema. Two recent studies report experiences with axillary reverse mapping in women with breast cancer.[28, 29] These studies show that there are variations in the location of lymphatics that drain the arm versus the breast regions. In some situations, arm lymphatics may be juxtaposed to or overlap with the sentinel lymph nodes. The idea that identification and preservation of these arm lymphatics may decrease the risk for lymphedema in women undergoing axillary surgery is currently being investigated.

Our finding that patients who undergo no axillary surgery or SLNB alone are still at risk for lymphedema (5.7% and 7.2% incidence at 4 years, respectively) is consistent with previous studies,[16-18] emphasizing that SLNB is not without associated morbidity and implying that other factors besides the removal of lymph nodes influences the development of lymphedema. We found no association between the type of axillary surgery performed (none, SLNB, ALND) and self-reported lymphedema. This finding is likely due to the high variability in the number of lymph nodes removed, regardless of axillary procedure performed. The high variability in the number of lymph nodes removed during SLNB is due to the surgeon's experience and SLNB technique. For ALND, the high variability is due to surgeon technique and completeness of pathologic assessment. This analysis by axillary surgery type is limited by Medicare claims billing issues. Using claims, we can identify those who underwent SLNB alone. However, patients who may have undergone SLNB initially and then underwent completion ALND at the same operation cannot be identified as the billing claims for the axillary part of the surgery would be only for ALND. Therefore, we could not perform an "intent-to-treat" analysis with respect to axillary surgery. In any case, we believe that the number of lymph nodes removed, and not the type of axillary surgery performed, is the important predictor of the development of lymphedema.

Our finding that the presence of lymph node metastasis is an independent predictor of lymphedema (OR 1.87, 95% CI 1.29-2.72) was not expected. Some previous studies have reported a similar finding [5, 7] while other studies have not found an association between lymph node status (positive/negative or number of positive nodes) and lymphedema.[6, 8-11] A possible explanation for our finding may be that patients with lymph node metastases were more likely to receive chemotherapy and/or axillary radiation but these effects may not be appreciated due to the relatively small number of patients who received chemotherapy (18% of cohort) and possible axillary radiation therapy. We are unable to identify patients who underwent axillary/regional nodal radiation as radiation therapy billing codes do not differentiate between whether or not the breast, chest wall, and/or regional lymph nodes are treated.

In contrast to previous older studies that involved women who more routinely underwent ALND and axillary radiation therapy,[4, 5] the receipt of radiation therapy in this contemporary cohort was not associated with the development of lymphedema. This lack of association between radiation therapy and lymphedema development is consistent with more recent studies[7-10] and is likely due to more modern radiation techniques that are confined largely to the breast and chest wall and limited use of axillary/regional nodal radiation therapy. Since axillary surgery results in the iatrogenic disruption and damage of lymphatic channels, we hypothesized that surgeon technique may play a role in the development of lymphedema. Surgeon technique, however, cannot be studied directly. By using surgeon case volume as a surrogate for technical expertise, we found no association between surgeon case volume and the development of lymphedema. However, there are significant limitations to using surgeon case volume as a surrogate marker of surgical technique. Another possible limitation of using surgeon case volume derived from Medicare care claims is that it may not be an accurate proxy of overall surgeon volume. However, approximately half of all incident breast cancer

cases occur in women 65 years or older and there is no reason to believe that surgeon case volume would be systematically biased by measuring it in this age group. Other investigators have used this approach to determine surgeon case volume in both cancer and non-cancer operations and hospital case volume for cancer operations and it appears that there is a high correlation between a surgeon's/hospital's Medicare case volume and overall volume for most operations.[30, 31]

As expected, we found no association between patient age, tumor size, type of breast cancer, extent of breast surgery, and receipt of chemotherapy or hormonal therapy with the development of self-reported lymphedema. These findings are also consistent with the majority of recently published studies.[5, 6, 8-10] Compared to women with invasive breast cancer, women with DCIS had a lower overall risk of developing lymphedema (6.0% vs. 16.4%). However, after accounting for the number of lymph nodes removed as part of their surgical treatment and lymph node status, women with DCIS had the same risk of developing lymphedema as invasive cancer patients. Our analysis of age as a risk factor for lymphedema is limited by our older cohort of women (ages 65-89). Our findings can only be applied to older women as results could differ for younger women. Paskett et al. conducted a multi-center study in the United States involving 622 women who were 45 years or younger at the time of breast cancer diagnosis.[9] After adjusting for numerous factors, they found that the receipt of chemotherapy (HR 1.76, 95% CI 1.10-2.82) was an independent predictor of self-reported lymphedema in this young cohort of breast cancer survivors. To our knowledge, this is the only study that reports such an association and may be explained by the more aggressive treatment offered to these younger patients.

A limitation of this study is that lymphedema was measured by self-report. Previous studies have defined lymphedema by self-report.[8-11] In addition, Armer et al. have shown a high predictive ability (*c* = 0.919) between objective measures of swelling

and self-report of arm swelling and heaviness.[32] Several studies have demonstrated that self-reported measures of arm swelling and other symptoms correlate with breast cancer-specific quality of life measures.[21, 33, 34] One potential problem with using self-report of lymphedema is recall bias; however, this is unlikely as the biggest predictor of lymphedema in this study was the removal of more than five lymph nodes; many patients probably would not know how many lymph nodes they had removed.

Perhaps most important is the fact that there is no current standardized definition of lymphedema. Frequently used measures of lymphedema include circumferential measures at various points along the arm, volumetric measures using limb submersion in water, or skin tonometry. However, there is currently no standardization of how and when these measurements should be performed and the reliability of these measures is variable.[4, 23, 35] In addition, arm measurements before surgery are rarely performed, so asymmetric measurements found postoperatively may be attributed to baseline arm differences rather than the development of lymphedema. Furthermore, studies defining lymphedema by one of the above measures may be confounded by lymphedema treatment. Patients with lymphedema who are either not undergoing treatment or receiving inadequate treatment will have abnormal measurements and be determined to have lymphedema. However, patients who are undergoing appropriate therapy for lymphedema will likely have “near normal” measurements and therefore may not be identified as having lymphedema. For these reasons, we believe that the self-report of lymphedema is the most clinically relevant and readily available measure and should be the standard definition of lymphedema for survey studies.

In summary, this study found that the four-year incidence of self-reported lymphedema was 14.4% in a contemporary, population-based, geographically diverse, large cohort of over 1,300 older breast cancer survivors operated on by over 700 predominantly community-based surgeons. The only independent predictors of

lymphedema in this representative cohort of older breast cancer women were the removal of more than five lymph nodes and the presence of lymph node metastases. Future studies with larger numbers of patients will further evaluate the relationship between number of lymph nodes removed, type of axillary surgery, pathologic nodal status and the risk of lymphedema. If it is confirmed that the risk of lymphedema is substantial with the removal of more than five lymph nodes or perhaps even fewer lymph nodes, this finding will be of significant clinical importance for patients undergoing SLNB alone, as the actual number of lymph nodes removed is a modifiable factor that is controlled by the surgeon. As more women with breast cancer undergo only SLNB for nodal staging, it is essential that they still be counseled on their risk for lymphedema.

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Table 1. Characteristics of 1,338 women who underwent initial breast cancer surgery in 2003, by lymphedema category.

Characteristic	Lymphedema (%) N = 193	No Lymphedema (%) N = 1145	*P* Value [a]
Patient Age (years)			0.169
Mean (SD)	71.9 (5.2)	72.9 (5.6)	
65 – 74	70.5	63.8	
75 – 84	27.5	32.8	
85 – 89	2.1	3.4	
Race			0.256
White	88.6	90.6	
Black	2.1	3.1	
Hispanic	6.2	3.4	
Other	3.1	3.0	
Tumor size (mm)			0.005
Mean (SD)	20.0 (19.2)	17.0 (23.5)	
0 – 20	63.7	73.5	
21 – 50	25.9	16.3	
> 50	5.2	3.0	
Missing	5.2	7.2	
Tumor grade			0.532
1	23.3	26.0	
2	42.0	41.5	
3	21.2	18.5	
4	2.6	4.2	
Missing	10.9	9.8	

Tumor stage	7.8	18.3	< 0.0001
0	43.0	54.3	
I	38.9	22.9	
II	6.2	1.7	
III	1.0	0.7	
IV	3.1	2.1	
Missing			
Lymph node status			< 0.0001[b]
Negative	60.1	82.8	
Positive	39.4	15.6	
Not performed	0.5	1.6	
No. lymph nodes examined			< 0.0001[c]
Mean (SD)	10.4 (7.6)	5.5 (6.2)	
0	5.7	18.4	
1 – 5	24.4	44.9	
6 – 10	24.4	16.2	
11 – 15	21.8	12.3	
16 – 25	19.7	6.1	
> 25	3.6	0.7	
Not performed	0.5	1.2	
Type of breast surgery			< 0.0001
Breast-conserving surgery	48.7	68.1	
Mastectomy	51.3	31.9	
Type of axillary surgery performed			< 0.0001
None	7.3	20.3	
Sentinel lymph node biopsy	11.9	25.8	
Axillary lymph node dissection	80.8	52.7	

Missing	0	1.2	
Receipt of radiation therapy			0.101[b]
Yes	60.6	66.7	
No	39.4	33.1	
Missing	0	0.2	
Receipt of chemotherapy			< 0.0001[b]
Yes	29.5	16.2	
No	70.5	83.5	
Missing	0	0.3	
Receipt of hormonal therapy			0.306[b]
Yes	72.5	68.2	
No	26.4	30.2	
Missing	1.0	1.5	
Annualized volume of surgeon's Medicare operations (SD)[d]	10.6 (9.9)	11.6 (11.1)	0.206[c]

Abbreviations: SD, standard deviation.

[a] All *P* values calculated from Pearson chi-square test unless otherwise noted.

[b] *P* value calculated by Fisher's exact test.

[c] *P* value calculated by Mann-Whitney *U*-test.

[d] Volume is averaged over patients, not surgeons. For the 707 surgeons who operated on the entire cohort, the mean annualized volume of Medicare operations per surgeon was 6.9 and the median was 5.4.

Table 2. Variables associated with lymphedema development in multivariate logistic regression analysis.

Variable	Category	Odds Ratio	95% CI	*P* Values
No. lymph nodes examined				**< 0.0001**
	None	1.00		
	1 – 5	2.11	0.65 – 6.78	0.21
	6 – 10	4.68	1.36 – 16.08	**0.01**
	11 – 15	5.61	1.59 – 19.74	**< 0.01**
	≥16	10.50	2.88 – 38.32	**< 0.01**
Lymph node metastasis				**< 0.01**
	No	1.00		
	Yes	1.98	1.21 – 3.24	
Type of breast cancer				0.94
	Invasive cancer	1.00		
	DCIS	1.03	0.41 – 2.60	
Tumor size (mm)				0.89
	0 – 20	1.00		
	21 – 50	1.10	0.69 – 1.75	0.69
	> 50	1.17	0.48 – 2.86	0.73
Type of breast surgery				0.84
	BCS	1.00		
	Mastectomy	0.95	0.56 – 1.61	
Type of axillary surgery				0.46
	None	1.00		
	SLNB	0.67	0.25 – 1.83	0.44
	ALND	0.98	0.39 – 2.46	0.96

Receipt of radiation therapy				0.82
	No	1.00		
	Yes	1.06	0.64 – 1.76	
Receipt of chemotherapy				0.13
	No	1.00		
	Yes	0.66	0.38 – 1.13	
Receipt of hormonal therapy				0.42
	No	1.00		
	Yes	1.18	0.79 – 1.78	
Patient age (years)				0.22
	65 – 74	1.00		
	75 – 84	0.72	0.48 – 1.08	0.11
	85 - 89	0.56	0.16 – 1.97	0.36
Annual surgeon case volume of				0.46
Medicare operations	< 6	1.00		
	6 – 12	0.76	0.49 – 1.18	0.22
	> 12	0.84	0.54 – 1.32	0.45

Abbreviations: ALND, axillary lymph node dissection; BCS, breast-conserving surgery; CI, confidence interval; DCIS, ductal carcinoma in situ; SLNB, sentinel lymph node biopsy.