JOURNAL OF WOMEN'S HEALTH
Volume 12, Number 9, 2003

Factors Associated with Arm Swelling after Breast Cancer Surgery

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ABSTRACT

Purpose: **As life expectancy improves for women with breast cancer, more women will be living with symptoms of lymphedema. This study reports the incidence of arm or hand swelling and associated risk factors in women with invasive breast cancer following surgery.**

Methods: **Data were obtained from baseline and follow-up interviews of women with invasive breast cancer ($n = 145$), and mammography and pathology records. The Kaplan-Meier method was used to estimate the probability of developing arm or hand swelling over time. Univariate and multivariate logistic regression analyses were conducted to identify risk factors for arm or hand swelling.**

Results: **Of women in this study, 38% self-reported arm or hand swelling. There was a significantly increased risk of arm swelling if women were under 50 years of age, had axillary node dissection, received chemotherapy, worked outside the home, and had a high household income. There was no association of body weight with swelling. A significantly decreased risk of arm swelling was found in women who were on treatment for high blood pressure. After adjustment for nodal dissection, only age had a significant independent effect.**

Conclusions: **Our study highlights two important areas of future research that could reduce the incidence of lymphedema. There is a need to better understand the role that treatment for high blood pressure may play in protecting women from arm edema. Second, the potential effect of weight as a modifiable lymphedema risk factor needs to be studied in more detail in light of the conflicting results of different studies.**

INTRODUCTION

Approximately 211,300 women in the United States will be diagnosed this year with breast cancer.[1] As life expectancy improves for women with breast cancer, more women will be living with possible side effects due to treatment for the disease. One of the complications of treatment for breast cancer is lymphedema, an accumulation of protein-rich fluid in the arm as a result of a disruption of axillary lymphatic drainage, causing swelling of the arm, hand, chest. In addition to this physical debilitation, lymphedema has been associated with psychological morbidity.[2] Although the use of sentinel node surgery in place of removing the axillary

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This work was supported by cooperative agreement U01CA70013 from the National Cancer Institute. However, all opinions and findings are the sole responsibility of the authors, and the views expressed do not necessarily represent those of the U.S. government.

nodes may decrease the incidence of arm edema, it will not eliminate this side effect completely.[3]

The true incidence of lymphedema is unknown, although estimates reported in previous studies ranged from 0 to 56% for different populations.[4] The variation in incidence reports may be attributed to the methods used to define and measure lymphedema, the patient populations studied, and the interval between breast cancer diagnosis and the collection of data. Symptoms can start almost immediately after surgery or as late as 30 years after surgery.[5]

Three types of risk factors for breast cancer-related lymphedema have been reported: type of treatment, disease status, and woman-specific characteristics.[6] Treatment-related factors include type of surgery, axillary node dissection, radiation therapy, and chemotherapy. Disease-related factors are stage at diagnosis, tumor size, and nodal involvement. Demographic characteristics, weight or body mass index (BMI), and comorbidity comprise the woman-specific factors related to lymphedema.

In this paper, we report the occurrence of arm or hand edema after the diagnosis and treatment of invasive breast cancer. The cases for this study were drawn from a larger study in which lymphedema was not the focus of the study. We explore the association of various risk factors with the self-reported symptom of arm or hand swelling.

MATERIALS AND METHODS

In the larger study that was designed to measure problems related to breast biopsy, women with malignant and benign breast biopsies were randomly selected from those with breast pathology reports in the Vermont Breast Cancer Surveillance System. A detailed description of the Vermont Breast Cancer Surveillance System can be found elsewhere.[7] In brief, all breast imaging and breast pathology and cytology reports performed in Vermont are sent regularly to the Vermont Breast Cancer Surveillance System. Patients were randomly selected and then invited into this study by their surgeons. Written informed consent was received from each participant before the baseline interview. The Institutional Review Board at the University of Vermont approved the methods used to protect human subjects in this study. Women with a previous history of breast cancer were excluded from the study.

In 1996 and 1997, 343 women (55% participation rate) were interviewed in their homes, 227 of them with breast cancer and 116 with benign breast biopsies. A second telephone interview was done approximately 26 months later with 190 of the women with breast cancer and 94 women with benign breast biopsies. The remaining 37 women with breast cancer were not reinterviewed for the following reasons: 2 had hearing problems, 3 were deceased, 17 declined to participate, 3 subjects' first survey data were unreliable, and 12 were unable to be reached. In the rest of this paper, we report mainly the results of the 145 women diagnosed with invasive breast cancer who completed both interviews. Initial interviews were conducted an average of 9.7 months (range 6–21 months) from the date of biopsy diagnosis, and follow-up telephone interviews were conducted an average of 26.0 months (range 19–40 months) after the breast biopsy. Interviewers were uniformly trained by one staff member. Some demographic and breast cancer risk information was collected prospectively at the mammography visit just prior to the breast biopsy. Information about the types of surgery and other treatments was collected at the first interview. In addition, we used data from the pathology reports following surgery to confirm or correct the self-reported data and to complete missing information.

Questions about arm or hand swelling and subsequent treatment were asked at the follow-up interview. Women were asked, "Since the time your breast problem was diagnosed, have you had any arm or hand swelling of either your arm or hand?" followed by, "If yes, which side?" and "When did the swelling begin?" This information was used to calculate how long after surgery the symptoms developed. Women who experienced swelling were also asked if they still had swelling and, if not, when it stopped. Additional questions pertained to the types of treatment they received for arm or hand swelling.

Statistical analysis

Several statistical tests were used in this analysis. The Kaplan-Meier method was used to estimate the probability of developing arm or hand swelling over time. Women were grouped according to whether or not they reported arm or hand swelling by the time of their follow-up interview to understand the association of types of treatment, disease status, and woman-specific characteristics with the occurrence of lymph-

edema. Differences between groups with regard to interval-scale measures, including maximum dimension of tumor, age, height, weight, and BMI, were assessed with two-sample *t*-tests. Pearson's chi-square tests or Fisher's exact tests were used to assess the association of swelling with categorical variables, including the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) cancer stage, axillary node dissection, axillary node status, type of surgery, receipt of radiation and chemotherapy, concurrent treatment for high blood pressure, ethnicity, education, household income, employment, and marital status. The construct validity of self-report was examined by comparing the incidence of reported arm swelling among women with benign biopsies, carcinoma *in situ* (CIS), and invasive cancers and by comparing the laterality of the breast cancer to the laterality of arm swelling. All tests were two-sided and were considered statistically significant at $p < 0.05$.

Univariate odds ratios (OR) were estimated by logistic regression. A risk factor was considered significant if the associated 95% confidence interval (95% CI) did not include one. Because axillary node dissection is a recognized cause of lymphedema, it was included in subsequent models as a control variable to examine if the effect of each of the remaining risk factors could be due to its association with axillary node dissection. Models with interaction terms were fitted to test for an interaction between the effects of axillary node dissection and each risk factor. Factors that were statistically significant after adjustment for axillary node dissection were included together in a multivariate logistic regression model to assess their independent effects on lymphedema risk.

RESULTS

Thirty-eight percent (55 of 145) of women with invasive breast cancer reported arm swelling compared with only 3.2% (3 of 94) of women with benign disease and 1.8% (1 of 45) of women with CIS. The self-reported laterality of arm swelling was perfectly correlated to the laterality on biopsy, with 3 women having missing information regarding laterality of swelling. Time from surgery to first onset of swelling is shown in Figure 1 for the women with invasive cancer. Of the 55 women who reported swelling, 49 provided date of first occurrence of symptoms, and for these women, mean time to onset of symptoms was 10.4 months after surgery (range 0–35 months). A Kaplan-Meier survival analysis was performed to estimate the probability of developing arm or hand swelling among invasive cancer patients, treating the time between surgery and follow-up interview for the women who reported no swelling as right-censored observations. As shown in Figure 1, the estimated probability of developing arm or hand swelling within 1 year is 0.18 and within 2 years is 0.35. Also, note that the cumulative probability plot flattens at 27 months, reflecting censored observations from women who had not developed swelling symptoms at the time of the follow-up interview.

Seventy-eight percent of the women who reported swelling were still experiencing it at the time of the interview, and their symptoms had lasted from 1 to 32 months (mean 17 months). There were 12 women whose symptoms had stopped, but only 6 could remember both when their swelling began and when it ended. The average duration of swelling for these women was 2 months. Nine of the women not experiencing swelling at the time of the interview could recall when their symptoms had started, and only 1 had an onset within the first year following surgery. Sixty-five percent of all the women who reported swelling had received treatment for lymphedema, 66% of those still experiencing symptoms and 58% of those whose symptoms had stopped.

Table 1 presents mean values of woman-specific and disease characteristics measured on interval scales for women with and without swelling. Only age at diagnosis differed significantly between the two groups, with the mean age of women reporting symptoms (49.7) being about 10 years younger than the mean age of women with no swelling (59.5). There were no significant differences in height, weight, BMI, or tumor size. All the women in the study were Caucasian.

Table 2 shows the proportion of women having swelling by woman-specific, disease-related, and treatment-related characteristics. Sample sizes do not total to 145 for some characteristics because women either could not supply the requested information or declined to do so. There was a significantly increased risk of arm swelling if women were <50 years of age, had axillary node dissection, received chemotherapy, worked outside the home, and had a high household income. A significantly decreased association with arm swelling was found in women who were in treatment for high blood pressure. The corre-

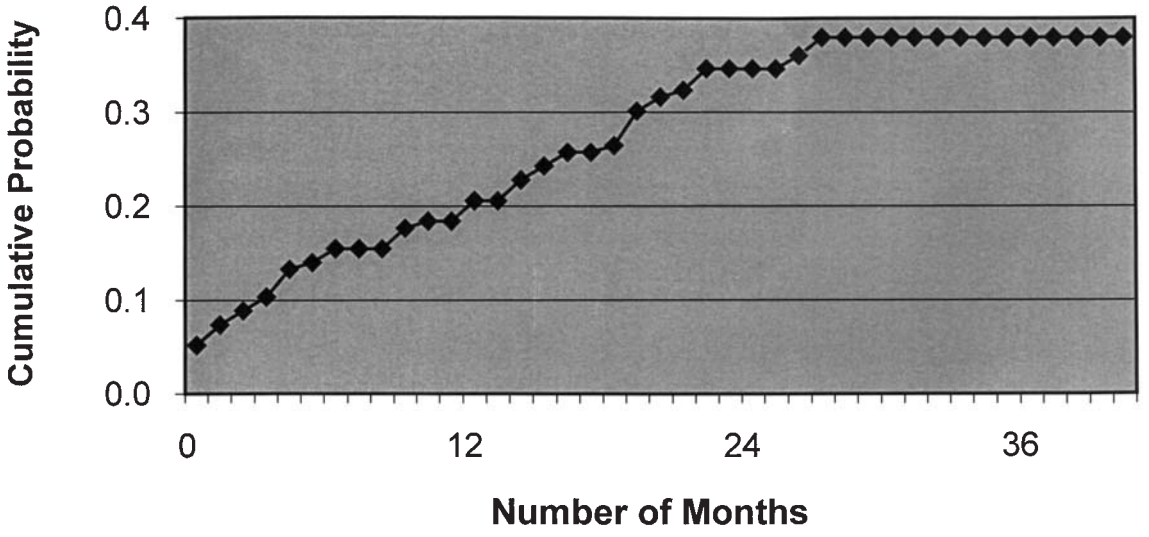

FIG. 1. Time from surgery to swelling among women with invasive breast cancer. Kaplan-Meier estimated probability of women self-reporting the development of arm swelling over time.

sponding univariate ORs are presented in Table 3, together with the ORs after adjustment for the effect of axillary node dissection. As indicated by the adjusted ORs, only age remained statistically significant after controlling for axillary node dissection. There were no significant interactions between the effects of axillary node dissection and each of the other risk factors. When axillary node dissection, age, treatment for high blood pressure, and household income were included together in a logistic regression model, only age had a significant independent effect.

DISCUSSION

Arm or hand edema is a serious side effect from treating breast cancer. Our observational results confirm some previously published findings and contradict others. This discussion focuses on comparing our results to other studies and pointing out the differences and similarities among the studies. Because the time since treatment, study population, and measurement used to define lymphedema vary so widely in the published studies, the incidence and the predictive factors also have varied. Results can vary because studies with differing sample sizes do not have the same statistical power to detect associations between predictive factors and lymphedema. With 143 women and a cumulative incidence of 38%, our study had 80% power to detect associations corresponding to relative risks (*RR*) of about 3.0 for most predictors but had lower power for detecting weaker associations.

Table 1. Personal and Disease Characteristics of Women with Invasive Breast Cancer: Comparison of Women with and without Arm Swelling

Characteristic	*Swelling* n = *55* *mean (SD)*	*No swelling* n = *90* *mean (SD)*	p *value*[a]
Age (years)	49.7 (8.5)	59.5 (12.4)	< 0.01
Height (inches)	64.1 (3.0)	64.4 (2.5)	0.51
Weight (pounds)	153.3 (38.9)	155.6 (30.9)	0.69
BMI (kg/m^2)	26.1 (5.4)	26.4 (5.0)	0.75
Tumor size (cm)	2.2 (1.5)	2.1 (1.6)	0.69

[a]*p* value of two-sample *t*-test.

Table 2. Percent of Women with Arm Swelling by Personal Characteristics, Procedures, and Treatments

Characteristic	*Total* n *in category*	*Swelling* n	*Swelling* (%)	p *value*[a]
Axillary node dissection				
No	20	1	(5.0)	
Yes	125	54	(43.2)	< 0.01
Axillary node status				
Positive	54	26	(48.1)	0.36[b]
Negative	71	28	(39.4)	
Type of surgery				
Breast conserving	90	31	(34.4)	
Mastectomy	55	24	(43.6)	0.29
Radiation therapy				
No	47	13	(27.7)	
Yes	98	42	(42.9)	0.10
Chemotherapy				
No	68	19	(27.9)	
Yes	77	36	(46.8)	0.03
SEER stage				
Local	76	26	(34.2)	0.13[b]
Regional/distant	52	24	(46.1)	
Unknown	17	5	(29.4)	
Age (years)				
≥ 50	93	25	(26.9)	
< 50	52	30	(57.7)	< 0.01
Education				
<High school	6	4	(66.7)	0.37
High school	39	15	(38.5)	
>High school	100	36	(36.0)	
Household income				
<$50,000	90	27	(30.0)	0.02
≥$50,000	51	26	(51.0)	
Working outside the home				
No	60	17	(28.3)	
Yes	85	38	(44.7)	0.05
Married (%)				
No	44	12	(27.3)	
Yes	100	42	(42.0)	0.09
BMI (kg/m^2)				
< 25.0	65	27	(41.5)	0.69
25.0–29.9	42	14	(33.3)	
≥ 30.0	28	11	(39.3)	
Treated for high blood pressure				
No	117	51	(43.6)	
Yes	28	4	(14.3)	< 0.01

[a]*p* value of chi-square or Fisher's exact test for association between characteristic and swelling group.
[b]Unknown category excluded from statistical analysis (*n* varies with each variable because of missing data).

Cumulative incidence

Symptoms of lymphedema can begin almost immediately after surgery, or they can be delayed as long as 30 years, so the cumulative incidence depends on the period of time over which women are followed and the method used to estimate incidence. In a study of women with early stage breast cancer by Kiel and Rademaker,[8] the cumulative incidence of lymphedema was 8% at 1 year and 35% after a median time of 20 months follow-up (range 6-72 months). We estimated a higher cumulative incidence (18%) at 1 year, but our Kaplan-Meier estimate of the cumulative incidence at 2 year was 35%, agreeing well with the findings of Kiel and Rademaker at 20 months.

Table 3. Risk Factors for Lymphedema among Women with Invasive Breast Cancer

Factor	Unadjusted OR[a]	(95% CI)	Adjusted[b] OR	(95% CI)
Axillary node dissection				
No	1.0	—		
Yes	14.5*	(1.81 − 111.3)		
Type of surgery				
Breast conserving	1.0	—	1.0	—
Mastectomy	1.5	(0.7 − 3.0)	1.1	(0.6 − 2.3)
Radiation therapy				
No	1.0	—	1.0	—
Yes	2.0	(0.9 − 4.2)	1.7	(0.8 − 3.8)
Chemotherapy				
No	1.0	—	1.0	—
Yes	2.3*	(1.1 − 4.6)	1.5	(0.7 − 3.1)
SEER stage				
Local	1.0	—	1.0	—
Regional/distant	1.7	(0.8 − 3.4)	1.2	(0.6 − 2.5)
Age (years)				
≥ 50	1.0	—	1.0	—
< 50	3.7*	(1.8 − 7.6)	3.1*	(1.5 − 6.5)
Household income				
< $50,000	1.0	—	1.0	—
≥ $50,000	2.4*	(1.2 − 5.0)	1.9	(.9 − 4.1)
Working outside the home				
No	1.0	—	1.0	—
Yes	2.0	(1.0 − 4.2)	1.5	(0.8 − 3.4)
Married				
No	1.0	—	1.0	—
Yes	1.9	(0.9 − 4.2)	1.5	(0.6 − 3.3)
Treated for high blood pressure				
No	1.0	—	1.0	—
Yes	0.2*	(0.07 − 0.7)	0.3	(.09 − 1.0)

[a]OR, odds radio; CI, confidence interval.
[b]Odds ratio for each risk factor adjusted for axillary node dissection.
*$p \leq 0.05$.

Our results were also consistent with those of Bosompra et al.,[9] who interviewed Vermont women 3–4 years after surgical treatment of breast cancer and found that 35% noticed swelling in an area related to surgery with up to 4 years follow-up time, and the cumulative incidence of 39% from a recently published Australian study with follow-up of 4 or more years.[10] In a study that followed women for 15 years after treatment with surgery and radiation therapy, at 0–2 years, 23% of the women had symptoms of lymphedema, and at 12–14 years, 35% had symptoms.[11] Another study with long-term follow-up reported a cumulative incidence of 49% reported in women followed for 20 years.[12] A higher cumulative incidence was reported by Gerber et al.,[13] who found that 40% of the 131 women studied had an increase in arm circumference of 2 cm or greater compared with the contralateral arm (a common definition of lymphedema) at 1 year after surgery, and at the 2-year follow-up, 57% of 69 women had this increase.[13] Most studies report only the crude incidence, which does not take into account variation in the length of follow-up for different women, and this will account for some of the discrepancies in cumulative incidence between studies.

Defining lymphedema

Self-report of symptoms of swelling is an easier tool than clinical measures for physicians to use to diagnose lymphedema and make appropriate referrals for treatment. Although there have been some studies to validate self-report questions and correlate the results of self-reported symptoms with clinical measures, research is needed to be more precise. There are at

least two ways to clinically measure lymphedema, arm circumference measurements and water displacement volumetry, and several ways to interpret the results of these measures.[14–16] Self-reported edema has also been measured using a variety of questions.[17] In addition, self-report and objective measures do not always agree. In fact, objective measures may not be sensitive enough to pick up subtle changes that cause symptoms or may be measuring effects that cause no symptoms. In two studies that compared clinical measurement with self-reported symptoms, the incidence of lymphedema seemed to be underestimated clinically (more women reported symptoms than were diagnosed with an objective measure).[18,19] In another study, patients tended to underreport symptoms when compared with objective measures. Kissan et al.[14] found that 9% of the patients who had clinical measures of lymphedema did not report symptoms.

A limitation of our study is that we did not have objective measures to compare with the self-reported data. In our study, to explore the construct validity of the self-reported measure, we correlated women's self-report of the laterality of their arm swelling with the side of the surgery that was substantiated with the pathology report. We found that it corresponded precisely. We obtained information about when the swelling started, how long it persisted, and whether or not it had been treated but not about its severity. Most of the women were still experiencing swelling at the time of the interview 19–40 months after breast cancer diagnosis, indicating it was not a transient problem associated with surgery or radiation. This is a possibility for a few of the women who were no longer experiencing symptoms, but we did not have enough information to make this determination and, therefore, included in our analysis all women who reported swelling.

Women-specific factors

No other published study we are aware of examined the use of medications for treatment of comorbidities and their relationship to arm swelling. We asked about treatment for several health conditions and found that treatment for hypertension was a significant protective factor for arm or hand swelling in the univariate analysis and approached significance in the adjusted OR. A study conducted in Germany found that women with high blood pressure had a higher rate of lymphedema than women with normal blood pressure.[6] The German study measured whether or not the women had high blood pressure but did not report if they were on medications, whereas we asked about if women were treated for high blood pressure. It could be that by lowering the blood pressure, less fluid leaks out through the capillaries than would have done so had the high blood pressure not been treated. An alternative explanation is that women with axillary deep venous thrombosis, a rare occurrence caused by axillary dissection or possibly radiation to the axilla, are more likely to develop lymphedema because high venous pressure can cause an increase in the intralymphatic system and lead to retrograde lymphatic flow. Some types of blood pressure medications, aimed at lowering arterial pressure, may also lower venous pressure. Two studies suggest that diurectics have little if any benefit for treating lymphedema.[20,21] It may be that treatment for hypertension is a protective factor in the development of arm edema, but once the edema exists, diuretics are unable to satisfactorily treat the symptoms. Our results warrant further investigation of this issue.

Height, weight, and BMI were not related to arm or hand swelling in our study. In fact, we did not observe a linear relationship of BMI with risk, as shown in the study by Werner et al.,[22] in which the higher the BMI, the greater the chance of arm edema. Werner et al. found both BMI and weight were associated with lymphedema in a univariate analysis. However, in a multivariate analysis, none of the variables (BMI, height, weight, brassiere and cup size, clinical T stage, nodal involvement, and use of adjuvant systemic treatment) were significant. Segerstrom et al.[23] and McCredie et al.[10] found that being overweight correlated with edema and Segerstrom et al. surmised that increased weight may lead to an increase in radiation dose, which may be associated with lymphedema. As obesity is a risk factor for delayed wound healing and infection, it would be helpful to control for infection and radiation dose in future analyses that look at weight as a predictor variable.

Our measurements of height and weight were collected at the time of the mammogram that preceded the diagnosis of breast cancer. Women have been known to gain weight after the treatment of breast cancer,[24] and most of the other studies acquired height and weight data after

treatment for breast cancer, at the same time that information about lymphedema was collected.[19,23] Petrek et al.[12] found that women who gained more than 10 pounds since diagnosis were more likely to develop lymphedema than women who lost weight or had no weight change. Perhaps it is an increase in weight after treatment for breast cancer and not absolute weight that is associated with the risk of lymphedema. As weight may be a modifiable risk factor, it is important to continue to study its role in the development of lymphedema.

Two demographic variables that have not been previously studied were found in our study to be significantly related to arm or hand swelling before adjusting for axillary node dissection. Our univariate analysis showed that women who worked outside the home and women whose household income was $\geq$ \$50,000 were significantly more likely to report arm or hand swelling, although when we controlled for axillary node dissection, these variables were no longer significant. Women who work outside the home may be younger, have higher household incomes, and may use their arms more.

The relationship of the age of the woman to edema varied in many studies. Being a younger woman (<50) in our study was highly correlated with reporting symptoms. Kiel and Rademacker[8] found that clinical measurements suggest that older age (>55) is a risk factor. Tengrup et al.,[18] Edwards,[19] and McCredie et al.[10] found no correlation with age, whereas Warmuth et al.[25] stated that younger women report more symptoms than older women and, similar to our findings, that younger age was associated with arm swelling.

Treatment-related factors

Breast cancer treatments have been found to be inconsistent predictors of developing lymphedema. Although axillary node dissection appears to be the best predictor of lymphedema in our study as well as others, women without axillary node dissection report symptoms of arm or hand swelling. A study using self-report of arm edema found that 21.9% of women without axillary node dissection reported swelling.[10] In a study that used clinical measures, 10% of the women with lymphedema did not have axillary node dissection.[14] Our study found that only 1 woman without axillary dissection reported swelling (5%). This woman had a mastectomy and had not received either radiation or chemotherapy.

Another type of treatment, radiation therapy, was not associated with swelling in our study. Several studies did not find that radiotherapy affected arm symptoms during the first 3 years after surgery.[19,26] Mortimer et al.[11] found a relationship between lymphedema and radiation therapy only after 3 years following surgery that grew stronger over time (up to 15 years). Segerstrom et al.[23] did not find that having an axillary node dissection without irradiation was the main risk factor for the edema but did find that the arm edema was related to receiving high-dose radiation with few fractions directly to the axilla.[23] Our study is limited to less than 3 years of follow-up, and we did not have radiation dosage or location of beams. Therefore, our findings are neither unexpected nor different from previously published studies.

Our study found no relationship between arm swelling and two other treatments, type of surgery and receipt of chemotherapy, after adjusting for axillary dissection. Two studies found that women who had a mastectomy with axillary sampling or dissection were more likely to have lymphedema than women who received a lumpectomy with axillary node dissection,[11,19] yet in two other studies, with results similar to our findings, there was no significant difference between these two groups.[10,13] Unlike our study, Kiel and Rademacher[8] found that women were less likely to develop edema after chemotherapy, but their study included ductal CIS (DCIS) cases that were not likely to be treated with chemotherapy. At the other extreme, Werner et al.[22] found no treatment related factors associated with arm edema.

Disease-related factors

In both the univariate and multivariate analyses, we found no disease-related factors, such as axillary node status or stage at diagnosis associated with swelling. These findings confirm the findings of Warmuth et al.[25] but contradict the findings of Kissan et al.[14] and Werner et al.[22] that showed a late stage at diagnosis was associated with increased risk of lymphedema. Werner et al.[22] found that positive nodes and clinical tumor stage were significantly related to arm edema in a univariate analysis but were not significant in the multivariate analysis.

Study population

The incidence will change if *in situ* cancer cases are included with invasive cancer because most women with an *in situ* diagnosis do not have their axillary nodes removed. One study included DCIS,[8] whereas others were not explicit about whether they included noninvasive cancers.[10,11,18,19,23] We found that in the 45 women with DCIS in our study, only 1 woman (1.8%) reported arm or hand edema. If we had included DCIS cases, the incidence in this study would have decreased from 38% to 29%. Other population characteristics, such as age, were discussed earlier.

CONCLUSIONS

Our study adds to the growing body of research focused on understanding the incidence and etiology of lymphedema. Based on our study, there are three important areas of future research to pursue because they could reduce the incidence of lymphedema. The role that treatment for high blood pressure may play in protecting women from arm edema needs further study. Second, the potential effect of weight, weight gain, and BMI as a modifiable risk factor for lymphedema needs to be studied in more detail in light of the conflicting results of different studies. Finally, it is clear that there is a need for validation of self-reported and clinically significant lymphedema.

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