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ORIGINAL REPORT

# Lymphedema in Breast Cancer Survivors: Incidence, Degree, Time Course, Treatment, and Symptoms

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## ABSTRACT

### Purpose
To examine the incidence, degree, time course, treatment, and symptoms of lymphedema in breast cancer survivors.

### Methods
We conducted a 5-year, population-based prospective study of 631 randomly selected Philadelphia and Delaware County, Pennsylvania female residents with incident breast cancer who were diagnosed from 1999 to 2001. Using a questionnaire previously validated against physical therapists' measurement-based clinical criteria, we assigned a score indicating the degree of lymphedema (none, mild, or moderate/severe) to each month of follow-up based on the respondent's perceived differences in hand/arm size. Standard survival analysis methods permitted maximum use of follow-up.

### Results
Five-year cumulative incidence of lymphedema was 42 (42%) per 100 women. Among the 238 affected women, lymphedema first occurred within 2 years of diagnosis in 80% and within 3 years in 89%. Among 433 women observed for 3 years, 23% reported no more than mild lymphedema, 12% reported moderate/severe lymphedema, and 2% reported chronically moderate/severe lymphedema. Women with mild lymphedema were more than three times more likely to develop moderate/severe lymphedema than women with no lymphedema. Thirty-seven percent of women with mild lymphedema and 68% with moderate/severe lymphedema received treatment. Increasing proportions of women with increasing degree of lymphedema reported symptoms (eg, jewelry too tight, tired/thick/heavy arm). Symptoms present before the first occurrence of lymphedema were associated with a higher probability of later lymphedema (eg, hazard ratio for jewelry too tight = 7.37; 95% CI, 4.26 to 12.76).

### Conclusion
Lymphedema after breast cancer is common but mostly mild. Subtle differences in self-reported hand/arm size and symptoms can be early signs of progressing lymphedema.

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## INTRODUCTION

Although lymphedema is considered one of the most distressing and debilitating complications of breast cancer treatment,[1-5] its incidence, degree of swelling, time course, and symptoms are not well understood.[6] Most prior studies have been retrospective, limited to single institutions, and lacking data on the time course of lymphedema.[4,7-10] Among recent prospective studies,[11-18] few are population-based, limiting generalizability.[12,17] Inconsistencies in measuring and defining lymphedema remain barriers to research and reporting.[4,9,19,20] Limb circumference and volume are most commonly used,[19,21] but there are no consistent measurement-based criteria for diagnosis.[4,7-9,19-22] Clinicians and researchers have emphasized the importance of patient self-report,[8,19,21,23,24] which is increasingly used, alone or combined with arm measurement, to study lymphedema.[12,15-17,25-29] We observed a population-based random sample of women with incident breast cancer over 5 years using a validated questionnaire to estimate the incidence, degree, and time course of lymphedema along with associated treatment and symptoms.

## METHODS

### *Study Population*

After institutional review board approvals, residents of Philadelphia and Delaware Counties in Pennsylvania with first diagnosis of histologically confirmed primary

 

**Table 1.** Study Participants Available by Year of Follow-Up and Age at Breast Cancer Diagnosis

| | Age < 50 Years (n = 199) | | Age 50-79 Years (n = 366) | | Age 80+ Years (n = 84) | | All Participants (N = 649) | |
|---|---|---|---|---|---|---|---|---|
| Year of Follow-Up | No. of Participants | % | No. of Participants | % | No. of Participants | % | No. of Participants | % |
| Eligible at start of follow-up* | 196 | 100 | 354 | 100 | 81 | 100 | 631 | 100 |
| Start of year 2 | 181 | 92 | 338 | 95 | 77 | 95 | 596 | 94 |
| Start of year 3 | 164 | 84 | 308 | 87 | 65 | 80 | 537 | 85 |
| Start of year 4 | 138 | 70 | 256 | 72 | 39 | 48 | 433 | 69 |
| Start of year 5 | 133 | 68 | 238 | 67 | 34 | 42 | 405 | 64 |
| End of year 5 | 119 | 61 | 219 | 62 | 24 | 30 | 362 | 57 |

*Eighteen enrolled participants were found to be ineligible at start of follow-up because there was no unaffected comparison side and lymphedema could not be evaluated, including 17 participants who had simultaneous bilateral mastectomies at the reference date (histologic confirmation of breast cancer diagnosis) and one participant with a pre-existing size difference affecting the entire arm. Among the 631 remaining eligible study participants, an additional six participants recalled a size difference in their hand, lower arm, or upper arm that preceded their breast cancer diagnosis. Five of these six participants had pre-existing size differences in only one part. These pre-existing size differences were not used to calculate incidence of lymphedema, although these six women contributed to estimating incidence rates based on the parts of the arm that were the same at diagnosis.

breast cancer (invasive or in situ) from May 1, 1999 to September 30, 2001 were identified from 30 (of 39) hospitals estimated to treat 95% of all newly diagnosed breast cancer patients residing in these counties (B. Wright, personal communication, April 2000). We then chose an age-stratified (< 50, 50 to 79, and 80+ years) random sample of potential participants, beginning with a 33% sample and subsequently increasing sampling fractions up to 100% for the youngest and oldest groups to ensure adequate representation. Eligible women were English speaking, physically and mentally capable of being interviewed, and household residents.

### *Data Collection*

Physician permission was obtained before patient contact; all participants provided written informed consent for interviews and medical records review. The first interview was in person, followed by telephone interviews scheduled approximately 7 to 9 months apart. This interval was chosen to maximize recall accuracy across the interview period and to minimize response burden and selective dropouts. The study was funded for 2 years of follow-up and then for 3 more years.

### *Assessing Lymphedema*

To assess presence and degree of lymphedema, we developed a structured questionnaire and scoring system that we validated against expert physical therapists' measurement-based clinical criteria.[7] At the first interview, respondents were asked whether, between the month/year of breast cancer diagnosis (the reference date) and the interview month/year, their right and left hands seemed to differ in size. Subsequent interviews covered the time period back to the previous interview (interview period). The question was repeated for the lower and upper arms separately. No difference was assigned a degree score of 0. Women noting differences rated them as follows: "1: very slight; you are the only person who would notice this"; "2: noticeable to people who know you well but not to strangers"; or "3: very noticeable." The degree score was summed over the three locations and could range from 0 to 9, resulting in the following categories: any lymphedema = degree score of more than 0 and limb on side of surgery larger; mild lymphedema = degree score of 1 to 3; and moderate/severe lymphedema = degree score of 4 to 9. A score of $\geq 4$ required size differences at two or more locations because the largest score possible at any one location was 3. Months in which lymphedema was reported were recorded. Respondents were asked whether a health professional was consulted about the size difference; what, if any, treatments were prescribed; the date treatment started; and whether treatment was ongoing.

### *Lymphedema Symptoms*

We adapted the format of the Memorial Symptom Assessment Scale[30] to study symptoms of lymphedema.[7] Symptoms were not used to assess lymphedema but to better understand the lymphedema experience by examining symptoms according to degree of lymphedema, including none. At each interview, all study participants, regardless of reported size differences, were asked whether jewelry or clothing were too tight, whether they could not see the knuckles or veins in the hand, and whether they noted puffiness, indentations, pain, firm or leathery skin, tiredness, thickness, heaviness, swelling after exercise, or difficulty writing. For each symptom noticed, patients indicated the side and rated its frequency (1 = rarely to 4 = almost constantly), severity (1 = slight to 4 = very severe), and level of associated distress (0 = not at all to 4 = very much). Responses to symptom questions were assigned to the entire interview period because symptom start and stop dates were not asked.

**Table 2.** Incidence of Lymphedema by Year and Cumulative Incidence of First Occurrence of Lymphedema by Age Group at Breast Cancer Diagnosis, by All Ages Combined, and Weighted to the Breast Cancer Population of Philadelphia and Delaware Counties During 1999 to 2001

| | Age < 50 Years | | | Age 50-79 Years | | | Age 80+ Years | | | All Patients | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Year | No. of New Lymphedema Diagnoses | No. of Participants at Risk at Start of Year* | Cumulative Incidence† | No. of New Lymphedema Diagnoses | No. of Participants at Risk at Start of Year | Cumulative Incidence | No. of New Lymphedema Diagnoses | No. of Participants at Risk at Start of Year | Cumulative Incidence | No. of New Lymphedema Diagnoses | No. of Participants at Risk at Start of Year | Cumulative Incidence | Weighted‡ Cumulative Incidence |
| Year 1 | 59 | 196 | 0.31 | 86 | 354 | 0.25 | 15 | 81 | 0.19 | 160 | 631 | 0.26 | 0.25 |
| Year 2 | 12 | 124 | 0.38 | 16 | 253 | 0.30 | 3 | 61 | 0.23 | 31 | 440 | 0.31 | 0.30 |
| Year 3 | 8 | 102 | 0.43 | 12 | 215 | 0.34 | 0 | 49 | 0.23 | 20 | 366 | 0.36 | 0.34 |
| Year 4 | 6 | 82 | 0.47 | 11 | 171 | 0.38 | 0 | 29 | 0.23 | 17 | 282 | 0.40 | 0.38 |
| Year 5 | 4 | 74 | 0.50 | 5 | 150 | 0.40 | 1 | 25 | 0.26 | 10 | 249 | 0.42 | 0.41 |

*Denominators are reduced by loss to follow-up and by censoring at time of first lymphedema occurrence.
†Cumulative incidence using standard survival analysis methods.
‡Weighted by age distribution of breast cancer population of Philadelphia and Delaware Counties.

**Table 3.** Time Course of Lymphedema* in First 3 Years of Study Among 433 Respondents With 3 Full Years of Follow-Up

| Lymphedema | Respondents | | Month of First Lymphedema | | | No. of Person-Months With Lymphedema Present | | |
|---|---|---|---|---|---|---|---|---|
| | No. | % | Mean | Median | Range | Mean | Median | Range |
| No lymphedema | 283 | 65.4 | | | | | | |
| Any lymphedema | 150 | 34.6 | 8.5 | 5 | 0-33 | 17.4 | 15.5 | 2-36 |
| Acute mild† | 24 | 5.5 | 13.4 | 13.5 | 2-33 | 3.6 | 3.5 | 2-5 |
| Chronic mild† | 20 | 4.6 | 16.5 | 18 | 0-30 | 19.5 | 18 | 6-36 |
| Improving: mild → none† | 30 | 6.9 | 6.3 | 4.5 | 0-21 | 12.6 | 11 | 6-27 |
| Wax/wane: mild ⇆ none† | 26 | 6.0 | 4.7 | 4 | 0-15 | 19.0 | 18.5 | 5-30 |
| Acute moderate/severe | 2 | 0.5 | 18 | 18 | 4-32 | 4 | 4 | 4-4 |
| Chronic moderate/severe | 10 | 2.3 | 9.1 | 7 | 1-25 | 26.9 | 29 | 11-35 |
| Improving: moderate/severe → mild/none | 4 | 0.9 | 2.8 | 2.5 | 0-6 | 24.5 | 26 | 10-36 |
| Progressing: mild → moderate/severe | 10 | 2.3 | 9.4 | 6.5 | 0-27 | 26.5 | 29.5 | 8-36 |
| Wax/wane: moderate/severe ⇆ mild/none (regardless of initial degree) | 24 | 5.5 | 3.3 | 2 | 0-22 | 26.1 | 27 | 14-35 |

*Any lymphedema was defined as a degree score greater than 0 and the limb on the side of surgery was larger. Mild lymphedema was defined as a degree score of 1 to 3. Moderate/severe lymphedema was defined as a degree score of 4 to 9.
†Lymphedema did not progress beyond mild.

### *Data Analysis*

Each woman's follow-up period was divided into months (0 to 59 months) from the reference date, and exposures or events were converted from calendar time into months from that date. A lymphedema degree score was assigned to every month based on when a size difference was first noticed, whether the difference was ongoing at the interview, and, if not, the month the difference disappeared.

Incidence of lymphedema by year and cumulative incidence of first occurrence of lymphedema were calculated using standard survival analysis methods to accommodate loss to follow-up.[31,32] Once a participant reported a size difference, she no longer contributed person-months to the calculation of incidence, although she continued to be interviewed. If, during follow-up, a woman was diagnosed with breast cancer or had a mastectomy or lymph node surgery on the side opposite to the original surgery, data on past exposures and outcomes were retained, but further follow-up was ignored for calculating incidence because there was no longer an unaffected side for comparing sizes.

To describe patterns of lymphedema within persons over time, we focused on the first 36 months of observation among respondents completing at least 3 full years of follow-up. Unlike calculations of cumulative incidence, this analysis started with the onset of lymphedema and described one of five mutually exclusive time courses, as follows (rare episodes lasting only 1 month were ignored): acute = a single episode of all mild or all moderate/severe lymphedema lasting 2 to 5 months; chronic = a single episode of all mild or all moderate/severe lymphedema lasting ≥ 6 months with the observation interval ending with lymphedema; improving = a single episode of lymphedema lasting ≥ 6 months with moderate/severe lymphedema followed by mild or no lymphedema or with mild lymphedema followed by no lymphedema; progressing = a single episode of lymphedema lasting ≥ 6 months with mild

**Table 4.** Treatment for Lymphedema in First 3 Years of Follow-Up Among the 150 Respondents With Any Lymphedema in the First 3 Years: Overall and by Time Course

| Degree of Lymphedema | No. of Respondents With Lymphedema | Talked to Provider | | Received Treatment* | | Treatment Intervention (No. of respondents) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No. of Respondents | % | No. of Respondents | % | Exercise | Wrap | Sleeve | Pump | Elevation | Medication | Massage | Other |
| Any lymphedema | 150 | 119 | 79.3 | 71 | 47.3 | 55 | 28 | 37 | 8 | 40 | 23 | 47 | 16 |
| Mild lymphedema | | | | | | | | | | | | | |
| Acute mild† | 24 | 15 | 62.5 | 10 | 41.7 | 7 | 1 | 3 | 1 | 4 | 2 | 8 | 5 |
| Chronic mild† | 20 | 13 | 65.0 | 7 | 35.0 | 1 | 2 | 4 | 0 | 3 | 2 | 3 | 0 |
| Improving: mild → none† | 30 | 20 | 66.7 | 6 | 20.0 | 4 | 2 | 3 | 0 | 4 | 3 | 5 | 2 |
| Wax/wane: mild ⇆ none† | 26 | 24 | 92.3 | 14 | 53.8 | 11 | 1 | 4 | 0 | 5 | 8 | 8 | 3 |
| Moderate/severe lymphedema | | | | | | | | | | | | | |
| Acute moderate | 2 | 2 | 100.0 | 0 | 0.0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Chronic moderate | 10 | 9 | 90.0 | 6 | 60.0 | 5 | 3 | 3 | 1 | 5 | 1 | 5 | 0 |
| Improving: moderate/severe → mild/none | 4 | 4 | 100.0 | 4 | 100.0 | 4 | 2 | 3 | 1 | 4 | 1 | 1 | 2 |
| Progressing: mild → moderate/severe | 10 | 8 | 80.0 | 6 | 60.0 | 6 | 5 | 4 | 1 | 4 | 1 | 4 | 0 |
| Wax/wane: moderate/severe ⇆ mild/none (regardless of initial degree) | 24 | 24 | 100.0 | 18 | 75.0 | 17 | 12 | 13 | 4 | 11 | 5 | 13 | 4 |

*Respondents were asked to respond (yes/no) to a list of specific treatments. Treatments are not mutually exclusive.
†Lymphedema did not progress beyond mild.

  

**Table 5.** Symptoms in the First 3 Years by Degree of Lymphedema: Presence and Average Frequency, Severity, and Distress Among the 433 Respondents With 3 Full Years of Follow-Up

| Symptom | Moderate/Severe | | | | | Mild | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Presence | | Average Score* | | | Presence | | Average Score* | | |
| | No. of Person-Months | % of Person-Months With Symptom | Frequency† | Severity‡ | Distress§ | No. of Person-Months | % of Person-Months With Symptom | Frequency† | Severity‡ | Distress§ |
| All 3-year completers | 852 | | | | | 1,764 | | | | |
| Jewelry too tight | 682 | 80.0 | 3.50 | 2.66 | 2.78 | 777 | 44.0 | 2.92 | 1.95 | 1.42 |
| Clothing too tight | 488 | 57.3 | 3.00 | 2.49 | 2.78 | 588 | 33.3 | 2.83 | 1.89 | 1.65 |
| One side was puffy | 748 | 87.8 | 3.37 | 2.63 | 2.62 | 1,032 | 58.5 | 2.74 | 1.75 | 1.39 |
| Could not see knuckles/ veins | 474 | 55.6 | 3.35 | 2.90 | 2.83 | 252 | 14.3 | 2.65 | 2.13 | 1.57 |
| Skin felt different | 481 | 56.5 | 3.34 | 2.67 | 2.32 | 504 | 28.6 | 2.74 | 2.10 | 1.82 |
| Skin felt tired/thick/heavy | 692 | 81.2 | 3.12 | 2.67 | 2.69 | 857 | 48.6 | 2.55 | 2.09 | 1.96 |
| Pain | 568 | 66.7 | 2.86 | 2.70 | 2.89 | 700 | 39.7 | 2.52 | 2.14 | 2.08 |
| Indentations in skin | 608 | 71.4 | 3.09 | 2.60 | 2.18 | 354 | 20.1 | 2.60 | 1.89 | 1.48 |
| Swelled after exercise | 392 | 46.0 | 3.03 | 2.55 | 2.34 | 274 | 15.5 | 2.54 | 2.09 | 1.96 |
| Difficulty writing | 187 | 21.9 | 2.77 | 2.68 | 2.91 | 190 | 10.8 | 2.50 | 2.17 | 2.39 |
| Any symptoms | 852 | 100.0 | | | | 1,485 | 84.2 | | | |
| % of months with symptoms | | | | | | | | | | |
| No symptoms | | 0.0 | | | | | 15.8 | | | |
| 1-2 symptoms | | 5.8 | | | | | 29.9 | | | |
| 3-4 symptoms | | 17.6 | | | | | 24.0 | | | |
| 5+ symptoms | | 76.6 | | | | | 30.3 | | | |

(continued on following page)

*Average calculated only with those person-months in which symptom was present.
†Frequency: 1 = rarely, 2 = occasionally, 3 = frequently, and 4 = almost constantly.
‡Severity: 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe.
§Distress: 0 = none, 1 = a little bit, 2 = somewhat, 3 = quite a bit, and 4 = very much.

followed by moderate/severe lymphedema; and waxing and waning = episodes of lymphedema that increased and decreased in degree with at least two changes in degree over time.

Analyses of symptom frequency, severity, and distress were based on person-months of exposure and were grouped by lymphedema status. For example, analyses combined months with mild lymphedema over all respondents to calculate average frequency, severity, and distress scores in months with mild lymphedema in which the symptom was present, acknowledging that a person could contribute months to any category of lymphedema.

To identify symptoms that might forewarn lymphedema onset, we compared presence or absence of symptoms in interview periods with no (and no prior) lymphedema to the presence or absence of lymphedema in the next interview period. For example, we asked whether individuals experiencing a tired/thick/heavy arm were more likely to first notice lymphedema in the next interview period than women not experiencing this symptom. Because this analysis contrasted the outcome of a following interview period with symptoms reported in the preceding period, women interviewed only once or whose onset of lymphedema occurred in the first interview period were excluded. We used a Cox proportional hazards model with time-varying covariates contrasting two risk sets (all periods in which the symptom was present *v* all periods in which the symptom was absent) in terms of the rate of lymphedema appearing in the next period.[33]

## RESULTS

### Ascertainment

We ascertained 4,551 breast cancer diagnoses from the hospitals, locating 97% of breast cancer patients diagnosed in the two counties during the study period.[34] Median time from breast cancer diagnosis to ascertainment was 2 months (range, 0 to 33 months).

### Study Enrollment and Response Rates

Among 1,589 randomly selected potentially eligible patients, 649 (41%) were enrolled. One hundred ninety-nine patients (31%) were younger than 50 years old, 366 patients (56%) were 50 to 79 years old, and 84 patients (13%) were 80+ years old; the age distribution of the sample was slightly younger than the breast cancer population of Philadelphia and Delaware Counties over the study period (20%, 66%, and 14%, respectively).[34] Patient refusal accounted for only 25% of nonenrollment; other reasons included physician noncooperation (35%), unable to locate physician to give consent (8%), restrictive hospital requirements for patient contact (13%), death (6%), illness (3%), ineligibility as a result of physical or mental incapability (3%), and inaccessibility (8%).

### Loss to Follow-Up

Lymphedema could not be evaluated for 18 of the 649 enrolled study participants (Table 1). Among the 631 remaining eligible participants at start of follow-up, 61%, 62%, and 30% of those aged ≤ 50, 50 to 79, and 80+ years, respectively, completed all 5 years of follow-up (Table 1). Overall, yearly retention was generally high at near or greater than 90%; however, retention dropped to 81% (433 of 537 participants) the third year of follow-up, which was the transition

**Table 5.** Symptoms in the First 3 Years by Degree of Lymphedema: Presence and Average Frequency, Severity, and Distress Among the 433 Respondents With 3 Full Years of Follow-Up (continued)

| | No Current Lymphedema | | | | | No Lymphedema Ever | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Presence | | Average Score* | | | Presence | | Average Score* | | |
| Symptom | No. of Person-Months | % of Person-Months With Symptom | Frequency† | Severity‡ | Distress§ | No. of Person-Months | % of Person-Months With Symptom | Frequency† | Severity‡ | Distress§ |
| All 3-year completers | 2,784 | | | | | 10,188 | | | | |
| Jewelry too tight | 762 | 27.4 | 2.47 | 1.82 | 1.30 | 678 | 6.7 | 2.16 | 1.69 | 1.22 |
| Clothing too tight | 284 | 10.2 | 2.30 | 1.68 | 1.61 | 127 | 1.2 | 2.21 | 1.59 | 1.32 |
| One side was puffy | 589 | 21.2 | 2.51 | 1.77 | 1.59 | 297 | 2.9 | 2.07 | 1.70 | 1.40 |
| Could not see knuckles/ veins | 146 | 5.2 | 2.73 | 2.35 | 2.31 | 21 | 0.2 | 2.81 | 2.52 | 1.52 |
| Skin felt different | 369 | 13.3 | 2.65 | 2.08 | 1.80 | 326 | 3.2 | 2.50 | 1.89 | 1.39 |
| Skin felt tired/thick/heavy | 858 | 30.8 | 2.67 | 2.10 | 1.94 | 1,140 | 11.2 | 2.20 | 1.83 | 1.70 |
| Pain | 872 | 31.3 | 2.47 | 2.05 | 1.92 | 1,542 | 15.1 | 2.35 | 1.95 | 1.83 |
| Indentations in skin | 260 | 9.3 | 2.40 | 1.99 | 1.87 | 178 | 1.7 | 1.87 | 1.58 | 1.06 |
| Swelled after exercise | 234 | 8.4 | 2.34 | 1.84 | 2.01 | 156 | 1.5 | 2.08 | 1.57 | 1.47 |
| Difficulty writing | 289 | 10.4 | 2.70 | 2.10 | 2.31 | 479 | 4.7 | 2.79 | 2.09 | 2.01 |
| Any symptoms | 1,718 | 61.7 | | | | 2,772 | 27.2 | | | |
| % of months with symptoms | | | | | | | | | | |
| No symptoms | | 38.3 | | | | | 72.8 | | | |
| 1-2 symptoms | | 35.7 | | | | | 22.0 | | | |
| 3-4 symptoms | | 14.1 | | | | | 4.1 | | | |
| 5+ symptoms | | 12.0 | | | | | 1.1 | | | |

*Average calculated only with those person-months in which symptom was present.
†Frequency: 1 = rarely, 2 = occasionally, 3 = frequently, and 4 = almost constantly.
‡Severity: 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe.
§Distress: 0 = none, 1 = a little bit, 2 = somewhat, 3 = quite a bit, and 4 = very much.

year between the original study and continuation funding. The longer time between contacts during this year resulted in more loss to follow-up (Table 1). The most common reasons for loss to follow-up were refusal, death, unavailability, and becoming ineligible; all reasons had approximately equal proportions. Among the 362 women (57%) completing all 5 years of follow-up, the median time from diagnosis to first interview was 11 months (range, 7 to 28 months). The median time between subsequent interviews was 9 months (range, 3 to 38 months), resulting in a median of six interviews (range, three to seven interviews).

### *Lymphedema Incidence*

Overall cumulative 5-year incidence of lymphedema was 42 (42%) per 100 women; 5-year rates of lymphedema were 50%, 40%, and 26% among respondents younger than 50, 50 to 79, and 80+ years old, respectively (Table 2). Eighty percent of the 238 women with lymphedema first experienced it within 2 years of breast cancer diagnosis, and 89% experienced it within 3 years (Table 2).

Most lymphedema was mild. Among women observed for 3 years, 23.1% (100 of 433 women) experienced mild lymphedema only (lymphedema degree score = 1 to 3) that generally resolved or waxed and waned between mild and none (Table 3). Of the 100 women with mild lymphedema, 83 had no degree score exceeding 1 ("very slight; you are the only person who would notice this") in any location, 16 had a maximum degree score of 2 ("noticeable to those who know you well but not to strangers") in a single location, and only one had a degree score of 3 ("very noticeable") in a single location.

An additional 50 (11.5%) of the 433 3-year completers reported moderate/severe lymphedema (degree score = 4 to 9), but only 10 had chronic moderate/severe lymphedema. Of the 50 women with moderate/severe lymphedema, 24 (48%) noticed a size difference scored as 3 in at least one part of the arm; eight women each reported a score of 3 in all three parts, two parts, and one part of the arm.

Among all 2,616 person-months of lymphedema in the first 3 years, 61.2% involved the hand, 54.5% involved the lower arm, and 72.1% involved the upper arm (percentages add to > 100% because lymphedema often occurred in more than one part). Among women with 3 full years of follow-up, those with mild lymphedema were at greater risk of progression to moderate/severe lymphedema (cumulative incidence = 0.24) than women who progressed from no lymphedema directly to moderate/severe lymphedema (cumulative incidence = 0.07).

### *Lymphedema Treatment*

Overall, 79.3% of 3-year completers with lymphedema talked to a health provider about the size difference between their arms, and 47.3% received at least one type of treatment (Table 4). Women experiencing moderate/severe lymphedema were more likely to be treated than those with only mild lymphedema. Among treated women, more than 50% used exercise, sleeve, elevation, or massage.

  

### *Lymphedema Symptoms: Frequency, Severity, and Distress*

Table 5 lists symptoms in women with and without lymphedema. For each month of follow-up, a respondent was classified as having moderate/severe, mild, or no lymphedema in that month. We further classified months with no lymphedema into the following two categories according to the respondent's entire 36-month experience: no lymphedema ever or no current lymphedema (no lymphedema in that month, although lymphedema was present in prior or subsequent months). The median numbers of symptoms per month out of a possible 10, by lymphedema status, were as follows: moderate/severe, seven symptoms (range, zero to 10 symptoms); mild, three symptoms (range, zero to nine symptoms); none currently, one symptom (range, zero to nine symptoms); and none ever, zero symptoms (range, zero to eight symptoms). The proportion of person-months with symptoms decreased as degree of lymphedema decreased from moderate/severe to no lymphedema. However, ratings of severity and distress by symptom seemed relatively similar for months with mild and no lymphedema and were lower than ratings in months with moderate/severe lymphedema (Table 5). For example, in months with moderate/severe lymphedema, average distress score for jewelry being too tight across all person-months was 2.78, but in months with mild lymphedema, no current lymphedema, and no lymphedema ever, the average distress scores were 1.42, 1.30, and 1.22, respectively.

Some symptoms offered early indications of an increased likelihood of developing lymphedema (Table 6). Compared with interview periods with no symptoms present and no current or prior lymphedema, interview periods with symptoms were associated with a greater rate of lymphedema in the next period, with the highest hazard ratio being 7.37 (95% CI, 4.26 to 12.76) for jewelry being too tight. Specifically, the symptom of jewelry too tight was reported in 64 interview periods in which lymphedema had not yet occurred. In 19 (29.7%) of 64 periods, lymphedema occurred in the next period. Conversely, there were 819 interview periods in which this symptom was not reported and lymphedema had not yet occurred; lymphedema was reported in 40 subsequent periods (4.9%).

## DISCUSSION

Previously, we developed and validated against clinical criteria a brief questionnaire for lymphedema that was easy to use and score.[7] Given the large study size required to estimate lymphedema incidence, multiple home visits for arm measurement were cost prohibitive. Our measure relies solely on perceived differences in size between the limbs, unlike some other questionnaires developed for self-reported lymphedema assessment in which swelling has been combined with additional factors, such as discomfort, decreased functional activity, movement limitation, and need for a compression sleeve.[12,27,35,36]

In the validation study,[7] the physical therapists agreed in advance on the clinical criteria; a circumferential difference between limbs of more than 2 cm at any one location indicated moderate/severe lymphedema, and mild lymphedema corresponded to a difference of $\leq$ 2 cm. No lower bound was specified; the clinicians used their judgment for borderline decisions, considering texture and handedness. Sensitivity and specificity of self-reported moderate/severe lymphedema were high (each approximately 0.90). Although sensitivity for any lymphedema, including mild, was also high, specificity was lower (ie, there were instances in which a respondent's questionnaire indicated mild lymphedema but the physical therapist did not diagnose lymphedema). However, when two physical therapists independently assessed a group of patients, disagreements at the border between mild and no lymphedema sometimes occurred, with one classifying the patient as having mild lymphedema whereas the other found none, or vice versa. As underscored by many clinicians and investigators, the patient may be the better judge of lymphedema, especially at the milder end.

The importance of mild lymphedema is becoming clearer.[16,24] We found that although lymphedema was a common sequela of breast

**Table 6.** Presence or Absence of Symptoms on the Side of Cancer Diagnosis in the Interview Period* Before Onset of Lymphedema and Lymphedema Status in the Next Interview Period by Symptom

| Symptom | Symptom Present | | | Symptom Absent | | | Hazard Ratio | 95% CI |
|---|---|---|---|---|---|---|---|---|
| | No. of Interview Periods With Symptom Present and No Lymphedema Yet | Immediately Following Interview Periods With Lymphedema | | No. of Interview Periods With Symptom Present and No Lymphedema Yet | Immediately Following Interview Periods With Lymphedema | | | |
| | | No. | % | | No. | % | | |
| Jewelry too tight | 64 | 19 | 29.7 | 819 | 40 | 4.9 | 7.37 | 4.26 to 12.76 |
| Clothing too tight | 13 | 4 | 30.8 | 870 | 55 | 6.3 | 5.47 | 1.98 to 15.10 |
| Puffiness | 29 | 5 | 17.2 | 854 | 54 | 6.3 | 4.20 | 1.66 to 10.62 |
| Could not see veins or knuckles in hand | 2 | 0 | 0.0 | 881 | 59 | 6.7 | —† | — |
| Skin felt different | 33 | 5 | 15.2 | 850 | 54 | 6.4 | 3.12 | 1.24 to 7.82 |
| Skin felt tired/thick/heavy | 106 | 16 | 15.1 | 777 | 43 | 5.5 | 3.52 | 1.97 to 6.27 |
| Pain | 141 | 16 | 11.3 | 742 | 43 | 5.8 | 2.42 | 1.36 to 4.32 |
| Indentations in skin | 15 | 2 | 13.3 | 868 | 57 | 6.6 | 1.88 | 0.46 to 7.71 |
| Swelling after exercise | 17 | 3 | 17.6 | 866 | 56 | 6.5 | 3.45 | 1.08 to 11.05 |
| Difficulty writing with dominant hand | 43 | 3 | 7.0 | 423 | 24 | 5.7 | 1.35 | 0.41 to 4.49 |

*Interview period is the time between month and year of the prior interview (reference date if the first interview) and current interview date.
†Cannot calculate hazard ratio and CI because of sparse data.

cancer, most lymphedema was mild. The wide range of reported incidences might reflect some studies measuring any lymphedema and others measuring moderate/severe lymphedema and may also reflect different modes of measurement and populations studied. Among recent prospective studies, 3-year rates of lymphedema varied from 15%[13] to 21%[11,12] to 54%.[16] The first two studies used circumferential measurements but with differing methods for establishing a criterion for lymphedema,[11,13] and the third and fourth studies assessed arm swelling by self-report.[12,16] Our finding of a 35% incidence of lymphedema by 3 years falls within this range of estimates.

Women with mild lymphedema rarely had differences between their arms that exceeded "very slight, you are the only one who would notice this." Nonetheless, they differed from women without lymphedema; they were more than three times as likely to develop moderate/severe lymphedema within 3 years as women with no lymphedema, and the number of symptoms they experienced was intermediate between women with moderate/severe and no lymphedema.

Armer et al[19] found that heaviness in the past year was predictive of current lymphedema. Our results confirm this finding and extend it to multiple symptoms associated with later emergence of lymphedema, such as jewelry being too tight.

The strengths of this study are as follows. First, it is prospective; only by observing a well-described and enumerated group of women over time can we obtain accurate estimates of cumulative incidence or risk as well as progression and regression of this condition. Second, the study is population based; aside from a few recent studies,[12,17] the incidence of lymphedema after community-based breast cancer treatment is unknown. Finally, this study is among the largest studies; of six studies as large or larger than ours, only one was population based and prospective,[12] two were prospective but not population based,[13,16] and three were retrospective.[37-39]

Despite population-based sampling, selective enrollment and loss to follow-up are potential sources of bias. Only 41% of potentially eligible participants enrolled, mainly because of restrictive hospital requirements for patient contact, physician refusal, or inability to find the physician, rather than patient refusal. We have no evidence that physician/hospital noncooperation was related to developing lymphedema. Instead, noncooperation reflected global concerns about patient privacy, which was especially salient because the new Health Insurance Portability and Accountability Act regulations were being discussed. Removing from the denominator of potentially eligible patients those patients not enrolled because of physician/hospital noncooperation or who died before initial contact, moved, or could not be located, the percentage enrolled increased to 62% (649 of 1,046 patients). Regarding loss to follow-up, yearly retention was high, most swelling occurred within the first 2 years, and survival analysis maximized use of follow-up months. Reasons for dropout varied, with no indication that loss to follow-up occurred predominantly in persons at higher or lower risk of lymphedema.

We lacked information on size differences between the arms before cancer diagnosis, which is a potential limitation.[25] Enumerating the population of women with incident breast cancer required identifying potential participants after cancer diagnosis. However, only six of the 631 eligible study participants recalled a size difference in their hand, lower arm, or upper arm that preceded breast cancer diagnosis (Table 1).

This prospective population-based study has addressed incidence, degree, and time course of lymphedema in breast cancer survivors along with related symptoms. Our conclusions are limited to lymphedema of the arm/hand; we did not assess breast or truncal lymphedema. Subtle differences in self-reported arm/hand size and symptoms can be early signs of progressing lymphedema. Whether prompt treatment when symptoms appear might forestall the emergence of lymphedema and whether progression from mild to moderate/severe lymphedema could be slowed with earlier detection and treatment merit further investigation.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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