

Lymphedema in a Cohort of Breast Carcinoma Survivors 20 Years after Diagnosis

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BACKGROUND. To the authors' knowledge, there are no long-term cohort studies of lymphedema, despite the substantial morbidity of arm swelling. The goal of this study was to identify prevalence of breast carcinoma-related lymphedema, time of onset, and associated predictive factors.

METHODS. A cohort of 923 women consecutively treated with mastectomy and complete axillary dissection at our center between 1976 and 1978 was observed intensively for 20 years. Two hundred sixty-three study subjects (28.5%) who were alive and recurrence free constituted the cohort for the current study. A subset of 52 women (20% of study population) with contralateral mastectomy was analyzed separately. Subjects reported circumferential arm measurements taken using a validated instrument. In addition to providing analysis of clinical and treatment variables, this study is the first to the authors' knowledge to analyze possible etiologic factors in the posttreatment years, such as occupation, general physical activity, and sports/leisure activities. Univariate and multivariate analytic methods were used.

RESULTS. At 20 years after treatment, 49% (128 of 263) reported the sensation of lymphedema. Arm swelling measurements were severe (≥ 2.0 in [5.08 cm]; patients reported measurement in inches) for 13% (33 of 263 women). Seventy-seven percent (98 of 128) noted onset within 3 years after the operation; the remaining percentage developed arm swelling at a rate of almost 1% per year. Of the 15 potential predictive factors analyzed, only 2 were statistically significantly associated with lymphedema: arm infection/injury and weight gain since operation ($P < 0.001$ and $P = 0.02$, respectively).

CONCLUSIONS. This defined cohort, treated by axillary dissection 20 years ago, documents the high prevalence of lymphedema and its time course. Two significantly associated factors, both potentially controllable, are identified. The current study provides further support for treatments that limit lymph node dissection. The authors are prospectively evaluating patients undergoing sentinel lymph node biopsy. *Cancer* 2001;92:1368-77. © 2001 American Cancer Society.

KEYWORDS: lymphedema, breast carcinoma, mastectomy, axillary dissection, infection, injury, weight gain, occupation, leisure activities, incidence.

There are approximately 2,000,000 breast carcinoma survivors in the United States. Assuming a conservative incidence rate of 10%, approximately 200,000 women cope with the consequences of lymphedema on a daily basis, including deformity of the arm due to swelling, and associated physical discomfort and disability. Scientific evaluation of lymphedema has been scant; this situation is most likely because of the following factors:

1. Patients experience prolonged susceptibility to lymphedema throughout their survivorship.

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- Clinical attention is directed toward cancer recurrence rather than concerns about arm disability.
- There is relatively little research interest and available support for quality-of-life issues such as lymphedema.

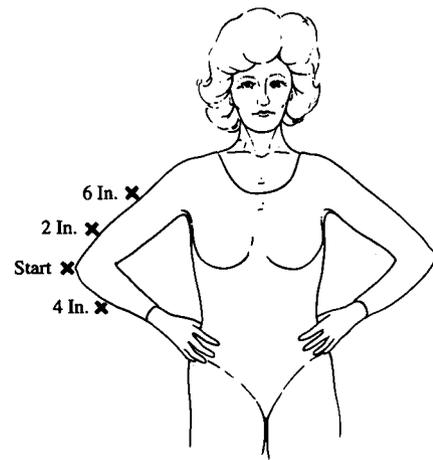
In a 1998 review article¹ of 7 large reports published since 1990, the incidence of lymphedema ranged from 6% to 30% among breast carcinoma patients treated in 5 Western countries. Comparisons across studies have been complicated by differences in the definition of lymphedema used, as well as differences in measurement techniques, breast carcinoma treatment, study patient criteria, and length of follow-up. The current study documents assessment of lymphedema in a consecutively treated cohort with long-term follow-up (20 years). The goal of this study was to assess the incidence, time of onset, and suspected etiologic factors of lymphedema, including both treatment and clinical variables and posttreatment experience factors such as specific occupation, hobbies, sports, activity level, and comorbid conditions. Although they are unreported in scientific publications, activities in the years subsequent to diagnosis must be considered by physicians, because patients often ask about the wisdom of continuing specific hobbies and work-related activities that may cause arm swelling after axillary dissection. Thus far, little information has been available to physicians with which to address these concerns.

METHODS

Study Population

The breast carcinoma cases included in the current study involve 20-year survivors from a cohort consecutively treated at Memorial Sloan-Kettering Cancer Center by members of the Breast Surgery Service between October of 1976 and June of 1978. During this 21-month treatment interval, all patients with newly diagnosed breast carcinoma were invited to participate in a study of epidemiologic and pathologic factors. Greater than 97% participated ($n = 923$). Epidemiologic information was obtained through personal interviews conducted during the patients' postoperative hospitalizations, and a complete pathologic review was conducted. The cohort was evaluated annually. Several published reports linked epidemiologic factors, pathologic factors, and prognosis.²⁻⁸

The original cohort of 923 women was evaluated from the time of diagnosis, with annual contact by phone and/or mail; in addition, yearly physician-patient contact was maintained to obtain information on each patient's general medical status (illnesses, hospitalizations, and medications), breast carcinoma sta-



INSTRUCTIONS:

- Please record measurements in inches (red arrow marks indicated on the enclosed tape).
- Put the hand of the arm being measured on your hip (i.e. right hand on right hip). Please ask someone to assist you with the measuring of your arms.

	<u>RIGHT ARM</u>	<u>LEFT ARM</u>
3. Measure 2 inches above elbow (start at the pointy part of elbows)	_____	_____
Measure 6 inches above the elbow points	_____	_____
Measure 4 inches below elbow points	_____	_____

FIGURE 1. Standardized mailed instrument for self-reported arm-circumference measurements.

tus (diagnosis and treatment of recurrence), and contralateral breast carcinoma status. Although patients occasionally reported arm swelling during follow-up calls or in their letters, issues relating to lymphedema were not part of this 20-year database.

The current study was launched to obtain self-reported lymphedema information retrospectively. Approval from the institutional review board was obtained and a twofold research intervention undertaken. This intervention consisted of standardized telephone interviews conducted by a designated research nurse (M.P.) and a mailed questionnaire requesting participant responses in the form of standardized self-reported arm-circumference measurements (Fig. 1).

Our study was initiated in 1997 with the 543 members of the original cohort of 923 known to be alive and free of recurrence 10 years after treatment, as established by Senie et al.² in 1992. In this study,² the authors reported on disease free survival for the cohort at 10 years in relation to obesity at the time of diagnosis. From among the 923 women in the original study cohort of 10 years prior, the authors established that in total 543 women were known to be alive and recurrence free 10 years after treatment.

By 1997, 30% (165 of 543) of these 543 had died, either from breast carcinoma or other causes, and 12% (64 of 543) were unable or unwilling to participate. Two percent (12 of 543 women) were contacted and refused; 9.5% (52 of 543), although known to be alive, were mentally and/or physically incapacitated and could not participate. Nine percent (51 of 543) of the original cohort could not be located through standard research efforts, searches by Equifax Credit Services and OmniSearch Services, or the National Death Index of the United States. The median age of those lost to follow-up was 81 years, almost 10 years older than the median age of the study subjects.

The remaining 263 of the 543 10-year recurrence free survivors formed the cohort for our report. This study population represents a little greater than one-quarter (28.5%) of the original cohort of 20 years ago, and, as such, is the largest such cohort in the literature to be studied in relation to lymphedema to our knowledge.

Of the 263 study subjects in our study, 20% (52 of 263) had undergone contralateral breast carcinoma treatment with axillary dissection during the approximately 20-year interval since their initial breast carcinoma treatment. Only 1 of the 263 women currently was being treated for recurrence of the original breast carcinoma.

Data Collection Instrument for Arm-Circumference Measures and Current Weight

To assess the reliability of self-measurement of arm circumference and body weight, we conducted a pilot study with 25 breast carcinoma patients, none of whom was a member of the study cohort, who were scheduled for routine follow-up exams. Two to 3 weeks before the scheduled appointment, the research nurse telephoned each patient. Measurement instructions and protocol forms were mailed to patients and returned during the physician-conducted follow-up exams. At the time of the follow-up exam, the research nurse met with each patient to record current weight and to measure the circumference of both arms at the appropriate sites. Measurements recorded by patients then were compared with those obtained by the research nurse.

The results of this pilot study confirmed the reliability of self-measurement techniques among these patients: correlation coefficients were high for both parameters. For weight, the correlation was 0.99; the mean difference was 2.6 lbs (1.18 kg) (standard deviation [SD], 2.0 lbs [0.91 kg]). The correlation coefficients for the three arm-measurement sites ranged from 0.87 to 0.97.

Following the results of the pilot study described above, each of the 263 women in our study cohort was

asked to complete a validated form (Fig. 1) documenting her arm-circumference measurements (using a tape measure provided with the study form). Explanation and guidance were provided by the research nurse over the telephone, on request. The arm-circumference measurement sites, clearly marked on the diagram, were 2 and 6 in (5.08 and 15.24 cm) above the "point of the elbow" (the olecranon), and 4 in (10.16 cm) below the point of the elbow.

Current weight also was requested on the same form, and instructions for weighing oneself (light clothing, no shoes) were provided.

Baseline Data

Data collected at the time of initial diagnosis were obtained from the following three sources:

1. Personal interviews
2. Medical records (from which data on operative and postoperative course were abstracted)
3. Pathology records (on complete review).

Several factors were included in the baseline data file and were evaluated for association with lymphedema:

1. Age
2. Height and weight at diagnosis, measured at admission, and providing a measure of relative obesity
3. Formal education
4. Type of mastectomy
5. Size of primary cancer
6. Extent of axillary dissection, as shown by number of lymph nodes excised.

As in previously conducted analyses with this cohort,² the Metropolitan Life Insurance Table of Desirable Weights for Women, published in 1959, was used to assess weight relative to height.⁹ Patients were grouped into four weight categories based on actual weight as a percentage of optimal weight:

1. 90% or less: below ideal weight
2. 91–110%: optimal weight
3. 111–124%: moderately overweight
4. 125% or greater: obese.

In our study, as in a recently reported analysis of other populations,¹⁰ percentage of optimal weight was strongly correlated ($r = 0.92$) with body mass index, another commonly used measure of weight relative to height.

Three other factors, information on which was abstracted from the medical records, also were evaluated for association with lymphedema:

TABLE 1
Occupations after Breast Carcinoma Treatment

Occupation	No. of patients
Homekeeper	68
Office worker	61
Saleswoman, cashier, waitress	41
Teacher, baby caretaker, elder helper	36
Nurse's aide, physician	24
Office cleaner and private housekeeper	20
Outdoor worker, gardener, florist, veterinarian	7
Cook, baker	6

1. Specific surgical technique including excision of the thoracodorsal nerve complex
2. Excision of pectoralis minor muscle
3. Postoperative surgical drainage from the mastectomy site, measured as both volume and duration.

Events and Activities in the Years after Breast Carcinoma Treatment

Interviews conducted by the study research nurse assessed patients' past arm injuries and infections, patients' self-reports of arm swelling, and their general physical activity and exercise levels, occupational and leisure pursuits, and histories of chronic conditions. The interviews also reconfirmed patients' histories of contralateral breast carcinoma. These factors then were evaluated for association with lymphedema.

General Physical Activity and Exercise

Following the format used in the Women's Health Initiative, interviews included questions about exertion. A three-point activity index was created in relation to the proportion of hours expended in mild or no activity (sitting, standing still, or lying down), moderate activity (routine walking, housework, or any other activity more than mildly but not highly demanding), or high activity (aerobic exercise, heavy housework, climbing stairs, ballroom dancing, jogging, or "any other activity causing sweating or increased heart rate").

Two separate scales were used to rank the women's activities: percentage of time spent in moderate and high activity and percentage of time spent in high activity.

Principal Occupation and Leisure Activity

Table 1 shows the occupations included in responses to questions about employment after breast carcinoma treatment. Women were also asked to name their principal hobby or leisure activity in the years since breast carcinoma treatment, and when necessary, a list of 22 suggested hobbies and 20 suggested

TABLE 2
Most Common Principal Hobby or Leisure Activity after Breast Carcinoma Treatment

Activity	No. of patients
Reading	68
Watching television	52
Golf	48
Gardening or flower arranging	41
Working with sharp needles (needle point, embroidery, etc.)	31
Playing cards	20
Swimming	20
Bowling	15
Painting, doing art projects, crafts, jewelry making	15
Working with dull needles (knitting, crocheting)	13
Cooking, baking	12
Listening to music	11
Tennis	11
Shuffleboard and croquet	1

sports was provided. The most common hobbies included in their responses are listed in Table 2. Only 95 subjects could report any sport being among their pastime pursuits (Table 2), even when prompted, and only 10 women reported a sport to be their principal leisure activity.

Women whose profession or leisure activities involved heavy lifting or the risk of skin injuries such as cuts or burns were classified as having "at risk" occupations or hobbies.

Chronic Illnesses

Women were asked to name all current illnesses, all medications in their medicine cabinet, and any periods of hospitalization undergone in the past 20 years. Using these data, patients were placed in one of the following three categories:

1. Most healthy, with no chronic illnesses
2. Moderately healthy, with one chronic illness
3. Least healthy, with two or more chronic illnesses.

Arm-Specific Information

The final questions asked about arm swelling or enlargement were, "Is your arm larger on the side of the mastectomy?" and "Do you have arm swelling?" Positive responses were followed with specific questions regarding the year of onset and the visible site at onset (upper or lower arm, or hand). In the 52 women who subsequently had undergone contralateral breast carcinoma with axillary dissection, the same questions were asked about the contralateral arm, and a subjective comparison of lymphedema symptoms between the ipsilateral and contralateral arms was made.

The questionnaire also requested information on any events in the subsequent years involving injury, elective surgery, or infection in the treated side that required oral or intravenous antibiotics. Injury was defined as any event necessitating evaluation by a medical healthcare provider. Infection was defined as any episode for which a course of antibiotics, either oral or intravenous, was prescribed. The specific years of injury or infection were requested. When the patient could not provide the exact year of infection/injury, she was asked to specify within a 5-year range and to indicate whether the injury or infection had occurred before or after the onset of arm swelling.

Lymphedema Classification

Study participants' circumferential arm measurements were received by mail, on the completed forms, and combined with verbal reports of arm swelling obtained during telephone interviews. Using these data, patients were classified based on extent of lymphedema as follows: 1) no lymphedema, 2) mild lymphedema, 3) moderate lymphedema, or 4) severe lymphedema.

The difference in measurement between the treated side (ipsilateral arm) and the contralateral arm at the site of greatest difference was used to determine extent of lymphedema. Severe lymphedema was defined as enlargement (difference) of 2 in (5.08 cm) or more, and moderate lymphedema as enlargement greater than 0.5 in (1.27 cm) and up to 2 in (5.08 cm). Arm swelling involving a difference of less than 0.5 in (1.27 cm) between arms was considered mild lymphedema when accompanied by a patient self-report of arm enlargement or heaviness. Women who reported no arm swelling and arm measurements with a difference of 0.5 in (1.27 cm) or less between arms were placed in the no lymphedema category.

All subjects in the no lymphedema category reported no arm swelling during their telephone interview and reported arm measurements with a difference of 0.5 in (1.27 cm) or less between arms. All study subjects with arm measurements showing a difference of greater than 0.5 in (1.27 cm) between arms (all subjects classified as having moderate/severe lymphedema) also reported arm swelling during their telephone interview.

The mild lymphedema category, defined as a difference of 0.5 in (1.27 cm) or less in women reporting arm enlargement or heaviness, was designed to be inclusive, because arm sensations such as heaviness are sometimes attributable to factors other than lymphedema. We used these measurements even in cases involving contralateral axillary dissection, realizing, however, that the measurements of the con-

tralateral arm in such cases may not always be a valid control.

Data Analysis

Statistical procedures for univariate analysis included the chi-square test applied to categorical data and analysis of variants, and the Student *t* test for continuous variables. Correlation coefficients were used to provide an assessment of two related measurements. Multivariate statistical methods were used to test epidemiologic and pathologic characteristics potentially associated with the development of lymphedema during the 20-year follow-up interval. These procedures were performed with the whole study group with unilateral and bilateral axillary dissection ($n = 263$) and also with the group who had a unilateral mastectomy and axillary dissection only ($n = 211$).

RESULTS

Description of the Study Cohort

Table 3 lists the demographic and clinical characteristics of the study subjects.

Clinical Characteristics

At diagnosis, the 263 women in our study cohort ranged in age from 25 to 77 years, with a mean age of 52.3 years (SD, 9.9); 22% were younger than age 45, and 18% were 60 years or older. Information on patients' educational backgrounds obtained at time of diagnosis reflected the usual distribution for patients receiving care at Memorial Sloan-Kettering Cancer Center: most women (54%; 142 of 263) had attended college, 31% (81 of 263) had graduated from high school, whereas 15% (40 of 263) had not completed high school.

Weight at diagnosis was recorded at time of admission and classified in relation to ideal weight for height.² Weight ranged from 93 to 253 lbs (42.18 to 114.8 kg), with a mean of 139 lbs (63.0 kg) (SD, 25.4). Nineteen percent (50 of 263) of the women were moderately overweight at diagnosis, and 14% (38 of 263) were considered obese. There were similar results in the subset of 211 women with unilateral axillary dissection only (Table 3).

Surgical and Pathologic Variables

With regard to specific surgical technique of 20 years ago, all patients were treated by modified (43%; 113 of 263) or radical (57%; 150 of 263) mastectomy and axillary dissection; the thoracodorsal nerve bundle was removed in 35% (93 of 263) of cases; and the pectoralis minor muscle was excised in 95% (250 of 263) of cases.

In the period during which these women's disease

TABLE 3
Demographic and Clinical Characteristics of 263 Study Subjects and of a Subset of 211 Subjects with Unilateral Axillary Dissection Only

Characteristic	n = 263	n = 211 (%)
At diagnosis		
Education level		
Did not complete high school	15	12
High school graduates	31	29
High school and higher	54	58
Family history		
None	68	71
Primary only: mother, sister, daughter	11	11
Secondary only: other relatives	15	12
Both primary and secondary relatives	6	6
Weight in relation to height		
Ideal or lower	67	65
Moderately overweight	19	19
Obese	14	16
At 20-year follow-up		
Lymphedema ^a		
None	51	50
Mild	19	19
Moderate	17	18
Severe	13	13
Age (yrs)		
< 65	22	26
65-79	60	49
≥ 80	18	25
Weight change at follow-up		
No change or loss	38	36
≤ 10-lb 4.54-kg gain	30	31
> 10-lb 4.54-kg gain	32	33
Arm infection or injury		
No episodes	79	78
One episode	13	13
Two or more episodes	8	9
Level of activity ^a		
Limited	30	29
Moderate	31	32
High	39	38

^a Defined in "Methods."

was diagnosed and treated, discharge was delayed until all drains were removed. Daily drainage volume, recorded in the hospital record, enabled calculation of total volume. Both volume and number of days the drains remained in place were included in the database. The number of axillary lymph nodes excised ranged from 1 to 41 lymph nodes, with a mean of 21 lymph nodes (SD, 7.4). Thirteen women underwent radiation therapy in the "hockey stick" fashion (designed to treat the internal mammary and supraclavicular lymph nodes but not the chest wall). There were no immediate reconstructions (although breast reconstruction with the implant technique was performed at some later point in 16% [43 of 263]).

The size of the primary tumor (not measured in 35

women) ranged from 0.3 to 7.5 cm, with a mean of 2.1 cm (SD, 1.2); 52% (137 of 263) of the women had tumors 2 cm or smaller. Among this series of 263 long-term survivors, 29% had positive axillary lymph nodes: 19% had 1-3 positive lymph nodes, and 10% had 4 or more positive lymph nodes. Among the 211 women with unilateral axillary dissection only, 31% had positive axillary lymph nodes: 20% had 1-3 positive lymph nodes, and 11% had 4 or more positive lymph nodes.

Events in the Subsequent Years

The number of hours spent by study subjects in moderate and/or strenuous activity was measured using two scales. The first scale measured the number of hours spent in moderate or strenuous (high) activity per day and ranged from 0 to 8.5 hours per day for the study cohort, with a median of 2.5 hours. The second scale used measured the time spent in high activity per week and ranged from 0 to 7 hours per week for the study cohort, with a median of 0.5 hours. Fifty-one women had at risk occupations (occupations that involved heavy lifting or the risk of skin injuries such as cuts or burns), and 99 women had at risk hobbies. No women were at risk because of their sports participation.

In total, 33% (88 of 263) of the women were classified as most healthy, because they had no chronic illnesses and used no daily medicine. Twenty-one percent (56 of 263) had 1 chronic illness and were classified as moderately healthy. Forty-five percent (119 of 263) had 2 or more chronic illnesses each and therefore were classified as least healthy. The two most common chronic illnesses were hypertension, documented in 17.5% (46 of 263) of the women, and diabetes mellitus, in 11% (29 of 263).

Current body weight was compared with weight at diagnosis; the two measurements were strongly correlated ($r = 0.72$; $P = 0.001$). Three categories of weight gain were created: 1) no change, 2) gain 10 lbs (≤ 4.54 kg), and 3) gain greater than 10 lbs (4.54 kg); none of the women had lost greater than 10 lbs (4.54 kg) since diagnosis. Thirty-eight percent (101 of 263) of the study cohort had no change or had lost a slight amount of weight (10 lbs [≤ 4.54 kg]). Thirty percent (78 of 263) had gained less than or equal to 10 lbs (4.54 kg), and 32% (84 of 263) had gained greater than 10 lbs (4.54 kg) since their breast carcinoma diagnosis 20 years ago.

Most (79%; 208 of 263) of the women in our study could recall no arm infections, injuries, or elective surgery since diagnosis; however, 13% (34 of 263) of the women reported 1 episode of infection, and 8% (21 of 263) reported 2 or more episodes. Only one woman

reported an injury separate from an infection. None of the women had surgery on the ipsilateral arm.

Lymphedema Classification

After combining data collected during the follow-up telephone interviews with arm-circumference measurements, we identified evidence of lymphedema in 49% (128 of 263) of the women, and 51% (135 of 263) were recorded as having no lymphedema. Severe lymphedema, defined as an enlargement of 2 in (5.08 cm) or more at any 1 of the 3 sites for arm-circumference measurement, was noted in 13% (33 of 263) of the women, and 17% (45 of 263) were coded as having moderate lymphedema. An additional 19% (50 of 263) were categorized as having mild lymphedema.

Of the 211 women with unilateral axillary dissection only, the results were similar: no lymphedema, 50%; severe lymphedema, 13%; moderate, 18%; and mild, 19%.

Of the 52 breast carcinoma survivors who had subsequent contralateral breast carcinoma treatment, 40% (21 of 52) reported the sensation and symptoms of arm swelling on the ipsilateral arm, versus 51% of the 211 women with unilateral axillary dissection only. All of the 31 women with contralateral breast carcinoma treatment who claimed no swelling on the ipsilateral side also reported no swelling on the contralateral side. Among the 21 women with contralateral breast carcinoma treatment who experienced arm swelling, all reported less swelling in the contralateral arm than in the arm ipsilateral to the axillary dissection performed 20 years ago. Eleven of these 21 women reported the sensation of swelling on the contralateral side, although less intense than on the index side, and 10 reported no symptoms of swelling on the contralateral side.

Of the 128 women with lymphedema from among the group as a whole, 50% (64 of 128) indicated all sections of their arm were affected at onset; 33% reported enlargement of the upper portion of their arm only. Results were similar among the 211 women with unilateral axillary dissection only.

Etiologic Factors

Of the potential epidemiologic, surgical, and pathologic factors and events in the subsequent years, only two were associated with the presence of lymphedema: history of infection/injury and weight gain since treatment. Although patients who were overweight at diagnosis had an increased risk of developing lymphedema, weight gain in the posttreatment years was shown to be a stronger predictor ($P = 0.02$). Among the 128 patients classified as having mild to severe lymphedema, 70% (90 of 128) had gained

TABLE 4
Selected Variables and Association with Lymphedema in 263 Study Subjects and in a Subset of 211 Subjects with Unilateral Axillary Dissection Only

Variable	Study subjects as a whole ($n = 263$)		
	No lymphedema ($n = 135$) (%)	Evidence of lymphedema ($n = 128$) (%)	<i>P</i> value
Weight at diagnosis			
Ideal weight or lower ($n = 175$)	53	47	0.08*
Moderately overweight ($n = 50$)	38	62	
Obese ($n = 38$)	60	40	
Weight change			
No change ($n = 100$)	61	39	0.02
≤ 10-lb 4.54-kg ($n = 79$)	49	51	
> 10-lb 4.54-kg ($n = 84$)	40	60	
Infection/injury			
No episodes ($n = 208$)	58	42	0.001
One or more episodes ($n = 55$)	26	74	
Subset with unilateral axillary dissection only ($n = 211$)			
Variable	No lymphedema ($n = 106$) (%)	Evidence of lymphedema ($n = 105$) (%)	<i>P</i> value
Weight at diagnosis			
Ideal weight or lower ($n = 137$)	51	49	0.01
Moderately overweight ($n = 40$)	29	71	
Obese ($n = 34$)	66	34	
Weight change			
No change ($n = 76$)	56	44	0.1
≤ 10-lb 4.54-kg ($n = 65$)	49	51	
> 10-lb 4.54-kg ($n = 70$)	45	55	
Infection/injury			
No episodes ($n = 165$)	58	42	0.001
One or more episodes ($n = 46$)	22	78	

* When only those with severe lymphedema ($n = 33$) are compared with those without lymphedema; $P = 0.01$.

weight after diagnosis and treatment, including 22 (67%) of the 33 women with severe lymphedema.

A statistically significant association was observed between a history of arm infections requiring antibiotics or arm injuries and the presence of lymphedema at 20 years ($P < 0.001$; Table 4). Among the 55 (21%) of the 263 women with 1 or more episodes of infection, 75% (41 of 55) reported subjective or measurable lymphedema. Of the 41 women reporting arm swelling, 14 could not recall whether the first infection/injury occurred before or after the onset of arm swelling. Four women (10%) stated that the infection/injury occurred after the onset of arm swelling. In total, 23 women (56%) stated that the first infection/injury occurred before or at the same time as the arm

swelling was noted. Eleven of 15 women (73%) who reported multiple arm infections were found to have severe lymphedema. Fifty-two percent (17 of 33) of women with severe lymphedema had had at least 1 infection, and lymphedema also was reported by 68% (87 of 128) of patients who could recall no infections or injuries to the arm. Similar results for infection and weight gain were found when the 211 women with unilateral axillary dissection only were considered separately, as shown in Table 4.

Although not significant, there was a prevalence of lymphedema among the women with less than a complete high school education. Of the group of 263 women as a whole, there were 40 women with less than a complete high school education; of these women, 62% of women in this group reported arm swelling, compared with 42% of the women who were high school graduates, and 48% of those with some postsecondary education. Results based on education level were similar in the group of 211 women with unilateral dissection only.

Interval to Onset of Lymphedema Symptoms

Among the entire group of 263 study subjects, and taking into consideration all three categories of lymphedema, 77% of patients reported swelling occurring within 3 years of diagnosis, the criterion for classification as early onset lymphedema. The onset of symptoms in the remaining 30 patients occurred gradually over the subsequent 17 years after treatment, at a rate of approximately 10 patients per 5-year interval; these patients were classified as having late onset lymphedema (defined as lymphedema with onset occurring more than 3 years after diagnosis). Of the 50 women in the mild lymphedema category, 74% had early onset lymphedema; of the 45 women with moderate lymphedema, 89% had early onset lymphedema; and of the 33 women with severe lymphedema, 64%. None of the following factors was associated with early versus late onset: age, drainage, lymph node status, weight at diagnosis, or weight change. Infection/injury was the only factor significantly associated with late onset lymphedema. Results were similar when the 211 women with unilateral axillary dissection only were considered separately.

DISCUSSION

The results of our study raise three major points related to incidence, rate of development, and etiologic factors for lymphedema:

1. The proportion of women with lymphedema at 20 years was high: 11% had measurements indicating

severe lymphedema, and a total of 48% had at least subjective reporting of a swollen sensation.

2. Onset of lymphedema was noted by approximately three-quarters (77%) within the first 3 years after breast carcinoma treatment, although additional women developed lymphedema subsequently at a rate of nearly 1% per year. Late onset was associated with a history of infection and injury.
3. Multiple factors related to specific activities and events of the subsequent years were assessed using data acquired at interview approximately 20 years after diagnosis. None was significantly associated with lymphedema except the history of infection or injury and weight gain in the posttreatment years.

The current study assesses lymphedema at a single time point, 20 years after breast carcinoma diagnosis. Three categories (mild, moderate, and severe) were used to analyze lymphedema incidence to compensate for variations in the definition and quantification of lymphedema. Traditionally, arm-circumference measurements have been used to assess lymphedema and account for most of the reporting in the literature. Circumference measurements do not quantify the volume of extra lymph fluid, however. A 2.5-cm difference is the most common definition for lymphedema, although this may be quite disfiguring on a thin arm and virtually unnoticeable on an obese arm. Nevertheless, circumferential measurements are important, because they can be obtained by a physician, by a physical therapist, and by the patient at home and can be a rough basis for comparison.

A difference in arm circumference of 2 in (5.08 cm), the value we used, represents severe lymphedema. At the opposite end of the spectrum, low-grade lymphedema cannot be easily measured, but it can be experienced as the sensation of heaviness and/or as a slight difference in appearance. In our study, women in the mild lymphedema category ($n = 50$) who had no measurable difference between arms, may not have lymphedema; rather, they may have been describing sensations resulting from such conditions as intercostal brachial nerve palsy, muscular atrophy, etc. Therefore, statistical analyses were performed using only the severe category ($n = 33$) versus the no lymphedema category ($n = 135$) and all lymphedema (mild to severe) ($n = 128$) versus no lymphedema ($n = 135$); these categories also were used for a separate analysis of the subgroup of 211 women who underwent unilateral axillary dissection only.

There can be a slight natural difference between a subject's arms because of hypertrophied muscle in the

overused arm. Older women, however, usually have poorly developed musculature. Multiple measurement sites are necessary (instead of just one), because the extra lymphatic fluid can accumulate preferentially. Therefore, we defined lymphedema based on the extent of enlargement at the measurement site showing the greatest difference between arms.

Current breast carcinoma therapy includes partial mastectomy/radiation and modified radical mastectomy as routine surgical treatment. In our study, there was no difference in the rate of lymphedema incidence based on type of treatment received (modified radical mastectomy vs. radical mastectomy). This finding is supported by those of large reviews.^{11,12} In more recent literature reporting on cases involving lumpectomy, axillary dissection, and radiation versus mastectomy, the rate of lymphedema is similar for breast-conservation surgery and mastectomy.¹³⁻¹⁶ For many women treated with breast conservation only, the incidence of arm swelling greater than 2.5 cm was 19%.¹⁷ The median number of lymph nodes removed in our study was 20—similar to a level I and II dissection in current practice.

The only factors significantly associated with the presence of lymphedema at 20 years survival were history of arm infection/injury and posttreatment weight gain ($P < 0.001$ and $P = 0.02$, respectively). Obesity at diagnosis also was shown to be statistically significant ($P = 0.01$) when those with severe lymphedema only are compared with those with no lymphedema. The association of lymphedema—for both severe only and all categories—with history of infection, while intuitive, must be interpreted within the context of the study design. Because women are told to avoid infections and even minor injuries after axillary dissection, those with lymphedema might recall their infections more readily than women without lymphedema.

The factors of weight at diagnosis and weight gain after breast carcinoma treatment do not, however, rely on recall. Obesity at diagnosis was a significant risk factor when those with severe lymphedema ($n = 33$) were compared with those with no lymphedema ($n = 135$; $P = 0.01$). Heavier weight at diagnosis was itself related to greater weight gain over the ensuing 20 years. In this particular data set, two recognized factors for lymphedema development could not be shown: extent of surgical dissection and extent of axillary radiation. All study subjects had a similar extent of axillary dissection. The relation of the extent of axillary dissection to lymphedema development can best be observed in studies that compare no axillary dissection with sampling and with extensive dissections.¹⁸ Radiation directed to the axilla (and possibly

radiation scattered to the axilla during breast or chest wall field radiation) greatly increases the incidence of lymphedema.¹⁹ Nevertheless, less than 5% of the 263 study subjects underwent radiation therapy, and those that did were irradiated using the hockey stick design of supraclavicular and internal mammary irradiation. Radiation therapy as a possible contributing factor for lymphedema could not be evaluated, because of the small size of the study population.

The current study was meant to evaluate practical questions about events and activities in the years subsequent to diagnosis of breast carcinoma. Patients regularly ask their surgeons and physicians about the wisdom of pursuing specific leisure activities or occupations after treatment. In this study, no particular activity level, occupation, sport, or hobby was associated with lymphedema. This is reassuring, and it probably rules out the possibility of these activities playing a large causative role in the development of lymphedema; however, from the nature of the study design, an effect could exist and be undetermined.

Although one may doubt accurate recall of an event occurring during a 20-year period, the onset of lymphedema is such a momentous occurrence that the general time noted is probably accurate. Many of the women remarked on 5- and 10-year anniversaries of their diagnosis. That the incidence of developing lymphedema is quite low (unless it occurs soon after breast carcinoma treatment), and that later onset may be related to infection and injury, seems quite reassuring information to give the present-day patient.

Of particular importance for current breast carcinoma patients is our study finding concerning the risk of lymphedema should a contralateral breast carcinoma necessitate contralateral axillary dissection. In this situation, patients have no ideal place for blood pressure cuffs and venipuncture, and precautions for avoiding infection and injury are even more onerous. In our study, however, patients with contralateral axillary treatment ($n = 52$) had a lower incidence of subjective lymphedema in the ipsilateral arm than those who had unilateral axillary dissection only ($n = 211$). The basis for this is unknown, but this also was found to be the case in a large, recent series from England.²⁰ Perhaps a reiteration of arm and hand precautions after contralateral axillary dissection was instrumental, although other conjectures are possible.

Although additional research is required to confirm these findings, it appears that the most important events associated with the development of lymphedema in the years subsequent to initial diagnosis of breast carcinoma are infection and weight gain. Both of these factors are under the patient's control, particularly weight gain. On the basis of our findings, we

recommend renewed and intensified educational efforts for avoidance of weight gain and infection after breast carcinoma treatment.

Finally, the current study provides further support for the use of treatment approaches that limit lymph node dissection, such as sentinel lymph node biopsy. To our knowledge, the relation of the sentinel lymph node biopsy procedure to morbidity and lymphedema development has not yet been shown. A prospective evaluation of patients undergoing sentinel lymph node biopsy, currently under way at our institution, will help to answer this question.

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