

Incidence of Breast Carcinoma-Related Lymphedema

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BACKGROUND. Of the 2 million breast carcinoma survivors, perhaps 15–20% are living currently with posttreatment lymphedema. Along with the physical discomfort and disfigurement, patients with lymphedema also must cope with the distress derived from these symptoms.

METHODS. To review the medical literature for the question of lymphedema incidence, a comprehensive, computerized search was performed. All publications with subject headings designating breast carcinoma-related lymphedema from 1970 to the present (116 reports) were found, and each summary or abstract was read. Of the 116 reports, 35 discussed the incidence of lymphedema. Of these, seven reports since 1990 from five countries with the most relevance to current patients were then chosen for greater analysis and comparison.

RESULTS. The incidence of lymphedema ranged from 6% to 30%. The source of patients, length of follow-up, measurement techniques, and definition of lymphedema varied from report to report. In general, reports with shorter follow-up reported lower incidences of lymphedema.

CONCLUSIONS. The definitive study to determine the incidence of lymphedema has not been performed to date. There has been no prospective study in which patients have been followed at intervals with accurate measurement techniques over the long term. *Cancer* 1998;83:2776–81. © 1998 American Cancer Society.

KEYWORDS: breast carcinoma, lymphedema, quality of life, treatment complication.

In a recent statement to the press,¹ the director of the National Cancer Institute reported that 8.5 million Americans are living after the diagnosis of cancer, of which a large fraction, about 2 million, are breast carcinoma survivors. With such large numbers, it behooves clinicians and scientists to study the health-related quality of life after breast carcinoma treatment. Except for breast carcinoma recurrence, no event is more dreaded than the development of lymphedema.

Lymphedema is distressing. Along with the deformity, the swelling causes discomfort and disability. Recurrent episodes of cellulitis and lymphangitis may be expected. Added to the physical symptoms is the pain caused unintentionally by the clinicians who, interested in carcinoma recurrence, trivialize the nonlethal nature of lymphedema. The appearance of arm swelling is more distressing than that of a mastectomy, because the latter can be hidden easily, but the disfigured arm/hand is a constant reminder of the disease to the woman herself and a subject of curiosity to others.

Presentation

Lymphedema is the result of a functional overload of the lymphatic system in which lymph volume exceeds transport capabilities. The build-up of interstitial macromolecules leads to an increase in oncotic pressure in the tissues, producing more edema. Persistent swelling and stagnant protein eventually lead to fibrosis and provide an ex-

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cellent culture medium for repeated bouts of cellulitis and lymphangitis. With dilatation of the lymphatics, the valves become incompetent, causing further stasis.

Lymphedema can begin insidiously at variable periods after axillary treatment. The swelling may range from being mild and barely noticeable, especially in the early stages, to a seriously disabling enlargement.

Lymphedema Quantitation

Various methods in the medical literature have been used to measure the lymphedematous arm. The traditional method is the comparison of the two arms with tape-measured circumference usually 10 cm below or 10 cm above either the olecranon or the lateral epicondyle. Such measurements can vary according to the degree of constriction of the soft tissues with the tape. Measurement of more than one location of the lower arm and upper arm (instead of relying on a single value) is important since the shape of the arm can differ among individuals before and after swelling as well as in the same individual. Measurement of the arm volume by water displacement is more accurate and can be used with a single value, but the technique is unwieldy and infrequently employed. Other more sophisticated methods (of little clinical use) include dichromatic differential absorptiometry² and computed tomography.³ Conference papers in this supplement will discuss other techniques for quantitation.

There is no standard degree of enlargement which constitutes lymphedema. Although 2 cm difference between arms is the most common definition, such swelling could be severe in a thin arm and unnoticeable in heavy arms. Natural variation can rarely result in a 2 cm greater circumference in the dominant and asymmetrically muscled extremity.⁴ Thus, for more accuracy, measurement of both arms, including preoperatively, is necessary.

Scientific Evaluation of Lymphedema

Research in all areas of lymphedema has been notably limited. Reasons for the scanty evaluation of lymphedema include 1) the prolonged course for development with a greater percentage of women developing lymphedema with longer follow-up, 2) lack of contact with the treating physicians—the original surgeon and/or the radiotherapist—and, most importantly, 3) lymphedema, with other issues concerning quality of life, has been viewed as less important than the eradication of cancer and detection of recurrence.

METHODS

A computerized search of the medical literature was undertaken. By using the search engine, MEDLINE

(Ovid Technologies, Inc., New York, NY), the medical subject heading (MeSH) "lymphedema" was combined with one of three other MeSH terms: "breast cancer," "breast carcinoma," or "breast neoplasm." MEDLINE includes foreign language journals with an English summary and MeSH terms. There were 116 publications with these three MeSH term combinations found in the years from 1970 to the present (March 31, 1998).

Over the time period, there has been an absolute increase in the number of reports on breast carcinoma-related lymphedema. However, within the same time frame, there has also been an explosion of new medical journals with a consequent rise of reports on every topic, and it is not clear whether there has been any real increase relative to other scientific topics. Of the 116 total reports, there was 1 report from 1970 to 1974, 10 from 1975 to 1979, 9 from 1980 to 1984, 22 from 1985 to 1989, 38 from 1990 to 1994, and 36 from 1995 to 1997.

The authors publishing these reports were from the United States (48 reports), France (13 reports), Germany (13 reports), Japan (8 reports), and Italy (7 reports), and 27 reports were from 15 other countries.

The 116 reports were classified further according to content in the summary or abstract by the authors (see Fig. 1). There were 35 reports referring to the incidence of lymphedema. To review the question of the proportion of breast carcinoma survivors developing lymphedema, reports were chosen from the 35 reports for comparative analysis if they 1) were published since 1990, 2) defined the source of patients, 3) described the measurement methods, and 4) noted the interval of follow-up from treatment to measurement.

RESULTS

Lymphedema Incidence

From 35 possible reports, seven studies⁵⁻¹¹ were chosen for a comparative analysis and are displayed in Table 1. The reports of Ferrandez et al.¹⁰ and Schunemann and Willich¹¹ were translated from the French and German, respectively. The other five reports⁵⁻⁹ were written in the English language. Because only a few of the reports state the breast carcinoma treatment of their patient population, it was not possible to include this important variable in the comparative analysis. Nevertheless, by focussing on the more recently published reports, these seven studies should be most relevant to current patients and their treatments.

All reports on the incidence of lymphedema, including the seven chosen, are retrospective and suffer from the imprecision of the incidence of lymphedema.

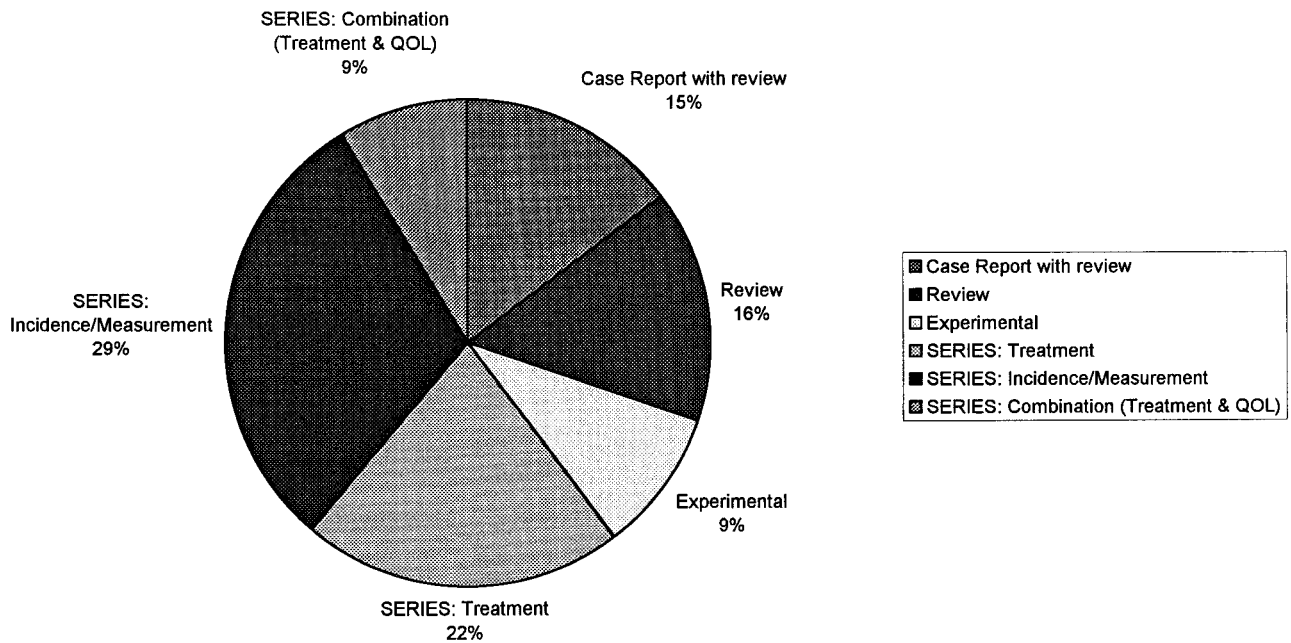


FIGURE 1. Classification of 116 medical literature reports on lymphedema between 1970 and 1997. QOL, quality of life.

TABLE 1
Seven Reports Published Since 1990 on the Incidence of Lymphedema

Yr	First author/journal	Country	Type of measurement	Definition	Incidence (%)	F/U	No. patients/source (treatment yrs)	
1991	Werner/ <i>Radiology</i> ⁵	United States	Circumference	≥2.5 cm	19.5	37 mos ^a	282/clinic F/U (1980-1989)	
1992	Ball/ <i>Ann R Coll Surg</i> ⁶	England	Circumference	>3 cm	6	>12 mos	50/one surgeon (1982-1990)	
1992	Ivens/ <i>Br J Surg</i> ⁷	England	Patient report	N/A	16	2 yrs ^a	106/clinic F/U (1986-1990)	
				Volumetric	>200 ml			10
					<3 cm			16
1993	Lin/ <i>J Clin Oncol</i> ⁸	United States	Circumference	3-4 cm	6	2 yrs ^a	283/four surgeons (1988-1990)	
					>4 cm			2
					≤4 cm			8.7
1986	Paci/ <i>Tumori</i> ⁹	Italy	Circumference	>4-8 cm	13.7	5 yrs ^a	238/tumor registry (1985-1986)	
					≥8 cm			7.9
					>3-<10 cm			14.3
1996	Ferrandez/ <i>Bull Cancer</i> ¹⁰	France	Circumference	≥10 cm	2.6	14 mos ^a	683/clinic F/U (1994)	
1997	Schunemann/ <i>Deutsch Med Wschr</i> ¹¹	Germany	Circumference	≥2 cm	24	11 yrs ^b	5868/clinic F/U (1972-1995)	

F/U: follow-up; N/A: not available.

^a Median time F/U.

^b Total.

In all reports, the denominator is unknown: the number of patients at risk for developing lymphedema in that particular population.

Table 1 shows that the incidence varied from 6%⁶ to 30%.⁹ The reported incidence of lymphedema varies along with the methods used to define lymphedema, the source of the patients, the completeness of the patient population follow-up, and the interval between axillary treatment and mea-

surement of lymphedema. The report with the lowest incidence of lymphedema⁶ also had the shortest follow-up and included patients returning to the clinic 12 months after axillary dissection. In this series, the patients were all operated by the same surgeon—one of the authors.

In the 1960s (before the time of the computerized search used in this review), when the radical mastectomy and modified radical mastectomy were the only

treatment, the incidence of lymphedema also varied greatly. In a review by American authors Britton and Nelson,¹² lymphedema incidence ranged between 6.7% and 62.5% among nine reports, and a similar review by British authors Hughes and Patel¹³ found a range of 41–70% among several reports.

In the first report of Table 1,⁵ 282 patients had breast conservation surgery, and all had radiation at Memorial Hospital where the report originated. Unselected patients were measured at a routine follow-up visit. The median interval between treatment and measurement was 37 months (range, 7–109). The 5-year actuarial rate of lymphedema (defined as circumference 2.5 cm larger on the treated side) was 16%.

The second report⁶ notes the lowest incidence of lymphedema. Fifty patients who had surgery for breast carcinoma between 1982 and 1990 by one surgeon were examined for lymphedema when they returned for routine follow-up at least 12 months after surgery. Six percent had an arm circumference difference of greater than 3 cm between arms. All patients had a full axillary clearance in conjunction with either a wide local excision or mastectomy as well as postoperative radiotherapy to the breast or chest wall skin flaps.

In a study of 106 women at the Royal South Harts Hospital,⁷ 10% of women returning for surgical follow-up were found to have lymphedema by volumetric displacement. A difference of 200 mL from the contralateral arm was defined as lymphedema. There was a median follow-up of 2 years.

In patients treated from 1988 to 1990 at Johns Hopkins University⁸ on cooperative group protocols, the lymphedema incidence was 16% (defined as 2 cm circumference difference between arms) at more than 1 year after breast carcinoma treatment. With only 43% of patients returning and thereby evaluated, the lymphedema incidence may be higher, because patients may not return to the doctor associated with the complication.

From the Tumor Registry in Florence, Italy, 238 women diagnosed with breast carcinoma in 1985 and 1986 agreed to be measured out of a possible 347 who were invited to participate.⁹ Lymphedema incidence was 30.2%. There were 8% who had extreme lymphedema with a difference of 8 cm between the two arms. The reason for the high incidence and severity of lymphedema is not suggested, although women with lymphedema may have been more likely to agree to become study subjects. Circumference measurements were taken at a median of 5 years after breast carcinoma surgery, making this data set one of the longer term evaluations.

In a retrospective study of 683 women in Avignon, France by Ferrandez et al.¹⁰ the incidence of upper arm lymphedema of greater than 3 cm was 16.9%. The proportion of women developing lymphedema was the same when they were divided into mastectomy or breast conserving treatment. However, of the lymphedematous patients, the mastectomy group had a substantially greater degree of swelling.

The last report in Table 1¹¹ is one of the largest on posttreatment lymphedema with long follow-up. In Bad Trissl, Germany, 5868 women registered in the Oncology Clinic were evaluated for lymphedema. There were 1405 cases of arm edema (24%) at measurement, with a median follow-up of 11 years. Lymphedema was defined as having a difference of arm circumferences of greater than or equal to 2 cm. There was frequent use of postoperative radiotherapy, which was used in more than half of women who had radical mastectomy, modified radical mastectomy, or breast conserving surgery. In each of the three surgical categories, the addition of radiotherapy substantially increased the incidence of lymphedema.

DISCUSSION

These studies are retrospective, and each has relatively small numbers of patients over a long time period, often from a single institution or department. The definition of lymphedema and its measurement varied from study to study. Nevertheless, the largest flaw is knowledge of the denominator. There is incomplete information on the total number of patients at risk from lymphedema versus the number with lymphedema; therefore, the incidence stated is imprecise.

Authors' Data

The definitive study on lymphedema would include a large population of consecutive patients with data acquired prospectively on multiple patient characteristics and treatment variables, accurate arm measurements preoperatively and at intervals during follow-up, data on suspected causative factors in subsequent years (such as arm infections), and minimal proportion lost to follow-up in a long term study. Knowing all of the rigid criteria for a definitive study, especially the several years of interval measurements and thereby the expense, the authors examined available hospital data sets for the possibility of useful information that could be obtained at present. With a grant from the federal government (DAMA 17-J-94-4276), a study on lymphedema was performed on a research patient cohort at Memorial Sloan-Kettering Cancer Center.

A preexisting research data set of 1216 consecutively treated patients at Memorial Sloan-Kettering

Cancer Center from 1976 to 1978 was used. Only 2% of the women diagnosed and treated during that time period were not entered. Patient characteristics and treatment variables were obtained prospectively. The cohort has been followed annually, with interval medical history for breast carcinoma recurrence and overall survival. Multiple funded research projects and publications have resulted: Obesity at diagnosis as a prognostic factor,¹⁴ the effect of histologic variables on outcome,¹⁵ risk of multicentricity and bilaterality,¹⁶ and others.¹⁷⁻¹⁹ However, before the present research project, nowhere in the 18-20 year course of follow-up were they assessed for lymphedema.

In 1997, various endpoints related to lymphedema and its suspected etiologic factors were assessed by the same research nurse in these patients. Self reported arm circumference measurements at two sites also were obtained by using a method validated on nonprotocol patients.

There were 336 women living in 1996 (only 42 patients had been lost to follow-up). Of these 336 women, 64 were unable (medical reasons) or refused to participate, and 272 women were study subjects on whom complete data and circumferential measurements were obtained. Of 272 study patients, 32 (12%) had enlargement of 2 inches or more in circumference over the contralateral arm that was designated as severe lymphedema. If those with some measurable enlargement, but less than 2 inches, are included, then an additional 43 women had lymphedema. About half of the patients with documented minimal enlargement (1-2 cm) suffer symptoms of "arm heaviness."²⁰

Based on these two categories, 75 of 272 patients (28%) have measurable lymphedema. Another 47 of 272 patients (17%) also stated in the research interview that their arm "felt" swollen. In the last category, there was no measurable difference, and they had not seen a medical professional for lymphedema. In another population of patients, a survey found that half of the patients acknowledging arm swelling in a mail questionnaire had never reported this problem to any doctor or other health care provider.²¹ An unknown proportion of breast carcinoma survivors may indeed have slight but unmeasurable lymphedema. Because that may be the case in these study patients, they are included in the "all" lymphedema category in the effort to be inclusive. To evaluate etiologic factors, the data were analyzed with all levels of lymphedema, with the two measurable levels and with severe lymphedema alone, and the results are undergoing statistical analysis.

Surprisingly, the treatment of a contralateral breast carcinoma was not associated with a higher incidence of lymphedema. Of the 272 women, 55

women were treated for contralateral breast carcinoma and had a lower incidence of lymphedema in the index arm (not significant) than those who received unilateral breast carcinoma treatment. Another large data set with contralateral breast carcinoma had similar findings.²²

CONCLUSIONS

In sum, objective lymphedema incidence in seven reports published in 1990, as noted in Table 1, was about 20%.⁵⁻¹¹ The range was 6%⁶ to 30%⁹ of the diverse study populations measured at various intervals after axillary dissection with arm circumferences or volumetric equipment. Table 1 is comprised of patients who underwent different surgical and radiotherapeutic procedures for breast carcinoma treatment in the United States, England, Italy, France, and Germany. In general, these reports show higher incidence and more severe swelling related to longer follow-up. However, in the reports with longer follow-up, more extensive breast carcinoma treatment was the standard in those years, and the treatment factor also may contribute to a higher risk of lymphedema.

The incidence of lymphedema seems to be decreasing in more modern times, according to practicing surgeons. This is probably due to earlier diagnosis of less advanced breast carcinomas that can be treated with lesser axillary procedures. In turn, this trend seems to be due to mammographic screening and public education efforts. Furthermore, the development of two modern techniques—sentinel lymph node biopsy technology, allowing less axillary surgery and more precise radiation planning, and delivery, allowing less radiation to the axilla—should also contribute to the decrease in the incidence of lymphedema.

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