

Lymphedema Beyond Breast Cancer

A Systematic Review and Meta-Analysis of Cancer-Related Secondary Lymphedema

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BACKGROUND: Secondary lymphedema is a debilitating, chronic, progressive condition that commonly occurs after the treatment of breast cancer. The purpose of the current study was to perform a systematic review and meta-analysis of the oncology-related literature excluding breast cancer to derive estimates of lymphedema incidence and to identify potential risk factors among various malignancies. **METHODS:** The authors systematically reviewed 3 major medical indices (MEDLINE, Cochrane Library databases, and Scopus) to identify studies (1972-2008) that included a prospective assessment of lymphedema after cancer treatment. Studies were categorized according to malignancy, and data included treatment, complications, lymphedema measurement criteria, lymphedema incidence, and follow-up interval. A quality assessment of individual studies was performed using established criteria for systematic reviews. Bayesian meta-analytic techniques were applied to derive summary estimates when sufficient data were available. **RESULTS:** A total of 47 studies (7779 cancer survivors) met inclusion criteria: melanoma (n = 15), gynecologic malignancies (n = 22), genitourinary cancers (n = 8), head/neck cancers (n = 1), and sarcomas (n = 1). The overall incidence of lymphedema was 15.5% and varied by malignancy ($P < .001$): melanoma, 16% (upper extremity, 5%; lower extremity, 28%); gynecologic, 20%; genitourinary, 10%; head/neck, 4%; and sarcoma, 30%. Increased lymphedema risk was also noted for patients undergoing pelvic dissections (22%) and radiation therapy (31%). Objective measurement methods and longer follow-up were both associated with increased lymphedema incidence. **CONCLUSIONS:** Lymphedema is a common condition affecting cancer survivors with various malignancies. The incidence of lymphedema is related to the type and extent of treatment, anatomic location, heterogeneity of assessment methods, and length of follow-up. *Cancer* 2010;116:5138-49. © 2010 American Cancer Society.

KEYWORDS: lymphedema, cancer, systematic review, meta-analysis, survivorship, surgery.

Lymphedema is a chronic, progressive, and often debilitating condition estimated to impact 2 to 3 million people in the United States,¹ with secondary or acquired lymphedema accounting for the majority of cases. Secondary lymphedema is the result of obstruction or disruption of the lymphatic system, which can occur as a consequence of tumors, surgery, trauma, and radiation therapy, and the resulting mechanical insufficiency can lead to the accumulation of fluid in the interstitial tissues.

Lymphedema has been described as 1 of the most significant survivorship issues after the surgical treatment of breast cancer and in this population has been documented to have significant physical,² functional, quality of life,³ and economic consequences.⁴ The reported incidence of lymphedema after breast cancer treatment varies widely, ranging from 6% to 63%,^{5,6} depending on the population studied, measurement criteria used, and the reported length of follow-up.

Apart from breast cancer, secondary lymphedema has been reported as a consequence of treatment for several solid tumors, including melanoma, head and neck, gynecological, and genitourinary malignancies. A common feature among these solid tumors is the pattern of disease progression, with the development of regional lymphatic metastases often occurring before distant metastatic disease. Particularly in the absence of effective systemic therapies, the oncologic principles for treating regional lymph node metastases in patients with these tumors often include complete lymph node dissection of the involved lymph node basin, whether it be axillary, inguino-femoral, or pelvic (iliac/obturator). Although soft tissue or bone

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sarcomas rarely metastasize to regional lymph nodes, primary sarcomas of the extremities and the treatment of such tumors can result in the obstruction or disruption of the lymphatic system, resulting in secondary lymphedema.

Risk factors for lymphedema have been examined primarily in patients with breast cancer. In this population, extent of surgery, tumor burden, and adjunctive treatments (eg, radiation therapy) have been identified as primary risk factors for breast cancer-related lymphedema.⁷ The adoption of sentinel lymph node biopsy in the pathologic staging of breast cancer, along with other malignancies, has drastically reduced the number of patients undergoing elective lymph node dissection; by allowing surgeons to avoid lymph node dissections in patients with lymph nodes that do not harbor metastases, the risk of developing lymphedema in lymph node-negative patients has likely decreased. However, secondary lymphedema has been shown to occur after even simple operations, such as wide local excision or sentinel lymph node biopsy.⁸

Acknowledging the lack of consistent, comprehensive lymphedema incidence estimates outside of the field of breast cancer, the aim of this study is to review the available body of oncology literature assessing post-treatment lymphedema in patients with other types of malignancies to broadly examine the incidence of lymphedema in the wider population of cancer survivors. In addition, we sought to identify risk factors associated with the development of lymphedema, to inform healthcare providers and promote awareness of this widespread and debilitating condition in the oncology community.

MATERIALS AND METHODS

The systematic review of the literature was performed in 2 phases. The initial phase was carried out by a reference research librarian, who searched 3 major medical indices (PubMed-MEDLINE, Cochrane Library databases, and Scopus) for articles published between 1972 and 2008. Ten search strategies were used, and for each search, “lymphedema” and “cancer” were used as keywords, along with specific malignancies: colorectal; gynecological including cervical, uterine, vulvar; genitourinary including prostate, penile, and bladder; sarcoma; melanoma; and head/neck cancers. The initial searches resulted in 1099 entries, which were then imported into Endnote X2.0 (Build 3210, Thomson Corporation, Stamford, Conn) to remove duplicates ($n = 230$). In the second phase of the review, articles in languages other than English ($n = 182$) were excluded, as well as case reports, letters, and reviews ($n = 314$). A total of 373 eligible studies remained after the selection process

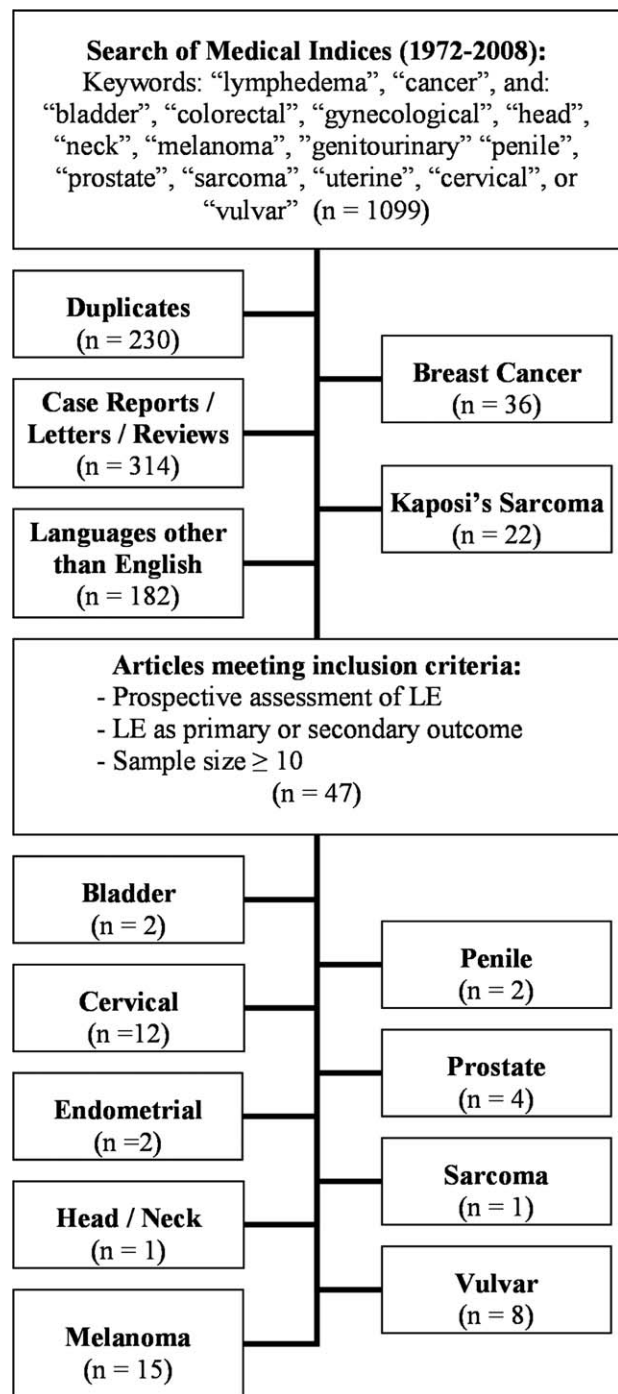


Figure 1. Search strategy and study selection are shown. LE indicates lymphedema.

(Fig. 1). After this, studies pertaining to lymphedema in patients with breast cancer ($n = 36$) or Kaposi sarcoma ($n = 22$) were excluded from further review.

A total of 315 articles were reviewed in detail with respect to predefined inclusion criteria requiring

prospective assessment of lymphedema as a primary or secondary study outcome and a sample size of at least 10 patients. Because the primary focus of this review was to estimate the incidence of treatment-related lymphedema, retrospective reviews that documented prospectively collected lymphedema-related data were also included. To ensure the search was sufficiently comprehensive, articles from the archives of the authors were also examined, including reference lists from related articles. A total of 47 studies met inclusion criteria. The 47 studies were subsequently categorized according to type of malignancy, and extracted data included number of patients, extent of operation, postsurgical infections, use of radiation therapy, length of follow-up, criteria for defining lymphedema, measurement methods, and incidence of lymphedema.

Quality Control

A 14-item methodological checklist adapted from established quality criteria for systematic reviews was used to assess the quality of the 47 individual studies.⁹⁻¹¹ Similar adaptations have recently been used in a systematic review of quality of life issues facing long-term breast cancer survivors.¹² Each article was independently scored by 2 authors (R.L.A. and J.N.C.), with 1 point assigned for each criterion fulfilled. Score discrepancies were resolved through group consultation.

Statistical Analysis

The various clinical definitions, measurement methods, and follow-up reported when assessing lymphedema limited the methods available for summary and subgroup analysis. Weighted averages based on study size were calculated as pooled summary statistics for lymphedema incidence, and stratification methods were used to examine the individual effects of study characteristics on the summary estimates. When possible, subgroup analyses of studies reporting characteristics of patient treatment groups in sufficient detail were examined separately and recorded along with their respective reported incidence of lymphedema. Study characteristics designated a priori for examination included sample size, type of lymphedema assessment (ie, subjective vs objective), measurement methods (circumference vs water displacement), and length of follow-up. The effects of postsurgical infections, radiation therapy, and deep pelvic lymph node dissections were also examined when data were available.

Meta-Analysis

For the meta-analysis, summary incidence estimates were obtained using a Bayesian random effects model assuming

a binomial distribution of the outcome.¹³ WinBUGS 1.4.2¹⁴ was used to perform Markov chain Monte Carlo simulations. With the first 5000 draws discarded, only the next 45,000 draws were used to obtain posterior estimates based on 3 separate chains with overdispersed starting values. The Brooks, Gelman, and Rubin convergence statistics¹⁵ were used to assess the models, and only properly converged models were considered further.

RESULTS

A total of 47 eligible studies were identified that examined secondary lymphedema in patients with melanoma ($n = 15$), gynecologic cancer ($n = 22$), genitourinary cancers ($n = 8$), head/neck cancers ($n = 1$), and sarcomas ($n = 1$). The reported incidence of postoperative lymphedema in these studies varied from 0% to 73%, and there was considerable heterogeneity among studies with respect to lymphedema measurement methods, lymphedema classification, and follow-up intervals (Tables 1-4). For the combined total of 7779 cancer survivors included, 15% were identified with lymphedema; however, the incidence varied widely according to the type of malignancy ($P < .001$). The median patient follow-up varied greatly among the studies, ranging from 6 to 118 months. Globally, the reported incidence of lymphedema was higher for studies with longer follow-up ($r = 0.38$, $P = .02$) (Fig. 2).

Type of Malignancy

A total of 15 studies were identified that assessed lymphedema in patients with melanoma between 1977 and 2008 (Table 1). In these studies, the reported incidence of lymphedema ranged from 1% to 66%, with an overall pooled incidence of 9% in 3676 patients. Melanoma patients were then stratified into 2 groups according to the anatomic region in which lymph node dissection was performed (ie, axillary and inguinofemoral). Six studies included both patients who had undergone axillary or inguinofemoral lymph node dissections,¹⁶⁻²¹; the dissection groups from these studies are listed separately in Table 1. The pooled incidence of lower extremity lymphedema after inguinofemoral lymph node dissection was higher (18%) than for upper extremity lymphedema after axillary lymph node dissection (3%). Twelve melanoma studies used objective measurements for lymphedema (ie, circumference or water displacement), with the remainder using subjective measures ($n = 3$). Follow-up for melanoma patients varied from 16 to 59 months, and the median quality score for these studies was 7 (range, 4-10).

Table 1. Published Articles Assessing Lymphedema in Melanoma Patients Stratified by Type of Dissection

Study	No. of Patients	Mean/Median Follow-up, mo	Lymphedema Measurement Method	LE Grade Criteria	Reported Incidence of LE, %	Quality Score
Axillary lymph node dissection						
de Vries 2005 ²⁹	14	59	Water displacement	>10%	7	8
Starrtt 2004 ³³	107	36	Water displacement/ circumference	>16%	17	10
Serpell 2003 ¹⁹	33	22	Subjective	—	6	5
Wrightson 2003 ²¹	1688	16	Subjective	—	1	10
Burmeister 2002 ¹⁷	56	—	Subjective	Grade 1: slight swelling; grade 2: obvious swelling; grade 3: treatment required; grade 4: incapacitating edema with ulceration	39	10
Lawton 2002 ¹⁸	106	22	Circumference	Mild: >2 cm; moderate: clinically apparent with reported heaviness; severe: obvious edema	5	10
Bowsher 1986 ¹⁶	28	53	Circumference	Mild: 0-1.9 cm; moderate: 2-4 cm; severe: >4 cm; LE delineated at moderate	3	4
Urist 1983 ²⁰	98	—	Circumference		1	5
Inguinofemoral lymph node dissection						
Brouns 2008 ²⁶	62	34	Circumference	Discrete: 2-4 cm; moderate: 4-8 cm; severe: >8 cm	61	7
de Vries 2006 ³⁰	66	51	Water displacement	Slight: 6.5%-20%; moderate: 20%-40%; severe: >40%	18	10
Wrightson 2003 ²¹	784	16	Subjective	—	6	10
Serpell 2003 ¹⁹	27	22	Subjective	—	29	5
Burmeister 2002 ¹⁷	33	—	Subjective	Grade 1: slight swelling; grade 2: obvious swelling; grade 3: treatment required; grade 4: incapacitating edema with ulceration	66	10
Lawton 2002 ¹⁸	56	24	Circumference	Mild: >2 cm; moderate: clinically apparent with reported heaviness; severe: obvious edema	14	10
Baas 1992 ³¹	151	48	Water displacement/ circumference	>6.5%; >3.5 cm	20	5
Bowsher 1986 ¹⁶	44	53	Circumference	>2 cm	35	4
Karakousis 1983 ⁶⁴	67	28	Circumference	Slight: 1.5-2.5 cm; moderate: 3-4.5 cm	21	9
Urist 1983 ²⁰	58	—	Circumference	Mild: 0-1.9 cm; moderate: 2-4 cm; severe: >4 cm; LE delineated at moderate	26	5
James 1982 ³²	33	—	Water displacement/ circumference	>100 mL; >0.5 cm	58	5
Holmes 1977 ²⁷	84	—	Circumference	>2 cm	24	6
Papachristou & Fortner 1977 ⁶⁵	81	—	Circumference	>1 inch	30	5

LE indicates lymphedema.

Axillary, n = 8 studies; inguinofemoral, n = 13 studies.

A total of 8 studies examining lymphedema associated with genitourinary cancers, which included penile, prostate, and bladder cancers, were published from 1978 to 2008 (Table 2). Of the 1060 combined patients with genitourinary cancers, 11% were identified with lymphedema. Among those with penile cancer (n = 244), prostate cancer (n = 549), and bladder cancer (n = 267), the incidence of lymphedema was 21%, 4%, and 16%, respectively. Only 1 study in this group used objective measurement methods (circumference), whereas the remainder assessed lymphedema subjectively. The length of follow-up ranged from 9 to 115 months, and the median quality score for these studies was 5 (range, 3-9).

For the 22 articles examining lymphedema associated with gynecological malignancies published from 1978 to 2008 (Table 3), the incidence of lymphedema ranged from 0% to 73%. Of the 2850 patients with gynecological malignancies, 716 (25%) were identified with lymphedema (cervical, n = 1544, 27% with lymphedema; vulvar, n = 890, 30% with lymphedema; endometrial, n = 168, 1% with lymphedema). Nearly all of these studies used subjective measurement methods, with the only exceptions noted in 1 study that used water displacement and circumference measures to evaluate cervical cancer patients and in another that used circumference measures to assess patients with vulvar cancer.^{22,23} The median quality score was 7 (range, 4-10) for studies of gynecological cancers, and follow-up ranged from 6 to 118 months.

Three studies were identified (1983 to 2008) that prospectively assessed lymphedema in patients with head and neck cancers (Table 4). Only Wolff et al reported mean follow-up (24 months),²⁴ and the study by Urist et al was the only 1 to use objective assessment measures (circumference).²⁰ The reported incidence of lymphedema ranged from 0% to 8%, and for the combined total of 139 patients, 4% were identified with lymphedema. The median quality score for these studies was 5 (range, 4-10). A single sarcoma study was published in 1991,²⁵ where 54 patients were followed for 50 months using subjective lymphedema measurement criteria. The quality of the study was rated at 7, and the incidence of lymphedema was reported at 30%.

Treatment Factors

When available, patient-level data related to the surgical procedure performed (eg, inguino-femoral with or without pelvic lymph node dissection), postoperative complications, and treatment with radiation therapy were extracted

Table 2. Published Articles Assessing Lymphedema in Patients With Genitourinary Malignancies (n=8)

Study	Type of Malignancy	No. of Patients	Mean/Median Follow-up, mo	Lymphedema Measurement Method	LE Criteria	Reported Incidence of LE, %	Quality Score
Jacobellis 2003 ⁶⁶	Penile	10	55	Subjective	—	20	4
Henningsohn 2002 ⁴³	Bladder	224	115	Subjective	—	15	9
Ravi 1993 ²⁸	Penile	234	—	Circumference	Mild: 0-1.9 cm; moderate: 2-4 cm; severe: >4 cm; LE delineated at moderate	21	5
Kavoussi 1993 ⁴⁴	Prostate	372	9	Subjective	—	1	5
Greskovich 1991 ⁴²	Prostate	65	29	Subjective	—	3	6
Rainwater & Zincke 1988 ⁵⁰	Prostate	30	80	Subjective	—	10	4
Lieskovsky 1980 ⁴⁶	Prostate	82	—	Subjective	—	18	5
Clark 1978 ³⁹	Bladder	43	—	Subjective	—	23	3

LE indicates lymphedema.

Table 3. Published Articles Assessing Lymphedema in Patients With Gynecologic Malignancies (n=22)

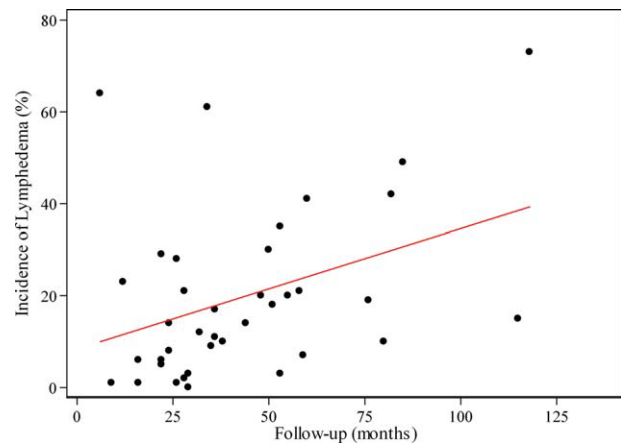
Study	Type of Malignancy	No. of Patients	Mean/Median Follow-up, mo	Lymphedema Measurement Method	LE Criteria	Reported Incidence of LE, %	Quality Score
Carlson 2008 ²²	Vulvar	137	6	Circumference	Mild: 0-2.9 cm; moderate: 3-5 cm; severe: >5 cm; LE delineated at moderate	64	10
Van der Zee 2008 ⁶⁷	Vulvar	383	35	Subjective	—	9	7
Moore 2008 ⁶⁸	Vulvar	31	29	Subjective	—	0	9
Tanaka 2007 ⁵²	Cervical (42%), endometrial (47%), ovaries (11%)	184	36	Subjective	Stage I: tissue indents when pressed and holds indentation; stage II: tissue bounces back with no indentation; stage III: lymphostatic elephantiasis	11	10
Zhang 2007 ⁶⁹	Vulvar	57	—	Subjective	—	37	4
Bellati 2005 ⁷⁰	Vulvar	14	58	Common Toxicity Criteria	—	21	7
Judson 2004 ⁷¹	Vulvar	61	—	Subjective	—	26	8
Gaarenstroom 2003 ⁷²	Vulvar	101	26	Subjective	—	28	4
Fujiwara 2003 ⁴¹	Cervical (66%), endometrial (34%)	64	—	Subjective	—	11	8
Bergmark 2002 ³⁶	Cervical	246	60	Subjective	—	41	7
de Hullu 2001 ⁷³	Vulvar	106	118	Subjective	—	73	4
Uno 2000 ⁵³	Cervical	98	76	Subjective	—	19	6
Kridelka 1999 ⁴⁵	Cervical	25	32	Subjective	—	12	7
Logmans 1999 ⁴⁷	Cervical	22	12	Subjective/MRI	—	23	5
Snijders-Keilholz 1999 ⁵¹	Cervical	220	38	Subjective	RTOG/EORTC classification	10	9
Yeh 1999 ⁵⁴	Cervical	179	82	Subjective	RTOG/EORTC classification	42	4
Chatani 1998 ³⁸	Cervical	128	85	Subjective	Grade 1: mild symptoms; grade 2: treatment required; grade 3: surgery required	49	7
Werngren-Elgstrom 1994 ²³	Cervical	54	—	Water displacement/circumference	Slight: 5-9.9%/3.5-6 cm; moderate: 10-14.9%/6.5-12 cm; severe LE: ≥15%/≥12.5 cm	41	7
Orr 1991 ⁴⁹	Endometrial	168	26	Subjective	—	1	5
Florica 1990 ⁴⁰	Cervical	50	28	Subjective	—	2	4
Bilek 1982 ³⁷	Cervical	120	44	Subjective	—	14	6
Martimbeau 1978 ⁴⁸	Cervical	402	—	Subjective	Mild: cosmetic only; moderate: treatment required; severe LE: treatment does not help and occupational difficulties	23	5

LE indicates lymphedema; MRI, magnetic resonance imaging; RTOG, Radiation Therapy Oncology Group; EORTC, European Organization for Research and Treatment of Cancer.

Table 4. Published Articles Assessing Lymphedema in Patients With Other Malignancies (n=4)

Study	Type of Malignancy	No. of Patients	Mean/Median Follow-up, mo	Lymphedema Measurement Method	LE Criteria	Reported Incidence of LE, %	Quality Score
Robinson 1991 ²⁵	Sarcoma	54	50	Subjective	—	30	7
Wolff 2009 ²⁴	Head/neck	50	24	Common Toxicity Criteria/late effects normal tissues criteria	—	8	4
Burmeister 2002 ¹⁷	Head/neck	41	—	Subjective	Grade 1: slight swelling; grade 2: obvious swelling; grade 3: treatment required; grade 4: incapacitating edema with ulceration	5	10
Urist 1983 ²⁰	Head/neck	48	—	Circumference	Mild: 0-1.9 cm; moderate: 2-4 cm; severe: >4 cm; LE delineated at moderate	0	5

LE indicates lymphedema.

**Figure 2.** Scatterplot of studies by median follow-up (in months) and reported incidence of lymphedema with linear prediction is shown.

and summarized. Twenty-two of the 47 articles identified a total of 2837 patients who had undergone pelvic lymph node dissection as a component of their cancer treatment. Overall, 22% of these patients developed lower extremity lymphedema. For those patients with melanoma undergoing iliac/obturator lymph node dissection (n = 132), the incidence of lymphedema was reported as 42%. For those undergoing pelvic lymph node dissection for genitourinary (n = 767) or gynecological cancers (n = 1938), the incidence of lymphedema was reported as 8% and 27%, respectively. A total of 18 articles examined the effect of radiation therapy on lymphedema, with a combined total of 1716 patients. Of those, 31% were identified with lymphedema. For those with melanoma undergoing radiation therapy (n = 106), 50% were noted to have lymphedema. For those with genitourinary (n = 284) or gynecological cancers (n = 1193) undergoing radiation treatment, the pooled incidence of lymphedema was reported as 16% and 34%, respectively.

Methods of Lymphedema Assessment

The most commonly reported objective measurement method was extremity circumference measurement (9 studies), with 7 studies using a difference threshold of >2 cm to define lymphedema.^{16,18,20,22,26-28} Two studies used water displacement methods exclusively for limb volume assessment, defining lymphedema thresholds of 6.5% and 10%,^{29,30} and another 4 studies used both circumference and water displacement.^{23,31-33} More subjective assessments of lymphedema included the Common Toxicity Criteria and the Late Effects Normal Tissues Scales,^{34,35} but the majority used ad hoc clinical

grading to define lymphedema such as skin-pinch tests or scales defined by the treating physician. Global comparisons revealed that patients were 91% more likely to be identified with lymphedema (relative risk, 1.91; 95% confidence interval [CI], 1.71-2.12; $P < .001$) when they were enrolled in studies using objective measurement methods (ie, volume and circumference measures) than those enrolled in studies using subjective (eg, self-report or provider observation) assessments.

Quality Assessment

The methodological quality of the 47 studies included in this review varied greatly. The maximum score possible from our quality assessment instrument was 14, but all ratings fell between 3 and 10 points, with a mean rating of 6.5 (standard deviation [SD], 2.2). The highest mean quality score was 7.3 (SD, 2.4) for melanoma studies, and the lowest mean quality score was 5.1 (SD, 1.8) for genitourinary cancers.

Meta-Analysis

The overall lymphedema incidence estimate derived from the random effect meta-analytic model (15.5%; 95% CI, 11.0-21.0) was nearly identical to the overall pooled incidence estimate of 15% (Table 5). However, greater differences in incidence estimates were observed in subgroup analysis. More specifically, for gynecologic malignancies and melanomas, differences between pooled and random effects incidence estimates ranged from 2% to 10%. However, all pooled incidence estimates fell within the 95% CIs of the random effects estimates.

The meta-analytic techniques further revealed that lymphedema incidence estimates for melanoma were 16.3% overall, 5.1% for melanomas of the upper extremity, and 28.0% for melanomas of the lower extremity. For gynecologic malignancies, 19.6% incidence was observed for lymphedema overall, with 21.8% for cervical and 24.9% for vulvar malignancies. For sarcomas, head and neck tumors, and endometrial tumors, random-effect estimates could not be calculated because of insufficient sample size. Further model refinement to include potential covariates was also inhibited by missing data (median patient follow-up) or inadequate distribution of study characteristics (measurement method/criteria).

DISCUSSION

The overall incidence of lymphedema for cancer survivors in this review was 15.5%. Incidence rates varied widely

among individual studies and according to primary tumor type. However, the observed disparity is more likely a function of the observed heterogeneity among study methods (eg, assessment methods and length of follow-up) than it is of the particular characteristics of the solid tumors reviewed. Increased lymphedema risk was observed for patients undergoing pelvic dissections (22%),^{18,23,26,30,36-54} as well as for those undergoing radiation therapy (31%).^{17,24,25,33,36-38,40,42,43,45,46,48,50-54} The high incidence of lymphedema observed for gynecological malignancies (20%) is not surprising given that approximately 70% of the patients in these studies were reported to have undergone pelvic lymph node dissections and/or radiation therapy. However, an equal percentage of patients with genitourinary malignancies underwent pelvic dissections, and the overall incidence of lymphedema was only 10%. The differences may be related to the lower percentage of genitourinary cancer patients undergoing adjunctive radiation therapy (27%). Lymphedema was only reported in 4% of patients with head and neck malignancies and 5% for upper extremity melanoma, with far fewer patients undergoing pelvic dissections and radiation therapy in these groups. The higher incidence of lower extremity lymphedema after inguino-femoral lymph node dissection may be because of anatomic variation, with fewer associated lymphatic collateral pathways, or be related to a specific response to increased hydrostatic pressure in the disrupted lower extremity lymphatics.⁵⁵

These findings are concordant with the primary risk factors for lymphedema identified in breast cancer survivors. Specifically, the surgical treatment for breast cancer, which often includes axillary lymph node dissection and/or mastectomy, is considered a major risk factor for lymphedema.^{7,56} The extent of lymph node dissection and tumor burden has also been shown to increase the risk of lymphedema.⁵⁶ Over the past decade, less invasive surgical techniques such as sentinel lymph node biopsy and breast-conserving surgery have reduced the overall incidence of lymphedema; however, conservative estimates for incidence after sentinel lymph node biopsy are still in the range of 7%.^{57,58} For high-risk patients treated with adjuvant radiation to a dissected axilla, the risk of subsequent lymphedema is greatly increased, with reported rates close to 45%.⁷ Other breast cancer-related lymphedema risk factors for which data were not available in this systematic review of nonbreast cancer lymphedema studies include patient age, obesity, tumor factors, lymph node status, the presence of postoperative seroma or infection, and the presence of venous obstruction. It is likely

Table 5. Incidence Estimates of Cancer-Related Secondary Lymphedema

Group	No. of Studies ^a	No. of Patients	Pooled Incidence, %	Range	Random Effects Incidence, %	95% CI
Overall	47	7779	15	0-73	15.5	11.0-21.0
Upper extremity ^b	8	2130	3	1-39	5.1	1.1-17.9
Lower extremity ^c	43	5456	20	1-66	19.9	14.3-26.8
Head and neck	3	139	4	0-8	NA	—
Melanoma (overall)	15	3676	9	1-66	16.3	8.6-27.8
Upper	8	2130	3	1-39	5.1	1.1-17.9
Lower	13	1546	18	6-66	28.0	17.2-42.2
Genitourinary (overall)	8	1060	11	1-23	10.1	3.2-25.2
Bladder	2	267	16	15-23	16.2	0-100
Penile	2	244	21	20-21	19.6	0-100
Prostate	4	549	4	1-18	4.8	0.1-71.7
Gynecologic (overall)	22	2850	25	0-73	19.6	11.1-31.0
Cervical	11	1544	27	2-49	21.8	11.6-35.8
Endometrial	1	168	1	—	NA	—
Vulvar	8	890	30	0-73	24.9	3.5-59.7
Sarcoma	1	54	30	—	NA	—

CI indicates confidence interval; NA, not available.

^aStudies were included in the overall estimates that could not be discretely assigned to subcategories due to insufficient granularity of the data, and some individual studies were included in >1 category when sufficient data were available for multiple subgroups.

^bIncludes melanomas only.

^cIncludes genitourinary and gynecologic malignancies and lower extremity melanomas.

that these risk factors do not account for the entire at-risk population. Indeed, even outside the field of oncology, many of these are independent risk factors (eg, obesity, chronic venous insufficiency) for secondary lymphedema.⁵⁹

Over the past decade there has been progress in the understanding of normal lymphatic function and the potential molecular pathways leading to lymphatic hypoplasia related to hereditary lymphedema. Several genes (*FLT4*, *FOXC2*, *SOX18*) have been shown to be associated and potentially responsible for the development of several variants of hereditary lymphedema.⁶⁰ Mutations in vascular endothelial growth factor receptor-3 (*VEGFR3*) as well as the VEGF-C/VEGFR3 signaling systems have been identified as key components to both normal and pathologic lymphangiogenesis.⁶¹ It has been hypothesized that mutations or variations in the genes responsible for underlying genetically linked, anatomical, and physiological variations in the lymphatic system may also increase the risk of secondary lymphedema.⁶² The identification of such mutations could potentially have important therapeutic implications.

Not surprisingly, patients enrolled in studies using objective measurement methods were twice as likely to be identified with lymphedema compared with studies that

used subjective scales. Currently, there is no gold standard measure or defining criteria for lymphedema assessment in the clinical setting, and the lack of a convenient, standardized, objective measurement method has resulted in reports of widely varying incidence. Although circumference measures may appear to be the most convenient, several problems exist, including problems with control of intra- and intermeasurer reliability. It is also time-consuming and requires considerable experience to obtain accurate measures. Although limb volume assessment using water displacement has historically been regarded as the most sensitive and accurate means to assess limb volume change, clinicians rarely use this cumbersome approach outside the research setting. To address these clinical challenges, several new devices have been introduced but have not yet become widely available. The perometer (JUZO, Cuyahoga Falls, Ohio) is an optoelectronic volumetry device that uses infrared light and an array of optoelectronic sensors to assess limb volume. In 2009, the US Food and Drug Administration approved the use of a bioelectrical impedance spectroscopy device (L-Dex U400, Impedimed, San Diego, Calif) for the clinical assessment of unilateral lymphedema of the arm in female breast cancer patients. Bioelectrical impedance spectroscopy measures tissue opposition (impedance) of

body tissues to a low, alternating electric current over a range of frequencies to determine extracellular fluid volume.⁶³ The magnitude of the impedance is used to determine the extracellular fluid volume and is expressed as an impedance ratio. Tissue tonometry is another method that measures the resistance of tissues to compression and quantifies tissue compliance. The degree of compressibility can then be correlated with limb swelling.

The strengths of this study include the large combined sample size for estimating lymphedema incidence, stratification by malignancy and extent of surgical resection, and the use of meta-analytic techniques. Specific eligibility criteria were used to exclude studies in which lymphedema was retrospectively assessed using medical records. Detailed patient-level data extraction was performed when possible to collate information related to radiation therapy and types of dissection. An assessment of methodological quality of the individual studies was included as an element of the systematic review to highlight the lack of methodological rigor in the current body of lymphedema literature. The weaknesses associated with this review can largely be attributed to the lack of consensus in the field of lymphedema. Because there are no precise consensus definitions or grading systems for lymphedema, clinicians and investigators have used a wide variety of independently developed, non-validated, subjective and objective diagnostic and rating criteria. In addition, limited patient-level data related to patient characteristics (ie, body mass index), radiation treatment, and postoperative complications did not allow for adjusted risk analyses. Furthermore, although a positive correlation was observed between length of follow-up and reported incidence, it is important to note that conclusions are limited by inherent variations among and between studies, including heterogeneity with respect to sample size, study quality, and clinical profile. Others, however, have previously reported a similar trend in studies of patients with breast cancer.⁶

In summary, cancer-related lymphedema is a common post-treatment condition. All persons undergoing lymph node dissection for the treatment of solid tumors should be considered at lifetime risk for developing lymphedema. In breast cancer patients, lymphedema has been described as an often overlooked, underdiagnosed, and undertreated condition, and the same can likely be said for patients with other malignancies. Early referral to lymphedema therapists for early intervention has been shown to reduce the risk of chronic lymphedema and to improve outcomes. As such, postoperative

surveillance evaluations should at a minimum include observation for signs (eg, swelling) and assessment of lymphedema-associated symptoms (eg, heaviness), because early detection and intervention hold the greatest promise of reducing the incidence of this widespread condition. Additional prospective longitudinal studies that incorporate validated instruments and objective measurements are needed to further define the magnitude of this condition.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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