# *Estimating the Population Burden of Lymphedema*

**STANLEY G. ROCKSON AND KAHEALANI K. RIVERA**

*Stanford Center for Lymphatic and Venous Disorders, Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California, USA*

**Lymphedema is a complex, regional edematous state that ensues when lymph transport is insufficient to maintain tissue homeostasis. The disorder is remarkably prevalent, but the population implications of lymphatic dysfunction are not well-studied. Prevalence estimates for lymphedema are relatively high, yet its prevalence is likely underestimated. The ability to estimate the burden of disease poses profound implications for current and future lymphedema patients, but the challenge to correctly surmise the incidence and prevalence of lymphedema is complex and the relevant medical literature is scanty. In the absence of the highly desired, prospectively designed and rigorously performed relevant epidemiologic studies, it is instructive to look at the existing studies of lymphedema disease burden. In the current review, the extant literature is examined in the context of the disease setting in which tissue edema is encountered. Incidence or prevalence estimates are provided or inferred, and, where feasible, the size of the subject population is also identified. It is extremely attractive to contemplate that future approaches will entail formal, prospectively designed studies to objectively quantitate incidence and prevalence statistics for individual categories, as well as for the global lymphedema population.**

*Key words:* **cancer-related lymphedema; lymphedema epidemiology; trauma-related lymphedema; tissue edema**

Lymphedema, the regional, complex edematous state that ensues when lymph transport is insufficient to maintain tissue homeostasis, is remarkably prevalent, but the population implications of lymphatic dysfunction are not well studied.[1–3] Prevalence estimates for lymphedema are relatively high, yet its prevalence is likely underestimated.[4] Attempts to identify the population impact of lymphedema are hampered by the fact that this chronic, debilitating disease is frequently underrecognized or misdiagnosed: treatment delays are common and many patients never receive treatment.[4] Recent prevalence estimates suggest that chronic edema is present between 1.33 per thousand[5] to 1.44 per thousand.[6] Nevertheless, underestimation of disease prevalence emanates, at least in part, from the problem of ascertainment of disease by health care professionals: not all patients are likely to receive treatment for the condition,[6] a factor that is particularly relevant to lymphedema. Another confounding attribute is the variable manner in which lymphedema is clinically detected and defined.[3,7] In the absence of a repeatable, valid, and accepted definition for the presence of lymphedema,[3] the reported incidence and prevalence estimates for lymphedema must be scrutinized with regard to the methods in which tissue edema is sought, identified, and quantitated.

The ability to estimate the population burden of disease poses profound implications for current and future lymphedema patients, having an impact upon risk stratification of an elusive disease, and profound implications for insurance and reimbursement issues. Furthermore, the motivation of pharmaceutical and biotechnology sectors to undertake the development of new treatment strategies is heavily linked to the accurate perception of the disease burden.[8]

The challenge to correctly surmise the incidence and prevalence of lymphedema is complex and the relevant medical literature is scanty.[3] Nevertheless, in the absence of the highly desired, prospectively designed and rigorously performed relevant epidemiologic studies, it is instructive to examine, in some detail, the existing reports that enumerate the lymphedema disease burden. In the current review, the extant literature will be examined in the context of the disease setting in which tissue edema is encountered. Incidence or prevalence estimates are provided or inferred, and,

Address for correspondence: Stanley G. Rockson, M.D., Stanford Center for Lymphatic and Venous Disorders, Division of Cardiovascular Medicine, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94305. Voice: +1-650-725-7571; fax: +1-650-725-1599.
srockson@cvmed.stanford.edu

**TABLE 1. Primary lymphedema**

| Diagnosis | Incidence/Prevalence | References |
|---|---|---|
| Primary lymphedema | 1.15/100,000 persons < age 20 y | 12 |
| Genital lymphedema | 49% of male genital edema is accompanied by primary lower extremity lymphedema ($n = 33$ males)<br>39% had hydrocele | 22 |
| Lymphedema–distichiasis syndrome | 94.2% penetrance of lymphedema ($n = 74$); 49% varicose veins of early onset | 13 |
| Turner's syndrome | 30% prevalence of lymphedema ($n = 23$)<br>Congenital lymphedema in 17% ($n = 23$)<br>15.4% had cystic hygroma<br>Fetal diagnosis of cystic hygroma in 75% | 15–19 |
| Aagenaes' syndrome | 100% of affected individuals | 14 |
| Trisomy 18 | 15.4% had cystic hygroma | 17 |

where feasible, the size of the subject population is also identified (TABLES 1–3).

The simplest schema for the classification of lymphedema patients relies upon a differentiation between causes that are designated as *primary* or *secondary* (also known as *acquired*).[1]

## Primary Lymphedema

Primary lymphedema may be present at birth or develop at predictable points in the patients' natural history. Therefore, the primary lymphedemas are often further classified according to the age of the patient when the edema is first detected. Congenital lymphedema is apparent at birth or becomes recognized within the first 2 years of life. *Lymphedema praecox* is most commonly detected at the time of puberty, but may appear as late as the third decade of life. *Lymphedema tarda* is typically first detected after age 35.

Reported estimates of the incidence of primary lymphedema suggest that this condition is neither common nor rare.[9] While current published figures for the incidence and prevalence are scanty, small observational analyses have suggested that, for example, 8% of newly diagnosed lymphedema clinic patients had primary forms of the disease.[10] In published observations of chronic outpatient lymphedema care, among those with non-cancer-related disease, 28% were diagnosed with primary lymphedema.[11]

Prevalence estimates for all forms of primary lymphedema (TABLE 1) suggest that the disease, without regard to pathogenesis, may affect 1.15/100,000 individuals younger than 20 years of age.[12]

Among the disease entities within this category, there are several identified heritable diseases.[2] When cases of congenital lymphedema cluster in families, an autosomal dominant pattern of transmission is most frequently described, such as in the lymphedema–distichiasis syndrome,[13] whereas Aagenaes' syndrome[14] represents an autosomal recessive expression of disease. In addition to specific gene mutations, Turner's syndrome[15–19] and trisomy 18[17] should be considered in this context. While genetically predetermined forms of the primary lymphedema are relatively frequently encountered, sporadic instances of primary disease are more common.[20] Specific categories for which prevalence estimates are available include fetal cystic hygroma[21] and genital lymphedema.[22]

A disease category that, clinically, can readily be confused with primary lymphedema is the entity known as *lipedema*. This condition, both confused with and mistaken for lymphedema, lacks confident prevalence estimates.[23]

## Secondary Lymphedema

The obliteration of previously normal lymphatic channels is the hallmark of the acquired form of lymphedema. The most common cause of acquired lymphedema in developed countries, including the United States, is iatrogenic, reflecting predominantly the large patient group in whom lymphatic trauma is a direct consequence of surgical and radiotherapeutic interventions for cancer.[24] Lymphedema can also be acquired from other forms of lymphatic vascular trauma. These include burns and large or circumferential wounds to the extremity, but relative prevalence estimates are difficult to ascertain.

### *Cancer-related Lymphedema*

In the context of cancer therapeutics, lymphedema is most commonly associated with surgical excision of lymph nodes or their irradiation (TABLE 2). In survivors of late cervical, axillary, or inguinal lymphadenectomy, the 14.9% observed incidence of late lymphedema was the most commonly encountered complication, particularly after groin dissection,[25] where an incidence of

**TABLE 2. Cancer-related lymphedema**

| Diagnosis | Incidence/Prevalence | References |
|---|---|---|
| Breast cancer | Node-negative disease ($n = 1031$): 5% after sentinel node biopsy<br>13% after standard axillary dissection | 56 |
| | 22% after surgery and radiotherapy | 54 |
| | Sentinel node biopsy: 6.9% at 6 months ($n = 4975$) | 57 |
| Malignant melanoma | 26% lymphedema after groin lymph node dissection ($n = 204$) | 60 |
| | 10% after prophylactic lymph node dissection ($n = 44$); 23% after therapeutic lymph node dissection ($n = 64$) | 61 |
| | Lymphedema 28.3% ($n = 367$) | 63 |
| Cervical cancer | Prevalence in Stage I-IIA 31% ($n = 228$) | 105 |
| | Early-stage disease: 21% in first year ($n = 167$) | 106 |
| | Stage IB-IIA: radical hysterectomy alone, 5%; adjuvant external irradiation, 22% ($n = 320$) | 28 |
| | Stage I-IIA: radical hysterectomy, 10%; surgery and preoperative radiation, 11% ($n = 233$) | 68 |
| | Stage IB-IIA, radical hysterectomy and postoperative radiation: 42% ($n = 179$) | 107 |
| | T1b-2b cervical cancer, surgery, pelvic lymphadenectomy and postoperative radiation: 42% at 5 y and 49% at 10 y ($n = 128$) | 69<br>69 |
| Endometrial cancer | Surgery ± radiotherapy 4.6% ($n = 517$) | 72 |
| | Early disease 0.7% ($n = 168$) | 70 |
| | Early disease 1.8% ($n = 396$) | 71 |
| | Surgical therapy 3.4% ($n = 122$) | 108 |
| | Uterine corpus cancer 2.4% ($n = 1289$) | 74 |
| | Uterine cancer 17.7% ($n = 141$) | 73 |
| Vulvar cancer | Squamous cell carcinoma of vulva 26% ($n = 61$) | 80 |
| | Irradiation or lymphadenectomy 16% ($n = 48$) | 76 |
| | Resection and inguinofemoral lymphadenectomy 28% ($n = 187$) | 79 |
| | Radical vulvectomy 48%; modified vulvectomy 12% ($n = 149$) | 78 |
| | Stage 1–IV 13% ($n = 60$) | 77 |
| | Squamous cell carcinoma 47% ($n = 83$) | 75 |
| Prostate cancer | Stage A2–C 3.1% ($n = 289$) | 84 |
| | Stage A2–C 7.7% ($n = 65$) | 82 |
| | Radiotherapy and staging lymphadenectomy 13% ($n = 16$) | 83 |
| | Prostatectomy 2%; surgery and radiotherapy 9% ($n = 442$) | 81 |
| Penile cancer | Penile cancer 23% ($n = 53$) | 87 |
| | Surgery with groin dissection 33% chronic edema ($n = 67$) | 85 |
| | Inguinal (25%) and ilioinguinal (29%) lymphadenectomy ($n = 234$) | 86 |
| Soft tissue sarcoma | Survivors of therapeutic intervention: 30% with lymphedema ($n = 54$) | 109 |
| | Limb-sparing surgery and radiotherapy 19% ($n = 145$) | 90 |
| | Soft tissue sarcoma 3% ($n = 156$) | 88 |
| | Pre- (16%) versus postoperative (23%) radiotherapy ($n = 129$) | 89 |

**TABLE 3. Trauma-related and iatrogenic lymphedema**

| Diagnosis | Incidence/Prevalence | References |
|---|---|---|
| Peripheral arterial disease | 30% of Stage II patients<br>80% of Stage III and IV patients | 98 |
| Varicose vein surgery | 0.5% of patients (retrospective questionnaire reflecting >184,000 surgeries) | 99 |
| Saphenous vein harvesting for aortocoronary bypass | 10% incidence of lymphedema ($n = 50$) | 100 |
| Burns | 1% prevalence in a burn unit (retrospective file review) | 101 |
| Circumcision and buried penis repair | 1.3% incidence of lymphedema of the penile shaft ($n = 83$) | 102 |
| Intrathecal infusion for analgesia of non-cancer-related pain | Development of lymphedema in 22% after pump insertion ($n = 23$) | 103 |
| Sirolimus administration after organ transplantation | Lymphedema in 6% (file review of 18 patients) | 104 |

up to 40% has been observed. These surgical complications of tumor nodal metastasis staging and nodal therapeutics do occur, most commonly, in association with breast cancer, malignant melanoma, gynecologic malignancy (cervical, endometrial, and vulvar), urologic malignancy (penile and prostate), and soft tissue sarcomas. The reported frequency of leg edema after pelvic or genital cancer surgeries, particularly when there has been inguinal and pelvic lymph node dissection or irradiation, varies between 1% and 47%.[26,27] Pelvic irradiation increases the frequency of leg lymphedema after cancer surgery.[28,29]

### *Breast Cancer–related Lymphedema*

Breast cancer–associated lymphedema is the most extensively studied cause of acquired lymphatic vascular insufficiency.[30] Clearly, this reflects the fact that the problem of breast cancer–associated lymphedema is the one most commonly encountered. Axillary lymph node dissection and adjuvant radiation therapy are both predisposing factors, particularly when the axilla is included in the radiation field.[31] Ever since Halsted first described this seemingly unavoidable complication of breast cancer intervention,[32] the medical literature has been replete with descriptions of this phenomenon, persisting into the modern surgical and radiotherapeutic era[5,33–50] (TABLE 2). The accrual of new cases is linear-to-exponential in the first 3 years after interventions; thereafter, new case appearance diminishes in number, but persists throughout the natural history of the survival period. Incidence estimates vary broadly, but the most recent observations suggest that lymphedema of the arm is likely to occur in approximately 20% of breast cancer patients after axillary clearance.[5,44] Factors that influence the likelihood of lymphedema development include the extent of axillary dissection[42,44,47,48,51,52] and the use of radiotherapy,[37,38,41–44] particularly when the two treatment modalities are used adjunctively.[33,34,39,47,49,53,54] Systemic factors[1,31,37,45,48] and other surgical variables[33,37–39,44,45,51] may play a role in the incidence of breast cancer–related lymphedema.

Even with recent improvements in surgical and radiotherapeutic techniques, lymphedematous complications cannot be obviated and are, in fact, not uncommon.[40,43,50,55] While incidence of lymphedema is diminished with the sentinel node technique, the risk is certainly not eliminated.[56,57]

### *Lymphedema and Malignant Melanoma*

In malignant melanoma, lymph node dissection for tumor nodal metastasis staging engenders substantial risk for the development of lymphedema (TABLE 2). Early reports have suggested an incidence approaching 80%,[58] but more recent reports suggest a more modest, yet quite substantial risk that ranges from 6% to 29%.[59–66] As is the case for breast cancer staging and therapeutics, sentinel node biopsy substantially reduces the likelihood of developing lymphedema.[67] Furthermore, prophylactic lymph node dissection appears to be associated with a lesser incidence of lymphedema than therapeutic lymph node excision.[61]

### *Lymphedema and Gynecologic Malignancy*

The treatment of cervical, endometrial, and vulvar malignancies is associated with a significant incidence of acquired lymphedema (TABLE 2). In cervical cancer treated with radical hysterectomy alone, the incidence has been observed to be as low as 5–10%[28,68]; however, adjunctive pelvic irradiation will augment the risk to as high as 49% at 10 years after treatment.[69] The reported frequency of lymphedema after uterine cancer therapy is somewhat more modest,[70–74] while the treatment of vulvar malignancies occasions a comparable degree of lymphedema.[75–80]

### *Lymphedema and Urologic Malignancy*

Groin dissection, nodal staging, and radiotherapy play a substantial role in the treatment of urologic malignancy as well. In prostate cancer, with some dependence upon the grade of neoplastic disease, the incidence of lymphedema has been reported as 3–8%[81–84]; the adjunctive use of radiotherapy has a three- to fourfold augmenting effect upon the likelihood of developing lymphedema.[81,83] In the treatment of penile cancer, where inguinal and ilio-inguinal lymphadenectomy are common, lymphedema has been observed in 23–33% of the small series of patients studied.[85–87]

### *Lymphedema and Soft Tissue Sarcoma*

Therapy of soft tissue sarcoma often entails wide local excision and radiotherapy, thereby invoking the classic risk factors for lymphedema development (TABLE 2). Soft-tissue sarcoma has a reported association of 3%[88] to 30% with acquired lymphedema development.[109] As in the other settings of antineoplastic therapy, the use of irradiation, either pre-[89] or postoperatively,[89,90] seems to increase substantially the risk of development of lymphedema.

## *Infection*

Recurrent episodes of bacterial lymphangitis lead to thrombosis and fibrosis of the lymphatic channels and are one of the most common causes of lymphedema.[91] The etiologic bacteria are almost always streptococci that are prone to enter through breaks in the skin or fissures induced by trichophytosis. Recurrent bacterial

lymphangitis is also a frequent complicating factor of lymphedema from any cause. Incidence and prevalence estimates for this cause of lymphedema are generally lacking.

Lymphatic filariasis, a nematode infection endemic to 83 countries within the endemic regions of Asia, Africa, and the Americas, is the most common cause of secondary lymphedema in the world. Common tropical filariae include *Wuchereria bancrofti* and *Brugia malayi* or *timori*.[92,93] Other *Brugia* species are found in North America and occasionally cause lymphatic obstruction.[94] In endemic areas of the world, up to 54% of the population may have microfilariae detectable in the blood.[95] The microfilariae are transmitted by an obligate mosquito vector and induce recurrent lymphangitis and, eventually, fibrosis of lymph nodes.

Lymphatic filariasis is estimated to infect more than 129 million people in tropical and subtropical areas throughout the world.[96,97] In most of the infected individuals, the condition is subclinical, but the acute manifestations can include filarial adenolymphangitis, acute dermatolymphangioadenitis, and tropical eosinophilia.[96] It has been estimated that 14 million people suffer from lymphedema and elephantiasis of the leg caused by lymphatic filariasis. Filariasis is recognized as one of the world's most disabling diseases.[97]

### *Traumatic and Iatrogenic Causes*

There are a number of non-cancer-related settings in which the acquisition of lymphedema is described and predictable (TABLE 3). Many of these circumstances relate to disorders of the nonlymphatic vasculature. Although the observations are limited in scope and number, lymphedema has been described in patients with occlusive peripheral arterial disease (up to 80% of patients)[98] and after varicose vein surgery (0.5%)[99] and saphenous vein harvesting for aortocoronary bypass surgery 10%.[100]

Lymphedema has been described in burn patients,[101] as well as in those who undergo non-cancer-related penile surgery.[102] One very interesting iatrogenic context for acquired lymphedema is in drug administration: both intrathecal pump insertion[103] and sirolimus administration[104] have been associated with the development of lymphedema in subsets of these patients.

It is notable, in contrast to these iatrogenic settings for acquired lymphedema, that there were no instances of lymphedema after prophylactic mastectomy in a series of 1356 patients.

## Conclusion

This review of the epidemiology of lymphedema is intended to focus upon the clinical settings in which the incidence and prevalence of lymphedema have been perceived to be substantial. The settings in which this disorder does occur suggests that the population-based problem of lymphedema is at least substantial, and, quite possibly, profound. The prevalence of lymphatic filariasis and neoplastic diseases alone implies a large global burden of lymphatic disease. The data presented in this review represent, regrettably, only the aggregate of many small observations, often retrospective, and almost never rigorously undertaken. It is extremely heartening to contemplate future approaches that will entail formal, prospectively designed studies to objectively quantitate incidence and prevalence statistics for individual categories, as well as for the global lymphedema population. These statistics will facilitate future stratification of risk and will encourage more rapid development of diagnostic and therapeutic strategies to reduce the burden of disease.

### Conflicts of Interest

The authors declare no conflicts of interest.

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