

Risk Factors of Arm Lymphedema in Breast Cancer Patients

Zafer Kocak and Jens Overgaard

From the Danish Cancer Society, Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark

Correspondence to: Dr J Overgaard, Danish Cancer Society, Department of Experimental Clinical Oncology, Aarhus University Hospital, Norrebrogade 44, Bldg. 5, DK-8000 Aarhus C, Denmark. Tel: + 45 89 49 26 29. Fax: + 45 86 19 71 09. E-mail: deco@onko.aau.dk

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Chronic lymphedema is a life-long, potential complication of axillary treatment for breast cancer patients. In this article we focus on risk factors in the development of arm lymphedema and also discuss definition, type and stage, and incidence of arm edema.

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In the industrialized countries, cancer and cancer treatment are the most common causes of lymphedema (1). This complication can develop at any time and has been reported as late as 30 years after treatment (2). Arm edema may be disfiguring and can therefore greatly affect quality of life. Once established lymphedema cannot be cured, therefore it is essential to prevent or minimize this condition. In this article we focus on risk factors in the development of lymphedema and also discuss the definition, type and stage, and incidence of arm edema in breast cancer patients.

DEFINITION, TYPE AND STAGE

Lymphedema is the result of the functional overload of the lymphatic system in which lymph volume exceeds transport capabilities.

Lymphedema can be classified as primary or secondary, and acute or chronic (3) (Table 1). Primary lymphedema may be caused by the congenital absence or abnormality of lymph tissue. Secondary lymphedema occurs as a result of obstruction or interruption of the lymph system due to infection, malignancy, or surgical or radiation treatment. Acute lymphedema is usually transient and self-limiting and lasts for less than 3 to 6 months (4). Chronic lymphedema is present for at least 3 months, with noticeable skin changes, known as brawny edema (3).

Three stages of lymphedema have been defined (1) (Table 2). Stage I (acute phase) is characterized by a pitting edema and is reversible with elevation of the arm.

If the condition worsens, stage II or the chronic phase begins. This stage, which is not considered to be 'spontaneously reversible', constitutes protein-rich edema and a proliferation of connective tissue. There is much less or no skin pitting. Stage III is known as elephantiasis, characterized by massive swelling and cartilage-like hardening.

INCIDENCE

All women who have had surgical resection of the lymph channels are at risk for lymphedema. In Halsted's time, lymphedema occurred in up to 62% of patients (5). Few recent trials of modern therapies have addressed this problem. The report from Germany is one of the largest on post-treatment lymphedema with long follow-up. The incidence of lymphedema was 24% in 5 868 patients with a median follow-up of 11 years (6). According to the analysis performed by Petrek & Heelan (7), the incidence of lymphedema varied from 6% to 30%. They reported that the incidence of arm edema varied along with

- the methods used to define lymphedema
- the source of the patients
- the completeness of the patient population follow-up
- the interval between axillary treatment and measurement of lymphedema.

RISK FACTORS

Risk factors in the development of arm lymphedema are still poorly understood, and there have been few trials

Table 1
Types of lymphedema (3)

Types	Etiology	Duration	Presentation
Primary	Congenital obstruction-infection		
Secondary			
Acute		<3–6 months	Within 6 weeks of surgery, less edema in morning more edema at night
Chronic		At least 3 months	less pitting, brawny edema; peau d'orange

relating to this subject in the literature. Nevertheless, risk factors can be grouped into three main categories. The first category consists of treatment-related factors (these factors will not be discussed): surgery, irradiation, systemic treatment (chemotherapy, tamoxifen), and combined treatment; the second category consists of disease-related factors: stage at diagnosis, pathologic node status, the number of lymph nodes with positive pathologic findings, and the location of the tumor in the breast. The third category consists of patient- and clinical-related factors: patient age at diagnosis, obesity-body mass index, hypertension, history of infection-inflammation, handedness and excessive use of the limb, appearance of early lymphedema, and time interval since treatment (Table 3).

DISEASE-RELATED FACTORS

Advanced stage at diagnosis is a major predictive factor for developing lymphedema (6, 8, 9). A study from Germany, which is the largest on post-treatment lymphedema with long-term follow-up, demonstrated that the incidence of arm edema in patients with in situ carcinoma (Tis) tumors was 6.7%, whereas the incidence was 16.9% in patients with T1 tumors and 34.9% in patients with T4 tumors. Furthermore, the risk of lymphedema was 24.8% in patients with N1 tumors, compared with 44.4% for those with N3 tumors (6) (Table 4). According to the univariate analysis performed by Kissin et al. (8), T-stage was significantly associated with lymphedema ($p = 0.002$). However, it should be emphasized that patients with more advanced nodal disease are likely to have more aggressive surgery along with axillary radiotherapy.

Pathological nodal status is the independent risk factor

for developing lymphedema (8). Schunemann & Willich (6) reported that the incidence of arm edema was 17.9% for node-negative patients (N0), compared with 38.5% for node positive (N+) patients (Table 4). Despite these findings, it is difficult to distinguish them as independent risk factors, because they show nodal stage of the disease and, furthermore, patients with positive nodal disease receive more aggressive treatment.

The study from Sweden (10) demonstrated that the number of pathologically positive lymph nodes was the significant factor contributing to lymphedema, but others did not find a correlation between number of positive lymph nodes and lymphedema (9, 11).

Correlation between site of the primary tumor and development of arm edema has not been demonstrated (9, 12, 13).

PATIENT AND CLINICAL-RELATED FACTORS

In contrast to Werner et al. (9), Kiel & Rademacker (14) have reported that the most statistically significant factor leading to the development of arm edema is the age of the patient at diagnosis. The study showed that the actuarial incidence of arm edema at 3 years was 56% for women older than 55 years and 23% for women younger than 55 years ($p = 0.0005$), which suggests that the risk of developing lymphedema is higher in older patients. Marcks (3) claims that this may be attributed to the formation of lymphovenous anastomosis in younger patients. Autopsy results have shown that these lymphovenous anastomoses are much less common in older patients, because of the ageing process (13).

Table 2
Stages of lymphedema (1)

Stage	Severity	Difference in circumference and volume	Symptoms
I	Mild	<3 cm (150–400 ml)	Pitting edema, reversible with elevation of the arm
II	Moderate	3–5 cm (400–700 ml)	Progressive hardening of the extremity; edema does not decrease with elevation
III	Severe	>5 cm (>750 ml)	Hardened tissue with skin changes

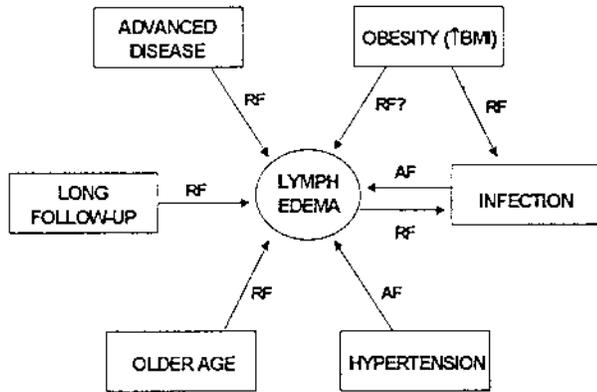


Fig. 1. Factors related to the development of lymphedema. RF = risk factor, AF = aggravating factor, BMI = body mass index.

In the literature there is support for the view that obesity is a risk factor in postmastectomy arm edema (11, 15–17). Few studies have examined the risk associated with obesity and increased patient size in patients treated conservatively. The study from Memorial Sloan Kettering Cancer Center showed that the most statistically significant predictive factor was body mass index (BMI) in patients treated with conservative surgery and radiotherapy (9). The findings of this study showed that in patients with BMIs greater than 29.2 kg/m², the 5-year incidence of lymphedema rose to 36% compared with 12% for those with lower BMIs. Although it is not clear that obesity is a direct risk factor for arm edema, it is certainly a risk factor for infection and poor wound healing (3).

In a series of studies by Bohler et al. (18), the effects of hypertension were investigated. Bohler and colleagues

Table 3

Classification of risk factors for lymphedema

Main groups	Subgroups
Treatment-related factors	Surgery Irradiation Systemic treatment (chemotherapy, tamoxifen) Combined treatment
Disease-related factors	Stage at diagnosis Pathologic node status Number of lymph nodes with positive pathologic findings Location of the tumor in the breast
Patient- and clinical-related factors	Patient age at diagnosis Obesity – body mass index Hypertension History of infection-inflammation Handedness and excessive use of the limb Appearance of early lymphedema Time interval since treatment

Table 4

Frequency of lymphedema according to tumor size (T) and nodal stage (N) (6)

T	Tx	Tis	T1	T2	T3	T4
n	179	7	362	657	98	102
%	43.6	6.7	16.9	24.8	35.4	34.9
N	N0	N+	N1	N2	N3	
n	525	168	443	241	28	
%	17.9	38.5	24.8	36.9	44.4	

noted that the incidence of arm edema in patients treated with both axillary surgery and irradiation was 35% among patients with normal blood pressure but 61% for patients with hypertension (p < 0.005).

A correlation between recurrent or late infections and arm edema has been reported in several studies (17, 19, 20), but it is difficult to accept this as a causative factor for lymphedema. The lymphedematous tissues are extremely sensitive to infections, and any simple burns and puncture wounds can develop into generalized erysipelas, which may produce further lymphatic destruction and blockage (4). Accumulated lymph in the edematous arm provides a rich culture medium for bacteria. As reported by Segerström et al. (17), the recurrent infections may be secondary to the edema, rather than the cause of the condition.

There is no evidence linking these factors with an increased risk for developing arm edema: handedness (operation on the dominant arm), excessive use of the limb, appearance of early lymphedema (8, 11, 17).

Many trials (14, 21, 22) report that lymphedema has a significant tendency to increase with time. Moretimer et al. (21) noted that there was a significant increase in prevalence with increasing time since treatment in patients who had received radiotherapy, but not in patients treated with surgery alone. Moreover, they suggested that at least 3 years' follow-up was required for this tendency to manifest itself, particularly following radiotherapy.

CONCLUSIONS

Owing to lack of studies performing multivariate analyses and to lack of prospective data, it is difficult to draw any definitive conclusions about risk factors from a review of the literature. Nevertheless, there seems to be a higher risk for developing lymphedema in patients with advanced disease at diagnosis, older age, greater BMI (obesity), and longer follow-up (see Fig. 1). Hypertension and infection are important comorbidities and may be initiating factors, but more likely they aggravate existing lymphedema.

REFERENCES

1. Brennan MJ, DePompolo RW, Garden FJ. Focused review: postmastectomy lymphedema. *Arch Phys Med Rehabil* 1996; 77 (Suppl 3): 74–80.
2. Brennan MJ, Weitz J. Lymphedema thirty years after radical mastectomy. *Am J Phys Med Rehabil* 1992; 71: 12–4.
3. Marcks P. Lymphedema: pathogenesis, prevention, and treatment. *Cancer Practice* 1997; 5: 32–8.
4. Aitken D, Minton J. Complications associated with mastectomy. *Surg Clin North Am* 1983; 63: 1331–52.
5. Lobb AW, Harkins HN. Postmastectomy swelling of the arm with note on effect of segmental resection of the axillary vein at time of radical mastectomy. *West J Surg* 1949; 57: 550–7.
6. Schunemann H, Willich N. Lymphoedema of the arm after treatment of cancer of the breast. A study of 5868 cases. *Deutsch Med Wschr* 1997; 122: 536–41.
7. Petrek JA, Heelan MC. Incidence of breast carcinoma-related lymphedema. *Cancer* 1998; 83 (Suppl 12): 2776–81.
8. Kissin MN, Qerci dello Rovero G, Easton D, Westburry G. Risk of lymphoedema following the treatment of breast cancer. *Br J Surg* 1986; 73: 580–4.
9. Werner RS, McCormick B, Petrek J, et al. Arm edema in conservatively managed breast cancer: obesity is a major predictive factor. *Radiology* 1991; 180: 177–84.
10. Suneson B, Lindholm C, Hamrin E. Clinical incidence of lymphoedema in breast cancer patients in Jönköping county, Sweden. *Eur J Cancer Care* 1996; 5: 7–12.
11. Warmuth MA, Bowen G, Prosnitz LR, et al. Complications of axillary lymph node dissection for carcinoma of the breast. A report based on a patient survey. *Cancer* 1998; 83: 1362–8.
12. Larson D, Weinstein M, Goldberg I, et al. Edema of the arm as a function of the extent of axillary surgery in patients with stage I–II carcinoma of the breast treated with primary radiotherapy. *Int J Radiat Oncol Biol Phys* 1986; 12: 1575–82.
13. Pezner DP, Patterson MP, Hill LR, et al. Arm lymphedema in patients treated conservatively for breast cancer: relationship to patient age and axillary node dissection technique. *Int J Radiat Oncol Biol Phys* 1986; 12: 2079–83.
14. Kiel KD, Rademacker AW. Early stage breast cancer: arm edema after wide excision and breast irradiation. *Radiology* 1996; 198: 279–83.
15. Say CC, Donegan W. A biostatistical evaluation of complications from mastectomy. *Surg Gynecol Obstet* 1974; 138: 370–6.
16. Hughes JH, Patel AR. Swelling of the arm following radical mastectomy. *Br J Surg* 1966; 53: 4–14.
17. Segerström K, Bjerle P, Graffman S, Nyström A. Factors that influence the incidence of brachial oedema after treatment of breast cancer. *Scand J Plast Reconstr Hand Surg* 1992; 26: 223–7.
18. Bohler FK, Rhomberg W, Doring W. Hypertonie als Risikofaktor für erhöhte Nebenwirkungsraten in Rahmen der Mammakarzinombestrahlung. *Strahlenther Onkol* 1992; 168: 344–9.
19. Fernandez JC, Serin D, Bauges S. Fréquence des lymphoedemes du membre supérieur après traitement du cancer du sein. Facteurs du risque. A propos de 683 observations. *Bull Cancer* 1996; 122: 536–41.
20. Mozes M, Papa MZ, Karasik A, Reshef A, Adar R. The role of infection in postmastectomy lymphedema. *Surg Ann* 1982; 14: 73–83.
21. Mortimer PS, Bates DO, Brassington HD, Stanton AWB, Strachon DP, Lewick JR. The prevalence of arm edema following treatment for breast cancer. *QJM* 1996; 89: 377–80.
22. Casley-Smith J. Alterations of untreated lymphedema and its grades over time. *Lymphology* 1995; 28: 174–85.