Risk factors of upper-arm lymphedema after breast cancer treatment

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Background
Lymphedema is one of the most problematic complications after breast cancer treatment. The risk factors (RFs) for breast cancer-related lymphedema (BCRL) are multifactorial and are not fully understood.

Aim
The aim of this study was to determine the RFs for breast cancer-related upper-arm lymphedema.

Patients and methods
This is a case–control study including patients with arm lymphedema as cases and patients without arm lymphedema as controls. The included patients had breast carcinoma ($n = 128$) and all had operable breast cancer that could undergo locoregional therapy (surgery ± radiotherapy). Diagnosis of lymphedema was made by the measurement method, in which a difference of up to 2 cm either above or below the olecranon process between the two arms is generally accepted for diagnosis of lymphedema. Assessment of lymphedema and RFs was performed by logistic regression.

Results
Univariate analysis showed significant difference between the groups of patients with and those without lymphedema with respect to older age (0.016), BMI greater than 30 (0.007), hard work (0.004), ipsilateral dominant arm (0.021), history of injury (0.001) and infection (0.001) to the ipsilateral arm, positive lymphadenopathy (0.020), advanced stage of cancer (0.009), positive human epidermal growth factor receptor-2/neu receptor (0.001), level III axillary dissection (0.001), and lack of information about BCRL and/or not following prophylactic advice (0.001). Meanwhile, multiple logistic regression analysis showed only old age (0.005), history of injury (0.016), cellulitis (0.033), level III axillary dissection (0.011), lack of information about BCRL, and not following prophylactic advice (0.012) to have a significant relation to lymphedema.

Conclusion
Healthcare personnel and patients must be aware of the prevention and early treatment of lymphedema.

Keywords:
breast carcinoma, lymphedema, risk factors

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Introduction

According to the National Cancer Institute and the Surveillance Epidemiology and End Results database, the mortality rate for breast cancer has been in significant decline, resulting in more than 2.5 million breast cancer survivors [1]. Although 5-year overall survival rates following breast cancer generally exceed 80%, treatment-associated morbidity is common and persists well beyond the active treatment period, specifically lymphedema, which develops in approximately one-fifth of these cancer survivors, with this incidence increasing over time [2].

Thus, breast cancer-related lymphedema is one of the main and most fearful complications of breast cancer and its therapies, and can have long-term physical and psychosocial consequences for patients [3].

Lymphedema is abnormal, regional accumulation of protein-rich fluid in the interstitial space that can result in edema formation and chronic inflammation [4].

The reported incidence of lymphedema after breast cancer treatment varies widely, ranging from 6 to 63%, depending on the population studied, measurement criteria used, and the reported length of follow-up [5,6].

Risk factors (RFs) for breast cancer-related lymphedema (BCRL), although not found to be the same in all studies, include treatment-related factors (extent of surgery: radiation, and chemotherapy),

disease-related factors (stage at diagnosis: pathologic nodal status, and number of dissected lymph nodes), and patient-related factors (age at diagnosis: BMI, and presence of a sedentary lifestyle). As shown by the nature of these RFs, BCRL is viewed as the consequence of a traumatic event [7].

Axillary lymph node dissection (ALND) and axillary radiation therapy have been mentioned as the principal RFs for lymphedema [8].

The pathophysiology of arm lymphedema has been attributed to an obstruction of the lymphatics after surgical dissection of the axilla, resulting in an increased downstream pressure, which is transmitted to the interstitium [9]. The increased hydrostatic pressure in the lymph vessel can damage the strength of the vessel walls and the effectiveness of the valves in the lymph vessels. This creates a backflow of lymph fluid and stagnation of fluids in the interstitium, leading to an increase in fluid volume in the tissue, which results in lymphedema [10].

Patients with lymphedema have chronic, progressive swelling, pain, recurrent infections, and significantly decreased quality of life [11].

When treated conservatively in the earliest stages, complications of lymphedema may be diminished or reversed. Unfortunately, lymphedema may progress to irreversible swelling and fibrosis, requiring lifelong attention and management [12].

Identification of RFs and their effects are keys to reduce lymphedema occurrence. Early detection and intervention hold the greatest promise in reducing this widespread condition [13].

Patients and methods

Study design

The study was a case–control investigation involving patients who developed lymphedema during the follow-up period, serving as cases (group I, n = 64), and those without lymphedema, serving as controls (group II, n = 64). It was carried out at El-Kasr El-Aini Hospital, Cairo, Egypt, from January 2012 to December 2013. This study was approved by ethical committee in faculty of medicine , Cairo University and the consent was taken from all patients who participate in this study.

The objectives of the study were to identify the RFs for breast cancer-related ipsilateral arm lymphedema.

(1) Inclusion criteria included all patients with operable breast cancer who underwent locoregional therapy
(2) Exclusion criteria included recurrence of disease, distant metastases, and loss to follow-up or death.

Methods

This study included all patients with operable breast cancer who will undergo locoregional therapy (surgery ± radiotherapy). Neoadjuvant, adjuvant, and hormonal therapies were given according to pathological stage and receptor status. The minimum follow-up period was 1 year from the start of treatment of breast cancer.

Sociodemographic characteristics

Data pertaining to age, educational level, occupation (hand use), menopausal status, BMI, presence of comorbidity, ipsilateral upper-extremity injury or infection, and dominant arm were collected.

Medical review

Information on the date and technique of breast cancer diagnosis, tumor size, location, grade, hormone receptor status, LNs status, number of nodes examined, number of positive LNs, stage, type of definitive cancer surgery, axillary dissection, and reconstructive surgery if any was obtained. Hormonal and chemoradiotherapy information was gathered from medical oncology office records.

Breast cancer characteristics

Using the tumor, lymph node and metastasis (TNM) classification, we classified stage as I, II–III (T1, T2, and T3) and N grade (N0, N1, N2, and N3). We classified primary tumor therapy as breast cancer conservative surgery or modified radical mastectomy. Axillary LNs dissection was reported as yes/no, as were adjuvant radiotherapy, chemotherapy, hormonal therapy, and presence of postoperative complications. LN status was classified as positive or negative [14].

RFs considered were age, occupation/hobby (hand use), TNM stage, number of dissected nodes, number of positive nodes, LN status, type of surgery, level of axillary dissection, tumor size, receptor status, radiotherapy, chemotherapy, postoperative complications, tumor side (dominant hand), injury, infection, comorbidity (diabetes mellitus and hypertension), and BMI. The relation between these factors and development of lymphedema was assessed to identify the RFs of BCRL.

Assessment of lymphedema was made through measurement of both arms at 3-month intervals after surgery for a total period of 12 months. Both arms

were measured with a circumferential tape 10 cm above and below the olecranon process [15]. A difference of up to 2 cm at either level between the two arms is generally accepted for a diagnosis of lymphedema [10]; a difference of more than 5–10% in circumference is described as mild lymphedema; a difference from 10 to 30% is described as moderate lymphedema; and a difference of more than 30% is described as severe lymphedema [16].

Statistical methods

Data were analyzed using statistical package for the social sciences program for Windows, version 17 (SPSS; SPSS Inc., Chicago, Illinois, USA), and continuous variables were summarized as mean ± SD and categorical variables as frequency and percentage.

Univariate logistic regression analysis of RFs contributing to the presence of lymphedema was performed and was tested for significance using Pearson's χ^2-test for discrete variables and the independent *t*-test for continuous variables.

Independent variables that were statistically significant in the univariate analysis or of considerable theoretical interest were included in the multivariate analysis.

Multivariate logistic regression models were used to explore associations between RFs of lymphedema. The strength of the associations was expressed as odds ratios (OR) with 95% confidence intervals. The level of significance was set at *P* values less than 0.05 and all tests were two-sided.

Results

Totally, 128 patients with breast cancer were included in this study: 64 patients had upper-arm lymphedema and 64 patients did not.

Regarding patients with upper-arm lymphedema after breast cancer treatment, using linear logistic regression analysis, the study showed that there was a statistically significant association between old age, higher BMI, injury to and cellulitis in the ipsilateral arm postoperatively, hard work, tumor in the dominant arm, positive lymphadenopathy, stages II and III, presence of positive human epidermal growth factor receptor-2 (HER-2)/neu type receptors, level III of axillary dissection, and not following postoperative prophylactic advice, with development of upper-arm lymphedema after breast cancer treatment, as shown in Table 1.

The study showed that there was no statistically significant association between tumor size, pathological type of tumor, number of dissected LNs and number of positive LNs, estrogen receptor and progesterone receptor status, type of operative procedures, hormonal and chemoradiotherapy, and postoperative infection and seroma with development of postoperative upper-arm lymphedema.

In multiple logistic regression analysis only old age, history of injury, cellulitis, level III axillary dissection, and not following prophylactic advice were significantly related to lymphedema (Table 2).

In our study most cases of lymphedema appeared within the first 2 years after mastectomy. The mean time of appearance of upper-arm lymphedema postoperatively was 14.23 ± 13.93 months; 67.2% of cases appeared in the first year and 84.4% of cases appeared within 2 years. The severity of lymphedema increased with time. The mean difference between the two arms above the elbow was 6.47 ± 4.136 cm and

Table 1 Logistic regression analysis for risk factors of lymphedema

Variables	Linear logistic regression		
	Odds ratio	95% CI	*P*
Age	1.048	1.009-1.090	0.016
BMI	1.096	1.025-1.172	0.007
Hard work (yes)	2.858	1.38-5.919	0.004
Injury	15.968	5.186-49.164	0.001
Cellulitis	24.111	5.422-107.216	0.001
Dominant arm (right)	2.284	1.124-4.639	0.021
LN status (positive)	2.778	1.151-6.703	0.020
TNM stages II and III (locally advanced)	1.980	1.612-2.348	0.009
HER-2/neu	3.686	1.731-7.847	0.001
Level III dissection	3.477	1.655-7.323	0.001
Did not followed advice	2.648	1.671-3.626	0.001

CI, confidence interval; HER-2, human epidermal growth factor receptor-2; LN, lymph node; TNM, tumor, lymph node and metastasis.

Table 2 Multiple logistic regression analysis for risk factors of lymphedema

	Multiple logistic analysis		
	Odds ratio	95% CI	*P*
Age	1.095	1.028-1.167	0.005
BMI	1.029	0.936-1.131	0.560
Hard work (yes)	2.012	0.412-9.827	0.388
Injury	11.919	1.572-90.339	0.016
Cellulitis	15.302	1.249-188.995	0.033
Dominant arm (right)	0.533	0.160-1.918	0.351
LN status (positive)	0.233	0.026-2.060	0.190
TNM stages II and III	1.007	0.240-4.225	0.933
HER-2/neu	2.451	0.789-7.666	0.123
Level III dissection	6.186	1.517-25.220	0.011
Did not followed advice	5.829	1.484-22.901	0.012

CI, confidence interval; HER-2, human epidermal growth factor receptor-2; LN, lymph node; TNM, tumor, lymph node and metastasis.

that below the elbow was 5.55 ± 3.333 cm. The mean maximum difference between the two arms at any point was 7.297 ± 4.173. On the basis of the difference in circumference between the two arms, the severity of lymphedema was divided into three categories: mild, moderate, and severe (Table 3).

Discussion

Lymphedema is one of the most problematic complications following breast cancer treatment. It represents failure of the lymphatic system to adequately drain fluid and proteins from the interstitial tissue and to circulate lymphocytes. Removal or damage to the LNs or lymphatic vasculature during cancer treatment may impede proper physiological function of this network [17].

In the current study, older age had increased risk for lymphedema, similar to the report by Ashikaga *et al.* [18]. In contrast to our study, Boccardo *et al.* and colleagues [5,19,20] found no significant relation of age to lymphedema.

The higher incidence of lymphedema in older patients observed in some studies may be due to a progressive loss of the lymphovenous anastomoses because of the aging process [21].

In our study, patients with higher BMI had significant risk for lymphedema. This is similar to the report by Clough-Gorr and colleagues [14,22–24], who stated that BMI up to 30 resulted in a significantly higher risk for lymphedema. Meanwhile, other studies such as Hinrichs and colleagues [25,26] reported no significant relationship with BMI.

It is unclear as to how obesity influences the development of lymphedema but the proposed mechanisms include an increased risk for postoperative complications including infection, reduced muscle pumping efficiency within loose tissues, additional fat deposition contributing to arm volume, and separation of deep lymphatic channels by additional subcutaneous fat [27].

In our study, there is a strong relationship between arm injury postoperatively and lymphedema development. It is consistent with the report by Paiva and colleagues [21,22,28].

Table 3 Degree of severity of upper-arm lymphedema

Degree of lymphedema	*n* (%)	Mean time (months)
Mild	23 (35.9)	10.65±8.77
Moderate	25 (39.1)	12.80±11.719
Severe	16 (25.0)	21.63±23.125
Total	64 (100)	14.23±13.93

In the current study, infection and cellulitis increased the risk for lymphedema. This is very close to that reported by McLaughlin and colleagues [28–30], but differed from that reported by Avraham *et al.* [31], where infections of the ipsilateral arm were not a significant RF for the development of lymphedema.

The occurrence of minor injuries, such as cuts, bruises, minor burns, and infection, triggers an inflammatory response. This translates into an increase in fluid filtered by the arterial capillaries into the interstitium, capillaries and lymphatic vessels, which overloads the lymphatic system already damaged by lymphadenectomy [21].

With regard to the relation of tumor pathological type and lymphedema, we found that the incidence of lymphedema is higher among ductal carcinoma patients than among lobular carcinoma patients, but with no statistical significance. This corresponds to the report by Yan *et al.* [32].

In our study, there was no statistical significance between tumor size, number of dissected LNs, and number of positive LNs with regard to the risk for lymphedema. This agrees with the reports of Goldberg and colleagues [22,33,34]. In contrast, Smoot *et al.* [35] reported that patients with lymphedema had more LNs removed as well [36,37].

The current study shows that positive lymphadenopathy resulted in a higher rate of lymphedema than negative ones, which concurs with the report by Yen and colleagues [37,38]. However, Purushotham *et al.* [39] reported no significant differences between arm volume increases and lymphedema among node-positive patients.

Concerning TNM staging, in this study there was a higher rate of lymphedema in stage II–III than in stage I, with statistical significance ($P = 0.009$). This resembled the reports of Clough-Gorr and colleagues [14,23,34], who stated that women with stage II–III disease had increased risk for lymphedema.

In our study we found a strong relation between positive HER-2/neu type receptors and the presence of lymphedema ($P = 0.001$ and OR = 3.686). Yet this relation is not fully understood and we did not find any literature on this relation between HER-2/neu status and lymphedema.

In the current study, level III axillary dissection was strongly related to the development of postoperative lymphedema.

In the present study we found that radiotherapy was not a RF for lymphedema. This is consistent with the

reports of Newman and colleagues [17,20,23,30,40,41], who found no significant relation of radiotherapy with lymphedema.

However, Deo *et al.* [42] reported that lymphedema developed in 42.4% of patients who received radiotherapy, versus only 13.4% who did not. Similarly, Ashikaga and colleagues [18,36] reported that radiotherapy to the axilla was associated with significant risk for lymphedema ($P = 0.007$ and 0.001). In the present study we examined only the effect of overall radiation therapy, rather than radiation therapy to the axilla.

In the present study, lack of information about BCRL and/or not following prophylactic advice had significant relation to lymphedema ($P = 0.001$ and OR = 2.648). This matches with the study of Fu *et al.* [43] in which they found that breast cancer survivors who received information about BCRL appeared to have significantly increased knowledge about BCRL and reduced BCRL symptoms when compared with patients who did not receive information.

Regarding postoperative complications in our study, there was no statistical significance between postoperative complications and lymphedema, which concurs with the report by Avraham *et al.* [31], whereas other studies Hayes and colleagues [44,45] stated that postoperative complications had increased risk for lymphedema.

The mean time to diagnosis of upper-arm lymphedema postoperatively in our study was 14.23 months, which varied from the study presented by Kwan *et al.* [23], who reported a mean time to diagnosis of 8.3 months (range: 0.7–27.3 months), while Gautam *et al.* [46] reported that the time from mastectomy was 2.08 ± 0.65 years.

This study showed that 67.2% of cases of lymphedema appeared in the first year and 84.4% developed within the first 2 years after primary treatment, similar to the studies by Hayes *et al.* [44], who reported that 70% of cases developed within the first year, and Norman *et al.* [47], who reported that lymphedema occurred within 2 years of diagnosis in 80% of cases and within 3 years in 89%. However, Nesvold *et al.* [48] reported a higher percentage of lymphedema in the first year (80%).

As per the National Cancer Institute, lymphedema is graded as follows:

Grade 1 (mild): lymphedema with 5–10% interlimb discrepancy in volume or circumference at the point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting edema.

Grade 2 (moderate): more than 10–30% interlimb discrepancy in volume or circumference at the point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour.

Grade 3 (severe): more than 30% interlimb discrepancy in volume circumference at the point of greatest visible difference; lymphorrhea; gross deviation from normal anatomic contour; interfering with activities of daily living [16].

In our study we found that mild lymphedema presented in 35.9% of cases, moderate lymphedema in 39.1% of cases, and severe lymphedema in 25% of cases; the severity of lymphedema increased with time. In contrast to our study, in the study by Paskett *et al.* [40] 70% of the cases of lymphedema were reported as mild, 25% were reported as moderate, and 5% were reported as severe. In addition, Cidon *et al.* [38] reported that 67% of cases of lymphedema were mild, 25% were moderate, and 7% were severe.

In many patients in the current study arm lymphedema was due to injury and cellulitis and this explains the higher incidence of severe degree of lymphedema.

The short duration of follow-up in the present study is a limitation and hence a number of questions remain unanswered and more research is needed to answer these.

Conclusion

Old age, history of injury, cellulitis, level III axillary dissection, and lack of information about BCRL and not following prophylactic advice are significantly related to the development of lymphedema.

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Conflicts of interest

There are no conflicts of interest.

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