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RESEARCH REPORT

UPPER LIMB LYMPHEDEMA FOLLOWING BREAST CANCER SURGERY: PREVALENCE AND ASSOCIATED FACTORS

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Abstract

Introduction: Lymphedema is one of the main complications following breast cancer surgery, and affects the quality of life of patients. This study aimed to determine the prevalence of lymphedema in women following breast cancer treatment, as well as associated risk factors. **Methods**: A cross-sectional study was carried out with 394 women undergoing breast cancer surgery. Personal data, tumor size, treatment and post surgical complications were collected. Risk estimates between lymphedema and selected independent variables were ascertained as odds ratios (OR) and their 95% confidence intervals were calculated. Unconditional logistic regression was performed to select the model that better explained the risk of lymphedema after breast cancer treatment. **Results**: The prevalence of lymphedema was 20.8%. The best adjusted model included the following variables: axillary radiotherapy (OR = 4.44; CI 95% 1.97 – 9.96), obesity (OR = 3.11; CI 95% 1.22 – 7.93), arm infection (OR = 5.01; CI 95% 1.80 – 13. 95), and reduced shoulder range of movement (ROM) (OR = 2.64; CI 95% 1.13 – 6.14). **Conclusion:** The prevalence of lymphedema was 20.8%. The variables which best explained the development of lymphedema were axillary radiotherapy, obesity, ROM and history of arm infection.

Keywords: Lymphedema, prevalence, breast cancer, complications.

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Introduction

Breast cancer is a major public health problem, due to the magnitude of its incidence and mortality worldwide. The management strategy advocated for women with breast cancer depends, directly, on tumor stage (TNM); thus, as the tumor is diagnosed in more advanced stages, therapeutic resources become more limited and mutilating, with increased post-treatment morbidity. In Brazil, late diagnoses are still part of daily practice, and therefore a significant number of women have to live with physical and functional sequels as a result of more aggressive treatments. Among the complications resulting from breast cancer treatment, upper limb lymphedema is a major one. The onset of lymphedema following surgical treatment of breast cancer leads to major physical, social and psychological changes and its symptoms should not be disregarded on account of its non-lethal condition [1].

The prevalence of post breast cancer surgery upper limb lymphedema ranges between 9% and 40% in different studies, depending on the follow-up time, on the classification and criteria used for its definition, and on the time elapsed after surgery[2]. The risk factors associated with lymphedema described in the literature can be divided into three major categories: factors associated with the treatment; with the tumor; with practice and the patient[3]. A more in-depth understanding of the factors associated with lymphedema is required, so one is able to intervene preventively, changing life activities of women at risk as little as possible. The aim of this study was to determine the prevalence of lymphedema in a cohort of women undergoing medical follow-up after breast cancer treatment in a public referral hospital, as well the factors associated with its development.

Materials and Methods

A study on the prevalence of lymphedema in women undergoing medical follow-up for breast cancer surgical treatment in the outpatient service of a public referral hospital, was conducted from April to August 2000. Excluded from the study were women with: bilateral breast cancer; absence of axillary lymphadenectomy; active locoregional or distant disease; reported functional change in upper limbs prior to treatment for breast cancer; surgical treatment performed less than 6 months before the date of the interview; treatment in other hospitals; and those who were in no condition to answer the questions. Women who met the inclusion criteria were informed about research objectives, and upon acceptance, signed an informed consent. Data was attained through a semi-structured interview and physical examination, and complemented through a review of patient's records. All measurements were performed by a single professional (A.B.) following intra-observer standardization of procedures. Data collection was carried out through standardized devices and validated through the application of a pre-test in 20 women undergoing follow-up in a

different institution, and also performed by the same researcher (A.B.). The lymphedema case definition adopted was based on the volume of the limb, estimated from five circumference measurements (21 cm, 14 cm and 11.5 cm above the olecranon; 7.5 cm, 14 cm and 24 cm below the olecranon), treating every limb segment as a pair of circumferences (truncate cone). The segment volume was given by: $V = h * (C^2 + Cc + c^2) / (\pi * 12)$, where V is the limb segment volume, C and c are the circumferences between the points, and h is the distance between circumferences (C,c). The sum of the differences for every point equaled the estimated final volume[7], in which differences equal to or greater than 200 ml were considered as lymphedema. Variables studied were the ones associated with patient characteristics (age at diagnosis, ethnic background, marital status, educational background, predominant side, reported remunerated work at the date of interview, menopause prior to breast cancer, smoking at the date of surgery, body mass index, background of systemic hypertension, and presence of mycosis in the upper limb), treatment characteristics (time of postoperative follow-up, type of breast surgery performed, type of axillary surgery, reported total days with suction tube and surgical stitches, performance of radiotherapy, drainage chains irradiation, neo and/or adjuvant chemotherapy, hormone therapy, performance of breast reconstruction, side of the surgery and number of axillary lymph nodes removed), tumor characteristics (status of the axillary lymph nodes, tumor stage, tumor location, histological type, and tumor size), and postoperative complications (reported early edema, reported infection in the upper limb on the affected side or in the surgical scar associated with the use of antibiotics, reported necrosis, reported seroma with required aspiration/puncture, reported sensory symptoms at the intercostobrachial nerve area, presence of winged scapula, reduced shoulder joint amplitude and hematoma requiring surgical intervention). The characteristics of women meeting inclusion criteria were compared by using the χ^2 test with a 5% ($p < 0.05$) level of significance. Means and medians were presented for continuous variables, and a frequency distribution was present for categorical variables. Logistic regression analysis was performed using the enter method to select a model to best represent the risk for lymphedema. Epi-Info 6.0 and SPSS 8.0 softwares were used for data analysis.

Six hundred and fifty one women came to the outpatient service for follow-up. Of the total, 189 (29%) were excluded because they failed to meet inclusion criteria and 68 (14.72%) refused to participate. Comparison between data obtained from medical records of the eligible women and of those who refused to participate did not show statistically significant differences, in relation to age, educational background, stage or number of lymph nodes removed. The type of surgery performed showed a borderline statistical level of significance between both groups, with a slight predominance of radical surgery among the ones who agreed to participate ($\chi^2 = 3.72$; p value = 0.05). Axillary status differed statistically between both groups, i.e., women participating in the

study presented a greater number of impaired lymph nodes, as compared to the ones who refused ($\chi^2 = 5.28$; p value = 0.02).

Results

The prevalence of lymphedema ascertained in the study was 20.8%, based on the diagnostic criteria established. Table 1 shows the distribution of continuous variables statistics in the study. Considering women altogether, the mean volume difference between the affected limb and the counterlateral one, estimated by the circumference, was 112.7 ml (median = 68.28; percentile 25 = 20.52; percentile 75 = 172.46).

Table 1 – Mean, median, standard deviation and amplitude of variance of continuous variables

Variable	Mean	SD	Median	Variance amplitude
Age at diagnosis (years)	55.3	11.1	54	28 - 94
Follow-up (months)	59.5	48.9	46	7 - 287
Closed suction drainage (days)	9.3	4.9	8	0 - 30
Number of lymph nodes removed	17.2	6.9	16	2 - 48
Number of metastatic lymph nodes	1.9	4.2	0	0 - 38
Body Mass Index (BMI)	27.4	4.5	27.3	16 - 44
Sum difference in limb volume (ml)	112.6	68.3	68.3	- 362 / 1873

Most women were Caucasians (60%) with incomplete elementary school (63%). In regard to their marital status, 43.4% shared a home with a companion, having household chores as their main occupation (80%). Menopause was already present at the time of breast cancer diagnosis in more than half the women (59%), and on the date of the interview, there was an additional of approximately 25% due to the breast cancer treatment.

Surgeries performed were mostly radical ones (73%). According to patient records, axillary lymphadenectomy (three axillary levels) was the most frequently found (60%). Postoperative radiotherapy treatment was performed in 56.0 % of women, 19.7% of them also had the axillary irradiated. Chemotherapy was performed in 61.2% and hormone therapy with Tamoxifen was given to 44% of women. Injury to the intercostobrachial nerve, seroma and pain were reported in more than half the women examined. Winged scapula was found in 6.3% and reduced shoulder range of movement in 15% (table 2).

Variables with a statistically significant association with lymphedema in the bivariate analysis are shown in Table 3. The other variables showed no statistical significance in this study.

Table 2 – Prevalence of patient characteristics

Variable	N	%
Surgery performed		
Halsted Mastectomy	18	06.2
Modified radical Patey mastectomy	203	70.0
Modified radical Madden mastectomy	69	23.8
Conservative	101	25.6
Axillary Lymphadenectomy		
Partial (up to level II)	237	60.2
Total (up to level III)	81	20.6
Adjuvant Treatment		
Chemotherapy	241	61.2
Radiotherapy	221	56.1
Radiotherapy (with lymph drainage chains)	39	17.6
Hormone therapy	172	43.7
Stage		
0	5	01.3
I	59	15.0
II	209	53.1
III	108	27.4
Postoperative complications		
Arm infection	36	09.1
Seroma	214	54.3
Necrosis	14	03.6
Sensory symptoms at intercostobrachial nerve	218	55.3
Winged scapula	25	06.3
Reduced shoulder range of movement (ROM)	60	15.0

Table 3 – Non-adjusted prevalence ratios and respective 95% confidence intervals

Independent variable	**Lymphedema**			
	Yes	No	RP*	CI**
Axillary radiotherapy				
Yes	20	19	2.81	1.79 – 4.41
No	29	130		
BMI				
Overweight	70	204	2.53	1.43 – 4.50
Adequate / Thinness	12	107		
Arm infection				
Yes	16	20	2.41	1.58 – 3.69
No	66	292		
Stage				
> II B	51	129	2.01	1.33 – 3.05
up to II A	28	171		
Metastatic lymph nodes				
Yes	48	121	1.84	1.24 – 2.72
No	34	186		
Radiotherapy				
Yes	57	164	1.76	1.15 – 2.70
No	25	146		
Shoulder range of movement				
Limited	19	40	1.76	1.14 – 2.71
Normal	61	272		
Total of days with tube				
8 days and +	58	179	1.60	1.04 – 2.46
up to 7 days	24	133		
Early edema (report)				
Yes	32	84	1.51	1.03 – 2.23
No	50	224		
Early edema (symptoms)				
Yes	43	125	1.48	1.01 – 2.18
No	39	187		

* Prevalence ratio

** 95% confidence interval

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Logistic regression was performed in order to find the model that best explained the risk for a woman to present with lymphedema after breast cancer treatment. The model which showed the best adjustment (explaining 80% of variance) was the one that included the following variables: radiotherapy in drainage chains, overweight or obesity, history of arm infection, and reduced shoulder range of movement (ROM) homolateral to surgery (table 4).

Table 4 – Adjusted odds ratio and corresponding 95% confidence intervals for axillary radiotherapy, BMI, Arm infection and ROM.

Independent variable	OR	CI
Axillary radiotherapy		
Yes	**4.44**	**1.97 – 9.96**
No		
BMI		
Overweight	**3.11**	**1.22 – 7.93**
Adequate / Thinness		
Arm infection		
Yes	**5.01**	**1.80 – 13.95**
No		
Shoulder range of movement		
Limited	**2.64**	**1.13 – 6.14**
Normal		

Estimated by unconditional logistic regression adjusted by selected variables.

Discussion

The prevalence of lymphedema in this study was similar to results reported by other authors, considering the differences in methods used for the diagnosis of lymphedema, follow-up interval, type of treatment performed and chosen cut-off point for edema distributions [4-7].

The women selected to take part in this study, but who refused to participate, presented a significantly higher frequency of conservative surgeries as well as lesser lymph node impairment than participants, which could have caused overestimation of the prevalence observed. However, we do not find the fact significant, since there was no difference in regard to the number of lymph nodes removed or the axillary lymphadenectomy level.

Age was not associated with lymphedema, and this result was similar to that observed by some other authors [5,7-12]. Other studies found an increased risk for the elderly [13,14] and a further one for a younger age [4].

Obesity was the only variable related to the patients' characteristics that showed association with lymphedema. This is in agreement with results of other studies[5,6,10,12,13,15,16]. According to Kocak and Overgaard [3], the risk factors involved in the physiopathology of upper limb lymphedema

associated with obesity remain unknown. However, obesity represents a risk factor for infection and delayed wound healing, and it may indirectly play a role in the development of lymphedema.

Time of follow-up was not associated with the development of lymphedema in the bivariate analysis, regardless of the cut-off point (2, 3, 4 or 5 years). Such results are in agreement with the ones reported by Kissin et al [17]. After lymphatic obstruction, compensating mechanisms are put into action in order to avoid the onset of lymphedema[18]. Such mechanisms aim to reestablish lymphatic circulation and maintain the affected upper limb without edema. However, this balance can be altered by other factors such as: "depletion" of the compensating mechanism; fibrosclerosis of the lymphatic vessels as of the fourth decade of life; local trauma; surgical lesion of collectors; inflammation; excessive muscle stress; exposure to high temperatures; and atmospheric pressure changes. Thus, it should be expected that the longer the time elapsed since lymphatic obstruction, the greater would be the risk for a lymphatic system unbalance, leading to the onset of lymphedema. Some studies have shown a significant trend towards an increased incidence of lymphedema along time, corroborating the theory described above [13,18,19].

Women undergoing radical treatment presented an increased risk for lymphedema, although without statistical significance. Other studies did not report a significant association of this variable with lymphedema either [8,13-16]. A possible explanation for the increased risk found in the current study, could be that the later the diagnosis the more radical the performed surgeries usually are.

Axillary radiotherapy played a major role in the development of lymphedema. Similar results were found by others authors [6,7,11,14,20-22]. We recommended that women with an indication for axillary radiotherapy be included in rehabilitation programs, aiming at the prevention of lymphedema.

Women with metastatic axillary lymph nodes were at a significantly higher risk for the development of lymphedema, but this observation was not sustained subsequently in the logistic regression performed. Similar results were found in other studies [4,5,14,20].

Women diagnosed at late tumor stages (> II B) presented a statistically greater risk for the development of lymphedema, as compared to those diagnosed at early stages, but when confounding and interaction were controlled, that variable lost its statistical significance. Heard-Smith et al [14], Ozaslan and Kuru [6] and Hinrichs et al [7] found no association between this variable and lymphedema.

Early edema was not associated with lymphedema in our results. Arm edema occurring shortly after surgery is usually transient, and tends to disappear after the development of compensating mechanisms [3,23].

Upper limb infection was associated with lymphedema in our study, a result also found by Petrek et al [13]. This variable should be investigated in depth, in order to establish the relationship between lymphedema and infection. The results of such studies could influence the current view concerning preventive guidance and adaptive management for women undergoing treatment for breast cancer [23,24].

Hematoma was a major risk factor for lymphedema in this study, but due to the limited sample size the observation was not statistically significant. This variable was not analysed in other studies.

Reduced shoulder range of movement was associated with lymphedema. Nevertheless, we cannot consider it to be a risk factor, given it was not possible to establish a true trend, and it may be acting either as a cause or as a consequence. Women with joint restriction should be encouraged to join a rehabilitation program, aiming to fully recover joint amplitude of the affected limb.

As information is achieved simultaneously in cross-sectional studies, it is often impossible to establish whether the condition preceded or resulted from the disease. A further limitation of this design derives from the fact that prevalent cases were analyzed and so the data may reflect disease survival determinants. As a result, cross-sectional studies may suggest possible risk factors, rather than establish the etiology of the disease [25]. Prospective studies are required if the major risk factors in the etiology of lymphedema are to be established.

Conclusion

The observed prevalence of lymphedema was 20.8%, which is in agreement with the results achieved in other reports. Sensory symptoms as intercostobrachial nerve, seroma and pain were present in more than half of the women examined. The variables which best explained the development of lymphedema were axillary radiotherapy, obesity, reduced shoulder range of movement and history of arm infection.

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