Risk Factors Associated with Lymphedema among Postmenopausal Breast Cancer Survivors after Radical Mastectomy and Axillary Dissection in China

Hua-Ping Huang^a Jian-Rong Zhou^a Qing Zeng^b

^aNursing College of Chongqing Medical University,

^bDepartment of Public Health, Chongqing Medical University, Chongqing, China

Keywords

Breast cancer · Lymphedema · Nursing · Chinese women

Summary

Background: Lymphedema is the major complication following breast cancer treatment and can persist long periods of time and affect breast cancer survivors' quality of life. Accurate estimation of the risk factors for lymphedema is of significant importance. In this article we report the factors for secondary lymphedema among postmenopausal breast cancer patients after radical mastectomy in China. **Patients and Methods:** A total of 126 consecutive postmenopausal breast cancer patients who received radical mastectomy were admitted to the Chongqing Breast Cancer Center between July 2009 and June 2010. Circumferential measurement was used to diagnose lymphedema. **Results:** Among the 126 postmenopausal women with breast cancer, 54 (42.9%) had lymphedema. Body mass index (BMI), lymph nodes status, and radiotherapy were associated with lymphedema. BMI ≥ 25 kg/m² (adjusted odds ratio (OR) = 7.5; 95% confidence interval (CI) 2.8–20.1) and radiotherapy (adjusted OR = 3.0; 95% CI 2.0–9.2) were independent predictors of lymphedema. **Conclusion:** BMI, lymph nodes status, and radiotherapy were the risk factors for lymphedema among Chinese postmenopausal breast cancer patients who underwent radical mastectomy. Clinicians should provide sufficient information for patients and their caregivers to prevent this complication, especially for those who are at high risk of developing lymphedema.

Schlüsselwörter

Mammakarzinom · Lymphödem · Pflege · Chinesische Frauen

Zusammenfassung

Hintergrund: Lymphödeme sind eine der Hauptkomplikationen der Mammakarzinomtherapie. Sie können über einen langen Zeitraum persistieren und die Lebensqualität der betroffenen Patientinnen beeinträchtigen. Eine genaue Einschätzung der Risikofaktoren für die Lymphödementstehung ist von signifikanter Wichtigkeit. In der vorliegenden Arbeit berichten wir von den Risikofaktoren für sekundäre Lymphödeme bei postmenopausalen Mammakarzinompatientinnen nach radikaler Mastektomie in China. **Patientinnen und Methoden:** Zwischen Juli 2009 und Juni 2010 wurden insgesamt 126 postmenopausale Mammakarzinompatientinnen an das Chongqing Breast Cancer Center überwiesen, bei denen eine radikale Mastektomie durchgeführt wurde. Das Vorliegen eines Lymphödems wurde mittels Umfangsmessung diagnostiziert. **Ergebnisse:** Von den 126 postmenopausalen Mammakarzinompatientinnen hatten 54 (42,9%) ein Lymphödem. Body mass index (BMI), Lymphknotenstatus und Radiotherapie waren mit dem Vorliegen eines Lymphödems assoziiert. BMI ≥ 25 kg/m² (adjustierte Odds Ratio (OR) = 7,5; 95%-Konfidenzintervall (KI) 2,8–20,1) und Radiotherapie (adjustierte OR = 3,0; 95%-KI 2,0–9,2) wurden als unabhängige Prädiktoren identifiziert. **Schlussfolgerung:** BMI, Lymphknotenstatus und Radiotherapie waren Risikofaktoren für die Entstehung eines Lymphödems bei postmenopausalen Mammakarzinompatientinnen in China, die mit radikaler Mastektomie behandelt wurden. Behandelnde Ärzte sollten insbesondere bei Bestehen eines hohen Lymphödemrisikos Patienten und Pfleger diesbezüglich ausreichend informieren, um dieser Komplikation vorzubeugen.

Introduction

Lymphedema is a major but overlooked complication following breast cancer treatment, which often occurs when the amount of high-protein lymph fluid that needs to be removed from the interstitial tissues exceeds the maximum transport capacity of the lymphatic system [1]. Patients with lymphedema may report sensations such as arm swelling, heaviness, immobility, and pain [2]. Recent studies have reported on the physical, psychological, and overall quality of life of patients with this condition [3, 4]. Lymphedema can emerge immediately or years after treatment [5], but the majority of women with lymphedema develop it within the first 12–18 months following treatment [6]. A range of risk factors including surgery – especially when accompanied by axillary lymph node dissection (ALND), number of lymph nodes removed, lymph node status, radiotherapy, chemotherapy, age, and overweight or obesity are associated with lymphedema [5–10]. However, findings varied in previous studies because of inconsistencies among diagnostic criteria employed, small sample sizes, and length of follow-up [7, 11]. The clinical treatment of lymphedema encompasses a wide variety of strategies, including manual lymphatic drainage, compression garments, pneumatic pumps, multilayer bandaging, and surgery [12]. Although these methods can decrease the severity of lymphedema, providing patients with adequate and effective knowledge regarding lymphedema and changing their understanding and behavior towards the condition may be a more effective way of preventing and managing this complication [13].

Similar to other cancers, age is the most important risk factor for breast cancer. The chances of getting breast cancer increase with age, and more than 50% of women are 50 years or older when they are diagnosed. Currently, although more women are eligible for less invasive breast surgery such as breast conserving surgery (BCS) and sentinel lymph node biopsy (SLNB) which has gradually replaced ALND as the standard of care, women with early-stage breast cancer may opt for mastectomy because of contraindications to radiation therapy or personal preference [14]. Very few studies have reported on lymphedema in older breast cancer survivors, which may arise due to adverse effects of treatment along with improved survival rates in China. This study aims to explore the relationship between risk factors and lymphedema among Chinese postmenopausal breast cancer patients who received radical mastectomy.

Patients and Methods

Participants

After Institutional Review Board (IRB) approval, 126 consecutive patients with breast cancer who received radical mastectomy and ALND were recruited from the Chongqing Breast Cancer Center from July 2009 to June 2010. The Chongqing Breast Cancer Center was established in 1996, and has the most outpatients in Chongqing. All participants signed

an informed consent form prior to being interviewed. Eligibility criteria covered Chinese women who i) were > 50 years of age which was selected in compliance with the Surveillance, Epidemiology, and End Results (SEER) definition of older and younger cohorts of breast cancer patients; ii) had been diagnosed with primary breast cancer; iii) had been actively treated for breast cancer (i.e. surgery and/or radiotherapy and/or chemotherapy) for ≥ 6 months; and iv) were Chinese speaking and capable of being interviewed. Exclusion criteria included i) bilateral surgery for invasive breast cancer; ii) recurrent breast cancer; iii) presence of other diseases that could cause edema (e.g. heart failure, renal disease); and iv) lumpectomy. A final sample of 126 patients participated in this study. The sample size was calculated with 95% confidence level (CI) and 5% error bound. We assumed that the conservative proportion of patients developing lymphedema was 10% in order to get the sample size [7].

Data Collection

Personal data regarding age and height were obtained through self-report during the first interview. Details of treatment and disease including number of lymph nodes removed, lymph node status (positive/negative), radiation therapy, chemotherapy, tumor size, histological grade, co-morbidities (hypertension, diabetes), and affected limb (left/right) were determined from the medical records. The number of lymph nodes removed and the lymph node status were confirmed by the final pathology report. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and then classified as normal ($\text{BMI} < 25 \text{ kg/m}^2$) or overweight/obese ($\text{BMI} \geq 25 \text{ kg/m}^2$).

Circumferential measurement was used to diagnosis lymphedema. With the olecranon as reference, a plastic tape measure with an accuracy of 1 mm was placed around the arm, and the arm circumference was measured 10 cm above and 5 cm below the elbow. The contralateral arm was measurement at the corresponding sites for comparison. A difference of ≥ 2 cm at any level between the affected and non-affected limbs was indicative of upper extremity lymphedema [7].

The first interview was held when patients were discharged, and then the lymphedema assessment was carried out every 6 months during a 12–24 month period after breast cancer surgery. In this study, 12 trained nurses with a college degree or above and at least 3 years of work experience joined in the measurement of lymphedema. Once lymphedema was confirmed, patients were required to receive complex decongestive treatment which includes manual lymphatic drainage, compression with multilayer bandages, exercises, and skin care.

Statistical Analysis

Data were analyzed using SPSS 17.0. (SPSS Inc., Chicago, IL, USA). Descriptive statistics (mean, standard deviation (SD), percentage, range) were used to describe the baseline demographics and medical characteristics. Univariate analyses for significant differences in the development of lymphedema according to baseline characteristics were performed by chi square test. The independent variables entered into the multivariate logistic regression analyses included the risk factors with univariate associations under the defined p value, and risk factors that were examined as predictors of lymphedema by other studies even though they were not significant on univariate analysis. All tests were two-sided, and $p < 0.05$ was taken as statistically significant.

Results

Lymphedema developed at a median of 18 months postoperatively (SD = 4; range 13–24 months). A total of 54 (42.9%) patients had lymphedema. Table 1 shows baseline demographic, medical, and disease characteristics of the 126 consecutive patients with breast cancer, who underwent radical

Table 1. Baseline demographic, medical, and disease characteristics (n = 126)

Characteristic	Patients, n (%)
Age ^a , years	
50–59	92 (73)
60–75	34 (27)
BMI, kg/m ²	
< 25	89 (71)
≥ 25	37 (29)
Co-morbidities	
Hypertension	24 (19)
Diabetes	9 (7)
Affected limb	
Left	64 (51)
Right	62 (49)
Tumor size ^b , cm	
≤ 2	53 (42)
> 2	73 (58)
Histological grade	
1	14 (11)
≥ 2	112 (89)
Lymph nodes removed ^c , n	
1–15	51 (41)
> 16	75 (59)
Lymph node status	
Positive	57 (45)
Negative	69 (55)
Radiotherapy	25 (20)
Chemotherapy	
Pre surgery	65 (52)
Post surgery	61 (48)

^aM ± SD (range): 58 ± 6 (50–75).^bM ± SD (range): 3 ± 2 (1–14).^cM ± SD (range): 16 ± 4 (1–29).

M = Medium; SD = standard deviation; BMI = body mass index.

Table 2. Relationship between personal, medical, and disease characteristics and lymphedema (n = 126)

Characteristics	Patients, n (%)		p
	lymphedema	no lymphedema	
Age, years			
50–59	40 (74)	52 (72)	0.8
60–75	14 (26)	20 (28)	
BMI, kg/m ²			
< 25	28 (48)	61 (85)	0.0
≥ 25	26 (52)	11 (15)	
Affected limb			
Left	27 (50)	37 (51)	1.0
Right	27 (50)	35 (49)	
Tumor size, cm			
≤ 2	18 (33)	35 (49)	0.1
> 2	36 (67)	37 (51)	
Histological grade			
1	3 (6)	11 (15)	0.2
≥ 2	51 (94)	61 (85)	
Lymph nodes removed, n			
1–15	18 (33)	33 (46)	0.2
> 16	36 (67)	39 (54)	
Lymph node status			
Positive	33 (61)	24 (46)	0.0
Negative	21 (39)	48 (54)	
Radiotherapy			
Yes	17 (32)	8 (11)	0.0
No	37 (68)	64 (89)	
Chemotherapy			
Post surgery	22 (41)	39 (54)	0.2
Pre surgery	32 (59)	33 (46)	

BMI = Body mass index.

Table 3. Results of the logistic regression analysis of personal, medical, disease characteristics and lymphedema (n = 126)

Characteristics	Adjusted OR (95% CI)	p
Age < 60 vs. ≥ 60 years	1 (0.4–2.5)	1.0
BMI < 25 vs. ≥ 25 kg/m ²	8 (2.8–20.1)	0.0
Affected limb left vs. right	1 (0.5–2.7)	0.7
Tumor size, ≤ 2 vs. > 2 cm	2 (0.7–3.9)	0.3
Histological grade 1 vs. ≥ 2	3 (0.5–12.8)	0.2
Lymph nodes removed 1–15 vs. > 16	1 (0.5–3.2)	0.5
Lymph node status negative vs. positive	2 (0.9–6.8)	0.1
Radiotherapy no vs. yes	3 (2.0–9.2)	0.0
Chemotherapy pre vs. post surgery	1 (0.3–2.7)	1.0

OR = Odds ratio; CI = confidence interval; BMI = body mass index.

mastectomy and ALND. Table 2 shows the relationship between personal, treatment-related, and disease-related factors and lymphedema. BMI ($\chi^2 = 16$, $p = 0.0$), lymph node status ($\chi^2 = 10$, $p = 0.0$), and radiotherapy ($\chi^2 = 8$, $p = 0.0$) were associated with upper extremity lymphedema. Other risk factors showed no statistically relevant association with lymphedema development. Table 3 shows the results of the logistic regression analysis of personal, treatment-related, and disease-related factors and lymphedema. Patients who were overweight or obese had an 8 times higher relative risk (adjusted 95% CI 2.8–20.1) of developing lymphedema compared with patients who had a normal BMI. Patients who received radiotherapy were 3 times (adjusted 95% CI 2.0–9.2) more likely to develop lymphedema than those who did not receive radiotherapy.

Discussion

In this study, we found that patients who were overweight or obese had an 8-times higher relative risk of developing lymphedema compared with patients who had a normal BMI. Overweight and obesity have been reported as an important factor that increases the risk of lymphedema development [5–9]. However, weight gain commonly occurs among women with breast cancer, and may both negatively affect quality of life and be a predictor for the development of lymphedema [5]. A recent clinical trial has shown that weight loss can significantly reduce the breast cancer-related lymphedema incidence [15]. On this basis, weight reduction should be a recommendation when managing lymphedema. Oncologists and nurses should encourage their breast cancer survivors to exercise routinely and give dietary advice to maintain a normal body weight.

Lymph node status is an important predictor for prognosis and treatment options in women with breast cancer. Positive lymph nodes mean adjuvant treatments such as chemotherapy, radiotherapy, endocrine therapy, or combined therapy, which may be more than is offered to lymph node-negative patients and may increase the damage to the lymphatic system and surrounding tissues. This may explain why lymph node-positive patients are more prone to lymphedema.

Radiation therapy has been found to be a major and independent risk factor of lymphedema development in some studies [7, 8]. In our study, patients who received radiotherapy had a 3 times higher lymphedema incidence than those who did not. The underlying pathophysiology is that radiotherapy can aggravate edema by causing fibrosis of tissues and muscles surrounding the lymph vessels. Women with breast cancer and a high recurrence risk after BCS or mastectomy would receive radiotherapy as would women with 5 or more positive lymph nodes. With regard to the latter, it should be noted that axillary radiotherapy is applied more commonly in older breast cancer patients.

Other risk factors in this study showed no association with edema in older women with breast cancer. For example, we did not find the number of lymph nodes removed to be significantly associated with lymphedema, which is in contrast with the work of Yen et al. [10] who found the opposite to be the case. This may be in part due to the fact that all women in our cohort received ALND, which limits the study power. Another potential reason is that the number of lymph nodes removed was confirmed by the final pathology report, and many factors such as node size, method of pathologic evaluation, and individual variation contribute to the number of nodes identified.

In summary, the present study examined the risk factors of lymphedema among Chinese postmenopausal breast cancer women. BMI, lymph node status, and radiotherapy were the risk factors of upper extremity lymphedema. BMI and radiotherapy were the independent predictors of upper extremity lymphedema. This study has several limitations: First, we did not measure lymphedema at baseline before surgery, which can affect the incidence of lymphedema in women. Second, the small sample size and data from just a single cancer center limit the ability to generalize the study findings. Third, this study related to older surgical techniques as over 90% of

Chinese postmenopausal breast cancer women are likely to receive mastectomy to prevent recurrence, which is partly due to cultural differences. The last one is that we did not assess all potential risk factors of lymphedema in older women.

Conclusion

Lymphedema is a distressing complication in older women with breast cancer. BMI, lymph node status, and radiotherapy were found to be risk factors of lymphedema development. Early detection and treatment of lymphedema are of the highest importance. Clinicians should provide sufficient information to patients and their caregivers to observe and assess lymphedema-related signs and symptoms. Nurses should provide reasonable dietary recommendations to patients who are overweight or obese and encourage them to take exercise to minimize the risk of developing lymphedema. When receiving radiotherapy, nurses and oncologists should accurately locate the site of exposure to avoid normal tissue being irradiated. Once lymphedema is diagnosed, early intervention (e.g. manual lymph drainage, compression garments) should occur as soon as possible.

Acknowledgement

We thank the Chongqing Breast Cancer Center and all contributors to this study.

Disclosure Statement

No potential conflicts of interest were disclosed.

References

- 1 Fu MR, Ridner SH: The pathophysiology of lymphedema. *Am J Nurs* 2009;7:48–54.
- 2 Fu MR, Rosedale M: Breast cancer survivors' experiences of lymphedema-related symptoms. *J Pain Symptom Manage* 2009;38:849–859.
- 3 McWayne J, Heiney SP: Psychological and social sequela of secondary lymphedema: a review. *Cancer* 2005;104:457–466.
- 4 Mak SS, Mo KF, Suen JJS, Chan SL, Ma WL, Yeo W: Lymphedema and quality of life in Chinese women after treatment for breast cancer. *Eur J Oncol Nurs* 2009;13:110–115.
- 5 Petrek JA, Senie RT, Peters M, Rosen PP: Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. *Cancer* 2001;92:1368–1377.
- 6 Clark B, Sitzia J, Harlow W: Incidence and risk of arm edema following treatment for breast cancer: a three-year follow-up study. *Q J Med* 2005;98:343–348.
- 7 Lawenda BD, Mondry TE, Johnstone PAS: Lymphedema: a primer on the identification and management of a chronic condition in oncologic treatment. *CA Cancer J Clin* 2009;59:8–24.
- 8 Park JH, Lee WH, Chung HS: Incidence and risk factors of breast cancer lymphedema. *J Clin Nurs* 2008;17:1450–1459.
- 9 Clough-Gorr KM, Ganz PA, Silliman RA: Older breast cancer survivors: factors associated with self-reported symptoms of persistent lymphedema over 7-years of follow up. *Breast J* 2010;16:147–155.
- 10 Yen TWF, Fan XL, Sparapani R, Laud PW, Walker AP, Nattinger AB: A contemporary, population based study of lymphedema risk factors in older women with breast cancer. *Ann Surg Oncol* 2009;16:979–988.
- 11 Armer JM: The problem of post-breast cancer lymphedema: impact and measurement issues. *Cancer Inves* 2005;1:76–83.
- 12 Moseley AL, Carati CJ, Piller NB: A systematic review of common conservative therapies for arm lymphedema secondary to breast cancer treatment. *Ann Oncol* 2007;18:639–646.
- 13 Fu MR, Chen CM, Haber J, Guth, AA, Axelrod D: The effect of providing information about lymphedema on the cognitive and symptom outcomes of breast cancer survivors. *Ann Surg Oncol* 2010;17:1847–1853.
- 14 Maughan KL, Lutterbie MA, Ham PS: Treatment of breast cancer. *Am Fam Physician* 2010;81:1339–1346.
- 15 Shaw C, Mortimer P, Judd PA: A randomized controlled trial of weight reduction as a treatment for breast cancer-related lymphedema. *Cancer* 2007;110:1868–1874.