The Breast 36 (2017) 67–73

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Incidence and risk factors of lymphedema after breast cancer treatment: 10 years of follow-up

Ana Carolina Padula Ribeiro Pereira [a], Rosalina Jorge Koifman [a], Anke Bergmann [b, *]

[a] National School of Public Health, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil
[b] National Cancer Institute, Rio de Janeiro, Brazil

ARTICLE INFO

Article history:
Received 6 June 2017
Received in revised form
21 September 2017
Accepted 27 September 2017
Available online 6 October 2017

Keywords:
Lymphedema
Breast neoplasm
Incidence
Risk factors

ABSTRACT

Purpose: To evaluate the incidence and risk factors of lymphedema 10 years after surgical treatment for breast cancer.
Methods: Prospective observational hospital-based cohort of women undergoing axillary lymph node dissection. Lymphedema was assessed by indirect volume, measured by circumference, and diagnosed if there was a difference of 200 mL between the arms or if the patient was treated for it. Independent variables were patient, tumour and treatment characteristics. Descriptive statistics were conducted as survival analysis using the Kaplan-Meier estimate. Cox regression was performed, considering a 95% confidence interval (95%CI).
Results: The study evaluated 964 women. The cumulative incidence of lymphedema observed was 13.5% at two years of follow-up, 30.2% at five years and 41.1% at 10 years. Final model showed an increased risk for lymphedema among women that underwent radiotherapy (HR = 2.19; 95%CI 1.63–2.94), were obese (HR = 1.52; 95%CI 1.20–1.92), had seroma formation after surgery (HR = 1.46; 95%CI 1.14–1.87), underwent chemotherapy infusion in the affected limb (HR = 1.45; 95%CI 1.12–1.87) or advanced disease staging (HR = 1.41; 95%CI 1.11–1.80).
Conclusions: Cumulative incidence of lymphedema was 41.1%. Women undergoing axillary radiotherapy, obese, who developed seroma, underwent chemotherapy infusion in the affected limb and with advanced disease had a higher risk of lymphedema.

1. Introduction

Breast cancer represents the most common neoplasm among women, and is responsible for 28.2% of all neoplasm cases. In the year 2012, there was an estimated 1.67 million new cases and 522,000 deaths from this cancer worldwide [1]. When detected in the early stages, the disease tends to have a good prognosis. Population-based studies have shown a mean relative survival in five years of 80% in developed countries and of 60% in developing countries [2,3].

Brazil is a developing country which still performs disease diagnosis in advanced stages. A large study conducted in the country reported that 53.5% of the cases diagnosed between the years 2000 and 2009 were classified as advanced stages (≥IIB) [4]. Late diagnosis leads to the need of employment of more aggressive treatments, carrying to several complications such as lymphedema [5–7]. Lymphedema is an impairing and chronic condition, which leads to important physical, social and psychological problems [8,9].

Most of the studies published in the current literature report the cumulative incidence of lymphedema in a 5-year follow-up period, which ranges from 3% to 42.2% depending on the assessment of the outcome and characteristics of the sample [10–18]. Considering a 10-year median follow-up, an incidence of 29% of lymphedema, as a self-reported outcome, was found among US multiethnic patients who had undergone breast cancer treatment [19]. In a meta-analysis, the estimated pooled incidence was 16.6%. Among patients who had undergone more aggressive treatment like Brazilian patients (axillary lymph node dissection), polled incidence estimated was 19.9% [20]. Considering studies with follow-up period ≥5 years, pooled incidence was 15.6%. A previous analysis of the present cohort was published in 2012 and reported a cumulative

* Corresponding author. André Cavalcanti Street, 37/2nd floor - Centro, Rio de Janeiro, 20231-050, Brazil.
E-mail addresses: carol_padula@hotmail.com (A.C.P. Ribeiro Pereira), rosalina.koifman@hotmail.com (R.J. Koifman), abergmann@inca.gov.br (A. Bergmann).

https://doi.org/10.1016/j.breast.2017.09.006
0960-9776/

incidence of 30.3% after a 5-year follow-up, using indirect volumetry (volume >200 ml) as the diagnosis method [21].

Several factors have been associated with the occurrence of lymphedema after breast cancer. Performance of mastectomy, axillary lymph node dissection (ALND), having positive lymph nodes, undergo to regional lymph node irradiation, higher body mass index (BMI), age and the occurrence of post-surgical complications were related to an increase in the risk of lymphedema [10,13–18,20–30].

To date, there are few studies that have assessed the incidence and associated factors of lymphedema in a 10-year follow-up period. As breast cancer has a good prognosis when diagnosed early, and patients will live with the impact of the treatment, it is essential to know the incidence and risk factors of lymphedema in the long term after treatment so that preventive measures can be incorporated into clinical practice.

This study aimed to evaluate the cumulative incidence and risk factors associated with the occurrence of lymphedema after ALND for breast cancer in a hospital-based cohort during 10 years of follow-up.

2. Material and methods

2.1. Study population and follow-up

This was a prospective cohort study, which included women undergoing ALND as surgical treatment for breast cancer from August 2001 to November 2002, in a single reference institution for cancer treatment. The following criteria for exclusion were considered: patients who underwent a sentinel Lymph node mapping; prior oncologic treatment provided at another institution, a previous contralateral or a synchronous bilateral breast cancer, previous lymphedema or functional alteration of one of the upper extremities, a palliative surgery, presence of distant metastasis and inability to answer the study questionnaire. Such women were initially prospectively followed for 60 months with the specific aim of determining the incidence and the predictive factors for lymphedema. The methodologic features of this cohort have been previously published [21].

The initial population of this study was composed of 1243 women, of which 189 did not fulfill eligibility criteria. This resulted in a total of 1054 women that participated in the lymphedema incidence evaluation during a five year follow-up from the surgical procedure [21]. For this study, all women with early lymphedema (developed in the first six months after the surgical procedure) ($n = 70$) and those with a follow-up of less than six months after surgery ($n = 27$) were excluded. Other 7 patients were excluded by mistake in the 5-year follow-up analysis and were reincluded. Thus, a total of 964 women were analyzed.

2.2. Data collection

Medical records from patients without lymphedema at 60 months were reviewed to identify information about the diagnosis of lymphedema after this period, disease progression or death. Women without this information in their medical records were invited for a physical examination at 10 years after surgery.

Demographic data (age, marital status, education level, occupation, race and BMI), treatment characteristics (type of surgery, radiotherapy, chemotherapy, hormonal therapy) and clinical events (recurrence, death) were obtained from medical records. Tumour characteristics (histological type, tumour size, lymph node status, tumour staging, number of axillary lymph nodes surgically removed and number of nodes involved) were abstracted from histopathology reports. Complications related to the healing process (wound infection, seroma, haematoma) were obtained from reports in medical charts. Post treatment complications (axillary web syndrome, early oedema, paresthesia of the intercostobrachial nerve, winged scapula) were abstracted from the routine physical therapy evaluation for the first six months post-surgery.

The outcome “lymphedema” was assessed at baseline (before surgical procedure) and during the follow-up using a circumference measure that was taken at 14 and 7 cm above, and 6, 14 and 21 cm below, the elbow joint. The volume of each arm was estimated by the formula for the volume of the frustum of a cone [31], and lymphedema was diagnosed if there was a difference of 200 ml between the arms.

2.3. Statistical analysis

Baseline demographics, treatment and clinical characteristics of the cohort were described using measures of central tendency and dispersion for continuous variables and proportions for categorical data.

Survival analysis was conducted by the Kaplan-Meier method, to identify the cumulative incidence and the possible differences in the curves for each exposure group. Censoring was considered for those women who completed 10 years free of lymphedema, those who were lost during follow-up and those who developed local recurrence, distant metastasis or death. The diagnosis of lymphedema was considered the event.

The univariate Cox regression analysis was performed in order to estimate the crude risk factors for the different exposure groups. Variables with $p < 0.20$ were selected for the multivariate model. The multivariate survival analysis was made using Cox regression model. The variables with $p < 0.05$ were retained in the final model.

2.4. Ethical standard

This study was approved by the institutional review board under the protocol 42/02. All patients signed an informed consent before being included in the study.

3. Results

Demographic and clinical characteristics of the 964 analyzed patients at the time of surgery are described in Table 1. The majority of women were married (47.6%), did not complete elementary school (45.1%) and performed housework (61.2%). Considering nutritional status, the mean BMI was 27.72 ($SD = 5.37$) where 36.7% was obese. Regarding treatment, chemotherapy was performed in the majority of patients, and 27.6% had at least one cycle of chemotherapy in the affected upper limb. Adjuvant radiotherapy and hormonal therapy was also performed by the majority of patients. In most of the cases, women had a mastectomy (65.1%), ALND until level III (83.8%), a mean of 17.85 ($SD = 7.52$) lymph nodes removed and 4.46 positive lymph nodes ($SD = 4.84$).

The stages IIA and IIB together represented more than half of the studied sample.

The occurrence of surgical complications is described in Table 2. The suction drain was kept for a mean period of 12.59 ($SD = 2.90$) days. The observed complications, related to the surgical wound, were seroma (62.6%), nechrosis (40.7%) and infection (12.9%). Considering functional complications, 81.7% had paresthesia in the intercostobrachial nerve, 33.8% had axillary web syndrome and 66.3% had winged scapula.

The conditional probability of lymphedema occurrence, according to the Kaplan-Meier curve, in a 10-year follow-up is shown in Fig. 1. The cumulative incidence of lymphedema was 13.5% in two

Table 1
Socio-demographic, clinical and treatment characteristics of the patients at the time of the surgical procedure (n = 964).

	N (%)
Age [mean (SD)]	55.31 (12.98)
Marital status	
Married	454 (47.6)
With partner	3 (0.3)
Divorced/separated	76 (8.0)
Widow	188 (19.7)
Single	233 (24.4)
Educational level	
Illiterate	63 (6.8)
Incomplete elementary school	417 (45.1)
Complete elementary school	167 (18.1)
Incomplete high school	34 (3.7)
Complete high school	174 (18.8)
Incomplete college	17 (1.8)
Completed college	53 (5.7)
Occupation	
Housework	450 (61.2)
Housekeeper	80 (10.9)
Trade	51 (6.9)
Office	47 (6.4)
Seamstress	23 (3.1)
Cook	14 (1.9)
Healthcare	20 (2.7)
Other	50 (6.8)
Body mass index [mean (SD)]	27.72 (5.375)
Nutritional status	
Underweight (BMI <18.5)	16 (1.7)
Normal (BMI 18.5–24.9)	289 (30.0)
Overweight (BMI 25.0–29.9)	305 (31.6)
Obesity (BMI ≥30.0)	354 (36.7)
Chemotherapy	
No	281 (29.1)
Neoadjuvant and Adjuvant	117 (12.1)
Only Neoadjuvant	96 (10.0)
Only Adjuvant	470 (48.8)
Chemotherapy infusion in the affected limb	
No	698 (72.4)
1-3 cycles	126 (13.1)
≥4 cycles	140 (14.5)
Radiotherapy	
No	335 (34.8)
Neoadjuvant and Adjuvant	1 (0.1)
Only Neoadjuvant	16 (1.7)
Only Adjuvant	611 (63.4)
Regional lymph node irradiation	
No	685 (71.1)
Yes	279 (28.9)
Hormonal therapy	
No	304 (31.5)
Neoadjuvant and Adjuvant	16 (1.7)
Only Neoadjuvant	4 (0.4)
Only Adjuvant	640 (66.4)
Surgical procedure	
Mastectomy	622 (65.1)
Breast-conserving	334 (34.9)
Surgical side	
Right	461 (47.8)
Left	503 (52.2)
Axillary lymph node dissection level	
I	51 (5.6)
II	96 (10.5)
III	764 (83.8)
Excised lymph nodes [mean (SD)]	17.85 (7.52)
Positive lymph nodes [mean (SD)]	4.46 (4.84)
Histopathological staging	
0	33 (3.4)
I	181 (18.9)
IIA	311 (32.5)
IIB	233 (24.3)
IIIA	52 (5.4)
IIIB	147 (15.4)

* Total of patients that have performed the treatment.

Table 2
Complications in the surgical wound and in physic functional state of the upper limb (n = 964).

Variables	N (%)
Maintenance of suction drain, days [mean (SD)]	12.59 (2.90)
Seroma	
Yes	575 (62.6)
No	344 (37.4)
Nechrosis	
Yes	374 (40.7)
No	546 (59.3)
Surgical wound infection	
Yes	119 (12.9)
No	801 (87.1)
Paresthesia in the intercostobrachial nerve	
Yes	788 (81.7)
No	176 (18.3)
Axillary web syndrome	
Yes	326 (33.8)
No	638 (66.2)
Winged scapula	
Yes	639 (66.3)
No	325 (33.7)

years, 30.2% in five years and 41.1% in 10 years (Table 3).

Table 4 shows differences in the probability of developing lymphedema between stratums of different exposure variables, according to the Kaplan-Meier method.

Considering socio-demographic and clinical characteristics, only obesity has shown statistically significant differences (HR = 1.52; 95%CI = 1.21–1.90; p < 0.001). Age at surgery, marital status, educational level and occupation did not seem to influence the lymphedema risk in 10 years of follow-up.

Regarding characteristics of breast cancer treatment, statistically significant differences in the conditional probability of lymphedema were observed when the sample was stratified by the type of breast surgery (HR = 1.31; 95%CI = 1.03–1.68; p = 0.027), ALND level (HR = 1.53; 95%CI = 1.07–2.20; p = 0.020), performance of chemotherapy in the affected upper limb (HR = 1.83; 95% CI = 1.44–2.33; p < 0.001), performance of radiotherapy (HR = 2.32; 95%CI = 1.76–3.06; p < 0.001) and regional lymph node irradiation (HR = 3.01; 95%CI = 2.47–3.89; p < 0.001) (Table 4). Furthermore, having advanced disease staging (HR = 1.60; 95% CI = 1.28–2.01; p < 0.001) and having at least four positive lymph nodes (HR = 1.72; 95%CI = 1.32–2.25; p < 0.001), also increased the probability of developing lymphedema.

Women with seroma showed a higher lymphedema incidence during the follow-up period (HR = 1.47; 95%CI = 1.15–1.88; p = 0.002), whereas other wounds and functional complications did not have a significant association with the occurrence of the outcome.

After adjustment, an increased risk of lymphedema was observed among women that underwent radiotherapy (HR = 2.19; 95%CI 1.63–2.94), were obese (HR = 1.52; 95%CI 1.20–1.92), had seroma formation after surgery (HR = 1.46; 95%CI 1.14–1.87), underwent chemotherapy infusion in the affected limb (HR = 1.45; 95%CI 1.12–1.87) or advanced disease staging (HR = 1.41; 95%CI 1.11–1.80) (Table 5).

4. Discussion

Cumulative incidence of lymphedema in a cohort of women surgically treated for breast cancer, after 10 years of follow-up, was 41.1%. To our knowledge, this is the first study to prospectively analyze the occurrence of lymphedema and associated factors in a

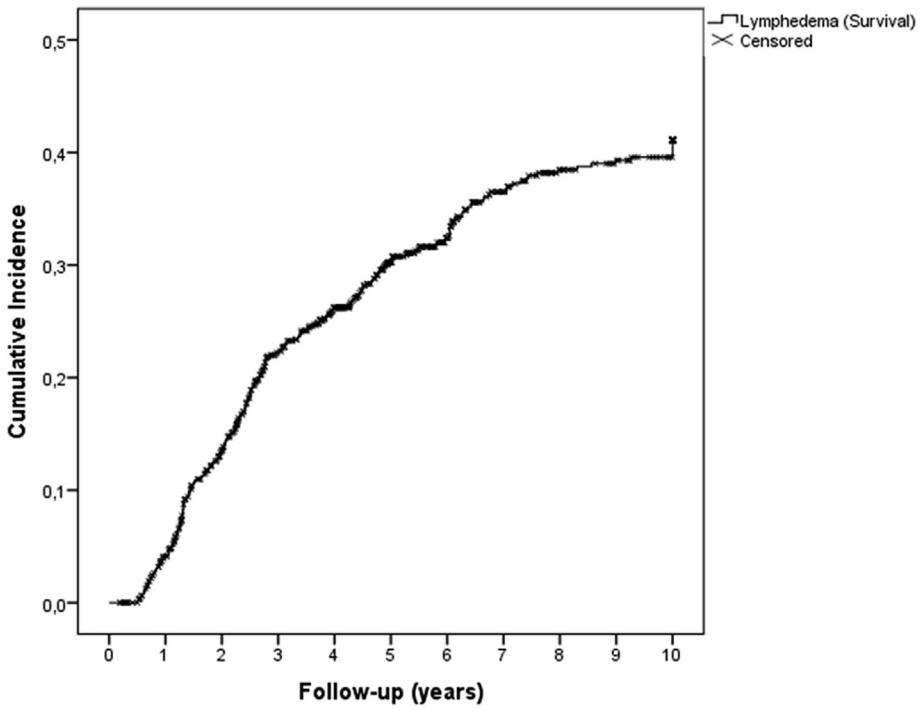

Fig. 1. Conditional probability of lymphedema in 10 years, according to Kaplan-Meier method.

Table 3
Lymphedema probability calculation, 10-years follow-up, according with Kaplan-Meier method.

Years after surgical procedure	N, in the beginning of the year	Lymphedema cases	Censored	Conditional probability of lymphedema
6 months to year 1	964	39	35	0.041
2	890	84	54	0.135
3	752	73	68	0.222
4	611	30	56	0.262
5	525	26	84	0.302
6	415	12	68	0.324
7	335	19	48	0.365
8	268	8	29	0.385
9	231	3	12	0.393
10	216	6	210	0.411

10-year follow-up using objective measures.

Some studies reported the incidence of lymphedema five years post-surgery, and noted an incidence ranging from 3% to 42.2% [10–18,23,32,33]. Only three studies assessed a 10-year follow-up. Wernicke and colleagues (2011) described a historical cohort of women with early stage disease that had undergone sentinel lymph node dissection and noted an incidence of 34.8%, assessed through objective measures [12]. Togawa and colleagues (2014) prospectively assessed self-reported lymphedema in a cohort of women that undergone none, sentinel biopsy or ALND and found an incidence of 29% [19]. Johansson & Branje (2010) retrospectively assessed lymphedema through objective measures in women with axillary dissection and found an incidence of 38.7% [34].

This great variability in literature seems to be due to differences in methods of assessing the outcome and characteristics of the population, especially regarding axillary surgery. As reported in a meta-analysis, when measure was stratified by the method to assess lymphedema, the following estimates were found: 5.0%, lymphoscintigraphy; 15.9%, bioelectrical impedance; 12.5%, self-reported clinical diagnosis; 12.6%, clinical diagnosis; 14.8%, circumference; 16.4%, perometry; 20.4%, self-reported swelling; 28.2%, more than one measure. Considering the axillary surgery, the incidence of lymphedema was 5.6% and 19.9% among patients that underwent sentinel lymph node dissection and ALND, respectively [20].

In our sample, all patients underwent ALND, lymphedema was assessed by circumference and higher estimates were found. Thus, this difference may be attributed to the duration of follow-up, which, also in accordance with data from DiSipio et al. (2013), provides discrepant measures (ranging from 10.3% in <6 months to 15.6% in >5 years) [20]. Considering this aspect, an increase in cumulative incidence was found in the study across the follow-up: 13.5% in two years, 30.2% in five years and 41.1% in ten years. Norman et al. conducted a study that assessed the occurrence of lymphedema in a 5-year follow-up period, using a standard questionnaire, and an increase in the estimate was also observed: 26.0%, in first year; 31.0% in second year; 36.0% in third year; 40.0% in fourth year; and 42.0% in fifth year. Although Norman et al. (2009) found higher estimates, the cases occurred during the first two years of the follow-up and in our cohort 75.3% of the cases occurred in the first four years [35]. Therefore, although these studies reinforce the importance of a close follow-up, data shows that the majority of lymphedema cases are observed within a few years after surgery.

As a secondary aim, the risk factors associated with the occurrence of lymphedema after surgical treatment for breast cancer were assessed. In multivariate model, performance of radiotherapy, obesity, seroma, chemotherapy infusion in the affected limb and staging were independently associated with lymphedema.

Regarding the performance of radiotherapy, our study showed a crude hazard ratio of 2.32 and adjusted risk of 2.19. This variable has been studied by several authors, and is one of the variables most associated with the occurrence of lymphedema after breast cancer treatment. Tsai et al. (2009) and Wang et al. (2016) found an increase in the risk of lymphedema of 1.91 (95%CI = 1.54–2.37) and

Table 4
Occurrence and lymphedema risk in accordance with demographic, clinical, treatment and disease variables and several complications.

Variable	Frequency (%)	Events (%)	Censored (%)	Mean follow-up without lymphedema (years)	Log rank p-value	Crude HR	95%CI
Demographic and clinical characteristics							
Age at the surgery							
≥65 years	241 (25.0)	69 (28.6)	172 (71.4)	7.48	0.898	1.02	0.78–1.33
<65 years	721 (74.9)	229 (31.8)	492 (68,2)	7.35			
Marital status at the surgery							
With partner	457 (47.9)	144 (31.5)	313 (68.5)	7.41	0.615	1.06	0.84–1.33
Without partner	497 (52.1)	156 (31.4)	341 (68.6)	7.27			
Educational level at the surgery							
Complete elementary school	647 (69.9)	213 (32.9)	434 (67.1)	7.21	0.080	1.26	0.97–1.63
High school or more	278 (30.1)	78 (28.1)	200 (71.9)	7.64			
Occupation at the surgery							
Housework	450 (61.2)	138 (30.7)	312 (69.3)	7.42	0.801	1.03	0.79–1.35
yWork out	285 (38.8)	90 (31.6)	195 (68.4)	7.38			
Obesity at the surgery							
Yes (BMI≥30)	354 (36.7)	136 (38.4)	218 (61.6)	6.79	**<0.001**	**1.52**	**1.21–1.90**
No (BMI<30)	610 (63.3)	164 (26.9)	446 (73.1)	7.70			
Treatment and disease characteristics							
Breast surgery							
Mastectomy	622 (65.1)	204 (32.8)	418 (67.2)	7.11	**0.027**	**1.31**	**1.03–1.68**
Conservative	334 (34.9)	96 (28.7)	238 (71.3)	7.76			
Staging							
Above IIB	432 (45.1)	154 (35.6)	278 (64.4)	6.75	**<0.001**	**1.60**	**1.28–2.01**
Until IIA	525 (54.9)	144 (27.4)	381 (72.6)	7.82			
Positive limph nodes							
≥4	174 (18.0)	70 (40.2)	104 (59.8)	6.34	**<0.001**	**1.72**	**1.32–2.25**
<4	790 (82.0)	230 (29.1)	560 (70.9)	7.57			
Removed lymph nodes							
≥15	652 (67.6)	210 (32.2)	442 (67.8)	7.33	0.690	1.05	0.82–1.35
<15	312 (32.4)	90 (28.8)	222 (71.2)	7.46			
Axillary lymph node dissection level							
Total	764 (83.8)	250 (32.7)	514 (67.3)	7.23	**0.020**	**1.53**	**1.07–2.20**
Partial	148 (16.2)	33 (22.3)	115 (77.7)	8.07			
Chemotherapy							
Yes	683 (70.8)	224 (32.8)	459 (67.2)	7.22	0.105	1.24	0.96–1.61
No	281 (29.1)	76 (27.0)	205 (73.0)	7.70			
Chemotherapy infusion in the affected limb							
Yes	266 (27.6)	104 (39.1)	162 (60.9)	6.32	**<0.001**	**1.83**	**1.44–2.33**
No	698 (72.4)	196 (28.1)	502 (71.9)	7.73			
Radiotherapy							
Yes	628 (65.1)	237 (37.7)	391 (62.3)	6.81	**<0.001**	**2.32**	**1.76–3.06**
No	336 (34.9)	63 (18.7)	273 (81.3)	8.41			
Regional lymph node irradiation							
Yes	279 (28.9)	142 (50.9)	137 (49.1)	5.47	**<0.001**	**3.01**	**2.47–3.89**
No	685 (71.1)	158 (23.1)	527 (76.9)	8.11			
Hormonal therapy							
Yes	660 (68.5)	215 (32.6)	445 (67.4)	7.33	0.553	1.08	0.84–1.39
No	304 (31.5)	85 (28.0)	219 (72.0)	7.45			
Complications							
Seroma							
Yes	575 (62.6)	200 (34.8)	375 (65.2)	7.02	**0.002**	**1.47**	**1.15–1.88**
No	344 (37.4)	91 (26.4)	253 (73.5)	7.80			
Nechrosis							
Yes	374 (40.6)	119 (31.8)	255 (68.2)	7.17	0.413	1.10	0.87–1.39
No	546 (59.4)	172 (31.5)	374 (68.5)	7.42			
Infection							
Yes	119 (12.9)	35 (29.4)	84 (70.6)	7.23	0.818	1.04	0.73–1.48
No	801 (87.1)	255 (31.8)	546 (68.2)	7.34			
Paresthesia							
Yes	788 (81.7)	240 (30.5)	548 (69.5)	7.46	0.107	0.79	0.60–1.05
No	176 (18.3)	60 (34.1)	116 (65.9)	6.91			
Winged scapula							
Yes	639 (66.3)	209 (32.7)	430 (67.3)	7.27	0.263	1.15	0.90–1.47
No	325 (33.7)	91 (28.0)	234 (72.0)	7.55			
Axillary web syndrome							
Yes	326 (33.8)	93 (28.5)	233 (71.5)	7.60	0.135	0.83	0.65–1.06
No	638 (66.2)	207 (32.4)	431 (67.6)	7.24			

Bold values are those with statistical significance.

Table 5
Cox multivariate model to assess the effect of variables with statistic and clinical importance in the development of lymphedema.

Variables	HR	95%CI	p-value
Radiotherapy	2.19	1.63–2.94	<0.001
Obesity (BMI≥30)	1.52	1.20–1.92	<0.001
Seroma	1.46	1.14–1.87	0.003
Chemotherapy infusion in the affected limb	1.45	1.12–1.87	0.005
Staging	1.41	1.11–1.80	0.005

4.285 (95%CI = 2.078–8.835), respectively, after radiotherapy to lymph node basin and/or breast/chest wall [22,30]. Other studies reported an increase of the risk of lymphedema after radiotherapy ranging from 1.44 to 3.24, however only when lymph node basin were involved [13–16,27]. In a meta-analysis the performance of regional lymph node irradiation was considered as weak/inconclusive evidence and the performance of radiotherapy, independently of the site, was considered as moderate level of evidence [20]. Regardless of discrepancies in the literature, radiotherapy is an important factor to consider in clinical practice in order to avoid the occurrence of lymphedema.

Patients with BMI ≥30, characterized as obese, at the time of the surgery had an increased risk of lymphedema (HR = 1.52) in both univariate and multivariate analyses. DiSipio et al. (2013) described a higher BMI as a variable strongly associated with the occurrence of lymphedema, increasing the risk by 1.4 times. In studies published after the conduction of this meta-analysis, a higher BMI is also reported as a risk factor for lymphedema, with association measures that range from 1.05 to 3.58 [13,27–29,36].

Post-surgical seroma formation was another variable associated with lymphedema and increased the risk by 1.47 and 1.46 times in univariate and multivariate analyses, respectively, corroborating the results from previous studies. When seroma was assessed as an independent variable, the risk of developing lymphedema varied from 1.59 to 1.92 times [32,37]. When assessing a combined variable of surgical infection and early edema, seroma increased the risk of developing lymphedema by 1.51 times [30]. As seroma is not an avoidable condition, its occurrence should be a concern that leads to close monitoring of patients for lymphedema.

The chemotherapy infusion in the affected limb was also associated with the occurrence of lymphedema, increasing the risk by 1.83 and 1.45 times in univariate and multivariate analyses, respectively. This finding still persists from the analysis in 24 and 60 months, however, to our knowledge, this association had never been described in other studies before [21,38]. Similar factors that could increase the risk of lymphedema such as ipsilateral injections and blood pressure measurements were not assessed since all patients from the institution are instructed not to perform these procedures in the arm ipsilateral to surgery. Fergusson et al. (2016) assessed the association between lymphedema and blood draws, injections, blood pressure readings, trauma, cellulitis in the at-risk arm, and air travel, and none of these variables were significantly associated [39]. This highlights the need of more studies assessing variables related not only to treatment and disease characteristics but also to patients' behavior.

The staging at diagnosis increased the risk of developing lymphedema by 1.60 and 1.41 times in univariate and multivariate analyses, respectively. Some studies previously published found an increase in the risk of developing lymphedema among patients diagnosed with later stages of the disease ranging from 1.49 to 6.93 [10,16,18,26,40]. However, in a systematic review, the stage was classified as having weak or inconclusive evidence to be supported as an independent risk factor [20].

Although our study provides new information about the incidence of lymphedema and associated risk factors in a long-term follow-up including a large Brazilian cohort, this study have some limitations. The lack of information on some demographic and clinical variables (race, comorbidities) may have impaired adequate control of the confounding bias. Another limitation is related to classification bias, since limb volume was obtained by indirect volumetric (frustum of a cone), and no using more sensitive methods (such as perometry, bioimpedance and water displacement). Women who presented a difference in arm volume above 200 mL in the first six months after surgical procedure were also excluded because it could be due to an acute condition (early oedema).

However, this sample was still representative of the Brazilian population due to the late diagnosis and the need for more aggressive treatment. Thus, major strengths of the study are the assessment of lymphedema using objective measures in a long term follow-up (10-year period), the use of data from Brazil which is a middle-income country with few data published in international literature, and the confirmation of previously reported risk factors.

This study highlights the need for strategies to prevent lymphedema in all stages of breast cancer, from diagnosis to long-term follow-up. In addition, it reinforces the importance of early diagnosis of breast cancer, so that less aggressive treatment strategies can be possible aiming to improve the quality of life.

5. Conclusion

After a 10-year follow-up period of this hospital-based cohort of women that underwent ALND as part of the surgical treatment for breast cancer, there was a cumulative lymphedema incidence of 41.1%. Although most of the lymphedema cases occurred in the beginning of the follow-up period, the cumulative incidence kept increasing throughout the evaluated years.

Final model showed that women that performed radiotherapy, obese, with seroma formation, that have performed chemotherapy infusion in the affected limb or diagnosed in an advanced stage of disease, are at increased risk of developing lymphedema.

In summary, our results show that even after a long period after breast cancer diagnosis, patients still need to be followed in order to diagnose and minimize the consequences of the treatment performed.

Funding sources

This work was supported by Oswaldo Cruz Foundation.

Acknowledgments

We want to thank the Physical Therapy Service from the National Cancer Institute.

References

[1] Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11 [internet]. Lyon, France: International Agency for Research on Cancer; 2013.
[2] Maughan KL, Lutterbie MA, Ham PS. Treatment of breast cancer. Am Fam Physician 2010;81:1339–46.
[3] Coleman MP, Quaresma M, Berrino F, Lutz J-M, De Angelis R, Capocaccia R, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). Lancet Oncol 2008;9:730–56. https://doi.org/10.1016/S1470-2045(08)70179-7.
[4] Abrahão KDS, Bergmann A, De Aguiar SS, Thuler LCS. Determinants of advanced stage presentation of breast cancer in 87,969 Brazilian women. Maturitas 2015;82:365–70. https://doi.org/10.1016/j.maturitas.2015.07.021.
[5] Lee BL, Liedke PER, Barrios CH, Simon SD, Finkelstein DM, Goss PE. Breast

cancer in Brazil: present status and future goals. Lancet Oncol 2012;13:e95–102.
[6] Rezende MCR, Koch HA, Figueiredo J de A, Thuler LCS. Causas do retardo na confirmação diagnóstica de lesões mamárias em mulheres atendidas em um centro de referência do Sistema Único de Saúde no Rio de Janeiro. Rev Bras Ginecol E Obs 2009;31:75–81.
[7] Alves Nogueira Fabro E, Bergmann A, Amaral E Silva B, Padula Ribeiro AC, Souza Abrahão K, Costa Leite Ferreira MG, et al. Post-mastectomy pain syndrome: incidence and risks. Breast 2012:1–5. https://doi.org/10.1016/j.breast.2012.01.019.
[8] Bergmann A, Mattos IE, Koifman RJ. Incidência e prevalência de linfedema após tratamento cirúrgico do câncer de mama: revisão de literatura. Rev Bras Cancerol 2007;53:461–70.
[9] Stamatakos M, Michael S, Stefanaki C, Charikleia S, Kontzoglou K, Konstantinos K. Lymphedema and breast cancer: a review of the literature. Breast Canc 2011;18:174–80. https://doi.org/10.1007/s12282-010-0246-1.
[10] 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 2011;16:147–55. https://doi.org/10.1111/j.1524-4741.2009.00878.x.Older.
[11] Goldberg JI, Wiechmann LI, Riedel ER, Morrow M, Van Zee KJ. Morbidity of sentinel node biopsy in breast cancer: the relationship between the number of excised lymph nodes and lymphedema. Ann Surg Oncol 2010;17:3278–86.
[12] Wernicke AG, Goodman RL, Turner BC, Komarnicky LT, Curran WJ, Christos PJ, et al. A 10-year follow-up of treatment outcomes in patients with early stage breast cancer and clinically negative axillary nodes treated with tangential breast irradiation following sentinel lymph node dissection or axillary clearence. Breast Cancer Res Treat 2011;125:893–902. https://doi.org/10.1007/s10549-010-1167-6.A.
[13] Warren LEG, Miller CL, Horick N, Skolny MN, Jammallo LS, Sadek BT, et al. The impact of radiation therapy on the risk of lymphedema after treatment for breast cancer: a prospective cohort study. Int J Radiat Oncol Biol Phys 2014;88:565–71. https://doi.org/10.1016/j.ijrobp.2013.11.232.
[14] Jung SY, Shin KH, Kim M, Chung SH, Lee S, Kang HS, et al. Treatment factors affecting breast cancer-related lymphedema after systemic chemotherapy and radiotherapy in stage II/III breast cancer patients. Breast Cancer Res Treat 2014;148:91–8. https://doi.org/10.1007/s10549-014-3137-x.
[15] Kim M, Kim SW, Lee SU, Lee NK, Jung SY, Kim TH, et al. A model to estimate the risk of breast cancer-related lymphedema: combinations of treatment-related factors of the number of dissected axillary nodes, adjuvant chemotherapy, and radiation therapy. Int J Radiat Oncol Biol Phys 2013;86:498–503. https://doi.org/10.1016/j.ijrobp.2013.02.018.
[16] Kim M, Shin KH, Jung S-Y, Lee S, Kang H-S, Lee ES, et al. Identification of prognostic risk factors for transient and persistent lymphedema after multimodal treatment for breast cancer. Cancer Res Treat 2016:4–11. https://doi.org/10.4143/crt.2015.463.
[17] Kim M, Park IH, Lee KS, Ro J, Jung S-Y, Lee S, et al. Breast cancer–related lymphedema after neoadjuvant chemotherapy. Cancer Res Treat 2014;47:416–23. https://doi.org/10.4143/crt.2014.079.
[18] Ugur S, Arıcı C, Yaprak M, Mescı A, Arıcı GA, Dolay K, et al. Risk factors of breast cancer-related lymphedema. Lymphat Res Biol 2013;11:72–5. https://doi.org/10.1089/lrb.2013.0004.
[19] Togawa K, Ma H, Sullivan-Halley J, Neuhouser ML, Imayama I, Baumgartner KB, et al. Risk factors for self-reported arm lymphedema among female breast cancer survivors: a prospective cohort study. Breast Cancer Res 2014;16:414. https://doi.org/10.1186/s13058-014-0414-x.
[20] DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol 2013;14:500–15. https://doi.org/10.1016/S1470-2045(13)70076-7.
[21] Bevilacqua JLB, Kattan MW, Changhong Y, Koifman S, Mattos IE, Koifman RJ, et al. Nomograms for predicting the risk of arm lymphedema after axillary dissection in breast cancer. Ann Surg Oncol 2012. https://doi.org/10.1245/s10434-012-2290-x.
[22] Tsai RJ, Dennis LK, Lynch CF, Snetselaar LG, Zamba GKD, Scott-Conner C. The risk of developing arm lymphedema among breast cancer survivors: a meta-analysis of treatment factors. Ann Surg Oncol 2009;16:1959–72. https://doi.org/10.1245/s10434-009-0452-2.
[23] Hayes SC, Janda M, Cornish B, Battistutta D, Newman B. Lymphedema after breast cancer: incidence, risk factors, and effect on upper body function. J Clin Oncol 2008;26:3536–42. https://doi.org/10.1200/JCO.2007.14.4899.
[24] Meeske K a, Sullivan-Halley J, Smith AW, McTiernan A, Baumgartner KB, Harlan LC, et al. Risk factors for arm lymphedema following breast cancer diagnosis in Black women and White women. Breast Cancer Res Treat 2009;113:383–91. https://doi.org/10.1007/s10549-008-9940-5.
[25] Ahmed RL, Schmitz KH, Prizment AE, Folsom AR. Risk factors for lymphedema in breast cancer survivors, the Iowa women's health study. Breast Cancer Res Treat 2011;130:981–91. https://doi.org/10.1007/s10549-011-1667-z.
[26] Kwan ML. Risk factors for lymphedema in a prospective breast cancer survivorship study. Arch Surg 2010;145:1055. https://doi.org/10.1001/archsurg.2010.231.
[27] Jammallo LS, Miller CL, Singer M, Horick NK, Skolny MN, Specht MC, et al. Impact of body mass index and weight fluctuation on lymphedema risk in patients treated for breast cancer. Breast Cancer Res Treat 2013;142:59–67. https://doi.org/10.1007/s10549-013-2715-7.
[28] Swaroop MN, Ferguson CM, Horick NK, Skolny MN, Miller CL, Jammallo LS, et al. Impact of adjuvant taxane-based chemotherapy on development of breast cancer-related lymphedema: results from a large prospective cohort. Breast Cancer Res Treat 2015;151:393–403. https://doi.org/10.1007/s10549-015-3408-1.
[29] Voss RK, Cromwell KD, Chiang YJ, Armer JM, Ross MI, Lee JE, et al. The long-term risk of upper-extremity lymphedema is two-fold higher in breast cancer patients than in melanoma patients. J Surg Oncol 2015;112:834–40. https://doi.org/10.1002/jso.24068.
[30] Wang L, Li H-P, Liu A-N, Wang D-B, Yang Y-J, Duan Y-Q, et al. A scoring system to predict arm lymphedema risk for individual Chinese breast cancer patients. Breast Care 2016:52–6. https://doi.org/10.1159/000443491.
[31] Casley-Smith JR. Measuring and representing peripheral oedema and its alterations. Lymphology 1994;27:56–70.
[32] Toyserkani NM, Jørgensen MG, Haugaard K, Sørensen JA. Seroma indicates increased risk of lymphedema following breast cancer treatment: a retrospective cohort study. The Breast 2017;32:102–4. https://doi.org/10.1016/j.breast.2017.01.009.
[33] Goldberg JI, Wiechmann LI, Riedel ER, Morrow M, Van Zee KJ. Morbidity of sentinel node biopsy in breast cancer: the relationship between the number of excised lymph nodes and lymphedema. Ann Surg Oncol 2010;17:3278–86. https://doi.org/10.1245/s10434-010-1155-4.
[34] Johansson K, Branje E. Arm lymphoedema in a cohort of breast cancer survivors 10 years after diagnosis. Acta Oncol 2010;49:166–73. https://doi.org/10.3109/02841860903483676.
[35] Norman S a, Localio a R, Potashnik SL, Simoes Torpey H a, Kallan MJ, Weber AL, et al. Lymphedema in breast cancer survivors: incidence, degree, time course, treatment, and symptoms. J Clin Oncol 2009;27:390–7. https://doi.org/10.1200/JCO.2008.17.9291.
[36] Kilbreath SL, Refshauge KM, Beith JM, Ward LC, Ung OA, Dylke ES, et al. Risk factors for lymphoedema in women with breast cancer: a large prospective cohort. Breast 2016;28:29–36. https://doi.org/10.1016/j.breast.2016.04.011.
[37] Monleon S, Murta-Nascimento C, Bascuas I, Macià F, Duarte E, Belmonte R. Lymphedema predictor factors after breast cancer surgery: a survival analysis. Lymphat Res Biol 2015;13:268–74. https://doi.org/10.1089/lrb.2013.0042.
[38] Bergmann A. Incidência e fatores de risco do linfedema após tratamento cirúrgico para câncer de mama: estudo de uma coorte hospitalar. Escola Nacional de Saúde Pública, Fundação Oswaldo Cruz; 2005.
[39] Ferguson CM, Swaroop MN, Horick N, Skolny MN, Miller CL, Jammallo LS, et al. Impact of ipsilateral blood draws, injections, blood pressure measurements, and air travel on the risk of lymphedema for patients treated for breast cancer. J Clin Oncol 2016;34:691–8. https://doi.org/10.1200/JCO.2015.61.5948.
[40] Park JH, Lee WH, Chung HS. Incidence and risk factors of breast cancer lymphoedema. J Clin Nurs 2008;17:1450–9. https://doi.org/10.1111/j.1365-2702.2007.02187.x.