Survival and Risk Factors in Women with Breast Cancer: the Relationship of Lymphedema

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Sobrevivência e Fatores de Risco em Mulheres com Câncer de Mama: a Relação do Linfedema

Supervivencia y Factores de Riesgo en Mujeres con Cáncer de Mama: la Relación del Linfedema

Laís Corsino Durant[1]; Aniele Tomadon[2]; Franciele Foschiera Camboin[3]; Joselici da Silva[4]; Regiane Bezerra Campos[5]; Thais de Oliveira Gozzo[6]

Abstract

Introduction: Lymphedema related to breast cancer is the main complication of the treatments for this neoplasm, affecting the upper limb homolateral to the compromised breast. **Objective:** To analyze the incidence, risk factors and impact on overall survival of lymphedema secondary to breast cancer. **Method:** Retrospective cohort study with 709 women attended at a rehabilitation center for breast cancer, between 1989 and 2014. The categorical absolute frequencies were compared to the Chi-square test. Overall survival rate was calculated using Kaplan Meier method and the Cox proportional hazard regression model was used to evaluation of prognostic factors, the definition of indicators associated with lymphedema incidence was calculated with logistic regression. **Results:** White women predominated, mean age 61.5 years. Women with lymphedema (33.24%), 85.8% were diagnosed at an advanced stage, a higher frequency of axillary lymphadenectomy (p=0.064) and low sentinel lymph node biopsy (p<0.0001). In the survival status the women with lymphedema presented a higher death rate due to the cancer (50.2%), with a survival rate of 0.996 up to five years. Women death predictors were advanced cancer stage and the amount of compromised lymph nodes. **Conclusion:** Women with lymphedema present a greater chance to die from cancer than the other group, but they remain alive for a longer period. The advanced stage and non-performance of sentinel lymph node biopsy were considered risk factors for the development of lymphedema and the predictive characteristics of death.

Key words: Breast Neoplasms; Lymphedema; Survival Analysis; Risk Factors.

Resumo

Introdução: O linfedema relacionado ao câncer de mama é a principal complicação dos tratamentos para essa neoplasia, acometendo o membro superior homolateral à mama comprometida. **Objetivo:** Analisar a incidência, fatores de risco e o impacto na sobrevida global do linfedema secundário ao câncer de mama. **Método:** Estudo de coorte retrospectivo com dados de 709 mulheres atendidas em núcleo de reabilitação de câncer de mama, entre 1989 e 2014. Realizou-se comparação de frequências absolutas categóricas com o teste qui-quadrado. As funções de sobrevida foram calculadas por meio do método de Kaplan Meier e o modelo de riscos proporcionais de Cox foi utilizado para avaliação de fatores prognósticos; utilizou-se a regressão logística para definir fatores associados à incidência de linfedema. **Resultados:** Predominaram mulheres brancas, média de idade de 61,5 anos. Das mulheres com linfedema (33,24%), 85,8% foram diagnosticadas em estadiamento avançado, maior frequência de linfadenectomia axilar (p=0,064) e baixa realização da biópsia de linfonodo sentinela (p<0,0001). No *status* de sobrevida, as mulheres com linfedema apresentaram maior frequência de óbito por causas relacionadas ao câncer (50,2%), com taxa de sobrevivência de 0,996 até cinco anos. As principais características preditoras ao óbito dessas mulheres foram o estadiamento avançado e a quantidade de linfonodos comprometidos. **Conclusão:** As mulheres com linfedema apresentaram maior chance de óbito por câncer do que o outro grupo, porém permaneceram vivas por período maior. O estadiamento avançado e a não realização da biópsia do linfonodo sentinela foram considerados fatores de risco para o desenvolvimento do linfedema e como características preditoras de óbito.

Palavras-chave: Neoplasias da Mama; Linfedema; Análise de Sobrevida; Fatores de Risco.

Resumen

Introducción: El linfedema relacionado con el cáncer de mama es la principal complicación de los tratamientos para esta neoplasia, afectando al miembro superior homolateral a la mama comprometida. **Objetivo:** Analizar la incidencia, factores de riesgo y impacto en la supervivencia global del linfedema secundario al cáncer de mama. **Método:** Estudio de cohorte retrospectivo con 709 mujeres atendidas en un núcleo de rehabilitación de cáncer, entre 1989 y 2014. Se realizó la comparación de sus series completas con la prueba Chi-cuadrado. Funciones de sobrevida fueran calculadas por método de Kaplan Meier y el modelo de evaluación de Cox fue utilizado para la evaluación de factores pronósticos, regresión logística fue usada para la definición de indicadores asociados al incidencia de linfedema. **Resultados:** Predominaron mujeres blancas, media de edad 61,5 años. Las mujeres con linfedema (33,24%), 85,8% fueron diagnosticadas en estadio avanzado, mayor frecuencia de linfadenectomía axilar (p=0,064) y baja realización de la biopsia de ganglio centinela (p<0,0001). En el estatus de sobrevida, mujeres con linfedema presentaron mayor frecuencia de muerte por cáncer (50,2%), con tasa de supervivencia de 0,996 hasta cinco años. Las características predictoras de muerte fueran estadio avanzado y la cantidad de ganglios linfáticos comprometidos. **Conclusión:** Las mujeres con linfedema presentan mayor probabilidad de muerte por cáncer que el otro grupo, sin embargo, permanecen vivas por período mayor. El estado avanzado y la no realización de la biopsia del ganglio centinela fueron considerados factores de riesgo para el desarrollo del linfedema y como características preditorias del óbito.

Palabras clave: Neoplasias de la Mama; Linfedema; Análisis de Supervivencia; Factores de Riesgo.

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INTRODUCTION

Breast cancer is the malignant most incident neoplasm worldwide among women, being considered a serious problem of public health due to the necessity of high financial investments to devise the diagnosis, treatment and possible adverse events arising from the therapies [1-3].

Breast cancer related lymphedema is the principal complication from the treatment of this neoplasm with incidence of until 50% of women, affecting in its majority the ipsilateral upper limb of the compromised breast[4,5]. After onset, cancer-related lymphedema can be irreversible because of the conventional therapeutic techniques available, and remains with the women during their whole life, making it a progressive and debilitating sequelae[4,6].

The occurrence of breast cancer-related lymphedema is associated to several risks as more aggressive surgeries, dissection of axillary lymph nodes, elevated Body Mass Index, radiotherapy over the lymph nodal region, age and postoperative complications[7-9].

So far, it is noticed that there are few studies which evaluate the risk factors and survival of women with breast cancer-related lymphedema within a follow up period over 10 years[10,11]. The survival of women with breast cancer and who develop lymphedema appears as a necessity for improvement of the care provided to these women by the healthcare providers, considering that this population, in its majority, results from late and more aggressive treatments with potential to produce worst prognosis. Furthermore, it could help to better understand the trajectory of its development, ameliorate the approach and management of lymphedema associated to strategies of prevention, with the intent to value the quality of life added to the years of the women with breast cancer.

This study had the objective to analyze the incidence, risk factors and impact over the global survival of secondary lymphedema to breast cancer in women assisted in a rehabilitation facility.

METHOD

Documental, retrospective cohort study with women diagnosed with breast cancer and followed up in a rehabilitation facility in a Municipality of the State of São Paulo.

The data were obtained through the evaluation of charts of the referenced unit with all the women signed in between May 1989, when the service was inaugurated until December 2014.

It were analyzed 1,300 charts of women that had been signed in at the service. Of these, 861 met the inclusion criteria: age, older than 18 years and treated for breast cancer in a university hospital in the same municipality. From this total, 152 were excluded because of incomplete data and chart not found, forming a final sample of 709 women (Figure 1).

It was used a structured questionnaire to collect the data with information to characterize the sample as age at the diagnosis, tobacco addiction or not, race, education[12]. In addition to these information, considering the clinical factors to be investigated to assess the risk of death, it were selected as independent variables the presence or

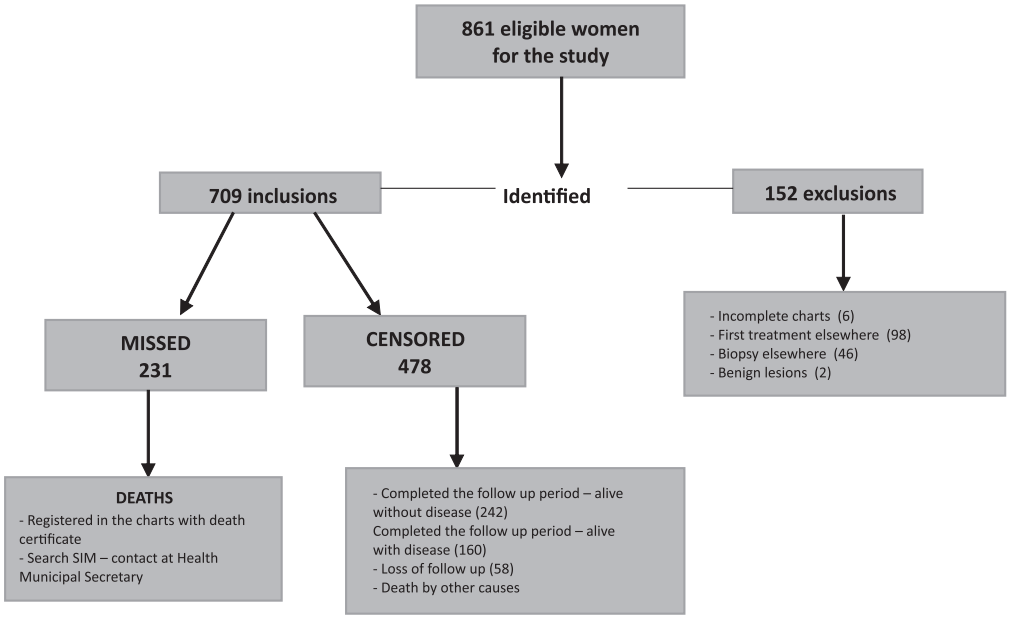

Figure 1. Flowchart of follow up of the patients of the study

not of lymphedema with differences greater than 200 ml between the members, calculated by the formula of the cone $V = \frac{\pi h}{3}[R^2 + Rr + r^2]$, and the *status* (alive with disease, alive without the disease, cancer-related death and cancer-unrelated death). The control variables were biopsy of the sentinel lymph node, axillary lymphedema (present or not), radiotherapy (neoadjuvant or adjuvant)[13].

Death was determined based in the death certificate attached to the chart and through the "*Sistema de Informação sobre Mortalidade*" (Mortality Reporting System) of "*Secretaria Municipal da Saúde*" (Municipal Health Secretary) of the city where the hospital of the study is located.

All the women whose death was cancer-related in the follow up period, until December 2014 were considered missed. It were considered censored those who survived upon completion of the follow up period, with loss to follow up or alive at the time when data were collected, but who had been transferred to another health service, those who moved away from the city, state or country and whose death was due to other than breast cancer and its progression, considering for analysis, the date of the last follow up registered in the medical chart or date of death (censorship at right).

Frequency tables of the categorical variables were elaborated to characterize the profile of the participants. The absolute frequencies of the categories of the variables were compared among the group of women with and without lymphedema through the chi-square test for independence. Where the hypothesis to apply this test was not feasible, it was applied the permutation test of Monte Carlo to adjust the chi-square distribution.

Upon the verification of the variables, the survival curve analysis was made through the Kaplan-Meier method and Log-rank test with level of significance of 5% with the probability of survival cumulative in months, according to the variable of interest.

To calculate the *hazard ratio* (HR), it was utilized the analysis of Mantel Hanzel. After, it was adjusted to the Cox proportional hazards model with confidence interval of 95%.

Once identified the significant variables for the development of lymphedema, it is used the model of logistic regression. This analysis was conducted to define the odds of developing lymphedema. For this, it was adjusted a mathematical model by the method of binary logistic regression method.

Some stages were fulfilled to conduct the binary logistic regression: a) selection of predictive variables of the model using the criteria of *P<0.10* of the odds ratio (OR) being equivalent to 1; b) obtain a model with reduced number of variables selected from the application of the criteria of *P<0.05* of the adjusted odds ratio being equivalent to 1; c) obtain a final model after the test for all the possible multiple iterations, utilizing the maximization of the function of Wald; d) to verify the adjustment of the models, it was utilized the statistic of Hosmer & Lemeshow.

Once decided the final model of logistic regression for each one of the objectives referenced, the probabilities were calculated with the formula $Pr=1/[1+e-(\alpha + \sum(\beta i\ xi)]$, being α the constant of the model.

At last, the data of the specific survival period (death by cancer) of women with and without lymphedema were evaluated with the date of the diagnosis and the date of the final outcome of the last visit.

For all the analyzes, it was assumed the level of significance of 0.05, being utilized the software XLSTAT® Version 2016.05.35209.

The Institutional Review Board of "Escola de Enfermagem de Ribeirão Preto" of "Universidade de São Paulo", approved the study, report CAAE: 24916813.0.0000.5393.

RESULTS

It were not found information in the charts about the development of lymphedema for 8 of 709 women; therefore, of the 701 women, 233 (33.24%) had lymphedema. It was noticed that the mean age of the participants was 61.5 years old (standard deviation, 12.70), with equivalence of the distribution of frequency of the age ranges between the groups of women with lymphedema and without lymphedema (p=0.327). There was no statistic difference between the groups in relation to the variables Tobacco Addition, Race and Education ($p > 0.05$), indicating that the groups are equivalent in their characteristics. Table 1 shows the distribution of women for the stratified sociodemographic variables among those who had or did not have lymphedema.

Regardless whether women have developed or not lymphedema, the majority (94% and 88.7%, respectively) was submitted to the surgical procedure of axillary lymphadenectomy, a data that was significantly more frequent among women with lymphedema (p=0.064; Table 2).

In the evaluation of frequency of biopsy of the sentinel lymph node it was verified that there was difference amidst the groups ($p < 0.0001$), occurring with more frequency among those with lymphedema (19.4%; Table 2).

As for the number of lymph nodes removed, it was noticed that the distribution of frequency was equivalent among the two groups ($p = 0.135$). However, in relation to the number of lymph nodes compromised, it was

Table 1. Distribution of the sociodemographic variables for women with and without lymphedema (N=701)

Variable	Lymphedema		Without lymphedema		p-value
	F	%	F	%	
Age at diagnosis					
21 to 30	0	0	5	1.1	0.327
31 to 40	12	5.2	17	3.6	
41 to 50	38	16.3	81	17.3	
51 to 60	54	23.2	120	25.6	
61 to 70	49	21	138	29.5	
>70	80	34.3	107	22.9	
Tobacco addiction					
Yes	33	14.2	85	18.2	0.155
No	199	85.4	383	81.8	
Not informed	1	0.4	0	0	
Race					
Caucasian	195	83.7	401	85.7	0.486
Others	38	16.3	67	14.3	
Education					
No education	20	8.6	34	7.3	0.239
Until 4 years	68	29.2	111	23.7	
5 to 8 years	94	40.3	201	42.9	
9 to 12 years	36	15.5	69	14.7	
>12 years	15	6.4	51	10.9	
Not informed	0	0	2	0.4	

observed that, in women with lymphedema, 13.3% had 11 to 20 lymph nodes compromised (p = 0.004; Table 2).

For women who submitted to neoadjuvant radiotherapy treatment it were observed significant statistic differences (p<0.0001) and among the women with lymphedema, the procedure represented 11.6%; for those who did not have lymphedema, it was 4.3%. Among women who submitted to adjuvant radiotherapy, significant statistic differences were not verified (p=0.363; Table 2).

Considering the status of survival, meaning the outcome in relation to the life condition of women with and without lymphedema, it was verified that there were significant statistical differences (p<0.0001), and those with lymphedema presented higher frequency of death for cancer-related causes (50.2%), while among those without lymphedema, it was observed higher frequency of being alive without cancer (39.5%) or with cancer (25.6%; Table 2).

In regard to staging, it was possible to notice significant statistical differences among the groups (p<0.0001), with more frequency of cases in staging IIIB and IIIC among women with lymphedema (27% and 3.9%, respectively), while women without lymphedema presented significantly more frequency in staging I and IIA (13.7% and 28%; Table 2).

For the calculation of the survival, 709 women were evaluated, and 246 presented lymphedema, the event of interest. In regard to lymphedema, 233 presented this morbidity and 468 did not, totaling 701 women. It can be observed that the mean survival period of the women with lymphedema was 162 months (CI 95%: 136-187 weeks), with 117 deaths for cancer-related causes. While for the women without lymphedema, the average survival was 203 months (CI95%: 190-216 weeks), with 110 deaths/cancer-related events (Figure 2). It was possible to verify that there was difference in the survival curve that was statistically significant in the model (p<0.0000), and the women with lymphedema presented significantly more survival time than those without lymphedema, but the number of deaths in women with lymphedema is proportionally bigger (Figure 2).

Among women with or without lymphedema who survived for less than one year, the rates were 0.996% and 0.998% respectively. For survival between one and five years, the rate for those with lymphedema was 0,993 and was 0.996 for those who had no lymphedema. At last, the value of survival in a ten years period was 0.982 for those with lymphedema and 0.991 for those without lymphedema, indicating a lower survival rate for all periods for the women with lymphedema, despite being observed among those who survived, a total extended period for the women with lymphedema that survived for more time. Concurring with Kaplan Meier, in relation to the Cox proportional hazards model where the hazard

Table 2. Characteristics related to cancer and treatment among women with and without lymphedema (N=701)

Variable	With lymphedema		Without lymphedema		p-value
	F	%	F	%	
Axillary lymphadenectomy					
Yes	219a	94	415b	88.7	0.327
No	14b	6	51a	10.9	
Not informed	0	0	2	0.4	
Biopsy of the sentinel lymph node					
Yes	18b	7.7	91a	19.4	
No	215a	92.3	375b	80.1	
Not informed	0	0	2	0.4	
Number of lymph nodes removed					
0 to 10	45	19.3	111	23.7	0.155
11 to 20	116	49.8	213	45.5	
21 to 30	45	19.3	97	20.7	
> 30	2	0.9	13	2.8	0.486
Not informed	25	10.7	34	7.3	
Number of lymph nodes compromised					
0 to 10	174b	74.7	398a	85.0	
11 to 20	31a	13.3	28b	6.0	
21 to 30	3	1.3	9	1.9	0.239
> 30	2	0.9	4	0.9	
Not informed	23	9.9	29	6.2	
Neoadjuvant Radiotherapy					
Yes	27a	11.6	20b	4.3	
No	205b	88	448a	95.7	<0.0001
Not informed	1	0.4	0	0.0	
Adjuvant Radiotherapy					
Yes	172	73.8	349	74.6	
No	60	25.8	119	25.4	0.363
Not informed	1	0.4	0	0	
Status					
Alive without cancer	55b	23.6	185a	39.5	
Live with cancer	40b	17.2	120a	25.6	
Death by cancer	117a	50.2	110b	23.5	<0.0001
Death not by cancer	6	2.6	13	2.8	
Losses	15	6.4	40	8.5	
Clinical Staging					
Staging 0	3	1.3	17	3.6	
Staging I	19b	8.2	64a	13.7	
Staging IIA	42b	18	131a	28	
Staging IIB	42	18	81	17.3	
Staging IIIA	30	12.9	71	15.2	< 0.0001
Staging IIIB	63a	27	70b	15	
Staging IIIC	9a	3.9	3b	0.6	
Staging IV	13	5.6	15	3.2	
Not informed	12	5.1	16	3.4	

Note: Different letters indicate significant statistic differences among the categories lymphedema and without lymphedema (p<0.05).

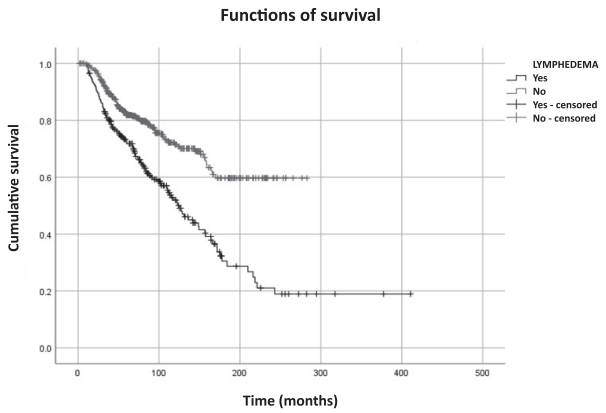

Figure 2. Function of free survival of women with and without lymphedema (N=701)

ratio of the event to occur was evaluated, those who had lymphedema presented 2.131 more risk of death (HR=2.131; CI=1.642-2.766)

To evaluate which factors were associated to the occurrence of the risk of developing lymphedema, it was performed the analysis of logistic regression. The variables considered as significant by the method were the number of lymph nodes compromised, biopsy of the sentinel lymph node and radiotherapy (Table 3). According to the model generated, the women who developed lymphedema had as predictive characteristics: higher number of compromised lymph nodes (>30), axillary lymphedema and advanced staging. In regard to the number of lymph nodes compromised, the odds of developing lymphedema was bigger among women with more than 30 compromised lymph nodes (OR=10,.; CI=0.977-113.024). The biopsy of the sentinel lymph node was considered a protective factor for the development of the morbidity. Women who had biopsy of the sentinel lymph node presented 66% less chance of developing lymphedema (OR=0,345; CI=0.203-0.588).

Whether radiotherapy was done or not had was not significant (OR=1.023; CI=0.714-1.466). To have axillary lymphadenectomy was considered a risk factor to develop lymphedema (OR=1.922; CI=1.041-3,551), (Table 3).

DISCUSSION

Lymphedema is an adverse and chronic condition that affects a considerable number of survivals of breast cancer, being estimated in a meta-analysis that more than one in five women who survive breast cancer will develop this complication[14]. In the population studied, the incidence of lymphedema was 33.24% similar to the study of Myungsoo el al.[15] where in that study, it was observed in 34.5% of a sample with 1,073 women in treatment for breast cancer. The literature presents great variations in the incidence of this condition, of 5% until close to 60%, this being explained by the difference among the treatments adopted, based in the disease staging and the caregiver and technique utilized to diagnose the lymphedema[16,17].

As Brazil is a country in development, which favors breast cancer-related complications as lymphedema, because the majority of the diagnosis are done at an advanced staging, needing more aggressive therapies. As seen in a study carried out in Brazil, 53.5% of the breast cancer cases diagnoses between 2000 and 2009 were classified as advanced staging (IIB)[18]. These data approach to what was found, because in the study, 46% of the women were classified in staging IIA; however, of those who developed lymphedema, 27% were diagnosed in more advanced staging (IIIB).

Table 3. Parameters obtained for the model created through the application of logistic regression to find the factors associated to women who died (N=699)

Source	Value	Standard Deviation	p-value	OR	OR(-95%)	OR(+95%)
Number of lymph nodes compromised						
0 to 10	0.000	0.000				
11 to 20	1.778	0.357	< 0.0001	5.919	2.939	11.919
21 to 30	0.935	0.674	0.165	2.547	0.680	9.539
> 30	2.352	1.212	0.052	10.508	0.977	113.024
Sentinel lymph node biopsy						
No	0.000	0.000				
Yes	1.0640	0.272	0.001	0.345	0.203	0.588
Axillary lymphadenectomy						
No	0.000	0.000				
Yes	0.654	0.313	< 0.0001	1.922	1.041	3.551
Radiotherapy						
No	0.000	0.000				
Yes	0.023	0.184	0.901	1.023	0.714	1.466

Caption: OR = *odds ratio*

The biopsy of the sentinel lymph node is considered, today, a reference for axillary staging in initial stage by the *American College of Surgeons*[19], provoking until 75% less morbidity than lymphadenectomy[20]. In this study, it was noticed that lymphadenectomy occurred more frequently when compared to biopsy of the sentinel lymph node, and can be explained by the presence of advanced staging of the disease and by the time of observation. This situation reflected over the incidence of lymphedema, where 94% of the women who developed this comorbidity were previously submitted to the more aggressive procedure, lymphadenectomy.

The association between radiotherapy and lymphedema is frequently studied. In this study, neoadjuvant radiotherapy was significant in the group lymphedema ($p<0.0001$) and other studies showed that radiotherapy can increase the risk of lymphedema in 2.19 until 4,285 times[10,21].

In relation to the *status* of survival of the women, it was observed that those with lymphedema presented significantly more frequency of cancer-related deaths when compared to the women without lymphedema. These data converge towards the results of other studies that, evaluating the survival of women with breast cancer and its prognostic factors, encountered bigger death rates for unrelated causes to neoplasms than for unrelated causes to the disease [22,23].

Lymphedema may be considered an important factor of prognosis and is related to the increase, of two to three-fold the risk of death in the first six years after the diagnosis of breast cancer[24]. Data corroborate what was observed, where death risk for women with lymphedema is approximately two times higher (52.8%) in relation to the risk of death for women without lymphedema (26.3%).

However, in a retrospective study, that evaluated 622 patients with breast cancer and compared the variables among women with and without lymphedema, it was encountered mean time of survival longer in women with lymphedema.(95.7 × 76.1 months, $p=0.002$). The authors justified this finding with the fact that the patients with lymphedema represent a group of survivals and, therefore, could have been a selection bias[25].

In relation to Brazil, the studies that analyze the overall survival of the persons that were diagnosed with cancer, especially breast cancer, presented a variation of the rates of survival between 75% and 87.7%[22,26].

The mortality of breast cancer relates to the staging at which the disease is diagnosed; which means that the delay of the diagnosis allows the progression of the disease that evolves and affects more intensely the lymph nodes, which justifies the presence of both as a facilitating factor of deaths [27].

Another essential issue are the treatments offered to these women, that can cause the increase or diminishing of the death risk with its complementation. It was shown in the present study that the adjuvant radiotherapy was associated to a worst survival of women with breast cancer, data that corroborated what was observed during the study[23], which also encountered significantly unfavorable survival in women who submitted to radiotherapy.

It is worth mentioning that lymphedema is a chronic disease of difficult management, control and where morbidity is highly prevalent in the treatment of breast cancer, resting behind only of fatigue and pain[28,29]. When comparing the survival of this study with the data estimated of others cited, it is necessary to be judicious with the differences encountered, considering the population studied, the eligibility criteria and the methods adopted for analysis.

The strength of this study is the number of participants with symptoms of lymphedema in a populational sample and the capacity of studying innumerable variables. The limitations of this study comprehend the lack of data that favored milestones for the appearance and development of lymphedema as well as the classification of the levels of lymphedema. It should also be highlighted the possibility of bias of confounding of the association between lymphedema and death because the adjusted analysis was not done.

CONCLUSION

The presence of lymphedema is a chronic condition that directly influences the quality of life of these women. This study, when it identified the increase of survival under these conditions brings the reflection about preventive actions of this condition and improvement of the quality of the daily activities for this population specifically.

The findings indicate that the women with lymphedema die more of cancer than those without lymphedema. In relation to the predictive characteristics of death, it were identified: higher number of compromised lymph nodes (>30), biopsy of sentinel lymph node not done and advanced staging (IV).

The results of this study can help to improve the care provided to the women with breast cancer with strategies of prevention and early identification of lymphedema.

CONTRIBUTIONS

Laís Corsino Durant participated of the conception, planning of the research trial, analysis and interpretation of the data. Aniele Tomadon and Franciele Foschiera Camboin participated of the analysis and interpretation of

the data and critical review. Joselici da Silva participated of the analysis and interpretation of the data. Regiane Bezerra Campos participated of the critical review. Thais de Oliveira Gozzo participated of the conception, planning of the research trial, analysis and interpretation of the data and final approval of the final version for publication.

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DECLARATION OF CONFLICT OF INTERESTS

There are no conflict of interests to declare.

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