

Prevalence of lymphedema after breast cancer treatment in overweight patients

Prevalência de linfedema após tratamento de câncer de mama em pacientes com sobrepeso

La prevalencia de linfedema tras tratamiento de cáncer de mama en mujeres con sobrepeso

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ABSTRACT | Breast cancer is the neoplasia with the highest incidence in the population worldwide, and lymphedema is one of the most frequent complications in the treatment. Body mass index increase is one of the risk factors for lymphedema after breast cancer treatment. The objective of this study was to verify the incidence of lymphedema in mastectomized women with overweight and obesity. The risk of lymphedema in women with overweight and obesity was four times greater (Odds Ratio, OR = 3.887). The higher the body mass index, the higher was the probability of lymphedema, with increase in the relative risk of 40% for obesity II.

Keywords | Breast Neoplasias; Lymphedema; Obesity.

RESUMO | O câncer de mama é a neoplasia de maior ocorrência no mundo, e o linfedema é uma das complicações mais frequentes do tratamento. O aumento do índice de massa corporal é um dos fatores de risco para linfedema após o tratamento do câncer de mama. O objetivo deste estudo foi verificar a incidência de linfedema em mulheres mastectomizadas com sobrepeso e obesidade. Os resultados mostraram que o risco de

linfedema em mulheres com sobrepeso e obesidade foi quatro vezes maior (Odds Ratio, OR=3,887). Quanto maior o índice de massa corporal, maior a probabilidade de linfedema, com aumento do risco relativo de 40% para obesidade II.

Descritores | Neoplasias de Mama; Linfedema; Obesidade.

RESUMEN | El cáncer de mama es la neoplasia que más ocurre en el mundo, y el linfedema es una de las complicaciones más frecuentes de su tratamiento. El aumento del índice de masa corporal es uno de los factores de riesgo para el linfedema tras el tratamiento de cáncer de mama. El propósito de este estudio fue verificar la incidencia de linfedema en mujeres sometidas a mastectomía y que están con sobrepeso y obesidad. Los resultados mostraron que el riesgo de linfedema en mujeres con sobrepeso y obesidad ha sido cuatro veces mayor (Odds ratio, OR=3,887). Cuanto mayor es el índice de masa corporal, mayor es la probabilidad de linfedema, con aumento de riesgo de 40% para obesidad II.

Palabras clave | Neoplasias de la Mama; Linfedema; Obesidad.

The research was conducted at the Cancer Hospital of Pernambuco (HCP) in the ambulatory service of breast physiotherapy – Recife (PE), Brazil.

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INTRODUCTION

Breast cancer is the neoplasia of highest incidence among women in developed or developing countries, achieving high rates of morbidity and mortality¹⁻⁴. Estimates from the American Cancer Society (ACS) for 2016 were approximately 246,660 new cases of breast cancer in women, with 40,000 cases of death for this year⁵. According to the National Cancer Institute of Brazil (INCA), in 2016, 57,960 new cases of breast cancer were estimated in the country².

Among the post-operative complications of breast cancer, the most frequent is lymphedema, a chronic condition caused by accumulation of liquid rich in proteins in the interstitial space⁶⁻¹⁰. The lymphedema development can happen immediately after surgery in rare cases, or years after the treatment¹¹⁻¹⁴. The lymphedema incidence varies in different studies, being observed in approximately 20% of cases. The rates may vary from 6 to 65%¹⁵⁻¹⁸.

The emergence of lymphedema is multifactorial and is associated with the dissection of the axillary lymph nodes, caused by radiotherapy, obesity, surgery, recurrence of cancer in the axillary lymph nodes, infection and lymphangitis^{13,19-21}. The lymphedema degree is associated with the degree of obesity, because the additional deposition of subcutaneous fat contributes to increase the arm volume and the separation of the deep lymphatic channels²². Weight gain after diagnosis of breast cancer is related to radiotherapy, chemotherapy and endocrine therapy²³. Obesity is a risk factor of infection and delay of the cicatrization process, tumorous reincidence and comorbidities, among other post-operative complications such as seroma, hematoma and axillary web syndrome²⁴. In addition, body mass index (BMI) increase, mainly in severe obese (BMI \geq 40 Kg/m²), causes serious health problems, such as increase in the risk factor for cardiovascular, metabolic, neoplastic and orthopedic diseases²⁵⁻²⁷.

Therefore, lymphedema is one of the main complications from the breast cancer treatment, and is associated with adverse psychosocial and physical consequences, interfering on the patient's quality of life¹⁹. The objective of this study was to verify the lymphedema incidence in mastectomized women with overweight and obesity.

METHODOLOGY

A descriptive, observational, transversal study, in which In total, participated 100 women who had undergone mastectomy and were under physical therapy treatment. The study was conducted from July 2013 to August 2014is at the physical therapy ambulatory of the Cancer Hospital of Pernambuco.

Data collection

The data were collected at the physical therapy ambulatory of the Cancer Hospital of Pernambuco. On their appointment days, the volunteers were invited to participate in the research. The objectives and benefits of our study were made explicit. In case of agreement, they were asked to sign the informed consent form, in accordance with resolution 466/12 from the National Health Council. After the explanation of the procedure to be performed and the signed form, the volunteers were submitted to physiotherapeutic evaluation of the upper limb perimetry.

The anthropometric assessment consisted of calculating the body mass index (BMI). BMI values between 25 and 30 were considered overweight, and BMI $>$ 30 was considered obesity²⁷. An evaluation form was developed for the selection of patients. All participants had BMI classified as overweight or obesity. Among them, 53% were married, 30% single, 9% divorced and 8% widow. The average age was 52.5 years (SD=7.9).

The lymphedema assessment was performed by perimetry of morbidity rates of the upper limbs. The measurements of the circumference (in centimeters) were taken in eight points. The point of reference was the crook of the arm, to mark the measurements. The latter were taken every 7 cm, in three points below the crook of the arm, with the limb supported, relaxed and in the position of supination and every 7 cm, in three points above the crook of the arm, in addition to the circumference of the wrist and the hand. The measuring tape was placed over the marks mentioned²⁸. Lymphedema was diagnosed when the circumference of one or more measurements in the affected side was 2.0 cm bigger than the circumference of the same point in the contralateral limb, according to the protocol established by the HCP of Pernambuco.

Instrumentation

Venosan brand tape was used for the perimetry evaluation. To measure body mass and height, a digital scale (Welmy) was used, reference W2005 (capacity of 200 kg) and Welmy stadiometer (200cm) (maximum height of 200cm), placed on a flat surface with good lighting. On the scale, the women were positioned erect and with heels together for the calibration of height and weight. Body mass index (BMI) was calculated by dividing the subject's mass by the square of their height. The mass was recorded in kilograms and the height in meters.

Statistical Analysis

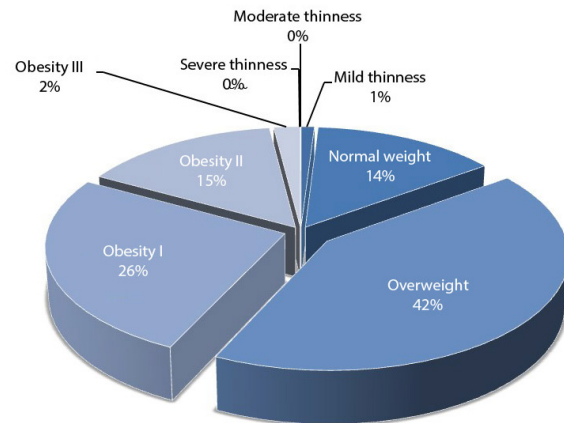
For the statistical analysis, we carried out a simple logistic regression, with the purpose of evaluating the prevalence of lymphedema as a dependent variable, in relation to the predictive factors "overweight" and "obesity" as independent variables. Separately, the predictive factors "overweight" and "obesity level I, II and III" were tested, with the aim to know the individual influence of each factor regarding lymphedema, through the Chi-square test.

To indicate the chance of a person – who is overweight or obese – having lymphedema, the prevalence ratio, the Odds Ratio (OR), the relative risk increase (RRI) and the number needed to cause the condition (NNC) were calculated. We used Microsoft Excel, SPSS18 and EpiInfo.

RESULTS

The population under study was classified according to the parameters stipulated in the body mass index (BMI) indicated by the World Health Organization. Severe thinness (BMI < 16 kg/m²): no elements present in the sample; moderate thinness (BMI between 16 and 17 Kg/m²): no elements in the sample; light thinness (BMI between 17 e 18.5 Kg/m²): one participant (1%); normal weight (BMI between 18.5 e 25 kg/m²): 14 participants (14%), overweight (BMI between 25 and 30 Kg/m²): 42 participants (42%); obesity I (BMI between 30 and 35 Kg/m²): 26 participants (26%); obesity II (BMI between 35 and 40 Kg/m²): 15 participants (15%), and obesity III (BMI ≥ 40 Kg/m²): 2 participants (2%), as shown in Chart 1.

BMI Classifications Percentage Distribution



Graph 1. Distribution of patients according to the classification of body mass index (BMI)

According to the logistic regression analysis, the chance of lymphedema emergence in women with predictive factors (overweight and obesity) was approximately 4 times (OR=3.887; $p < 0.05$), considering women that were submitted to the same surgical treatment, but did not present overweight or obesity. The probability for the development of lymphedema was 37.4% for women with a history of overweight and obesity, and 13.3% for those who did not have these risk factors.

The Chi-square test found no significant difference ($p = 0.308$) in the prevalence of lymphedema in overweight individuals, and 11 of them presented lymphedema (11/42). However, the overweight patient is twice more likely to develop lymphedema (OR=2.31), with 12.9% of relative risk increase.

Among the 26 cases of obesity degree I, 12 showed lymphedema (12/26) with a probability six times higher to develop the condition, compared with individuals without the predictive factor (OR=5.57), as shown in Table 1. For every four obese patients, one individual will present lymphedema (NNC=4), with RRI of 32.8% (Table 1).

Table 1. Comparison of lymphedema occurrences among predictive factors - Chi-square tests; relative risk increase (RRI) and the number needed to cause the condition (lymphedema) (NNH)

Study	Chi-square p-Value	Odds Ratio	RI	NNC
With overweight Without overweight	0.308	2.310	12.86%	8
With obesity I Without obesity I	0.033	5.570	32.82%	4
With obesity II Without obesity II	0.020	7.420	40.00%	3
With obesity III Without obesity III	0.201	6.500	36.67%	3

Concerning women that presented obesity II (15), this variable had the highest prevalence ratio (PR=4), as shown in Table 2. There was statistical significance (p=0.020) and OR=7.42, that is, a chance seven times higher for the emergence of lymphedema compared with a patient who is not obese (Table 2).

Table 2. Values for the occurrence of lymphedema in relation to predictive factors and the prevalence ratio

Classification/ Predictive factors	n	Presence of Lymphedema		Prevalence Ratio
		Yes (positive cases)	No (negative cases)	
Severe thinness	0	0	0	0
Moderate thinness	0	0	0	0
Light thinness	1	0	1	0
Normal weight	14	2	12	0
Overweight	42	11	31	1.964
Obesity I	26	12	14	3.462
Obesity II	15	8	7	4.000
Obesity III	2	1	1	3.750
TOTAL	100	34	66	

Two cases were observed for obesity III, of which one presented lymphedema, with prevalence ratio of 3.75. The Chi-square did not reach statistical significance. The OR indicated six times more chances of developing lymphedema.

DISCUSSION

A previous study¹⁹ reported that out of the 455 women evaluated, 124 presented lymphedema. Among these, 114 had BMI>25 Kg/m², that is, 91.9% of the overweight or obese women presented lymphedema¹⁹. People who have a higher BMI need more blood in circulation and higher efficiency of the lymphatic system to keep its flux. Possibly there is an imbalance of the transportation and absorption capacity of the lymph, which increases the risk of lymphedema^{29,30}.

The overweight patient is twice more likely to develop lymphedema (OR=2.31). Another study also found that the increase in the arm volume was related to BMI. It was observed that women with higher BMI tended to have a change in the upper limbs volume¹³. However, there was no stratification of overweight and obesity cases. Although the relative risk increase (RRI) has been low in this study, there is a risk to develop

the condition (lymphedema): for eight patients with overweight/obesity, one will present lymphedema (NNC=8).

For the cases that presented obesity level I, the risk of developing lymphedema was about six times higher. In other studies, 79% of patients (359 women) presented BMI≥25 and 32% (145 women) had lymphedema, with OR=3.94¹⁹. Another study reported that 92% of the patients with lymphedema had obesity, however the authors did not specify the obesity degree³¹. Women with BMI≥30 were 3.6 times more likely to develop lymphedema in six months³².

The reduction of body weight interferes on the arm volume reduction. The study of Shaw et al.²⁷ showed a reduction from 24%±12% to 15%±10%. According to Kwan et al.¹⁶, obese women present OR= 2.34; however, in their study the relationship with the obesity degree was not investigated. Proportionally, in our study, the increased relative risk was 40%, the NNC was only 3 individuals with overweight/obesity for the emergence of a new case of lymphedema.

For the cases of obesity level III, the reduced size of the sample impaired the estimation. Ahmed et al.⁶ observed that most women evaluated had BMI>30 Kg/m² and lymphedema. They associated this fact not only to obesity, but found that, at the time of the diagnosis, these women had larger tumors and dissection need of a bigger amount of lymph nodes. However, Demark-Wahnefried et al.¹⁰ found that BMI≥30 was not associated with increased risk of lymphedema in the assessment 30 months after surgery.

CONCLUSION

The analysis of significance indexes, probability and epidemiological indexes of the sample and the predictive factors (overweight and obesity) showed strong interaction between overweight and obesity and the presence of lymphedema.

REFERENCES

1. Dieli-Conwright CM, Mortimer JE, Schroeder ET, Courneya K, Demark-Wahnefried W, Buchanan TA, et al. Randomized controlled trial to evaluate the effects of combined progressive exercise on metabolic syndrome in breast cancer survivors: rationale, design, and methods. BMC Cancer. 2014;14(238):1-12.

2. Instituto Nacional de Câncer. Estimativa 2016: incidência de câncer no Brasil. Rio de Janeiro: INCA; 2016.
3. Kulie T, Slattengren A, Redmer J, Counts H, Eglasb A, Schrager S. Obesity and women's health: an evidence - based review. *J Am Board Fam Med.* 2011;24(1):75-85.
4. DeSantis C, Siegel R, Bandi P, Jemal A. Breast cancer statistics. *CA Cancer J Clin.* 2011;61(6):409-18.
5. American Cancer Society. Breast cancer facts and figures 2016. Atlanta: ACS; 2016.
6. Ahmed RL, Thomas W, Yee D, Schmitz KH. Randomized controlled trial of weight training and lymphedema in breast cancer survivors. *J Clin Oncol.* 2006;24(18):2765-72.
7. World Health Organization. BMI classification [acesso em 4 jul. 2013]. Disponível em: <http://bit.ly/KuJLJK>
8. Buchholz TA, Avritscher R, Yu TK. Identifying the "sentinel lymph nodes" for arm drainage as a strategy for minimizing the lymphedema risk after breast cancer therapy. *Breast Cancer Res Treat.* 2009;116(3):539-41.
9. Camargo MC, Marx AG. Reabilitação física no câncer de mama. São Paulo: ROCA; 2000.
10. Demark-Wahnefried W, Campbell LK, Hayes SC. Weight management and its role in breast cancer rehabilitation. *Cancer.* 2012;118(80):1-26.
11. Garther R, Jensen MB, Kronborg L, Ewertz M, Kehlet H, Kroman N. Self-reported arm-lymphedema and functional impairment after breast cancer treatment: a nationwide study of prevalence and association factors. *Breast J.* 2010;19(6):506-15.
12. Helyer LK, Varnic M, Le LW, McCready D. Obesity is a risk factor for developing postoperative lymphedema in breast cancer patients. *Breast J.* 2012;16(1):48-54.
13. Banin Hirata BK, Oda JMM, Losi Guembarovski R, Ariza CB, de Oliveira CEC, Watanabe MAE. Molecular markers for breast cancer: prediction on tumor behavior. *Dis Markers.* 2014; 2014(513158):1-12.
14. Lee HD, Ahn SG, Lee AS, Lee HM, Jeong J. Prospective evaluation of the feasibility of sentinel lymph node biopsy in breast cancer patients with negative axillary conversion after neoadjuvant chemotherapy. *Cancer Res Treat.* 2015;47(1):26-33.
15. Honnor A. Classification, aetiology and nursing management of lymphoedema. *Br J Nurs.* 2008;17(9):576-86.
16. Kwan ML, Darbinian J, Schmitz KH, Citron R, Partee P, Kutner SE, Kushi LH. Risk factors for lymphedema in a prospective breast cancer survivorship study: the pathways study. *Arch Surg.* 2010;145(11):1055-63.
17. Mahamaneerat WK, Chi-Ren S, Stewart BR, Armer JM. Breast cancer treatment, BMI, post-op swelling/lymphodema. *J Lymphoedema.* 2008;3(2):38-44.
18. Martín, ML, Hernández MA, Avendaño C, Rodríguez F, Martínez H. Manual lymphatic drainage therapy in patients with breast cancer related lymphedema. *BMC Cancer.* 2011;11(94):1471-76.
19. Meeske KA, Sullivan-Halley J, Smith AW, McTiernan A, Baemgartner 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(2):383-91.
20. Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM, et al. Randomized multicenter trial sentinel lymph node biopsy versus standard axillary treatment in operable breast cancer: the almanac trial. *J Natl Cancer Inst.* 2006;98(9):599-609.
21. Pereira AC, Freitas-Júnior R, Martins KA, Pereira AC, Pereira CE, Martins E. Alterações venosas e linfáticas em mulheres com linfedema após linfadenectomia axilar no tratamento do câncer de mama. *Rev Bras Ginecol Obstet.* 2013;35(4):171-7.
22. Pérez-Hernández AI, Catalán V, Gómez-Ambrosi J, Rodríguez A, Frunbeck G. et al. Mechanisms linking excess adiposity and carcinogenesis promotion. *Front Endocrinol.* 2014;5(65):1-17.
23. Petrek JÁ, Heelan MC. Incidence of breast carcinoma-related lymphedema. *Cancer.* 1998;83(15):2776-81.
24. Paskett ED, Dean JÁ, Oliveri JM, Harrosp P. Cancer-related lymphedema risk factors, diagnosis, treatment, and impact: a review. *J Clin Oncol.* 2012;30(30):3726-33.
25. Rezende LF, Pedras FV, Ramos CD, Gurgel, MSC. Avaliação das compensações linfáticas no pós-operatório de câncer de mama com dissecação axilar através da linfocintilografia. *J Vasc Bras.* 2008;7(4):370-5.
26. Ridner SH, Diefrich MS, Stewart BR, Armer JM. Body mass index and breast cancer treatment-related lymphedema. *Support Care Cancer.* 2011;19(6):853-7.
27. Shaw C, Mortimer P, Judd PA. A randomized controlled trial of weight reduction as a treatment for breast cancer-related lymphedema. *Cancer.* 2007;110(8):1868-74.
28. Thomson CA, Thompson PA, Wright-Bea J, Nardi E, Frey GR, Stopeck A. Metabolic syndrome and elevated C-reactive protein in breast cancer survivors on adjuvant hormone therapy. *J Womens Health (Larcmt).* 2009;18(12):2041-7.
29. Ahmed RL, Schmitz KH, Prizment AE, Folsom AR. Risk factors for lymphedema in breast cancer survivors, the low a women's health study. *Breast Cancer Res Treat.* 2011;130(3):981-91.
30. Shih YC, Xu Y, Cormier JN, Giordano S, Ridner SH, Buchholz TA, et al. Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: a 2-year follow-up study. *J Clin Oncol.* 2009;27(12):2001-14.
31. Ugur S, Arıcı C, Yaprak M, Mesci A, Arıcı GA, Dolay K, et al. Risk Factors of breast cancer-related lymphedema. *Lymphat Res Biol.* 2013;11(2):72-5.
32. Zhu YQ, Xiu YH, Liu FH, Guo Q, Shen PP, Tian Y. Systemic analysis on risk factors breast cancer related lymphedema. *Asian Pac J Cancer Prev.* 2014;15(6):6535-41.