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SHORT COMMUNICATION

Body mass index and breast cancer treatment-related lymphedema

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Abstract
Purpose The main purpose was to examine longitudinally the influence of body mass index (BMI) and obesity on the development of breast cancer treatment-related lymphedema. We asked, does elevated BMI increase lymphedema risk?
Methods A secondary analysis was conducted on de-identified data collected from 138 newly diagnosed breast cancer survivors who had arm-volume measurements and symptom assessment at pre-treatment baseline and measurements up to 30 months post-surgery in a prospective longitudinal parent study. Arm volume and weight data, part of the information collected during each participant visit, were examined.
Results Breast cancer survivors whose BMI was ≥30 at the time of breast cancer treatment were approximately 3.6 times more likely to develop lymphedema at 6 months or greater after diagnosis than those with a BMI<30 at the time of cancer treatment (95% confidence interval, C.I., for odds ratio, O.R., 1.42–9.04; $p = 0.007$). Those with a general BMI increase or a BMI rise to 30 or greater during their first 30 months of survivorship were not more likely to develop late-onset lymphedema than those who did not have similar changes in BMI.
Conclusions Pre-treatment BMI may be a risk factor for lymphedema. Weight gain post-treatment may not be. Further research is warranted.

Keywords Body mass index · Breast cancer · Lymphedema

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Introduction

Despite the increasing use of axillary-sparing sentinel node biopsies (SLNB), many breast cancer survivors experience permanent disruption of their lymphatic system and are at life-long risk for developing chronic arm lymphedema [1–5]. Lymphedema onset is a distressing, life-altering event [6, 7]. Those with lymphedema face a lifetime of burdensome self-care and risk for infection in the swollen arm. Although estimates vary greatly, even if conservatively 20% of breast cancer survivors develop lymphedema, many are at risk [8, 9]. Currently, there is no cure for lymphedema. Therefore, until a cure for lymphedema arises, identification of factors that place a breast cancer survivor at higher risk for developing lymphedema is paramount.

Studies suggest that an elevated body mass index (BMI) may be associated with breast cancer treatment-related lymphedema [10–14]. There are well-documented relationships between obesity and other health problems (e.g., heart disease, diabetes, asthma, arthritis) [15–18]. Possible explanations for the influence of obesity on health include: (1) the stress placed upon the body, particularly the circulatory systems, by the actual physical increase in fat

body mass; and (2) the increase of endocrine-like functions (increased secretory peptides, etc.) of fat cells as they enlarge [17, 19, 20]. Each mechanism may contribute to the development of treatment-related lymphedema in breast cancer survivors. Specifically, larger physical size places a greater demand on both the blood circulatory and lymphatic systems to move fluid. In breast cancer survivors with treatment-related lymphatic damage, it is possible that the additional demand created by a larger body size may cause an imbalance in lymphatic fluid volume and transport capacity. Increased secretory peptides may contribute to tissue inflammation and trigger lymphedema in at-risk arms as well.

Although, obesity and/or elevated BMI has been associated with lymphedema in breast cancer survivors in some studies, a causal relationship has yet to be established. As a result, the purpose of this secondary analysis was to examine longitudinally the influence of BMI in the development of breast cancer treatment-related lymphedema. The hypotheses were: (1) breast cancer survivors whose BMI is ≥30 at the time of breast cancer treatment are more likely to develop lymphedema than breast cancer survivors whose BMI is <30 at the time of treatment; (2) breast cancer survivors who experience an increase in BMI during their first 30 months of survivorship are more likely to develop lymphedema than breast cancer survivors who do not experience an increase in BMI during their first 30 months of survivorship; and (3) breast cancer survivors whose BMI rises to ≥30 after breast cancer experience lymphedema more frequently than those whose BMI remains <30.

Materials and methods

Design

This is a secondary analysis conducted on de-identified data collected from 138 newly diagnosed breast cancer survivors in a prospective longitudinal parent study. An Institutional Review Board approved parent study examined arm volume and symptoms up to 30 months post-diagnosis (pre-operative baseline, post-operative months 1, 3, 6, 9, 12, 18, 24, and 30). Same day weights and symptom data were obtained.

Sample and settings

Participants were 138 women undergoing breast cancer treatment at a midwestern cancer center, or nearby community cancer treatment centers, and who were followed over a 30 month period. They were over age 18, experiencing their first occurrence of breast cancer (stages I–IV), and able to give informed consent.

Instruments

Arm volume A Perometer 350S, manufactured by Pero-System GmbH, was used to determine arm volume [21]. The volume of each arm was measured three times during each visit, and the mean volume in milliliters served as the final data point.

Weight Participants were weighed on a balance scale in the lab or a digital scale in the clinic.

Symptoms The Lymphedema Breast Cancer Questionnaire was used to collect self-report symptom information [22]. Swelling and heaviness were the two symptoms of interest for this study.

Analyses

Lymphedema was defined as either a 200 ml or 10% increase in arm volume occurring on the side where breast cancer treatment (surgery and/or radiation) had occurred in the absence of a similar change in the contralateral side, as measured by the Perometer. To account for possible acute post-operative swelling or transient lymphedema, this change had to be documented 6 months or more after treatment. Descriptive statistics were used to summarize the sample characteristics and study variables at baseline and during the course of the data collection period. Associations (in the form of O.R.s) of BMI, as well as symptom reports of swelling and/or heaviness, with the primary outcome variable of whether or not a criterion for lymphedema was met, were summarized and tested using logistic regression. Associations of disease and treatment characteristics such as nodal involvement and type of surgery were also assessed and adjusted for in the logistic regression analyses. Receiver operator curve (ROC) analyses were used to assess the possible usefulness or accuracy of self-reports of arm swelling and heaviness for detecting a symptom that may be consistent with lymphedema.

Results

Sample The sample (N=138) consisted primarily of Caucasian women (96%), whose mean age was 58.9 years (SD=12.3, min=20, max=89) (see Table 1). The sample was almost equally divided between sentinel node (SLND) and axillary dissections (ALND).

Lymphedema Using either the 200 ml or 10% difference criteria, 19.6% (n=27) of the sample met the criteria for lymphedema at some point in the study 6 months or more after treatment. Of those 27, 19 (70%) had undergone

Table 1 Demographic and treatment history (n=138)

Age (years)	
Median	58
25th–75th inter-quartile range	50–67
Range (min, max)	20, 89
Characteristic:	*n* (%)
Ethnic group	
Caucasian	133 (96.4)
African–American	3 (2.2)
Hispanic	1 (0.7)
Native American	1 (0.7)
Level of education	
≤12 years	69 (50.0)
>12 years	67 (48.6)
Unknown	2 (1.4)
Type of lymph node dissection	
Sentinel node	66 (47.8)
Axillary node	64 (46.4)
None/unknown	8 (5.8)
Type of surgery	
Non-breast conserving	63 (45.7)
Breast conserving	71 (51.4)
None/unknown	4 (2.9)
Radiation	
No	62 (44.9)
Yes	74 (53.6)
Unknown	2 (1.4)

axillary lymph node dissection (ALND), while eight (30%) had SNLD. The minimum time since baseline assessment, for which lymphedema criteria were met, averaged 14.9 months (median, 12.0; min=7; max=35) for this group. Three of the 27 who met our criteria for lymphedema also met those criteria during the first six months after treatment and met the criteria on the first measurement point used in our analyses. An additional two participants had swelling sufficient to meet our criteria prior to six months after treatment; however, they had reduced differential swelling to the point that the criteria were not met six or more months after treatment. They were therefore not included in the group with chronic lymphedema in our analyses. Sixty-eight percent of the 138 participants had measurements up to 30 months post-surgery.

BMI at baseline The average BMI prior to breast cancer treatment was 30.4 (median=28.8, min=17.5, max=48.1). Based on the Centers for Disease Control and Prevention (2010) weight classifications of BMI (<18.5, underweight; 18.5 to 24.9, healthy weight; 25 to 29.9, overweight; and ≥30, obese), most participants in this study were obese prior to treatment. A total of 10 (12.7%) of 79 participants with a BMI <30 prior to treatment subsequently met the criteria for lymphedema (BMI<25, n=3 of 33, 9.1%; BMI 25–29.9, n=7 of 46,15.2%, p=0.419). Of 59 participants (42.8%) who had a BMI greater than or equal to 30, 17 (28.8%) subsequently met the criteria for lymphedema (p=0.007; O.R.=3.59; 95% C.I.; O.R., 1.42–9.04).

BMI and lymphedema The association of BMI per se with lymphedema (as opposed to an increase in BMI post-treatment) was tested in two different ways. First, of the 79 participants with BMI less than 30 prior to treatment, the BMIs of 14 (17.7%) subsequently increased to ≥30. Three of those 14 (21.4%) subsequently met the criteria for lymphedema; of the remaining 65 who did not increase their BMI≥ 30, five (7.7%) subsequently met the lymphedema criteria (p= 0.139; O.R.=3.27; 95% C.I., 0.68–15.72). Secondly, each participant's intercept (BMI prior to treatment) and slope of the change in their respective BMIs were included in a logistic model. After controlling for the baseline BMI value (p=0.001), no further statistically significant information was garnered by including either the linear (p=0.336) and/or the quadratic (p=0.632) values for the change in BMI. Of the key disease and treatment characteristics available for this sample, only type of nodal dissection, ALND versus SLND, demonstrated a statistically significant association with the development of lymphedema (ALND was higher than SLND, p=0.013). Nevertheless, after adjusting for that association, the association of the baseline BMI value with subsequent meeting of the criteria for lymphedema remained strong and statistically significant (p=0.004; O.R.=4.12; 95% C.I., 1.58–10.72). Thus, pre-treatment BMI was an independent predictor of lymphedema.

Self-reported symptoms Of the participants who met the criteria for lymphedema and had self-reported data (n=25), 20 (80.0%) reported an observation of swelling 1 year prior to, or simultaneously with, the time that the criteria for lymphedema via arm-volume assessments were met, while five (20.0%) of those participants had not reported such an observation. Participants not meeting the criteria for lymphedema did not report observed swelling (area under curve (AUC)=0.900; 95% C.I.=0.806–0.994, p<0.001). Participants who did not meet the lymphedema criteria did not report heaviness. Approximately half of those meeting the criteria for lymphedema (14 of 25, 56.0%) reported heaviness prior to or simultaneously with the time that arm volume criteria for lymphedema were met (AUC=0.780, 95% C.I.=0.655–0.905, p<0.001)

Discussion

This secondary analysis specifically targeted lymphedema only if the onset or occurrence was at or after the six-month

assessment and only if the selected 200-ml or 10% increase in volume criteria was met, without a corresponding change in the contralateral arm. Our analyses did not specifically include early-emerging lymphedema within 6 months following surgery because of concerns about falsely labeling acute swelling as lymphedema. We did note that three of the participants with lymphedema at 6 months developed swelling prior to our initial measurement. We also identified two additional participants who met the criteria prior to 6 months after surgery; however, differential swelling was not detected at 6 months after surgery. These two individuals may have had acute swelling that resolved or on-going swelling that would only be accounted for when using a more liberal definition for lymphedema (e.g., 5% change or lymphedema which resolved with treatment) [23].

It is notable that the majority of study participants met the CDC guidelines for overweight or obese at baseline, a finding which matches the characteristics of breast cancer survivors overall. Few participants were underweight, and a relatively modest number were of healthy weight. Thus, this study does not examine the low- and normal- weight women's risk of developing lymphedema in comparison to overweight and obese women.

Findings from this study support hypothesis 1, as breast cancer survivors whose BMI≥30.0 at the time of the breast cancer surgery were found to be approximately 3.6 times more likely to develop lymphedema at 6 months or greater after diagnosis than breast cancer survivors whose BMI was ≤30 at the time of cancer surgery. Hypotheses 2 and 3 were not supported.

These findings, in conjunction with the findings that, after controlling for baseline BMI, a change in BMI did not have a statistically significant effect, suggest that elevated pre-surgery BMI (≥30) has a greater influence on lymphedema development subsequent to surgery than increasing BMI post-surgery, a finding that differs from one previous study that found increased weight post-surgery was associated with lymphedema [24]. This difference may be attributable to the differences in women sampled and measurement methods, as the previous study included only survivors 20 years post-ALND who self-measured their arms with a tape.

Patient self-reported symptoms of swelling and heaviness were predominant in those with objective lymphedema, although five patients meeting the criteria for lymphedema did not self-report swelling. These findings corroborate the finding that post-operative perceived heaviness and swelling are associated with the development of lymphedema [22] and suggest such self-reports are key sources of data.

Findings from this study should be considered in light of its limitations (follow-up≤30 months, few gained weight, small sample size, and stage of breast cancer at time of treatment is not considered). A more prolonged follow-up is needed to confirm these findings. Despite these limitations, important practice implications arise from these findings. Health care professionals may need to inform patients whose BMI is ≥30 at time of treatment that they are at higher risk for developing lymphedema than if their BMI was at a lower level. Baseline arm measurements prior to treatment and monitoring after treatment may be especially critical in those patients with a BMI of ≥30. Clinical assessments subsequent to treatment should not only include volume but also an assessment of associated signs (e.g. observable swelling) and symptoms (e.g., heaviness). It may also be helpful to inform those with a BMI of <30 at the time of treatment that, while they are at less risk than others, they still are at risk for lymphedema. On-going assessment is also indicated in these patients.

Conclusion

A BMI≥30 prior to treatment is a risk factor for lymphedema development. As it is not feasible for patients to be asked to lose weight pre-treatment, vigilant monitoring of these at-risk patients, via self-report symptom assessments and/or physical measurement of the limb, is warranted post-treatment.

It is unknown if reduction of BMI to <30 subsequent to treatment, or if early detection of even small changes in limb volume in these high-risk patients, coupled with compression [25], would provide any reduction in the risk identified. Future studies in these areas are indicated based upon our preliminary findings.

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Conflict of interest statement None.

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