

BREAST CANCER TREATMENT, BMI, POST-OP SWELLING/LYMPHOEDEMA

Wannapa Kay Mahamaneerat, Chi-Ren Shyu, Bob R Stewart, Jane M Armer

Abstract

Background: Diagnosis of post-breast cancer lymphoedema is difficult because of inconsistent measurement approaches, measurement reliability and validity, and lymphoedema definition and criterion. **Aims:** To examine lymphoedema occurrence using a body mass index (BMI)-adjusted limb volume change (LVC) as a potentially sensitive alternative criterion for assessment and diagnosis of lymphoedema. Secondary aims were to examine the risk of lymphoedema occurrence in relation to post-operative swelling and limb dominance and the cancer-affected side. **Methods:** The volume calculated from circumferences of 193 breast cancer survivors was used to analyse lymphoedema assessment. A change $\geq 5\%$ in affected-arm volume over percent change in BMI in comparison to pre-operative baseline was considered indicative of lymphoedema. **Results:** For all participants, 63% met the 5% BMI-adjusted LVC criterion. Dominant limb and cancer-affected side were significantly related to lymphoedema occurrence only in those whose BMI ≥ 30 ($p=0.02$), while post-operative swelling significantly increased the lymphoedema risk irrespective of BMI ($p=0.01$). **Conclusions:** The proposed 5% BMI-adjusted LVC criterion provides a more sensitive estimation of post-breast cancer lymphoedema occurrence. **Declaration of interest:** None.

Key words

Breast cancer
Arm dominance
Post-operative swelling
Diagnosis of lymphoedema
Body mass index (BMI)

Over 200,000 American women and over one million women around the world are newly affected by breast cancer each year (American Cancer Society, 2007; Office for National Statistics, 2007). The two million breast cancer survivors living in the US and ten

million worldwide are at lifetime risk of developing lymphoedema (Ferlay et al, 2004; American Cancer Society, 2006;), a chronic condition involving accumulation of protein-rich fluid that affects physical, functional and psychosocial health and well-being (Hull, 1998; Beaulac et al, 2002;

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The percentage of breast cancer survivors who develop lymphoedema is not precisely known, although it is conservatively estimated that as many as half of survivors may experience

lymphoedema during their lifetime (Armer and Stewart, 2005; Armer, 2008, in press). The discrepancy between the reported percentages of 3% to 62.5% (Passik and McDonald, 1998; Petrek and Heelan, 1998; Sener et al, 2001) in the literature stems from difficulties in measurement, diagnosis, and follow up of lymphoedema (Meek, 1998; Passik and McDonald, 1998; Petrek and Heelan, 1998; Rockson, 1998; Armer, 2005; Armer and Stewart, 2005). Common quantitative criteria for lymphoedema include: two or more centimetres difference in limb girth between the affected and non-affected limb; a 200ml limb volume difference; or a 10% limb volume change (LVC) (Petlund, 1991; Armer and Stewart, 2005).

The reported incidence fluctuates greatly among groups of individuals at risk of developing lymphoedema (Armer et al, 2004; Armer and Fu, 2005). Although a number of factors have been implicated as being associated with increased risk of lymphoedema, including axillary dissection, radiation therapy, post-

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operative infection, age, and weight gain (Meek, 1998; Petrek and Heelan, 1998; Coen et al, 2003; Deutsch and Flickinger, 2003; Geller et al, 2003; Voogd et al, 2003; Ozaslan and Kuru, 2004), the diagnostic criteria themselves require further refinement in order to clarify actual occurrence of lymphoedema (Armer and Stewart, 2005). One of the dilemmas of the current forementioned anthropometric criteria for lymphoedema is that they are not calibrated to account for selected individual changes that commonly occur over the course of breast cancer treatment, such as fluid retention and changes in body mass index (BMI) (Armer et al, 2008 in press).

In the same way that it has been identified that increased BMI is associated with a higher risk of breast cancer and poorer outcome (Feigelson et al, 2004), including breast cancer recurrence (Chlebowski et al, 2002), second primary cancers, and higher morbidity and mortality (Johansson et al, 2002; Whiteman, et al, 2005), studies have identified a correlation between both BMI and BMI change and the development of lymphoedema after breast cancer treatment (Petrek et al, 2001; Soran et al, 2006). Unfortunately, the 2cm, 200ml, and even 10% LVC criteria do not take into account the changes experienced in the body that result in weight gain during or following treatment. The aim of this study was to develop and refine a BMI-adjusted criterion for lymphoedema occurrence (Armer et al, 2008 in press) that would consider the commonly-experienced fluctuations in weight during and following breast cancer treatment. In addition, the secondary aims were to examine the risk of lymphoedema occurrence in relation to post-operative swelling, and limb dominance and the cancer-affected side.

Methods

In this National Institute of Health (NIH)-funded prospective repeated-measures study, a convenience sample of 202 women with breast cancer were recruited to participate in the 30-month study starting from a pre-

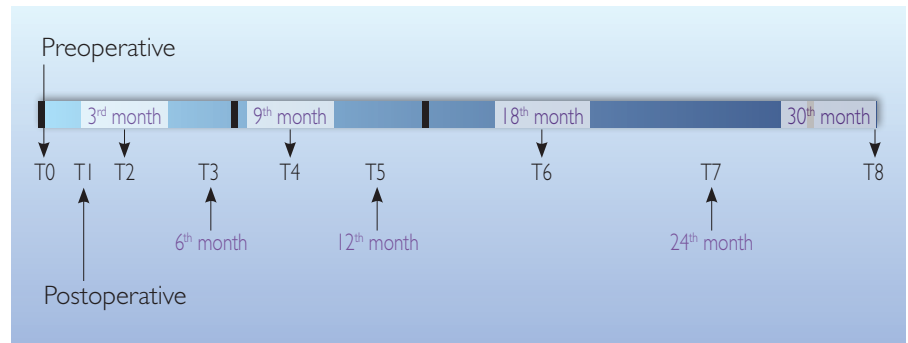


Figure 1. Timeline for data collection (pre-operative to 30 months following surgery).

operative visit (visit T0 after breast cancer diagnosis and before surgery). The selection criteria were first breast cancer diagnosis, enrolled prior to surgery, English-speaking, and capable of informed consent. Approval for research with human subjects was received through the University of Missouri Health Sciences Institutional Review Board (IRB) office prior to conducting the study. Participants were seen post-operatively every three months for 12 months, and then every six months for 18 months to a total of 30 months (Figure 1). Of all participants, 193 (95.5%) were unilateral breast cancer survivors. From this group, there were 105 (54.4%) participants whose cancer-affected side was their dominant limb (11 [10.5%] participants were left-handed, 94 [89.5%] participants were right-handed); whereas, there were 88 (45.6%) participants whose cancer-affected side was not their dominant limb. From the same group of 193 participants, there were 37 (19.2%) participants who experienced swelling to the extent of the proposed 5% BMI-adjusted LVC criterion at the post-operative visit (visit T1).

Arm circumferences were measured every 4cm using non-stretch tape measures (Callaway et al, 1988; Armer, 2005). Limb volume (LV) was calculated using a summation of cylinder volumes (v). A derived cylinder formula is as follows:

$$v = \frac{\pi(c_1^2 + c_2^2)}{2\pi}$$

Please note that a cylinder's base area was inferred from an average of two circular areas associated

with two consecutive circumference measurements (c_1 and c_2) starting from the wrist to the underarm. A cylinder's height is 4cm.

This research proposes a 5% BMI-adjusted LVC criterion; a participant meets this criterion when there is an LV increase of at least 5% greater than BMI change (with respect to the participant's pre-operative baseline BMI and LV in the cancer-affected side) during at least one visit after the post-operative visit. The BMI formula (Centers for Disease Control and Prevention, 2008) was defined as:

$$BMI = \frac{\text{weight (kg)}}{\text{height (m)}^2} \cong \left[\frac{\text{weight (lb)}}{\text{height (in)}^2} \right] \times 703$$

The 5% BMI-adjusted LVC criterion is a potentially more sensitive measure of lymphoedema occurrence because:

- ▶ Increased BMI is associated with higher risk of lymphoedema occurrence following breast cancer
- ▶ Current standards rarely consider simultaneous contralateral LVC
- ▶ Study participants' BMI ranged from 17.2 to 54.4 (average 30.5).

BMI categories used in this study follow the guideline of the Centers for Disease Control and Prevention (2008) (Table 1). The same table also shows the percentages of women in this study per BMI category, compared to women aged 18 years or older who answered the Behavioral Risk Factor Surveillance System (BRFSS) survey in year 2006 (Centers for Disease Control and Prevention, 2006). The BRFSS 2006 data showed that women in the state of Missouri (MO) had higher percentages for overweight and

obese categories than the national percentages. These statistics are consistent with the higher percentages of the same BMI categories among the participants in this study, although in this study, the percentage of the obese category (44%) is considerably higher than the obese category of MO (28.9%).

Analysis

Occurrence of lymphoedema was calculated from percent change in cancer-affected limb volume at each of eight post-operative time points (starting from one to four weeks to 30 months post-surgery) (T1 or T8), compared to pre-operative LV. Percent change in BMI during the same time periods were then calculated. A change of 5% or greater in affected-arm

volume over percent change in BMI with respect to the participant's pre-operative baseline BMI and LV in the cancer-affected side was considered to be indicative of lymphoedema. Two sets of statistical analyses were conducted between the cancer-affected dominant and non-dominant limbs, and those with and without post-operative (one to four weeks after surgery) swelling. Unpaired (two-sample or independent-sample) t-tests were used to determine statistical significance (Brink and Wood, 1998; Peat and Barton, 2005). Relative risk was calculated to estimate the magnitude of the difference.

Participants were grouped according to their BMI weight status (Centers for Disease Control and

Prevention, 2008), as shown in Table 1. To find whether there was an increased risk of developing lymphoedema on the dominant limb side that may be used more often, the first analysis compared risks of developing lymphoedema from three months to 30 months post-surgery (visits T2 to T8) between the group of participants whose cancer affected their dominant limb side and the group of participants whose cancer affected their non-dominant side.

To find whether there was an increased risk of developing lymphoedema that may be associated with the swelling caused by breast cancer surgery, the second analysis compared risks of developing lymphoedema during the same time period as the first analysis (visits T2 to T8) between the group of participants who met or exceeded the 5% BMI-adjusted LVC criterion at the post-operative visit (visit T1), and the group that did not meet this criterion at visit T1.

Results

All unilateral cancer-affected limb participants ($n=193$), 63% ($n=121$) met the 5% BMI-adjusted LVC criterion at some point following (excluding) the post-operative visit (mean time to criterion=nine months, standard deviation=seven months).

Cancer-affected dominant and non-dominant limbs

To answer the question of whether there was an increased risk of developing lymphoedema when a participant's cancer-affected limb was her dominant side, t-test and relative risk analyses were used to compare between two groups of participants: cancer-affected dominant limb group; and cancer-affected non-dominant limb group. Overall, the relative risk between these groups was 1.1, and there was not a significant difference (65.7% compared to 59.1%; $t=0.95$; $p=0.35$) (Table 2) (Figure 2).

Tests of statistical significance were also conducted for lymphoedema occurrence and non-occurrence in the three BMI categories—normal

Table 1

Adult women BMI weight status

BMI	Weight status	% of participants	BRFSS 2006	
			% of MO women*	% of US women*
Below 18.5	Underweight	1.6%	37.3%	40.3%
18.5–24.9	Normal	22.8%		
25.0–29.9	Overweight	31.6%	30.1%	28.7%
30.0 and above	Obese	44.0%	28.9%	24.0%

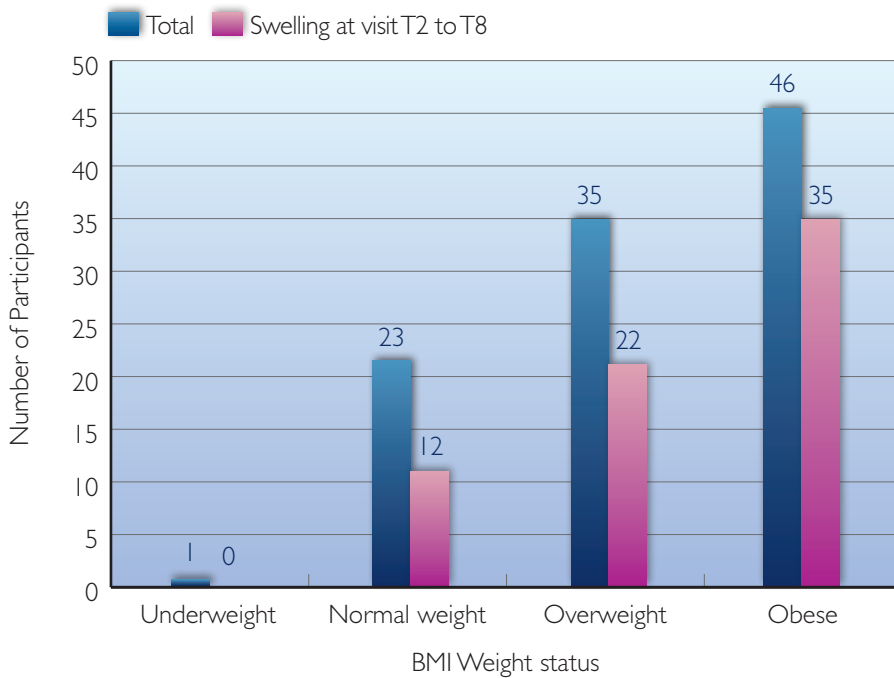
* 3.7% of MO women and 7% of US women did not respond

Table 2

Relative lymphoedema risk analysis between cancer-affected dominant and non-dominant sides

Dominance, cancer-affected side, and lymphoedema		BMI status				Total
		Under-weight	Normal weight	Over-weight	Obese	
Cancer-affected dominant limb	Total number of participants	1	23	35	46	105
	Swelling at visits T2 and T8	0 of 1 (0%)	12 of 23 (52.2%)	22 of 35 (62.9%)	35 of 46 (76.1%)	69 of 105 (65.7%)
Cancer-affected non-dominant limb	Total number of participants	2	21	26	39	88
	Swelling at visits T2 and T8	1 of 2 (50%)	13 of 21 (61.9%)	18 of 26 (69.2%)	20 of 39 (51.3%)	52 of 88 (59.1%)

(a) Cancer-affected dominant limb



(b) Cancer-affected non-dominant limb

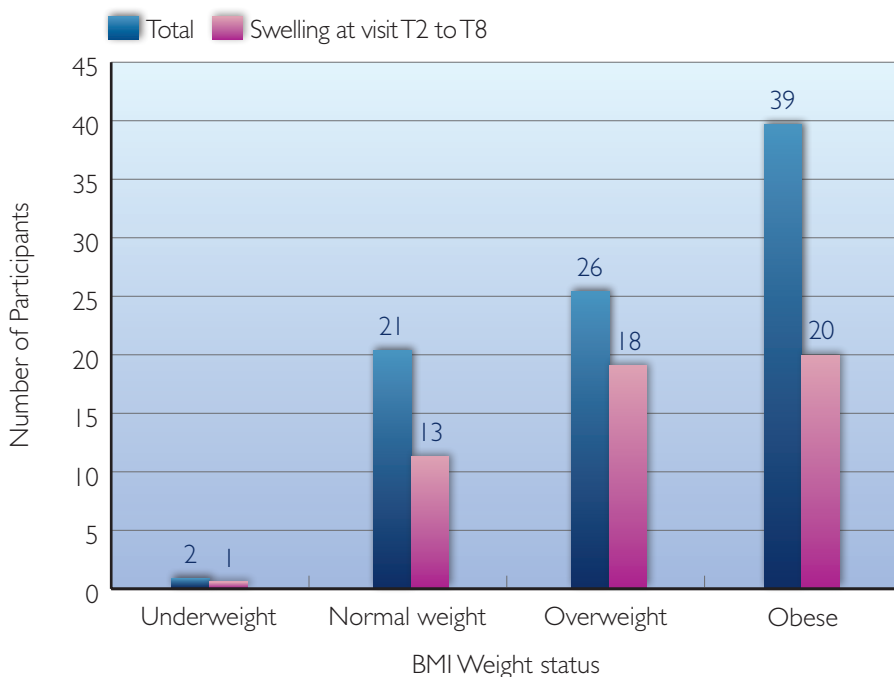


Figure 2. Number of participants whose (a) cancer affected their dominant limb or (b) cancer affected their non-dominant limb, categorised by body mass index status.

weight, overweight, and obese, with the reported relative risks of 0.84, 0.91, and 1.48, reported *t* values of 0.64, 0.51, and 2.44, and reported *p* values of 0.53, 0.61, and 0.02, respectively. Even though in the larger group analysis, limb dominance and cancer-

affected side were not significantly associated with the risk of developing lymphoedema, participants with BMI 30 and above had a significantly higher risk of developing lymphoedema if their cancer treatment was on the dominant side (relative risk [rr]=1.48, 48% higher

risk). Please note that the underweight group was not tested due to its small sample size.

With and without post-operative swelling

A relative risk analysis was calculated to compare the risk of developing lymphoedema at a later visit (visits T2 to T8) between the groups of participants with and without post-operative (visit T1) swelling. Overall, the relative risk between these two groups was 1.4, and there is a significant difference between the groups (81.1% compare to 58.3%; *t*=2.6; *p*=0.01) (Table 3) (Figure 3). Those with post-operative swelling had a 1.4 greater risk of developing lymphoedema at some later point compared to those without post-operative swelling.

Tests of statistical significance were also conducted for each of the three BMI categories — normal weight, overweight, and obese, with the reported relative risk values of 0.97, 1.4, and 1.6, reported *t* values of 0.08, 1.64, and 2.63, and reported *p* values of 0.93, 0.11, and 0.01 respectively. In addition to the larger group analysis in which post-operative swelling was significantly associated with the risk of developing lymphoedema, a sub-category analysis revealed participants with BMI above 25 had a higher relative risk of developing lymphoedema than the normal weight group (rr=1.4 and 1.6, 40% and 60% higher risk for overweight and obese, respectively). Please note that the underweight group was not tested due to its small sample size.

Further analyses showed the significance of having the pre-operative (before surgery) (T0) measurement, when the data from the three-month (following surgery) visit were substituted for the T0 pre-operative data. Without the pre-operative measurement, 49 participants who met the 5% BMI-adjusted LVC criterion at visit T2 would not have been recognised.

Discussion

For all participants, 63% met the

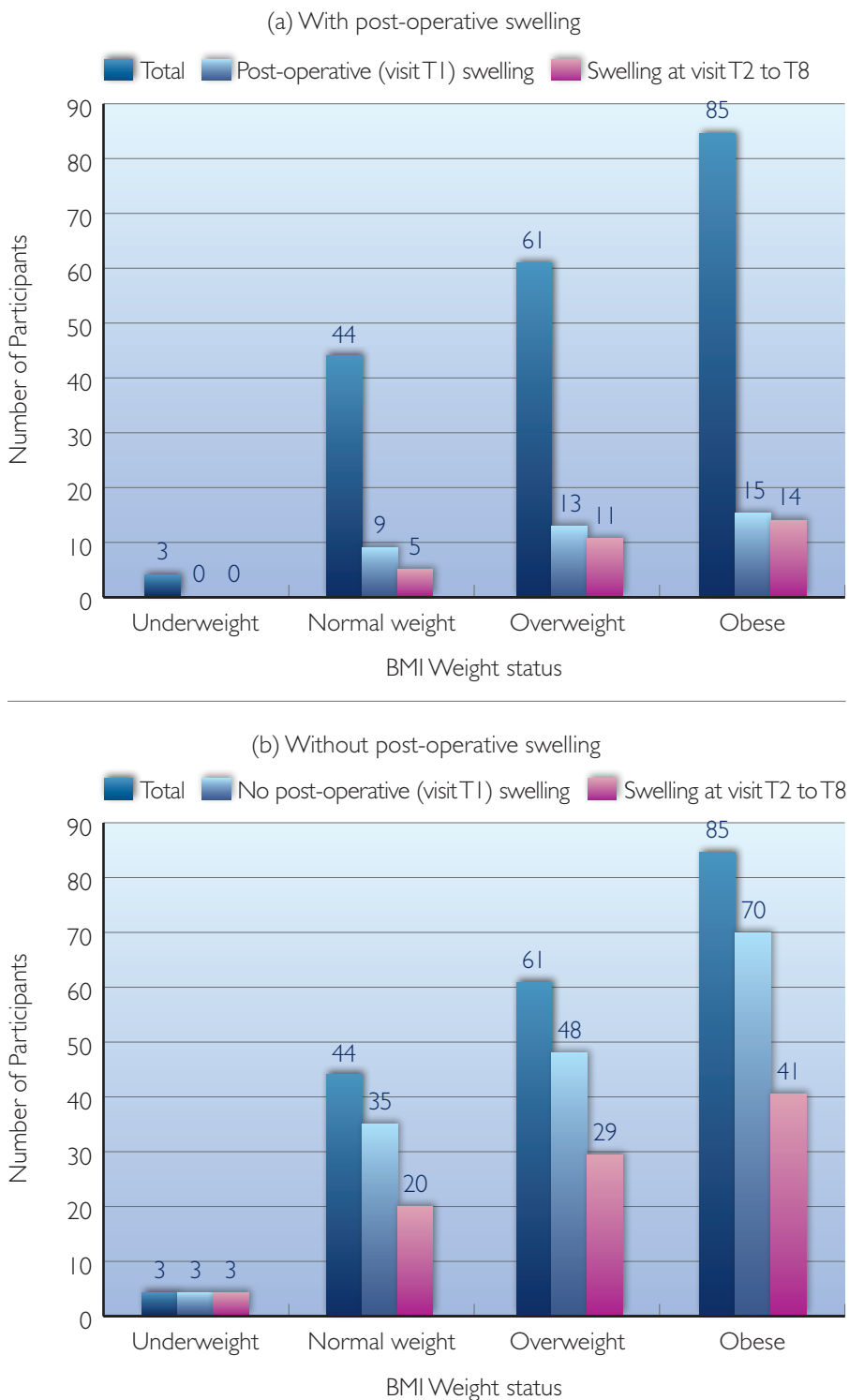


Figure 3. Categorised by their body mass index status, number of participants who: (a) experienced post-operative swelling; or (b) did not experience post-operative swelling.

5% BMI-adjusted LVC criterion at some point following (excluding) the post-operative visit. Limb dominance and cancer-affected side were not significantly associated with the development of post-surgery lymphoedema ($rr=1.1$) in the group as a whole. In the subgroup analysis,

those with BMI classified as obese showed a 48% greater lymphoedema risk in women whose cancer occurred on their dominant side. Further, post-operative swelling significantly increased the risk of later developing lymphoedema ($rr=1.4$) across the group as a whole. This means a

person who developed post-operative swelling was 40% more likely to develop lymphoedema at some later time (before 30 months) after surgery. In the subgroup analysis, this relative risk of developing lymphoedema was even higher in the overweight and obese BMI groups than for normal weight women (40% and 60% greater risk).

Also of importance, approximately 40% of those who met the 5% BMI-adjusted LVC criterion in this study would have been overlooked if the pre-operative measurements had not been available. Further, since post-operative swelling is associated with higher risk of developing lymphoedema, having the pre-operative baseline is an essential reference for detection of post-operative swelling. This finding supports the need for pre-operative assessment in the clinical setting.

A strength of the study is the 30-month follow-up with the pre-operative baseline measurements. This follow-up exceeds that of most studies (Deutsch and Flickinger, 2003; Rovere et al, 2003; Voogd et al, 2003; Armer and Stewart, 2005). However, more answers regarding long-term occurrence of lymphoedema will be discovered with seven-year follow-up with this cohort. In early findings from the 36–84 months follow-up, new cases of lymphoedema have been identified. The preliminary findings are consistent with the isolated studies which report late-occurring cases of lymphoedema (Petrek and Heeland, 1998; Petrek et al, 2001).

Conclusions

Using the 5% BMI-adjusted LVC approach to assessment of lymphoedema occurrence provides the opportunity for a more sensitive estimation of post-breast cancer lymphoedema occurrence. Also important is the capability to compare pre-operative LV measurements to post-operative volume. Based on this preliminary analysis, lymphoedema is a risk for approximately two-thirds of breast cancer survivors in the

30 months after surgery. These data suggest increased risk of lymphoedema in survivors with BMI classified as obese whose dominant limb was treated for cancer. Overall, breast cancer survivors with post-operative swelling have a significantly higher risk of developing lymphoedema than those who do not have post-operative swelling. It is the group with higher BMI (overweight or obese) who has the greatest risk of developing lymphoedema. Breast cancer survivors with higher BMI appear to have a cumulative risk of developing lymphoedema if the cancer is on the dominant side or if they experience post-operative swelling. This finding is also consistent with work by Ridner (2005) and Park et al (2008). The survivors who are overweight or obese will benefit from education on maintaining optimal BMI and lymphoedema risk reduction practices, as well as careful monitoring for limb and symptom changes. Further vigilance is required for overweight and obese survivors who have cancer treatment to the dominant side or experience post-operative swelling.

Further research to examine the constellation of risk factors that contribute to the development of lymphoedema in breast cancer survivors must include consideration of:

- ▶ Pre-diagnosis BMI
- ▶ BMI increase in survivorship
- ▶ Occurrence of post-operative swelling
- ▶ Cancer treatment to the dominant side.

Increased understanding of the cumulative impact of these and other known risk factors will enable researchers and clinicians to design and implement more targeted risk-reduction interventions.

Acknowledgements

The data for this project were supported by Grant Number 1 RO1 NR05342-01 (Armer, PI) from the National Institute for Nursing Research, National Institutes of Health, MU PRIME fund # PRM-01-007, University of Missouri, and Ellis

Table 3

Relative lymphoedema risk between participants with and without post-operative swelling

With and without post-operative swelling		BMI status				Total
		Under-weight	Normal weight	Over-weight	Obese	
Total number of participants		3	44	61	85	193
Post-operative swelling	Swelling at post-operative visit	0 of 3 (0%)	9 of 44 (20.5%)	13 of 61 (21.3%)	15 of 85 (17.6%)	37
	Swelling at visits T2 to T8	0 of 01 (N/A%)	5 of 9 (55.6%)	11 of 13 (84.6%)	14 of 15 (93.3%)	30 of 37 (81.1%)
No post-operative swelling	No swelling at post-operative visit	3 of 3 (100%)	35 of 44 (79.5%)	48 of 61 (78.7%)	70 of 85 (82.4%)	156
	Swelling at visits T2 to T8	1 of 3 (33.3%)	20 of 35 (57.1%)	29 of 48 (60.4%)	41 of 70 (58.6%)	91 of 156 (58.3%)

Fischel Cancer Center research gift funds and the first author received funding support by the Nuclear Science and Engineering Institute for Graduate Research Assistantship. The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official views of the National Institute of Health. The authors thank Tetsuya Kobayashi for preliminary computational implementation, Dr Richard Madsen and Isabella Zaniletti for the original database design and data cleaning, Orawan Nukaew and Nathan Armer for editing assistance, the research nurses and research assistants for data collection and entry, and the breast cancer survivors who participated in the study. The authors would like to thank the reviewers for their comments that helped improve the manuscript. **JL**

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Key points

- ▶▶ The unique contribution of this research is a proposed 5% BMI-adjusted limb volume change (LVC) approach, which considers a change of 5% or greater in breast cancer affected-arm volume over percent change in BMI compared to pre-operative baseline to be indicative of lymphoedema.
- ▶▶ Dominant limb and cancer-affected side significantly increased the risk (48% greater risk, $p=0.02$) of developing lymphoedema only in those whose BMI ≥ 30 .
- ▶▶ Breast cancer survivors who developed post-operative swelling had significantly higher risk (40% greater risk, $p=0.01$) of developing lymphoedema at some later time (before 30 months) after surgery, than those who did not develop post-operative swelling.
- ▶▶ Pre-operative limb measurement was an essential reference for detection of post-operative swelling. It is not recommended that researchers and clinicians substitute the measurement at the three-month (after surgery) visit, due to occurrences of limb swelling during the post-operative visit (one to four weeks after surgery) and lymphoedema at the three-month (after surgery) visit.

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