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Side of Cancer Does Not Influence Limb Volumes in Women Prior to Breast Cancer Surgery

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Abstract

Background: Understanding normal volume asymmetry is essential for accurate assessment of limb volume changes following breast cancer (BC) treatment in which lymphatic function is disrupted. The purposes of this study were to evaluate for differences in dominant and nondominant limb volumes and to evaluate for interactions between the effects of dominance and side of cancer on limb volume.
Methods and Results: This study evaluated preoperative limb volumes of 397 women enrolled in a prospective, longitudinal study of neuropathic pain and lymphedema. Volume was calculated from circumference. Limb resistance was measured with bioimpedance. Women were dichotomized into two groups: those whose cancer was on their dominant side and those whose cancer was on their nondominant side. Analyses of variance were used to evaluate for differences. In 47%, BC occurred on the side of the dominant limb. Except for the 30 to 40 centimeter (cm) limb volume segment, a main effect of dominance was found for all measures. The volume of the dominant limb was significantly greater than that of the nondominant limb. No main effects were found for side of cancer. A statistically significant interaction was found only at the 0 to 10 cm limb volume segment.
Conclusions: Prior to BC treatment, the dominant limb demonstrated lower bioimpedance resistance (−2.09%) and greater total limb volume (1.12%) than the nondominant limb. Segmental volume differences were greatest at the proximal forearm segment (2.31%) and least at the proximal arm segment (0.21%). This study provides evidence that preoperative volume assessment is important due to normal variability associated with limb dominance.

Introduction

Damage to axillary lymph nodes and vessels during breast cancer treatment results in impaired lymph transport and may lead to lymphedema (LE). This chronic and often disabling condition affects at least 1 in 5 women treated for breast cancer.[1] Detailed information on normal variability in pre-treatment limb volumes is required to determine if increases in volume following breast cancer treatment are clinically meaningful.[2] Accurate assessment of increases in limb volume is essential to determining prevalence, to initiating prompt treatment, and to monitoring responses to therapy.

Limb volume asymmetries have been evaluated in healthy adult women using circumference,[3] volumetry,[4] optoelectric perometry,[5,6] or bioimpedance.[3,6–8] Regardless of the measure used, the volume of the dominant limb was 1.6%[4] to 4.7%[5] greater than the nondominant limb. However, only five studies[2,9–12] evaluated for differences in volume between the affected limbs (i.e., limb on the side of the cancer) and unaffected limbs in patients prior to breast cancer surgery. In one study that used volumetry[11] ($n=61$) and two (reporting data from the same 196 women) that used optoelectric perometry,[9,10] no differences in preoperative interlimb volumes were found. Similarly, in a more recent large prospective study ($n=677$) by Ancukiewicz et al.,[12] no difference was found in the mean preoperative limb volumes between the affected and unaffected limbs using perometry. However, for 11.2% of patients, the preoperative volume of the affected limb exceeded the volume of unaffected limb

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by ≥ 5%.[12] Predictors for baseline volume differences were not evaluated in this study and none of these studies evaluated for interaction effects between limb dominance and side of cancer.

The most recent prospective study[2] used bioimpedance spectroscopy (BIS) to evaluate for differences in limb volumes between affected and unaffected limbs in women prior to breast cancer surgery. In a multivariate analysis of factors that predicted preoperative extracellular fluid ratio, side of cancer explained 6.7% of the variance in preoperative bioimpedance ratios. However, the interaction between limb dominance and side of cancer on interlimb volume differences was not evaluated.

Given the paucity of information on the effects of dominance and the side of cancer on interlimb volume differences in women prior to breast cancer surgery, the purposes of this study were to evaluate for differences in dominant and nondominant limb volumes using two common clinical measures (i.e., volume calculated from circumference, bioimpedance) and to evaluate for interactions between the effects of dominance and side of cancer on volume differences between limbs.

Materials and Methods

Patients and settings

This study is part of a larger study that evaluated for neuropathic pain and lymphedema in a sample of women who underwent breast cancer surgery.[13–16] Patients were recruited from Breast Care Centers located in a Comprehensive Cancer Center, two public hospitals, and four community practices. Patients were eligible to participate if they: were adult women (>18 years) who would undergo breast cancer surgery on one breast; were able to read, write, and understand English; agreed to participate, and gave written informed consent. Patients were excluded if they were having breast cancer surgery on both breasts and/or were known to have distant metastases at the time of diagnosis. A total of 516 patients were approached to participate, 410 were enrolled in the study (response rate 79.5%) and 397 completed the study questionnaires and preoperative volume and bioimpedance measurements. The major reasons for refusal were: too busy, overwhelmed with the cancer diagnosis, or insufficient time available to do the preoperative assessment prior to surgery.

Subjective measures

Patients completed a demographic questionnaire and the Karnofsky Performance Status (KPS) scale. The demographic questionnaire obtained information on age, education, ethnicity, marital status, employment status, living situation, financial status, and exercise. The KPS scale is widely used to evaluate general functional status in patients with cancer.[17,18] Patients rated their functional status using the KPS scale that ranged from 30 (I feel severely disabled and need to be hospitalized) to 100 (I feel normal; I have no complaints or symptoms).

Objective measures

Measurement of limb volume using arm circumference. Circumferential measurements of the upper limbs were done using a spring-loaded narrow tape measure at 10 centimeter (cm) intervals from the pisiform prominence of the wrist up to a total distance of 40 cm proximally. Volumes of each 10 cm segment of the limb were calculated using the average of the two circumferential measurements. Limb volume was calculated from circumference using the formula for volume of a truncated cone.[19] For each patient, each measure of arm circumference was repeated twice by the same research nurse. All of the nurses, who had at least 2 years of oncology nursing experience, were trained to do the circumferential measures. Every 6 months, the project director did inter-rater reliability assessments (using inter-class correlation) with all of our research nurses. At every evaluation, inter-rater reliabilities of >0.80 were achieved.

Bioimpedance. Bioimpedance analysis of both upper limbs was done using established procedures.[3,20,21] Patients were instructed to refrain from exercise and sauna for 8 hours and from drinking alcohol for 12 hours prior to bioimpedance assessment. Patients lay supine with their arms abducted 30 degrees and legs not touching for at least 10 minutes prior to the measurements. Bioimpedance measurements were taken using the Quantum X Bioelectrical Impedance Device (RJL Systems, Clinton Township, MI). Measurement electrodes were placed on the skin at either end of the 40 cm length over which the circumference measurements were made and the 'drive' electrodes were placed 8 cm to 10 cm distal to these measurement electrodes. As with the circumference measures, two readings of resistance from each limb were averaged.

Study procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco and by the Institutional Review Boards at each of the study sites. During the patient's preoperative visit, a clinician explained the study to the patient, determined her willingness to participate, and introduced the patient to the research nurse. The research nurse determined patient eligibility. After obtaining written informed consent, patients completed the study questionnaires, then the research nurse performed the following preoperative objective measurements: height, weight, limb circumference, and bioimpedance. Patients' medical records were reviewed for disease and treatment information.

Data analysis

Data were analyzed using PASW Statistics for Windows Version 18.0. (SPSS Inc. Released 2009. Chicago, IL). Descriptive statistics and frequency distributions were calculated for demographic and clinical characteristics. Paired *t*-tests were used to evaluate for interlimb differences in resistance and volume. Repeated measures analysis of variance (RM-ANOVA), with one within subjects factor and one between groups factor, was performed to evaluate for main effects of dominance and side of cancer, and to evaluate for the interaction between these two factors. The repeated (within group) factor was the dominant versus nondominant limb. Patients were dichotomized into those whose cancer was on the dominant side and those whose cancer was on their nondominant side and this was used as the between groups factor. Women who indicated they used both limbs equally were categorized as having cancer on their dominant side.

Table 1. Demographic and Clinical Characteristics of Patients (n = 397)

Characteristic	*Mean (SD)*
Age (years)	54.9 (11.6)
Body mass index (kilogram/meter^2)	26.8 (6.2)
Karnofsky Performance Status score	93.2 (10.3)
	n (%)
Affected side	
Right	188 (47.2)
Left	209 (52.8)
Dominant side	
Right	355 (89.4)
Left	31 (7.8)
Uses equally	11 (2.8)
Affected side = Dominant side	186 (47.0)
Exercise on a regular basis	275 (69.1)
Ethnicity	
Caucasian – White	255 (64.2)
Asian or Pacific Islander	50 (12.6)
Black	39 (9.8)
Other	36 (9.1)
Hispanic	17 (4.3)
Stage of cancer at diagnosis	
Stage 0	73 (18.4)
Stage I	151 (38.0)
Stage IIA and IIB	141 (35.5)
Stage IIIA-IV	32 (8.1)

Results

Patient characteristics

The patients' demographic and clinical characteristics are summarized in Table 1. Of the 397 women, 89.4% were right handed. In 47% of the patients, breast cancer occurred on the side of their dominant limb. Differences in limb volumes between dominant and nondominant limbs for the entire sample are presented in Table 2. Except for the 30 cm to 40 cm segment, the volume of the dominant limb was significantly greater than the nondominant limb.

Repeated Measures Analysis of Variance: Main effects and dominance x cancer-group interactions

Table 3 summarizes the RM-ANOVA results for each of the volume measures. The interlimb volume difference for women whose cancer was on their dominant side was 22.06 mL (95% confidence interval: 9.08, 35.05). For women whose cancer was on their nondominant side, the interlimb volume difference was 18.58 mL (95% CI: 7.70, 29.47). Except for the 30 cm to 40 cm segment, a main effect of dominance ($p < 0.001$) was found for all the measures. No main effects were found for side of cancer. Only one statistically significant interaction was found for the 0 cm to 10 cm volume segment ($F = 19.44$, $p < 0.001$). Although volume was greater in dominant limbs than nondominant limbs, the magnitude of the difference at the 0 cm to 10 cm segment was larger for women with cancer on the nondominant side.

Conclusions

This study is the first to report volume differences using both bioimpedance resistance and circumference measures between dominant and nondominant limbs in a large cohort of women assessed prior to breast cancer treatment, and to evaluate for the interaction effects between dominance and side of cancer. With both measures, very small, but statistically significant differences in volumes were found between dominant and nondominant limbs. Consistent with previous reports,[2,5,7] and regardless of the measure used, the volume of the dominant limb was significantly greater than the nondominant limb. Differences in volume between the dominant and nondominant limbs were similar, regardless of the side of cancer. Our findings suggest that there is no functional alteration in lymph transport prior to cancer treatment. However, following cancer treatment, the interaction between dominance and side of cancer may be more meaningful. Lymph transport is aided by skeletal muscle contraction. The larger muscle mass of the dominant limb, or a greater inclination to use the dominant limb following cancer treatment, could lead to greater lymphatic transport in the dominant limb than the nondominant limb. Thus, differences in interlimb volume may be less in women whose cancer treatment was on their dominant side than for those whose cancer treatment was on their nondominant side.

The segmental volume differences found in this study are within 2 mL of those reported by Dylke et al.[5] who assessed limb volume in 240 healthy older women using optoelectric perometry. This finding lends supports to the use of an inexpensive high quality tape measure to evaluate limb volume in the clinical setting. Of note, the largest volume difference (5.6 mL) was found at the proximal forearm segment (10–20 cm). The smallest volume difference (1.4 mL) was found at the proximal arm segment (30–40 cm), highlighting the potential importance of evaluating the segmental distribution

Table 2. Differences in Preoperative Volumes Between Dominant and Nondominant Limbs (n = 397)

Volume measure	*Dominant mean (SD)*	*Nondominant mean (SD)*	*Mean difference 95% confidence interval*	p*
Bioimpedance resistance (ohms)	253.18 (35.38)	258.58 (37.27)	−5.41 (−6.86, −3.95)	< 0.001
Volume from circumference (mL)				
Total limb volume	1830.91 (448.85)	1810.70 (451.52)	20.21 (11.85, 28.57)	< 0.001
0 cm to 10 cm segment	267.07 (51.45)	261.47 (52.32)	5.60 (4.40, 6.80)	< 0.001
10 cm to 20 cm segment	405.65 (82.59)	396.50 (83.53)	9.15 (7.28, 11.02)	< 0.001
20 cm to 30 cm segment	517.92 (128.03)	513.90 (127.03)	4.02 (1.12, 7.02)	0.009
30 cm to 40 cm segment	643.42 (197.23)	642.05 (198.35)	1.36 (−2.67, 5.39)	0.507

*Paired *t*-test.
cm, centimeter; mL, milliliter; SD, standard deviation.

Table 3. Main and Interaction Effects of Preoperative Volume Sifferences Between Dominant and Nondominant Limbs

Outcome	*Women with cancer on dominant side Mean (SD)* N=*186*	*Women with cancer on non-dominant side Mean (SD)* N=*211*	*Main effect of dominance* *F*	p	*Main effect of side of cancer (cancer group)* *F*	p	*Interaction effect Dominance x Cancer group* *F*	p
Bioimpedance resistance								
(ohms) Dominant limb	254.53 (35.22)	251.98 (35.56)	51.78	< 0.001	0.118	0.732	3.191	0.075
Nondominant limb	258.53 (36.66)	258.63 (37.88)						
Volume calculated from circumference (mL)								
Total limb volume								
Dominant limb	1833.80 (493.17)	1828.4 (407.2)	22.70	< 0.001	0.007	0.935	0.166	0.684
Nondominant limb	1811.7 (478.8)	1809.8 (427.1)						
0 cm to10 cm segment								
Dominant limb	264.88 (56.28)	269.00 (46.84)	282.36	< 0.001	0.082	0.775	19.44	< 0.001
Nondominant limb	262.09 (56.98)	260.85 (48.01)						
10 cm to 20 cm segment								
Dominant limb	404.15 (91.67)	406.97 (73.88)	90.68	< 0.001	0.016	0.899	3.431	0.065
Nondominant limb	396.87 (89.18)	396.17 (78.42)						
20 cm to 30 cm segment								
Dominant limb	518.87 (141.85)	517.08 (114.81)	6.835	0.009	0.025	0.874	.022	0.881
Nondominant limb	515.10 (135.21)	512.85 (119.66)						
30 cm to 40 cm segment								
Dominant limb	645.90 (212.37)	641.22 (183.33)	0.437	0.509	0.057	0.811	0.001	0.978
Nondominant limb	644.60 (208.88)	639.81 (189.05)						

cm, centimeters; mL, milliliters; SD, standard deviation.

of volume changes in addition to total limb volume. Limb volume changes do not occur evenly over the arm. Measures of total limb volume do not provide information on the distribution of the fluid in the limb. Segmental limb volume differences may appear prior to and be predictive of changes in total limb volume.[10]

A 200 mL interlimb volume difference or a 2 cm circumferential interlimb difference at any measurement location are the objective criteria most often used to diagnose LE.[22] However, these criteria do not account for preoperative asymmetry. Limiting limb volume assessment to postoperative comparisons of the affected side to unaffected side does not consider pre-existing asymmetry. Comparison of affected limb postoperative volume to affected limb preoperative volume does not account for bilateral changes that may occur with weight gain/loss or changes in muscle mass. Accurate assessment of volume changes following breast cancer surgery should include bilateral comparison and consideration of preoperative asymmetry. Comparison of postoperative volume ratios to preoperative ratios addresses these issues, as does comparison of bioimpedance resistance ratios. Kilbreath et al.[2] evaluated limb volume prospectively in 516 women before and 4 weeks after breast cancer surgery, using bioimpedance. A 0.10 increase in the bioimpedance resistance ratio postoperatively from preoperative assessment identified more women at risk for LE than using only previously published postoperative thresholds.

Several limitations need to be acknowledged. First, measurement of hand volume was not done. In spite of the small relative volume of muscle in the hand, van Velze et al.[23] found the dominant hand to be 3.43% larger than the nondominant hand in healthy working males. Thus, hand measurement should be included in future studies. Second, dominance was based on patients' self–report. While valid questionnaires are available to evaluate hand dominance, Gebruers[24] found high correlation between the Edinburgh Handedness Inventory (EHI) and self-reports of handedness ($r = 0.91$, $p < 0.01$).

While preoperative assessment of limb volumes is recommended[2,9,10] limited evidence is available to support that this recommendation improves the diagnosis of LE.[2] This study provides evidence that preoperative assessment is important because of the normal variability in preoperative volumes associated with limb dominance. While the mean interlimb differences were small, the degree of variability was large. In contrast to previous studies that used perometry to assess limb volume,[10,12] we used more common clinical tools, namely a flexible tape measure and a bioimpedance device. In this large cohort of women who were evaluated preoperatively, the dominant limb demonstrated greater limb volume, particularly in the forearm, and lower resistance than the nondominant limb. Preoperative variability and asymmetries in limb volume must be considered when assessing limb volume changes following breast cancer treatment, to determine if increases are clinically important and warrant treatment.

Author Disclosure Statement

No competing financial interests exist.

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