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IMPACT OF LYMPHEDEMA AND ARM SYMPTOMS ON QUALITY OF LIFE IN BREAST CANCER SURVIVORS

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ABSTRACT

Lymphedema is one of many arm problems reported by breast cancer survivors. Understanding the impact of lymphedema on quality of life requires consideration that arm symptoms may occur with or without lymphedema. It was hypothesized that specific arm symptoms and pain, related or unrelated to lymphedema, would be more associated with quality of life outcomes than arm swelling. The relation of arm swelling and of arm symptoms and associated severity with a range of quality of life outcomes following breast cancer treatment was assessed in a diverse sample of 295 women, 141 of whom had a clinical diagnosis of lymphedema. Arm swelling (as defined by interlimb volume or circumference differences) and lymphedema severity (defined by Common Toxicity Criteria) were less correlated with quality of life than total number of arm symptoms and specific individual symptoms. Pain in the affected arm correlated with poor quality of life outcomes, regardless of arm swelling. When evaluating the impact of lymphedema on quality of life, arm swelling may not be as important as the total number and specific types of arm symptoms present, as these may be more informative about quality of life outcomes in survivors of breast cancer with and without lymphedema.

Keywords: lymphedema, breast cancer, quality of life, pain, arm symptoms

Lymphedema is a chronic lymphatic condition that consists of interstitial accumulation of protein-rich fluid and subsequent inflammation, adipose tissue hypertrophy, and fibrosis, resulting in swelling, disfigurement, heightened risk of infection, and decreased mobility and function (1,2). Lymphedema of the ipsilateral upper extremity is a common side-effect in breast cancer patients undergoing radiation and surgical resection of axillary lymph nodes. It arises in approximately 15-30% of individuals treated for breast cancer, with lower incidence following sentinel node biopsy (3,4). About 60% of patients undergoing radical mastectomy develop lymphedema, compared to approximately 30% of women treated with modified radical mastectomies or breast-conserving surgery (2). Onset varies but a majority of patients who develop arm edema do so within four years following treatment (5); an estimated

38% of survivors struggle with arm problems at five years post- treatment (6).

Studies of long-term, recurrence-free breast cancer survivors suggest no significant differences from healthy controls in self-reported quality of life (QOL) (7). Arm problems and related complaints, however, have emerged as an exception and are one of the symptoms related to poorer QOL outcomes in survivors (7). Breast cancer patients and survivors who develop lymphedema following axillary lymph node dissection report decreased QOL, as indicated by low scores on the Medical Outcome Study – Short Form (SF-36) Emotional and Role Functioning and Bodily Pain subscales (8), as well as the subscales of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument (9). A subgroup of patients with lymphedema who also report considerable levels of pain tend to experience significant functional interference, psychiatric symptoms, intrusive thoughts, body image disturbance, and decreased sexual drive (10).

There is mixed evidence regarding whether the impact of lymphedema on quality of life is due to arm swelling versus arm symptoms. In a study of the effects of complete decongestive therapy on limb volume reduction and QOL in breast cancer survivors with lymphedema, QOL improved significantly following treatment (11). Interestingly, however, improvement was unrelated to actual volume decrease in the affected arm (11). Even though the incidence of lymphedema differs depending on the type of surgery performed QOL outcomes at one year post-surgery are not worse in women who had more invasive operations (12). Therefore, the question remains: is the effect of lymphedema on quality of life due to arm swelling? Or is it due to arm symptoms? The answer to this question will assist clinicians in deciding what is more important to treat to improve quality of life among breast cancer survivors.

This report, which uses baseline data from the recently completed Physical Activity and Lymphedema (PAL) Trial, assesses the way in which different definitions of arm swelling, and number and type of arm symptoms (13) differentially relate to a range of QOL outcomes in a diverse sample of almost 300 female survivors of breast cancer. The PAL trial cohort is uniquely able to address this issue as it includes breast cancer survivors with and without clinically diagnosed lymphedema who underwent assessments of limb volume, arm symptoms, pain, and QOL. It is hypothesized that arm symptoms will be more associated with QOL outcomes than arm swelling among breast cancer survivors with and without lymphedema. It is furthermore expected that pain will be significantly correlated with poorer outcomes in QOL domains in survivors with and without lymphedema.

METHODS

All methods were approved by the institutional review board at the University of Pennsylvania, and all participants provided written consent for their participation in the study.

Sample Characteristics

Participants were 295 female breast cancer survivors (mean age=55.98 years, SD=8.83, range: 36-80 years) taking part in a randomized controlled strength training intervention trial. Of the 295 participants, 141 entered the study with a prior diagnosis of lymphedema. Women with lymphedema were randomized into two equal sized groups, with a primary aim to assess the safety of strength training by comparing rates of lymphedema exacerbations (“flare-ups”) in the treatment and control groups. The other 154 participants entered the study with no evidence of lymphedema and were also randomized into two equal sized groups to assess the safety of strength training with a primary outcome of lymphedema onset. Women were primarily recruited through

letters sent in collaboration with the Pennsylvania and New Jersey state cancer registries. Study eligibility criteria for the entire sample included female gender, history of unilateral breast cancer, and a body mass index ≤ 50 kg/m^2. Eligibility criteria specific to those with lymphedema were that they were one to 15 years post-diagnosis, had at least one lymph node removed, and either had current evidence of lymphedema (10% interlimb difference or obscuration of anatomic architecture upon clinical exam by a qualified lymphedema therapist or pitting edema), or clinical documentation of a prior diagnosis. Lymphedema had to be "stable," defined as having, over the past three months, no therapist-delivered treatment, no more than one arm infection requiring antibiotics, no changes in the ability to complete activities of daily living due to lymphedema symptom changes, and no verified changes greater than 5% in arm swelling. There were no upper limits placed on the magnitude of interlimb difference allowable among women with lymphedema. Eligibility criteria specific to those without lymphedema were that they must have had at least two lymph nodes removed as part of treatment and a cancer diagnosis between one and 5 years prior to study entry. Based on the exclusion criteria specified, 1411 of the 3200 women who contacted study staff about participation were excluded. Of these, 13 women were excluded solely because they presented with unstable lymphedema. Women who were interested in the study who were currently experiencing a flare-up or cellulitic infection were asked to get treatment and call back after the arm had stabilized. The majority of the 13 women excluded due to unstable lymphedema called less than 3 months before the end of the recruitment period, so this option was not possible for them. The study started recruitment in October 2005 and completed recruitment in February 2007. All data included for this report were collected at baseline.

Measures

At baseline all participants completed a self-report battery of QOL measures, including the eight subscales of the Medical Outcome Study – Short Form (SF-36), Coopersmith Self-Esteem Inventory (SEI) – Adult Short Form, the Fatigue Symptom Inventory – Disruption Index, Life Orientation Test – optimism and pessimism subscales, the Medical Outcome Study (MOS) Social Support Scale, the Temporal Satisfaction with Life Scale, the Pittsburgh Sleep Quality Index (PSQI), and the three Body Image and Relationships Scale (BIRS) subscales (*Table 1*). All measures – with the exception of the recently developed BIRS – are widely used instruments; all have evidence for good reliability and validity.

Lymphedema presence and severity was assessed through objective measurement and clinician rating. Objective measures were made by study research staff at pre-randomization baseline, and used to categorize participants into lower, middle, and upper tertiles according to measures of interlimb difference in water volume (%) and of largest arm circumference difference (%). Both have been found to be reliable measures of lymphedema in clinical practice (14). Clinician ratings were assigned by a study clinician pre-randomization based on a physical examination. Participants with lymphedema were categorized according to the National Cancer Institute's Common Toxicity Criteria (CTC), ranging from 0: "normal or sub-clinical" to 4: "severe lymphedema limiting function with ulceration" (15).

Number and perceived severity of arm symptoms, regardless of lymphedema, were assessed using a 14-item self-report measure developed by Norman and colleagues (13), which describes the presence, frequency, severity and distress caused by individual arm symptoms commonly associated with lymphedema (symptoms listed in *Tables 3a and 3b*). Finally, participants were asked to

TABLE 1
Description of Quality of Life Assessment Instruments Administered to Respondents

Name of Instrument	Description
Coopersmith Self-Esteem Inventory (SEI) – Adult Short Form	A measure of patients' attitudes toward themselves. Aspects of self-esteem include self-approval or disapproval, and judgments of worthiness (16).
The Fatigue Symptom Inventory	A 13-item self-report inventory deigned to measure the duration and intensity of fatigue and its impact on quality of life (17).
Life Orientation Test (LOT-R) – 10 Item Revised	A measure of optimism or a general disposition to view things in a favorable light (18).
Medical Outcome Study Social Support Scale (MOS-SS)	A measure of three components of social support: emotional/ informational, affection, and positive social interaction. MOS-SS measures the degree that one's interpersonal relationships are perceived to satisfy particular functions with 5-point ratings from none to all of the time (19).
Medical Outcome Study – Short Form (SF-36)	The most widely used generic health profile. The SF-36 provides subscale scores for 8 domains of health-related quality of life – mental health, physical health, emotional role function, physical role function, social health, pain, vitality/energy, health perceptions, two overall summary scores (overall physical and overall mental health), and one health transition item (20-23).
The Pittsburgh Sleep Quality Index (PSQI)	A measure of sleep quality, based on recall of sleep behaviors in the past month. The PSQI is the most widely used standardized measure of sleep quality. The PSQI provides an overall score based on 7 domains of sleep: quality, latency, duration, efficiency (quotient of hours asleep divided by hours in bed), disturbances (like awakening to use the toilet), use of medications, and daytime dysfunction (24-25).
Quality of Life	Quality of life as assessed on a visual analogue scale, ranging from 0 = "worst possible quality of life" to 100 = "best possible quality of life."
Temporal Satisfaction with Life Scale (TSWLS)	A 15-item measure of life satisfaction or the cognitive or judgmental aspect of subjective well-being. The TSWLS evaluates current, past and future (anticipated) life satisfaction (26).
Body Image and Relationships Scale (BIRS)	Three-factor measure of the effects of breast cancer diagnosis and treatment in quality of life, including twelve items assessing "Strength and Health," or the perceived physical impairment related to treatment, including decreased energy, feeling "weak" and "unhealthy," and lack of subjective control over health and strength, nine items assessing "Social Barriers," or the perceived impairment in social interactions, including reduced social activity due to and embarrassment about physical or psychological symptoms, and eleven items assessing impact on "Appearance and Sexuality" or decreased enjoyment of and satisfaction with sexual activity, embarrassment about physical appearance, and altered perception of one's body as whole" and "natural" (27).

indicate whether they experienced any pain on the side of the body that was treated, and if so, to rate the severity of their pain on a scale of 0: "no pain" to 10: "worst pain imaginable." All measurements were administered to women with and without lymphedema.

Statistical Analyses

The relationship between QOL outcomes, lymphedema severity, and arm-related symptoms was assessed using Pearson's correlation coefficients. Time since diagnosis and race correlated significantly with a number of QOL measures and were controlled for in all analyses. Correlation analyses were conducted separately for groups of participants with and without a prior diagnosis of lymphedema, and for all participants combined. Groups were compared using chi-square, t-test analyses, and one-way analyses of variance (ANOVA). All significance tests were two-sided and conducted using a Type I error of 0.05. It was assumed here that lymphedema and arm-related symptoms impact QOL, and thus QOL was considered the outcome variable in all analyses.

RESULTS

Demographics

Respondents self-identified as Caucasian (n=194, 65.8%), African-American (n=95, 32.2%), Asian (n=6, 2.0%), American Indian/Alaskan Native (n=5, 1.7%), Hispanic (n=2, 0.7%), Native Hawaiian (n=1, 0.3%), and "other" (n=1, 0.3%). Approximately a third of all respondents had completed some college (34.2%, n=101), 23.1% (n=68) had a four-year college degree, and 26.8% (n=79) had a post-graduate degree. A majority of participants was married or living with a partner (61.3%, n=179); fewer respondents reported being divorced or separated (16.8%, n=49), widowed (11.0%, n=32), or never married (11.0%, n=32). Fewer than half of the respondents (42.4%, n=125) were primary caregivers for children living with them.

Description of Arm Swelling and Arm Symptoms in the PAL Cohort

The average interlimb volume difference among women with lymphedema was 16.12% (SD=15.19), and among women without lymphedema was -0.07% (SD=5.00; $t(293)= -12.07$, $p \leq 0.001$). Circumferential measurements were also taken. The differences between the affected and unaffected limbs at the point of the largest visible difference had an average of 14.14 cm (SD=10.91) among the women with lymphedema and 3.63 cm (SD=3.03; $t(285)=-10.96$, $p \leq 0.001$) among those without lymphedema. Using CTC categories of lymphedema severity a majority of all participants were categorized as "0" (i.e., "normal" or controlled lymphedema) (n=184, 62.4%), followed by 21.4% (n=63) of participants in category 2 (i.e., "moderate lymphedema, requiring compression"), 8.8% (n=26) in category 3 (i.e., "severe lymphedema limiting function"), and 7.5% (n=22) in category 1 (i.e., "mild lymphedema"). Of the women with a prior diagnosis of lymphedema 44.7% (n=63) fell into the CTC category "2," 21.3% (n=30) were categorized as "0," 18.4% (n=26) as "3," and 15.6% (n=22) as "1." Thus, the sample recruited represented a range of lymphedema severity.

Regardless of prior lymphedema status all participants were categorized into clinically defined tertiles based on interlimb volume differences as lowest (-11.0%-9.9%, n=203, 68.8%), middle (10.0%-19.9%, n=49, 16.6%), and highest tertiles (≤20.0%-, n=43, 14.6%). The values for the largest interlimb percent difference in arm or hand circumference ranged from 0.16% to 44.35% (M=8.72%, SD=9.48), yielding clinically defined tertiles of lowest (0.16%-9.9%, n=210, 71.2%), middle (10.0%-19.9%, n=41, 13.9%), and highest tertiles (≤20.0%, n=36, 12.2%) in the entire sample of participants.

Participants on average reported three out of a possible 14 arm symptoms (M=3.31, SD=3.17, range: 0-12). Participants who had previously been diagnosed with lymphedema on average reported a significantly higher number of symptoms (M=5.48, SD=2.83) than those who entered the study without a diagnosis (M=1.32, SD=1.92; $t(282)=-14.35$,

p≤0.001). Of those without a prior lymphedema diagnosis, 50.7% reported at least one symptom, 30.4% reported at least two symptoms, and 20.3% reported at least three symptoms; 7.4% reported five or more symptoms.

About half of the full PAL cohort (n=148, 50.5%) reported currently experiencing pain on the side of their body treated for breast cancer, including 50.7% of the women without lymphedema. Respondents who reported experiencing any pain rated the severity of their pain as relatively mild (M=2.30, SD=2.09, range: 0-8 on a scale of "0=no pain" to "10=worst pain imaginable"). Respondents with any pain symptoms reported significantly more total arm symptoms (M=4.15, SD=3.24) than those who did not currently experience any pain [M=2.47, SD=2.86; t(280)=-4.62, p≤0.001].

Criteria Overlap

Arm volume as measured by percent interlimb difference in water volume and percent difference in circumference correlated significantly with CTC categorization (r=0.88, p≤0.001 for water volume; r=0.80, p≤0.001 for circumference), total number of symptoms (r=0.50, p≤0.001; r=0.52, pœ0.001), and self-reported pain severity (r=0.24, p=0.003; r=0.32, p≤0.001). Common Toxicity Criteria categorization correlated significantly with number of arm symptoms (r=0.57, p≤0.001) and pain severity (r=0.24, p=0.01), and number of symptoms correlated significantly with pain severity (r=0.49, p≤0.001).

Lymphedema and Quality of Life: Lymphedema Defined by Interlimb Water Volume Difference

One-way ANOVAs that included all participants (with and without lymphedema) yielded no significant differences between the three tertile groups of largest, medium, and smallest percent interlimb water volume difference in terms of any of the QOL outcomes. In a separate analysis that included only those participants with a prior diagnosis of lymphedema, the continuous measure of water volume was also not significantly correlated with any QOL outcomes.

Lymphedema and Quality of Life: Lymphedema Defined by Largest Circumference Difference

In an analysis that included all participants (with and without lymphedema), the three tertile groups of largest, medium, and smallest percent interlimb circumference difference did not differ in any QOL outcomes, with the exception of scores on the SF-36 Physical Role Functioning Scale [F(2,281)=3.17, p=0.04], where those in the third tertile scored significantly higher (M=89.71, SD=24.71) than those in the second tertile (M=69.51, SD=41.65, p=0.03), with the first tertile mean scores falling in between (M=79.39, SD=34.52). In a separate analysis that included only those participants with a prior diagnosis of lymphedema, the continuous measure of circumference difference was not correlated significantly with any of the QOL outcomes, with the exception of scores on the PSQI (r=-0.24, p=0.04).

Lymphedema and Quality of Life: Lymphedema Defined by Common Toxicity Criteria

In the full cohort (those with and without lymphedema) there were no differences across CTC categories in any QOL outcomes, with the exception of scores on the Cooper-smith Self-Esteem Inventory [F(3,257)=2.60, p=0.05], where those in CTC category "0" scored significantly lower than those in category "1" (p=0.04). In those with an existing diagnosis of lymphedema significant differences emerged on the SF-36 Physical Role Functioning subscale [F(3,134)=2.90,

TABLE 2
Number of Arm Symptoms and Quality of Life Outcomes

	Correlations with Total Number of Symptoms – All Participants (n=295)	Correlations with Total Number of Symptoms – Participants with prior diagnosis of lymphedema (n=141)	Correlations with Total Number of Symptoms – Participants without prior diagnosis of lymphedema (n=154)
SF-36			
Physical Function	-0.42, p≤0.001***	-0.36, p=0.002**	-0.47, p≤0.001***
Physical Role Functioning	-0.34, p≤0.001***	-0.31, p=0.01**	-0.40, p≤0.001***
Emotional Role Functioning	-0.18, p=0.02*	-0.24, p=0.04*	-0.18, p=0.09
Social	-0.19, p=0.01**	-0.26, p=0.03*	-0.07, p=0.52
Bodily Pain	-0.44, p≤0.001***	-0.43, p≤0.001***	-0.43, p≤0.001***
Mental Health	-0.09, p=0.26	-0.13, p=0.27	-0.21, p=0.05*
Vitality	-0.18, p=0.02*	-0.11, p=0.33	-0.29, p=0.01**
General Health Perception	-0.33, p≤0.001***	-0.23, p=0.05*	-0.37, p=0.001***
Fatigue – Disruption Index	0.26, p=0.001***	0.19, p=0.10	-0.28, p=0.01**
Coopersmith SEI	0.06, p=0.44	0.07, p=0.56	0.22, p=0.04*
Quality of Life VAS	-0.11, p=0.15	-0.11, p=0.34	-0.03, p=0.76
Life Orientation Test - Optimism	-0.03, p=0.71	0.02, p=0.85	-0.35, p=0.001***
Life Orientation Test - Pessimism	0.10, p=0.20	0.10, p=0.37	0.33, p=0.002**
Satisfaction with Life	-0.09, p=0.28	0.03, p=0.82	-0.21, p=0.05*
Temporal Life Satisfaction	0.06, p=0.49	0.07, p=0.53	0.17, p=0.12
MOS Social Support	0.01, p=0.92	-0.04, p=0.76	-0.07, p=0.54
PSQI	-0.01, p=0.95	-0.05, p=0.70	0.15, p=0.16
BIRS - Strength and Health	0.23, p=0.003**	0.21, p=0.07	0.26, p=0.02*
BIRS - Social Barriers	0.24, p=0.002**	0.27, p=0.02*	0.11, p=0.31
BIRS - Appearance and Sexuality	0.22, p=0.004**	0.24, p=0.04*	0.18, p=0.09

* p≤0.05, ** p≤0.01, *** p≤0.001

p=0.04], with those with grade 3 lymphedema scoring significantly higher than respondents in grade 0 (p=0.02).

Arm Symptoms and Quality of Life: Number and Type

In an analysis that included all participants (with and without lymphedema) and controlling for time since diagnosis and race, total number of arm symptoms correlated significantly with the Physical Function, Physical Role Functioning, Emotional Role Functioning, Social, Bodily Pain, Vitality, and General Health Perceptions subscales of the SF-36, the Fatigue Scale Disruption Index, scores on the Quality of Life visual analog scale, and the Strength and Health, Social Barriers, and Appearance and Sexuality subscales of the BIRS in the entire sample of respondents (*Table 2*). In a separate analysis that included only those respondents with a prior diagnosis of lymphedema and controlling for time since diagnosis and race, total number of arm symptoms was correlated significantly with the Physical Function, Physical Role Functioning, Emotional Role Functioning, Social, Bodily Pain, and General Health Perceptions subscales of the SF-36, and the Social Barriers and the Appearance and Sexuality subscales of the BIRS (*Table 2*).

TABLE 3a
Correlations of Individual Symptoms with Quality of Life Outcomes (shaded boxes indicate significance of p<0.05)

	Rings too tight (n=78)	Watch too tight (n=41)	Bracelet too tight (n=34)	Clothing too tight (n=84)	One side puffy (n=136)	Couldn't see knuckles (n=40)	Couldn't see veins (n=47)
SF-36							
Physical Function	-0.20, p=0.001	-0.21, p≤0.001	-0.16, p=0.01	-0.19, p≤0.001	-0.22, p≤0.001	-0.17, p=0.003	-0.17, p=0.004
Physical Role Functioning	-0.22, p≤0.001	-0.16, p=0.01	-0.25, p≤0.001	-0.13, p=0.03	-0.12, p=0.04	-0.01, p=0.92	-0.02, 0.74
Emotional Role Functioning	-0.13, p=0.03	-0.001, p=0.98	-0.01, p=0.84	0.00, p=0.99	-0.03, p=0.60	0.02, p=0.68	0.05, p=0.43
Social	-0.17, p=0.004	-0.09, p=0.13	-0.06, p=0.33	-0.05, p=0.37	-0.08, p=0.18	0.01, p=0.89	0.003, p=0.95
Bodily Pain	-0.20, p=0.001	-0.17, p=0.003	-0.16, p=0.01	-0.19, p≤0.001	-0.20, p=0.001	-0.05, p=0.43	-0.09, p=0.11
Mental Health	-0.14. p=0.02	-0.01, p=0.81	0.02, p=0.69	-0.05, 0.41	-0.01, p=0.93	0.07, p=0.24	0.09, p=0.11
Vitality	-0.17, p=0.004	-0.02, p=0.70	-0.03, p=0.62	-0.06, p=0.35	-0.05, p=0.44	0.03, p=0.56	0.13, p=0.03
General Health Perception	-0.17, p=0.004	-0.15, p=0.01	-0.10, p=0.09	-0.16, p=0.01	-0.16, p=0.01	-0.03, p=0.64	0.06, p=0.34
Fatigue – Disruption Index	0.12, p=0.05	0.05, p=0.38	0.01, p=0.88	0.01, p=0.95	0.04, p=0.51	-0.11, p=0.07	-0.08, 0.20
Coopersmith SEI	0.13, p=0.03	0.02, p=0.71	0.06, p=0.36	-0.004, p=0.95	-0.06, p=0.35	-0.07, p=0.26	-0.11, p=0.08
Quality of Life VAS	-0.13, p=0.03	-0.05, p=0.40	-0.05, p=0.36	-0.04, p=0.47	-0.08, p=0.18	0.04, p=0.52	0.03, p=0.61
Life Orientation Test - Optimism	-0.03, p=0.58	-0.03, p=0.63	-0.06, p=0.31	-0.04, p=0.54	0.02, p=0.72	0.07, p=0.26	0.10, p=0.08
Life Orientation Test - Pessimism	0.06, p=0.33	-0.01, p=0.84	0.07, p=0.24	0.004, p=0.95	-0.004, p=0.94	0.01, p=0.84	-0.07, p=0.22
Satisfaction with Life	-0.09, p=0.14	-0.02, p=0.71	-0.04, p=0.51	-0.05, p=0.38	0.001, p=0.99	-0.06, p=0.28	0.11, p=0.06
Temporal Life Satisfaction	0.06, p=0.36	-0.07, 0.26	-0.02, p=0.75	0.01, p=0.92	0.001, p=0.98	0.02, p=0.74	-0.06, p=0.34
MOS Social Support	0.05, p=0.45	-0.03, p=0.61	-0.06, p=0.29	-0.05, p=0.44	-0.04, p=0.54	-0.06, p=0.35	0.03, p=0.57
PSQI	0.09, p=0.14	0.12, p=0.04	0.07, p=0.25	0.10, p=0.10	0.03, p=0.65	-0.03, p=0.63	-0.05, p=0.36
BIRS - Strength and Health	0.14, p=0.02	0.08, p=0.16	0.07, p=0.24	0.13, p=0.03	0.09, p=0.13	-0.03, p=0.63	-0.03, p=0.61
BIRS - Social Barriers	0.08, p=0.24	0.14, p=0.04	0.13, p=0.07	0.10, p=0.16	0.08, p=0.24	-0.04, p=0.58	-0.06, p=0.36
BIRS - Appearance and Sexuality	0.05, p=0.45	0.02, p=0.71	0.02, p=0.78	0.13, p=0.04	0.11, p=0.09	-0.03, p=0.63	-0.07, p=0.24

In yet another separate analysis that only included respondents without a prior diagnosis of lymphedema and again controlling for time since diagnosis and race, there were significant correlations between total number of symptoms and the Physical Function, Physical Role Functioning, Pain, Mental Health, Vitality, and General Health Perceptions subscales of the SF-36, the Fatigue Disruption Index, scores on the Coopersmith SEI, Life Orientation Test Optimism and Pessimism subscales, Satisfaction with Life, and the Strength and Health subscale of the BIRS (*Table 2*).

In terms of specific arm symptoms reported by the full sample of respondents, experiencing "pain in hand or arm on one side" was the most strongly associated with QOL outcomes, correlating significantly with 16 of the 20 measures administered. Having "rings too tight on one side" and experiencing "difficulty writing" each correlated significantly with 12 of the 20 QOL measures. Having one's "arm feeling tired, thick, or heavy on one side" correlated significantly with 10, and reporting "skin feeling different, firmer, or leathery on one side" correlated significantly with eight measures of QOL. Not being able to see your knuckles, noticing indentations in skin when leaning against something, and not being able to see veins in the hand on one side were the least associated with QOL outcomes, correlating only with one or two measures administered (*Tables 3a,3b*).

Lymphedema and Quality of Life: The Role of Pain

In an analysis that included all participants, regardless of lymphedema status, respondents with any pain differed significantly from individuals with no pain on all but one (MOS Social Support) measure of QOL outcomes. Pain severity correlated significantly with all SF-36 subscales, the Fatigue Symptom Inventory Disruption Index, the Coopersmith SEI, the Quality of Life Visual Analogue Scale, the Pessimism Index of the Life Orientation Test, the PSQI, and the Strength and Health and Social Barriers subscales of the BIRS (*Table 4*). It should be noted that there is some content overlap with items assessing pain included on the SF-36 as well as the total symptom score and that the scale for the BIRS is the reverse of the other scales (higher score is worse).

DISCUSSION

This report evaluated the relationship of arm swelling and arm symptoms with a battery of QOL measures to determine whether swelling or symptoms would be most associated with poor QOL adjustment following breast cancer treatment. It should be noted that participants with and without existing lymphedema diagnosis were assessed, thus results regarding the influence of arm symptoms on QOL reflect the full spectrum of experiences in breast cancer survivors. Number of arm symptoms correlated significantly with QOL outcomes in respondents with and without a prior diagnosis of lymphedema. Arm swelling, on the other hand, was only significantly correlated with an overall sleep score and a physical function subscale of the SF-36. A significant proportion of participants who had not been diagnosed with lymphedema previously reported experiencing symptoms, including pain. These findings are consistent with the hypothesis that arm symptoms and pain are more closely correlated with a negative impact on quality of life than arm swelling. The results emphasize the importance of recognizing that lymphedema is not just about the swelling, as well as the fact that lymphedema is only one arm-related issue on a spectrum of diverse upper body problems and pain in breast cancer survivors.

Several symptoms emerged as being particularly strongly correlated with poorer QOL outcomes. Pain in hand or arm on the side treated for breast cancer was the most strongly associated individual symptom in

TABLE 3b
Correlations of Individual Symptoms with Quality of Life Outcomes (shaded boxes indicate significance of p<0.05)

	Skin felt different (n=62)	Arm/hand felt tired, thick, heavy (n=128)	Pain in hand/ arm (n=92)	Indentations (n=75)	Swelling after exercise (n=41)	Difficulty writing (n=36)	Other (n=79)
SF-36							
Physical Function	-0.23, p≤0.001	-0.26, p≤0.001	-0.27, p≤0.001	-0.18, p=0.003	-0.16, p=0.01	-0.30, p≤0.001	-0.13, p=0.03
Physical Role Functioning	-0.21, p≤0.001	-0.18, p=0.002	-0.30, p≤0.001	-0.01, p=0.85	-0.08, p=0.18	-0.17, p=0.003	-0.09, p=0.15
Emotional Role Functioning	-0.09, p=0.13	-0.09, p=0.11	-0.18, p=0.003	-0.03, p=0.60	-0.02, p=0.71	-0.12, p=0.04	-0.19, p=0.001
Social	-0.12, p=0.04	-0.11, p=0.06	-0.22, p≤0.001	-0.10, p=0.93	-0.07, p=0.23	-0.16, p=0.01	-0.23, p≤0.001
Bodily Pain	-0.18, p=0.002	-0.20, p=0.001	-0.30, p≤0.001	-0.02, p=0.71	-0.09, p=0.14	-0.23, p≤0.001	-0.14, p=0.02
Mental Health	-0.06, p=0.32	-0.03, p=0.56	-0.13, p=0.03	0.06, p=0.31	-0.08, p=0.16	-0.09, p=0.15	-0.23, p≤0.001
Vitality	-0.09, p=0.11	-0.14, p=0.02	-0.15, p=0.01	0.02, p=0.75	-0.11, p=0.07	-0.13, p=0.02	-0.23, p≤0.001
General Health Perception	-0.14, p=0.02	-0.20, p=0.001	-0.21, p≤0.001	-0.04, p=0.49	-0.17, p=0.003	-0.15, p=0.01	-0.17, p=0.003
Fatigue – Disruption Index	0.14, p=0.02	0.12, p=0.04	0.21, p≤0.001	-0.05, p=0.41	0.06, p=0.35	0.17, p=0.01	0.27, p≤0.001
Coopersmith SEI	0.09, p=0.15	0.08, p=0.20	0.14, p=0.02	-0.09, p=0.14	0.03, p=0.63	0.15, p=0.02	0.13, p=0.04
Quality of Life VAS	0.02, p=0.77	-0.10, p=0.11	-0.18, p=0.002	0.03, p=0.64	-0.12, p=0.04	-0.08, p=0.19	-0.11, p=0.06
Life Orientation Test - Optimism	0.03, p=0.66	-0.08, p=0.20	-0.05, 0.37	0.10, p=0.10	-0.05, p=0.42	-0.07, p=0.26	-0.09, p=0.12
Life Orientation Test - Pessimism	0.04, p=0.52	0.08, p=0.20	0.13, p=0.02	-0.07, p=0.24	0.02, p=0.70	0.07, 0.25	0.20, p≤0.001
Satisfaction with Life	0.04, p=0.51	-0.13, p=0.03	-0.13, p=0.02	0.10, p=0.10	-0.07, p=0.24	-0.08, -.17	-0.17, p=0.004
Temporal Life Satisfaction	0.03, p=0.56	0.02, p=0.71	0.07, p=0.25	-0.04, p=0.50	0.02, p=0.69	0.15, p=0.01	0.11, p=0.06
MOS Social Support	0.05, p=0.44	-0.06, p=0.30	-0.10, p=0.08	0.05, p=0.43	-0.04, p=0.50	-0.09, p=0.14	-0.09, 0.15
PSQI	0.02, p=0.69	-0.03, p=0.63	0.05, p=0.42	-0.04, p=0.54	0.05, p=0.41	0.15, p=0.01	-0.002, p=0.98
BIRS - Strength and Health	0.12, p=0.04	0.16, p=0.01	0.15, p=0.01	0.03, p=0.66	0.12, p=0.04	0.15, p=0.01	0.15, p=0.01
BIRS - Social Barriers	0.25, p≤0.001	0.20, p=0.003	0.20, 0.003	0.07, p=0.34	0.24, p≤0.001	0.10, p=0.15	0.14, p=0.04
BIRS - Appearance and Sexuality	0.09, p=0.14	0.24, p≤0.001	0.22, p≤0.001	0.01, p=0.87	0.04, p=0.49	0.12, p=0.06	0.20, p=0.001

TABLE 4
Pain Symptoms and Severity and Quality of Life Measures

	Correlation with Pain severity (0=no pain to 10=worst pain imaginable)	Pain or Discomfort in Side of Body Treated for Breast Cancer		
		No (n=145, 49.5%)	Yes (n=148, 50.5%)	Statistic
SF-36				
Physical Function	r=-0.49, p≤0.001***	M=26.88, SD=3.43	M=25.20, SD=4.20	t(289)=3.75, p≤0.001
Physical Role Functioning	r=-0.31, p≤0.001***	M=7.48, SD=1.11	M=6.82, SD=1.57	t(289)=4.14, p≤0.001
Emotional Role Functioning	r=-0.21, p=0.01**	M=5.70, SD=0.75	M=5.32, SD=1.13	t(289)=3.40, p≤0.001
Social	r=-0.35, p≤0.001***	M=9.50, SD=1.14	M=8.69, SD=1.77	t(287)=4.63, p≤0.001
Bodily Pain	r=-0.50, p≤0.001***	M=10.34, SD=1.92	M=8.95, SD=2.16	t(289)=5.81, p≤0.001
Mental Health	r=-0.15, p=0.07	M=25.78, SD=3.47	M=24.02, SD=4.43	t(289)=3.77, p≤0.001
Vitality	r=-0.30, p≤0.001***	M=16.66, SD=3.94	M=14.50, SD=4.48	t(289)=4.36, p≤0.001
General Health Perception	r=-0.42, p≤0.001***	M=19.96, SD=3.50	M=18.43, SD=3.88	t(289)=3.52, p=0.001
Fatigue – Disruption Index	r=0.29, p≤0.001***	M=7.67, SD=10.19	M=13.56, SD=14.20	t(289)=-4.04, p=0.001
Coopersmith SEI	r=0.16, p=0.07	M=16.52, SD=16.24	M=22.85, SD=18.86	t(285)=-2.90, p=0.004
Quality of Life VAS	r=-0.14, p=0.09	M=84.97, SD=12.63	M=79.08, SD=16.81	t(288)=3.38, p=0.001
Life Orientation Test - Optimism	r=-0.02, p=0.80	M=11.02, SD=1.80	M=11.08, SD=2.26	t(287)=2.22, p=0.03
Life Orientation Test - Pessimism	r=0.18, p=0.03*	M=6.31, SD=2.21	M=6.94, SD=2.86	t(287)=-2.10, p=0.037
Satisfaction with Life	r=-0.01, p=0.94	M=16.24, SD=4.14	M=13.95, SD=4.44	t(288)=4.56, p≤0.001
Temporal Life Satisfaction	r=0.03, p=0.69	M=18.49, SD=2.77	M=19.21, SD=3.05	t(287)=-2.10, p=0.04
MOS Social Support	r=-0.05, p=0.54	M=73.81, SD=22.98	M=68.75, SD=27.14	t(285)=1.70, p=0.09
PSQI	r=0.16, p=0.06	M=0.24, SD=0.50	M=0.38, SD=0.59	t(289)=-2.11, p=0.04
BIRS - Strength and Health	r=0.27, p=0.001***	M=31.03, SD=8.46	M=35.02, SD=9.00	t(285)=-3.96, p≤0.001
BIRS - Social Barriers	r=0.26, p=0.01**	M=14.98, SD=4.95	M=18.38, SD=7.29	t(205)=-3.96, p<0.001
BIRS - Appearance and Sexuality	r=0.11, p=0.23	M=27.88, SD=5.33	M=31.81, SD=6.18	t(260)=-5.50, p≤0.001

* p≤0.05, ** p≤0.01, *** p≤0.001

the full cohort, regardless of lymphedema diagnosis. The importance of pain was reinforced by the fact that pain assessed in other ways (yes/no and severity scale) was also associated with poorer QOL. Other individual symptoms correlated with worse QOL included measures of functioning, such as difficulty writing and inability to wear rings, as well as heaviness in one arm or hand and changes in skin texture and appearance. These findings should be noted by clinicians as indicating the symptoms that would be most important to resolve to improve quality of life among breast cancer survivors, regardless of lymphedema diagnosis.

This study has many strengths that speak for the generalizability of findings. The large sample surveyed was highly diverse in terms of age, race, and ethnicity, making this one of the only studies highlighting QOL outcomes in breast cancer survivors of diverse backgrounds. Participants entered the study at a variety of time points from their initial diagnosis, represented a broad cross section of lymphedema severity (including 26 women with grade 3 lymphedema and 63 women with grade 2 lymphedema), and reported a range of arm symptoms, swelling, and pain, as well as widely varying levels of QOL. Measures used were manifold and of high quality, yielding a valid, reliable, and nuanced picture of the ways in which lymphedema and QOL are related. A limitation to be noted is that due to its cross-sectional design the present study cannot speak to the direction of association between the variables of interest. It is however unlikely that poorer QOL has a significant impact on upper body symptoms and pain, as opposed to vice versa.

In summary, the findings herein support the conclusion that arm symptoms and pain are more closely correlated to multiple domains of quality of life among breast cancer survivors than arm swelling. This was observed in a diverse cohort of breast cancer survivors with and without a diagnosis of lymphedema, including 63 women with inter-limb differences of 10-20% and 26 women with interlimb differences over 20%. Lymphedema is clearly not just about swelling. Clinicians who work with breast cancer survivors are urged to focus on arm symptoms and pain as much if not more than on arm swelling. Assessment and treatment of arm symptoms is warranted, even in survivors who do not meet full diagnostic criteria for lymphedema, as these may point to possible complications in psychosocial adjustment and QOL following treatment.

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