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Heavy-load lifting: Acute response in breast cancer survivors at risk for lymphedema

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**Purpose** Despite a paucity of evidence, prevention guidelines typically advise avoidance of heavy lifting in an effort to protect against breast cancer-related lymphedema. This study compared acute responses in arm swelling and related symptoms after low- and heavy-load resistance exercise among women at risk of lymphedema while receiving adjuvant taxane-based chemotherapy.

**Methods** This is a randomized, cross-over equivalence trial. Women receiving adjuvant taxane-based chemotherapy for breast cancer who had undergone axillary lymph node dissection (n=21) participated in low- (60-65% 1 repetition maximum (RM), two sets of 15-20 repetitions) and heavy-load (85-90% 1RM, three sets of 5-8 repetition) upper-extremity resistance exercise separated by a one-week wash-out period. Swelling was determined by bioimpedance spectroscopy and dual energy x-ray absorptiometry, with breast cancer-related lymphedema symptoms (heaviness, swelling, pain, tightness) reported using a numeric rating scale (0-10). Order of low- versus heavy-load was randomized. All outcomes were assessed pre-, immediately post-, and 24- and 72-hours post-exercise. Generalized estimating equations were used to evaluate changes over time between groups, with equivalence between resistance exercise loads determined using the principle of confidence interval inclusion.

**Results** The acute response to resistance exercise was equivalent for all outcomes at all time points irrespective of loads lifted, with the exception of extracellular fluid at 72-hours post-exercise with less swelling following heavy-loads (estimated mean difference -1.00, 95% CI -3.17 to 1.17).

**Conclusion** Low- and heavy-load resistance exercise elicited similar acute responses in arm swelling and breast cancer-related lymphedema symptoms in women at risk for lymphedema receiving adjuvant taxane-based chemotherapy. These represent important preliminary findings, which can be used to inform future prospective evaluation of the long term effects of repeated exposure to heavy-load resistance exercise.

**Keywords** arm swelling, breast cancer, dose response, strength training
Introduction

Breast cancer-related arm lymphedema (BCRL) is a chronic condition initially characterized by regional swelling of the arm or hand due to increases in protein-rich extracellular fluid, affecting approximately 20% of breast cancer survivors as a consequence of treatment (1, 2). The adverse effects of BCRL are well described in the literature, negatively impacting daily functions (3, 4), and social, emotional and psychological well-being (4, 5).

More extensive surgery to the chest wall, radiotherapy, chemotherapy, and being overweight and/or physically inactive have been consistently associated with increased BCRL risk (1). However, the extent of lymph node removal is considered the strongest risk factor, with BCRL incidence four times higher after axillary lymph node dissection compared to sentinel-node biopsy (1). Despite the high quality evidence in support of specific risk factors, the ability to predict who will develop BCRL is limited.

Historically, breast cancer survivors were advised to refrain from resistance exercise as a means of preventing BCRL (6, 7). However, results from systematic reviews of clinical trials consistently indicate that resistance exercise elicits gains in muscle strength and physical components of quality of life without increased risk of BCRL (6-9). Nonetheless, more work needs to be undertaken to confirm safety of resistance exercise, since those considered at high-risk of BCRL do not reflect the target sample of studies included in these reviews. Specifically, only one study explicitly included participants undergoing chemotherapy (10), of which 31% received adjuvant taxane-based chemotherapy. This is of importance as generalized edema with ensuing arm swelling is a known side-effect to this cytostatic agent (11). Additionally, just two studies (10, 12) specifically included women at risk for BCRL who had undergone axillary lymph node dissection, considered the greatest risk factor.

Limitations also exist with respect to exercise prescription as resistance load has not exceeded 80% of one repetition maximum (RM) or 8-12 repetitions in previous studies evaluating
resistance exercise and BCRL risk, due to concerns that heavier loads would trigger BCRL development (6-9, 13). Yet, exercise science literature indicates that a dose-response relationship exists between loads lifted and gains in muscular structure and function with heavier loads shown to be more effective in eliciting strength gains compared with lighter loads (14, 15).

To date, two prospective studies including women with clinically stable BCRL who had been diagnosed with breast cancer at least a year before study inclusion, have evaluated the potential of heavier load resistance exercise using 6-10 RM (16, 17). These studies found that the extent of arm swelling and associated BCRL symptoms remained stable both immediately post-, 24- and 72-hours after one bout of resistance exercise (16), and after twelve-weeks of regular resistance exercise irrespective of whether low- or heavy-loads were lifted (17). As such, these studies provide meaningful information for women with BCRL who have completed active treatment (chemotherapy and radiotherapy). These findings cannot however be generalized to the at-risk population undergoing taxane-based chemotherapy.

Therefore, the purpose of this study was to undertake a phase II trial to assess the initial lymphatic response to low-load compared with heavy-load resistance exercise in breast cancer survivors at risk of BCRL development. This was undertaken by comparing acute changes in extracellular fluid, arm volume and associated BCRL symptoms after a session of low- and heavy-load resistance exercise in women who had undergone axillary lymph node dissection and were receiving taxane-based chemotherapy during the conduct of this trial.

**Methods**

**Trial design**

Details of study design and methods have been previously described (18). In summary, this was a randomized, cross-over, equivalence trial whereby participants participated in an experimental low- and heavy-load upper-extremity resistance exercise session, with a seven
day wash-out period between sessions (Figure 1). It was hypothesized that response would be similar between resistance exercise loads for all outcomes. The study protocol was approved by the Danish Data Protection Agency (30-1430) and the Danish Capital Regional Ethics Committee (H-3-2014-147) and written informed consent was obtained from all participants.

**Participants**

A convenience sample of women receiving standard adjuvant chemotherapy for stage I-III breast cancer were screened for eligibility (>18 years of age, first diagnosis of breast cancer, unilateral breast surgery, axillary node dissection) at the Copenhagen Centre for Cancer and Health and from a waitlist to the Body & Cancer program (18, 19) at the University Hospitals Centre for Health Research between March 2015 and December 2016. Women with a known clinical diagnosis of lymphedema or who had conditions limiting resistance exercise of the upper-extremities (e.g., fibromyalgia, frozen shoulder) or who had participated in regular upper-extremity heavy resistance exercise (>1 / week) during the last month were excluded (Figure 1).

Those meeting eligibility were assessed for BCRL status by the first author (KB), after the third cycle of chemotherapy. BCRL was assessed using bioimpedance spectroscopy (BIS) (SFB7, Impedimed, Brisbane, Australia (20, 21)) and a visual inspection to detect differences in swelling between arms (Common Toxicity Criteria v3.0; (2)). Those with evidence of lymphedema according to standardised protocols for BIS (L-Dex > 10) or visual inspection were then referred to a lymphedema therapist for further assessment and were excluded from participating in the study.

**Exercise sessions**

All participants completed two familiarization sessions, followed by two experimental sessions (low- and heavy-load sessions) at exercise facilities located at the research centre.
All resistance exercise sessions lasted approximately 30 minutes including a 10-minute aerobic-based warm-up (rowing or cross-trainer) at low-moderate intensity. All sessions were supervised by the first author (KB) to ensure consistency of warm-up intensity and order of resistance exercises performed. None of the participants wore compression sleeves. During the first familiarization session, participants were introduced to four upper-extremity exercises consisting of the biceps curl performed with free weights, followed by the chest press, latissimus pull down and triceps extension using resistance exercise machines (Technogym®, Gamettola, Italy). Hereafter, a one RM strength test was performed in each exercise. During the second session, one set of 10-15 repetitions was performed, followed by a new one RM strength test. Subsequent resistance exercise prescription during the experimental sessions was based on these values. After completion of the familiarization sessions, resistance exercise load order for the experimental sessions was randomly allocated (that is, low- or heavy-load first) using a computer-generated random sequence (1:1 ratio). Women then participated in the experimental sessions which entailed the 10-minute aerobic-based warm-up, followed by the four resistance-based exercises. Resistance exercise load corresponded to 60-65% 1RM, (2 sets of 15-20 repetitions) for the low-load session and 85-90% 1RM (3 sets of 5-8 repetitions) for the heavy-load session. Participants were instructed to work to muscle fatigue (until they were unable to maintain appropriate technique) within the prescribed range and with rest periods of 60-90 seconds between sets.

The experimental sessions were consistently performed on the same day of the week and at the same time of day, with all outcomes assessed pre-, immediately post- (within 30 minutes) and 24- and 72-hours post-resistance exercise sessions. Blinded data collection was performed by medical technicians. Participants were instructed to maintain normal upper-body activities during the experimental period and to refrain from extraordinary activities involving the upper-extremities.
Primary Outcome

Extracellular fluid

BIS was used to directly measure and compare the impedance of extracellular fluid in the upper-extremities to electrical currents at a range of frequencies according to the manufacturer’s software (20). Using the principle of equipotentials, four single tab electrodes were placed in a tetrapolar arrangement and participants were measured in supine with arms and legs abducted from the trunk with palms facing down. To ensure accuracy, standard protocols from the manufacturer were followed (e.g. empty bladder, no excessive exercise or caffeine consumption within two hours). The ratio of impedance (at R0) between the at-risk and non-affected arm was calculated and converted into an L-Dex score taking arm dominance into account.

Secondary Outcomes

Inter-arm volume % difference

Measurements of arm volume were obtained using Dual energy x-ray absorptiometry (DXA) (Lunar Prodigy Advanced Scanner, GE Healthcare, Madison, WI). DXA measures tissue composition using a three-compartment model that is sensitive to changes in upper-extremity tissue composition (22). Using previously derived densities for fat (0.9 g/ml), lean mass (1.1g/ml) and bone mineral content (1.85 g/ml), DXA measurements were converted into estimated arm volumes. Lying supine on the scan-table with the arm separated from the trunk, each arm was scanned separately. If necessary, a Velcro band or the free arm was placed over the breast to ensure space between the arm and trunk. Small animal software (ENCORE version 14.10) was used to analyse the scans as described by Gjorup et al., (22). All scans were analysed by a clinical expert (PO) in DXA scan analysis. Inter-arm volume %
differences (at-risk arm minus unaffected arm/affected arm * 100) were then calculated for each participant.

Subjective assessment of BCRL symptoms

The severity of symptoms related to BCRL was monitored using a numeric rating scale (NRS). Participants rated their perceptions of swelling, heaviness, pain and tightness independently for each arm on a scale from 0 (no discomfort) to 10 (very severe discomfort)(21, 23).

Sample size calculation

Sample size calculation was based on changes in L-Dex scores between baseline and 72-hours post-resistance exercise sessions. From results of Cormie et al.(16), it was hypothesized that the standard deviation in the distribution of L-Dex scores would be 1.9 units. Based on clinical experience, for patients with BCRL, a change score of 2.0 L-Dex units would be considered clinically relevant. However, in the at-risk population no published normative change scores exist, nor does evidence regarding a threshold for a clinically significant acute change. A change in 2.0 L-Dex units was deemed too small in the at-risk population, based on the assumption that larger fluctuations would be seen within the normal range without clinical relevance. Therefore, a priori, we set the clinically relevant threshold for change as being 3.0 L-Dex units. Thus, if there was no difference between intensities, then 18 participants were needed to be 90% sure that the limits of a two one-sided 95% confidence interval (CI) would exclude a difference in means of more than 3.0 L-Dex units. To allow for drop-outs, 21 women were recruited.
**Statistical Analyses**

Descriptive statistics included counts (and percentages) for categorical values and mean ± standard deviation for normally distributed continuous variables, unless otherwise noted. Individual responses to resistance exercise loads were first assessed descriptively, including determination of the proportion that exceeded the predetermined clinically relevant threshold. Next, generalized estimating equations (GEE) (24) were used to evaluate the effects of time (pre-, post-, 24- and 72-hours post) and load (low-/heavy-load), and a time x load interaction. An exchangeable correlation structure was used to model the within-subject correlation of repeated measurements over time and across intensities.

To assess equivalence, the principle of confidence interval inclusion was used to calculate one-sided upper- and lower-95% confidence limits for all outcomes (25) (reported as two-sided 90% confidence limits). If the interval between the upper- and lower- confidence limits was within the predetermined equivalence margin, equivalence between resistance exercise intensities was declared. For the primary outcome, the margin of equivalence was set at ± 3.0 L-Dex units. Based on findings from Stout et al., (26) that volume increases of >3% from pre-operative measures were indicative of sub-clinical BCRL, an equivalence margin of ±3.0% was used for inter-arm volume % differences. For all subjective measures, inter-arm differences were calculated and an equivalence margin was set at ±1.0 points. This threshold was based on previous findings that suggest a 2 point or 30% change to be clinically meaningful for pain (23). Per-protocol principles were applied as this is considered the most conservative approach for determining equivalence (27). Analyses were conducted in R version 3.3.1 (28) using geepack 1.2.0.1 for GEE modelling (29).
Results

Participants

From the 216 women assessed for eligibility, 21 were eligible and consented to participate. Of these, three dropped out before initiation of the experimental exercise sessions due to time constraints and injury (Figure 1), one discontinued participation after the 24-hour post-exercise assessment in week one due to logistical considerations, and 17 (81%) completed all data collections.

Characteristics of the study population are presented in Table 1. Average age of participants was 45 years and mean body mass index (BMI) was 25.3 kg/m², with 11 (53%) participants presenting with a BMI ≥ 25.0. On average, women had 22 axillary lymph nodes removed during axillary node dissection and 62% of the participants had received a mastectomy. As per eligibility criteria, all participants received adjuvant taxane-based chemotherapy during the experimental sessions, however, the first ten participants received docetaxel, while the last 11 received paclitaxel, as standard chemotherapy changed midway through the study period.

Individual responses to resistance exercise sessions

For L-Dex and inter-arm volume outcomes, individual responses to resistance exercise sessions varied with no apparent group trend observed (Figure 2A, 2B). For BCRL symptoms we found that most participants were asymptomatic pre-exercise and remained asymptomatic throughout the subsequent data collections irrespective of loads lifted (Figure 2C-F).

Deviations from predetermined thresholds

When data were described according to clinically relevant changes from pre-exercise, sixteen women (89%) had experienced fluctuations in extracellular fluid beyond the predetermined threshold at one time point or more, ranging from -8.7 to 6.8 L-Dex units. Almost twice as many had fluctuations following the low-load session (n = 12 (71%)) compared to the high-
load session (n = 8 (44%)) (Table 2). Increases above the clinical threshold were observed for seven women (41%) following the low-load session, two of which had increased pre-post measures that remained elevated above the clinically meaningful threshold at 24- and 72-hours post-exercise (Figure 2A). None of these women had clinically meaningful increases in L-Dex following heavy-load resistance exercise. Four women (22%) had increases in L-Dex following the heavy-load session. Of these, two were observed immediately post- the heavy load session (one of these also showed an increase in inter-arm volume % difference; increases had dissipated in both cases by the 24-hours post follow-up), while the other two were observed at 72-hours post-exercise.

For inter-arm volume, four (24%) women experienced clinically meaningful fluctuations ranging from -4.1% to 4.6%. Three (18%) participants experienced increases after heavy-load exercise with two seen immediately post-exercise, and one at 24- hours post-exercise (Figure 2B). One participant (6%) experienced decreases after the low-load session immediately post-exercise (Table 2). None of these observations coincided with other outcome measures (except for the previously described L-Dex pre-post measure).

For BCRL symptoms, we found that 8 (44%) women responded with fluctuations ranging from -7 to 3 units. Specifically, six (33%) women reported decreases in symptoms, with reductions observed post-exercise and sustained over the subsequent time points, and were equally distributed between resistance exercise load conditions (Table 2). Increases in symptoms were reported by two (11%) women. One woman reported increases in pain and tightness at 24-hours post-heavy-load exercise (Figure 2D, 2E), while the other participant experienced increases in heaviness and swelling post-exercise after the heavy-load session (Figure 2C, 2F), and an increase in pain 24-hours after the low-load session (Figure 2D). None of these increases were sustained at the 72-hour post-session follow-up.
An overview of unadjusted means and standard deviations for all outcomes at each time point is presented in Table 3.

**L-Dex**

The estimated mean difference between resistance exercise loads and associated two-sided 90% CIs for L-Dex scores were contained within the predetermined equivalence margin of ±3.0 units immediately-, and 24-hours after resistance exercise indicating equivalence between intensities (-0.97(-2.09, 0.16) and -0.14(-1.63, 1.35), respectively) (Table 4). However, at 72-hours post-exercise, the lower CI exceeded -3.0 and equivalence between low- and heavy-load intensities could not be declared, favoring heavy-load resistance exercise.

**Inter-arm volume % difference**

Equivalence between intensities was observed at all time points for inter-arm volume % differences, as estimated mean differences and 90% CI were within the ±3.0 margin of equivalence (Table 4).

**BCRL symptoms**

Equivalence between resistance exercise intensities was found for all BCRL symptoms at all time points, as estimated mean differences and associated 90% CIs were within the equivalence margin of ±1.0 (Table 4).

No adverse events related to exercise (i.e. sprains or strains) were reported. However, two (11%) participants were advised to seek evaluation by a lymphedema therapist at the end of the study period as L-Dex scores had exceeded ten (Figure 2A). One participant had a pre-exercise L-Dex score of 7.9 in week one. Upon instigating the low-load session at week two, an L-Dex score of 11.7 was observed with subsequent measures decreasing. The other
participant initiated the heavy-load session at week one with a pre-exercise L-Dex score of 3.8, and subsequent measures fluctuating below 5.0 units. At week two, a pre-exercise L-Dex score of 9.5 was observed that increased to 12.7 post-exercise, with decreasing subsequent measures. Notably, this participant suffered from rapid weight gain due to generalized edema between weeks one and two that was effectively treated with diuretics. All other outcomes were within the predetermined clinical thresholds at all time points for both of these participants.

Discussion

The findings of this study support the hypothesis that acute changes in extracellular fluid, arm volume and BCRL related symptoms were similar irrespective of whether low- or heavy-load upper extremity resistance exercise was performed during adjuvant taxane-based chemotherapy in women with axillary lymph node dissection.

This is the first study to prospectively investigate lymphatic response to resistance exercise with heavy loads (85-90% 1RM, for 5-8 repetitions) in breast cancer survivors at risk of developing BCRL. Findings are consistent with observations from a cross-sectional study (n=149) that showed no association between participation in a multimodal exercise intervention including heavy-load resistance exercise during taxane-based chemotherapy and BCRL development (30). Further, our results are consistent with the findings of Cormie et al., demonstrating that participation in a bout of resistance exercise using 6-10RM loads did not acutely exacerbate swelling or BCRL symptoms in women with stable lymphedema (16). As such, this lends credibility to the results of the present study.

The equivalence design was considered the most appropriate for addressing our research question, and was formalized by defining equivalence margins for all outcomes. Equivalence margins ideally represent the maximum clinically acceptable difference that one is willing to accept in return for the secondary benefits of a new therapy (27), which in this study was
heavy-load resistance exercise. The value and impact of establishing equivalence depends on how well the equivalence margin can be justified in terms of relevant evidence and clinical judgement, where a narrower equivalence margin makes it more difficult to establish equivalence (27). The equivalence margin for the primary outcome was estimated as 3.0 L-Dex units. A priori, the threshold was chosen based on change scores considered to be clinically relevant for persons with BCRL, as no known normative change scores existed for persons without BCRL. However, new normative data recently published indicates that L-Dex scores fluctuate between 9-11 units (31). This is in line with our results, finding that sixteen (89%) participants experienced deviations from the predetermined L-Dex threshold. As such, while the equivalence margin for this outcome likely was unnecessarily narrow, this adds confidence to our findings. Furthermore, had we used broader L-Dex equivalence margins, the 90% CI at 72-hours post-exercise would have fallen within the margin of equivalence. Therefore, in light of these new normative data, it is likely that response to resistance exercise intensities were equivalent at all time points.

Equivalence was also established for all assessed BCRL symptoms at all time points, and although fluctuations beyond the predetermined thresholds were observed, it should be highlighted that the majority (82%) of these deviations indicated reductions in severity after resistance exercise with both intensities. This is relevant as symptoms can be the earliest indicator of an ensuing BCRL (32).

When interpreting the findings several limitations should be considered. In this study participants were excluded if they presented with evidence of BCRL according to standardised protocols for BIS (L-Dex >10) or visual inspection. It is however possible that these women were experiencing transient increases in extracellular fluid, either as a consequence of surgery or in response to chemotherapy (33), and/or may have been at greatest risk of developing BCRL. As such, these women may have been more likely than those
included in the study to demonstrate changes in extracellular fluid, and by excluding them it may have been easier to find equivalence between loads. Moreover, activities undertaken by participants within the 3 days following the bout of low- or high-load resistance may have influenced data collected at 24- or 72-hours post-exercise session. However, participants were advised to maintain normal activities throughout the study period, and efforts were made to standardize treatment burden by placing exercise bouts and consecutive data collections between chemotherapy cycles.

Strengths of this study include that all participants had received axillary node dissection, considered the largest single risk factor for developing BCRL, lending generalizability to breast cancer survivors at BCRL risk. Further, as all exercise sessions took place during the taxane-based cycles of chemotherapy the results extend to acute bouts of low- or high-load resistance type activities during taxane-based treatment. Finally, validated objective measurement methods sensitive to changes in extracellular fluid were used, and all data collection and analyses were blinded to resistance load lending credibility to the results.

Findings from this study are clinically relevant for a number of reasons. First, the safety of resistance exercise in regard to BCRL risk has previously been established based on exercise prescription using low- to moderate loads. For example, some resistance exercise programs started with little or no weight and slowly progressed with the smallest weight increment possible until loads lifted corresponded to weights that successfully could be lifted a minimum of 15 repetitions (12) or within a range of 10-12 repetitions (34), while others utilized loads corresponding to 60-80% 1RM at 8-12 repetitions (10, 13). As such, this work adds new information, providing initial evidence that resistance exercise prescription also can include heavier loads, specifically corresponding to 85-90% 1RM at 5-8 repetitions.

Second, a considerable rationale exists for participating in resistance exercise during chemotherapy as it has been found to elicit increases in muscle strength (10, 35, 36), lean
body mass (10) and self-esteem (10) as well as attenuating fatigue and quality of life (36). Moreover, it has been hypothesized that resistance exercise reduces taxane-related edema (37) through the effects of the muscle pump, and it is plausible that participation in heavy-load resistance exercise may instigate more effective lymphatic function change than low-load resistance exercise, and in doing so, potentially have a greater effect on reducing BCRL risk. As such, results from this study provide the necessary platform for future studies to explore whether additional benefits can be gained from repeated bouts of heavy-load resistance exercise during adjuvant taxane-based chemotherapy. Finally, breast cancer survivors commonly receive risk reduction advice cautioning against heavy lifting (24). This study however, found no evidence to suggest that participation in activities of daily living that include intermittent heavy-load lifting need be avoided. Further, a varied response to resistance exercise was observed for both intensities. This highlights the importance of an individualized approach to resistance exercise prescribed in accordance with signs and symptoms of BCRL, as well as an individualized approach to the risk reduction advice given to breast cancer survivors.

In conclusion, the acute lymphatic response was similar irrespective of whether low- or heavy-load resistance exercise was undertaken in women with axillary node dissection at risk for BCRL during adjuvant taxane-based chemotherapy. Future research needs to now investigate the longer term response to regular heavy-load resistance exercise. In the interim, these findings challenge existing risk reduction advice concerning avoidance of heavy lifting, and suggest that breast cancer survivors should be encouraged to participate in normal daily activities and to act accordingly if changes in sensations or BCRL symptoms are observed.
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Conflict of Interest

The authors declare no conflict of interest. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation and do not constitute endorsement by the ACSM.

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Table 1. Baseline characteristics of participants (n=21)

| Variables                           | Mean ± SD / Median (range) |
|-------------------------------------|----------------------------|
| Age (years)                         | 45.3 ± 9.2 / 46 (23-60)    |
| BMI (kg/m²)                         | 25.3 ± 4.7                 |
| Cancer stage n (%)                  |                            |
| Ⅱ                                   | 15 (71)                    |
| Ⅲ                                   | 6 (29)                     |
| Tumor size (mm)                     | 21.5 ± 12.9 / 18 (7-62)    |
| Breast surgery n (%)                |                            |
| Lumpectomy                          | 8 (38)                     |
| Mastectomy                          | 13 (62)                    |
| Surgery on dominant side n (%)      | 11 (52)                    |
| Axillary lymph nodes removed        | 21.7 ± 7.8                 |
| Metastatic lymph nodesᵃ             | 5.7 ± 7 / 2 (1-25)         |
| Seroma drainage n (%)               | 5.5 ± 3.4                  |
| Chemotherapy n (%)                  |                            |
| 3-wkly CE x 3 -> 3 wkly docetaxel x 3 | 10 (48)                    |
| 3-wkly CE x 3 -> 1 wkly paclitaxel x 9 | 11 (52)                    |
| Axillary webbing at screening n (%) | 8 (38)                     |
| L-Dex at screening                  | -0.08 ± 2.23               |

Abbreviations: CE (cyclophosphamide and epirubicin)

ᵃ) micro- and macrometastases
Table 2. Number (%) of participants exceeding equivalence margin from pre-exercise to immediately post-exercise and 24-and 72-hours post-exercise for all outcomes (n=17)

|                      | Δ Pre-Post | Δ Pre-24-hrs Post | Δ Pre-72-hrs Post |
|----------------------|------------|-------------------|-------------------|
| **L-Dex**            |            |                   |                   |
| Heavy load           | 2↑(11%)\(^a\) | 2↓(11%)\(^a\)    | 2↑(12%), 3↓(18%)  |
| Low load             | 4↑(24%), 1↓(6%) | 3↑(18%), 4↓(24%) | 4↑(24%), 4↓(24%)  |
| **% Inter-arm diff.**|            |                   |                   |
| Heavy load           | 2↑(12%)    | 1↑(6%)            | 1↑(6%)            |
| Low load             | 1↓(6%)     | 0                 | 1↓(6%)            |
| **Pain**             |            |                   |                   |
| Heavy load           | 2↓(11%)\(^a\) | 1↑(6%), 2↓(12%)  | 2↓(12%)           |
| Low load             | 2↓(12%)    | 1↑(6%), 1↓(6%)    | 1↓(6%)            |
| **Heaviness**        |            |                   |                   |
| Heavy load           | 1↑(6%), 1↓(6%)\(^a\) | 1↓(6%)  | 2↓(12%)           |
| Low load             | 2↓(12%)    | 2↓(12%)           | 2↓(12%)           |
| **Tightness**        |            |                   |                   |
| Heavy load           | 0\(^a\)    | 1↑(6%), 1↓(6%)    | 1↓(6%)            |
| Low load             | 1↓(6%)     | 1↓(6%)            | 2↓(12%)           |
| **Swelling**         |            |                   |                   |
| Heavy load           | 1↑(6%), 1↓(6%)\(^a\) | 1↓(6%)  | 1↓(6%)            |
| Low load             | 0          | 1↓(24%)           | 2↓(12%)           |

\(^a\)=higher than equivalence margin, \(\_\)=lower than equivalence margin. *) n =18
Table 3. Extent of swelling and breast cancer-related lymphedema symptoms for all outcomes (n= 17)

|                  | Pre-exercise | Post- exercise | 24-hrs Post-exercise | 72-hrs Post-exercise |
|------------------|--------------|----------------|----------------------|----------------------|
| L-Dex score      |              |                |                      |                      |
| Heavy load       | 1.7 ± 3.3\(^a\) | 1.9 ± 3.4\(^a\) | 1.0 ± 2.6\(^a\)      | 0.8 ± 3.9            |
| Low load         | 0.8 ± 5.0    | 1.9 ± 5.1      | 0.2 ± 4.4            | 0.7 ± 3.6            |
| % Inter-arm diff.|              |                |                      |                      |
| Heavy load       | 0.5 ± 4.4    | 1.0 ± 4.0      | 1.4 ± 4.2            | 1.1 ± 4.3            |
| Low load         | 1.3 ± 4.1    | 1.6 ± 4.8      | 1.0 ± 4.2            | 0.8 ± 4.4            |
| Pain             |              |                |                      |                      |
| Heavy load       | 0 (-1, 6)\(^a\) | 0 (-1, 2)\(^a\) | 0 (-1, 3)            | 0 (0, 2)             |
| Low load         | 0 (0, 5)     | 0 (-1, 1)      | 0 (-1, 2)            | 0 (-1, 4)            |
| Heaviness        |              |                |                      |                      |
| Heavy load       | 0 (0, 2)\(^a\) | 0 (0, 4)\(^a\) | 0 (0, 2)             | 0 (0, 2)             |
| Low load         | 0 (0, 5)     | 0 (0, 3)       | 0 (0, 2)             | 0 (0, 2)             |
| Tightness        |              |                |                      |                      |
| Heavy load       | 0 (0, 6)\(^a\) | 0 (0, 5)\(^a\) | 0 (0, 3)             | 0 (0, 3)             |
| Low load         | 0 (0, 7)     | 0 (0, 8)       | 0 (0, 8)             | 0 (0, 3)             |
| Swelling         |              |                |                      |                      |
| Heavy load       | 0 (0, 2)\(^a\) | 0 (0, 3)\(^a\) | 0 (0, 2)             | 0 (0, 2)             |
| Low load         | 0 (0, 2)     | 0 (-1, 3)      | 0 (0, 2)             | 0 (0, 2)             |

\(^a\) n = 18

L-Dex and inter-arm volume presented as mean ± SD
BCRL related symptoms presented as median (range)

Table 4. Equivalence between resistance exercise loads for all outcomes (n=17)

|                              | Estimated mean difference $^b$ | Equivalence 90% CI     |
|------------------------------|--------------------------------|------------------------|
| **L-Dex (±3.0)$^a$**         |                                 |                        |
| Post-exercise                | -0.97                           | -2.09 to 0.16          |
| 24-hrs Post-exercise         | -0.14                           | -1.63 to 1.35          |
| 72-hrs Post-exercise         | -1.00                           | **-3.17 to 1.17$^a$**  |
| **Inter-arm volume % difference (±3.0)$^a$** |                   |                        |
| Post-exercise                | 0.21                            | -0.89 to 1.31          |
| 24-hrs Post-exercise         | 1.09                            | 0.41 to 1.78           |
| 72-hrs Post-exercise         | 0.96                            | -0.09 to 2.02          |
| **Inter-arm difference Pain (±1.0)$^a$** |                   |                        |
| Post-exercise                | 0                               | -0.43 to 0.43          |
| 24-hrs Post-exercise         | -0.06                           | -0.58 to 0.46          |
| 72-hrs Post-exercise         | -0.06                           | -0.61 to 0.49          |
| **Inter-arm difference Heaviness (±1.0)$^a$** |                   |                        |
| Post-exercise                | 0.24                            | -0.23 to 0.70          |
| 24-hrs Post-exercise         | 0.18                            | -0.32 to 0.67          |
| 72-hrs Post-exercise         | 0.24                            | -0.38 to 0.85          |
| **Inter-arm difference Tightness (±1.0)$^a$** |                   |                        |
| Post-exercise                | -0.06                           | -0.45 to 0.34          |
| 24-hrs Post-exercise         | -0.11                           | -0.50 to 0.27          |
| 72-hrs Post-exercise         | 0.20                            | -0.37 to 0.77          |
| **Inter-arm difference Swelling (±1.0)$^a$** |                   |                        |
| Post-exercise                | 0                               | -0.33 to 0.33          |
| 24-hrs Post-exercise         | 0                               | -0.33 to 0.33          |
72-hrs Post-exercise 0.06 -0.42 to 0.54

a Equivalence margin. b Estimated mean difference calculated using a generalized estimating equations model with heavy-load as comparator (heavy minus low). c Equivalence not demonstrated

Captions for figures

Figure 1. Participant flow through resistance exercise and data collection sessions

Footnote for Figure 1.

Abbreviations: sentinel node biopsy (SNB), resistance exercise (RE)

Figure 2. Individual response related to low- and heavy-load resistance exercise sessions for all outcomes (n=17)

Footnote for Figure 2.

(n=18) Heavy-load L-Dex pre-, post-, 24-hours; (n=18) Heavy-load breast cancer-related lymphedema symptoms pre- and post- exercise

In sub-plots C-F (n=) refers to the number of participants with a symptom score of 0 at all time points.