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PhD thesis

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Heavy resistance exercise in breast cancer survivors at risk for lymphedema

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The University Hospitals Centre for Health Research (UCSF), University of Copenhagen, Rigshospitalet

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List of Manuscripts

This thesis is based on the following manuscripts:

Paper I
Bloomquist K, Karlsmark T, Christensen KB, Adamsen L. Heavy resistance training and lymphedema: Prevalence of breast cancer-related lymphedema in participants of an exercise intervention utilizing heavy load resistance training. Acta Oncol. 2014;53(2):215-25

Paper II
Bloomquist K, Hayes S, Adamsen L, Møller T, Christensen KB, Ejlertsen B, Oturai P. A randomized cross-over trial to detect differences in arm volume after low- and heavy-load resistance exercise among patients receiving adjuvant chemotherapy for breast cancer at risk for arm lymphedema: study protocol. BMC Cancer. 2016;16:517

Paper III
Bloomquist K, Oturai P, Steele M, Adamsen L, Møller T, Christensen KB, Ejlertsen B**,** Hayes S. Heavy-load lifting: Acute response in breast cancer survivors at risk for lymphedema. Med Sci Sports Exerc. 2018; 50(2):187-95

Paper IV
Bloomquist K, Adamsen L, Hayes S, Lillelund C, Andersen C, Christensen KB, Oturai P, Ejlertsen B, Tuxen MK, Møller T. Heavy-load resistance exercise in pre-diagnosis physically inactive women at risk of breast cancer-related lymphedema during adjuvant chemotherapy: a randomized trial. Manuscript prepared for submission to Acta Oncologica.

Abbreviations

ALND Axillary lymph node dissection

SLNB Sentinel lymph node biopsy

BCRL Breast cancer-related arm lymphedema

RH Rigshospitalet

HE Herlev Hospital

BIS Bioimpedance spectroscopy

DXA Dual-energy X-ray absorptiometry

EORTC QLQ-BR23 European Organization for Research and Treatment of Cancer quality of life questionnaire breast-23

NRS Numeric rating scale

RM Repetition maximum

WHO World Health Organization

ICC Intraclass correlation coefficient

SE Standard error of the mean

SD Standard deviation

IQR Interquartile range

ITT Intention- to- treat

GEE Generalized estimating equation

CDT Complete decongestive therapy

Summary

Background

Despite a paucity of evidence, breast cancer survivors have historically been advised to refrain from a number of activities including lifting heavy objects and resistance exercise in an effort to reduce the risk of breast cancer-related lymphedema. However, clinical trials carried out over the last two decades have consistently demonstrated that resistance exercise can be conducted without increased risk of lymphedema. Nonetheless, as previous work utilized exercise prescription with low- to moderate loads, uncertainty exists as to the upper-limits of resistance exercise loading, and breast cancer survivors at risk for lymphedema continue to be encouraged to avoid heavy-lifting. Yet exercise science literature indicates that a dose-response relationship exists between loads lifted and gains in muscular strength and function, of potential benefit for breast cancer survivors receiving chemotherapy. Therefore, the purpose of this thesis was to explore the safety of heavy-load resistance exercise among women at risk of developing breast cancer-related lymphedema while undergoing adjuvant chemotherapy.

Material and methods

Three studies were undertaken. **Study 1** This was a cross-sectional trial including women treated with chemotherapy for breast cancer (n = 149) who had participated in the *Body & Cancer* program between January 2010 and December 2011. The *Body & Cancer* program is a six-week multimodal exercise program including heavy-load resistance exercise. The primary outcome, self-reported diagnosis of breast cancer-related lymphedema, was obtained from a structured telephone interview carried out on average 14 months after participation in the exercise program. **Study 2** This was a randomized cross-over trial including women receiving adjuvant taxane-based chemotherapy for breast cancer who had undergone axillary lymph node dissection (n =21). Participants were randomly assigned to participate in a low- (two sets of 15–20 repetition maximum) and heavy-load (three sets of 5–8 repetition maximum) upper extremity resistance exercise session first, with a one week wash-out period between sessions. Swelling was determined by bioimpedance spectroscopy (BIS) and dual energy x-ray absorptiometry (DXA), and breast cancer-related lymphedema symptoms (heaviness, swelling, pain, tightness) were reported using a numeric rating scale (NRS) (0-10). Outcomes were assessed immediately pre- and post-exercise, 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. **Study 3** This was a parallel group, randomized trial. Screened pre-

diagnosis physically inactive women receiving adjuvant chemotherapy for breast cancer (n=153) participated in 12 weeks of 1) HIGH: supervised multimodal exercise including heavy-load resistance exercise (85-90% 1 repetition maximum (RM), three sets of 5-8 repetitions) or 2) LOW: walking supported by pedometer and one-on-one consultations. Outcomes were assessed at baseline, 12 and 39 weeks and included: swelling (BIS, L-Dex scores; DXA, inter-arm volume % difference; self-report, n(%)), lymphedema symptoms (NRS, 0-10), upper extremity strength (1 RM), and self-reported breast cancer specific function and symptoms (EORTC QLQ-BR23). Linear mixed models with a heterogeneous autoregressive (1) covariance structure were used to evaluate changes over time between groups. Equivalence was hypothesized for lymphedema outcomes, and was determined using the principle of confidence interval inclusion.

Results

Study 1 On average, 14 months (range 4-26 months) post-participation in *Body & Cancer*, 27.5% reported having been diagnosed with lymphedema by a clinician. When restricted to women with axillary node dissection, 44.4% reported a clinician diagnosis of BCRL. No statistically significant association between change in muscle strength during *Body & Cancer* and the development of lymphedema was observed, nor was self-reported participation in resistance exercise with heavy loads up to three months post-intervention. **Study 2** The acute response to resistance exercise with low and heavy loads was equivalent, with the exception of extracellular fluid at 72-hours post-exercise with less swelling following heavy-loads. **Study 3** Post-intervention equivalence between groups was found for L-Dex and self-reported heaviness, tightness and swelling. Non-equivalence was determined for inter-arm volume and pain, as deviations beyond equivalence margins indicated reductions associated with participation in the HIGH intervention for these two outcomes. Further, greater increases ($p < 0.05$) in upper extremity strength were seen in the HIGH group compared to LOW at all assessments, and clinically relevant within group reductions in breast and arm symptoms were observed in the HIGH group at 6 and 12 weeks.

Conclusion

The findings presented in this thesis indicate that breast cancer survivors at risk of breast cancer-related lymphedema, can participate in and benefit from heavy-load resistance exercise while receiving taxane-based chemotherapy, without an increased risk of exacerbating the development of lymphedema.

Perspectives

Previous clinical trials using low to moderate resistance exercise loads have found gains in muscle strength while mitigating adverse changes in physical components of quality of life, including fatigue in this population, and it has been hypothesized that resistance exercise reduces taxane-related edema. However, due to the dose-response relationship that exists between loads lifted and gains in muscular strength and function it is feasible that superior benefits can be gained with resistance exercise with heavier loads. Further it is plausible that participation in heavy-load resistance exercise may instigate more effective lymphatic function than low-load resistance exercise, and in doing so, potentially have a greater effect on reducing lymphedema risk. Therefore, as this thesis indicates that resistance exercise safely can be performed with heavy loads, future studies should carry out a head to head comparison between resistance exercise protocols to establish optimal resistance exercise prescription for breast cancer survivors.

Danish summary (Dansk resume')

Baggrund

Trods manglende evidens er brystkræftoverlevere blevet frarådet en række fysisk krævende aktiviteter, bl.a. løft af tunge genstande og styrketræning, i et forsøg på at reducere risikoen for brystkræftrelateret lymfødem. Igennem de sidste to årtier har kliniske forsøg imidlertid vist, at styrketræning kan udføres uden øget risiko for lymfødem blandt kvinder diagnosticeret med brystkæft. Der er dog fortsat uklarhed om de øvre grænser for vægtbelastningen ved styrketræning, da tidligere forsøg har anvendt lav til moderat vægt i de gennemførte interventioner. Den idrætsfysiologiske litteratur indikerer imidlertid, at der eksisterer et dosis-responsforhold mellem vægtbelastninger og fremgang i forhold til muskelstyrke og –funktion, af potentiel positiv betydning for brystkræftoverlevere, der modtager kemoterapi. Formålet med denne afhandling var derfor at undersøge, hvor vidt det er sikkert at styrketræne med tung belastning for kvinder, der er i risiko for at udvikle brystkræftrelateret lymfødem, under adjuverende kemoterapi.

Metode

Der blev gennemført tre studier. **Studie 1** var et tværsnitsstudie, som inkluderede kvinder behandlet for brystkræft med kemoterapi (n = 149), og som parallelt hertil deltog i *Krop & Kræft* i perioden januar 2010 til december 2011. *Krop & Kræft* er et seks-ugers multimodalt træningsprogram, som blandt andet indeholder tung styrketræning. Det primære effektmål var selvrapporteret brystkræftrelateret lymfødem. Data blev indsamlet med et struktureret telefoninterview gennemført i gennemsnit 14 måneder efter afsluttet deltagelse i *Krop & Kræft*. **Studie 2** var et randomiseret cross-over studie, som inkluderede kvinder med aksil-dissektion, der modtog adjuverende taxanbaseret kemoterapi for brystkræft (n=21). Deltagerne blev tilfældigt allokeret til at deltage i en styrketræningssession med lav (to sæt af 15-20 gentagelser) henholdsvis tung (tre sæt af 5-8 gentagelser) vægtbelastning, med en uges "wash-out" periode mellem de to styrketræningssessioner. Ekstracellulær væske i armene blev målt med bioimpedansspektroskopi (BIS) og dual X-ray absorptiometri (DXA), og symptomer relateret til brystkræftrelateret lymfødem (fornemmelse af stramhed, tyngde, hævelse, smerte) blev registreret med en numerisk rating skala (NRS) (0-10). Målingerne blev foretaget umiddelbart før og efter styrketræningssessionerne samt 24 og 72 timer efter. Til at evaluere ændringer over tid mellem grupperne blev generalized estimating equations anvendt. Ækvivalens mellem styrketræningssessionerne (lav / tung) blev bestemt ved anvendelse af confidence interval inclusion. **Studie 3** var et parallel-gruppe, randomiseret forsøg. Kvinder, der inden deres brystkræft diagnose var defineret som fysisk inaktiv

(screenet) og som modtog adjuverende kemoterapi (n = 153) deltog 12 uger i: 1) HIGH: Superviseret multimodalt træningsprogram med tung styrketræning (85-90% 1 repetitions maksimum (RM), tre sæt 5-8 gentagelser) eller 2) LOW: Gangtræningsintervention med skridttæller og face-to-face rådgivning. Data blev indsamlet ved baseline, samt efter 12 og 39 uger og inkluderede: hævelse af armene (BIS, L-Dex-score; DXA, inter-arm volumen % forskel; selvrapporteret hævelse, n (%)), lymfødem-symptomer (NRS, 0-10), muskelstyrke (1 RM) samt selvrapporteret brystkræftspecifik funktion og symptomer (EORTC QLQ-BR23). Linear mixed models med en heterogen autoregressiv (1) kovarians struktur blev anvendt til at evaluere ændringer over tid mellem grupperne. Ækvivalens blev bestemt ved anvendelse af confidence interval inclusion for effektmål relateret til lymfødem

.

Resultater

Studie 1 I gennemsnit 14 måneder efter deltagelse i *Krop & Kræft* (interval 4-26 måneder) rapporterede 27,5% at de var blevet diagnosticeret med lymfødem (lymfødemterapeut eller læge). Ved sub-analyse af kvinder med aksil-dissektion rapporterede 44,4% at være blevet diagnosticeret med lymfødem. Der blev ikke observeret en statistisk signifikant association mellem ændring i muskelstyrke og udvikling af lymfødem, hverken efter deltagelse i *Krop & Kræft* eller efter selvrapporteret deltagelse i styrketræning med tung belastning op til tre måneder efter deltagelse. **Studie 2** Det akutte respons til styrketræning med lav og tung vægtbelastning var ækvivalent, med undtagelse af ekstracellulær væske ved 72 timers opfølgning, som indikerede mindre væske efter tung vægtbelastning. **Studie 3** Post-intervention ækvivalens mellem grupper blev fundet for L-Dex og selvrapporterede symptomer (tyngde, stramhed og hævelse). For inter-arm volumen og smerte kunne ækvivalens ikke demonstreres, men indikerede større reduktioner associeret til deltagelse i HIGH interventionen sammenlignet med LOW for disse to effektmål. Analyser af muskelstyrke viste, at HIGH gruppen øgede muskelstyrken i overekstremiteterne ($p < 0,05$) sammenlignet med LOW. Desuden blev bryst- og arm-symptomer reduceret ved 6 og 12 uger i HIGH gruppen, uden signifikant forskel mellem grupperne.

Konklusion

Resultaterne fra denne afhandling indikerer, at kvinder med brystkræft i risiko for at udvikle brystkræftrelateret lymfødem kan deltage i og profitere af tung styrketræning under behandling med taxanbaseret kemoterapi uden øget risiko for udvikling af lymfødem.

Perspektivering

Set i lyset af det dosis-responsforhold der eksisterer mellem belastning og fremgang i muskelstyrke og -funktion, kan der antageligvis opnås større fordele ved styrketræning med tungere vægte. Det er ligeledes plausibelt at deltagelse i styrketræning med tung belastning potentielt kan medføre en mere effektiv lymfatisk funktion end styrketræning med lav belastning og dermed have en positiv effekt på risikoen for at udvikle lymfødem. Da denne afhandling indikerer, at styrketræning med tung belastning er sikker at udføre, bør fremtidige undersøgelser derfor sammenligne styrketræningsprotokoller for at klarlægge den optimale styrketræningsdosering for brystkræftoverlevere i risiko for at udvikle lymfødem.

Introduction

Breast cancer-related lymphedema (BCRL) is a feared adverse effect of breast cancer treatment (2, 3) affecting approximately one in five breast cancer survivors (4). At present, though evidence suggests a predisposition for developing BCRL (5, 6) ability to accurately predict who will develop BCRL is limited.

Historically, breast cancer survivors have been advised to refrain from a number of activities including lifting heavy objects and resistance exercise in an effort to avoid the development of BCRL (7-9). These recommendations were based on anecdotal concerns, that heavy-lifting would increase lymph production, which would then overload an impaired lymph system and thus trigger the development of BCRL (9).

During the last two decades, numerous studies have evaluated and consistently demonstrated that resistance exercise is beneficial to strength and outcomes of importance for quality of life, and can be conducted without increased risk of BCRL after treatment for breast cancer (7, 8, 10, 11). However, as previous work utilized exercise prescription with low- to moderate loads, breast cancer survivors continue to be encouraged to avoid heavy-lifting. Further, there is a paucity of evidence confirming upper-limits of resistance exercise loading for women at risk of BCRL.

At present, two prospective studies have evaluated the safety of resistance exercise with heavy loads in women with clinically stable BCRL who had been diagnosed with breast cancer at least a year before study inclusion (12, 13). Both studies found that the extent of arm swelling and associated BCRL symptoms remained stable immediately post-, 24- and 72-hours after one bout of resistance exercise (12), and after twelve-weeks of regular resistance exercise, irrespective of whether low- or heavy-loads were lifted (13). While these findings provide meaningful information for breast cancer survivors with BCRL who have completed chemotherapy and radiotherapy, they cannot be generalized to the at-risk population undergoing chemotherapy.

This thesis focuses therefore on the safety of resistance exercise with heavy loads during adjuvant chemotherapy in breast cancer survivors at risk for lymphedema.

Background

Breast cancer

Breast cancer is the second most common cancer in the world after lung cancer, and is the most frequent cancer among women with an estimated 1.67 million new cases diagnosed in 2012, representing 25% of all cancers in women (14). In 2015, 4,767 women were diagnosed with breast cancer in Denmark, corresponding to 24.8% of all cancers. Comparatively, just 38 men were diagnosed with breast cancer in the same period (15). Survival rates vary worldwide, but in general rates have improved especially in countries where breast cancer is detected early and there is access to improved treatment strategies (14). Treatment modalities for breast cancer include surgery, chemotherapy, radiotherapy as well as targeted and hormonal therapy, with subtype and stage of breast cancer determining treatment strategy (16). While these treatment modalities are increasingly effective in terms of survival, they are also associated with a range of treatment specific adverse acute and late side effects including fatigue, pain and lymphedema that negatively impact the quality of life of breast cancer survivors (17-19). In Denmark, breast cancer prevalence has increased over the past decades (Figure 1) and five year survival rates from 2014 were estimated at 86% (1). As such, with more people surviving breast cancer, adverse late effects, are a growing public health concern.

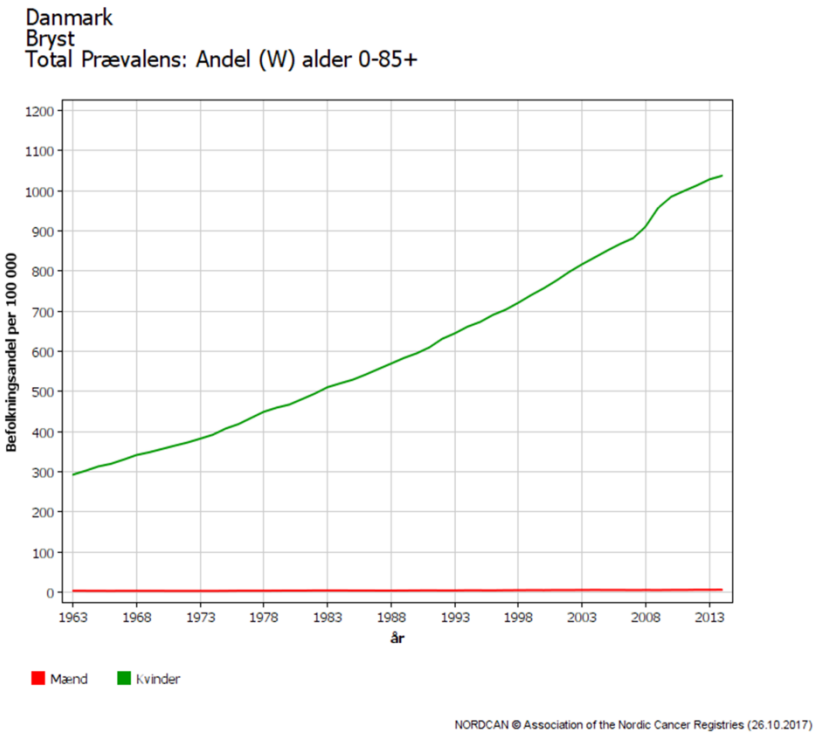


Figure 1. Age-standardized breast cancer prevalence in men and women in Denmark (1990-2014) Adapted from the NORDCAN database, ancr.nu (1).

Ramifications of breast cancer-related lymphedema

BCRL is initially characterized by accumulation of excess protein-rich extracellular fluid resulting in regional swelling of the hand, arm, breast or torso on the surgical side as a consequence of disruption or damage to the axillary lymphatic system due to breast cancer treatment (9, 20-23). This incurable condition is negatively associated with significant physical, functional, social and psychological burden (24-27) impacting daily living, work and quality of life (24, 28-30). BCRL and efforts to reduce the risk of BCRL impose limitations on the lives of breast cancer survivors, with some women reporting more distress related to the threat of BCRL than with breast cancer itself (3). BCRL is a persistent reminder of breast cancer and the physical and functional manifestations include decreased mobility, skin changes and visible swelling as well as sensory disturbances, discomfort and pain (3, 22). Considerable psychosocial effects are also associated with BCRL including negative perceptions of self-image, appearance and sexuality (25, 26). Further, breast cancer survivors with lymphedema are faced with extra financial burden due to the cost of lymphedema treatment (31) as well as the economic ramifications of reducing work hours, changing work places or exiting the workforce which can be a necessity especially for those with more severe lymphedema (25, 28, 32).

The lymphatic system and breast cancer

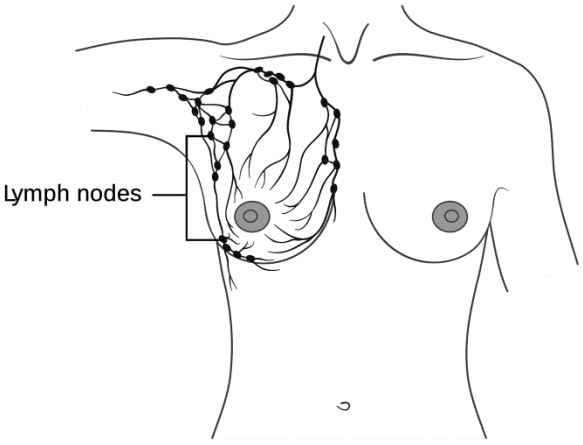
The lymphatics are a one-way transport system that carries fluid and plasma proteins that have leaked from tissues into the interstitial space, back into the cardiovascular system (33). The lymphatic system supports the cardiovascular and immune systems and has three major functions including maintenance of fluid balance (homeostasis), fat absorption by the intestinal lymphatics, and immunological defense (21). The lymphatic system aids in the removal of excess fat, water, cellular debris and foreign material from body tissues, as well as larger proteins by way of lymph fluid transport. Lymph fluid is derived from interstitial fluid upon entry into lymph capillaries that are found near the arteriovenous anastomoses that serve all systemic tissues (9, 21). Formation and propulsion of lymph through lymphatic vessels is primarily dependent on extrinsic mechanisms such as skeletal muscle contraction (muscle pump) and pressure changes due to respiration and arterial pressure pulsations (33). However, once lymph fluid moves beyond the lymphatic capillaries, movement of lymph is dependent on contraction of smooth muscle that line the contractile lymphatic vessels driven by pacemaker cells as well as one-way valves that help prevent backflow (lymphatic pump) (21, 33). The lymphatic system is comprised of a superficial layer (drainage for skin and subcutaneous tissues) and a deep layer (drainage for e.g. muscles, joints and

bones) that drain into site specific lymph nodes that filter foreign particles, process antigens and produce appropriate immune response (5). As such, bacteria, proteins and other materials from a specific body part are delivered to a specific lymph node that serves that tissue. Consequently, if lymph nodes are damaged or removed, the immune response is interrupted as well as the ability to remove excess fluid from the tissue supported by the specific lymph node and explains, in part, potential ensuing edema of that region (9, 21).

The lymphatic vessels that transport lymph from the breast to the axillary lymph nodes are the preferential route for the metastatic spread of breast cancer, with status of the axillary lymph nodes a determinant of breast cancer staging and subsequent treatment (6, 21, 34). The sentinel node (or nodes) is typically the first lymph node to which cancer cells spread from a primary tumor, and histopathological examination by means of a sentinel lymph node biopsy (SLNB) determines whether cancer cells are present. A negative SLNB suggests that cancer has not spread to nearby lymph nodes and no further surgery is warranted. However, in Denmark if the biopsy contains macrometastasis or micrometastasis/isolated tumorcells in 3 or more sentinel nodes, subsequent removal of the axillary lymph nodes, usually levels 1 and 2, known as axillary lymph node dissection (ALND) is performed (35). Consequently, as more lymph nodes are removed, compared to SLNB, ALND is associated with considerably more morbidity and an increased risk of developing BCRL(4). However, not all breast cancer survivors with ALND develop lymphedema, and cases of grade 1or higher lymphedema are seen in breast cancer survivors with only SLNB, irrespective of axillary radiotherapy. At present, though a predisposition for BCRL likely exists, the complex pathophysiology of BCRL remains unclear rendering limited ability to predict who will develop this condition (6, 21).

Epidemiology of BCRL

The incidence of BCRL is difficult to quantify with factors such as type of study design, time since- and type of breast cancer treatment and method of lymphedema assessment affecting incidence rates (4). In Denmark, an incidence of 860 to 1260 new cases per year has been estimated (31) and a nationwide study by Gartner et al. (36) found point prevalence of self-reported BCRL symptoms corresponding to 37%



in 2008 and 31% in 2012, in women who had received treatment for unilateral breast cancer in 2005 and 2006. To date, the best estimate of BCRL incidence is based on a systematic review and meta-analysis by Disipio et al., 2013, which found a cumulative incidence rate of 16.6% (95% CI 13.6 – 20.2), based on data from 72 studies (4). However, when restricted to 30 prospective cohort studies, the incidence estimate was 21.4% (14.9- 29.8). In breast cancer survivors with ALND, incident BCRL (18 studies) was approximately four times higher (19.9%, 13.5 – 28.2) as compared to SLNB (5.6%, 6-1 – 7.9%). Though risk of BCRL is lifelong, incident BCRL increased up to two years post- surgery (18.9%, 14.2 - 24.7) based on 24 studies, after which time, incidence decreased (15.6 %, 10.0 – 23.5). This is in line with findings from a prospective study by Norman et al. (37) that showed 80% of the women that developed BCRL, did so within 2 years post-surgery.

Findings from the aforementioned systematic review by Disipio and colleagues also collated risk factor findings from 29 studies and found that there was 'strong' evidence demonstrating the following characteristics increased risk of lymphedema: ALND / greater number of lymph nodes removed, more extensive breast surgery and higher body mass index (BMI) ≥ 25. Further, there was 'moderate' evidence suggesting that higher number of metastatic nodes, anti-cancer treatment with chemotherapy and radiotherapy as well as physical inactivity also increased risk of BCRL (4).

BCRL diagnosis and clinical progression

Though classification criteria for defining and grading BCRL severity have been developed including a staging system by the International Society of Lymphology and Common Toxicity Criteria from the National Cancer Institute (Table 1) (20, 22, 38), no universal definition of BCRL exists. Further, no gold standard assessment of BCRL exists as current measurement methods including circumferential measurements, self-report of symptoms, water displacement, perometry and bioimpedance spectroscopy have advantages and disadvantages, as well as varying diagnostic thresholds applied (4, 39). The inability to identify a gold standard definition and measure of lymphedema is in part due to several challenges inherent to BCRL presentation. First, many breast cancer survivors experience transient swelling related to surgery and taxane-based chemotherapy in the first year after surgery that resolves by itself (40). However, as there is no accepted time line for defining transient versus chronic lymphedema, some transient cases are mistakenly diagnosed as chronic. Importantly, though, transient swelling during the first year after surgery has been identified as a strong predictor of chronic BCRL at 18 months, why prospective monitoring of these patients is warranted (41). Further, the distribution of swelling can vary from person to person.

Swelling may for example be confined to a specific region such as the hand in some, while in others swelling is restricted to the forearm or upper arm (5). Additionally, early BCRL is characterized by a latent phase whereby an accumulation of excess extracellular fluid is present, but where no visible swelling is detected. As BCRL progresses this then manifests as visible swelling (22), and then in later stages the excess extracellular fluid initially characterizing BCRL is replaced with fibrotic and adipose tissue (21). Therefore, it has been proposed that the use of multiple measures, incorporating both objective and subjective measures may be the most comprehensive way to capture BCRL cases and to monitor BCRL over time (4, 39).

Table 1. Lymphedema staging and grading criteria: International Society of Lymphology (ISL) and National Cancer Institute Common Toxicity Criteria version 3 (CTC v3.0)

ISL staging	CTC v3.0 grading
0 Latent or subclinical LE No evidence of swelling Exists prior to overt edema	Normal
1 Pitting Elevation of limb reduces swelling <20% increase in limb volume	5%-10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomical architecture on close inspection: pitting edema
2 Elevation of limb does not reduce swelling Pitting is present in early Stage II due to tissue fibrosis 20% to 40% increase in limb volume	>10%-30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomical architecture; obliteration of skin folds; readily apparent deviation from normal anatomical contour
3 Lymphostatic elephantiasis Pitting is absent Trophic skin changes present >40% increase in limb volume	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomical architecture; interfering with activities of daily living
4	Progression to malignancy (e.g., lymphangiosarcoma); amputation indicated; disabling

BCRL treatment

The majority of BCRL is mild (20, 37) and the aim of treatment is to contain swelling and alleviate symptoms. The current standard of treatment for BCRL "complete decongestive therapy" (CDT) is comprised of multiple elements including a massage technique called manual lymph drainage, compression (bandaging or garments) of the affected area, remedial exercises, skin care and education in self-care (31, 38, 42). CDT is delivered by specially trained lymphedema therapists and involves two phases. The aim of the first phase is to reduce the extent of swelling. This intensive and time consuming phase can last up to four weeks and involves frequent therapist-

delivered treatment sessions including bandaging of the affected body part. After reaching a plateau in the extent of swelling, home-based maintenance (phase two) then begins to retain the effects of the intensive phase. Depending on the severity of the lymphedema this entails wearing a custom-fitted compression garment during the day, performing remedial exercises, wearing special night garments and using pneumatic compression devices (22). Though CDT involves two phases and contains these various components, the treatment delivered is based on the clinical presentation and could, for example, include only compression or manual lymph drainage. Other less common treatment strategies include pharmacological and surgical approaches such as liposuction, lymph node transplants, lymph-venous anastomosis (22, 23, 42), while the potential of stem cell surgery is being explored (43). The treatment of lymphedema will not be addressed further in the present thesis.

Risk reduction recommendations and exercise

Because uncertainty exists as to why some develop BCRL and others do not, and because prevention of BCRL is preferable to the mitigation of BCRL symptoms, breast cancer survivors are encouraged to adopt a range of precautionary behaviors in an effort to reduce the risk of BCRL (22, 44). The risk reduction guidelines or strategies are intended to minimize lymphatic overload of the at-risk extremity, and are based in large part on pathophysiological principals and expert opinion rather than scientific evidence (42, 45). These recommendations include avoiding constriction of the at-risk arm (including blood pressure cuffs), extreme temperatures (e.g. sauna) and trauma or injury and blood draws on the at-risk extremity (44, 45). Historically avoidance of vigorous, repetitive upper-body activities was also recommended as well as avoidance of heavy lifting, often with restrictions of not lifting more than 2-7 kilograms (9). As a consequence, daily living activities were restricted (vacuuming, child care, grocery shopping) along with upper-body, recreational activities including resistance exercise (9). However, a growing body of evidence has emerged over the last two decades, with studies consistently finding participating in resistance exercise to be a safe and effective exercise modality in breast cancer survivors at risk for lymphedema (7, 8, 10, 11). Nonetheless, as exercise prescription of previous work has been limited to loads considered to be low to moderately heavy, questions remain as to the safety of resistance exercise with heavy loads and lymphedema risk (7). Additionally, uncertainty still exists as to whether intermittent heavy-lifting in activities of daily living need be avoided (2, 46).

Resistance exercise

Skeletal muscle has the ability to alter its phenotypic profile in response to specific stimuli with aerobic and resistance exercise representing two exercise modalities with distinct ability to modify skeletal muscle (47). Specifically, resistance exercise is characterized by short periods of high contractile muscle performance against external load and is considered the optimal exercise modality to increase muscle mass and strength (48-50).

The extent of strength enhancement is dependent on a number of exercise prescription variables including the magnitude of loads lifted. The term repetition maximum (RM) is used to describe resistance exercise prescription, with RM corresponding to the maximal amount of weight lifted for a number of exercise movements. Thus, a 1 RM is the heaviest weight that can be lifted once and only once, corresponding to maximal strength or 100% RM (51). As such, an 8 RM is the heaviest weight that can be lifted only eight times. To induce desirable adaptations in muscle mass and strength the American College of Sports Medicine recommends that resistance exercise should be carried out at a minimum intensity corresponding to 60% 1 RM. Importantly, a dose-response relationship exists in regard to loads lifted and gains in muscle strength outcomes, with loads of 80-100% 1 RM or higher being recommended for continued, long-term progression in muscle strength (48, 50). Additionally, beyond skeletal muscle adaptations, resistance exercise with heavy loads has also been identified as an osteogenic exercise modality due to the adaptive nature of bone that requires heavier loads (52).

Heavy-load resistance exercise during adjuvant chemotherapy

There are several reasons why resistance exercise with heavy loads is relevant during adjuvant chemotherapy for breast cancer. First, participation in resistance exercise with low to moderate loads (60-80% of 1 repetition maximum (RM) for 8-15 RM) has been found to reduce or mitigate chemotherapy-related fatigue (53, 54) with evidence to suggest that a dose-response relationship exists between increasing loads lifted and reductions of fatigue (53). Further, reductions in physical activity contributing to weight gain, characterized as sarcopenic obesity, is common during adjuvant chemotherapy for breast cancer (55-57). Sarcopenic obesity is defined as no change or decline in muscle mass in the presence of increased body fat) (55), and is adversely associated with reductions in muscle strength and functional impairment (49, 58). As such, resistance exercise represents an important countermeasure (8, 54, 59) and is recognized as an effective modality to control or revert sarcopenia, thereby contributing to improved functional levels and overall health (48, 49).

Nonetheless, though increases in muscle strength and reductions in fatigue have been observed with resistance exercise-prescription using lower loads, it is feasible that resistance exercise with heavy loads, could yield superior reductions in fatigue and increases in muscle strength. In turn, this could positively influence functional aspects of quality of life in this population. Also, in Denmark, standard adjuvant chemotherapy for breast cancer consists of combination taxane-based chemotherapy (16) with generalized swelling characterized by an increased level of the interstitial component of extracellular fluid as a known side-effect (40, 60). For some breast cancer survivors this may manifest as transient arm swelling and for others as chronic lymphedema. It has been hypothesized that resistance exercise, through the effects of the muscle pump, could mitigate the extent of arm swelling (33, 40). At present, no studies evaluating the effect of resistance exercise and BCRL have explicitly included participants undergoing taxane-based chemotherapy why uncertainty remains as to the impact of resistance exercise and resistance exercise load on taxane-based swelling. This is especially relevant as the majority of individuals who receive chemotherapy for breast cancer, receive taxane-based chemotherapy. Therefore, in light of the potential for superior benefits, the safety of resistance exercise with heavy loads in regard to BCRL development during taxane-based chemotherapy should be established.

Body & Cancer

Against this back-drop, the author of this thesis has been affiliated with the *Body & Cancer* program since 2003. This program started in 2001 as a randomized controlled trial designed to compare the effectiveness of a multimodal exercise intervention to a wait-list control group on rate of cancer-related fatigue (61). Since 2007 *Body & Cancer* has been offered as an adjunct to chemotherapy in the Copenhagen area, and is today offered at seven hospitals throughout Denmark. To date, approximately 1800 participants representing over 21 diagnoses have participated in *Body & Cancer* in the Copenhagen area alone, with approximately half receiving chemotherapy for breast cancer.

The *Body & Cancer* program is a six-week, nine-hour weekly, group based (10-15 participants), multimodal exercise intervention comprised of both low-intensity components (relaxation techniques, body awareness training and Swedish massage) and high-intensity components (aerobic-and resistance exercise). Prior to each high intensity exercise session, participants are screened (e.g. musculoskeletal issues, temperature, blood pressure) to ensure safety of participation.

Table 2. *Body & Cancer* overview

<table>
<tr><th>Monday</th><th>Tuesday</th><th>Wednesday</th><th>Thursday</th><th>Friday</th></tr>
<tr><td>Aerobic and resistance exercise (1.5 h)</td><td rowspan="3">Body awareness (1.5 h)
Relaxation (.5 h)</td><td>Aerobic and resistance exercise (2 h)</td><td rowspan="3"></td><td>Aerobic and resistance exercise (1.5 h)</td></tr>
<tr><td>Relaxation training (.5 h)</td><td rowspan="2">Relaxation training (.5 h)</td><td>Relaxation training (.5 h)</td></tr>
<tr><td>Massage (.5 h)</td><td>Massage (.5 h)</td></tr>
</table>

In Copenhagen, exercise sessions are held at training facilities affiliated with the Copenhagen University Hospital, Rigshospitalet and supervised by a cancer nurse specialist and physical therapist. Of particular interest for this thesis is the high intensity component which consisted of an aerobic-based warm-up followed by heavy-load resistance exercise followed by 15-30 minutes of interval aerobic exercise on a stationary bike with peak loads of 85-95% of each participant's maximal heart rate. The resistance exercise program comprises of six machine-based exercises (Technogym®, Gamettola, Italy), each targeting major muscle groups of the body including the upper-extremities (chest press, latissimus pull down, abdominal crunch, back extension, leg press and knee extension). Resistance exercise loads are based on a 1 RM strength test for each exercise. During the first week participants are instructed to lift loads corresponding to 2-3 sets of 8-12 repetitions at 70% 1 RM, progressing to 80% 1 RM in week two. From week three forward, loads lifted correspond to 3 sets of 5-8 repetitions at 80-90% 1 RM. Participants who develop signs of BCRL (e.g. sensations of heaviness, visual swelling) or experience exacerbations of an existing BCRL are instructed to reduce loads or refrain from exercises of the upper extremities and are referred to a lymphedema therapist for evaluation and treatment. No data has previously been collected regarding BCRL in this cohort.

Aim

In light of the uncertainty surrounding heavy-load lifting in breast cancer survivors at risk for BCRL, the overall aim of this thesis was to explore the safety of heavy-load resistance exercise among women at risk of developing BCRL while undergoing adjuvant chemotherapy. To meet this aim, three studies were undertaken.

The specific aims of the three studies comprising this thesis were:

Study 1 To determine the prevalence of BCRL in breast cancer survivors who had participated in a six-week multimodal exercise intervention including heavy-load resistance exercise concomitant to receiving chemotherapy (*Body & Cancer*). Further, this study explored associations between engaging in resistance exercise with heavy-loads and the development of BCRL.

Study 2 To assess the initial lymphatic response to resistance exercise with low-compared to heavy-load resistance exercise in breast cancer survivors at risk of BCRL, by comparing acute changes in extracellular fluid, arm volume and 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 adjuvant chemotherapy.

Study 3 To prospectively evaluate the effect of a supervised, multimodal intervention including heavy-load resistance exercise compared with a home-based walking intervention on BCRL outcomes, muscle strength and breast cancer-specific quality of life domains in pre-diagnosis physically inactive breast cancer survivors during adjuvant chemotherapy.

Material and methods

Each of the three studies was conducted separately with the objective of addressing its specific research aim. The data collected within each study are not combined, but are summarized to form a comprehensive whole in the discussion and conclusion sections. Table 3 gives an overview of the included studies.

Design

Study 1

This PhD was pragmatically formed beginning with a cross-sectional study to determine prevalence of BCRL and associations with treatment related risk factors and heavy-load resistance exercise, among former participants of *Body & Cancer*. While causality cannot be established with this study design, findings from Study 1was hypothesis generating and provided the platform for the subsequent studies.

Study 2

Study 2 utilized a randomized, cross-over design to determine the acute lymphatic response to low- and heavy-load resistance exercise. As between-person variations are inherently eliminated, this design lends more statistical power with the practical advantage of a smaller sample size, providing the basis for an efficient comparison between the two resistance exercise loads (62). While results from this type of study can provide important preliminary information, specifically about the acute lymphatic response, a longitudinal study is required to determine the longer term effects of repeated exposure to heavy-load resistance exercise.

Study 3

Study 3 was conducted within the framework of an existing parallel group, randomized trial. The study evaluated the effect of a multimodal exercise intervention including heavy-load resistance exercise vs. a walking intervention supported by a pedometer and counselling, with aerobic capacity as the primary outcome. Therefore, BCRL results are based on secondary outcomes in this trial.

Table 3. Material and methods overview of the three studies comprising this thesis

Study / Paper	**1 / I**	**2 / II & III**	**3 / IV**
Hypothesis	Participation in an exercise intervention utilizing heavy-load resistance exercise would not be associated with incidence BCRL.	Response would be similar between resistance exercise loads for all outcomes.	Superior muscular strength and breast cancer-specific domains after HIGH compared to LOW. BCRL outcomes will be similar irrespective of intervention.
Design	Cross-sectional study	Randomized cross-over trial	Parallel-group randomized trial
Participants	(n = 149)	(n = 21)	(n = 153)
Sample	Breast cancer survivors who had participated in *Body & Cancer* during chemotherapy Excluded: BCRL diagnosis prior to *Body &Cancer* Recurrent disease and mortality at study initiation	Women receiving standard adjuvant chemotherapy for stage I-III breast cancer with no pre-existing cancer diagnosis Over 18 years of age Unilateral breast surgery and axillary node dissection Excluded: Existing BCRL Conditions limiting resistance exercise of the upper extremities Regular heavy resistance exercise (>1 / week) during the last month	Self-reported physically inactive women receiving adjuvant chemotherapy for stage I-III breast cancer. WHO performance status 0-1 Excluded: Symptomatic heart disease and/or pathological echocardiogram Diagnosed acute coronary syndrome within 6 months Contraindication to exercise Unable to read or understand Danish.
Randomized concealed allocation	Not applicable	Yes	Yes
Interventions	Not applicable	One session of low- load resistance exercise One session of heavy-load resistance exercise	HIGH: 12-week supervised, group-based intervention including heavy-load resistance exercise OR LOW: 12-week home-based individual walking intervention to support physical activity
Measurement methods	Telephone questionnaire Medical records *Body & Cancer* database	BIS DXA NRS	BIS DXA NRS Structured interview 1 RM EORTC QLQ-BR23
Outcomes	Self-reported clinically diagnosed BCRL	Primary: Arm extracellular fluid Secondary: Inter-arm volume BCRL symptoms	Arm extracellular fluid Inter-arm volume BCRL symptoms Self-reported swelling Muscle strength Functional & symptom domains
Blinded	Not applicable	Data collection & analyses	Data collection & analyses
Analysis	Prevalence / Associations	Equivalence	Superiority / Equivalence
Statistics	Point prevalence X^2-test Fisher's exact test	General estimating equation Confidence interval inclusion	Linear mixed model: heterogeneous autoregressive (1) covariance Confidence interval inclusion

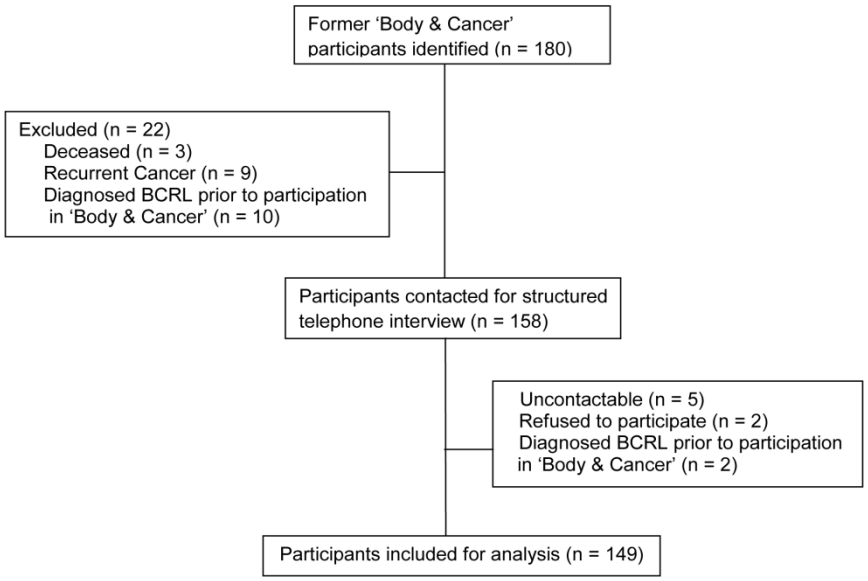
Abbreviations: **BCRL** breast cancer-related lymphedema, **WHO** World Health Organization, **BIS** Bioimpedance spectroscopy, **DXA** Dual X-ray absorptiometry, **NRS** Numeric rating scale, **RM** repetition maximum, **EORTC QLQ-BR23** European Organization for Research and Treatment of Cancer quality of life questionnaire breast-23

Participants

Study 1

Breast cancer patients who had participated in *Body & Cancer* between January 2010 and December 2011 were identified from the *Body & Cancer* database (n=149). Participants were eligible for *Body & Cancer* if they were receiving chemotherapy for cancer at a university hospital in the Copenhagen area, had a World Health Organization (WHO) performance status of 0-1, and otherwise had been approved to participate by the treating oncologist. Potential participants for the cross-sectional analysis were screened for BCRL, recurrent cancer and mortality status in medical records and excluded if identified. Figure 2 details the recruitment and exclusion process.

Figure 2. Flowchart over participants in Study 1

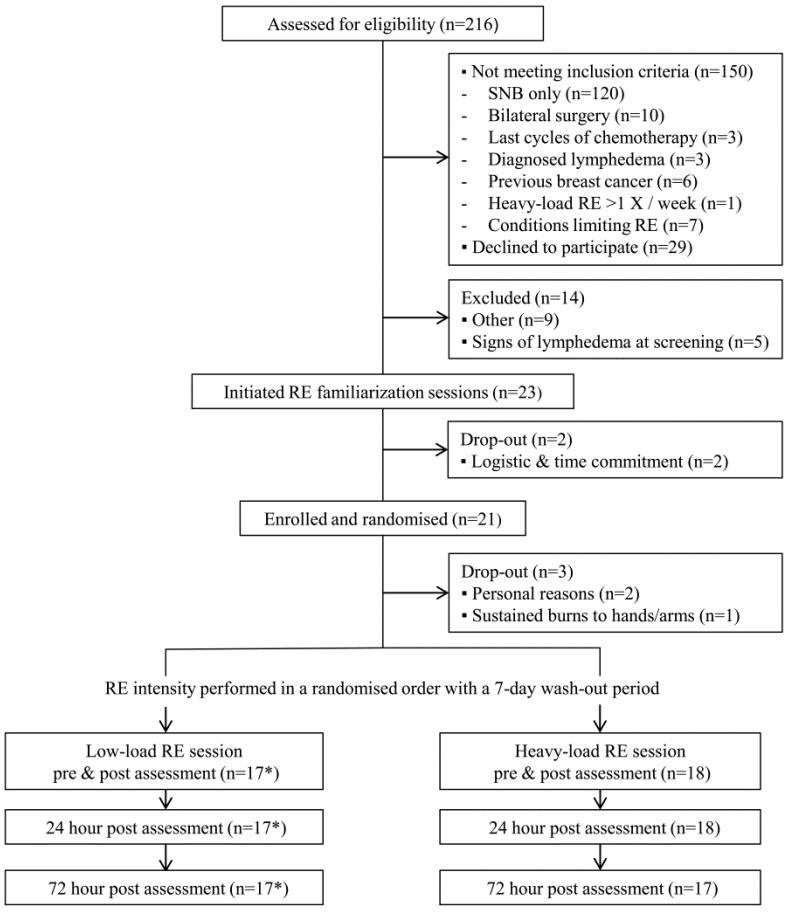


Study 2

A convenience sample of women (n =21) receiving adjuvant taxane-based chemotherapy for stage I-III breast cancer who had undergone ALND, were recruited from the Copenhagen Centre for Cancer and Health and from a waitlist to participate in *Body & Cancer* between March 2015 and December 2016. Potential participants were screened for eligibility (over 18 years of age, unilateral

breast surgery, first diagnosis of breast cancer) and excluded if they had a known clinical diagnosis of BCRL and/or had conditions limiting resistance exercise of the upper extremities, or had participated in regular (>1 × / week) upper extremity heavy resistance exercise during the last month. Those meeting eligibility were then assessed for BCRL after the third cycle of chemotherapy. Those with evidence of lymphedema (L-Dex >10 assessed using bioimpedance spectroscopy (BIS) or visual inspection (CTC v3.0) were excluded from participating in the study and referred to a lymphedema therapist for evaluation and treatment (Figure 3).

Figure 3. Flowchart over participants in Study 2

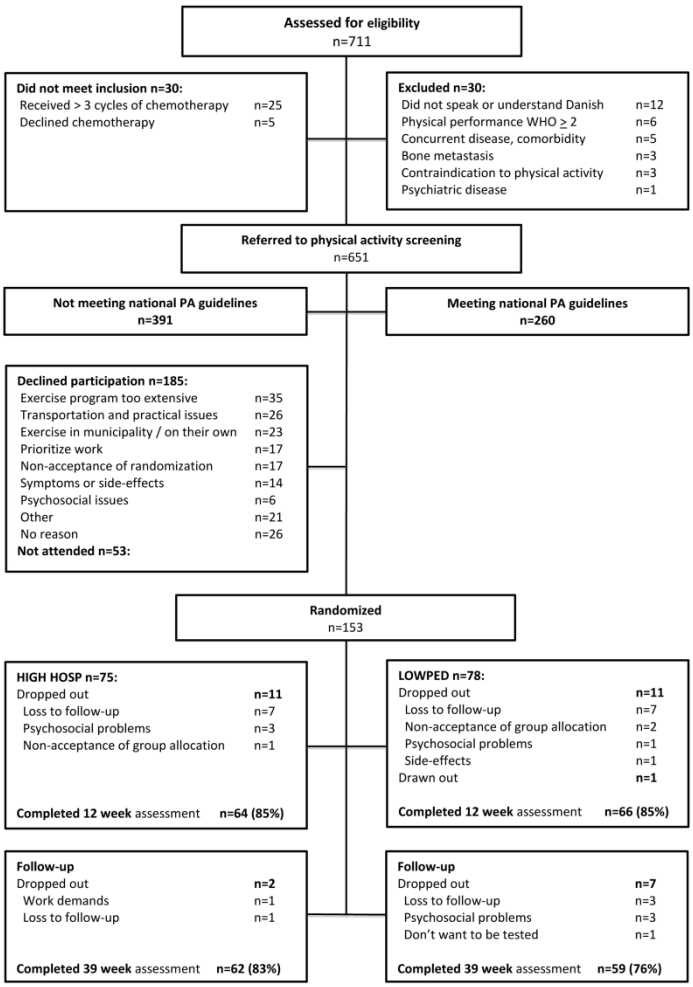


*One participant only participated in first week due to time constraints.

Study 3

Participants (n =154) were recruited between January 2014 and July 2016 at the oncology departments of The Copenhagen University Hospital, Rigshospitalet (RH) and Herlev Hospital (HE). Women were screened/interviewed for eligibility by nurses / physicians upon initiation of adjuvant chemotherapy for stage I-III breast cancer. Eligibility criteria included a WHO performance status of 0-1 and physical activity levels retrospectively rated as less than 150 minutes of regular, moderate- intensity and / or less than 2 x 20 minutes of high-intensity exercise per week (Danish national recommendations (63)), three months prior to diagnosis. Eligible participants were then referred to the research team and matched against exclusion criteria (diagnosed acute coronary heart syndrome within the past six months, symptomatic heart disease, pathological echocardiogram, contraindication for exercise noted in medical records, unable to read or understand Danish) (Figure 4).

Figure 4. Flow chart over participants in Study 3



Setting

The three studies have been carried out at exercise facilities located at the University Hospitals Centre for Health Research, University of Copenhagen, Rigshospitalet.

Randomization and blinding

Inherent to exercise studies, participants, nurses and physical therapists delivering the interventions in Study 2 and 3 were aware of group allocation.

Study 2

Resistance exercise order (low- or heavy-load first) for the experimental sessions was randomly allocated using a computer-generated random sequence (1:1 ratio). Blinded data collection was performed by medical technicians at the Department of Clinical Physiology and Nuclear Medicine, at the Copenhagen University Hospital, Rigshospitalet. Further all DXA scan analyses were performed blinded to intervention order. Subsequently, data was keyed by research assistants, and statistical analyses were performed with no knowledge of allocation by an external statistician.

Study 3

Following baseline assessment, participants were sequentially numbered and stratified by age (<48/48+ years) and hospital (RH/HE). Intervention allocation (1:1) was determined by a computerized, random number generated at the Copenhagen Trial Unit, an external clinical research unit. All data collection and subsequent data entry were performed blinded to group allocation by study staff. Further, all statistical analyses were performed blinded to group allocation by a senior statistician at the University of Copenhagen.

Interventions

Participants were encouraged to contact study personnel if signs or symptoms of BCRL developed (Studies 2 and 3) or exacerbation of an existing BCRL (Study 3) occurred during the study period, and were referred to a lymphedema therapist for evaluation and treatment. The type and duration of treatment delivered by the therapist was not recorded.

Study 2

Participants completed two familiarization sessions, followed by two experimental sessions (one low- and heavy-load) lasting 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 author 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 (free weights), followed by the chest press, latissimus pull down and triceps extension using resistance exercise machines (Technogym®, Gamettola, Italy). Hereafter, a 1 RM strength test was performed for each exercise. During the second session, one set of 10-15 repetitions was performed, followed by a new 1 RM strength test. Subsequent resistance exercise prescription during the experimental sessions was based on these values. Women then participated in the experimental sessions (performed on the same day of the week and at the same time of day) and were instructed to maintain normal upper-body activities and to refrain from extraordinary activities involving the upper extremities. Resistance exercise load corresponded to 60-65% 1 RM (2 sets of 15-20 repetitions) for the low-load session and 85-90% 1 RM (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, with rest periods of 60-90 seconds between sets.

Study 3

Following baseline testing, all participants received verbal and written information, highlighting current evidence-based risk factors for developing BCRL (e.g. lymph node removal, BMI, physical inactivity). Both groups received health promotion counselling including exploration of barriers and motivators for adopting regular physical activity as well as clinical advice concerning symptom management and feedback regarding physiological outcomes (64).

HIGH group

Participants randomized to the HIGH group participated in a twelve-week, group-based exercise program, supervised by a cancer nurse specialist and a physical therapist. The first six weeks consisted of *Body & Cancer* (61, 64) followed by six weeks of an 'All sport' exercise program. The 'All sport' program focused on moderate to high intensity aerobic activities and the high-intensity components of the previous six weeks (Table 4) (64). The resistance exercise program in *Body & Cancer* was carried out as previously described with resistance exercise loads adjusted every third week, based on new 1 RM testing to ensure progression. If participants developed signs of BCRL or experienced exacerbations of an existing BCRL, they were instructed to refrain from resistance exercise targeting the upper extremities or to decrease loads.

LOW group

The LOW group participated in an individualized, home-based, twelve-week walking program supported by a pedometer and counselling from a cancer nurse specialist or physical therapist (Table 4). Participants were issued an Omron Walking Style Pro pedometer 2.0, and were

encouraged to progressively increase steps to ultimately achieve 10,000 steps per day. Face-to-face meetings during weeks 2, 4, 6, 9 and 12 were held to discuss daily walking targets as well as barriers and motivators for achieving these targets. Participants were also encouraged to exercise (beyond walking) and to integrate physical activity into activities of daily living.

Table 4. Overview of HIGH and LOW interventions

HIGH intervention					
Monday	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	
Part I:*Body & Cancer* 6 weeks, 9 h/week					
Aerobic and resistance exercise (1.5 h) Relaxation (0.5 h) Swedish massage (0.5 h)	Body awareness (1.5 h) Relaxation (0.5 h)	Aerobic and resistance exercise (2 h) Relaxation (0.5 h)		Aerobic and resistance exercise (1.5 h) Relaxation (0.5 h) Swedish massage (0.5 h)	
Part II: 'All-sport' 6 weeks, 6 h/week					
Aerobic and resistance exercise and e.g. ballgames, dancing (2 h)		Aerobic and resistance exercise and e.g. ballgames, dancing (2 h)		Aerobic and resistance exercise and e.g. ballgames, dancing (2 h)	
LOW intervention					
Week 1 Pedometer consultation	**Week 2** Pedometer consultation	**Week 4** Pedometer consultation	**Week 6** Pedometer consultation	**Week 9** Pedometer consultation	**Week 12** Pedometer consultation
Both interventions					
Baseline Health promotion counselling	**Week 6** Health promotion counselling	**Week 12** Health promotion counselling	**Week 39** Health promotion counselling		

Measurement methods/outcomes

Study 1

Medical records

Data regarding surgery and treatment as well as BCRL, recurrent cancer and mortality status were obtained from electronic medical records.

Structured telephone interview

Structured telephone interviews, lasting 15 minutes on average, were conducted within a six week period by the PhD student. The primary outcome, a clinical diagnosis of BCRL, was recorded if the participant answered "yes" to having been diagnosed with lymphedema. Subsequently, participants were asked when and by whom the diagnosis was made, as well as which region was affected (hand, arm, breast, torso). Demographic, treatment, and physical activity characteristics were also

obtained as well as any information lacking from the medical records. Specifically, demographic characteristics included age, current BMI, relationship status, age of children living at home, education and current occupation. Treatment characteristics included whether surgery had been performed on the dominant side and whether they had been introduced to breast cancer-specific post-operative exercises. Behavioral characteristics included whether the participant had performed post-operative exercises before participating in *Body & Cancer*, whether they had engaged in resistance exercise 1-3x/week between surgery and *Body & Cancer*, and whether they had engaged in resistance exercise1-3x/week post intervention, and if so for how long, and with what load(s). In addition, leisure time physical activity was explored using the Salting-Grimby Physical Activity Level Scale (65).

Arm Circumference measurements

For participants who answered "yes" to having been diagnosed with BCRL, circumference measurements from the time of lymphedema assessment were obtained from medical records or by contacting the clinician that had diagnosed BCRL. No standardized protocol for measuring BCRL was used, with clinicians using measurement protocols ranging from five to seven measuring points. For this study, a participant was considered to have BCRL if an inter-arm difference of ≥ 2 cm at to two or more measures was reported (66).

Body & Cancer database

Baseline BMI and pre-illness physical activity levels (65) were obtained from the database, as well as baseline and post-intervention muscular strength (1 RM) of the upper and lower extremities (chest and leg press, respectively) and adherence to the *Body & Cancer* program.

Study 2

All outcomes were assessed pre-, immediately post- (within 30 minutes) and 24- and 72-hours post-resistance exercise sessions.

Extracellular fluid

Bioimpedance spectroscopy (BIS) (SFB7, Impedimed, Brisbane, Australia) was performed immediately after the DXA scans. This measurement method has a high reliability for detecting sub-clinical BCRL (67, 68) by directly measuring and comparing the impedance of extracellular fluid in the upper extremities to electrical currents at a range of frequencies (68). Participants were positioned in supine with arms and legs slightly abducted with palms facing down. Using the principle of equipotentials, four single tab electrodes were placed in a tetrapolar arrangement. Measurement electrodes were placed on the dorsum of the wrist midway between the styloid

processes. Current drive electrodes were placed five centimeters distally on the dorsal side over the third metacarpal of the hand, and approximately midway on the third metatarsal on the dorsum of the foot (69). 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 (70).

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 (71). 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 analyze the scans as described by Gjorup et al., (71). All scans were point typed and analyzed by a clinical expert. Inter-arm volume % differences (at-risk arm minus unaffected arm/unaffected arm * 100) were then calculated for each participant.

Subjective assessment of BCRL symptoms

The severity of BCRL symptoms (swelling, heaviness, pain, tightness) was monitored using a numeric rating scale (NRS). Participants rated their perception of symptoms for each arm on a scale from 0 (no discomfort) to 10 (very severe discomfort) (72, 73).

Study 3

All outcomes were assessed at baseline, 12 week follow-up (immediately post-intervention) and 39 week follow-up. 1 RM strength and self-reported data were also assessed at these time points as well as at 6 weeks post-baseline.

Extracellular Fluid

BIS was performed immediately after DXA as described in Study 2, and was consecutively obtained from participant 71 forward.

Inter-arm volume % difference

Arm volume was obtained using DXA. Lying supine on the scan-table with arms slightly abducted and hands in a mid-prone position, total body scans were performed fasting, at the same time of day (mornings) at all assessments. Scans were automatically analyzed using encore version 16, GE Healthcare Lunar software. From the total body scans, the measured weight of fat, lean mass and

bone mineral content of both arms were identified and converted into estimated arm volumes as in Study 2 with the region of interest extending from the gleno-humeral joint to the finger tips (74, 75). Inter-arm volume % differences (at-risk arm minus unaffected arm/unaffected arm * 100) were then calculated for each participant.

Self-reported BCRL symptoms

The severity of BCRL symptoms (heaviness, tightness, pain, swelling) on the surgical side was monitored using a NRS. Participants rated their perception of symptoms on the surgical side as compared to the non-surgical side on a scale from 0 (no discomfort) to 10 (very severe discomfort)(72).

Self-reported swelling

Participants reported if they had observed a difference in size between their surgical-and non-surgical side within the last week. If they answered "yes", they were then asked to report where: fingers, hand, forearm, upper arm (extremity) and breast, torso (body).

Upper extremity muscular strength

To assess maximal strength of the upper extremities, the 1 RM strength test (51) was performed using the chest press (Technogym®, Gamettola, Italy). Prior to the 1 RM attempt, a warm-up was performed consisting of 8-10 repetitions using a low weight ensuring no muscle fatigue. Hereafter, load was increased based on ease of performance, with one repetition lifted of each load, until the participant was unable to lift a respective load.

Breast cancer-specific functional and symptom domains

To assess breast cancer-specific quality of life domains (functional and symptom), the 23 item European Organization for Research and Treatment of Cancer (EORTC) breast cancer module (BR23) (76), version 3.0, was used. This validated breast cancer-specific module includes four functional scales as well as four symptom specific subscales. Each item is scored on a four point Likert scale from "not at all" to "very much", with raw scores summed and converted to a score out of 100. Higher levels of functioning are represented by higher functional scores and worse symptoms are represented by higher symptom scores (76, 77).

Data analysis

Statistical assistance was provided by associate professor, senior statistician Karl B. Christensen (Department of Biostatistics, University of Copenhagen) for all three studies, with additional assistance from PhD Megan L. Steele (Institute of Health and Biomedical Innovation, Queensland

University of Technology) in study 2. A two-tailed $P < .05$ was taken as evidence of statistical significance.

Study 1

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software (version 19) for Windows. Descriptive statistics are presented as counts (percentages) for categorical variables and as means and standard error (SE) for continuous variables unless otherwise noted. Mean changes in 1 RM muscular strength post *Body & Cancer* were assessed using a paired *t*-test, and were analyzed on a per-protocol basis, (only participants with data at baseline and 6 weeks) as well as on an intention to treat (ITT) basis using baseline observation carried forward. Point prevalence of BCRL was calculated on average 14 months post intervention (range 4 to 26 months)), and estimated retrospectively at the commencement of *Body & Cancer* as well as 1, 2, 3, and 4 months post *Body & Cancer*.

To compare differences between participants diagnosed with BCRL and those without, Chi-squared and Fisher's exact test were used for categorical variables and two-sample *t*-tests for continuous variables. Levene's test for equality of variances was performed and results presented use pooled variances unless otherwise noted.

Study 2

Sample size calculation was based on changes in L-Dex scores between baseline and 72-hours post-resistance exercise sessions. On the basis of clinical experience with patients with BCRL a change score of 2.0 L-Dex units was considered clinically relevant, and SD of the distribution of L-Dex units was estimated at 1.9 units based on results of Cormie et al.(12). However, upon study initiation no normative data existed in the at-risk population nor did a threshold for a clinically significant acute change. As such, 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. Therefore, *a priori*, the clinically relevant threshold was set at 3.0 L-Dex units. Eighteen 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.

Descriptive statistics included counts (and percentages) for categorical values and mean ± standard deviation (SD) 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) (78) 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, *a priori*, equivalence margins were determined for all outcomes. For extracellular fluid, the margin of equivalence was set at ± 3.0 L-Dex units (primary outcome). An equivalence margin of ±3.0% was used for inter-arm volume % differences based on findings from Stout et al., (79) showing that volume increases of >3% from pre-operative measures were indicative of subclinical BCRL. For all BCRL symptoms, inter-arm differences were calculated and an equivalence margin was set at ±1.0 points based on previous findings that suggest a 2 point or 30% change to be clinically meaningful for pain (72). The principle of confidence interval inclusion was used to calculate two one-sided upper and lower 95% confidence limits for all outcomes (80) (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. Per-protocol principles were applied as this is considered the most conservative approach for determining equivalence (81). Analyses were conducted in R version 3.3.1 (82) using geepack 1.2.0.1 for GEE modelling (83).

Study 3

Analyses were conducted using Statistical Analysis Software (SAS) version 9.4.
Descriptive statistics included counts (and percentages) for categorical variables and point prevalence of BCRL defined as L-Dex > 10, inter-arm volume difference > 5% or self-reported observation of swelling. For continuous variables means ± SD (normally distributed), or median with interquartile range (IQR) (not normally distributed) are presented.

Linear mixed models with a heterogeneous autoregressive (1) covariance structure were used to estimate changes over time in each group with an intention-to-treat (ITT) approach. An exchangeable correlation structure modelled the within-subject correlation of repeated measurements over time and across interventions, incorporating all available data including participants with incomplete data. Effect sizes were calculated for muscular strength (84). A two-sided significance level was set at 0.05 for outcomes where superiority was hypothesized (muscular strength and cancer-specific functional and symptom domains).
As with Study 2, *a priori*, clinically relevant equivalence margins were chosen for BCRL outcomes. For L-Dex, the margin of equivalence was set at ±5.0 units based on new normative data indicating

that L-Dex scores fluctuate between 9-11 units (70). An equivalence margin of ±3.0% was used for inter-arm volume % differences and at ±1.0 points for BCRL symptoms, and the principle of confidence interval inclusion (80) was used to calculate two one-sided upper and lower 95% confidence limits, (reported as 90% confidence limits) as in study 2. Further, a per-protocol analysis of participants with an adherence rate >65% to the HIGH intervention was performed to evaluate equivalence of BCRL outcomes to the predetermined equivalence margins.

Ethical approval

Study 1

Study 1 was performed in accordance with the Helsinki Declaration, and approved by the Danish Data Protection Agency**.**

Study 2

Study 2 was registered at Current Controlled Trials (ISRCTN97332727), approved by the Danish Data Protection Agency (30-1430) and the Danish Capital Regional Ethics Committee (H-3-2014-147).

Study 3

Study 3 was registered at Current Controlled Trials (ISRCTN24901641), approved by the Danish Data Protection Agency (2011-41-6349) and the Danish Capital Regional Ethics Committee (H-1-2011-131).

Results

The following section presents the main findings of the three studies.

Study 1

Participants

The mean age of participants was 47.7 years and mean self-reported BMI was 24.1, with 54 (36%) classified as overweight (BMI > 25). The majority reported being physically active before diagnosis 108 (72%). All had undergone chemotherapy, with 141 (95%) having received adjuvant taxane-based chemotherapy, 62 (42%) had received a mastectomy and 90 (60%) had ALND while 120 (81%) had received radiotherapy.

Body & Cancer participation

Over half of the participants (60%) had an adherence rate of at least 70% (17 of 24 training days). Significant increases in lower and upper extremity muscular strength were observed after six weeks of training (Table 5).

Table 5. Muscular strength post *Body & Cancer*

	Total Population				Total Population				ALND Population			
	Baseline		6 weeks	Change	No BCRL		BCRL		No BCRL		BCRL	
1 RM (kg)	n	Mean (SE)	Mean (SE)	Mean (SE)	n	Δ Mean (SE)	n	Δ Mean (SE)	n	Δ Mean (SE)	n	Δ Mean (SE)
Chest Press	125	27.2 (.66)	31.9 (.70)	**4.7 (.43)**	93	4.6 (.47)	32	5.0 (.98)	41	4.3 (.69)	31	4.5 (.88)
Leg Press	132	76.0 (2.00)	94.8 (2.45)	**18.8 (1.75)**	96	16.5 (1.82)	36	24.7 (4.07)	45	14.9 (2.48)	35	23.7 (4.06)

Δ Change between baseline and post *Body & Cancer*, **Bold** (p-value <0.05), No BCRL as reference

BCRL point prevalence

At an average follow-up of 14 months (range 4-26) post Body & Cancer, point prevalence of BCRL was 27.5% for the total sample (n=149). When analysis was restricted to include only women who underwent ALND, point prevalence was 44.4% (Table 6). Six percent of the total sample and 10% of those who underwent ALND reported that they had been diagnosed with BCRL during the intervention, with an additional 11.4% and 17.8% diagnosed within the first four months post *Body & Cancer*, respectively. All BCRL cases had ALND, with the exception of one participant (n = 89, 98.8%). Of the participants with a diagnosis of BCRL, one reported swelling in the hand only, three in the breast only, and one in the torso only. The remainder (n = 144) reported swelling in the arm only or in combination with the hand, breast and torso.

Arm circumference measurements were obtained for 38 of the 41 (93%) participants diagnosed with BCRL, from two hospitals and six private practice lymphedema therapists. Of these, 47.4% had an inter-arm difference ≥ 2 cm at two or more measures. Therefore, when applying this measurement method and cut-off, prevalence rates were lower than for those diagnosed with BCRL (Table 6).

Table 6. Point prevalence of lymphedema in relation to participation in *Body & Cancer*. Values are numbers of participants (%).

Time in relation to participation in *Body & Cancer*	**Diagnosed BCRL Total population (n = 149)**	**Circumference ≥ 2 Total population (n = 146)†**	**Diagnosed BCRL ALND population (n = 90)**	**Circumference ≥ 2 ALND population (n = 87)†**
During intervention	9 (6.0)	5 (3.4)	9 (10.0)	5 (5.8)
Within 1month post intervention	16 (10.7)	10 (6.8)	16 (17.8)	10 (11.5)
1-2 months post intervention	21 (14.1)	11 (7.5)	21 (23.3)	10 (11.5)
2-3 months post intervention	23 (15.4)	13 (8.9)	23 (25.6)	12 (13.7)
3-4 months post intervention	26 (17.4)	15 (10.3)	25 (27.8)	14 (16.1)
Total at study*	41 (27.5)	18 (12.3)	40 (44.4)	17 (19.5)

*On average 14 months (4-26) post *Body & Cancer*. † Circumference measurements not available for 3 participants

BCRL vs. No BCRL

When comparing characteristics of participants with and without diagnosed BCRL, significantly more ($p < 0.05$) participants with BCRL currently had a BMI > 25 (BCRL 21 (51%) vs. No BCRL 33 (31%), had undergone ALND (BCRL 40 (98%) vs. No BCRL 50 (46%)) and had received radiotherapy (BCRL 39 (95%) vs. No BCRL 81 (75%)). No between group differences were observed in regard to resistance exercise participation before or after *Body & Cancer*, nor to adherence to *Body & Cancer*, or to changes in muscular strength (Table 5).

A sub-analysis of participants with ALND showed that significantly more ($p < 0.05$) participants with BCRL were currently overweight or had been overweight upon commencing *Body & Cancer* (Table 7). No between group differences were found in regard to radiotherapy, however 93.3% of the participants with ALND had received radiotherapy. No between group differences were seen in regard to RE participation before or after *Body & Cancer* (Table 7), nor to changes in muscular strength (Table 5).

Table 7. BCRL vs. no BCRL in participants with ALND (n = 90). Values are numbers (%)

	No BCRL (n = 50)	**BCRL (n = 40)**	
Demographic characteristics			p
Age (years) mean (SD)	49.2 (9.0)	47.8 (8.0)	.436
Children in care < 7 years	9 (18.0)	4 (10.0)	.371
Married, cohabitating or in a relationship	37 (74.0)	28 (70.0)	.813
Education > secondary school	44 (88.0)	37 (92.5)	.726
Employed (full/part time)	40 (80.0)	29 (72.5)	.458
Not physically demanding work	27 (54.0)	19 (47.5)	.832
Moderately physically demanding work	11 (22.0)	9 (22.5)	
Very physically demanding work	2 (4.0)	1 (2.5)	
Health and medical characteristics			
Baseline BMI (kg/m$^{2)}$ > 25*	**13 (26.0)**	**20 (51.3)**	**.017**
Study BMI (kg/m$^{2)}$ > 25	**9 (18.0)**	**21 (52.5)**	**.001**
Mastectomy	25 (50.0)	18 (45.0)	.676
Non-dominant arm	32 (64.0)	23 (57.5)	.664
Chemotherapy			
3-wkly CE x 3 -> 3 wkly docetaxel x 3	33 (66.0)	29 (72.5)	.508
3-weekly CT x 6	13 (26.0)	10 (25.0)	
Other	4 (8.0)	1 (2.5)	
Received radiotherapy	46 (92.0)	38 (95.0)	.689
Received endocrine treatment	45 (90.0)	33 (82.5)	.358
Received trastuzumubab	8 (16.0)	2 (5.0)	.175
Physical activity level (self-reported)			
Pre-illness[†]			
Sedentary	1 (2.1)	1 (2.8)	.717
Walking or cycling for pleasure	11 (22.9)	9 (25.0)	
Regular physical exercise, at least 3 h/week	34 (70.8)	23 (63.9)	
Intense physical activity > 4 h/week	2 (4.2)	3 (8.3)	
Present			
Sedentary	0 (0.0)	1 (2.5)	.326
Walking or cycling for pleasure	7 (14.0)	10 (25.0)	
Regular physical exercise at least 3 h/week	25 (50.0)	15 (37.5)	
Intense physical activity > 4 h/week	18 (36.0)	14 (35.0)	
Training			
Performed exercises prescribed post-surgery[‡]			
No	10 (21.7)	3 (7.7)	.192
3 x weekly	8 (17.4)	7 (17.9)	
Daily	28 (60.9)	29 (74.4)	
RE 1-3x/wk between surgery and *Body & Cancer* [‡]	13 (28.3)	10 (25.6)	1.000
RE 1-3x/wk 3 months after *Body & Cancer*	24 (48.0)	22 (55.0)	.532
Utilized 2-3 sets of 5-8 RM	14 (28.0)	14 (35.0)	.769
Adherence ≥70% while in *Body & Cancer*	35 (70.0)	19 (47.5)	.051

Abbreviations: CE, cyclophosphamide & epirubicin; CT, cyclophosphamide & docetaxel; RE, resistance exercise *(n = 84, (n = 39 BCRL; n = 50 no BCRL) due to missing data. [†](n = 84) due to missing data.[‡] (n = 85,(n = 39 BCRL; n = 46 no BCRL) participants receiving neo-adjuvant (n = 4) or chemotherapy for advanced disease (n = 1) not included.

Study 2

Participants

Twenty one eligible participants were included in the study with seventeen (81%) completing all data collections. For details of participant flow see Figure 4. Characteristics of the study population are presented in Table 8. As per eligibility criteria, all participants received adjuvant taxane-based chemotherapy during the experimental sessions. However, as standard chemotherapy changed midway through the study period, the first ten participants received docetaxel, while the last 11 received paclitaxel.

Table 8. Characteristics of participants (n = 21)

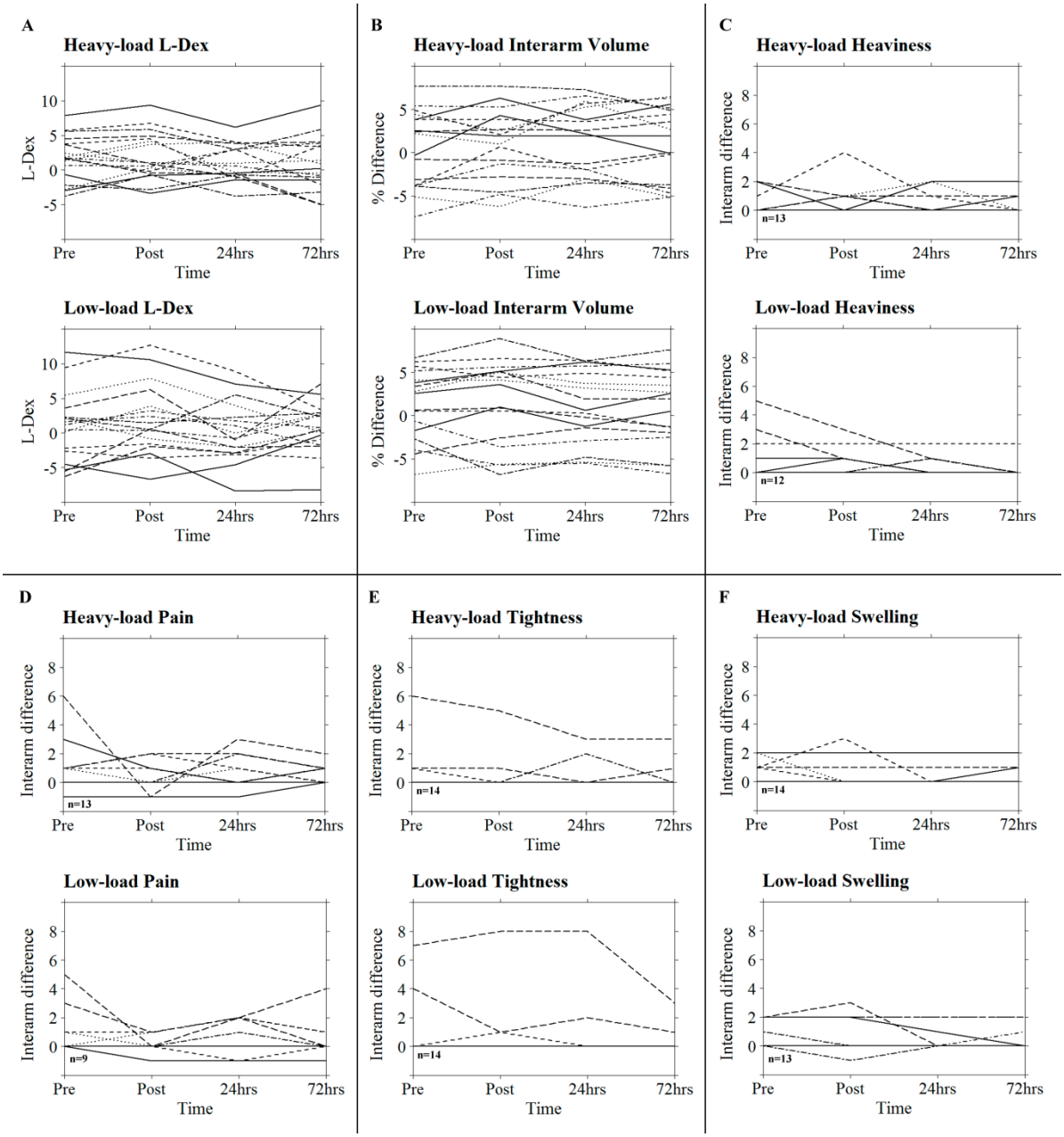
Variables	Mean ± SD / Median (range)
Age (years)	45.3 ± 9.2 / 46 (23-60)
BMI (kg/m$^{2)}$	25.3 ± 4.7
Cancer stage *n (%)*	
ll	15 (71)
lll	6 (29)
Tumor size (mm)	21.5 ± 12.9 / 18 (7-62)
Breast surgery *n (%)*	
Lumpectomy	8 (38)
Mastectomy	13 (62)
Surgery on dominant side n *(%)*	11 (52)
Axillary lymph nodes removed	21.7 ± 7.8
Metastatic lymph nodes[a]	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 & epirubicin [a]) micro- and macrometastases

Individual responses to resistance exercise

Individual responses to resistance exercise sessions varied with no apparent group trend observed for L-Dex and inter-arm volume % differences (Figure 5A, 5B). For BCRL symptoms, most participants were asymptomatic pre-exercise and remained asymptomatic throughout the subsequent data collections irrespective of loads lifted (Figure 5C-F).

Figure 5. Individual responses related to low- and heavy-load resistance exercise (n = 17)



Subplot A Heavy-load L-Dex pre-, post-, 24-hours (n = 18); Sub-plots C-F Heavy-load breast cancer-related lymphedema symptoms pre- and post- exercise (n = 18), Sub-plots C-F (n=) refers to the number of participants with a symptom score of 0 at all time points.

L-Dex

The estimated mean difference between resistance exercise loads and associated two-sided 90% CIs were within the predetermined equivalence margin of ±3.0 L-Dex units immediately-, and 24-hours after resistance exercise indicating equivalence between intensities (Table 9). However, at 72-hours post-exercise, the lower CI exceeded -3.0 and equivalence between low- and heavy-load intensities could not be declared, indicating a reduction of extracellular fluid post heavy-load resistance exercise.

Inter-arm volume % difference

Equivalence between resistance exercise loads 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 9).

BCRL symptoms

Equivalence between resistance exercise loads 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 9).

Adverse events

No adverse events related to exercise (i.e. sprains or strains) were reported. 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 5A). One participant had a pre-exercise L-Dex score of 7.9 in week one which remained elevated at week two, with a pre-exercise L-Dex score of 11.7 that decreased over the subsequent data collections. 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, the pre-exercise L-Dex score had increased to 9.5 that further increased to 12.7 post-exercise, followed by 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.

Table 9. Equivalence between resistance exercise intensities (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**[c]
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

Study 3

Participants

391 women receiving adjuvant chemotherapy for breast cancer were screened for eligibility with 153 (39%) included in the study between January 2014 and July 2016 (Figure 4). Baseline characteristics were balanced between the two intervention groups (Table 10). However, more participants with L-Dex data had received paclitaxel based chemotherapy (13 (20.3%) vs. 6 (6.7%). Further, the mean BMI of participants without inter-arm volume data was higher than participants with, as body dimensions exceeded the DXA scan area (31.3 ± 5.3 vs. 24.3 ± 3.6, respectively).

Table 10. Baseline characterеristics (n = 153)

Characteristics	Total (n = 153)	HIGH (n = 75)	LOW (n = 78)
Age (years), mean ± SD	51.7 ± 9.4	51.5 ± 9.6	52.0 ± 9.3
BMI (kg/m$^{2)}$, mean ± SD	26.1 ± 5.1	26.2 ± 5.3	26.0 ± 4.9
Cancer stage, n (%)			
Stage 1	56 (36.6%)	31 (41.3%)	25 (31.1%)
Stage 2	81 (52.9%)	36 (48.0%)	45 (57.7%)
Stage 3	16 (10.5%)	8 (10.7%)	8 (10.3%)
Breast surgery, n (%)			
Lumpectomy	90 (58.8%)	47 (62.7%)	43 (55.1%)
Mastectomy	56 (36.6%)	26 (34.7%)	30 (38.5%)
Mastectomy plus expander	7 (4.6%)	2 (2.7%)	5 (6.4%)
Axillary surgery, n (%)			
Axillary lymph node dissection	61 (39.9%)	26 (34.7%)	35 (44.9%)
Sentinel node biopsy	92 (60.1%)	49 (65.3%)	43 (55.1%)
Nodes removed, median (IQR)	3 (2-17)	3 (1-15)	5 (2-19)
Surgery on dominant side,* n (%)	76 (49.7%)	39 (52.0%)	37 (47.4%)
No. of seroma drainages, median (IQR)	1 (0-5)	1 (0-5)	1 (0-5)
Chemotherapy, n (%)			
3-wkly CE x 3 -> 3 wkly docetaxel x 3	130 (85.0%)	66 (86.7%)	64 (82.1%)
3-wkly CE x 3 -> 1 wkly paclitaxel x 9	19 (12.4%)	8 (10.7%)	11 (14.1%)
Other	4 (2.6%)	1 (1.3%)	3 (3.9%)
Observations of swelling,** n (%)			
Extremity (hand, underarm, overarm)	5 (3.3%)	2 (2.7%)	3 (3.9%)
Body (breast, torso)	31 (20.5%)	14 (18.9%)	17 (22.1%)
Both (body & extremity)	11 (7.3%)	3 (4.1%)	8 (10.4%)
Treatment related to lymphedema,** n (%)			
Preventatively	4 (2.6%)	1 (1.4%)	3 (3.9%)
Existing lymphedema	5 (3.3%)	1 (1.4%)	4 (5.2%)
Symptom subscales EORTC-BR23			
Arm symptoms, n, mean ± SD	152, 16.2±19.0	74, 15.6±20.1	78, 16.8±18.0
Breast symptoms, n, mean ± SD	151, 18.9±16.1	74, 18.6±16.4	77, 19.2±16.0
L-Dex[a], n, Mean ± SD	80, -0.3±5.1	39, -0.6±3.6	41, 0.1±6.2
Volume % difference[b], n, mean ± SD	118, 1.3±19.8	55, 0.6 ±19.7	63, 1.9±20.0
Upper extremity strength[c], n, mean ± SD	138, 29.4±8.3	71, 29.0±8.1	67, 29.8±8.

Not included: *n = 4 missing, **n = 2 missing, [a] n=3 (n = 1 missing, n = 2 bilateral axillary surgery), [b] n =35 (n = 5 bilateral axillary surgery, n = 30 left side estimated), [c] n = 15 (n = 14 post-surgery restrictions, n =1 precautionary due to arm swelling)
Abbreviations: BMI, body mass index; SD, standard deviation; CE, cyclophosphamide & epirubicin; pctl, percentile/IQR, interquartile range

Retention, adherence and adverse events

Outcome data were available for 130 participants (85%) at 12-weeks post-intervention, and for 121 (79%) at the 39 week follow-up (Figure 1). %). Four women never partook in the intervention and an additional six withdrew shortly after initiation of the program. A detailed description of reasons for non-attendance can be found elsewhere (article in submission, Møller et al.).

On average, participants in the HIGH group attended 66% (±18) of the planned exercise sessions. Adherence to resistance exercise prescription of the upper extremity corresponded to a median load of 10 RM during the first two weeks. From week three forward (heavy-load period), loads corresponded to 7 RM. Comparatively, loads lifted for the leg press were 14 RM and 8 RM, respectively. No exercise-related injuries were reported. Six participants in the HIGH and five participants in the LOW group experienced swelling during the 12-week intervention and received treatment delivered by a lymphedema therapist. Just one of the women in the HIGH group reduced loads (10-15 RM), whereas the other five continued lifting loads corresponding to 5-8 RM. Seven of these participants had received treatment for BCRL between the 12 and 39 week follow up, while three had not, and one was lost-to follow-up at 39 weeks.

Lymphedema

Point prevalence: Irrespective of assessment method, point prevalence of BCRL was similar between the HIGH and LOW group at all time points (Table 11). Point prevalence of BCRL varied depending on the method of assessment. For participants reporting an observation of swelling on the surgical side compared to the non-surgical side, it is worth noting that body only (breast and torso) accounted for 31 (66%), 8 (25.8%) and 17 (39.5%) of these cases at baseline, 12 and 39 weeks respectively. As BIS and DXA detect arm and hand swelling only, these methods of lymphedema were unable to detect these cases (Table 11).

Table 11. Lymphedema point prevalence. Number of participants (%)

	n	Baseline	n	12 weeks	n	39 weeks
L-Dex >10[a]						
HIGH	39	0 (0.0%)	33	3 (9.1%)	41	4 (9.8%)
LOW	41	2 (4.9%)	31	2 (6.5%)	34	3 (8.8%)
Inter-arm volume % difference > 5%[b]						
HIGH	55	15 (27.3%)	45	14 (31.1%)	50	12 (24.0%)
LOW	63	15 (23.8%)	51	13 (25.5%)	49	13 (26.5%)
Observed difference in size between sides within the last week[c]						
HIGH	74	19 (25.7%)	62	18 (29.0%)	62	21 (33.9%)
LOW	77	28 (36.4%)	63	13 (20.6%)	59	22 (37.3%)

Based on all available data for each outcome.[a] Maximum n = 81 due to bilateral axillary surgery (n =2) and BIS not available (n = 70). At 39 weeks BIS was available for twelve of these particicpants and included in the analysis ; [b] Maximum n = 148 due to bilateral axillary surgery (n = 5), n = 30, 28, 14 exceeded DXA scan area, respectively at baseline, 12 and 39 weeks and were therefore not included in the analysis); [c] Of the participants that observed swelling at: baseline n = 31 (66%), 12 weeks n = 8 (25.8%), 39 weeks n = 17 (39.5%) reported swelling located to the body (breast , torso) only

Self-reported diagnosis of BCRL at baseline: Five participants (3.3%) reported a diagnosis of BCRL which they were receiving or had received lymphedema treatment for; one of whom participated in the HIGH group and carried out the resistance exercise protocol without need for modification (e.g. less load). All five of these participants also reported observed swelling at baseline, two of whom reported localization to the torso only, which therefore could not be detected by BIS or DXA. Further, no DXA measurements were available for two participants as body dimensions exceeded the scan areas. Comparatively, one of these participants had an L-Dex >10, while no L-Dex was available for the other participant. Finally, one of the participants reported observed swelling of the overarm, breast and torso which BIS and DXA did not detect.

L-Dex: The mean difference in L-Dex scores between the HIGH and LOW group and associated two-sided 90% CIs were contained within the predetermined equivalence margin of ±5.0 units at both 12 and 39 weeks indicating equivalence between groups (Table 12). Equivalence to the predetermined equivalence margin in the per-protocol analysis at 12 weeks was also observed (Table 13). However, at the 39 week follow-up, the upper CI exceeded the predetermined margin.

Table 12. Equivalence between groups for BCRL outcomes

		Mean difference*	Equivalence 90% CI
L-Dex (±5.0)[a] (n =81)**	n		
12 weeks	64	0.4	-2.5 to 3.2
39 weeks	63	0.7	-2.2 to 3.6
Inter-arm volume % difference (±3.0)[a] (n =148)**			
12 weeks[ǂ]	86	**-3.5**	**-17.3 to 10.3[b]**
39 weeks[ǂ]	83	**-1.7**	**-7.7 to 4.3[c]**
Pain (±1.0)[a] (n =153)**			
12 weeks	124	**-0.7**	**-1.3 to 0[b]**
39 weeks	121	**-0.8**	**-1.5 to -0.1[b]**
Heaviness (±1.0)[a] (n =153)**			
12 weeks	124	-0.2	-0.6 to 0.2
39 weeks	121	0.0	-0.7 to 0.6
Tightness (±1.0)[a] (n =153)**			
12 weeks	124	-0.1	-0.8 to 0.6
39 weeks	121	**-1.0**	**-1.8 to 0.2[b]**
Swelling (±1.0)[a] (n =153)**			
12 weeks	124	0.2	-0.4 to 0.8
39 weeks	120	0.0	-0.8 to 0.7

*Mean difference between groups with HIGH as comparator (HIGH minus LOW); **Maximum n; ǂn = 38 and 30 not included at 12 and 39 weeks respectively, due to body dimension exceeding the DXA scan area; [a]Pre-determined equivalence margin; **Bold** = equivalence not demonstrated; [b]negative deviation reflecting reductions beyond the equivalence margin favoring the HIGH group [c]inconclusive as mean is within predetermined equivalence margin, but CI's exceed at both sides

Inter-arm volume % difference: Non-equivalence between groups was observed at all time points for inter-arm volume % differences with deviations inconclusive or indicating reductions in arm volume, favoring the HIGH group (Table 12). These observations were consistent with findings from the per-protocol analysis (Table 13).

BCRL symptoms: Equivalence between groups was found for all symptoms except for pain at 12 weeks and tightness and pain at 39 weeks favoring reductions for those in the HIGH group (Table 12). Consistent with the between group analysis, the per-protocol findings indicated equivalence to the predetermined margin or deviations indicating reductions in symptoms except for pain at 39 weeks as upper CI's exceeded the equivalence margin (Table 13).

Table 13. Per-protocol equivalence of BCRL outcomes in participants with >65% adherence to HIGH

Variable	Baseline Mean (SD)	12 weeks Mean (SD)	39 weeks Mean (SD)	12 weeks - baseline n	12 weeks - baseline Δ (90 % CI)	39 weeks-baseline n	39 weeks-baseline Δ (90 % CI)
L-Dex (±5.0)[a]	-0.8 (3.3)	0.9 (6.6)	1.5 (5.3)	21[*]	1.7 (-0.8 to 4.2)	21[*]	**3.2 (0.9 to 5.5)[c]**
Inter-arm volume % difference (±3.0)[a]	5.3 (23.0)	4.3 (27.2)	0.6 (7.4)	21[**]	**-3.1 (-19.5 to 13.4)[b]**	26[**]	**-5.0 (-12.8 to 2.9)[b]**
Pain (±1.0)[a]	1.0 (1.7)	0.6 (1.2)	1.4 (2.5)	32	-0.4 (-0.9 to 0.1)	33	**0.4 (-0.4 to 1.2)[c]**
Heaviness (±1.0)[a]	0.5 (1.3)	0.3 (1.1)	0.9 (1.7)	32	-0.2 (-0.4 to 0.1)	33	0.4 (0.0 to 0.8)
Tightness (±1.0)[a]	1.6 (2.4)	0.8 (1.9)	0.4 (0.8)	32	**-0.9 (-1.5 to -0.2)[b]**	33	**-1.2 (-2.0 to -0.5)[b]**
Swelling (±1.0)[a]	1.1 (2.0)	1.0 (1.8)	1.0 (1.8)	32	-0.1 (-0.7 to 0.6)	33	-0.1 (-0.6 to 0.5)

[a] Pre-determined equivalence margin; [*]maximum n = 21; **Bold =** equivalence not demonstrated;[**]maximum n = 32; [b] negative deviation reflecting reductions beyond the equivalence margin; [c] positive deviation reflecting increases beyond the equivalence

Upper extremity muscular strength

A significant ($p < 0.05$) increase in maximal upper extremity strength was observed in the HIGH group at all follow-up assessments which were significantly greater compared to those in the LOW group at 6 and 12 week follow-up (Table 14). Strength increases corresponded to an effect size of 0.55 (95% CI 0.40 – 0.75), 0.55 (0.35 – 0.70) and 0.35 (0.15 – 0.55) at 6, 12 and 39 weeks, respectively.

Breast cancer-specific functional and symptom domains

No between group differences were observed for any subscale score of the EORTC QLQ-BR23. However, both groups reported declines in breast symptoms at 6 and 12 weeks. Similarly, declines in arm symptoms were seen for both groups at 6 weeks, but only in the HIGH group at 12 week follow-up (Table 14 and Supplemental table).

Table 14. Changes in upper extremity strength and breast cancer-specific functional and symptom domains

	Δ 6 weeks-baseline			**Δ 12 weeks-baseline**			**Δ 39 weeks-baseline**		
Variable	n	Mean Δ (95% CI)	Group difference (95% CI)	n	Mean Δ (95% CI)	Group difference (95% CI)	n	Mean Δ (95% CI)	Group difference (95% CI)
Muscular strength 1 RM (kg)*									
Chest press									
HIGH	58	**5 (3 to 6)**	**4 (2 to 6)**	56	**4 (3 to 6)**	**3 (1 to 5)**	50	**3 (1 to 5)**	2 (0 to 5)
LOW	51	1 (-1 to 2)		55	1 (0 to 3)		44	1 (-1 to 3)	
EORTC QLQ-BR23 scores**									
Body Image									
HIGH	62	2 (-3 to 7)	4 (-3 to 10)	60	-3 (-9 to 2)	2 (-5 to 10)	61	**7 (2 to 11)[a]**	1 (-6 to 8)
LOW	61	-1 (-6 to 3)		62	-6 (-11 to -1)		56	**6 (1 to 11)[a]**	
Systemic therapy ǂ									
HIGH	63	**5 (1 to 10)[a]**	1 (-6 to 8)	61	**7 (2 to 12)[a]**	-2 (-9 to 6)	61	**-19 (-23 to -15)[b]**	1 (-5 to 7)
LOW	62	4 (-1 to 9)		65	**9 (4 to 14)[a]**		57	**-20 (-24 to -16)[c]**	
Breast symptoms									
HIGH	62	**-6 (-9 to -2)[a]**	1 (-4 to 6)	60	**-11 (-15 to -7)[b]**	-2 (-8 to 3)	59	-4 (-9 to 1)	-4 (-12 to 3)
LOW	62	**-7 (10 to -3)[a]**		64	**-9 (-12 to -5)[a]**		55	1 (-4 to 6)	
Arm symptoms									
HIGH	62	**-4 (-8 to 0)[a]**	1 (-5 to 7)	60	**-6 (-10 to -1)[a]**	-2 (-8 to 4)	59	-1 (-6 to 4)	-4 (-12 to 3)
LOW	62	**-5 (-10 to -1)[a]**		65	-4 (-8 to 1)		56	3 (-2 to 9)	

Abbreviations: CI, confidence interval; **Bold** = statistical difference ($p < 0.05$); *No upper extremity strength measures on one participant (LOW) at baseline due to visible and untreated swelling. No upper extremity strength assessment at subsequent data collections as the participant was receiving treatment for lymphedema. Three participants (2 HIGH, 1 LOW) were not assessed for upper extremity strength at 6, 12 and 39 weeks, as a precautionary measure due to swelling or because participants refused. An additional participant (HIGH) received treatment for lymphedema at 12 and 39 weeks and was therefore not tested; **Higher functional scores (body image) indicate higher levels of functioning, lower symptom scores (systemic therapy, arm and breast symptoms) indicate a reduction in symptoms; ǂ Perceived treatment burden; [a, b, c] Subjective significance of changes from baseline in terms of [a] "small", [b] "moderate", [c] "large" (Osoba, 1998)

Discussion

This thesis examined for the first time whether participation in heavy-load resistance exercise exacerbates development of lymphedema in breast cancer survivors at risk for lymphedema. This section provides a discussion of the main findings of the three studies/ four articles considered in the context of relevant literature. Further, methodological considerations including issues of internal and external validity will be addressed.

Lymphedema

Findings of Study 1 indicated no association between participation in a multimodal exercise intervention including heavy-load resistance exercise during taxane-based chemotherapy and BCRL development. While no conclusions regarding the safety of heavy-load resistance and BCRL could

be drawn from the conclusions of Study 1, it provided a platform for Studies 2 and 3 to prospectively evaluate the lymphatic response to heavy-load resistance exercise both acutely after a single bout of resistance exercise, and after repeated exposure over twelve weeks. In accordance with the hypothesis, Study 2 found that acute changes in extracellular fluid, arm volume and symptoms associated with BCRL were similar irrespective of whether low- or heavy-load upper extremity resistance exercise was performed at all time points with the exception of extracellular fluid at 72-hours post-exercise, with lower CI's indicating reductions in swelling after heavy loads. Further, though individual fluctuations beyond the predetermined thresholds were observed for BCRL symptoms, the majority of deviations (82%) indicated reductions in severity after resistance exercise with both intensities. Consistent with the results of Study 2, similar L-Dex scores and self-reported perceptions of heaviness, swelling and tightness post-intervention were found between the HIGH and LOW group in Study 3. Additionally, though equivalence was not demonstrated in inter-arm volume % differences or pain, negative deviations indicated reductions of these outcomes, favoring the HIGH group. Accordingly, per-protocol analysis of HIGH participants with >65% adherence also supported equivalence to- or reductions beyond the predetermined equivalence margins for all outcomes post-intervention.

These consistent findings are in agreement with previous research establishing the safety of resistance exercise in regard to BCRL based on exercise prescription using low- to moderate loads. The resistance exercise programs of previous work utilized loads corresponding to 60-80% 1 RM at 8-12 repetitions (59, 85) or 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 (86) or within a range of 10-12 repetitions (87). Further our findings are in agreement with the results of two studies by Cormie et al. (13, 73), demonstrating the safety of heavy-load resistance exercise in women with clinically stable BCRL who had been diagnosed with breast cancer at least a year before study inclusion. These studies found that the extent of arm swelling and associated BCRL symptoms remained stable immediately post-, 24- and 72-hours after one bout of resistance exercise (73), and after twelve-weeks of regular resistance exercise irrespective of low- or heavy-loads (75-85% of 1 RM using 6-10 RM) were lifted (13). The results from the present thesis indicate that heavy-load resistance exercise, specifically corresponding to 85-90% 1 RM at 5-8 repetitions, can be undertaken safely. Therefore, the current evidence base (7, 8, 10, 11) can now be extended to include participation in heavy-load resistance exercise.

Point prevalence

Post-intervention point prevalence rates were obtained in Studies 1 and 3 with variations depending on the method of measurement (Tables 6 and 11). This is in accordance with previous studies finding that applied diagnostic methods influences incidence and prevalence rates (4, 88) and exemplifies the challenges in providing accurate estimates of BCRL. Importantly however, similar point prevalence rates were observed between the HIGH and LOW group in Study 3 for any given measurement method. Beyond measurement methods, other factors influence estimates of BCRL prevalence including treatment burden (30) and timing of measurements post-surgery (4, 40) limiting comparisons between studies. To the authors knowledge, the only meaningful comparison is to a randomized controlled trial by Kilbreath et al. (n = 160) (66). This study evaluated eight weeks of low to moderate load resistance exercise, starting 4-6 post-surgery, and found point prevalent rates corresponding to 7% and 8% in the exercise group (rates were determined using BIS and Circumference >2 cm, respectively) (66). While the Kilbreath study provides a relevant comparison in regard to timing and measurement method, it should however be noted that over 95% of the participants in Studies 1 and 3 were receiving adjuvant taxane-based chemotherapy. In comparison about half (52.5%) of the participants in the Kilbreath study were receiving taxane-based chemotherapy. This is relevant, as generalized edema and ensuing arm swelling is a known side-effect to taxane-based chemotherapy. As such, our data estimating point prevalence of BCRL following a multimodal exercise intervention including heavy-load resistance exercise provides further evidence of the safety of this exercise modality.

Muscular strength

Significant post-intervention ($p < 0.05$) upper extremity strength increases were observed after six weeks of participation in *Body & Cancer* (Study 1), and after twelve weeks in the HIGH intervention (Study 3) (Tables 5 and 14). Further significant between group differences in strength were observed with an increase of 13% in the HIGH group, compared to a 3% increase in the LOW group. This is relevant as upper extremity strength in breast cancer survivors during cancer treatment (without intervention) has been found to be 12-16% lower compared to healthy women (89). Further, increases in upper extremity strength in the HIGH group corresponded to an effect size of 0.55 (95% CI 0.35-0.70), similar to pooled estimates from a systematic review (8). Specifically, fifteen randomized controlled trials evaluating populations with stable BCRL or at risk for developing BCRL were included in the systematic review, finding that participation in resistance exercise significantly increased muscular strength compared to controls with an effect

size 0.57 (95% CI 0.37-0.76). Therefore, the observed effect sizes after participation in the HIGH intervention are encouraging, especially considering that none of the studies in the systematic review exclusively included previously physically inactive breast cancer survivors receiving taxane-based chemotherapy. As such, the present study indicates that participation in a multimodal intervention incorporating heavy-load resistance exercise during chemotherapy can mitigate declines in muscle strength.

Though no between group differences were observed for any subscale score of the EORTC QLQ- B23 it should be highlighted that clinically relevant within group reductions in breast and arm symptoms were found in the HIGH group (90) at both 6- and 12 weeks. These data are similar to findings by the aforementioned studies of Kilbreath (66) and Cormie (13). Namely, that clinically relevant reductions were observed post-intervention in both studies, despite no statistically significant difference between exercise and control groups. Therefore, the data from the present thesis provide additional evidence that participation in heavy-load resistance does not precipitate BCRL, and likely alleviates breast and arm symptoms associated with breast cancer surgery and treatment.

Methodological considerations

Internal validity

Measurement methods

No objective measures of BCRL were obtained in Study 1 with a self-reported clinician diagnosis defined as a lymphedema case. Circumference measurements, taken at the time of diagnosis, were however obtained for 38 (93%) of the women that reported a diagnosis of BCRL confirming BCRL objectively. This measurement method is considered acceptable as a minimum standard provided that measurements are obtained using a non-stretch tape measure at multiple points on each arm, and is performed by health professionals with extensive training in this measurement method, in order to provide reliable measures (39). As the circumference data in Study 1 were collected by eight different clinicians using varying measurement protocols, circumference measurements provided are not standardized and the level of training of the various clinicians is unknown. Therefore, though the attainment of circumference measures adds strength to the study these limitations should be taken into consideration. Nonetheless, these data reflect the reality of clinical practice and provided a basis for Studies 2 and 3 where validated objective measurement methods were used to assess presence and severity of lymphedema.

Measurement methods such as circumference, water displacement, and perometry are limited in their ability to differentiate between tissue types and indirectly measure extracellular fluid (approximately 25% of the total limb), by measuring the total volume of the entire extremity (67, 88). In contrast, BIS directly measures lymph fluid change by measuring the impedance to a low level electrical current. This allows for a sensitive (74, 91) and reliable measurement method for detecting subclinical BCRL (91) (early BCRL characterized by an increase in extracellular fluid). Further, as impedance values are converted to an L-Dex score, inherent volume differences associated with hand dominance are taken into account (88, 91). However, as lymphedema progresses BIS loses its sensitivity as extracellular fluid is replaced with fibrotic and adipose tissues, and is therefore not considered an appropriate measurement method to monitor BCRL over time (74, 88). However, as the purpose of Studies 2 and 3 were to detect changes in extracellular fluid in women at risk for BCRL, the BIS measurements add strength to the results.

DXA provides a sensitive measure of tissue composition using a three-compartment model providing estimates of bone mass composition, fat mass and lean mass where the lean mass component includes extracellular fluid (71, 74, 75). DXA is sensitive to changes in tissue composition, and is therefore able to monitor BCRL over time as fluid components are replaced with adipose tissue. Further, DXA allows for analysis of separate regions of the arm, of potential clinical importance for patients where swelling is confined to a specific region of the arm or hand (71, 74, 75, 92). Two different DXA scan and analysis protocols were used in this thesis. In study 2, separate arm scans were performed and software with a high resolution was used as described by Gjorup et al., (71), allowing for more precise definition of the region of interest and correct definition of bone and soft tissue. In study 3, whole body scans were performed and analyzed with standard total body software (74, 75). However, due to body dimensions exceeding the scan area, 28% of the sample (n = 42) are missing inter-arm volume data, why caution should be applied when generalizing Study 3 findings to obese women, and is a limitation to this protocol. As an alternative for these individuals, the potential of performing separate arms scans exists.

In line with existing recommendations advocating for subjective symptom assessment alongside objective measurements (39), breast and arm symptoms were monitored using a validated questionnaire (EORTC QLQ-BR23) in Study 3, as well as the severity of swelling, heaviness, pain and tightness using a numeric rating scale (72, 73) in Study 2 and 3. This is relevant as breast cancer survivors at risk for lymphedema may experience a variety of symptoms, which can be the earliest indicator of an ensuing BCRL (93). Further, assessment of symptoms provides a more

comprehensive evaluation of BCRL that takes the participant's perceptions into consideration, which arguably is more important than any objective measurement. Finally, as complete BIS and DXA data were not available in Study 3, the self-report measures ensured that 100% data for at least one outcome was available adding strength to the findings.

Blinding

Inherent to exercise intervention studies, Studies 2 and 3 were not double-blinded. However, considerable effort was made to reduce the potential of assessor bias as data was collected blinded by medical technicians and study assessors with no knowledge of group allocation. Further, outcomes were obtained objectively and assessors followed detailed protocols, with previous test results concealed at follow-up assessments so that neither the participant nor the assessor knew their previous scores. Keying of data and statistical analyses were also performed blinded to group allocation.

Equivalence margins

As it was hypothesized that lymphatic response would be similar between groups in Study 2 and 3, the equivalence design was considered the most appropriate analysis of BCRL outcomes. This was formalized by defining equivalence margins for each outcome, which ideally represent the maximum clinically acceptable difference that one is willing to accept in return for the secondary benefits of a new therapy (heavy-load resistance exercise) (81). 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 (81). This is exemplified by equivalence margins for L-Dex being set at ± 3.0 in Study 2 rendering conclusions of nonequivalence between heavy- and low-loads at 72 hours. *A priori*, this 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, in the interim to Study 3, normative L-Dex data were published indicating that L-Dex scores fluctuate between 9-11 units, (70) which is why equivalence margins were set at ±5.0. As such, equivalence would have been declared at all time points in Study 2 and illustrates the challenges in defining meaningful margins in equivalence trials. The chosen equivalence margins in Studies 2 and 3 were purposely set as more conservative (narrower) in order to ensure credibility. Arguably though, this may have created confidence limits with an unnecessarily narrow interval rendering conclusions of nonequivalence. While this may not be the case due to over-conservative equivalence margins, the negative deviations favoring the Heavy-load or HIGH group add

confidence to the overall conclusion, that heavy-load resistance exercise does not exacerbate the development of BCRL acutely or after twelve weeks of repeated exposure.

Follow-up data

39 weeks follow-up data were collected in Study 3, with findings indicating that the longer term effect of the LOW and HIGH intervention was similar between groups or indicated reductions favouring the HIGH group. These findings were consistent with the per-protocol analysis, with the exception of L-Dex and pain as upper CIs indicated a slight increase beyond the predetermined equivalence margin. However, in general, care should be taken when interpreting the 39 week follow-up results as no data regarding upper extremity resistance exercise behaviour was collected post-intervention. Consequently, we cannot determine whether effects seen at 39 weeks were a result of resistance exercise or other unknown factors and is an additional limitation of this study.

External validity

When generalizing the results of the thesis to the larger breast cancer population at risk for lymphedema a number of issues should be considered.

In Study 2, five women were excluded at baseline screening if they presented with evidence of BCRL according to standardized protocols for BIS (L-Dex > 10) or visual inspection (CTC v3.0). These women could however have been experiencing transient swelling. Further, though participants were not screened for BCRL and excluded before participation in Studies 1 and 3, transient cases were not specifically addressed. As such, the findings of this thesis do not extend to breast cancer survivors displaying increased levels of extracellular fluid, but who have not been diagnosed with- or received treatment for BCRL. Clinically, this is important as uncertainty exists as to whether these women would respond in a positive or negative way to heavy-load resistance exercise. Indeed, though previous studies have found resistance exercise, including heavy-load, to be both safe and beneficial for breast cancer survivors with lymphedema, these studies have included women presenting with a clinical diagnosis of BCRL (94) or specifically diagnosed stable BCRL (e.g. no treatment within the last three months)(7, 8, 95, 96). Therefore, a paucity in knowledge remains as to the appropriate resistance exercise prescription for women presenting with potentially transient, unstable lymphedema.

Another limitation to this thesis was that participants making up our sample were on average younger than women diagnosed with breast cancer. Further, inherent to exercise studies, there may also have been a selection bias towards women motivated to exercise. Nonetheless, 60%

of the total cohort (n =194 (n = 41 Study 1, n =153 Study 3)) reported that they were physically inactive pre- diagnosis which extends generalizability to this vulnerable groups. This is relevant as fear of lymphedema has been identified as a barrier for physical activity, and especially vigorous or strength activities (2), which in turn may lead to avoidance and non-adoption of regular physical activity further increasing risk of BCRL (4). Also, recent work has found that attitude towards exercise can be transformed from having no priority to being highly prioritized if support to adopt exercise is received in physically inactive breast cancer survivors during adjuvant chemotherapy (97). While it is not known whether this translates to long-term behavioral change, the potential for long term adoption of exercise exists, ultimately leading to better health outcomes (98, 99).

Further, 96% (311) of the participants involved with Study 1, 2 or 3 were receiving taxane-based adjuvant chemotherapy. As such, findings from this body of work are highly generalizable to the majority of breast cancer survivors receiving adjuvant chemotherapy as taxane-based chemotherapy is considered standard first line treatment (16, 100). Further, when considering other evidence-based risk factors for developing BCRL, participants had an average BMI of 25, 172 (53%) had ALND, and 138 (43%) had undergone a mastectomy. Therefore, as multiple risk factors for developing BCRL are well represented, applicability extends to breast cancer survivors at additional risk for developing lymphedema.

Conclusion and clinical implications

In conclusion, across studies, we found no evidence to suggest that participating in heavy-load resistance exercise during adjuvant taxane-based chemotherapy for breast cancer increased the risk of developing BCRL. Further, benefits were observed in upper extremity strength, as well as clinically relevant reductions in breast cancer-specific arm and breast symptoms related to participation in a multimodal exercise intervention including heavy-load resistance exercise. Importantly, as this thesis targeted breast cancer survivors with multiple risk factors for developing BCRL (axillary surgery, physically inactive, taxane-based chemotherapy), applicability extends to those considered at high-risk for developing BCRL. Therefore, breast cancer survivors should be encouraged to adopt exercise including heavy-load resistance exercise without fear of exacerbating BCRL development during adjuvant chemotherapy and beyond.

Breast cancer survivors commonly receive risk reduction advice cautioning against heavy lifting (2, 46) despite revisions from the National Lymphedema Network, omitting this particular risk reduction strategy (9). Findings from the present thesis lend clinical evidence that

supports these revisions, as we found no evidence indicating that intermittent activities of daily living including heavy-load lifting need be avoided. These results are in accordance with previous research finding that unrestricted activity of the upper extremities did not alter BCRL risk (86). Further, Round et al. found that the best functional outcomes were found in those who followed minimal activity restrictions and used their at-risk extremity as much as the contralateral extremity (101). As such, breast cancer survivors should be encouraged, without restrictions, to participate in activities of daily living in accordance with signs and symptoms of BCRL.

Perspectives and future research

The findings from this thesis are in support of current lymphedema risk reduction recommendations from The National Comprehensive Cancer Network and The American Society of Breast Surgeons (39). These recommendations advocate for patient education which encourages participation in regular exercise (without restrictions) and weight management, while also providing information about early signs and symptoms of BCRL (e.g. tightness, heaviness and swelling) and individual lifetime risk for developing BCRL. This is relevant as early self-detection combined with prompt intervention has been associated with better outcomes (102). Indeed, a paradigm shift in BCRL surveillance has occurred with increasing support for early-detection strategies whereby reversible stages of lymphedema (stage 0 -1) are identified. Identifying subclinical lymphedema facilitates early, less time consuming and less cumbersome intervention (e.g. compression garment, self-care, self-MLD) which likely reduces BCRL progression and is likely more cost-effective than waiting for obvious swelling to occur (22, 103). Various prospective surveillance models have been proposed to facilitate early detection. However, consensus is lacking with regard to the optimal frequency and duration of surveillance, and with respect to who should be regularly surveyed (102). Further, the detection of subclinical lymphedema has in large part been made possible due to the increased sensitivity of measurement methods such as BIS and perometry, as well as tissue dielectric constant and DXA. However, agreement as to the optimal measurement method or methods is lacking as advantages and disadvantages exist for each of these diagnostic tools (102).Therefore, though current data supports the implementation of prospective surveillance (102), future work should provide prospective comparisons of measurement methods and current prospective models with long-term follow-up and cost-benefit analyses in order to elucidate the best early detection strategy (or strategies).

A considerable rationale exists for participating in resistance exercise during adjuvant chemotherapy as previous clinical trials using low to moderate loads have found that resistance exercise elicits gains in muscle strength while mitigating adverse changes in physical components of quality of life, including fatigue, without increased risk of BCRL (7, 8, 10, 11, 54). Moreover, it has been hypothesized that resistance exercise reduces taxane-related edema through the effects of

the muscle pump (33, 40). Due to the dose-response relationship that exists between loads lifted and gains in muscular structure and function it is feasible that additional benefits can be gained. Further 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. Therefore, a head to head comparison between resistance exercise loads should be undertaken with results from this thesis providing the necessary evidence to carry out this work.

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