Morbidity after lymph node dissection in patients with cancer: Incidence, risk factors, and prevention
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CHAPTER 5

Conservative interventions for preventing clinically detectable upper-limb lymphoedema in patients who are at risk of developing lymphoedema after breast cancer therapy

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ABSTRACT

Background
Breast cancer related lymphoedema is one of the most bothersome long term sequelae of breast cancer treatment. A number of studies have investigated the effectiveness of different treatment strategies to reduce the risk of breast cancer related lymphoedema.

Objectives
To provide an overview of current evidence on the effectiveness of conservative (non-surgical and non-farmacological) interventions for prevention of clinically detectable upper limb lymphoedema after breast cancer treatment.

Search methods
We searched the Cochrane Breast Cancer Group's (CBCG) Specialised Register, CENTRAL, MEDLINE via PubMed, EMBASE via Ovid, CINAHL, PEDRO, PsychINFO, and the WHO International Clinical Trials Registry Platform. We reviewed the reference lists of included trials and of relevant other reviews that were identified in the search. Eligible were all randomised controlled trials that used lymphoedema as the primary outcome, and that compared any conservative intervention to either no intervention or to another conservative intervention, in patients of both sexes and all ages at risk of developing lymphoedema in the upper limb after treatment for breast cancer. We excluded studies that were non-randomised, studies that had included patients who had been diagnosed with lymphoedema or cancer recurrence, or studies that had not used a pre-defined, objective measure to assess lymphoedema. All studies identified through the electronic searching were screened for eligibility by two authors (MS and MT) independently.

Data collection and analysis
Three review authors independently extracted data on study characteristics, risk of bias, and outcomes after interventions from reports of the included studies. Outcome measures included lymphoedema, infection, range of motion of the shoulder, pain, psychosocial morbidity, level of functioning in activities of daily life (ADL), and health-related quality of life (HRQoL). Where possible, meta-analyses were performed to generate summary estimates of effectiveness, in the form of relative risks or hazard ratios for lymphoedema incidence and other dichotomous outcomes, and mean differences for range of motion and patient reported outcomes on a continuous scale.

Results
We were able to include ten trials. Overall, the quality of the evidence generated by these trials was low, due to risk of bias and inconsistency in the results.
**manual lymph drainage**

Four studies (385 patients) studied the effectiveness of manual lymph drainage (MLD). In two of these studies MLD was added to education and/or exercises. The addition of MLD to standard physiotherapy resulted in lower lymphoedema incidence compared to standard physiotherapy in only one of these studies. Two other studies compared MLD combined with compression and exercise respectively to education only. Both studies found lower incidence of lymphoedema in patients receiving the combined intervention compared to patients who received education only.

Manual lymph drainage combined with either exercise or compression resulted in better shoulder mobility for abduction and forward flexion in the first weeks after breast cancer surgery, compared to education only (abduction 21.8 degrees; 95% CI: 13.6 to 30.1; forward flexion 14.4 degrees; 95% CI: 7.1 to 21.8). At medium term follow up the mean difference in improvement was 3.10 degrees (95% CI: -4.45 to 10.65) for abduction, and 0.40 degrees (95% CI: -8.25 to 9.05) for forward flexion, in patients receiving education only compared to patients receiving MLD and compression. The mean difference in abduction was 16.90 degrees (95% CI: 10.12 - 23.68) and in flexion 14.30 degrees (95% CI: 7.11 - 21.49) in patients receiving MLD and exercise compared to patients receiving exercise and education only.

Two of the studies on MLD reported on pain, with inconsistent results. Results on HRQOL in two studies on MLD were also contradictory. One study reported on functioning in activities of daily life. Infection, and psychosocial morbidity had not been evaluated in any of the studies on MLD.

**comprehensive outpatient follow-up**

One study investigated the effects of a comprehensive outpatient follow-up program, consisting of patient education, exercise, monitoring of lymphoedema symptoms and early intervention for lymphoedema, compared to education only. Lymphoedema incidence at 24 months was lower in the intervention group (RR: 0.34; 95% CI: 0.10 to 1.15). Patients in the intervention group had significantly faster recovery of shoulder abduction.

**early versus delayed start of shoulder mobilising exercises**

Three studies (378 patients) had compared early versus delayed (>7 days postoperative) start of shoulder mobilising exercises. The relative risk of lymphoedema after a delayed start was 0.59 (95% CI: 0.33 to 1.06). Shoulder mobility for forward flexion was better at one month and six months follow-up after early exercise, compared to delayed exercise (two studies), but no meta-analysis could be performed due to statistical heterogeneity. At 12 months follow-up (one study), there was no difference in forward flexion between early and late start of exercise. One of the studies had evaluated infection; the rates were 11% for an early start and 13% for a delayed start of exercise. One study had evaluated ADL functioning: the mean difference at one year follow-up was 0.2 on the shoulder disability questionnaire. One other study looked at pain: median scores were comparable at any point up to two years follow-up. The study that had evaluated HRQoL reported a difference at one year follow-up of 1.6 (95% CI: -2.14 to 5.34) on the Trial Outcome Index of the FACT-B. Two studies reported on wound drainage volumes, one of which found higher volume in the early exercise group.
**resistance training**

Two studies (351 patients) reported that resistance training does not increase the risk of developing lymphoedema, provided that symptoms are monitored and treated immediately if they occur (RR 0.58; 95% CI: 0.30 to 1.13). One of these studies reported on pain and found that in the exercise group patients reported pain more often at 3 months and 6 months. One of the studies reported on HRQoL: the difference in %change at 12 months follow-up was 0.2 for the mental component score and 2.5 for the physical component score. One study reported a risk of musculoskeletal injury in the resistance training group of 3.4 per 100, compared to 0 in the control group. None of the other outcome measures of interest were reported in these trials.

**Authors’ conclusions**

Because of the heterogeneity, the limited precision due to a low number of study participants, and the risk of bias, the results of this review should be interpreted with caution. Based on the current available evidence, we cannot draw firm conclusions about the effectiveness of physiotherapy interventions containing MLD.

The current evidence does not indicate a higher risk of lymphoedema after early postoperative start of exercises compared to a >7 days delay. Shoulder mobility is better at short-term follow-up after early start of exercises, but wound drainage volumes may be increased. Progressive resistance exercise therapy does not increase lymphoedema risk, provided that symptoms are closely monitored and adequately treated if they occur.

High quality trials are needed to further evaluate all the interventions studied in this review.
Background

Breast cancer is the most common type of cancer among women. Worldwide, it has been estimated that 1.38 million new cases were diagnosed in 2008. The incidence is especially high in the developed countries of the world, with an estimated age standardised incidence in 2008 of 76 cases per 100,000 women in the United States, 83.2 per 100,000 in Canada, 84.8 per 100,000 in Australia and 89.7 per 100,000 women in Western Europe. Advances in breast cancer treatment have resulted in better survival after diagnosis. As a consequence, an increasing number of people are confronted with early and late side effects of breast cancer treatment.

One of the most important side-effects of breast cancer treatment is secondary lymphoedema. The reported incidence of lymphoedema following breast cancer treatment varies from 6% to 54%. A recent systematic review and meta-analysis estimated the risk of developing arm lymphoedema to be 16.6%, taking all studies into account, and 21% based on meta-analysis of cohort studies. Lymphoedema incidence increases with the time since treatment. The variability in reported incidence is due, in part, to differences in the criteria used to define lymphoedema.

Lymphoedema can be a debilitating condition that negatively affects health-related quality of life, body image, finances, social participation and activity level. The economic burden of breast cancer related lymphoedema was studied in a two-year follow-up study after breast cancer treatment in which insurance claims data were used. The estimated difference in the two-year costs between women who were diagnosed with breast cancer related to lymphoedema and those without lymphoedema ranged from USD 14,877 to USD 23,167. The true costs may have been underestimated in that study because of the use of claims data and the limited duration of follow-up.

Pathophysiology of lymphoedema

Lymphoedema is the accumulation of interstitial fluid as a result of insufficient lymph drainage. After breast cancer treatment, secondary lymphoedema may occur as a result of insufficient lymph drainage from the upper limb. This is due to partial or total destruction of the lymphatic system with surgery or radiotherapy. Additionally, cancer treatment may induce qualitative changes in the structure of the skin and subcutaneous tissues of the arm or trunk, such as scarring or subcutaneous fibrosis. Insufficient lymph drainage due to these changes can also lead to the development of lymphoedema.

Diagnosis of lymphoedema

A variety of diagnostic criteria for the presence of lymphoedema are used. Lymphoedema may be defined as a certain amount of absolute or relative change in limb circumference. Circumference can be measured using a tape measure or perometry. Other criteria are absolute or relative changes in total limb volume. Volume can be estimated from circumference measurements, water displacement or laser scanning. Bioimpedance spectrometry can be used to estimate the amount of extracellular fluid. The diagnosis of lymphoedema is sometimes made by self-reporting of symptoms. The wide variety of ways to define and diagnose lymphoedema complicates the interpretation of research on its incidence, prevalence, risk factors, treatment and prevention.

Risk factors

Findings in the literature on treatment-related and patient-related risk factors are inconsistent. The treatment factor most consistently associated with lymphoedema is the extent of surgery. Besides the extent of local surgery, this specifically includes axillary lymph node dissection and the
number of lymph nodes removed. Radiotherapy has been associated with an elevated risk of lymphoedema in some studies, but not in others. This inconsistency may be due, in part, to the heterogeneity of radiotherapy treatment protocols. Of the clinical characteristics associated with an increased risk of developing lymphoedema, higher body mass index (BMI) and higher body weight are the most consistent. Other clinical risk factors include positive lymph nodes and advanced disease. Coming from a black race has also been suggested as a risk factor, although other studies found no such association. Higher age has been identified both as a risk factor and as a protective factor. Higher education or socioeconomic status has also been identified both as a risk factor and as a protective factor.

Interventions
Various preventive interventions are employed to minimise the risk of developing lymphoedema after treatment for breast cancer. For this review, we considered conservative interventions: non-surgical and non-farmacological interventions. These include, but may not be limited to, the interventions as described below.

Exercise
Performing exercise has been debated to be both a risk factor and a risk-reducing factor. Exercise increases blood flow and the blood pressure in the upper limb, and consequently increases lymph production. On the other hand, muscle activity in the limb stimulates lymph flow (often referred to as the ‘muscle pump’), improving lymph drainage. Interindividual physiological variation seems to exist with regards to changes in lymphatic drainage during exercise. Exercises that specifically aim to stimulate lymph flow from the extremity towards the thorax may, if effective, lower the risk of developing lymphoedema. Exercises that improve the range of motion and strength of the upper limb may also improve daily use of the arm thus improving lymph drainage though muscle activity.

Patient education
Patient education can be provided verbally, or through written materials. Education is intended to help patients understand the changes in fluid regulation in the affected limb and the influence of external factors on fluid regulation. Risk minimisation strategies may additionally be discussed as part of the education, including lifestyle advice, such as maintaining activity levels and a healthy BMI, information on early self-detection of lymphoedema, and measures that can be taken in case of swelling. Although education may be effective in encouraging preventive self-care measures, it may also unintentionally reduce other forms of behaviour, such as activities involving the arm on the affected side.

Monitoring and early intervention
Monitoring involves regular follow-up appointments to objectively judge the status of the affected limb and to reinforce behaviour that is thought to be beneficial for preventing lymphoedema. Subclinical lymphoedema may be diagnosed with the help of techniques such as bioimpedance spectrometry or whole limb perometry. The rationale for monitoring is that the sooner lymphoedema is diagnosed then the sooner it can be adequately addressed, thus limiting morbidity.
Compression therapy

Compression therapy may consist of wearing compression garments in various compression classes, and using bindings or pneumatic compression devices. The rationale for compression therapy is based on providing resistance to swelling, as well as improving the ‘muscle pump’ function. Compression therapy has been recommended for the treatment and control of manifest lymphoedema of the limbs, but is also sometimes used for prevention of lymphoedema.

Manual lymph drainage

Manual lymph drainage (MLD) is a massage technique that involves gentle compression of the skin to stimulate lymph flow and manual stimulation of lymph nodes to increase their activity. MLD generally aims at improving the quality of the oedema and reducing or stabilising lymphoedema. Reducing lymphoedema is achieved by stimulating the formation of physiological lymphatic shunts or alternative pathways for lymph drainage. Some evidence suggests that MLD could be effective in reducing upper limb volume in patients with existing lymphoedema although it is usually combined with other treatment modalities. Some advocate the use of MLD to prevent lymphoedema by activating alternative drainage pathways. Techniques of manual lymph drainage may also be used to improve tissue consistency and tissue compliance of the surgical scar, with the objective to improve lymphatic flow through the tissue and range of motion.

Lymph taping (Kinesiotape)

The concept of lymph taping is relatively novel. This therapy involves the application of elastic, thermo-adhesive tape in such a way that lymph drainage towards the lymph nodes is facilitated. Kinesiotape has been suggested as a replacement for bandaging in the treatment of lymphoedema.

Why it is important to do this review

Considering the impact of lymphoedema on the quality of life of patients after breast cancer therapy and the associated societal costs, efforts should be made to prevent its occurrence. Unfortunately, there is no conclusive evidence to date on the optimal strategy to prevent lymphoedema. Preventive treatments carry with them direct and indirect costs that should be balanced against possible gains. A research recommendation for a systematic review addressing this subject was made in the NHS Database of Uncertainties about the Effects of Treatments. The review presented here aims to summarize current evidence in such a way that it can be used to guide clinical decisions, and support the development of evidence-based guidelines for the prevention of lymphoedema in patients with breast cancer.

Objectives

To estimate the effectiveness of conservative therapies for the prevention of lymphoedema in (specific subgroups of) patients who are at risk of developing lymphoedema after treatment for breast cancer.

To compare the effectiveness of the different interventions.
Methods

Criteria for considering studies for this review

Types of studies
We considered all types of randomised controlled trials (RCTs) eligible for inclusion that had reported secondary lymphoedema as the primary outcome, and had compared a conservative intervention to either usual care, placebo intervention, or some other intervention.

Types of participants
We included trials in patients of both sexes and all ages at risk of developing lymphoedema in the upper limb after treatment for breast cancer. Treatments for breast cancer could include: surgical treatment for breast cancer with axillary lymph node dissection, sentinel lymph node biopsy or axillary sampling, with or without radiotherapy to the axilla or the supraclavicular fossa or both; or radiotherapy alone. Trials in patients who had been diagnosed with lymphoedema or cancer recurrence were not eligible for inclusion.

Types of interventions
We considered trials of exercise therapy, patient education, monitoring and early intervention, manual lymph drainage (MLD), compression therapy (bandages, a compression sleeve, pneumatic compression) and lymph taping; or any combination of these interventions. We also considered trials with other non-farmacological and non-surgical interventions eligible for inclusion if they were identified in the search, provided that the studies met the other inclusion criteria.

Types of outcome measures

Primary outcomes
The primary outcome in our review is the occurrence of lymphoedema. This could be reported as either a dichotomous outcome or as a continuous outcome (volume or percentage volume change). Time-to-event data, with lymphoedema as the event, was also used, if reported. Because of the variety of ways in which lymphoedema can be defined and diagnosed, studies were only considered eligible if they had used a predefined criterion for establishing lymphoedema that was based, at least in part, on an objective assessment. This included circumference measurements, water displacement methods, bioimpedance measurements, laser scanning, perometry and dual energy X-ray absorptiometry (DEXA) scanning. This means we did not include studies that had evaluated an intervention based solely on a diagnosis of lymphoedema made by a healthcare professional or on self-reported swelling or complaints of oedema.

Secondary outcomes
Secondary outcome measures of interest were:

- infection, defined as any inflammation (redness, pain, heat and swelling) for which antibiotics are prescribed;
- active range of motion (AROM) of the upper limb;
- level of functioning in activities of daily living (ADL), as a self-reported measure or as rated by an assessor using a validated measurement instrument.
The following self-reported measures were also included as secondary outcomes, whenever assessed with a validated measurement instrument:

- pain;
- health-related quality of life (including both physical and mental well-being);
- psychosocial morbidity (emotional or psychosocial distress).

Any reported adverse effects of the preventive treatments were documented.

**Search methods for identification of studies**

No language or publication date restrictions were imposed. We only considered research that has been published in peer-reviewed scientific journals.

**Electronic searches**

We searched the following databases.


(b) MEDLINE via PubMed. See Appendix 1 for the search strategy.

(c) EMBASE via Ovid (1980 to May 2013). See Appendix 2 for the search strategy.

(d) The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/Default.aspx) for all prospectively registered and ongoing trials. See Appendix 3 for the search strategy.

(e) The Cumulative Index to Nursing and Allied Health Literature (CINAHL) through EBSCO (1980 to May 2013). See Appendix 4 for the search strategy.


(g) PsycINFO through Ovid (1980 to May 2013). See Appendix 6 for the search strategy.

(h) The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 4, April 2013). See Appendix 7.

**Searching other resources**

References of included articles and relevant identified reviews were handsearched for previously unidentified studies.

**Data collection and analysis**

**Selection of studies**

All the studies identified through the electronic searching were screened for eligibility by two authors independently (MS and MT or CA). An initial selection was carried out based on the title of the study.
Articles were classified as potentially eligible if the title indicated a randomised controlled trial (RCT) on the prevention of lymphoedema using a conservative therapy. If no judgment could be made about the eligibility of a study based on the title, the judgment was based on title and abstract. Any disagreements about eligibility were resolved in consensus meetings. The same procedure was applied to references found in included studies. Review articles identified in the search were screened for relevance and reference lists were checked to identify additional potentially eligible studies. Final decisions about inclusion for all articles judged potentially eligible were based on the full text of the study report.

**Data extraction and management**

Two authors (MS and MT) performed data extraction independently, using data collection forms that were developed and pretested for the purpose of this study. In the case of disagreement, agreement was reached in a consensus meeting. If no consensus could be reached, the decision was made by a third author (CA).

For each included study, the following characteristics were collected:

1. study information (year, country, setting, sample size, method of randomisation, blinding and method of outcome assessment including the definition of lymphoedema in the case of a dichotomous outcome, duration of follow-up);
2. baseline characteristics of study participants (age, disease stage);
3. intervention used for the prevention of lymphoedema (type of treatment, dosage of treatment, description of usual care condition);
4. comparator (alternative intervention or follow-up only);
5. aggregated outcomes (event rates for dichotomous data or means and standard deviations for continuous data);
6. adverse effects reported; and
7. loss to follow-up (number and reasons).

If the data and methods reported were insufficient for data extraction or risk of bias assessment, the authors of included studies were contacted for additional information.

**Assessment of risk of bias in included studies**

Risk of bias was assessed using the Cochrane risk of bias tool for the appraisal of RCTs, as outlined in the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0. The tool contains six domains and each domain was assigned a judgement related to the risk of bias. The judgement could be ‘low risk’, ‘high risk’, or ‘unclear risk’. The latter judgement was assigned if the risk of bias of a characteristic in an included study was judged to be unclear, or if there was insufficient information on which to base the judgement.
The six domains are:

1. sequence generation;
2. allocation concealment;
3. blinding of participants, personnel and outcome assessors;
4. incomplete outcome data;
5. selective outcome reporting; and
6. other sources of bias.

Other sources of bias specifically addressed were comparability of the groups at baseline, intention to treat analysis, and equal treatment of groups except for the allocated intervention. Specifically, additional contact with a healthcare professional due to the nature of the intervention may also reinforce risk-reduction behaviour, such as self-care; this may result in overestimation of the effect. Since the effectiveness of self-care and other risk reduction behaviour is unclear, risk of bias from other sources was set to unclear if this was the only potential source of bias, or high if there were additional concerns related to risk of bias from other sources. Judgements on comparability of groups at baseline were based on magnitude of the differences rather than statistical significance.

Two authors (MS and MT) independently assessed each included trial for risk of bias. Results were compared and discussed in a consensus meeting. If no consensus could be reached, a third author (CA) made the decision. In cases where no clear judgement could be reached based on the trial report, the trial authors were contacted to obtain additional details. The risk of bias is reported with a risk of bias table and graph for each outcome measure.

Measures of treatment effect
Statistics to express treatment effects are reported for each outcome separately. We used the measure of effect as estimated in the intention-to-treat analysis. The method of assessment is reported for each outcome.

Dichotomous outcomes
For studies reporting event rates, we used the relative risk as a measure of effect. For dichotomous outcomes, such as a diagnosis of lymphoedema, the treatment effect was expressed as a risk ratio with 95% confidence intervals.

Continuous outcomes
For continuous outcomes, such as limb volume, and self-reported measures, such as health-related quality of life, psychosocial morbidity, level of ADL functioning and active range of motion of the upper limb, the treatment effect was expressed as the mean difference or the standardised mean difference, if different scales had been used. If no mean differences and confidence intervals were reported, they were calculated from the available summary data using Review Manager software (The Nordic Cochrane Centre, The Cochrane Collaboration).

For outcome variables measured with the same instrument, final scores and change scores (the difference between baseline scores and final scores) could be reported in the included trials. If final scores and change scores could be pooled, they were presented for subgroups in the corresponding forest plot. If it was not possible to extract standard deviations for a particular outcome,
attempts were made to obtain the standard deviations from the study authors. If no further details could be obtained, missing standard deviations were imputed using the square root of the average of the variances (standard deviation squared) from all other included studies for that measure.

**Time-to-event outcomes**

For time-to-event outcomes, such as time to diagnosis of lymphoedema, the treatment effect was expressed as a hazard ratio.

**Dealing with missing data**

For trials listed in trial registers, reported outcomes were compared with those specified in the protocol. If outcomes as described in the methods section of the publication or the trial registration file were not presented in the available publications, the authors were contacted for additional details.

**Assessment of heterogeneity**

Three authors (MS, MT and CA) jointly judged the extent of clinical heterogeneity for studies that had comparable goals and type of intervention, but differences with respect to treatment protocols or population. Outcomes that were judged potentially eligible for meta-analyses were used to generate summary measures of treatment effect. Subsequently, statistical heterogeneity was assessed by visual inspection of the forest plots and quantified using the Chi² statistic and the I² statistic, as provided by Review Manager software. For the Chi² statistic, a P value of 0.10 was set to indicate statistically significant heterogeneity, rather than the conventional value of 0.05. The I² statistic indicates the percentage of the variability in effect estimates that is due to heterogeneity. We considered an I² statistic greater than 50% as large. The value of the I² statistic was evaluated alongside the magnitude and direction of effect and the P value for the Chi² statistic for heterogeneity.

**Data synthesis**

Treatment effects from studies with comparable interventions and outcomes were visualized in forest plots. Summary estimates were calculated only if statistical heterogeneity was within the pre-specified limits of acceptability. The results were stratified according to the duration of follow-up, combining studies with short follow-up (< six months) and medium length follow-up (6 months up to two years) and long term follow-up (> 2 years) in separate plots.

For continuous outcomes, mean differences (MD) were used for limb volume and standardised mean differences (SMD) for self-reported measures.

Fixed-effect (inverse-variance method) analyses were conducted on all occasions considering the small number of studies. All analyses were performed using Review Manager software in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and R 3.0.1.

**Results**

A total of 2570 records were identified in the initial search, of which six were relevant reviews. In the reference lists of these reviews, one additional potentially eligible study was identified. Figure 1 provides full information on study selection. After removing duplicates 1702 unique titles remained. Of these, 1679 were excluded based on title and abstract.
**Included studies**

Twenty-three of the 1702 unique records were retrieved for full text evaluation. Of these ten fulfilled all inclusion criteria. For three of the included studies additional publications were available. These publications concerned reports on additional outcome measures, a publication on the trial protocol, and a paper on adverse events.

**Meta analyses on secondary outcome (shoulder range of motion):**
- 2 physiotherapy + MLD studies in 2 meta-analyses
- 3 postoperative exercise studies in 1 meta-analysis
- 2 postoperative exercise studies in 1 meta-analysis

**Meta analyses on primary outcome:**
- 2 resistance exercise studies
- 3 postoperative exercise studies
All included studies had evaluated the occurrence of lymphoedema, but different study questions and interventions had been addressed.

- Four trials in five publications investigated the effectiveness of manual lymph drainage, alone or in combination with other interventions, for the prevention of lymphoedema after breast cancer surgery.\textsuperscript{29,30,37,42,43}
- Two studies in four publications were non-inferiority trials investigating the safety of progressive resistance exercise after breast cancer surgery, with regard to lymphoedema risk.\textsuperscript{39,40,45,47}
- Three studies investigated the influence of different postoperative rehabilitation protocols: early versus late start of shoulder mobilization exercises after surgery for breast cancer, on the risk of subsequent secondary lymphoedema.\textsuperscript{36,38,41}
- One study investigated the effects of a comprehensive out-patient physiotherapy program for women surgically treated for breast cancer, that included education, monitoring, exercise and early intervention for prevention of lymphoedema.\textsuperscript{25}

Six studies included shoulder range of motion as a secondary outcome measure.\textsuperscript{29,36-38,41,42}
Four studies reported pain as a secondary outcome measure.\textsuperscript{29,36,37,39}
Four studies included HRQoL as a secondary outcome measure.\textsuperscript{30,37,41,45}

We did not identify any studies evaluating the effectiveness of lymph taping for prevention of lymphoedema. Full details on trial characteristics and outcomes are provided in Table 1.

**Excluded studies**
Thirteen full-text publications were excluded. These publications and the reasons for exclusion are listed in Table 2.

**Ongoing studies**
Two ongoing studies were identified; see Table 3 for trial characteristics.

**Risk of bias in included studies**
Information on one or more items related to risk of bias was unclear or not-reported in seven studies.\textsuperscript{25,29,30,36-38,43} The authors of these studies were contacted for further clarification, and the missing information was obtained in all but one case.\textsuperscript{38}
All studies had used a randomization, but allocation concealment was not sufficiently ensured in three studies.\textsuperscript{25,36,43} None of the studies relied on blinding of study participants, and outcome assessment of measured outcomes was judged sufficiently blinded in only four studies.\textsuperscript{37,38,40,41} Although compliance to the experimental intervention was measured and reported in some studies, this was not the case for the compliance to the control condition in all but two studies.\textsuperscript{39,40} Risk of bias due to attrition or selective reporting was low in most studies. Other sources of risk of bias were associated with patients having more contact with a healthcare professional compared to the control group,\textsuperscript{37,39,43} and baseline imbalances.\textsuperscript{37,38}
Detailed information on risk of bias for all studies is described in Table 1. Figure 2 summarizes risk of bias per domain for all studies.
Figure 2
Risk of bias (white: no risk of bias, grey: unclear risk of bias, black: high risk of bias) in included studies.

Effects of interventions

**Manual lymph drainage (MLD)**

*Incidence of treatment failure (occurrence of lymphoedema)*

Four trials tested MLD alone or in combination with other interventions. In two of these studies, manual lymph drainage as an added intervention to usual care was investigated, allowing for the evaluation of the unique effect of MLD.\(^{30,43}\). Two other studies investigated the effect of MLD in combination with another intervention, compared to education alone.\(^{29,37}\).

In one study, both cumulative incidence up to each follow-up point and point prevalence at each follow-up point were reported.\(^{30}\). In three other studies no explicit distinction was made and reported numbers were treated as cumulative incidence.\(^{29,37,43}\).

Due to substantial clinical and statistical heterogeneity both for short-term (<6 months) and medium-term (>6 months, <24 months) follow-up, \(I^2 = 86\%\); \(P=0.008\) and \(I^2 = 84\%\); \(P < 0.001\) respectively for RR and I2 = 84%, \(P=0.01\) for the unadjusted HR), no meta-analyses were performed. A narrative summary of the results is provided below.
Physiotherapy including MLD versus physiotherapy without MLD

One study that investigated MLD in addition to routine physiotherapy consisting of exercises of the upper limb and chest, compared to a control group that had routine physiotherapy only, found a large lymphoedema risk-reducing effect of MLD (RR=0.14, 95% CI: 0.04 - 0.58, at 3 month follow-up; RR=0.02, 95% CI: 0.00 - 0.33, at 6 months follow-up) 43. Risk of bias in this study was high. Another study, with moderate risk of bias, found no added value of MLD in combination with routine physiotherapy consisting of exercises and education, in comparison to routine physiotherapy only (RR=1.40, 95% CI: 0.51 - 3.86, at 3 month follow-up; RR=0.96, 95% CI: 0.45 - 2.05, at 6 month follow-up, RR=1.26, 95% CI: 0.69 - 2.32, at 12 month follow-up) 30. In this study, comparisons were also made for time-to-event for the occurrence of lymphoedema. There was no statistically significant difference between the groups (unadjusted HR 1.3, 95% CI: 0.6-2.5). Results on lymphoedema risk as defined by a different criterion (an increase of 2cm or more in the difference in arm circumference between the affected and healthy side at two or more adjacent measurement points compared with the difference before surgery), which was included as a secondary outcome measure, were qualitatively similar.

MLD in combination with other interventions versus education only

One study compared a combined intervention of MLD, compression, scar massage and education to education alone. This study reported a reduction in lymphoedema risk, for the intervention group, but the 95% confidence interval as calculated from the available data was wide and included 1 (RR=0.17, 95% CI: 0.02 - 1.28, reported P=0.042 at 8 month follow-up) 37. Risk of bias in this study was moderate. A second study compared MLD combined with exercise therapy and education to education only 29. In this study, there was a statistically significant reduction in lymphoedema risk at the 12 month follow-up in favour of the intervention group (RR=0.28; 95% CI: 0.10-0.79). Time-to-event in this study was also statistically significantly in favour of the intervention group (unadjusted HR 0.26; 95% CI: 0.09-0.79). Risk of bias in this study was high.

Infection

No data on this outcome

Active range of motion (AROM) of the upper limb

Two studies examined the effect of early physiotherapy consisting MLD plus exercise on shoulder range of motion 29,42. Both studies had high risk of bias. Pooling the results of the early postoperative phase (≤ 3 weeks) resulted in a mean difference for abduction of 21.8 degrees (95% CI: 13.6 to 30.10, Analysis 1.1), and a mean difference for forward flexion of 14.4 degrees (95% CI: 7.1 to 21.8 degrees, Analysis 1.2). At medium term follow-up (≥6 months ≤ 24), one of the studies reported a small and statistically non-significant difference in improvement of shoulder range of motion from first postoperative day at the 12 month follow-up of 3.10 degrees (95% CI: - 4.45 to 10.65) for abduction, and of 0.40 degrees (95% CI: -8.25 to 9.05) for forward flexion, in favour of the control group 29. The other study reported a statistically significant mean difference of 16.90 degrees (95% CI: 10.12 - 23.68) for abduction and 14.30 degrees (95% CI: 7.11 - 21.49) for forward flexion, in favour of the intervention group 42. No meta-analyses could be performed due to considerable statistical heterogeneity ($I^2 = 93\%$, and $I^2 = 85\%$, for abduction and forward flexion respectively). Only one of the studies included range of motion for rotations and found
a small and statistically non-significant difference in recovery of medial rotation (15 versus 9.8 degrees improvement; 95% CI for the difference in means: 3.6 to 10.77) and lateral rotation (7.6 versus 6.8 degrees improvement, 95% CI for the difference in means: 1.09 to 5.91) in favour of the early physical therapy group at respectively three weeks and 12 months after the first postoperative day.

### Analysis 1.1

**Short term range of motion for shoulder abduction, early physiotherapy including MLD vs no physiotherapy or physiotherapy without MLD**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (degrees)</td>
<td>SD (degrees)</td>
<td>Total</td>
<td>Mean (degrees)</td>
</tr>
<tr>
<td></td>
<td>134</td>
<td>25.1</td>
<td>33</td>
<td>121.6</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>33</td>
<td>34</td>
<td>12.40 (1.96, 26.76)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.85 (P = 0.06)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.5.2 Studies reporting change scores

<table>
<thead>
<tr>
<th>Studies</th>
<th>Mean (degrees)</th>
<th>SD (degrees)</th>
<th>Total</th>
<th>Mean (degrees)</th>
<th>SD (degrees)</th>
<th>Total</th>
<th>IV, Fixed, 95% CI (degrees)</th>
<th>IV, Fixed, 95% CI (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torres 2010</td>
<td>82.6</td>
<td>23.6</td>
<td>59</td>
<td>56.1</td>
<td>31.2</td>
<td>57</td>
<td>66.9%</td>
<td>26.50 (16.41, 36.59)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>59</td>
<td>57</td>
<td>26.50 (16.41, 36.59)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.15 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 92 | 91 | 100.0% | 21.84 (13.58, 30.10) |

1.5.3 Analysis 1.1: Short term ranges of motion for shoulder abduction, early physiotherapy including MLD vs no physiotherapy or physiotherapy without MLD

1.5.4 Analysis 1.2: Short term range of motion for shoulder forward flexion, early physiotherapy including MLD vs no physiotherapy or physiotherapy without MLD

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (degrees)</td>
<td>SD (degrees)</td>
<td>Total</td>
<td>Mean (degrees)</td>
</tr>
<tr>
<td></td>
<td>134.6</td>
<td>22.4</td>
<td>33</td>
<td>126.3</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>33</td>
<td>34</td>
<td>8.20 (3.21, 19.61)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.41 (P = 0.16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.5.5 Analysis 1.2: Short term range of motion for shoulder forward flexion, early physiotherapy including MLD vs no physiotherapy or physiotherapy without MLD

<table>
<thead>
<tr>
<th>Studies</th>
<th>Mean (degrees)</th>
<th>SD (degrees)</th>
<th>Total</th>
<th>Mean (degrees)</th>
<th>SD (degrees)</th>
<th>Total</th>
<th>IV, Fixed, 95% CI (degrees)</th>
<th>IV, Fixed, 95% CI (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torres 2010</td>
<td>67.8</td>
<td>24.6</td>
<td>59</td>
<td>48.9</td>
<td>26.2</td>
<td>57</td>
<td>58.3%</td>
<td>18.90 (9.28, 28.54)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>59</td>
<td>57</td>
<td>18.90 (9.28, 28.54)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.84 (P &lt; 0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 92 | 91 | 100.0% | 14.44 (7.08, 21.81) |

1.5.6 Analysis 1.2: Short term range of motion for shoulder forward flexion, early physiotherapy including MLD vs no physiotherapy or physiotherapy without MLD

### ADL function

No data on this outcome.

### Pain

Two studies, both with high risk of bias, addressed pain as a secondary outcome and both evaluated combined interventions including MLD versus education alone. In one study, patients who received manual lymph drainage, exercise and education reported greater improvement in pain score from baseline at three weeks (-4.2 versus -3.8 on a 0-10 scale, 95% CI: -0.72 to 1.72) but less improvement at 12 months (-4.5 versus -5.0, 95% CI: -1.62 to 0.62), compared to patients who received education alone.
In the other study, patients receiving MLD and using a compression sleeve for 8 months reported lower pain scores on a 0-10 scale, compared to patients who received education only. The mean difference between groups and the corresponding 95% CI: as calculated from the provided means and 95%CI of per group was -2.37 points (95% CI: -4.52 to -0.22) 37.

**Health-related quality of life (HRQoL)**

**MLD in combination with other interventions versus education only**

Two studies on MLD assessed HRQoL as a secondary outcome measure 30,37. Due to clinical heterogeneity meta-analysis was deemed inappropriate and a narrative synthesis is provided here. One of these studies found no statistically significant differences in the mental and physical summary component scores of the 36-item Medical Outcomes Study Short-Form (SF-36) between patients who received MLD in combination with exercise and education and patients who received exercise and education only 30. This study had moderate risk of bias. In the other study, patients receiving MLD plus compression had statistically significantly better scores than patients receiving education only, for physical functioning (144 versus 109), social functioning (144 versus 124), fatigue (47 versus 71) and financial difficulties (6 versus 14) as measured with the EORTC-QLQ-C30 questionnaire 37. Risk of bias in this study was high. In particular, there were baseline differences in several domains of the QLQ-C30 (see ‘other types of bias’ in for Castro-Sanchez 2011 in Table 1).

**Psychosocial morbidity**

No data on this outcome.

**Adverse events**

No data on this outcome.

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**Exercise**

**Incidence of treatment failure (occurrence of lymphoedema)**

**Early versus delayed onset of mobilising shoulder exercises after breast cancer treatment**

Three trials, all with high risk of bias for the primary outcome, investigated the influence of early versus delayed onset of full range mobilising shoulder exercises after breast cancer surgery 36,38,41. Meta-analysis resulted in a summary estimate of the difference in risk of lymphoedema at medium-term follow-up (6-12 months) between early or late start of full range exercises of 0.59 (95% CI: 0.33 to 1.06) (Analysis 2).
Analysis 2

**Lymphoedema risk after early versus delayed start of postoperative shoulder exercises**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Delayed exercise Events</th>
<th>Early exercise Events</th>
<th>Total Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendz 2002 (1)</td>
<td>4</td>
<td>104</td>
<td>5</td>
<td>19.3% 0.78 [0.21, 2.61]</td>
</tr>
<tr>
<td>Cinar 2008 (2)</td>
<td>6</td>
<td>30</td>
<td>5</td>
<td>20.0% 1.08 [0.37, 3.14]</td>
</tr>
<tr>
<td>Todd 2008 (3)</td>
<td>6</td>
<td>58</td>
<td>16</td>
<td>60.8% 0.38 [0.16, 0.89]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>192</td>
<td>186</td>
<td>100.0%</td>
<td>0.59 [0.33, 1.06]</td>
</tr>
</tbody>
</table>

Total events: 16 26

Safety of progressive resistance exercise after breast cancer treatment

The meta-analysis of two non-inferiority studies indicated that weight training after breast cancer treatment did not increase lymphoedema risk (summary RR 0.58; 95% CI: 0.30 to 1.13; Analysis 3)\(^{39,40}\). One of these studies compared a supervised physiotherapy program of moderate progressive resistance exercises (starting at 0.5 kg) 2-3 times a week, with a regimen of activity restriction (i.e. avoiding heavy or strenuous physical activities, including aerobic or other types of exercise classes involving heavy upper limb physical activity, and lifting and carrying objects over 3 kg) and physiotherapy (passive mobilization and massage) once a week for 6 months. In both groups, lymphoedema treatment was started if patients reported symptoms\(^{39}\). RRs calculated from reported point prevalences were 0.69 (95% CI: 0.23 to 2.09), 0.52 (95% CI: 0.16 to 1.67) and 1.04 (95% CI: 0.51 to 2.09) at three months, six months and 24 months respectively. This study had high risk of bias.

The second study, with moderate risk of bias, compared progressive resistance exercise (starting with the lowest weight, and using the smallest possible increments) plus immediate treatment of lymphoedema at first symptoms versus no exercise, and accepted the equivalence hypothesis on lymphoedema risk (RR=0.64; 95% CI: 0.28 to 1.45)\(^{40}\).

Analysis 3

**Lymphoedema risk of progressive resistance exercises**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sagen 2009 (1)</td>
<td>4</td>
<td>104</td>
<td>8</td>
<td>39.0% 0.48 [0.15, 1.55]</td>
</tr>
<tr>
<td>Schmitz 2010 (2)</td>
<td>8</td>
<td>72</td>
<td>13</td>
<td>61.0% 0.64 [0.28, 1.45]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>176</td>
<td>175</td>
<td>100.0%</td>
<td>0.58 [0.30, 1.13]</td>
</tr>
</tbody>
</table>

Total events: 12 21

Heterogeneity: Chi\(^2\) = 0.16, df = 1 (P = 0.69); I\(^2\) = 0%  
Test for overall effect: Z = 1.60 (P = 0.11)

(1) 6 month follow up  
(2) 12 month follow up
Infection

Early versus delayed onset of mobilising shoulder exercises after breast cancer treatment

Infection rates were reported in one study. No statistically significant differences in wound infection rates were observed between early supervised start of mobilising shoulder exercises compared to a delayed start (RR: 0.83; 95% CI: 0.20 to 3.39). Risk of bias for this outcome was unclear.

Active range of motion (AROM) of the upper limb

Early versus delayed onset of mobilising shoulder exercises after breast cancer treatment

Three studies reported on early versus delayed full range shoulder mobilisation after breast cancer surgery. Two of the studies reported on short-term results, and included a one month follow-up measurement. Data-pooling was possible for shoulder internal rotations only, due to statistical heterogeneity for forward flexion ($I^2 = 97\%$), abduction ($I^2=97\%$) and external rotation ($I^2=89\%$). In both studies, patients with an early start of exercises had better forward flexion at one month; 7 degrees (95% CI: 3 to 11) and 36 degrees (95% CI: 27 to 45), respectively. Abduction did not differ significantly at one month in one study. In the other study, the early exercise group had better shoulder function at one month: mean difference for abduction 43 degrees, (95% CI: 32 to 55). External rotation did not differ significantly at one month in one study. In the other study, the early exercise group had better function at one month (mean difference 15 degrees, 95% CI: 7 to 23). The pooled estimate for internal rotation at one month showed no statistically significant or potentially clinically relevant difference as indicated by the 95% confidence interval, between early and delayed shoulder exercises (Analysis 4.1).

All three studies reported medium-term follow-up, of which two reported a 6 month follow-up and one a 12 months follow-up. Data-pooling was possible for shoulder internal rotations only, due to statistical heterogeneity for forward flexion ($I^2=90\%$), abduction ($I^2=92\%$) and external rotation ($I^2=58\%$). Forward flexion was statistically significantly better at 6 months for patients who started early with full range shoulder exercises compared to patients who followed a delayed approach. The difference was 5 degrees (95% CI: 2 to 8) and 15 degrees (95% CI: 11 to 20), respectively. In the third study there was no difference in forward flexion at 12 months follow-up. One of the studies also included a measurement at two years follow-up and found a difference of 3 degrees (95% CI: 0 to 6), once again in favour of the early start.

Abduction at medium term follow-up in one study with high risk of bias, was not significantly better at 6 months, for patients who started early with shoulder exercises compared to patients with a delayed start. At 2 years follow-up, there was a small but statistically significant difference of 9 degrees (95% CI: 2 to 16) in favour of an early start. In a second study, with unclear risk of bias, patients in the early mobilisation group also had statistically significant better abduction at six months (mean difference 21 degrees; 95% CI: 13 to 30). In the third study, patients in both groups had declined range of motion for abduction at 12 months compared to baseline. Although the difference in abduction between the groups was not statistically significant, it was observed that the early mobilisation group had worse shoulder function than the delayed mobilisation group, and the 95% CI included a clinically relevant difference (mean difference -8.30, 95% CI: -16.97 to 0.37). Risk of bias in this study was low for this outcome. The summary estimate for internal rotation at medium-term follow-up was 2.39 degrees (96% CI: -0.14 to 4.92) (Analysis 4.2). Risk of bias in this study was low for this outcome.
Analysis 4.1

Short term range of motion for shoulder internal rotation, early vs delayed start of postoperative shoulder exercises

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early Mean [degrees]</th>
<th>SD [degrees]</th>
<th>Total Mean [degrees]</th>
<th>SD [degrees]</th>
<th>Total Mean [degrees]</th>
<th>SD [degrees]</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI (degrees)</th>
<th>Mean Difference IV, Fixed, 95% CI (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendz 2002 (1)</td>
<td>66</td>
<td>9</td>
<td>101</td>
<td>68</td>
<td>11</td>
<td>104</td>
<td>78.7%</td>
<td>0.00 [-2.75, 2.75]</td>
<td></td>
</tr>
<tr>
<td>Cair 2008 (2)</td>
<td>86.84</td>
<td>10.3</td>
<td>27</td>
<td>85.76</td>
<td>9.98</td>
<td>30</td>
<td>21.3%</td>
<td>1.08 [4.20, 6.38]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>128</td>
<td></td>
<td>134</td>
<td></td>
<td>100.0%</td>
<td>0.23 [-2.21, 2.67]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: CH² = 0.13, df = 1 (P = 0.72), I² = 0%
Test for overall effect: Z = 0.18 (P = 0.85)

(1) 1 month
(2) 1 month

Analysis 4.2

Medium term range of motion for shoulder internal rotation, early vs delayed start of postoperative shoulder exercises

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early Mean [degrees]</th>
<th>SD [degrees]</th>
<th>Total Mean [degrees]</th>
<th>SD [degrees]</th>
<th>Total Mean [degrees]</th>
<th>SD [degrees]</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI (degrees)</th>
<th>Mean Difference IV, Fixed, 95% CI (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.3.1 Studies reporting final scores Bendz 2002 (1)</td>
<td>70</td>
<td>10</td>
<td>101</td>
<td>68</td>
<td>12</td>
<td>104</td>
<td>70.1%</td>
<td>2.00 [-1.02, 5.02]</td>
<td></td>
</tr>
<tr>
<td>Cair 2008 (2)</td>
<td>90</td>
<td>10</td>
<td>27</td>
<td>84.45</td>
<td>18.54</td>
<td>30</td>
<td>11.0%</td>
<td>5.55 [-2.08, 13.18]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>128</td>
<td></td>
<td>134</td>
<td></td>
<td>91.1%</td>
<td>2.48 [-0.33, 5.29]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: CH² = 0.72, df = 1 (P = 0.40), I² = 0%
Test for overall effect: Z = 1.73 (P = 0.08)

2.3.2 Studies reporting change scores Todd 2006 (3) 3.1 13 58 1.1 18.6 58 18.9% 2.00 [-3.62, 7.62]
Subtotal (95% CI) 56 58 18.9% 2.00 [-3.62, 7.62]

Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)

Total (95% CI) 186 192 100.0% 2.39 [-0.14, 4.92]

Heterogeneity: CH² = 0.74, df = 2 (P = 0.69), I² = 0%
Test for overall effect: Z = 1.85 (P = 0.06)
Test for subgroup differences: CH² = 0.02, df = 1 (P = 0.88), I² = 0%
(1) ROM at 6 months follow up
(2) ROM at 6 months follow up
(3) ROM at 6 months follow up

ADL function

Early versus delayed onset of mobilising shoulder exercises after breast cancer treatment

Only one of the studies reported on ADL function. In this study, there were no differences between early mobilisation and delayed mobilisation in Shoulder Disability Questionnaire score at one year follow-up (a mean of 1.7 positively scored items versus 1.9 for early and delayed start respectively). Risk of bias for this outcome was low.

Pain

Early versus delayed onset of mobilising shoulder exercises after breast cancer treatment

Only one study, with high risk of bias, examined the effects of early versus delayed exercise on pain. No statistically significant differences were found for pain scores at any follow-up point up to 2 years in patients who started early with mobilization exercises and patients who had a delayed start of exercises.
Progressive resistance exercise
One study with moderate risk of bias for this outcome, examined the effect of progressive resistance exercise on pain \(^{39}\). Patients who were engaged in moderate progressive resistance exercise reported pain significantly more often at 3 months and 6 months, but not at 24 months, compared to a control group with 6 months of activity restrictions, massage and passive mobilisation: 78% vs 45% at 3 months, 60% vs 36% at 6 months, and 39% vs 34% at 24 months.

Health related quality of life (HRQOL)
Early versus delayed onset of mobilising shoulder exercises after breast cancer treatment
One study that compared early versus delayed start of exercises reported on HRQoL \(^{41}\). The average scores on the Functional Assessment of Cancer Therapy-Breast Trial Outcome Index at 12 months follow-up were 32.5 for patients who started early with mobilization exercises and 30.9 for patients who had a delayed start. This difference was smaller than the 5 points difference that was considered to be clinically important by the authors. The study had low risk of bias for this outcome.

Progressive resistance exercise
There were no statistically significant differences in the mental and physical summary component scores of the SF-36 between patients who engaged in progressive resistance exercise and those who did not increase their activity level, at 12 months follow-up (mean %change in mental component score: 3.3 versus 3.1, mean %change in physical component score: 6.6 versus 4.1, for exercise and control group respectively)\(^{40,45}\). Risk of bias in this study was unclear.

Psychosocial morbidity
No data on this outcome

Adverse events
Early versus delayed onset of mobilising shoulder exercises after breast cancer treatment
Although this was not specifically described as an adverse event, statistically higher wound drainage volume was reported in the early mobilisation group compared to the delayed mobilisation group in one study with low risk of bias for this outcome \(^{41}\), but not in another study with unclear risk of bias \(^{38}\). Absolute values of drainage volume were not reported.

Safety of progressive resistance exercise after breast cancer treatment
Self-reported (musculoskeletal) injury was assessed with a 1-year recall, using a survey, in one of the studies. The OR for musculoskeletal injury in the weight lifting group compared to the control group was 5.6, 95% CI: 0.31 to 26.1 \(^{47}\). Another study noted a 1.5% incidence of musculoskeletal adverse events (2 patients with a frozen shoulder, one with a supraspinatus tendinopathy), but did not specify in which of the groups these occurred \(^{39}\).
Patient education, monitoring and early intervention

Incidence of treatment failure (occurrence of lymphoedema)
There were no studies that evaluated either patient education, or monitoring and early intervention alone. One study, with high risk of bias, employed an extensive program ('PMCP') consisting of patient education, supervision of exercises and adjustment of self-directed shoulder exercises, and monitoring of lymphoedema symptoms and early intervention for lymphoedema or shoulder problems if deemed necessary. The control group received an instruction booklet only. 25.

Absolute numbers of patients at risk in each group at each time point were not available from the published reports. From a survival curve obtained from the authors of the study, the number of patients in each group was obtained by subtracting the number of censored patients up to that time point. 2x2 Tables were then constructed for each follow-up point and risk estimates were calculated. No statistically significant difference in prevalence of lymphoedema, as defined by a >200ml or 10% change from preoperative volume, was found between the control group and the intervention group at 1 month (RR: 1.03, 95% CI: 0.07 to 15.8), 3 months (RR: 0.40, 95% CI: 0.12 to 1.37), 6 months (RR: 0.22, 95% CI: 0.03 to 1.78), 12 months (RR: 0.52, 95% CI: 0.10 to 2.60) and 24 months (RR: 0.34, 95% CI: 0.10 to 1.15). There also were no statistically significant differences at each follow-up point by any of the other criteria for lymphoedema.

Infection
No data on this outcome.

Active range of motion (AROM) of the upper limb
The recovery pattern for range of motion of shoulder abduction was more favourable for patients receiving the PMCP intervention than for the control group. Shoulder function in the intervention group returned to preoperative levels at 3 months, compared to 6 months in the control group (P=0.001) 25, 44. No statistically significant differences between groups were observed for recovery pattern of the other shoulder movements (forward flexion, extension, and rotations).

ADL function
No data on this outcome.

Pain
No data on this outcome.

Health related quality of life (HRQoL)
No data on this outcome.

Compression therapy
The effect was studied in a single study in which it was combined with MLD and education. A separate evaluation of compression therapy is therefore not possible.
Outcome measures in this study included lymphoedema occurrence, pain and health related quality of life 37. The results are presented in the manual lymph drainage section.
Discussion

Summary of main results
In this systematic review we included ten randomised controlled trials investigating different types of interventions to reduce the risk of secondary lymphoedema after breast cancer treatment.

Manual Lymph Drainage
Four studies with a total of 385 participants studied the effectiveness of MLD. The main results are summarized in Summary of findings table 1. The evidence on the effectiveness of MLD on lymphoedema risk is conflicting. Differences in dosage and administration of the MLD intervention in the two studies that allowed for evaluation of the effectiveness of MLD only may in part account for the observed differences in effect. It should also be noted however, that compared to the study that found no effect, overall risk of bias in the study that did find statistically significant effects was higher. In particular, allocation concealment and blinding of outcome assessment were lacking, both of which are typically associated with larger effect estimates.

The results of two other studies on MLD suggest that a combined physiotherapy intervention containing MLD may reduce the risk of developing lymphoedema compared to education only. The extent to which MLD accounts for the observed effect cannot be estimated from these studies. Therefore, it is unclear whether the observed positive effects resulted from the concurrent compression therapy or exercise therapy rather than MLD or vice versa. Also, the results should be interpreted with caution, since both trials suffered from risk of bias at several points.

No conclusions can be drawn from the available studies with regard to effects of MLD, with or without additional intervention, on pain.

The observed effects on shoulder function suggest that MLD combined with exercise may lead to better shoulder intervention in the first few weeks after surgery compared to education only. Results on long term effects were inconsistent. These findings too, should be interpreted with caution due to the overall low quality of the evidence.

Early versus delayed shoulder mobilisation
Three of the included trials compared early versus delayed full range shoulder exercises after axillary dissection in a total of 378 breast cancer patients at risk for lymphoedema. The main findings of these studies are summarized in Summary of findings table 2. The meta-analysis did not yield a statistically significant elevated risk of lymphoedema after early start of exercises. However, the point estimate favoured a delayed start. A delayed start of exercises does not seem to have a negative influence on recovery of shoulder range of motion in medium term, but immediate postoperative start of exercise leads to better shoulder function in the short term (up to 6 months).

Progressive resistance exercise
Two studies evaluated the safety of progressive resistance exercises after breast cancer surgery including axillary lymph node dissection, in a total of 351 participants. The results of these studies (summarized in Summary of findings table 3) support the hypothesis that resistance training does not increase lymphoedema risk, and may even reduce the risk, provided that lymphoedema symptoms are closely monitored and adequate treatment is initiated as soon as symptoms become apparent.
Overall completeness and applicability of evidence

The number of studies that investigated the effectiveness of a conservative intervention for prevention of lymphoedema after breast cancer surgery was small, and the type of interventions studied was limited. None of the included studies investigated the effect of compression therapy only, either by bandaging, compression sleeves or pneumatic compression, or of lymph taping. There were no studies evaluating the effect of education or risk-reduction advice compared to no education, or surveillance and early intervention.

Not all relevant outcome measures were used in the identified studies. ADL functioning in relation to the affected arm was measured in with a validated self-report measure in only one study. Infection was reported in one study, but none of the other studies included it as an outcome measure or adverse effect. None of the included studies addressed psychosocial morbidity (depression or anxiety).

Quality of the evidence

The overall quality of the evidence ranged from very low to low, with the exception of the comparison of progressive resistance training with no exercise, which was graded as moderate (See summary of findings tables). Lack of blinding accounted for an important part of the reasons for downgrading the quality of the evidence, as it was judged to be unclear or insufficient in the majority of studies. The type of interventions under investigation made it very difficult, if not impossible to adequately blind patients. The impact of this on the observed outcomes is difficult to estimate and may differ between types of interventions. Since adherence to the assigned intervention was not explicitly addressed in eight of the studies, this may have introduced bias towards the null hypothesis in superiority trials, and towards the alternative hypothesis in non-inferiority trials.

The definitions used for lymphoedema among the included studies differed, with some studies reporting on lymphoedema based on several different criteria. Since all of the studies included a volume criterion to define incident cases, we extracted the results based on this criterion for studies reporting on several definitions but failing to specify the definition used as the primary outcome. In one study the primary outcome measure for lymphoedema as defined in the methods section was not reported. Since incident cases of lymphoedema were reported and the authors provided a sufficiently objective criterion, we used this outcome for our analyses. Even though all studies included a volume criterion, these too differed between studies. Also, different ways of measuring limb volume were used. These variations added to the observed heterogeneity.

Most studies reported cumulative incidence of lymphoedema, but a number of the studies did this by reporting the prevalent cases at a certain follow-up point. Since limb volume is variable over time, and transient episodes of lymphoedema may occur, the reported number of cases observed at a particular follow-up measurement could be considered point prevalence rather than cumulative incidence.

The use of a priori power calculation was not included in the risk of bias assessment. It should be noted, however, that sample size calculations were not performed in five studies. Power calculations were performed based on volume differences rather than incidence of lymphoedema in two studies. All studies reporting a-priori power calculations recruited the targeted number of patients.
Potential biases in the review process
We performed a comprehensive search in the most relevant databases. We refrained from using a methodological filter to make sure that no relevant studies would be missed due to misclassification in the databases. Neither did we impose a language restriction. The studies identified included both studies with positive findings and studies with negative findings. Although the number of studies per outcome and intervention was too small to make a formal analysis, we have found no clues that indicate possible publication bias.
We corresponded with the authors of six studies to obtain additional information on risk of bias related to study characteristics, and additional outcome data. These data were obtained in most cases, which makes our review more complete. On the other hand, it also means that some of the details on study methodology and study results have not yet gone through a peer-review process.
An important limitation of this review was that we included only studies that used lymphoedema as the primary outcome. As a result of this restriction, studies may have been missed that reported on lymphoedema as a secondary outcome in trials on exercise, postoperative rehabilitation protocols or other interventions.

Agreements and disagreements with other studies or reviews
A Cochrane systematic review studied the effect of exercise interventions on upper limb dysfunction due to breast cancer treatment 51. This review included a number of studies that reported lymphoedema as a secondary outcome. The reported results with regard to the effects of early versus late start of exercise on lymphoedema incidence are congruent with our results.
A second systematic review also summarized the evidence on the effectiveness of exercise programmes on shoulder mobility and lymphoedema 50. While that review included some studies that did not meet the inclusion criteria of the current review, the authors also conclude that exercise is safe with regard to lymphoedema risk.
Some of the results that we calculated, based on the available data and using RevMan, were inconsistent with the results as reported in the source publications. Castro-Sanchez et al. reported a statistically significant difference in lymphoedema incidence at 8 month follow-up 37. Using the data as reported, our analysis did not show a statistically significant reduction in lymphoedema risk for patients receiving a combined intervention of MLD, exercise, scar massage and education, compared to those receiving education alone (RR=0.13, 95% CI: 0.02 to 1.28, P = 0.07). We have no explanation for this difference. Conversely, Castro-Sanchez et al. reported a clinically relevant, but statistically non-significant difference in pain scores (reported P=0.056) whereas in our analysis based on the reported mean scores and 95%CIs, this difference was statistically significant (calculated P=0.03). We also do not have an explanation for this difference; it seems unlikely that differences occurred due to rounding, since confidence intervals were reported precisely (up to 2 decimals). The results as reported by Box et al. 25 were also not entirely consistent with our calculations based on the available data, but this did not result in a qualitatively different conclusion.

Authors’ conclusions
Implications for practice
The aim of this review was to summarize current evidence and thus provide information that can be used to guide clinical decisions and guideline development. Unfortunately, the overall low quality
of the evidence does not allow for firm conclusions on the effect of MLD, compression, exercise or a combination of these interventions for prevention of upper limb lymphoedema in patients at risk after breast cancer treatment.

Although the comparison of early versus delayed start of shoulder exercises showed no significant influence on lymphoedema incidence, the point estimate showed a lower risk of lymphoedema after delayed start. An early start may result in better range of motion in the short-term compared to a late start, but this difference disappears from 6 months onward. Other studies have shown that delaying postoperative shoulder rehabilitation reduces postoperative wound drainage volumes and wound drainage time, although it does not reduce incidence of seroma formation. Clinicians who consider early recovery of shoulder function as very important may want to consider early onset of exercise. Otherwise, delaying exercise for a week after the operation could be considered.

Current evidence supports that progressive resistance exercise is safe, and potentially beneficial for reducing lymphoedema risk in patients treated for breast cancer. The beneficial effects of resistance training on physical functioning, fatigue and quality of life are well established. Breast cancer survivors can therefore be actively encouraged to engage in such exercise and can be informed that this will not increase their risk of developing chronic upper limb lymphoedema, provided that they monitor their symptoms and see to it that lymphoedema is treated in a timely manner should it occur.

**Implications for research**

Considering the low number of studies identified, the heterogeneity of interventions applied in these studies, and the overall low quality of the evidence available to date, future studies are needed. Many of the included studies in this review did not report on important methodological characteristics related to risk of bias. Therefore, we would stress the importance of adhering to the CONSORT guidelines for reporting future clinical trials.

Using a commonly agreed on criterion for clinically detectable lymphoedema would greatly facilitate the interpretation of future studies, but unfortunately no such single criterion currently exists. Alternatively, future studies could choose to incorporate a number of methods to assess lymphoedema and report results based on each of those, while clearly specifying the criterion used as the primary outcome variable. Future studies should preferably use survival analysis to assess the effectiveness of interventions, as this takes into consideration that even if lymphoedema is not prevented, its onset may be postponed by the intervention. Including infection, pain, limitations in ADL functioning, quality of life and mood and adverse events as secondary outcomes is recommended.

Further research is needed to provide more robust evidence on the (combined) interventions as described in this review, as well as to examine the effectiveness of preventive compression and MLD as a single intervention, kinesiotaping, and early intervention for subclinical lymphoedema. Although results from an observational study suggest that early detection by self-examination and subsequent treatment with conservative interventions may reduce the severity of lymphoedema, randomised controlled trials are needed to confirm these findings. The effect of patient education also needs further study in randomised controlled trials. While it is generally agreed upon that providing risk-reduction advice should be part of routine care after breast cancer treatment, it is currently unclear whether the benefits outweigh potential harm. In addition, the cost-effectiveness from a societal perspective should be evaluated for all interventions.
### Table 1

**Characteristics and risk of bias of included studies**

**Bendz 2002**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Cluster randomized controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Women treated for breast cancer with radical mastectomy or quadrantectomy, including ALND, with or without radiotherapy to the chestwall. Mean age 58 (SD 11).</td>
</tr>
</tbody>
</table>
| Interventions      | **Intervention group (n=101)**
Immediate full range exercise supervised by a physical therapist: Preoperative instructions to use the arm as much as comfortable, avoiding lifting and carrying heavier items and avoid forced movements for 14 days. From day 14 forward, full range mobilizing exercises were given to both groups, to be performed 3 times a day. 

**Control group (n=104)**
Delayed full range exercise: Preoperative instruction on shoulder/arm exercise programme, to be started on the first postoperative day. No abduction or elevation for three days, slowly increasing to elevation and abduction to 90° during 14 days.

| Outcomes           | **Primary outcome:**
Lymphoedema, defined as 10% or greater change in volume of the operated arm, corrected for preoperative differences, using the formula: (volume difference between operated and non-operated arm at baseline - volume difference at follow-up)/ postoperative volume of the operated arm * 100.

**Secondary outcomes:**
Range of motion (goniometer) for shoulder flexion, abduction and rotation; Pain (4 point ordinal scale based on visual analogue scale); Hand grip strength (Vigorimeter); Subjective estimation of heaviness and tension (VAS)

<table>
<thead>
<tr>
<th>Follow up</th>
<th>1 month, 6 months, 24 months follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country, setting</td>
<td>Sweden, University Hospital</td>
</tr>
<tr>
<td>Year of conduct</td>
<td>1994-1996</td>
</tr>
</tbody>
</table>
## Risk of bias table for Bendz 2002

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>“Cluster randomisation was used to alternate periods of 4 weeks”. The way the sequence of allocation was generated is not described, but earlier randomised studies by the senior author clearly use randomization procedures.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>There is no mention of allocation concealment</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Unclear risk</td>
<td>Neither patients nor personnel were blinded for the intervention, but due to the nature of the intervention and the use of cluster randomisation, performance bias seems unlikely.</td>
</tr>
<tr>
<td>(performance bias) Measured outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Unclear risk</td>
<td>Neither patients nor personnel were blinded for the intervention, but due to the nature of the intervention and the use of cluster randomisation, performance bias seems unlikely.</td>
</tr>
<tr>
<td>(performance bias) Patient reported outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>High risk</td>
<td>Outcome assessors were not blinded.</td>
</tr>
<tr>
<td>Measured outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Patients were not blinded, but the trial was cluster randomised and it seems unlikely that patients self report of pain would be influenced by knowledge of group allocation.</td>
</tr>
<tr>
<td>Patient reported outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Drop out rates at two years follow-up were twice as high in the early exercise group compared to the delayed exercise group (16 versus 8) and reasons for drop out differed between groups. Also twenty-five patients dropped-out before the first assessment and were not included in any of the subsequent analyses.</td>
</tr>
<tr>
<td>Measured outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Drop out rates at two years follow-up were twice as high in the early exercise group compared to the delayed exercise group (16 versus 8) and reasons for drop out differed between groups. Also twenty-five patients dropped-out before the first assessment and were not included in any of the subsequent analyses.</td>
</tr>
<tr>
<td>Patient reported outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Outcomes for all variables are reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>It is unclear whether the groups were comparable on all relevant risk factors such as number of removed nodes and BMI. There is no explicit statistical consideration for the cluster randomisation.</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>Parallel group randomized controlled trial, stratification by surgical procedure (complete local excision or modified radical mastectomy)</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Patients treated surgically for breast cancer (all stages except advanced disease), complete local excision or modified radical mastectomy, including ALND. Mean age (SD) 56 (10.6)</td>
<td></td>
</tr>
</tbody>
</table>
| **Interventions** | **Intervention Group (n= 32)**  
Physiotherapy Management Care Plan (PMCP). PMCP includes preoperative individual risk assessment, identification of possible risk factors, education on the lymphatic system, education about early signs of lymphoedema and introduction of risk minimisation strategies for identified precipitating factors in the preoperative phase. Postoperatively, outpatient reviews are scheduled (monitoring of shoulder ROM, progression of exercise, provision of LO awareness, individualized intervention if required).  
**Control Group (n=33)**  
No physiotherapy. |
| **Outcomes** | **Primary outcome:**  
Lymphoedema defined as:  
1. Increase of 5cm or more from preoperative sum of circumferences of the arm, operated arm versus non operated side  
2. Increase of 200ml or more from preoperative total arm volume difference between the operated and non operated side.  
3. Multifrequency Bioelectrical Impedance Measurement: A MFBIA ratio of the arm operated side and and non operated side lower than 95%Conficence Interval from preoperative data, or a 10% change from baseline in the ratio operated arm:unoperated arm  
**Secondary outcome:**  
Range of motion (goniometer) for shoulder flexion, abduction extension and rotations;  
Non-validated functional tasks questionnaire |
| **Follow up** | 1, 3, 6, 12 months |
| **Country, setting** | Australia, University Hospital |
| **Year of conduct** | 1996-1999 |
## Risk of bias table for Box 2002

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer generated random number table</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Chronological recruitment with allocation from random number table, without attempts at blinding</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) Measured outcomes</td>
<td>Low risk</td>
<td>Medical and nursing staff were blinded for group allocation, patients were not. Contamination seems unlikely due to the nature of the intervention.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) Patient reported outcomes</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Measured outcomes</td>
<td>High risk</td>
<td>Outcome measurements were taken by a blinded PT for “as many women as possible”, it is unclear in how many cases this was actually the case.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Patient reported outcomes</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) Measured outcomes</td>
<td>Low risk</td>
<td>There is a 9% loss to follow-up, for reasons unrelated to the outcome</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) Patient reported outcome</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcomes mentioned in the methods sections are reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Women in the treatment group on average had more lymph nodes removed (16 versus 13), more often had level 2 (81 versus 64) or 3 (16 versus 9) axillary dissection, and more often had radiotherapy (66 versus 49). No sensitivity analysis or adjusted analysis were performed due to the low number of events. Analyses on shoulder function measurements were adjusted for age, number of removed lymph nodes, level of ALND, history of shoulder problems, radiotherapy, chemotherapy and wound infection.</td>
</tr>
</tbody>
</table>
## Methods
Parallel group randomised controlled trial

## Participants
Woman aged 30-60, treated for breast cancer (stages not specified) including partial axillary dissection and adjuvant radiotherapy

## Interventions
**Intervention group (n=24)**
Elastic compression sleeve + manual lymph drainage 5 times a week for 6 months; Lecuc method transthoracical and thoraco-abdominal and manual lymph drainage of the arm.

**Control group (n=24)**
Patient education

## Outcomes
**Primary outcome:**
Lymphoedema, defined as:
Between group mean difference in percentage upper arm volume difference (from circumference measurements) between affected versus non-affected side (not reported).

**Secondary outcomes:**
Incident cases of lymphoedema, defined as > 2cm increase in the circumferential measurements at two adjacent marked points in comparison with the corresponding contralateral arm.

Volume of the arm
Body composition: fat-free mass (g/kg/d), fat mass (kg), amount of extracellular water (l) as measured with bio impedance measurements.

Temperature of the back of the hand, anterior forearm and elbow.

Health related quality of life (EORTC-QLQ c30)

Pain (10 point visual analogue scale)

Functional Shoulder rating scale UCLA (composite score of self report complaints and limitations, ROM measurements and strength measurements)

## Follow up
8 months

## Country, setting
Spain, 2 university hospitals

## Year of conduct
2008-2009
## Risk of bias table for Castro-Sanchez 2011

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>A computer generated random number table was used.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Randomization cards were placed in opaque envelopes that were opened by a therapist who was not involved in baseline assessments.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) Measured outcomes</td>
<td>Unclear risk</td>
<td>Participants and personnel were not blinded for the intervention. The risk of contamination is unclear.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) Patient reported outcomes</td>
<td>Unclear risk</td>
<td>Patients and therapist were not blinded for the intervention. The risk of contamination is unclear.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Measured outcomes</td>
<td>Low risk</td>
<td>Outcome assessor was blinded for group allocation</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Patient reported outcomes</td>
<td>High risk</td>
<td>Self report for pain and HRQOL may be affected by patients’ knowledge of group allocation.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) Measured outcomes</td>
<td>Low risk</td>
<td>There is no loss to follow-up</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) Patient reported outcome</td>
<td>Low risk</td>
<td>There is no loss to follow-up</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Reported incident cases with lymphoedema are based on a different criterion than defined the methods section.</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Baseline imbalance in limbvolume (intervention group: 307ml control group: 378ml) not controlled for in analysis. At baseline, the intervention group had lower scores than the control group for the EORTC QLQ c30 domains of: Physical functioning (114 versus 123), Role functioning (88 versus 96), Social functioning (120 versus 126), Global health (73 versus 87), Constipation (4 versus 11), Diarrhea (44 versus 53), Financial difficulties (8 versus 14). No corrections were made to take these differences into account. The intervention group had more contacts with a therapist, which may reinforce other behaviour such as compliance to exercises and self-care measures.</td>
</tr>
</tbody>
</table>
## Cinar 2008

<table>
<thead>
<tr>
<th>Methods</th>
<th>Parallel groups randomised controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Women (mean age 53, range 29-72), surgically treated for breast cancer with radical modified mastectomy</td>
</tr>
</tbody>
</table>
| Interventions    | **Intervention group (n=27)**  
Early postoperative shoulder mobilisation:  
Shoulder immobilisation on first day, PT supervised active exercises hand and elbow. Gradually increasing shoulder mobilising exercises from day 2 onwards, with passive stretching from day 5 forward. After removal of wound drain 15 sessions of individual PT out-patients setting mobilising and strengthening exercises for the shoulder upper limb. Home based exercise in following 8 weeks, and education on risk reducing behavior.  

**Control group (n=30)**  
Delayed approach to shoulder exercises, starting after removal of the wound drain. Homebased after initial physiotherapist delivered exercise instruction, and education on risk reducing behavior. |
| Outcomes         | **Primary outcome:**  
Lymphoedema defined as 1.5-3cm difference in circumference of the treated versus the non-treated upper limb (mild oedema), 3-5 cm difference (moderate), >5 cm difference (severe)  

**Secondary outcome:**  
Non validated questionnaire on functional activities involving the shoulder |
| Follow up        | 5 days, 1, 3, 6 months |
| Country, setting | Turkey, hospital |
| Year of conduct  | <2007 |
## Risk of bias table for Cinar 2008

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>It is mentioned that treatment allocation was randomised, the method is not stated.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) Measured outcomes</td>
<td>Unclear risk</td>
<td>Participants and personnel were not blinded for the intervention. The risk of contamination is unclear.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) Patient reported outcomes</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Measured outcomes</td>
<td>Low risk</td>
<td>Outcome assessor was blinded to group allocation</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Patient reported outcomes</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) Measured outcomes</td>
<td>Unclear risk</td>
<td>No attrition was reported, but the number of patients at follow-up is not reported and there is no consort diagram</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) Patient reported outcome</td>
<td>Unclear risk</td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcomes are reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Women in the treatment group on average less often had radiotherapy treatment (10; 37% versus 14; 47% ). The intervention group had more contacts with a therapist, which may reinforce other behaviour such as compliance to exercises and self-care measures.</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>Parallel groups randomized controlled trial, stratification for Body Mass Index and adjuvant radiotherapy</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Patients treated for breast cancer (all stages except advanced disease) including ALND</td>
<td></td>
</tr>
</tbody>
</table>
| **Interventions** | **Intervention group (n=79)**  
Provision of guidelines about prevention of lymphoedema, passive shoulder mobilisation, active shoulder exercises, scar massage and manual lymph drainage (40 one-hour sessions/week, 3 times/week, 40 sessions in total)  
**Control group (n=81)**  
Provision of guidelines about prevention of lymphoedema, passive shoulder mobilisation, active shoulder exercises, scar massage |
| **Outcomes** | **Primary outcome**  
Cumulative incidence of lymphoedema defined as:  
1. 200ml or more increase in arm volume difference between healthy and operated side compared to the difference before surgery.  
2. Time to develop lymphoedema, by same criterion  
**Secondary outcome**  
Cumulative incidence of lymphoedema defined as 2 cm or more increase in arm circumference difference at any two adjacent points between healthy and operated side.  
Time to develop lymphoedema by the same criterion.  
Point prevalence of lymphoedema using both criteria  
Point prevalence of subjective lymphoedema  
Increase of arm volume  
Health related quality of life (MOS Short Form 36 component scores for physical and mental health)  
Range of motion of the upper limb (not reported)  
Lymphscintigraphic examination (not reported)  
Lymph-SBP questionnaire (not reported) |
| **Follow up** | 12 months |
| **Country, setting** | Belgium, University Hospital |
| **Year of conduct** | 2007-2009 |
### Risk of bias table for De Voogdt 2011

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Randomization using permuted blocks, stratification for Body Mass Index and adjuvant radiotherapy</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Allocation to treatment groups was concealed.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) Measured outcomes</td>
<td>Unclear risk</td>
<td>Participants and personnel were not blinded for the intervention. The risk of contamination is unclear.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) Patient reported outcomes</td>
<td>Unclear risk</td>
<td>Participants and personnel were not blinded for the intervention. The risk of contamination is unclear.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Measured outcomes</td>
<td>Unclear risk</td>
<td>Outcome assessors were blinded. However, lymphoedema was assessed at scheduled follow-up measurements or in case of self reported symptoms. Participants were not blinded for the intervention which may have induced differences in propensity towards reporting symptoms based on knowledge of group allocation.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Patient reported outcomes</td>
<td>Unclear risk</td>
<td>Self report for pain and HRQOL may be affected by patients' knowledge of group allocation.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) Measured outcomes</td>
<td>Low risk</td>
<td>There was a very low dropout rate. A sensitivity analysis by the review authors supported the conclusions.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) Patient reported outcome</td>
<td>Low risk</td>
<td>There was a very low dropout rate.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Range of motion was measured according to the trial protocol, but not reported. Data were not yet available at the time of writing for this review.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>A higher percentage in the intervention group had level III dissection (43 versus 33%) and a higher percentage had radiotherapy on the axilla (10 versus 6), which may lead to increased risk for the intervention group.</td>
</tr>
</tbody>
</table>
**Methods**  
Parallel group randomised controlled trial.  

**Participants**  
Women aged 32-75, treated for early stage breast cancer with mastectomy or breast-conserving therapy with ALND (level I en II), with or without radiotherapy, chemotherapy or hormone treatment.  

**Interventions**  
**Intervention (n=104)**  
Supervised physiotherapy consisting of moderate progressive resistance exercise training 2-3 times a week, without restriction in activities.  

**Control (n=100)**  
Restricted activity for the affected limb for 6 months (avoidance of heavy or strenuous activities, carrying or lifting over 3 kg). Supervised physiotherapy consisting of passive manual mobilization, light massage, once a week.  

**Outcomes**  
**Primary outcome:**  
Lymphoedema defined as 10% or more increase in Voldiff= (volume of the affected - volume of the heterolateral arm)/volume of the heterolateral arm *100, measured by water displacement volumetry.  

**Secondary outcome:**  
Pain (ordinal scale with three categories, based on visual analogue scale)  
Sensation of Heaviness (VAS)  

**Follow up**  
24 months  

**Country, setting**  
Norway, 2 University Hospitals  

**Year of conduct**  
1999-2003  

**Notes**  
The study question was based on an equivalence hypothesis, but the study was analysed as a superiority trial.
<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Block randomisation by computer program</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>sealed envelopes</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) Measured outcomes</td>
<td>Unclear risk</td>
<td>Participants and personnel were not blinded. Self-reported physical activity scores were lower in the control group than in the intervention group at 3 and 6 months.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) Patient reported outcomes</td>
<td>Low risk</td>
<td>Participants and personnel were not blinded. Self-reported physical activity scores were lower in the control group than in the intervention group at 3 months and 6 months.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Measured outcomes</td>
<td>Unclear risk</td>
<td>The blinded outcome assessor was not involved in the interventions performed at the outpaient clinics. However, LO treatment was given whenever necessary during the 6 month intervention and whenever requested between the 6 month and 2 year follow-up. Since patients were not blinded, there may have been differences in reporting symptoms of LO between experimental and control group.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Patient reported outcomes</td>
<td>Unclear risk</td>
<td>Participants were not blinded. Self-reported pain may be affected by participants knowledge of group allocation.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) Measured outcomes</td>
<td>High risk</td>
<td>Loss to follow-up in the no activity restriction group was higher compared to the exercise group: 13 vs 10, 14 vs 3 and 36 vs 16 at 3, 6 and 24 months respectively. A last observation carried forward procedure was employed. Since lymphoedema incidence increases over time, this approach is questionable.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) Patient reported outcome</td>
<td>High risk</td>
<td>More patients were lost to follow-up in group 1 (no activity restriction) compared to group 2: 13 versus 10, 14 versus 3 and 36 versus 16 at 3, 6 and 24 months respectively. A last observation carried forward procedure was employed. Data on 17 patients in group 1 and 15 patients in group 2 were not reported at 3-months follow-up and apparently imputed at six months and two years.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcomes mentioned in the methods section are reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Patients in the activity restriction group also received usual care physiotherapy treatment once a week, which included massage, while patients in the exercise group did not receive massage. The intervention group had more contacts with a therapist, which may reinforce other behaviour such as compliance to exercises and self-care measures. Arm lymphoedema was treated in both groups, both during the intervention period and during follow-up. The figures as reported are based on point-prevalence at follow-up points, not as cumulative incidence. It is therefore unclear how many patients in each group developed lymphoedema at some point during the follow-up that resolved as a result of therapy. This may lead to a biased interpretation of equivalence.</td>
</tr>
</tbody>
</table>
Methods | Parallel groups equivalence trial
---|---
Participants | Female sex, unilateral BRCA, non-metastatic 1-5 yrs post treatment, BMI<50, currently cancer free, no medical conditions limiting exercise, weight stable, no weight lifting in the year before study entry, no plans for surgery or leave >1 month during study period, not actively trying to loose weight, > 1 LN removed, no current LO

Interventions | **Intervention group (n=77)**
1 year membership to community fitness center, progressive resistance exercises in groups of 2-6, supervised for 13 weeks. Unsupervised for the rest of the study period. Progressive resistance exercises with dumbbells or machines, in 3 sets of 10 reps, increasing weight with the smallest possible increment after completing 2 sessions of 3x10 reps without symptoms of lymphoedema

**Control group (n=77)**
Controls were asked not to change baseline level of exercise during study period.

Outcomes | **Primary LO outcome:**
Lymphoedema defined as: Interlimb difference of >5%, determined by water displacement volumetry: (affected arm volume – unaffected arm volume) / unaffected arm volume

**Secondary LO outcomes:**
Lymphoedema defined as: greatest circumferential difference of >5% and clinician based diagnosis based on CTCAE 3.0
Health related quality of life (SF36)
Body image (Body Image and Relationships Scale)
Pain (not reported)
Musculoskeletal adverse events

Follow up | 12 months
Country, setting | USA, University Medical Center
Year of conduct | 2005-2008
### Risk of bias table for Schmitz 2010

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Minimization balancing for age, NRN, obesity and RT</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Computerized sequence generation</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) Measured outcomes</td>
<td>High risk</td>
<td>Patients and personnel were not blinded for the intervention. Although patients in the control group were asked not to change their baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>physical activity level, average self reported physical activity in MET-min/week increased with 370 MET-min/week and 360MET-min/week in the control group.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>It is unclear whether this involved strength training as well, although there was no significant increase in strength in the control group.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) Patient reported outcomes</td>
<td>High risk</td>
<td>Patients and personnel were not blinded for the intervention</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Measured outcomes</td>
<td>Low risk</td>
<td>Outcome observers LO were blinded to group allocation. Participants were asked not to reveal group assignment before measurement sessions.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Patient reported outcomes</td>
<td>Unclear risk</td>
<td>Participants were not blinded. Self reported HRQoL may be affected by participants knowledge of group allocation.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) Measured outcomes</td>
<td>Low risk</td>
<td>The drop-out rate and reasons for drop-out were comparable between groups for the primary outcome, sensitivity analysis (best case/worst case scenario) was performed and findings were robust.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) Patient reported outcome</td>
<td>Unclear risk</td>
<td>For patient reported outcomes, the attrition rate was 23.3% in the intervention group and 20.8% in the control group at the 12 month follow-up. Time since diagnosis of the evaluable patients in the control group was on average 5 months more than in the intervention group.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>There were no results reported on pain.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other potential sources of bias were identified</td>
</tr>
</tbody>
</table>
### Todd 2008

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT, parallel groups, single blind</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Women with early breast cancer admitted for surgery including ALND</td>
</tr>
</tbody>
</table>
| Interventions | Intervention group (n=58)  
 Delayed (1 week) full-range shoulder mobilisation exercises. During the first week, exercise was limited to below 90 degrees in all planes of movement. Exercises were to be performed four times per day, until full shoulder movement was restored. |
| Outcomes      | Primary outcome:  
 Lymphoedema defined as:  
 200 ml or more volume difference between the arms on the operated side and the non-operated side.  
 Secondary outcome:  
 Range of motion of the shoulder for flexion, abduction, medial rotation and lateral rotation as measured with a goniometer.  
 HRQOL using the Trial Outcome Index of the Functional Assessment of Cancer Therapy-Breast (FACT-B)  
 Grip strength (JAMAR)  
 Shoulder disability (Shoulder disability questionnaire) |
| Follow up     | 12 months |
| Country, setting | Two secondary care National Health Service trusts, UK. |
| Year of conduct | 2003-2006 |
## Risk of bias table for Todd 2008

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Randomisation using random number table and sealed envelopes</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Women were randomised by an objective third person after completion of baseline measures</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Patients and personnel were not blinded for group allocation, but only one patient in the delayed mobilisation group did not receive the allocated intervention.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Patients and personnel were not blinded for group allocation, but only one patient in the delayed mobilisation group did not receive the allocated intervention.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Measured outcomes</td>
<td>Low risk</td>
<td>Outcome observer was blinded, and participants were instructed not to reveal group allocation during follow-up visits</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Patient reported outcomes</td>
<td>Low risk</td>
<td>Patients were not blinded, but HRQOL was assessed at one year follow-up. Given the nature and the duration of the intervention, it seems unlikely that knowledge of group allocation would have influenced patients self report HRQOL.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) Measured outcomes</td>
<td>High risk</td>
<td>Results for lymphoedema were imputed using last observation carried forward; sensitivity analysis yields the possibility of a non-significant difference (whereas a significant difference is reported).</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) Patient reported outcome</td>
<td>Low risk</td>
<td>Drop-out was limited</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcome measures mentioned in the methods section are reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>It is unclear how many patients in each group were treated for lymphoedema in the period between baseline and follow-up measurements (this was dependent on self report lymphoedema complaints and subsequent clinical evaluation).</td>
</tr>
</tbody>
</table>
## Torres 2010

<table>
<thead>
<tr>
<th>Methods</th>
<th>Parallel groups randomised controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Women after unilateral breast cancer surgery including ALND, mean age 52.9 (SD 11.6), (N=120). Eighty percent of the women received radiotherapy treatment, 82% chemotherapy</td>
</tr>
</tbody>
</table>
| Interventions    | **Intervention group (n=60)**  
Manual Lymph Drainage (thorax, breast, axilla and upper arm), scar massage and exercise therapy (stretching, functional activities, active and assisted exercises of the shoulder) for three weeks (3 visits/week) & education.  
**Control group (n=60)**  
Education only |
| Outcomes         | **Primary outcome:**  
Lymphoedema, defined as a 2cm or greater increase in the circumference of any two adjacent points compared with measurements in the other arm.  
**Secondary outcome:**  
Pain (VAS);  
Range of motion of the shoulder;  
Lymphoedema by other criteria (not reported)  
Time to event for lymphoedema |
| Follow up        | 1, 3, 6 and 12 months (event rates for lymphoedema only available for 12 months) |
| Country, setting | Spain, University hospital |
| Year of conduct  | 2005 - 2007 |
### Risk of bias table for Torres 2010

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>randomisation was done based on a computer generated randomisation table</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Patients were enrolled in order of arrival. Randomisation was performed by a different person from the recruiter.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) Measured outcomes</td>
<td>Unclear risk</td>
<td>Participants and personnel were not blinded for the intervention. The risk of contamination is unclear.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) Patient reported outcomes</td>
<td>Unclear risk</td>
<td>Patients and therapist were not blinded for the intervention. The risk of contamination is unclear.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Measured outcomes</td>
<td>Unclear risk</td>
<td>An independent observer performed all follow-up measurements, however participants were not blinded for the intervention which may have induced differences in propensity towards reporting symptoms based on knowledge of group allocation. This may have biased the estimation of lymphoedema incidence, but not measurements of range of motion of the shoulder.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Patient reported outcomes</td>
<td>High risk</td>
<td>Self report for pain and HRQOL may be affected by patients’ knowledge of group allocation.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) Measured outcomes</td>
<td>Low risk</td>
<td>Data is available for all included patients.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) Patient reported outcome</td>
<td>Low risk</td>
<td>Data is available for all included patients.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Data on secondary outcomes are not reported in the publication, but were made available by the researchers.</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Radiotherapy was more often given to patients in the control group (+11%). Trial analysis was per protocol. 3 patients in the control group and one 1 patient in the intervention group who did not receive the allocated intervention were excluded from the analysis.</td>
</tr>
</tbody>
</table>
### Zimmermann 2012

<table>
<thead>
<tr>
<th>Methods</th>
<th>Parallel groups randomised controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Women after breast cancer surgery, mean age 67 (range 34 - 81)</td>
</tr>
</tbody>
</table>
| Interventions            | **Intervention group:** Manual lymphdrainage (Modified Földi and Strössenreuther method), 5 times a week during first 2 weeks, then twice a week from day 14 until 6 months, in addition to standardized physiotherapy (exercises of upper limb and chest).  
**Control group:** Self drainage and standardized physiotherapy |
| Outcomes                 | **Primary outcome:** Lymphoedema, measured through the water displacement method. Volume of lymphoedema is expressed as the ratio of the difference between arm volume on the operated and nonoperated sides/ arm volume nonoperated side. Cutoff points used for lymphoedema: <5% absence, 5-10% mild, 10-20% moderate >20% substantial.  
**Secondary outcome:** Range of motion (goniometer) for shoulder flexion, abduction, extension.  
Follow up                | 2, 7, 14 days, 3 months, 6 months |
| Country, setting         | Germany, teaching hospital |
| Year of conduct          | 2003 - 2004 |
## Risk of bias table for Zimmermann 2012

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>block randomisation using computerized list</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>fixed block length, no mention of blinding of allocation</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) Measured outcomes</td>
<td>Unclear risk</td>
<td>Participants and personnel were not blinded for the intervention. The risk of contamination is unclear.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) Patient reported outcomes</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Measured outcomes</td>
<td>High risk</td>
<td>No attempts at blinding were made.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Patient reported outcomes</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) Measured outcomes</td>
<td>Low risk</td>
<td>Outcome is complete for all participants</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) Patient reported outcome</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcome data is available</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>The intervention group had more contacts with a therapist, which may reinforce other behaviour such as compliance to exercises and self-care measures.</td>
</tr>
<tr>
<td>Study</td>
<td>Reason for exclusion</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Ahmed 2006</td>
<td>In both groups patients were included who already had lymphoedema. Allocation was not stratified for presence of lymphoedema, hence no subgroups could be examined.</td>
<td></td>
</tr>
<tr>
<td>Anderson 2012</td>
<td>Lymphoedema was not the primary outcome in this study on the effect and safety of a structured exercise program with lymphoedema prevention module on quality of life.</td>
<td></td>
</tr>
<tr>
<td>Boccardo, 2009</td>
<td>The intervention was in part non-conservative (microsurgical operation in case of appearance of lymphoedema, as established by lymphoscintigraphy).</td>
<td></td>
</tr>
<tr>
<td>Box, 2009</td>
<td>Not a primary study, but a synopsis of Todd 2008</td>
<td></td>
</tr>
<tr>
<td>Campisi, 2002</td>
<td>The intervention was in part non-conservative (microsurgical lymhatic-venous anastomoses in patients non responsive to early physical therapy for lymphoedema, as established by lymphscintigraphy).</td>
<td></td>
</tr>
<tr>
<td>Chandrakaladharan, 2009</td>
<td>Full text could not be obtained from the author; study was published as an abstract only.</td>
<td></td>
</tr>
<tr>
<td>de Rezende, 2006</td>
<td>The study evaluated shoulder function and wound drainage volumes. Lymphoedema was not an outcome.</td>
<td></td>
</tr>
<tr>
<td>Hayes 2012</td>
<td>Lymphoedema was not as primary outcome in this study on effect of exercise on quality of life, and the outcome measure used was not sufficiently objective.</td>
<td></td>
</tr>
<tr>
<td>Le-Vu, 1997</td>
<td>The primary outcome was seroma formation. Lymphoedema was assessed at some point between 8 and 24 months, but only by self report questionnaire or clinician-based diagnosis.</td>
<td></td>
</tr>
<tr>
<td>Oliveira, 2009</td>
<td>The primary outcome was range of motion of the shoulder. Arm circumferences were included as secondary outcome measure. No results on lymphoedema are reported except that there was no statistically significant difference between the groups at all follow-up points.</td>
<td></td>
</tr>
<tr>
<td>Sarri, 2010</td>
<td>The primary outcome was lymphatic flow as measured by lymphscintigraphy, as a surrogate endpoint for lymphoedema.</td>
<td></td>
</tr>
<tr>
<td>Sisman, 2012</td>
<td>Not a randomised controlled trial</td>
<td></td>
</tr>
<tr>
<td>Wang, 2005</td>
<td>No clear and sufficiently objective measure for lymphoedema was defined</td>
<td></td>
</tr>
</tbody>
</table>
Table 3  Characteristics of ongoing studies

<table>
<thead>
<tr>
<th>Study id</th>
<th>Study name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ben Selvan 2008</td>
<td>The influence of prophylactic application of the class 2 upper limb stockings in carcinoma breast patients in reducing the incidence of Breast cancer related lymphedema</td>
</tr>
<tr>
<td>Pain 2012</td>
<td>Prevention of breast cancer-related lymphoedema following axillary lymph node clearance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study name</th>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ben Selvan 2008</td>
<td>Parallel group single blinded randomised controlled trial, 36 month follow-up, N=178</td>
</tr>
<tr>
<td>Pain 2012</td>
<td>Parallel group randomised controlled trial, 36 month follow-up, N=178</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients who need surgery for breast cancer</td>
<td>Class-2 elastic compression stockings: for a period of three months from the first post operative period, versus no stocking</td>
</tr>
<tr>
<td>Pain, S, Norfolk &amp; Norwich Univeristy Hospital Coiney Lane Norwich Norfolk NR4 7UY, United Kingdom</td>
<td>Manual lymph drainage, in addition to skin care, compression garments and exercise versus skin care, compression garments and exercise only.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Starting date</th>
<th>Contact information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: percentage of reduction in arm volume (circumference measurements) in the study group. Secondary outcome: Incidence of lymphoedema on the 10th post operative day and at three months follow up</td>
<td>Registered on 27-11-2008</td>
<td>Ben Selvan, C.K. Christian medical college, department of surgery, 632004, Vellore, Tamil Nadu India. <a href="mailto:drckben@yahoo.com">drckben@yahoo.com</a></td>
</tr>
<tr>
<td>Limb volume using circumference measurements, validation of bio-impedance technology</td>
<td>01-10-11</td>
<td>Pain, S, Norfolk &amp; Norwich Univeristy Hospital Coiney Lane Norwich Norfolk NR4 7UY, United Kingdom, <a href="mailto:simon.pain@nnuh.nhs.uk">simon.pain@nnuh.nhs.uk</a></td>
</tr>
</tbody>
</table>

Registry ID

<table>
<thead>
<tr>
<th>Study id</th>
<th>Registry ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ben Selvan 2008</td>
<td>CTRI/2008/091/000249</td>
</tr>
<tr>
<td>Pain 2012</td>
<td>ACTRN12612000639820</td>
</tr>
</tbody>
</table>
### Summary of Findings Table 1

**early physiotherapy including MLD for patients at risk for secondary upper limb lymphoedema after breast cancer treatment**

**Patient or population:** patients at risk for secondary upper limb lymphoedema after breast cancer treatment  
**Intervention:** early physiotherapy including MLD

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI) (studies)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **Time to event (Lymphoedema) volumetry**  
Follow-up: 12 months | Control | Early physiotherapy including MLD | Low | Not estimable | HR ranged 270 from 0.26 to 1.3 | 2 | very low^1,2,3 |
| | High | | | Not estimable | |
| **Lymphoedema - short term follow up**  
Volumetry  
Follow-up: mean 3 months | Control | Early physiotherapy including MLD | Low | Not estimable | RR ranged 226 from 0.14 to 1.4 | 2 | very low^5,6 |
| | High | | | Not estimable | |
| **Lymphoedema - medium term follow up**  
Volumetry  
Follow-up: 6-12 months | Control | Early physiotherapy including MLD | Low | Not estimable | RR ranged 385 from 0.02 to 1.26 | 4 | very low^8,9 |
| | High | | | Not estimable | |
**Pain - medium term follow-up**
Visual analogue scale. Scale from: 0 to 10
Follow-up: 8-12 months

<table>
<thead>
<tr>
<th></th>
<th>Not estimable</th>
<th>The mean pain - medium term follow-up in the intervention group ranged from 2.4 lower to 0.5 higher</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>164 (2 studies)</td>
<td></td>
</tr>
</tbody>
</table>

**Shoulder range of motion for abduction - short term follow up**
goniometer. Scale from: 0 to 180.
Follow-up: 2-4 weeks

|  | The mean shoulder range of motion for abduction - short term follow up in the intervention groups was 21.84 higher (13.58 to 30.1 higher) |
|  | 183 (2 studies) |

**Shoulder range of motion for forward flexion - short term follow up**
goniometer. Scale from: 0 to 180.
Follow-up: 2-4 weeks

|  | The mean shoulder range of motion for forward flexion - short term follow up in the intervention groups was 14.44 higher (7.08 to 21.81 higher) |
|  | 183 (3 studies) |

**Shoulder range of motion for abduction - medium term follow up**
goniometer. Scale from: 0 to 180.
Follow-up: 6-12 months

|  | Not estimable | The mean shoulder range of motion for abduction - medium term follow up in the intervention group ranged from 3.1 lower to 16.9 higher |
|  | 183 (3 studies) |

**Shoulder range of motion for forward flexion - medium term follow up**
goniometer. Scale from: 0 to 180.
Follow-up: 6-12 months

|  | Not estimable | The mean shoulder range of motion for forward flexion - medium term follow up in the intervention group ranged from 0.4 lower to 14.3 higher |
|  | 183 (3 studies) |

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

**CI:** Confidence interval; **RR:** Risk ratio; **HR:** Hazard ratio;

**GRADE Working Group grades of evidence**

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

1 A higher percentage in the intervention group had level III dissection (43 vs 33%) and a higher percentage had radiotherapy on the axilla (10 vs 6) in one study (de Voogd 2011). Radiotherapy was more often used in control group in one study (Torres 2010). No blinding of participants and personnel both studies. Per protocol analysis in one study (Torres 2010).
2 No evidence of effect in one study (deVoogd 2011), large effect in one study (Torres 2010). Contradicting point estimates.
3 No meta analysis was possible due to statistical heterogeneity; 95%CI includes clinically relevant values in both directions in one study (de Voogd, 2011)
4 No allocation concealment in one study (Zimmermann 2012), no blinding of outcome assessment in one study (Zimmermann 2011).
5 No evidence of effect in one study (de Voogd 2011), large effect in the second study (Zimmermann 2012).
6 No meta-analysis was possible, one study with a very large confidence interval (Zimmermann 2012) one study with small confidence interval (de Voogd 2011)
7 No allocation concealment in one study (Zimmermann 2012), selective outcome reporting in one study (Castro-Sanchez 2011), No blinding of outcome assessment in 3 studies (Castro-Sanchez 2011, Torres 2010, Zimmermann 2011). No intention-to-treat analysis in one study (Torres 2010), groups not comparable at baseline in one study (Castro-Sanchez 2011, Torres 2010), treatment of groups differed apart from assigned intervention (Castro-Sanchez 2011, Torres 2010).
8 strong statistical heterogeneity
9 Broad 95% confidence intervals including clinically relevant effects in both directions in three studies (Castro-Sanchez 2011, Torres 2011, de Voogd 2011).
10 No allocation concealment in one study (Zimmermann 2012) No blinding of outcome assessment in both studies. No intention-to-treat analysis in one study (Torres 2010), treatment of groups differed apart from assigned intervention (Torres 2010).
11 No allocation concealment in one study (Zimmermann 2012) No blinding of outcome assessment in both studies. No intention-to-treat analysis in one study (Torres 2010), groups not comparable at baseline in one study for radiotherapy treatment (Castro-Sanchez 2011, Torres 2010), treatment of groups differed apart from assigned intervention (Torres 2010).
12 Large effect in favour of intervention in one study (Zimmermann 2012), small non-significant effect favouring the control group in another study (Torres 2010).
13 Broad 95% CI in one non-significant study includes potentially clinically relevant effects in both directions (Torres 2010).
## Early shoulder mobilising exercises compared to Delayed shoulder mobilising exercises for patients surgically treated for breast cancer

**Patient or population:** patients at risk for secondary upper limb lymphoedema after breast cancer treatment  
**Settings:** Hospital  
**Intervention:** early shoulder mobilising exercises  
**Comparison:** delayed shoulder mobilising exercises

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **Lymphoedema - medium term follow up**  
Volumetry/Circumference  
Follow-up: 6-12 months | **Low**  
5 per 100  
3 per 100 (2 to 5) | RR 0.59  
(0.33 to 1.06) | 378  
(3 studies) | #3#3#3#3 very low1,2,3 |  |
| **High**  
20 per 100  
12 per 100 (7 to 21) |  |  |  |  |  |

| **Shoulder range of motion for abduction - short term follow up**  
goniometer. Scale from: 0 to 180.  
Follow-up: 1 months | Not estimable | The mean shoulder range of motion for abduction - short term follow up in the intervention group ranged from 6 to 43 higher | 262  
(2 studies) | #3#3#3 very low1,4 |  |

| **Shoulder range of motion for abduction - medium term follow up**  
goniometer. Scale from: 0 to 180.  
Follow-up: 6-12 months | Not estimable | The mean shoulder range of motion for abduction - medium term follow up in the intervention group ranged from 8.3 lower to 21.3 higher | 378  
(3 studies) | #3#3#3 very low5,6,7 |  |

| **Shoulder range of motion for forward flexion - short term follow up**  
goniometer. Scale from: 0 to 180.  
Follow-up: 1 months | Not estimable | The mean shoulder range of motion for forward flexion - short term follow up in the intervention group ranged from 7 to 35.7 higher | 262  
(2 studies) | #3#3#3 low1,8 |  |

| **Shoulder range of motion for forward flexion - medium term follow up**  
goniometer. Scale from: 0 to 180.  
Follow-up: 6-12 months | Not estimable | The mean shoulder range of motion for forward flexion - medium term follow up in the intervention group ranged from 0.6 lower to 5 higher | 321  
(3 studies) | #3#3#3 very low5,6,9 |  |
<table>
<thead>
<tr>
<th>Study Design</th>
<th>Risk Estimate</th>
<th>Participants</th>
<th>GRADE Evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder range of motion for external rotation - short term follow up</td>
<td>Not estimable</td>
<td>20 per 100 (7 to 21)</td>
<td>Low</td>
<td>No allocation concealment in one study (Bendz 2002), no blinding of outcome assessment in one study (Bendz 2002), no explicit statistical consideration for cluster randomisation (Bendz 2002), unclear risk of bias for allocation procedure and concealment and attrition in one study (Cinar 2008), unequal treatment of groups besides intervention in one study (Cinar).</td>
</tr>
<tr>
<td>Shoulder range of motion for external rotation - medium term follow up</td>
<td>The mean shoulder range of motion for external rotation - medium term follow up in the intervention group ranged from 1 lower to 8 higher</td>
<td>262 (2 studies)</td>
<td>Very low</td>
<td></td>
</tr>
<tr>
<td>Shoulder range of motion for internal rotation - short term follow up</td>
<td>The mean shoulder range of motion for internal rotation - short term follow up in the control groups was 1 degrees higher (2.21 lower to 2.67 higher)</td>
<td>262 (2 studies)</td>
<td>Very low</td>
<td></td>
</tr>
<tr>
<td>Shoulder range of motion for internal rotation - medium term follow up</td>
<td>The mean shoulder range of motion for internal rotation - medium term follow up in the intervention groups was 2.43 higher (0.14 lower to 4.9 higher)</td>
<td>378 (3 studies)</td>
<td>Very low</td>
<td></td>
</tr>
</tbody>
</table>

The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

**GRADE Working Group grades of evidence**

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

1. No allocation concealment in one study (Bendz 2002), no blinding of outcome assessment in one study (Bendz 2002), No explicit statistical consideration for cluster randomisation (Bendz 2002), unclear risk of bias for allocation procedure and concealment and attrition in one study (Cinar 2008), unequal treatment of groups besides intervention in one study (Cinar).
2. Large and statistically significant effect in favour of intervention in one study (Todd 2008), statistically non-significant effect in favour of control group in another study (Bendz 2002).
3. Broad 95% confidence interval including clinically relevant effect in non-significant meta-analysis.
4. Small and non significant effect in one study (Bendz 2002), large statistically significant effect in another study (Cinar 2008). Data pooling could not be performed due to significant statistical heterogeneity.
5. No allocation concealment in one study (Bendz 2002), no blinding of outcome assessment in one study (Bendz 2002), high risk of attrition bias in one study (Todd 2008), no explicit statistical consideration for cluster randomisation (Bendz 2002), unclear risk of bias for allocation procedure and concealment and attrition in one study (Cinar 2008), unequal treatment of groups besides intervention in one study (Cinar).
6. No metaanalysis could be performed due to significant statistical heterogeneity, with contradicting effect estimates in three studies: (Bendz 2002; Cinar 2008; Todd 2008).
7. Very broad 95% confidence intervals including both neutral values and large clinically relevant effects in two studies (Bendz 2002, Todd 2008). Data pooling was not possible due to significant statistical heterogeneity.
8. No data pooling was possible due to significant statistical heterogeneity, but point estimates are in favour of early mobilisation and statistically significant in both studies (Bendz 2002, Cinar 2008).
9. 95% confidence interval includes both neutral and potentially clinically relevant values in one study (Todd 2008), and a small clinically irrelevant effect in the lower boundary of the CI in a second study (Bendz 2002).
10. 95%CI in one study included both small and very large effect (Cinar 2008).
11. Pooled data are from 6 month follow up (Bendz 2002) and 12 month follow up (Todd 2008).
12. Two studies with non-significant effect with point estimate favouring delayed exercise (Bendz 2002, Todd 2008), one study with a large statistically significant effect favouring early exercise (Cinar 2008).
progressive resistance exercise for patients at risk for secondary upper limb lymphoedema after breast cancer treatment

**Patient or population:** patients at risk for secondary upper limb lymphoedema after breast cancer treatment

**Settings:**

**Intervention:** progressive resistance exercise

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>Progressive resistance exercise</td>
<td>RR 0.58 (0.3 to 1.13)</td>
<td>351 (2 studies)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Lymphoedema Volumetry Follow-up: 12-24 months</td>
<td>Low</td>
<td>0 per 100 (0 to 0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>17 per 100</td>
<td>10 per 100 (5 to 20)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio.

**GRADE Working Group grades of evidence**

- **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very low quality:** We are very uncertain about the estimate.

† Both studies did not blind participants for the intervention. In one study, activity levels over time increased in both experimental and control group, despite requests to the control group not to increase activity levels during study period. One study (Sagen 2009) had more patients lost to follow up in the experimental group, data were imputed using last observation carried forward. Contact with a physiotherapist was more frequent in the experimental group in one study, which may reinforce self-care/ risk reducing behaviour (Sagen 2009).

**Acknowledgements**

The authors would like to thank Faridi van Jetten, Academic Medical Center - Univeristy of Amsterdam for her help with developing the search strategy; Chen Xiao Chen, BM, University of Winsconsin-Madison - School of Nursing, and Anna Miquel Cases, The Netherlands Cancer Institute for their help with translation of the non-English language studies; all authors of included studies who were very helpful by clarifying details about the study and providing additional data; the Cochrane Breast Cancer Group and especially Dr. Melina Willson, editor, for her support with developing this review and Fergus Tai for his help with the searches.
REFERENCES


Search strategies used for ‘Conservative interventions for preventing clinically detectable upper-limb lymphoedema in patients who are at risk of developing lymphoedema after breast cancer therapy

1. MEDLINE via Pubmed (1980 to present)


2. EMBASE via Ovid (1980 to present)

1. exp breast cancer/ or (breast cancer* or breastcancer* or breast tumor* or breast tumour* or mammary neoplasm* or mammary carcinoma* or breast neoplasm* or breast carcinoma*).ti,ab.

2. lymphedema/ or elephantiasis/ or (lymphoedema or lymphedema or lymphedema or lymphatic edema or oedema or edema).ti,ab.

3. prevention/ or early diagnosis/ or risk/ or *risk reduction/ or probability/ or prevalence/ or prediction/ or (prevent* or risk* or reducing or restrict* or prevalence*).ti,ab.

4. 1 and 2 and 3

5. limit 4 to embase

3 WHO ICTRP Search Portal

Basic Searches:

1. Conventional interventions for preventing clinically detectable upper-limb lymphoedema in patients who are at risk of developing lymphoedema after breast cancer therapy

2. Lymphoedema AND prevent*

3. Lymphedema AND prevent*
Advanced Searches:

1. Title: Conventional interventions for preventing clinically detectable upper-limb lymphoedema in patients who are at risk of developing lymphoedema after breast cancer therapy. Recruitment Status: ALL

2. Condition: breast cancer AND (lymphoedema OR lymphedema OR lymphatic oedema OR lymphatic edema OR oedema OR edema) Intervention: prevention OR control OR early diagnosis OR risk reduction behavior OR exercise OR patient education OR early intervention OR monitoring OR compression therapy OR manual lymph drainage OR lymph taping OR kinesiotape

3. Recruitment Status: ALL

---

4 The Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO (1980 to present)

S4 S1 and S2 and S3

S3

( (MH "Early Diagnosis+") or (MH "Relative Risk") or (MH "Probability") or (MH "Prevalence") ) or ( ( TI restrict* OR AB restrict* ) or ( TI prevalence* OR AB prevalence* ) ) or ( ( TI prevent* OR AB prevent* ) or ( TI risk* OR AB risk* ) or ( TI reducing OR AB reducing ) ) or ( TI predict* or AB predict* ) or (MH "Risk Factors+")

S2

( (MH "Lymphedema+") or ( ( TI lymphoedema or AB lymphoedema ) or ( TI lymphedema or AB lymphoedema ) or ( TI lymph edema or AB lymph edema ) ) or ( ( TI lymphatic edema or AB lymphatic edema ) or ( TI oedema or AB oedema ) or ( TI edema or AB edema ) ) ) or ( ( TI swelling or AB swelling ) or ( TI elephantias* or AB elephantias* )

S1

( (MH "Breast Neoplasms+") or ( ( TI breast cancer* or AB breast cancer* ) or ( TI breastcancer* or AB breastcancer* ) or ( TI breast tumor* or AB breast tumor* ) ) or ( ( TI breast tumour* or AB breast tumour* ) or ( TI mammary neoplasm* or AB mammary neoplasm* ) or ( TI mammary carcinoma* or AB mammary carcinoma* ) or ( TI breast neoplasm* or AB breast neoplasm* ) or ( TI breast carcinoma* or AB breast carcinoma* )

---

5 Physiotherapy Evidence Database (PEDro) via http://pedro.org.au (1980 to present)

1. Abstract and title: cancer

2. Problem: oedema
6 PsycINFO via Ovid (1980 to present)

1. lymphoedema.id. or (lymphoedema or lymphedema or lymphatic edema or oedema or edema or swelling or elephantias*).ti,ab.

2. risk factors/ or risk factors.id. or (prevent* or risk* or reducing or restrict* or prevalence*).ti,ab.

3. breast neoplasms/ or breast cancer.id. or (breast cancer* or breastcancer* or breast tumor* or breast tumour* or mammary neoplasm* or mammary carcinoma* or breast neoplasm* or breast carcinoma* or breast malignan* or breast metastas* or mammary malignan* or mammary metastas*).ti,ab.

4. 1 and 2 and 3

7 CENTRAL

1. MeSH descriptor: [Lymphedema] explode all trees

2. lymphoedema* or lymphedema* or lymphatic oedema* or lymphatic edema* or oedema* or edema* or swelling

3. MeSH descriptor: [Elephantiasis] explode all trees

4. #1 or #2 or #3

5. MeSH descriptor: [Breast Neoplasms] explode all trees

6. breast neoplasm or breast cancer or breast tumour or breast tumor or breast carcinoma

7. #5 or #6

8. #4 and #7

9. ‘prevention and control’ or prevent* or control or early diagnosis or risk reduction behavior or exercise or patient education or early intervention or monitoring or compression therapy or manual lymph drainage or lymph taping or kinesiotape

10. #8 and #9