National Institute for Health and Care Excellence

Early and locally advanced breast cancer: diagnosis and management

[O] Evidence reviews for the non-pharmacological prevention of lymphoedema in people who have, or have had, breast cancer.

NICE guideline NG101

Evidence reviews underpinning recommendations 1.1.1 to 1.1.4 and research recommendations in the NICE guideline

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Draft for consultation

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1 Non-pharmacological prevention of lymphoedema

1.1 Review question

In people who have, or have had, breast cancer, what non-pharmacological strategies are effective and cost-effective for reducing the risk of developing lymphoedema?

1. Lymphoedema Education
2. Early intervention
3. Worn prevention
4. Exercise and movement.
5. Surgery
6. Skincare

1.1.1 Introduction

The NICE surveillance review (June 2023) identified some studies that showed that various interventions such as vascularised lymph node transfer may decrease the risk of lymphoedema in people with breast cancer. The current recommendations in NG101 and CG81 focus on preventing lymphoedema in people with early and locally advanced breast cancer and do not include people with advanced breast cancer. As such, there is a need to expand the evidence reviews to cover all people with breast cancer, as well as review any new evidence on the prevention and management of lymphoedema in people with breast cancer.

1.1.2 Summary of the protocol

Table 1: PICOS inclusion criteria

Population	All adults (aged 18 or over) who have, or have had, breast cancer and are at risk of developing lymphoedema of the upper limb (including axilla, hands and fingers), chest wall or breast. Exclusion: None identified
Interventions	Any intervention (or combination of interventions) with the aim of reducing the risk of lymphoedema: 1. Lymphoedema Education (for example, increased awareness, advice on interventions to avoid [including venepuncture, injection to affected tissues, blood pressure checks, tattoos], advice on behaviour change to achieve healthy weight) 2. Early intervention (for example, monitoring and self-measurements [including, functional assessments, questionnaires], active management of infection and injury) 3. Worn prevention (for example, wired/non-wired bras, compression garments, foam inserts, spaghetti foam)

	4. Exercise and movement (for example, range of motion exercises, physiotherapy) 5. Surgery (for example: immediate lymphatic reconstruction, lymphaticovenous anastomosis, vascularised lymph node transfer) (see 1.1.3.2) 6. Skincare (for example, keeping skin clean and use of moisturisers)
Comparator	1. No intervention aimed at preventing lymphoedema (usual care) 2. Each other 3. Contralateral arm or breast
Outcomes	1. Incidence of lymphoedema 2. Severity of lymphoedema (for example, limb or breast volume/swelling using ultrasound/tissue dielectric constant, arm mobility (including, DASH scores), bioimpedance) 3. Patient reported outcomes (for example pain, psychological distress, limb function) 4. Adverse events (for example, infection) 5. Quality of life (for example, LYMQOL, FACT B+4, EQ5D and EORTC-QoL-C30)
Study type	1. SRs of RCTs 2. SRs of cohort studies 3. RCTs 4. Prospective cohort studies.

For the full protocol see appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.3.1 Methods specific for this review

Each of the 6 subsections (families of interventions) of the review protocol was treated as a separate evidence syntheses to allow for tailored approaches to the evidence for each of the

subsections, and they are presented sequentially in this evidence review (sections 2 to 7). Evidence synthesis for each subsection was done taking a stepped approach:

1. For subsections where a recent systematic review was found that covered all interventions identified by the committee, that systematic review was used as the primary source of evidence. The outcomes and results from the systematic review were reported in the relevant sections. Primary studies used in the systematic reviews were not checked for additional outcomes not reported by the systematic review. If NICE searches found RCTs not included in the SR (because they were more recent), or that covered interventions in the subsection not covered by the SR then these were reported separately. Due to the heterogenous nature of the existing systematic reviews, it was not appropriate to update meta-analyses with the new studies.

2. For areas where several SRs were found covering all or part of the subsection, these were reported alongside a table of inclusions for each review that shows the overlap and differences. Where relevant, for example because an intervention is not covered in the SRs, or because newer RCTs are available, RCTs will be reported as above.

3. Where no SRs are available, the NICE team have presented data in GRADE from relevant RCTs but were unable to perform meta-analyses due to the data being too heterogenous.

Study selection for systematic reviews:

1. Systematic reviews of randomised controlled trials were only included if they:

    a. Matched the review protocol for the question (including the relevant interventions, comparators, and outcomes).

    b. Included a quantitative analysis of the studies (i.e. a meta-analysis, with appropriate statistics).

    c. Where more than one systematic review with the same criteria, for the same intervention category was found, the more recent systematic review was selected for inclusion.

    d. Where more than one systematic review was found for each subset of interventions, each systematic review for each subset of interventions was included.

2. Systematic reviews of non-randomised trials were only included if they:

    a. No systematic reviews of randomised trials were included.

    b. Matched the review protocol for the question (including the relevant interventions, comparators and outcomes).

    c. Included a quantitative analysis of the studies (i.e. a meta-analysis with appropriate statistics).

    d. Where more than one systematic review with the same criteria for the same intervention was found, the more recent systematic review was selected for inclusion.

e. Where more than one systematic review was found for each subset of interventions, each systematic review was included.

Study selection for randomised controlled trials and observational studies:

1. Randomised controlled trials (RCTs) were only included if:
    a. They matched the review protocol of the question.
    b. They were not included as primary studies in any of the systematic reviews selected for inclusion.
2. Observational studies were only included if:
    a. Less than 3 RCTs were found for each subset of interventions.
    b. The studies matched the review question protocol (including relevant interventions, comparators, and outcomes).
3. If <3 RCTs were found for each subset of interventions, and no observational studies were found, the RCTs were included.

Defining clinical decision thresholds

Clinical decision thresholds for minimally important differences (MIDs) were used to interpret the evidence. Where there were known published MIDs for an outcome, these were used as the clinical decision thresholds.

- For continuous outcomes, where there were no published MIDs:
    - Where a mean difference (MD) was reported, the NICE default clinical decision threshold of 0.5 of the standard deviation (SD) of the control group for each outcome was used. Where the SD was not reported, the line of no effect was used was used as a clinical decision threshold and a sample size of n <400 was used to provide the second domain to downgrade for imprecision.
    - Where a standardised mean difference (SMD) was reported, the NICE default of +-0.5 was used for the clinical decision thresholds.
- For dichotomous outcomes, where there were no published MIDs the NICE default clinical decision thresholds of 0.8 and 1.25 were used..

GRADE summary tables

The following criteria were used to interpret the effect (column of 'Interpretation of effect') in the summary GRADE tables:

For all outcomes, evidence statements are divided into 2 groups as follows:

- We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect
- The evidence could not differentiate between comparators if the 95% CI crosses the line of no effect

1.1.3.2 Search methods

The searches for the effectiveness evidence were run on 19 February 2024. The following databases were searched: Allied and Complementary Medicine (AMED) (Ovid); Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley); Cochrane Database of Systematic Reviews (CDSR) (CRD); Database of Abstracts of Reviews of Effectiveness (DARE) (CRD); Embase (Ovid); Emcare (Ovid); Epistemonikos; Health Technology Assessment (HTA) (CRD); International Health Technology Assessment Database (INAHTA); Medline ALL (Ovid). Full search strategies for each database are provided in appendix B

The searches for the cost effectiveness evidence were run on 22 February 2024. The following databases were searched: EconLit (Ovid); Embase (Ovid); International Health Technology Assessment Database (INAHTA); Medline ALL (Ovid); NHS EED (CRD). Full search strategies for each database are provided in appendix B.

A NICE information specialist conducted the searches. The MEDLINE strategy was quality assured by a trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement.

1.1.3.3 Protocol deviations

The committee highlighted that preventative surgery for lymphoedema can be conducted concurrently with any primary interventions for breast cancer. There is an existing evidence base for its use in the prevention of breast cancer-related lymphoedema. As the NICE searches and search terms were not intervention specific, the studies covering surgical interventions for the prevention of lymphoedema were considered as part of the evidence for this review.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 2912 references (see appendix B for the literature search strategy).

These 2912 references were screened at title and abstract level against the review protocol, with 2833 excluded at this level. 10% of references were screened separately by two reviewers with 100% agreement. Discrepancies were resolved by discussion.

The full texts of 79 systematic reviews, RCTs and cohort studies were ordered for closer inspection. 5 SRs and 16 RCTs met the criteria specified in the review protocol (appendix A). For a summary of each of included studies see summary tables in sections 2 to 7 in the evidence review

The clinical evidence study selection is presented as a PRISMA diagram in appendix C .

See section 1.1.14 References – included studies for the full references of the included studies.

1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in appendix J.

2 Lymphoedema Education

2.1 Summary of studies included in the effectiveness evidence

Table 2 Summary of studies included in the effectiveness evidence – Randomised controlled trials

Study details	Population	Intervention	Comparison	Outcome	Risk of bias
Bland et al., 2019 N=119 RCT Follow up: Up to 3 years	Breast cancer patients undergoing surgery	Structured preoperative lymphoedema education class plus refresher (n=64)	Standard preoperative counselling and booklet (n=55)	• Quality of life, • lymphoedema incidence and severity	Moderate
Shi et al., 2023 N=108 RCT Follow up time:4 months	Women aged ≥18 with stage I-III unilateral breast cancer undergoing surgery and adjuvant chemotherapy	Perioperative education, exercise guidance, peer support (n=52)	Usual care control (n=56)	• Incidence of lymphoedema • handgrip strength • arm disability.	Low
Temur et al., 2019 N=72 RCT Follow up time:6 months	Patients aged 18-65 who underwent modified radical mastectomy or breast-conserving surgery with axillary lymph node dissection	Self-management programmesmes with education, exercises, massage (n=30)	Education only control (n=31)	• Severity of lymphoedema • quality of life • arm disability, symptoms	Low

2.2 Summary of the effectiveness evidence

GRADE summary tables

Table 3:Structured training + preoperative counselling vs preoperative counselling

Outcomes	Effect estimate (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Quality of life (higher scores represent better quality of life)				
Quality of life FACT-B scores ±MID 7-8 points follow-up: mean 1 years	MD **12.74 lower** (28.86 lower to 3.38 higher)	119 (1 RCT Bland, 2019)	Very low	Could not differentiate
Lymphoedema (incidence) (RR less than 1 represents lower incidence)				
Incidence of acute lymphoedema MID 0.8 to 1.25 follow-up: mean 1 years	**RR 1.09** (0.76 to 1.57)	119 (1 RCT Bland, 2019)	Very low	Could not differentiate
Incidence of chronic lymphoedema MID 0.8 to 1.25 follow-up: mean 1 years	**RR 0.74** (0.26 to 2.06)	119 (1 RCT Bland, 2019)	Very low	Could not differentiate

Table 4:Summarised preoperative education vs routine preoperative education

Outcomes	Effect estimate (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Lymphoedema (incidence) (RR less than 1 represents lower incidence)				

Outcomes	Effect estimate (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Incidence of lymphoedema MID 0.8 to 1.25 follow-up: 18 weeks	**RR 1.04** (0.95 to 1.13)	108 (1 RCT Shi, 2023)	Moderate	Could not differentiate
Lymphoedema (arm function) (higher scores represent better handgrip strength; lower DASH scores represent less disability)				
Handgrip strength ±MID -2.32 to 2.32 follow-up: 18 weeks	MD **3.58 higher** (1.66 higher to 5.5 higher)	108 (1 RCT Shi, 2023)	Low	Favours summarised preoperative education
Arm & shoulder function (DASH scores) ±MID: MD –7 to +7 points follow-up: 18 weeks	MD **6.42 lower** (8.51 lower to 4.33 higher)	108 (1 RCT Shi, 2023)	Low	Could not differentiate

1

Summary of other effectiveness evidence

For some of the evidence, it was not possible to complete GRADE due to incomplete reporting of data and as such evidence statements were produced to summarise the evidence narratively.

Self-management vs usual care

A randomised controlled trial **(Temur et al., 2019**) at low risk of bias compared the effects of a lymphoedema self-management programmes (SMLP) to usual care in preventing breast cancer-related lymphoedema and improving quality of life. The SMLP group (n=30) received education on lymphoedema symptoms, risk factors, evaluation, prevention, skin care, maintaining ideal weight, exercise, and simple lymphatic drainage massage. The control group (n=31) received usual care, which included routine preoperative and postoperative education and follow-up, but no specific lymphoedema prevention intervention and found:

Lymphoedema

- No lymphoedema development in the SMLP group, while 61.2% of controls developed lymphoedema by 6 months (p=0.000)
- Significantly lower upper extremity circumference measurements in the SMLP group at 1, 3 and 6 months compared to control group (p<0.05)

Arm function and mobility

- Significantly lower median DASH scores (less disability) in the SMLP group vs controls at 1 month (15.0 vs 34.2), 3 months (7.5 vs 57.5), and 6 months (2.9 vs 75.0) (p=0.000 at all timepoints).

Quality of life

- Significantly higher quality of life scores on the EORTC QLQ-C30 questionnaire in the SMLP group for global health status, physical, role, emotional, cognitive and social functioning (p≤0.05).
- Significantly lower symptom scores (fatigue, pain, insomnia) on the EORTC QLQ-C30 questionnaire in the SMLP group at 3 and 6 months (p≤0.05).
- Lower symptom scores on the EORTC QLQ-BR23 questionnaire (therapy side effects, breast/arm symptoms, hair loss) in the SMLP group at 3 and 6 months.

3 Early intervention

3.1 Summary of studies included in the effectiveness evidence.

Table 5 Summary of studies included in the effectiveness evidence - Systematic reviews

Authors	Experimental group	Control group	Duration/follow-up	Outcome measures
Rafn, 2022				
Box et al., 2002 N= 65 Location: Australia	Early Management Group Physiotherapy after surgery - education, exercise, massage, skin care, compression garments	Usual care (not specified)	24 months	• Incidence and severity of lymphoedema
Ridner et al., 2019 N=508 Location: United States	Prospective surveillance with bioimpedance spectroscopy (BIS)	Prospective surveillance with circumference measurements	18 months	• Incidence of chronic lymphoedema
Rafn,2018 N= 41 Location: Canada	Prospective surveillance with education, exercise, and compression garments	Usual care - preoperative education by clinic staff and educational booklet	12 months	• Incidence of lymphoedema • Health-related quality of life
Boccardo et al., 2009 N= 49 Location: Italy	Prospective protocol with pre-surgery assessment, post-op surveillance every 3 months for 2 years, early management with massage, compression	Compression garments only after lymphoedema was detected	24 months	• Incidence of lymphoedema
Stuiver, 2015				
Bendz et al., 2002	101 (Early shoulder exercises)	104 (Delayed exercises)	24 months	• Lymphoedema incidence • Shoulder ROM

N= 205 Location: Sweden				• Pain
Box et al., 2002 N=65 Location: Australia	32 (Physiotherapy management care plan)	33 (No physiotherapy)	12 months	• Lymphoedema incidence • shoulder ROM
Castro-Sanchez et al., 2011 N=48 Location: Spain	24 (MLD + compression)	24 (Education only)	8 months	• Lymphoedema incidence • Pain • QoL
Cinar et al., 2008 N=57 Location: Turkey	27 (Early shoulder exercises)	30 (Delayed exercises)	6 months	• Lymphoedema incidence • shoulder ROM
Devoogdt et al., 2011 N=160 Location: Belgium	79 (MLD + exercise + education)	81 (Exercise + education)	12 months	• Lymphoedema incidence • QoL
Sagen et al., 2009 N=204 Location: Norway	104 (Progressive resistance exercise)	100 (Activity restriction)	24 months	Lymphoedema incidence pain
Schmitz et al., 2010 N=154 Location: USA	72 (Progressive resistance exercise)	75 (No exercise)	12 months	• Lymphoedema incidence • QoL • adverse events
Todd et al., 2008	58 (Early shoulder exercises)	58 (Delayed exercises)	12 months	• Lymphoedema incidence • shoulder ROM

N=116 Location: UK				• QoL
Torres-Lacomba et al., 2010 N=120 Location: Spain	60 (MLD + exercise + education)	60 (Education only)	12 months	• Lymphoedema incidence • Pain • shoulder ROM
Zimmermann 2012 N=67 Location: Germany	33 (MLD + exercise)	34 (Exercise only)	6 months	• Lymphoedema incidence • shoulder ROM

Table 6 Summary of studies included in the effectiveness evidence – Randomised controlled trials

Study details	Population	Intervention	Comparison	Outcome	Risk of bias
Paskett et al., 2021 N=554 RCT Follow up time:18 months	Women aged ≥18 with newly diagnosed stage I-III breast cancer who underwent lymph node dissection	Education plus exercise programmes with compression sleeves (n=312)	Education only control (n=242)	• Incidence of lymphoedema • self-reported • range of motion • adherence	Moderate
Thakur et al., 2016 N=20 RCT Follow up time:3 weeks	Women who underwent unilateral breast cancer surgery with axillary lymph node dissection	Early physiotherapy with manual lymphatic drainage, exercises (n=10)	Education only control (n=10)	• Severity of lymphoedema, • quality of life	Low

3.2 Summary of the effectiveness evidence

GRADE summary tables

Table 7:Prospective surveillance vs usual care

Outcomes	Effect estimate (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Lymphoedema (incidence) (RR less than 1 represents lower incidence)				
Incidence of chronic breast cancer-related arm lymphoedema MID 0.8 to 1.25 follow-up: mean 12 months	**RR 0.31** (0.10 to 0.95)	106 (2 RCTs) Rafn,2022	Low	Favours prospective surveillance

Table 8:Early shoulder mobilising exercises vs delayed shoulder mobilising exercises

Outcomes	Effect estimate (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Lymphoedema (incidence) (RR less than 1 represents lower incidence)				
Incidence of lymphoedema MID 0.8 to 1.25 assessed with: Volumetry/ Circumference follow-up: range 6 months to 12 months	**RR 1.69** (0.94 to 3.01)	378 (3 RCTs) Stuiver,2015	Very low	Could not differentiate

Table 9:Progressive resistance exercise vs control

Outcomes	Effect estimate (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Lymphoedema (incidence) (RR less than 1 represents lower incidence)				
Incidence of lymphoedema MID 0.8 to 1.25 assessed with: Volumetry follow-up: range 12 months to 24 months	**RR 0.58** (0.30 to 1.13)	351 (2 RCTs) Stuiver,2015	Very low	Could not differentiate

Table 10:Early exercise vs delayed exercise

Outcomes	Effect estimate (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Lymphoedema (arm mobility) (higher scores are better)				
Shoulder range of motion for internal rotation follow-up: mean 3 months	MD **0.23 higher** (2.21 lower to 2.67 higher)	262 (2 RCTs) Stuiver, 2015	Very low	Could not differentiate
Shoulder range of motion for internal rotation follow-up: mean 6 months	MD **2.48 higher** (0.33 lower to 5.29 higher)	262 (2 RCTs) Stuiver, 2015	Very low	Could not differentiate

Table 11:Education + Exercise vs Education Only

Outcomes	Effect estimate (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Lymphoedema (incidence) (RR less than 1 represents higher rates of lymphoedema)				
Lymphoedema-free rates MID 0.8 to 1.25 follow-up: mean 18 months	**RR 0.88** (0.87 to 1.31)	568 (1 RCT) Paskett,2021	Low	Could not differentiate
Lymphoedema (severity) (lower scores are better)				
severity of lymphoedema assessed with as defined by changes in arm circumference at the site of greatest difference follow-up: mean 12 months	MD **0.04 lower** (0.97 lower to 0.88 higher)	568 (1 RCT) Paskett,2021	Moderate	Could not differentiate

Table 12:Early physiotherapy including MLD vs no early physiotherapy or physiotherapy without MLD

Outcomes	Effect estimate (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Lymphoedema (incidence) (RR less than 1 represents lower incidence)				
Lymphoedema incidence MID 0.8 to 1.25 follow-up: mean 6 months	**RR 0.02** (0.00 to 0.33)	67 (1 RCT, Zimmermann 2012) In Stuiver 2015 SR*	Low	Favours early physiotherapy including MLD

Outcomes	Effect estimate (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Lymphoedema incidence MID 0.8 to 1.25 follow-up: mean 8 months	**RR 0.17** (0.02 to 1.28)	48 (1 RCT, Castro-Sanchez 2011) In Stuiver 2015 SR*	Very low	Could not differentiate
Lymphoedema incidence MID 0.8 to 1.25 follow-up: mean 12 months	**RR 0.28** (0.10 to 0.79)	116 (1 RCT, Torres 2010) In Stuiver 2015 SR*	low	Favours early physiotherapy including MLD
Lymphoedema incidence MID 0.8 to 1.25 follow-up: mean 12 months	**RR 1.26** (0.69 to 2.32)	154 (1 RCT, Devooght 2011) In Stuiver 2015 SR*	Very low	Could not differentiate

*Individual RCTs were not pooled in the Stuiver 2015 systematic review so are also reported separately here.

Summary of other effectiveness evidence

For some of the evidence, it was not possible to complete GRADE due to incomplete reporting of data and as such evidence statements were produced to summarise the evidence narratively.

Thakur et al. (2016) conducted a randomised controlled trial on 20 women after modified radical mastectomy to evaluate the effectiveness of early physiotherapy in reducing the risk of lymphoedema compared to an educational strategy only. The early physiotherapy group (n=10) received manual lymph drainage, scar massage, progressive shoulder exercises and an educational strategy. The control group (n=10) received the educational strategy only. Both groups were treated for 3 weeks

Lymphoedema

- Significantly less increase in arm volume in the early physiotherapy vs education only group at 3 weeks (mean increase 4.00 mL vs 39.50 mL, $p<0.0001$)
- At 3 weeks, the early physiotherapy group showed a smaller final arm volume compared to the education only group (mean 106.50 mL vs 145.50 mL, $p<0.0001$)

Quality of Life

- Significantly lower (improved) Quality of Life Questionnaire scores in the early physiotherapy vs education only group at 3 weeks (mean 52.40 vs 56.70, $p<0.0001$)
- Significantly greater improvement in Quality-of-Life Questionnaire scores in the early physiotherapy group compared to the education only group (mean improvement 9.80 vs 3.66, $p=0.001$)

4 Worn prevention

4.1 Summary of studies included in the effectiveness evidence

Table 13 Summary of studies included in the effectiveness evidence - Randomised controlled trials

Study details	Population	Intervention	Comparison	Outcome	Risk of bias
Hansdorfer-Korzon et al., 2016 N=37 RCT Follow up time:7 months	Women undergoing mastectomy and axillary lymph node dissection for breast cancer	Low-pressure compression corsets on operated chest/trunk side (n=19)	No physiotherapeutic treatment control (n=18)	• Severity of lymphoedema • pain	Moderate
Nadal Castells et al., 2021 N=70 RCT Follow up time:2 years	Women aged 18-85 undergoing unilateral breast cancer surgery with axillary lymph node dissection	Compression garments for ≥8 hours/day for 3 months plus education and exercise (n=35)	Education and exercise only control (n=35)	• Incidence of arm swelling	Low
Ochalek et al., 2017 N=45 RCT Follow up time:12 months	Women undergoing breast cancer surgery with axillary lymph node dissection or sentinel lymph node biopsy	Compression sleeves plus exercise programmes (n=23)	Exercise programmes only control (n=22)	• Incidence of lymphoedema • health-related quality of life	Low
Ochalek et al., 2019 N=44 RCT Follow up time:24 months	(Same as Ochalek 2017)	Compression sleeves plus exercise programmes (n=22)	Exercise programmes only control (n=22)	• Incidence of lymphoedema • quality of life	Low
Paramanandam et al., 2022 N=301	Women aged ≥18 undergoing unilateral breast cancer surgery with axillary lymph node dissection	Compression sleeves ≥8 hours/day plus	Usual care control (n=152)	• Incidence of arm swelling • quality of life	Low

Study details	Population	Intervention	Comparison	Outcome	Risk of bias
RCT Follow up time:1 year		usual care (n=154)			

4.2 Summary of the effectiveness evidence

GRADE summary tables

Table 14:Low-Pressure Compression Corsets Vs No Physiotherapeutic Treatment

Outcomes	Effect estimate (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Lymphoedema (incidence) (RR less than 1 favours represents lower incidence)				
Incidence of lymphoedema MID 0.8 to 1.25 follow-up: mean 7 months	**RR 0.04** (0.00 to 0.65)	37 (1 RCT) Hansdorfer-Korzon,2016	Moderate	Favours low-pressure compression corsets
Patient-reported outcomes (pain) (RR less than 1 **represents pain reduction**)				
Pain reduction MID 0.8 to 1.25 assessed with: based on the Visual Analog Scale (VAS) follow-up: mean 7 months	**RR 1.74** (0.81 to 3.70)	37 (1 RCT) Hansdorfer-Korzon,2016	Low	Could not differentiate

Table 15:Compression garments vs conventional preventative therapy

Outcomes	Effect estimate (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Lymphoedema (incidence) (RR less than 1 represents lower incidence)				
Incidence of lymphoedema MID 0.8 to 1.25 follow-up: mean 2 years	**RR 1.00** (0.26 to 3.82)	65 (1 RCT) Nadal Castells 2021	Very low	Could not differentiate

Table 16:Compression garments vs no compression sleeves

Outcomes	Effect estimate (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Lymphoedema (incidence) (RR less than 1 represents lower incidence)				
Incidence of lymphoedema MID 0.8 to 1.25 assessed with: mean arm volume change follow-up: mean 12 months	**RR 0.17** (0.02 to 1.33)	41 (1 RCT) Ochalek 2019	Very low	Could not differentiate

Table 17:Compression sleeves vs Education

Outcomes	Effect estimate (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Lymphoedema (incidence) (HR less than 1 represents lower incidence)				
Incidence of lymphoedema (Arm swelling incidence) MID 0.8 to 1.25 assessed with: based on bioimpedance spectroscopy follow-up: mean 1 years	**HR 0.61** (0.43 to 0.85)	306 (1 RCT) Paramanandam,2022	Low	Favours compression sleeves
Incidence of lymphoedema arm volume increase ≥10%, MID 0.8 to 1.25 assessed with: bioimpedance spectroscopy follow-up: mean 1 years	**HR 0.56** (0.33 to 0.96)	306 (1 RCT) Paramanandam,2022	Low	Favours compression sleeves
Quality of life (RR less than 1 represents better quality of life)				
EORTC-QLQ-C30 Questionnaire and the Breast and Arm Symptom Scales of the BR23 Questionnaire (Global Health Decreased) MID 0.8 to 1.25 follow-up: mean 12 months	**RR 0.79** (0.59 to 1.05)	273 (1 RCT) Paramanandam,2022	Low	Could not differentiate
EORTC-QLQ-C30 Questionnaire and the Breast and Arm Symptom Scales of the BR23 Questionnaire (Physical Functioning Decreased) MID 0.8 to 1.25 follow-up: mean 12 months	**RR 1.20** (0.91 to 1.60)	285 (1 RCT) Paramanandam,2022	Low	Could not differentiate

Outcomes	Effect estimate (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
EORTC-QLQ-C30 Questionnaire and the Breast and Arm Symptom Scales of the BR23 Questionnaire (breast symptoms increased) MID 0.8 to 1.25 follow-up: mean 12 months	**RR 1.04** (0.83 to 1.31)	282 (1 RCT) Paramanandam,2022	Low	Could not differentiate
EORTC-QLQ-C30 Questionnaire and the Breast and Arm Symptom Scales of the BR23 Questionnaire (arm symptoms increased) MID 0.8 to 1.25 follow-up: mean 12 months	**RR 1.14** (0.96 to 1.36)	281 (1 RCT) Paramanandam,2022	Low	Could not differentiate

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Summary of other effectiveness evidence

For some of the evidence, it was not possible to complete GRADE due incomplete reporting which meant that standard deviation could not be calculated and as such evidence statements were produced to summarise the evidence narratively.

Compression therapy vs No Compression

A randomised controlled trial (**Ochalek, 2017**) at low risk of bias evaluated the effectiveness of using light compression sleeves (15-21 mmHg) in preventing early postoperative swelling and arm lymphoedema up to one year after breast cancer surgery with axillary lymph node interventions. Compression group (CG, n=23): received class I compression sleeves (15-21 mmHg) for daily wear postoperatively; control group (NCG, n=22): received no compression. Both groups received a standardised physical exercise programmes and found:

Lymphoedema

- Significantly lower arm volumes in the compression vs no compression group at 3, 6, 9 and 12 months (e.g. at 12 months, median 1969 mL vs 2257 mL, p=0.007)
- Significantly less arm oedema (excess volume) in the compression vs no compression group at 3, 6, 9 and 12 months (e.g. at 12 months, median -67.6 mL vs +114.5 mL, p<0.001)
- At 12 months, 4/23 patients (17.4%) in the compression group vs 6/22 (27.3%) in the no compression group developed lymphoedema (defined as >10% excess volume compared to pre-surgery)

Quality of Life

- No significant differences in health-related quality of life between groups at any timepoint

5 Exercise and movement

5.1 Summary of studies included in the effectiveness evidence.

Table 18 Summary of studies included in the effectiveness evidence - Randomised controlled trials

Study details	Population	Intervention	Comparison	Outcome	Risk of bias
Ammitzboll et al., 2019 N=158 RCT Follow up time: 12 months	Women aged 18-75 with primary unilateral breast cancer who underwent axillary lymph node dissection	Progressive Resistance Training (n=82)	Usual care control (n=76)	• Arm lymphoedema, patient-reported symptoms, • limb strength, • range of motion, • soft tissue mass difference	Low
Bloomquist et al., 2019 N=153 RCT Follow up time:39 weeks	Women receiving adjuvant chemotherapy for stage I-III breast cancer who were physically inactive pre-diagnosis	12-week supervised heavy-load resistance training (n=75)	Home-based walking programmes (n=78)	• Lymphoedema severity • upper-extremity strength • quality of life	Moderate
Bloomquist et al., 2021 N=68 RCT Follow up time:12 months	Women aged 18-75 who received surgery for stage I-III breast cancer and completed adjuvant therapy within 5 years	Supervised group football training twice weekly for 52 weeks (n=46)	No intervention control (n=22)	• Lymphoedema • patient-reported breast/arm symptoms • upper extremity function	Moderate
Donmez et al., 2017 N=52 RCT Follow up time:6 weeks	Women diagnosed with breast cancer undergoing surgery	Simple lymphatic drainage and physical activity programmes (n=25)	Usual care control (n=27)	• Upper extremity circumference • lymphoedema symptom severity • upper extremity function	Moderate

Study details	Population	Intervention	Comparison	Outcome	Risk of bias
Zhang et al., 2016 N=1000 RCT Follow up time:12 months	Women with breast cancer undergoing modified radical mastectomy	Self-manual lymph drainage plus physical exercise (n=500)	Physical exercise only control (n=500)	• Severity of lymphoedema • scar formation. • shoulder abduction	Low

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5.2 Summary of the effectiveness evidence

GRADE summary tables

Table 19:Progressive Resistance Training vs usual care

Outcomes	Effect estimate (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Lymphoedema (lower scores or OR of less than 1 represent lower incidence)				
Incidence of lymphoedema assessed with mean change in interlimb volume difference follow-up: mean 12 months	MD **0.3 higher** (1.7 lower to 2.3 higher)	158 (1 RCT) Ammitzbøll,2019	Very low	Could not differentiate
Incidence of lymphoedema MID 0.8 to 1.25 assessed with: Incidence of >3% increase in interlimb volume difference follow-up: mean 1 years	**OR 1.2** (0.5 to 2.8)	82 (1 RCT) Ammitzbøll,2019	Very low	Could not differentiate
Incidence of clinically relevant lymphoedema MID 0.8 to 1.25 follow-up: mean 12 months	**OR 1.1** (0.5 to 2.8)	158 (1 RCT) Ammitzbøll,2019	Very low	Could not differentiate

Table 20:Heavy-load resistance exercise vs home based walking programmes

Outcomes	Effect estimate (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Lymphoedema (incidence) (lower scores are better)				

Outcomes	Effect estimate (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Incidence of lymphoedema assessed with: L-Dex score - difference in extracellular fluid follow-up: mean 39 weeks	MD **0.7 higher** (2.2 lower to 3.6 higher)	75 (1 RCT) Bloomquist,2019	Very low	Could not differentiate
Lymphoedema (volume) (lower scores are better)				
Inter-arm volume % difference follow-up: mean 39 weeks	MD **1.7 lower** (7.7 lower to 4.3 higher)	99 (1 RCT) Bloomquist,2019	Very low	Could not differentiate
Patient-reported outcomes (pain) (lower scores are better)				
Pain follow-up: mean 39 weeks	MD **0.8 lower** (1.5 lower to 0.1 lower)	(1 RCT)	Moderate	Favours exercise
Quality of life (lower scores are better for symptoms and systemic therapy burden; higher scores better for body image)				
EORTC QLQ-BR23 scores assessed with: Breast symptoms follow-up: mean 39 weeks	MD **4 lower** (12 lower to 3 higher)	114 (1 RCT) Bloomquist,2019	Very low	Could not differentiate
EORTC QLQ-BR23 scores assessed with: Arm symptoms follow-up: mean 39 weeks	MD **4 lower** (12 lower to 3 higher)	115 (1 RCT) Bloomquist,2019	Very low	Could not differentiate
EORTC QLQ-BR23 scores assessed with: Systemic therapy burden follow-up: mean 39 weeks	MD **1 higher** (5 lower to 7 higher)	118 (1 RCT) Bloomquist,2019	Very low	Could not differentiate
EORTC QLQ-BR23 scores assessed with: Body Image follow-up: mean 39 weeks	MD **1 higher** (6 lower to 8 higher)	117 (1 RCT) Bloomquist,2019	Very low	Could not differentiate

Table 21:Football Fitness Training Vs Physical Activity

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Lymphoedema (incidence and severity) (Lower scores are better)				
L-Dex score ±MID -2.76 to 2.76 follow-up: mean 12 months	MD **2.5 SD lower** (5.85 lower to 0.85 higher)	46 (1 RCT) Bloomquist,2021	Very low	Could not differentiate
Inter-arm volume difference ±MID-4.4 to 4.4 follow-up: mean 12 months	MD **2 higher** (1.88 lower to 5.88 higher)	48 (1 RCT) Bloomquist,2021	Very low	Could not differentiate
Lymphoedema (arm function) (Lower scores are better)				
DASH score ±MID-7 to 7 follow-up: mean 12 months	MD **3.9 higher** (0.85 lower to 8.65 higher)	47 (1 RCT) Bloomquist,2021	Very low	Could not differentiate
Quality of life (Lower scores are better)				
EORTC QLQ BR23 breast symptom score ±MID -7.8 to 7.8 follow-up: mean 12 months	MD **2.5 lower** (11.1 lower to 6.01 higher)	47 (1 RCT) Bloomquist,2021	Very low	Could not differentiate
EORTC QLQ BR23 arm symptom score ±MID-14.5 to 14.5 follow-up: mean 12 months	MD **6.6 higher** (3.41 lower to 16.61 higher)	47 (1 RCT) Bloomquist,2021	Very low	Could not differentiate

Table 22: Physical exercise with simple lymphatic drainage vs physical exercise

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Lymphoedema (incidence and severity) (RR less than 1 represents lower incidence)				
Incidence of Upper limb lymphoedema ±MID 0.8 to 1.25 follow-up: mean 3 months	**RR 0.26** (0.11 to 0.64)	1000 (1 RCT) Zhang,2016	Moderate	Favours physical exercise with simple lymphatic drainage
Incidence of Upper limb lymphoedema ±MID 0.8 to 1.25 follow-up: mean 6 months	**RR 0.36** (0.17 to 0.76)	1000 (1 RCT) Zhang,2016	Moderate	Favours physical exercise with simple lymphatic drainage
Incidence of Upper limb lymphoedema ±MID 0.8 to 1.25 follow-up: mean 12 months	**RR 0.21** (0.10 to 0.43)	1000 (1 RCT) Zhang,2016	Moderate	Favours physical exercise with simple lymphatic drainage
Scar formation (RR less than 1 represents reduced scar formation)				
Scar formation ±MID 0.8 to 1.25 follow-up: mean 3 months	**RR 0.33** (0.11 to 1.03)	1000 (1 RCT) Zhang,2016	Low	Could not differentiate
Scar formation ±MID 0.8 to 1.25 follow-up: mean 6 months	**RR 0.06** (0.02 to 0.20)	1000 (1 RCT) Zhang,2016	Moderate	Favours physical exercise with simple lymphatic drainage
Scar formation ±MID 0.8 to 1.25 follow-up: mean 12 months	**RR 0.05** (0.02 to 0.14)	1000 (1 RCT) Zhang,2016	Moderate	Favours physical exercise with simple lymphatic drainage

Summary of other effectiveness evidence

For some of the evidence, it was not possible to complete GRADE due to incomplete data reporting and as such evidence statements were produced to summarise the evidence narratively.

Clinical physical activity programmes vs home-based activity programmes

A prospective randomised controlled trial (**Dönmez 2017**) at moderate risk of bias (n=52) investigating the effectiveness of a clinical and home-based physical activity programmes (PAP) and simple lymphatic drainage (SLD) in preventing breast cancer-related lymphoedema and found:

Lymphoedema

- No significant change in mean upper extremity circumference measurements over 6 weeks in the intervention group, but a statistically significant gradual increase in all measurement points in the control group compared to the intervention group ($p<0.05$)

Patient reported outcomes

- A significant decrease in lymphoedema-related symptom scores (pain, limitation of daily activities, heaviness, tension, numbness) over time in the intervention group ($p<0.05$), while scores were significantly higher at week 2 and did not change thereafter in the control group.

Arm function and mobility

- Significantly lower DASH scores (less disability) in the intervention vs control group over time, though scores decreased in both groups ($p<0.05$)

6 Surgery

6.1 Summary of studies included in the effectiveness evidence.

Table 23 Summary of studies included in the effectiveness evidence - Systematic reviews

Authors	Experimental group	Control group	Follow-up (months)	Outcome measures
Chun et al., 2022				
Agarwal, 2020 N=35 Location: India	LYMPHA	None	12	• Lymphoedema incidence (lymphoscintigraphy)
Schwarz, 2019 N=60 Location: United States	LPS	None	29	• Lymphoedema incidence (circumferential limb measurements)
Johnson, 2019 N=142 Location: United States	LYMPHA	None	12	• Lymphoedema incidence (circumferential arm measurements, perometry, bioimpedance spectroscopy)
Hahamoff. 2018 N=177 Location: United States	LYMPHA	None	24	• Lymphoedema incidence (circumferential arm measurements, therapist evaluation, bioimpedance spectroscopy)
Gomberawalla, 2017 N=52 Location: United States	LYMPHA	None	41	• Lymphoedema incidence (circumferential arm measurements, bioimpedance spectroscopy)
Spiguel, 2016 N=13 Location: United States	LYMPHA	None	1	• Did not report outcomes of relevance to this review
Feldman, 2015 N=40 Location: United States	LYMPHA	None	24	• Lymphoedema incidence (circumferential arm measurements)

Boccardo, 2014 N=78 Location: Italy	LYMPHA	None	48	• Lymphoedema incidence (volumetry)
Boccardo, 2011 N=49 Location: Italy	LYMPHA	No LVA (n=33)	18	• Lymphoedema incidence (volumetry)
Boccardo, 2009 N=19 Location: Italy	LYMPHA	None	12	• Lymphoedema incidence (circumferential limb measurements)
Cook et al. 2022				
Boccardo, 2014 N= 74 Location: Italy	ILR Patients also received compression sleeves, manual lymphatic drainage, and exercises if lymphoedema developed.	compression, manual lymph drainage, and microsurgery	48 months	• Volumetry, lymphoscintigraphy, • Lymphoedema incidence
Cook,2020 N= 26 Location: USA	ILR	underwent axillary lymph node dissection (ALND) alone. No lymphatic reconstruction (in cases where bypass could not be performed)	10 months	• Arm circumference, clinical assessment. • Lymphoedema incidence
Feldman, 2015 N= 37 Location USA	ILR	underwent axillary lymph node dissection (ALND) alone.	6 months	• Arm circumference bioimpedance spectroscopy. • Lymphoedema incidence

Shaffer, 2020 Location: USA N=46	ILR	None specified	14.6 months	• Arm circumference. • Clinical assessment. • Lymphoedema incidence
Johnson, 2021 N= 88 Location USA	ILR	underwent axillary lymph node dissection (ALND) alone.	11.4 months	• Perometry, bioimpedance spectroscopy • lymphoedema incidence
Markkula et al., 2019				
Boccardo et al., 2009 N= 49 Location: Italy	LVA Group	physical therapy and compression garments alone	24 months	• Development of lymphoedema (defined as >200 mL increase from baseline)
Boccardo et al., 2011 N=46 Location: Italy	LVA Group	local standard practice	24 months	• Development of lymphoedema (defined as >100 mL increase from preoperative volume)

LYMPHA: Lymphatic Microsurgical Preventative Healing Approach; LVA: Lymphaticovenous anastomosis; ILR: Immediate Lymphatic Reconstruction;ALND: Axillary lymph node dissection

Table 24 Summary of studies included in the effectiveness evidence – Randomised controlled trials

Study details	Population	Intervention	Comparison	Outcome	Risk of bias
Coriddi 2023 N=144 RCT Follow up time:24 months	Women undergoing axillary lymph node dissection for breast cancer	Immediate lymphatic reconstruction during surgery (n=72)	No lymphatic reconstruction control (n=72)	• Incidence of breast cancer-related lymphoedema, • bioimpedance spectroscopy, • quality of life,	Moderate

Study details	Population	Intervention	Comparison	Outcome	Risk of bias
				• compression garment usage	

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6.2 Summary of the effectiveness evidence

GRADE summary tables

Table 25:Lymphaticovenular anastomosis vs physical and compression therapy

Outcomes	Effect estimate (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Lymphoedema (incidence) (RR less than 1 represents lower incidence)				
Incidence of lymphoedema MID 0.8 to 1.25 assessed with: Arm circumference, bioimpedance spectroscopy & Perometry, Bioimpedance spectroscopy	**RR 0.20** (0.06 to 0.63)	95 (2 RCTs) Markkula,2019	Low	Favours lymphaticovenular anastomosis

Table 26:Immediate Lymphatic Reconstruction after axillary lymph node dissection vs axillary lymph node dissection only

Outcomes	Effect estimate (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Lymphoedema (limb volume) (lower scores are better)				
Changes in Bioimpedance Values From Baseline ±MID -5.2 to 5.2 follow-up: mean 24 months	MD **1.2 lower** (7.57 lower to 5.17 higher)	40 (1 RCT) Coriddi 2023	Low	Could not differentiate

Summary of other effectiveness evidence

For some of the evidence, it was not possible to complete GRADE due to incomplete data reporting or non-comparative data and as such evidence statements were produced to summarise the evidence narratively.

Immediate lymphatic reconstruction

One systematic review (**Chun et al., 2022**) of 13 observational studies at low to high risk of bias, found:

Lymphoedema

- Pooled analysis of 10 non-comparative studies on immediate lymphatic reconstruction (ILR) during axillary lymphadenectomy for breast cancer found that the overall incidence of lymphoedema was 2.7% (95% CI: 1.1%-4.4%) over an average follow-up of 11.6 ± 7.8 months. The incidence appeared to be highest approximately 1 to 2 years post-operation.
- Pairwise analysis of two studies (**Feldman, 2015; Boccardo, 2011**) compared ILR to a control group (no ILR) following axillary lymphadenectomy. There was no statistically significant difference in the relative risk of developing lymphoedema between the ILR and control groups at immediate, 1 month, 2 months, 6 months, 8 months, 12 months, and 18 months post-operation.

One systematic review, (**Cook, 2022**) of 5 observational studies at moderate to high risk of bias, found:

- One prospective cohort study (**Boccardo,2014**) at unclear risk of bias (n=88) compared immediate lymphatic reconstruction and found 3 patients (3.4%) developed lymphoedema at a median 10 months with lymphatic reconstruction outcomes in the no lymphatic reconstruction group were not reported.
- One retrospective study (**Cook,2020**) at unclear risk of bias (n=24) compared immediate lymphatic reconstruction to no lymphatic reconstruction and found 3 patients (12.5%) developed lymphoedema at a median 17 months with lymphatic reconstruction, over a 10-month follow-up. Outcomes in the no lymphatic reconstruction group were not reported.
- One prospective cohort study (**Feldman,2015**) at unclear risk of bias (n=27) compared immediate lymphatic reconstruction to no lymphatic reconstruction and found 3 patients (11.1%) developed lymphoedema at a median 8 months with lymphatic reconstruction versus 33.3% without lymphatic reconstruction, over a 6-month follow-up.
- One prospective cohort study (**Shaffer,2020**) at unclear risk of bias (n=52) compared immediate lymphatic reconstruction to no lymphatic reconstruction and found 5 patients (9.6%) developed lymphoedema at a median 9.4 months with lymphatic reconstruction, over a 14.6-month follow-up. Outcomes in the no lymphatic reconstruction group were not reported.

- One retrospective study (**Johnson, 2021**) at unclear risk of bias (n=60) compared immediate lymphatic reconstruction to no lymphatic reconstruction and found 1 patient (1.7%) developed lymphoedema at 3 months with lymphatic reconstruction versus 25% without lymphatic reconstruction, over an 11.4-month follow-up.

7 Skincare

No evidence identified.

8 Economic evidence

8.1 Included studies

A search was performed to identify published economic evaluations of relevance to this guideline update. This search retrieved 121 studies (appendix G). Based on title and abstract screening, all of the studies were excluded for this question. Therefore, no studies were identified for this review question.

8.2 Excluded studies

See Appendix J for excluded studies and reasons for exclusion.

9 Economic model

An economic model was not developed for this review question.

10 The committee's discussion and interpretation of the evidence

10.1 The outcomes that matter most

The committee discussed the range of outcomes and agreed that that incidence and severity of lymphoedema and adverse events such as infections or surgical complications were the most important in decision making for lymphoedema prevention. The committee were particularly interested in Disabilities of Arm Shoulder and Hand (DASH) scores and limb volume reductions. The committee also discussed the importance of quality-of-life measures, and patient reported outcomes. The committee agreed that all these outcomes are important to clinical decision-making and ensuring that people's preferences and needs are met during treatment.

The committee also wanted to consider cosmetic impact of lymphoedema however this was not widely reported in the literature, and it was limited to scar contracture. They agreed that cosmetic effect of lymphoedema on people's body image should be considered. This suggests a need for future research to better understand and address these aspects of the patient experience. Therefore, the committee made a research recommendation for the assessments of core outcomes sets for diagnosis of lymphoedema. This research recommendation can be found in evidence review for management of lymphoedema (see evidence review B) .

10.2 The quality of the evidence

Overall, the quality of the evidence ranged from high to Very low with the main reasons for downgrading being due to imprecision of the evidence and risk of bias. In some of the evidence, imprecision was serious or very serious with the 95% confidence intervals crossing one or two ends of the defined minimally important differences (MIDs) thresholds. Some of the included RCTs were downgraded for risk of bias due to lack of blinding, imbalanced baseline characteristics, selective reporting of outcomes, and unclear definitions of outcome measures.

The committee discussed the challenges with respect to the evidence base for lymphoedema. There was significant variation in interventions and comparators. For example, early intervention differed between the studies and comprised of interventions such as early physiotherapy, early exercise and early exercise with manual lymphatic drainage. Early intervention was also compared to exercise, education or a combination of exercise and education. Where the interventions were similar, there were differences with the duration, when the intervention was administered as well as different severities of lymphoedema at baseline. There was variability in measurement techniques for example the location of circumference measurements (in the wrist, axilla or elbow) and timing of assessment. Some studies reported follow-ups for up to 12 months while other studies recorded the outcomes after 4 weeks. The committee noted that many of the studies did not report long-term follow-up. This also indicates that there is a need for longitudinal studies to understand the natural history of the breast cancer-related lymphoedema (BCRL) and the long-term effects of different preventative strategies. The committee were also concerned that all the evidence was for women, with no male participants in the included studies.

Therefore, the committee could not be certain whether the effectiveness of different interventions would differ for men and women.

Another factor the committee considered was the variation in outcome measures. In the committee's experience, lymphoedema assessment varies in practice due to factors such as local hospital protocols and availability of equipment. Although, the studies reported outcomes that matched our protocol, data analysis was difficult because the outcome measures used in the literature varied, which reflects practice. For example, lymphoedema incidence and severity were reported in different ways across the studies which reported the outcome as measures of volume, circumference, severity scores like L-DeX or tissue dielectric constant (TDC) ratios which cannot be pooled in a meta-analysis. However, the committee noted that volume difference measurements were most commonly used and reliable for assessing lymphoedema.

10.3 Benefits and harms

The committee were presented with evidence on a range of interventions including, early intervention, exercise, education, worn prevention and surgery for the prevention of lymphoedema. The committee noted that for many of the outcomes, the evidence could not differentiate between effectiveness of the intervention and comparators because the 95% confidence intervals for the outcomes crossed the line of no effect. But the committee put this down to lack of long-term follow-up and lack of consistent definitions used by clinicians for diagnosis.

Lymphoedema education

The committee discussed the importance of lymphoedema education. The committee agreed that early information exchange is key so that people can identify and look for the signs of lymphoedema. They also agreed educating people about their risk of lymphoedema is very important, as it allows them to be prepared and take steps to reduce their risk (for example maintaining a healthy body weight, being aware of ways to reduce their risk of infection, and following advice on skincare, movement and exercise). Giving people information on these topics, including information to take away so they can review it in their own time and refer back to later, was therefore recommended.

The committee discussed regular hospital monitoring where baseline measurements such as limb volume for people can be recorded, and any early changes can be identified would be difficult to implement in practice, so the committee suggested that it would be beneficial for practitioners to teach people how to self-monitor according to local practices as when early lymphoedema is identified, it can be treated non-surgically , possibly preventing the progression to a more advanced, chronic lymphoedema.. The committee wanted to emphasise self-monitoring as a crucial component of lymphoedema prevention, this approach aims to empower people to be actively involved in their care. They discussed that providing information and advice on how to self-monitor and detect changes in their condition will help to empower people to be actively involved in their care. By providing information on signs and symptoms, people are guided on what to look for. The committee discussed that self-monitoring should include awareness of skin changes, feelings of swelling, and signs of recurrence of primary disease or axillary disease (lymphadenopathy). It' is important to be aware for signs of infection, such as redness, rash, swelling, and pain. People should be aware of any skin changes in colour or the appearance of rashes, as well

as obvious swelling in the arm, hand, wrist, fingers, breast, or chest wall. Additionally, people should pay attention to subjective feelings such as heaviness or aching in the affected areas.

Early intervention

In their discussion of the effectiveness of early intervention for prevention, the committee discussed that the evidence was unclear on whether the treatments used were for preventing lymphoedema or monitoring signs and symptoms. The committee considered how the evidence for the individual interventions included in the systematic reviews for early intervention, was also considered as standalone interventions in this evidence review (for example, exercise and education). The committee were concerned that there was no clear evidence of benefit for the prospective monitoring, and if implemented, would also create more work and pressure on hospital services .

Worn prevention

The committee carefully considered the evidence on compression therapy for both the prevention and management of breast cancer-related lymphoedema. The evidence did not support the use of compression therapy as a preventive measure for BCRL and showed no clinical benefit which reflected the committee's experience. The evidence on using compression therapy as a preventive strategy for breast cancer-related lymphoedema is currently insufficient and mixed. The effectiveness appeared to vary depending on the type of compression used (e.g., compression sleeves) and the comparator (e.g., education, light compression sleeves). Given this inconsistency in the evidence, the committee decided not to make a recommendation on the use of compression therapy for lymphoedema prevention at this time. They also discussed a limitation with how some of the studies did not report adherence to compression garments use, and noted that adherence is usually higher in clinical trial settings than in practice. The committee also highlighted that the studies required people to wear compression garments for prolonged periods of time which may be uncomfortable and not desirable. As such, this supports the committee's experience of them not being used in practice. The committee also considered the additional cost associated with this and therefore decided to make a do not offer recommendation.

Exercise and movement

The committee considered the evidence on exercise for the prevention of lymphoedema which demonstrated some improvement in quality of life for people who exercised compared to those who did not. There may be some benefit of exercise for the incidence and severity of lymphoedema, but the evidence was uncertain.

Surgery

The committee considered evidence on different surgical interventions including immediate lymph venous anastomosis and Lymphovenous anastomosis Evidence supports the use of surgical treatments for lymphoedema prevention for reducing the excess limb volume, , decreasing the need for conservative therapy, improving patient quality of life, and improving physical function. While these studies suggest some benefit to immediate lymph venous anastomosis during axillary lymph node dissection (ALND), further research is needed, the committee highlighted that the majority of the evidence was based on lower limb lymphoedema, the small studies that looked at upper limb lymphoedema failed to show its efficacy, the committee also considered that the added operative time associated costs and need for specialised microsurgical training must be considered if preventive surgical

intervention is to be widely adopted for all patients at risk of breast cancer related lymphoedema. The committee agreed to refer to the NICE guidelines on Lymphovenous anastomosis during axillary or inguinal node dissection for preventing secondary lymphoedema for further advice on this intervention and to emphasise the need for research in this area..

The committee discussed that there is potential for surgical interventions as preventative strategy for secondary lymphoedema, however the current evidence does not provide clear benefit of effectiveness of surgical intervention for prevention The committee also recognised that studies in NICE's interventional procedures guidance were not UK-based and primarily focused on lower limb lymphoedema. While lower limb lymphoedema is well studied there is an evidence gap for truncal and upper limb lymphoedema. which are more relevant to breast cancer patients. Therefore, they made research recommendations for surgical interventions including lymphovenous anastomosis during axillary lymph node dissection as well as vascularised lymph node transfer which is not covered by the NICE interventional procedure's guidance

They agreed that this research is needed to address evidence gaps for upper limb and truncal lymphoedema, to generate UK-relevant data on these interventions and explore the potential of these surgeries in prevention as well as management

Skincare

No evidence was identified for skincare, the committee agreed that skincare should be included in recommendations for preventing breast cancer-related lymphoedema as well as for management of lymphoedema for several key reasons. Skincare is consistently incorporated as part of treatments in clinical trials, indicating its widespread acceptance as a included in usual standard of care.

The committee agreed that this explained why no standalone studies on skincare were identified, as withholding it from a control group would be unreasonable. The widespread use of skincare in lymphoedema management suggests that its efficacy is generally assumed by researchers and clinicians. The committee agreed on the importance of skincare in lymphoedema care. Furthermore, skincare is a low-risk intervention with potential benefits, making its inclusion in the recommendations important. Although there may be a lack of new specific evidence on skincare, these factors supported its inclusion as part of comprehensive care recommendations for breast cancer-related lymphoedema. The committee suggested that skin care advice may include using an appropriate emollient or moisturiser daily, using sunscreen SPF to prevent sunburn, avoiding and promptly treating any breaks, bites, or other skin injuries, and monitoring them for signs of infection until fully healed. These practices help maintain skin integrity, reduce infection risks, and promote overall skin health which are crucial in managing and reducing the risk of lymphoedema

10.4 Cost effectiveness and resource use

No health economic evidence was identified for this review.

The committee discussed the clinical evidence and made various recommendations on providing adequate information about risk factor, prevention and early identification of lymphoedema. These reflect current practice and are expected to improve people accessibility to information about prevention without requiring additional NHS resources.

The committee discussed the clinical evidence on surgical treatments for lymphoedema prevention. Although some potential benefits were identified in the clinical review, the committee acknowledged that the evidence was not sufficient to make a recommendation for all people potentially at risk of lymphoedema. In particular, the committee were aware that only a few centres currently provide this service, and the cost of training microsurgeons and setting up more centres could be significantly higher. Moreover, due to the relatively low incidence of lymphoedema after sentinel lymph node dissection and the significant cost associated with longer operative time, it is unclear whether surgery for lymphoedema prevention would be a cost-effective use of NHS resource in the UK. However, the committee agreed to signpost to the NICE Interventional Procedure guidance on lymphovenous anastomosis during axillary or inguinal node dissection for preventing secondary lymphoedema (IP785) in the guideline. This recommendation is not expected to have any resource use impact.

10.5 Other factors the committee took into account

The committee recognised that while breast cancer predominantly affects women, men can also be diagnosed with this disease. And that while clinical trials do not tend to include men in the studies the committee felt that it was appropriate to extrapolate the evidence where possible to make comprehensive recommendations that address the needs of all breast cancer patients, regardless of gender.

10.6 Recommendations supported by this evidence review.

This evidence review supports the recommendation 1.12 to 1.14 and research recommendations.

11 References – included studies

11.1 Effectiveness

Randomised controlled trials

Ammitzboll, Gunn, Johansen, Christoffer, Lanng, Charlotte et al. (2019) Progressive resistance training to prevent arm lymphoedema in the first year after breast cancer surgery: Results of a randomized controlled trial. Cancer 125(10): 1683-1692

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Bloomquist, Kira, Krustrup, Peter, Fristrup, Bjorn et al. (2021) Effects of football fitness training on lymphoedema and upper-extremity function in women after treatment for breast cancer: a randomized trial. Acta oncologica (Stockholm, Sweden) 60(3): 392-400

Coriddi, Michelle, Dayan, Joseph, Bloomfield, Emily et al. (2023) Efficacy of Immediate Lymphatic Reconstruction to Decrease Incidence of Breast Cancer-related Lymphoedema: Preliminary Results of Randomized Controlled Trial. Annals of surgery 278(4): 630-637

Donmez, Ayse Arikan and Kapucu, Sevgisun (2017) The effectiveness of a clinical and home-based physical activity programmes and simple lymphatic drainage in the prevention of breast cancer-related lymphoedema: A prospective randomized controlled study. European journal of oncology nursing : the official journal of European Oncology Nursing Society 31: 12-21

Fan, A., Yan, J., He, Y. et al. (2016) Combining manual lymph drainage with physical exercise after modified radical mastectomy effectively prevents upper limb lymphoedema. Lymphatic Research and Biology 14(2): 104-108

Hansdorfer-Korzon, R., Teodorczyk, J., Gruszecka, A. et al. (2016) Relevance of low-pressure compression corsets in physiotherapeutic treatment of patients after mastectomy and lymphadenectomy. Patient Preference and Adherence 10: 1177-1187

Nadal Castells, Maria J, Ramirez Mirabal, Eliot, Cuartero Archs, Jordi et al. (2021) Effectiveness of Lymphoedema Prevention Programmess With Compression Garment After Lymphatic Node Dissection in Breast Cancer: A Randomized Controlled Clinical Trial. Frontiers in rehabilitation sciences 2: 727256

Ochalek, Katarzyna; Gradalski, Tomasz; Partsch, Hugo (2017) Preventing Early Postoperative Arm Swelling and Lymphoedema Manifestation by Compression Sleeves After Axillary Lymph Node Interventions in Breast Cancer Patients: A Randomized Controlled Trial. Journal of pain and symptom management 54(3): 346-354

Ochalek, Katarzyna, Partsch, Hugo, Gradalski, Tomasz et al. (2019) Do Compression Sleeves Reduce the Incidence of Arm Lymphoedema and Improve Quality of Life? Two-Year Results from a Prospective Randomized Trial in Breast Cancer Survivors. Lymphatic research and biology 17(1): 70-77

Paramanandam, Vincent S, Dylke, Elizabeth, Clark, Gary M et al. (2022) Prophylactic Use of Compression Sleeves Reduces the Incidence of Arm Swelling in Women at High Risk of Breast

Cancer-Related Lymphoedema: A Randomized Controlled Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 40(18): 2004-2012

Paskett, Electra D, Le-Rademacher, Jennifer, Oliveri, Jill M et al. (2021) A randomized study to prevent lymphoedema in women treated for breast cancer: CALGB 70305 (Alliance). Cancer 127(2): 291-299

Shi, Bohui, Lin, Zihan, Shi, Xiaowei et al. (2023) Effects of a lymphoedema prevention programmes based on the theory of knowledge-attitude-practice on postoperative breast cancer patients: A randomized clinical trial. Cancer medicine 12(14): 15468-15481

Temur, Kubra and Kapucu, Sevgisun (2019) The effectiveness of lymphoedema self-management in the prevention of breast cancer-related lymphoedema and quality of life: A randomized controlled trial. European journal of oncology nursing : the official journal of European Oncology Nursing Society 40: 22-35

Thakur, R.R.; Bhat, A.; Kaur, A. (2016) Effectiveness of early physiotherapy to prevent lymphoedema after breast cancer related surgery. Indian Journal of Physiotherapy and Occupational Therapy 10(3): 96-101

Systematic reviews

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Cook, Julia A, Sinha, Mithun, Lester, Mary et al. (2022) Immediate Lymphatic Reconstruction to Prevent Breast Cancer-Related Lymphoedema: A Systematic Review. Advances in wound care 11(7): 382-391

Markkula, Silja P, Leung, Nelson, Allen, Victoria B et al. (2019) Surgical interventions for the prevention or treatment of lymphoedema after breast cancer treatment. The Cochrane database of systematic reviews 2: cd011433

Rafn, Bolette S, Christensen, Jan, Larsen, Anders et al. (2022) Prospective Surveillance for Breast Cancer-Related Arm Lymphoedema: A Systematic Review and Meta-Analysis. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 40(9): 1009-1026

Stuiver Martijn M, ten Tusscher Marieke R, Agasi-Idenburg Carla S, Lucas Cees, Aaronson Neil K, Bossuyt Patrick MM (2015) Conservative interventions for preventing clinically detectable upper-limb lymphoedema in patients who are at risk of developing lymphoedema after breast cancer therapy. Cochrane Database of Systematic Reviews: Reviews issue2

11.2 Economic

No economic evidence was identified.

Appendices

Appendix A – Review protocol

Review protocol for reducing the risk of developing lymphoedema in people who have, or have had breast cancer

ID	Field	Content
0.	PROSPERO registration number	CRD42024521526
1.	Review title	The effectiveness and cost-effectiveness of non-pharmacological strategies for reducing the risk of developing lymphoedema in people who have or have had breast cancer.
2.	Review question	In people who have, or have had, breast cancer, what non-pharmacological strategies are effective and cost-effective for reducing the risk of developing lymphoedema?
3.	Objective	To determine effective strategies for reducing the risk of developing lymphoedema for people who have, or have had, breast cancer. This will include assessing existing interventions, their efficacy, and their impact on patient outcomes.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • HTA (Health Technology Assessment) • DARE (Database of Abstracts of Reviews of Effectiveness) • Embase • Emcare • MEDLINE ALL • INAHTA • Epistemonikos • AMED (Allied and Complementary Medicine)

		For the economics review the following databases will be searched: • Embase* • MEDLINE ALL* • Econlit • INAHTA • HTA (Health Technology Assessment) • NHS EED Searches will be restricted by: • Date of last search (October 2013) • English language • Human studies • Abstracts, conference presentations and theses will be excluded. • Systematic reviews and RCTs and observational studies. The full search strategies for MEDLINE database will be published in the final review. The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion.
5.	Condition or domain being studied	Lymphoedema in all people who have, or have had, breast cancer.
6.	Population	Inclusion: All adults (aged 18 or over) who have, or have had, breast cancer and are at risk of developing lymphoedema of the upper limb (including axilla, hand and fingers), chest wall or breast. Exclusion: none identified.
7.	Intervention	Any intervention (or combination of interventions) with the aim of reducing the risk of lymphoedema: 1. Lymphoedema Education (for example, increased awareness, advice on interventions to avoid

		[including venepuncture, injection to affected tissues, blood pressure checks, tattoos], advice on behaviour change to achieve healthy weight) 2. Early intervention (for example, monitoring and self-measurements [including, functional assessments, questionnaires], active management of infection and injury) 3. Worn prevention (for example, wired/non-wired bras, compression garments, foam inserts, spaghetti foam) 4. Exercise and movement (for example, range of motion exercises, physiotherapy) 5. Surgery (for example: immediate lymphatic reconstruction, lymphaticovenous anastomosis, vascularised lymph node transfer) 6. Skincare (for example, keeping skin clean and use of moisturisers)
8.	Comparator	• No intervention aimed at preventing lymphoedema (usual care) • Each other • Contralateral arm or breast

9.	Types of study to be included	We will search for • SRs of RCTs • SRs of cohort studies • RCTs • Prospective cohort studies. Due to time and resource restraints, the best evidence will be included for each intervention and evidence from lower categories in the hierarchy of evidence will be excluded, so for example we will only include cohort studies for an intervention if there is no/poor RCT evidence for that intervention. Adequacy of evidence will be discussed on an intervention-by-intervention basis between the team and QA lead.
10.	Other exclusion criteria	• Abstracts, conference presentations and theses • Non-human studies • Non-English language studies
11.	Context	The NICE surveillance review (June 2023) identified some studies indicating that surveillance and early intervention reduce the risk of chronic lymphoedema in people with breast cancer. The current recommendations in NG101 and CG81 focus on prevention in people with early breast cancer and do not include people with advanced breast cancer. As such, there is a need to expand the evidence reviews to cover all people with breast cancer, as well as review any new evidence on surveillance and early intervention or prevention of lymphoedema in people with breast cancer.
12.	Primary outcomes (critical outcomes)	At all reported timepoints in 6-monthly intervals where applicable (e.g. 0-6 months, 7-12 months): • Incidence of lymphoedema • Severity of lymphoedema (for example, limb or breast volume/swelling using ultrasound/tissue dielectric constant,

		arm mobility (including, DASH scores), bioimpedance)
13.	Secondary outcomes (important outcomes)	At all reported timepoints in 6-monthly intervals where applicable (e.g. 0-6 months, 7-12 months): • Patient reported outcomes (for example pain, psychological distress, limb function) • Adverse events (for example, infection) • Quality of life (for example, LYMQOL, FACT B+4, EQ5D and EORTC-QoL-C30)
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).
15.	Risk of bias (quality) assessment	Risk of bias for RCTs and systematic reviews will be assessed using the Cochrane Risk of Bias v.2.0 or ROBIS respectively. Risk of bias for cohort and non-randomised studies will be assessed using the ROBINS-I tool (Risk Of Bias In Non-randomised Studies - of Interventions).
16.	Strategy for data synthesis	Where possible, meta-analyses of outcome data will be conducted for all comparators that are reported by more than one study, with reference to the Cochrane Handbook for Systematic Reviews of Interventions.

		Where data can be disaggregated it will also be separated into the subgroups identified in section 17 (below).Pooled relative risks will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. Absolute risks will be presented where possible. Continuous outcomes will be analysed as mean differences, unless multiple scales are used to measure the same factor. In these cases, standardised mean differences will be used instead. Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be deemed to be inappropriate if one or both of the following conditions is met: • Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$. GRADE will be used to assess the quality of the outcomes. Data from randomised controlled trials and cohort studies will be initially rated as high quality, with the quality of the evidence for each outcome then downgraded or not from this initial point. Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically (visually) assess the potential for publication bias. Imprecision will be based on default values of 0.8 and 1.25 for dichotomous outcomes,

		and 0.5*median SD of the control groups for continuous outcomes.		
17.	Analysis of sub-groups	Where disaggregation is possible/applicable: • Axillary intervention • Type of treatment (surgery or radiotherapy) • Risk factors for lymphoedema (for example, age, obesity, comorbidities) • Duration/intensity of treatment		
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	February 2024		
22.	Anticipated completion date	June 2024		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐

		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** Centre for Guidelines, NICE. **5b Named contact e-mail** breastcancerupdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and Guideline Development Team.		
25.	Review team members	From the Guideline Development Team: • Alfredo Mariani, Senior health economist • Chris Carmona, Technical adviser • Clare Dadswell, Senior technical analyst • Daniel Tuvey, Senior information specialist • Lindsay Claxton, Health economist adviser • Omnia Bilal, Technical analyst		
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Development Team which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the		

		development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: Early and locally advanced breast cancer:
29.	Other registration details	None.
30.	Reference/URL for published protocol	None.
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Breast cancer; lymphoedema; non-surgical interventions
33.	Details of existing review of same topic by same authors	None.
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published

		☐ Completed, published and being updated ☐ Discontinued
35.	Additional information	None.
36.	Details of final publication	www.nice.org.uk

1

2

Appendix B – Literature search strategies

Background and development

Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches for the evidence review. The searches were run on 19 February 2024 (effectiveness search) and 22 February 2024 (cost effectiveness search).

This search report is compliant with the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

The MEDLINE strategies below were quality assured (QA) by a trained NICE SIS. All translated search strategies were peer reviewed by another SIS to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

The principal search strategies were developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess "low-probability" matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The search strategy was based on the strategies used for NG101 and CG81.The strategy was updated to include additional lymphoedema terms.

Search limits and other restrictions

Formats

Limits were applied in adherence to standard NICE practice and the review protocol to exclude:

- Animal studies
- Editorials, letters, news items and commentaries
- Conference abstracts and posters
- Papers not published in the English language.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from:

> Dickersin K, Scherer R & Lefebvre C. (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Date limits

A date limit of October 2013 to February 2024 was applied, as stated in the review protocol, because the last update search for GG81 was in October 2013. The update search for NG101 was carried out in 2017. We were aware that there would be some duplicate records for the NG101 population (2013-2017).

Allied and Complementary Medicine (AMED) was searched up until October 2023. This is due to the British Library cyberattack. Full access to AMED has yet to be restored.

Search filters and classifiers

Effectiveness searches

Randomised controlled trials filter

The MEDLINE RCT filter was McMaster Therapy – Medline - "best balance of sensitivity and specificity" version.

The standard NICE modifications were used: the MeSH heading *randomized controlled trial/*, which is equivalent *to randomized controlled trial.pt* was exploded to capture newer, narrower *terms equivalence trial/ and pragmatic clinical trial*. The free-text term *randomized.mp* was also changed to the (more inclusive) alternative *randomi?ed.mp.* to capture both UK and US spellings.

The Embase RCT filter was McMaster Therapy – Embase "best balance of sensitivity and specificity" version.

Systematic reviews filters:

Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. BMC Medical Research Methodology, 12(1), 51.

- In MEDLINE, the standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.
- In Embase, the standard NICE modifications were used: pubmed.tw added to line medline.tw.

Observational studies

The terms used for observational studies are standard NICE practice that have been developed in house.

Cost effectiveness searches

In line with the review protocol, the sensitive version of the validated NICE cost utility filter was used in the MEDLINE and Embase strategies without amendment.

Hubbard W et al. (2022) Development and validation of paired MEDLINE and Embase search filters for cost-utility studies. *BMC Medical Research Methodology*, 22(1), 310.

Note: Several modifications have been made to these filters over the years that are standard NICE practice.

1 ## Effectiveness searches

Database results

2

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Allied and Complementary Medicine (AMED)	19/02/24	Ovid	1985 to October 2023	69
Cochrane Central Register of Controlled Trials (CENTRAL)	19/02/24	Wiley	Issue 2 of 12, February 2024	560
Cochrane Database of Systematic Reviews (CDSR)	19/02/24	Wiley	Issue 2 of 12, February 2024	11
Database of Abstracts of Reviews of Effectiveness (DARE)	19/02/24	CRD	-	13
Embase	19/02/24	Ovid	1996 to 2024 February 16	2,400
Emcare	19/02/24	Ovid	1995 to 2024 Week 06	882
Epistemonikos	19/02/24	Epistemonikos		503
Health Technology Assessment (HTA)	19/02/24	CRD	-	4
International Health Technology Assessment Database (INAHTA)	19/02/24	https://database.inahta.org/	-	9
Medline ALL	19/02/24	Ovid	1946 to February 16, 2024	1,938

Search strategy history

Database name: Allied and Complementary Medicine (AMED)

Searches
1 exp breast neoplasms/ 1933 2 exp Breast/ 104 3 breast*.ti,ab. 2872 4 2 or 3 2908 5 (breast adj milk).ti,ab. 37 6 (breast adj tender*).ti,ab. 5 7 5 or 6 42 8 4 not 7 2866 9 exp neoplasms/ 18086 10 8 and 9 2213 11 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab. 2470 12 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab. 101 13 10 or 11 or 12 2630 14 1 or 13 2799 15 (duct* carcinoma* in situ or DCIS).ti,ab. 2 16 14 or 15 2799 17 exp lymphoedema/ 289 18 (lymphed* or lymphoed*).ti,ab. 344 19 elephantiasis.ti,ab. 15 20 ((arm* or hand* or finger* or upper limb* or chest wall or trunc* or trunk* or axilla* or thoracic) adj4 (morbidity or swell* or swollen or pain* or oedema* or edema*)).ti,ab. 1317 21 (breast* adj4 (morbidity or swell* or swollen or oedema* or edema*)).ti,ab. 27 22 (lymph* adj4 (oedema* or edema*)).ti,ab. 37 23 or/17-22 1707 24 16 and 23 197 25 limit 24 to english 175 26 limit 25 to yr="2013 -Current" 69

Database name: Cochrane Central Register of Controlled Trials (CENTRAL)

Searches
#1 MeSH descriptor: [Breast Neoplasms] explode all trees 19974 #2 MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees 1001 #3 MeSH descriptor: [Carcinoma, Lobular] this term only 217 #4 MeSH descriptor: [Carcinoma, Medullary] this term only 21 #5 MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] this term only 305 #6 {OR #1-#5} 20272 #7 MeSH descriptor: [Breast] explode all trees 1142 #8 breast*:ti,ab 60058 #9 #7 or #8 60167 #10 (breast NEXT milk):ti,ab 2709 #11 (breast NEXT tender*):ti,ab 261 #12 #10 or #11 2969 #13 #9 not #12 57198

Searches
#14 MeSH descriptor: [Neoplasms] explode all trees 123386 #15 #13 and #14 20312 #16 (breast* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab 43053 #17 (mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab 282 #18 MeSH descriptor: [Paget's Disease, Mammary] explode all trees 3 #19 (paget* and (breast* or mammary or nipple*)):ti,ab 18 #20 {OR #15-#19} 44070 #21 #6 or #20 45463 #22 ((duct* carcinoma* in situ or DCIS)):ti,ab,kw 1013 #23 #21 or #22 45560 #24 MeSH descriptor: [Lymphoedema] explode all trees 906 #25 (lymphoed* or lymphed*):ti,ab,kw 1896 #26 (elephantiasis):ti,ab,kw 182 #27 (((arm* or hand* or finger* or upper limb* or "chest wall" or trunc* or trunk* or axilla* or thoracic) NEAR/4 (morbidity or swell* or swollen or pain* or oedema* or edema*))):ti,ab,kw 11433 #28 ((breast* NEAR/4 (morbidity or swell* or swollen or oedema* or edema*))):ti,ab,kw 371 #29 ((lymph* NEAR/4 (oedema* or edema*))):ti,ab,kw 237 #30 #24 OR #25 OR #26 OR #27 OR #28 OR #29 13511 #31 #23 AND #30 1762 #32 MeSH descriptor: [Breast Cancer Lymphoedema] this term only 155 #33 #31 OR #32 1766 #34 (((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp))):an (Word variations have been searched) 494506 #35 #33 NOT #34 1236 #36 ("conference"):pt 236547 #37 #35 NOT #36 with Cochrane Library publication date Between Oct 2013 and Feb 2024, in Cochrane Reviews 11 #38 #35 NOT #36 with Publication Year from 2013 to 2024, in Trials 560

Database name: Cochrane Database of Systematic Reviews (CDSR)

Searches
#1 MeSH descriptor: [Breast Neoplasms] explode all trees 19974 #2 MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees 1001 #3 MeSH descriptor: [Carcinoma, Lobular] this term only 217 #4 MeSH descriptor: [Carcinoma, Medullary] this term only 21 #5 MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] this term only 305 #6 {OR #1-#5} 20272 #7 MeSH descriptor: [Breast] explode all trees 1142 #8 breast*:ti,ab 60058 #9 #7 or #8 60167

Searches
#10 (breast NEXT milk):ti,ab 2709
#11 (breast NEXT tender*):ti,ab 261
#12 #10 or #11 2969
#13 #9 not #12 57198
#14 MeSH descriptor: [Neoplasms] explode all trees 123386
#15 #13 and #14 20312
#16 (breast* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab 43053
#17 (mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab 282
#18 MeSH descriptor: [Paget's Disease, Mammary] explode all trees 3
#19 (paget* and (breast* or mammary or nipple*)):ti,ab 18
#20 {OR #15-#19} 44070
#21 #6 or #20 45463
#22 ((duct* carcinoma* in situ or DCIS)):ti,ab,kw 1013
#23 #21 or #22 45560
#24 MeSH descriptor: [Lymphoedema] explode all trees 906
#25 (lymphoed* or lymphed*):ti,ab,kw 1896
#26 (elephantiasis):ti,ab,kw 182
#27 (((arm* or hand* or finger* or upper limb* or "chest wall" or trunc* or trunk* or axilla* or thoracic) NEAR/4 (morbidity or swell* or swollen or pain* or oedema* or edema*))):ti,ab,kw 11433
#28 ((breast* NEAR/4 (morbidity or swell* or swollen or oedema* or edema*))):ti,ab,kw 371
#29 ((lymph* NEAR/4 (oedema* or edema*))):ti,ab,kw 237
#30 #24 OR #25 OR #26 OR #27 OR #28 OR #29 13511
#31 #23 AND #30 1762
#32 MeSH descriptor: [Breast Cancer Lymphoedema] this term only 155
#33 #31 OR #32 1766
#34 (((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp))):an (Word variations have been searched) 494506
#35 #33 NOT #34 1236
#36 ("conference"):pt 236547
#37 #35 NOT #36 with Cochrane Library publication date Between Oct 2013 and Feb 2024, in Cochrane Reviews 11
#38 #35 NOT #36 with Publication Year from 2013 to 2024, in Trials 560

1 **Database name: Database of Abstracts of Reviews of Effectiveness (DARE)**

Searches
1 MESH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES
2 MESH DESCRIPTOR Neoplasms, Ductal, Lobular, and Medullary EXPLODE ALL TREES
3 MESH DESCRIPTOR Carcinoma, Lobular
4 MESH DESCRIPTOR Carcinoma, Medullary
5 MESH DESCRIPTOR Carcinoma, Intraductal, Noninfiltrating
6 #1 OR #2 OR #3 OR #4 OR #5
7 MESH DESCRIPTOR Breast EXPLODE ALL TREES
8 breast*

Searches
9 #7 or #8 10 (breast NEXT milk) 11 (breast NEXT tender*) 12 #10 or #11 13 #9 not #12 14 MESH DESCRIPTOR Neoplasms EXPLODE ALL TREES 15 #13 and #14 16 (breast* NEAR5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)) 17 (mammar* near5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)) 18 MESH DESCRIPTOR Paget's Disease, Mammary EXPLODE ALL TREES 19 (paget* and (breast* or mammary or nipple*)) 20 #15 OR #16 OR #17 OR #18 OR #19 21 #6 or #20 22 ((duct* carcinoma* in situ or DCIS)) 23 #21 or #22 24 MESH DESCRIPTOR Lymphoedema EXPLODE ALL TREES 25 (lymphoed* or lymphed*) 26 (elephantiasis) 27 (((arm* or hand* or finger* or upper limb* or "chest wall" or trunc* or trunk* or axilla* or thoracic) NEAR4 (morbidity or swell* or swollen or pain* or oedema* or edema*))) 28 ((breast* NEAR4 (morbidity or swell* or swollen or oedema* or edema*))) 29 ((lymph* NEAR4 (oedema* or edema*))) 30 #24 OR #25 OR #26 OR #27 OR #28 OR #29 31 #23 AND #30 32 MESH DESCRIPTOR Breast Cancer Lymphoedema 33 #31 OR #32 34 * IN DARE FROM 2013 TO 2015 35 #33 AND #34 36 * IN HTA FROM 2013 TO 2018 37 #33 AND #36 34 * IN DARE FROM 2013 TO 2015 35 #33 AND #34

1 **Database name: Embase**

Searches
1 exp breast cancer/ 529909 2 exp breast carcinoma/ 76840 3 exp medullary carcinoma/ 10990 4 ductal breast carcinoma in situ/ 2803 5 exp breast tumor/ 592337 6 lobular carcinoma/ 3428 7 or/1-6 601890 8 exp breast/ 90238 9 breast*.ti,ab,kf. 707921 10 8 or 9 723315 11 (breast adj milk).ti,ab,kf. 18056 12 (breast adj tender*).ti,ab,kf. 642 13 11 or 12 18692 14 10 not 13 704623 15 exp neoplasm/ 4809452

Searches
16 14 and 15 543759 17 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 559182 18 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 30184 19 exp Paget nipple disease/ 7002 20 (paget* and (breast* or mammary or nipple*)).ti,ab,kf. 1496 21 or/16-20 610142 22 7 or 21 720727 23 (duct* carcinoma* in situ or DCIS).ti,ab,kf. 15980 24 ductal breast carcinoma in situ/ 2803 25 23 or 24 17216 26 22 or 25 721602 27 lymphoedema/ 17927 28 hand edema/ or arm edema/ 2843 29 (lymphed* or lymphoed*).ti,ab,kf. 16315 30 elephantiasis.ti,ab,kf. 968 31 elephantiasis/ 1104 32 ((arm* or hand* or finger* or upper limb* or chest wall or trunc* or trunk* or axilla* or thoracic) adj4 (morbidity or swell* or swollen or pain* or oedema* or edema*)).ti,ab,kf. 29338 33 (breast* adj4 (morbidity or swell* or swollen or oedema* or edema*)).ti,ab,kf. 2543 34 (lymph* adj4 (oedema* or edema*)).ti,ab,kf. 2558 35 or/27-34 56148 36 26 and 35 9822 37 breast cancer-related lymphoedema/ 1026 38 36 or 37 9909 39 limit 38 to english language 9267 40 nonhuman/ not (human/ and nonhuman/) 4078001 41 39 not 40 9181 42 41 not (letter or editorial).pt. 8841 43 42 not (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 6199 44 limit 43 to dc=20131028-20240219 3924 45 random:.tw. 1891142 46 placebo:.mp. 454874 47 double-blind:.tw. 203299 48 or/45-47 2106089 49 44 and 48 657 50 (MEDLINE or pubmed).tw. 428339 51 exp systematic review/ or systematic review.tw. 533668 52 meta-analysis/ 299840 53 intervention$.ti. 260952 54 or/50-53 988821 55 44 and 54 455 56 Clinical study/ 114620 57 Case control study/ 208200 58 Family study/ 23056 59 Longitudinal study/ 198747 60 Retrospective study/ 1538275 61 comparative study/ 833607 62 Prospective study/ 884095

Searches
63 Randomized controlled trials/ 268881
64 62 not 63 873100
65 Cohort analysis/ 1104832
66 cohort analy$.tw. 19876
67 (Cohort adj (study or studies)).tw. 483757
68 (Case control$ adj (study or studies)).tw. 167323
69 (follow up adj (study or studies)).tw. 61088
70 (observational adj (study or studies)).tw. 265849
71 (epidemiologic$ adj (study or studies)).tw. 107694
72 (cross sectional adj (study or studies)).tw. 356283
73 case series.tw. 151642
74 prospective.tw. 1070934
75 retrospective.tw. 1266191
76 or/56-61,64-75 5181172
77 44 and 76 1466
78 49 or 55 934

Database name: Emcare

Searches
1 exp breast cancer/ 87822
2 exp breast carcinoma/ 10647
3 exp medullary carcinoma/ 1186
4 ductal breast carcinoma in situ/ 47
5 exp breast tumor/ 91820
6 lobular carcinoma/ 292
7 or/1-6 92792
8 exp breast/ 19500
9 breast*.ti,ab,kf. 173755
10 8 or 9 175714
11 (breast adj milk).ti,ab,kf. 6979
12 (breast adj tender*).ti,ab,kf. 215
13 11 or 12 7191
14 10 not 13 168523
15 exp neoplasm/ 586574
16 14 and 15 78895
17 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 119680
18 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 3570
19 exp Paget nipple disease/ 1094
20 (paget* and (breast* or mammary or nipple*)).ti,ab,kf. 254
21 or/16-20 127587
22 7 or 21 146722
23 (duct* carcinoma* in situ or DCIS).ti,ab,kf. 3191
24 ductal breast carcinoma in situ/ 47
25 23 or 24 3195
26 22 or 25 147059
27 lymphoedema/ 3290
28 hand edema/ or arm edema/ 601
29 (lymphed* or lymphoed*).ti,ab,kf. 4027
30 elephantiasis.ti,ab,kf. 234
31 elephantiasis/ 202

Searches
32 ((arm* or hand* or finger* or upper limb* or chest wall or trunc* or trunk* or axilla* or thoracic) adj4 (morbidity or swell* or swollen or pain* or oedema* or edema*)).ti,ab,kf. 8658
33 (breast* adj4 (morbidity or swell* or swollen or oedema* or edema*)).ti,ab,kf. 742
34 (lymph* adj4 (oedema* or edema*)).ti,ab,kf. 477
35 or/27-34 14711
36 26 and 35 2696
37 breast cancer-related lymphoedema/ 199
38 36 or 37 2702
39 limit 38 to english language 2550
40 nonhuman/ not (human/ and nonhuman/) 366923
41 39 not 40 2539
42 41 not (letter or editorial).pt. 2428
43 42 not (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 2390
44 limit 43 to dc=20131028-20240219 1549
45 random:.tw. 617894
46 placebo:.mp. 124509
47 double-blind:.tw. 61710
48 or/45-47 673244
49 44 and 48 306
50 (MEDLINE or pubmed).tw. 168156
51 exp systematic review/ or systematic review.tw. 196322
52 meta-analysis/ 60710
53 intervention$.ti. 127911
54 or/50-53 386930
55 44 and 54 192
56 Clinical study/ 43682
57 Case control study/ 30075
58 Family study/ 9975
59 Longitudinal study/ 52483
60 Retrospective study/ 173031
61 comparative study/ 93270
62 Prospective study/ 138331
63 Randomized controlled trials/ 52706
64 62 not 63 136396
65 Cohort analysis/ 146137
66 cohort analy$.tw. 5531
67 (Cohort adj (study or studies)).tw. 162921
68 (Case control$ adj (study or studies)).tw. 46523
69 (follow up adj (study or studies)).tw. 19973
70 (observational adj (study or studies)).tw. 82242
71 (epidemiologic$ adj (study or studies)).tw. 31731
72 (cross sectional adj (study or studies)).tw. 148946
73 case series.tw. 40415
74 prospective.tw. 305265
75 retrospective.tw. 305940
76 or/56-61,64-75 1192781
77 44 and 76 458
78 49 or 55 424

1 Database name: Epistemonikos

Searches
(advanced_title_en:((breast* AND (neoplasm* OR cancer* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR dcis OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignanc*)) OR (mammar* AND (neoplasm* OR cancer* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR dcis OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)) OR (paget* AND (breast* OR mammary OR nipple*)) OR (duct* carcinoma* in situ OR dcis)) OR advanced_abstract_en:((breast* AND (neoplasm* OR cancer* OR tumo?r* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR dcis OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)) OR (mammar* AND (neoplasm* OR cancer* OR tumo?r* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR dcis OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignanc*)) OR (paget* AND (breast* OR mammary OR nipple*)) OR (duct* carcinoma* in situ OR dcis))) AND (advanced_title_en:((lymphoed* OR lymphed*) OR (elephantiasis) OR (((arm* OR hand* OR finger* OR upper limb* OR "chest wall" OR trunc* OR trunk* OR axilla* OR thoracic) AND (morbidity OR swell* OR swollen OR pain* OR oedema* OR edema*))) OR ((breast* AND (morbidity OR swell* OR swollen OR oedema* OR edema*))) OR ((lymph* AND (oedema* OR edema*)))) OR advanced_abstract_en:((lymphoed* OR lymphed*) OR (elephantiasis) OR (((arm* OR hand* OR finger* OR upper limb* OR "chest wall" OR trunc* OR trunk* OR axilla* OR thoracic) AND (morbidity OR swell* OR swollen OR pain* OR oedema* OR edema*))) OR ((breast* AND (morbidity OR swell* OR swollen OR oedema* OR edema*))) OR ((lymph* AND (oedema* OR edema*))))) [Filters: classification=systematic-review, cochrane=missing, protocol=no, min_year=2013, max_year=2024]

2 Database name: Health Technology Assessment (HTA)

Searches
1 MESH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES
2 MESH DESCRIPTOR Neoplasms, Ductal, Lobular, and Medullary EXPLODE ALL TREES
3 MESH DESCRIPTOR Carcinoma, Lobular
4 MESH DESCRIPTOR Carcinoma, Medullary
5 MESH DESCRIPTOR Carcinoma, Intraductal, Noninfiltrating
6 #1 OR #2 OR #3 OR #4 OR #5
7 MESH DESCRIPTOR Breast EXPLODE ALL TREES
8 breast*
9 #7 or #8
10 (breast NEXT milk)
11 (breast NEXT tender*)
12 #10 or #11
13 #9 not #12
14 MESH DESCRIPTOR Neoplasms EXPLODE ALL TREES
15 #13 and #14
16 (breast* NEAR5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*))
17 (mammar* near5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*))
18 MESH DESCRIPTOR Paget's Disease, Mammary EXPLODE ALL TREES
19 (paget* and (breast* or mammary or nipple*))
20 #15 OR #16 OR #17 OR #18 OR #19

Searches
21 #6 or #20 22 ((duct* carcinoma* in situ or DCIS)) 23 #21 or #22 24 MESH DESCRIPTOR Lymphoedema EXPLODE ALL TREES 25 (lymphoed* or lymphed*) 26 (elephantiasis) 27 (((arm* or hand* or finger* or upper limb* or "chest wall" or trunc* or trunk* or axilla* or thoracic) NEAR4 (morbidity or swell* or swollen or pain* or oedema* or edema*))) 28 ((breast* NEAR4 (morbidity or swell* or swollen or oedema* or edema*))) 29 ((lymph* NEAR4 (oedema* or edema*))) 30 #24 OR #25 OR #26 OR #27 OR #28 OR #29 31 #23 AND #30 32 MESH DESCRIPTOR Breast Cancer Lymphoedema 33 #31 OR #32 34 * IN DARE FROM 2013 TO 2015 35 #33 AND #34 36 * IN HTA FROM 2013 TO 2018 37 #33 AND #36

Database name: International Health Technology Assessment Database (INAHTA)

Searches
(((((paget* and (breast* or mammary or nipple*)))[Title] OR ((paget* and (breast* or mammary or nipple*)))[abs]) OR ("Paget's Disease, Mammary"[mh]) OR (((duct* carcinoma* in situ or DCIS))[Title] OR ((duct* carcinoma* in situ or DCIS))[abs]) OR (((breast* AND (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)))[Title] OR ((breast* AND (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)))[abs]) OR (((mammar* AND (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)))[Title] OR ((mammar* AND (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)))[abs]) OR (("Carcinoma, Intraductal, Noninfiltrating"[mh]) OR ("Carcinoma, Medullary"[mh]) OR ("Carcinoma, Lobular"[mh]) OR ("Neoplasms, Ductal, Lobular, and Medullary"[mhe]) OR ("Breast Neoplasms"[mhe])) AND ((((lymph* AND (oedema* or edema*)))[Title] OR ((lymph* AND (oedema* or edema*)))[abs]) OR (((breast* AND (morbidity or swell* or swollen or oedema* or edema*)))[Title] OR ((breast* AND (morbidity or swell* or swollen or oedema* or edema*)))[abs]) OR ((((arm* or hand* or finger* or upper limb* or chest wall or trunc* or trunk* or axilla* or thoracic) AND (morbidity or swell* or swollen or pain* or oedema* or edema*)))[Title] OR (((arm* or hand* or finger* or upper limb* or chest wall or trunc* or trunk* or axilla* or thoracic) AND (morbidity or swell* or swollen or pain* or oedema* or edema*)))[abs]) OR ((elephantiasis)[Title] OR (elephantiasis)[abs]) OR ((Lymphoedema)[mh]) OR ((lymphed* or lymphoed*)[Title] OR (lymphed* or lymphoed*)[abs])))) OR ("Breast Cancer Lymphoedema"[mh])

Database name: Medline ALL

Searches		
1	exp Breast Neoplasms/	350560
2	exp "Neoplasms, Ductal, Lobular, and Medullary"/	47659
3	Carcinoma, Lobular/	6144

Searches
4 Carcinoma, Medullary/ 3414 5 Carcinoma, Intraductal, Noninfiltrating/ 10797 6 or/1-5 370386 7 exp Breast/ 54252 8 breast*.ti,ab,kf. 572489 9 7 or 8 582466 10 (breast adj milk).ti,ab,kf. 16563 11 (breast adj tender*).ti,ab,kf. 591 12 10 or 11 17151 13 9 not 12 565315 14 exp Neoplasms/ 3937769 15 13 and 14 367555 16 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 431026 17 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 37160 18 Paget's Disease, Mammary/ 819 19 (paget* and (breast* or mammary or nipple*)).ti,ab,kf. 1539 20 or/15-19 483927 21 6 or 20 541054 22 (duct* carcinoma* in situ or DCIS).ti,ab,kf. 9660 23 21 or 22 541289 24 exp Lymphoedema/ 14418 25 (lymphed* or lymphoed*).ti,ab,kf. 13195 26 elephantiasis.ti,ab,kf. 1679 27 ((arm* or hand* or finger* or upper limb* or chest wall or trunc* or trunk* or axilla* or thoracic) adj4 (morbidity or swell* or swollen or pain* or oedema* or edema*)).ti,ab,kf. 20575 28 (breast* adj4 (morbidity or swell* or swollen or oedema* or edema*)).ti,ab,kf. 1955 29 (lymph* adj4 (oedema* or edema*)).ti,ab,kf. 1976 30 or/24-29 42155 31 23 and 30 6171 32 Breast Cancer Lymphoedema/ 464 33 31 or 32 6184 34 animals/ not humans/ 5164263 35 33 not 34 6147 36 limit 35 to ed=20131028-20240219 2743 37 limit 35 to dt=20131028-20240219 3272 38 36 or 37 3381 39 limit 38 to english language 3235 40 limit 39 to (letter or historical article or comment or editorial or news or case reports) 463 41 39 not 40 2772 42 exp Randomized Controlled Trial/ 610711 43 randomi?ed.mp. 1105735 44 placebo.mp. 253935 45 or/42-44 1172955 46 41 and 45 510 47 (MEDLINE or pubmed).tw. 348643 48 systematic review.tw. 291515 49 systematic review.pt. 252884 50 meta-analysis.pt. 195422

Searches		
51	intervention$.ti.	210163
52	or/47-51	727387
53	41 and 52	364
54	Observational Studies as Topic/	9480
55	Observational Study/	152445
56	Epidemiologic Studies/	9493
57	exp Case-Control Studies/	1483235
58	exp Cohort Studies/	2575193
59	Cross-Sectional Studies/	493306
60	Controlled Before-After Studies/	748
61	Historically Controlled Study/	231
62	Interrupted Time Series Analysis/	1999
63	Comparative Study.pt.	1913680
64	case control$.tw.	164265
65	case series.tw.	108819
66	(cohort adj (study or studies)).tw.	341314
67	cohort analy$.tw.	12718
68	(follow up adj (study or studies)).tw.	57657
69	(observational adj (study or studies)).tw.	173410
70	longitudinal.tw.	339087
71	prospective.tw.	744373
72	retrospective.tw.	791851
73	cross sectional.tw.	547954
74	or/54-73	5666064
75	41 and 74	1206
76	46 or 53	732

1

Cost-effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
EconLit	22/02/24	Ovid	Econlit 1886 to February 15, 2024	0
(NHS) EED	22/02/24	CRD	-	0
Embase	22/02/24	Ovid	Embase 1996 to 2024 February 21	96
Health Technology Assessment (HTA)	22/02/24	CRD	-	4
International Health Technology Assessment Database (INAHTA)	22/02/24	https://database.inahta.org/	-	9
Medline ALL	22/02/24	Ovid	MEDLINE(R) ALL 1946 to February 21, 2024	79

Search strategy history

Database name: Econlit

Searches
1 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 396
2 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 1
3 (duct* carcinoma* in situ or DCIS).ti,ab,kw. 3
4 (paget* and (breast* or mammary or nipple*)).ti,ab,kw. 0
5 or/1-4 398
6 (lymphed* or lymphoed*).ti,ab,kw. 0
7 elephantiasis.ti,ab,kw. 0
8 ((arm* or hand* or finger* or upper limb* or chest wall or trunc* or trunk* or axilla* or thoracic) adj4 (morbidity or swell* or swollen or pain* or oedema* or edema*)).ti,ab,kw. 11

Searches	
9	(breast* adj4 (morbidity or swell* or swollen or oedema* or edema*)).ti,ab,kw. 5
10	(lymph* adj4 (oedema* or edema*)).ti,ab,kw. 0
11	or/6-10 16
12	5 and 11 2
13	limit 12 to english 2
14	limit 13 to yr="2013 -Current" 0

Database name: NHS EED

Searches
1 MESH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES 1798
2 MESH DESCRIPTOR Neoplasms, Ductal, Lobular, and Medullary EXPLODE ALL TREES 65
3 MESH DESCRIPTOR Carcinoma, Lobular 7
4 MESH DESCRIPTOR Carcinoma, Medullary 7
5 MESH DESCRIPTOR Carcinoma, Intraductal, Noninfiltrating 13
6 #1 OR #2 OR #3 OR #4 OR #5 1820
7 MESH DESCRIPTOR Breast EXPLODE ALL TREES 97
8 breast* 3002
9 #7 or #8 3002
10 (breast NEXT milk) 58
11 (breast NEXT tender*) 14
12 #10 or #11 72
13 #9 not #12 2930
14 MESH DESCRIPTOR Neoplasms EXPLODE ALL TREES 12016
15 #13 and #14 2071
16 (breast* NEAR5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)) 2414
17 (mammar* near5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)) 7
18 MESH DESCRIPTOR Paget's Disease, Mammary EXPLODE ALL TREES 1
19 (paget* and (breast* or mammary or nipple*)) 4
20 #15 OR #16 OR #17 OR #18 OR #19 2455
21 #6 or #20 2477
22 ((duct* carcinoma* in situ or DCIS)) 46
23 #21 or #22 2477
24 MESH DESCRIPTOR Lymphoedema EXPLODE ALL TREES 50
25 (lymphoed* or lymphed*) 77
26 (elephantiasis) 6
27 (((arm* or hand* or finger* or upper limb* or "chest wall" or trunc* or trunk* or axilla* or thoracic) NEAR4 (morbidity or swell* or swollen or pain* or oedema* or edema*))) 82
28 ((breast* NEAR4 (morbidity or swell* or swollen or oedema* or edema*))) 15
29 ((lymph* NEAR4 (oedema* or edema*))) 3
30 #24 OR #25 OR #26 OR #27 OR #28 OR #29 168
31 #23 AND #30 64
32 MESH DESCRIPTOR Breast Cancer Lymphoedema 0
33 #31 OR #32 64
34 * IN NHSEED FROM 2013 TO 2015 3345
35 #33 AND #34 0

Database name: Embase

Searches
1 exp breast cancer/ 530109
2 exp breast carcinoma/ 76856
3 exp medullary carcinoma/ 10993
4 ductal breast carcinoma in situ/ 2810
5 exp breast tumor/ 592548
6 lobular carcinoma/ 3430
7 or/1-6 602104
8 exp breast/ 90259
9 breast*.ti,ab,kf. 708228
10 8 or 9 723627
11 (breast adj milk).ti,ab,kf. 18068
12 (breast adj tender*).ti,ab,kf. 642
13 11 or 12 18704
14 10 not 13 704923
15 exp neoplasm/ 4815765
16 14 and 15 544005
17 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 559419
18 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 30192
19 exp Paget nipple disease/ 7002
20 (paget* and (breast* or mammary or nipple*)).ti,ab,kf. 1496
21 or/16-20 610395
22 7 or 21 720985
23 (duct* carcinoma* in situ or DCIS).ti,ab,kf. 15984
24 ductal breast carcinoma in situ/ 2810
25 23 or 24 17223
26 22 or 25 721860
27 lymphoedema/ 17932
28 hand edema/ or arm edema/ 2844
29 (lymphed* or lymphoed*).ti,ab,kf. 16320
30 elephantiasis.ti,ab,kf. 968
31 elephantiasis/ 1104
32 ((arm* or hand* or finger* or upper limb* or chest wall or trunc* or trunk* or axilla* or thoracic) adj4 (morbidity or swell* or swollen or pain* or oedema* or edema*)).ti,ab,kf. 29351
33 (breast* adj4 (morbidity or swell* or swollen or oedema* or edema*)).ti,ab,kf. 2544
34 (lymph* adj4 (oedema* or edema*)).ti,ab,kf. 2560
35 or/27-34 56168
36 26 and 35 9827
37 breast cancer-related lymphoedema/ 1027
38 36 or 37 9914
39 limit 38 to english language 9271
40 nonhuman/ not (human/ and nonhuman/) 4079755
41 39 not 40 9185
42 41 not (letter or editorial).pt. 8845
43 42 not (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 6202
44 limit 43 to dc=20131028-20240222 3927
45 cost utility analysis/ 12719

Searches
46 quality adjusted life year/ 36546 47 cost*.ti. 170922 48 (cost* adj2 utilit*).tw. 12813 49 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. 366211 50 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. 64840 51 (qualit* adj2 adjust* adj2 life*).tw. 27688 52 QALY*.tw. 27269 53 (incremental* adj2 cost*).tw. 29195 54 ICER.tw. 13436 55 utilities.tw. 14726 56 markov*.tw. 39567 57 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. 67998 58 ((utility or effective*) adj2 analys*).tw. 37326 59 (willing* adj2 pay*).tw. 14913 60 (EQ5D* or EQ-5D*).tw. 26893 61 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. 5431 62 (european* adj2 quality adj3 ("5" or five)).tw. 1026 63 or/45-62 591958 64 44 and 63 96

1 **Database name: Health Technology Assessment (HTA)**

Searches
1 MESH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES 1798 2 MESH DESCRIPTOR Neoplasms, Ductal, Lobular, and Medullary EXPLODE ALL TREES 65 3 MESH DESCRIPTOR Carcinoma, Lobular 7 4 MESH DESCRIPTOR Carcinoma, Medullary 7 5 MESH DESCRIPTOR Carcinoma, Intraductal, Noninfiltrating 13 6 #1 OR #2 OR #3 OR #4 OR #5 1820 7 MESH DESCRIPTOR Breast EXPLODE ALL TREES 97 8 breast* 3002 9 #7 or #8 3002 10 (breast NEXT milk) 58 11 (breast NEXT tender*) 14 12 #10 or #11 72 13 #9 not #12 2930 14 MESH DESCRIPTOR Neoplasms EXPLODE ALL TREES 12016 15 #13 and #14 2071 16 (breast* NEAR5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)) 2414 17 (mammar* near5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)) 7 18 MESH DESCRIPTOR Paget's Disease, Mammary EXPLODE ALL TREES 1 19 (paget* and (breast* or mammary or nipple*)) 4 20 #15 OR #16 OR #17 OR #18 OR #19 2455 21 #6 or #20 2477 22 ((duct* carcinoma* in situ or DCIS)) 46 23 #21 or #22 2477

Searches	
24	MESH DESCRIPTOR Lymphoedema EXPLODE ALL TREES 50
25	(lymphoed* or lymphed*) 77
26	(elephantiasis) 6
27	(((arm* or hand* or finger* or upper limb* or "chest wall" or trunc* or trunk* or axilla* or thoracic) NEAR4 (morbidity or swell* or swollen or pain* or oedema* or edema*))) 82
28	((breast* NEAR4 (morbidity or swell* or swollen or oedema* or edema*))) 15
29	((lymph* NEAR4 (oedema* or edema*))) 3
30	#24 OR #25 OR #26 OR #27 OR #28 OR #29 168
31	#23 AND #30 64
32	MESH DESCRIPTOR Breast Cancer Lymphoedema 0
33	#31 OR #32 64
34	* IN DARE FROM 2013 TO 2015 17124
35	#33 AND #34 13
36	* IN HTA FROM 2013 TO 2018 4606
37	#33 AND #36 4

Database name: International Health Technology Assessment Database (INAHTA)

Searches
(((((paget* and (breast* or mammary or nipple*)))[Title] OR ((paget* and (breast* or mammary or nipple*)))[abs]) OR ("Paget's Disease, Mammary"[mh]) OR (((duct* carcinoma* in situ or DCIS))[Title] OR ((duct* carcinoma* in situ or DCIS))[abs]) OR (((breast* AND (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)))[Title] OR ((breast* AND (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)))[abs]) OR (((mammar* AND (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)))[Title] OR ((mammar* AND (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)))[abs]) OR (("Carcinoma, Intraductal, Noninfiltrating"[mh]) OR ("Carcinoma, Medullary"[mh]) OR ("Carcinoma, Lobular"[mh]) OR ("Neoplasms, Ductal, Lobular, and Medullary"[mhe]) OR ("Breast Neoplasms"[mhe]))) AND ((((lymph* AND (oedema* or edema*)))[Title] OR ((lymph* AND (oedema* or edema*)))[abs]) OR (((breast* AND (morbidity or swell* or swollen or oedema* or edema*)))[Title] OR ((breast* AND (morbidity or swell* or swollen or oedema* or edema*)))[abs]) OR ((((arm* or hand* or finger* or upper limb* or chest wall or trunc* or trunk* or axilla* or thoracic) AND (morbidity or swell* or swollen or pain* or oedema* or edema*)))[Title] OR (((arm* or hand* or finger* or upper limb* or chest wall or trunc* or trunk* or axilla* or thoracic) AND (morbidity or swell* or swollen or pain* or oedema* or edema*)))[abs]) OR ((elephantiasis)[Title] OR (elephantiasis)[abs]) OR ((Lymphoedema)[mh]) OR ((lymphed* or lymphoed*)[Title] OR (lymphed* or lymphoed*)[abs]))) OR ("Breast Cancer Lymphoedema"[mh])

Database name: Medline ALL

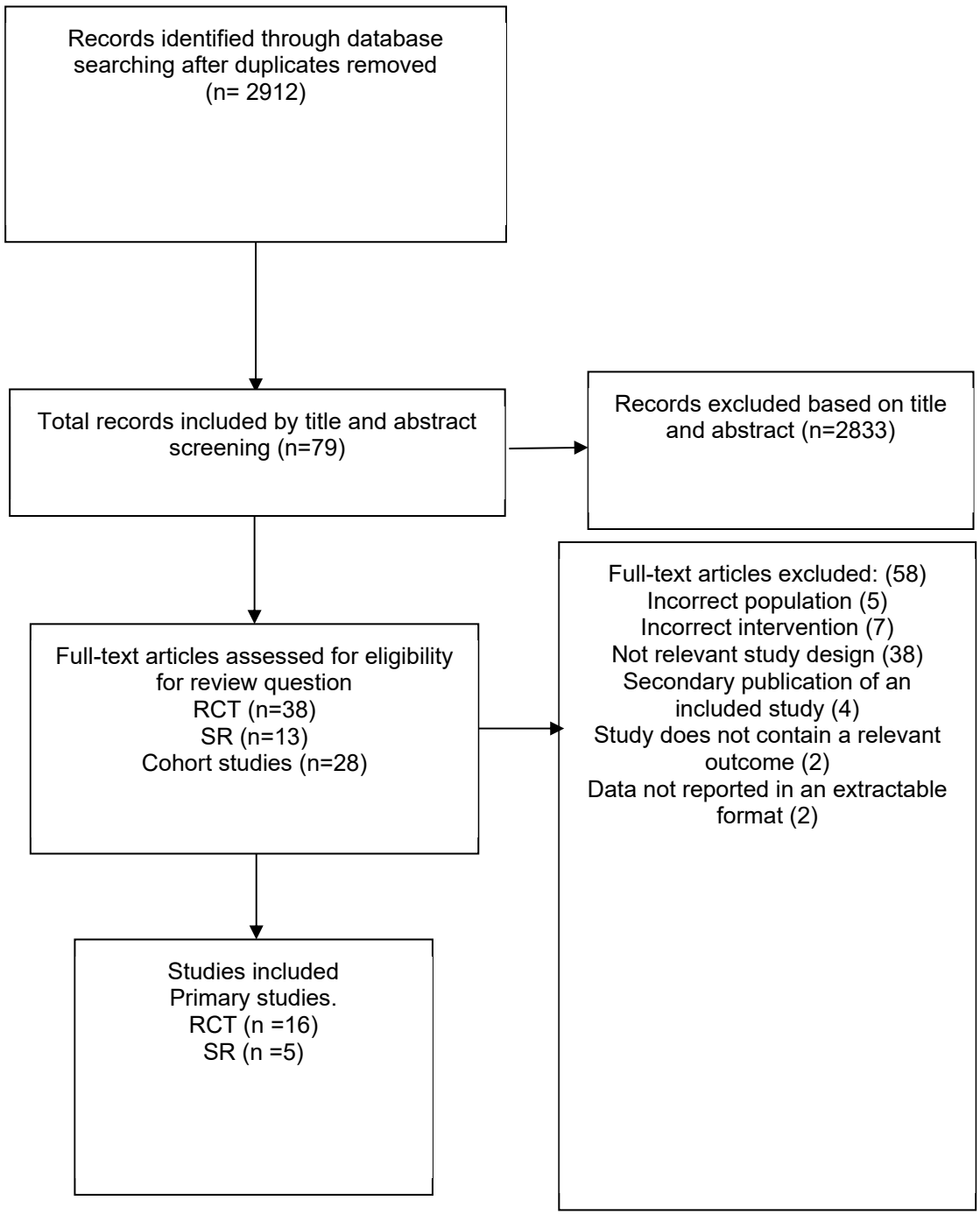
Searches	
1	exp Breast Neoplasms/ 350464
2	exp "Neoplasms, Ductal, Lobular, and Medullary"/ 47625
3	Carcinoma, Lobular/ 6142
4	Carcinoma, Medullary/ 3414
5	Carcinoma, Intraductal, Noninfiltrating/ 10794
6	or/1-5 370256

Searches
7 exp Breast/ 54248 8 breast*.ti,ab,kf. 572438 9 7 or 8 582416 10 (breast adj milk).ti,ab,kf. 16564 11 (breast adj tender*).ti,ab,kf. 591 12 10 or 11 17152 13 9 not 12 565264 14 exp Neoplasms/ 3937191 15 13 and 14 367429 16 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 430956 17 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 37150 18 Paget's Disease, Mammary/ 819 19 (paget* and (breast* or mammary or nipple*)).ti,ab,kf. 1538 20 or/15-19 483859 21 6 or 20 540948 22 (duct* carcinoma* in situ or DCIS).ti,ab,kf. 9658 23 21 or 22 541183 24 exp Lymphoedema/ 14413 25 (lymphed* or lymphoed*).ti,ab,kf. 13192 26 elephantiasis.ti,ab,kf. 1678 27 ((arm* or hand* or finger* or upper limb* or chest wall or trunc* or trunk* or axilla* or thoracic) adj4 (morbidity or swell* or swollen or pain* or oedema* or edema*)).ti,ab,kf. 20586 28 (breast* adj4 (morbidity or swell* or swollen or oedema* or edema*)).ti,ab,kf. 1954 29 (lymph* adj4 (oedema* or edema*)).ti,ab,kf. 1977 30 or/24-29 42160 31 23 and 30 6168 32 Breast Cancer Lymphoedema/ 463 33 31 or 32 6181 34 animals/ not humans/ 5163561 35 33 not 34 6144 36 limit 35 to ed=20131028-20240222 2739 37 limit 35 to dt=20131028-20240222 3269 38 36 or 37 3378 39 limit 38 to english language 3231 40 limit 39 to (letter or historical article or comment or editorial or news or case reports) 464 41 39 not 40 2767 42 Cost-Benefit Analysis/ 94087 43 Quality-Adjusted Life Years/ 16166 44 Markov Chains/ 16084 45 exp Models, Economic/ 16263 46 cost*.ti. 148113 47 (cost* adj2 utilit*).tw. 7946 48 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. 285690 49 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. 48640 50 (qualit* adj2 adjust* adj2 life*).tw. 18401 51 QALY*.tw. 14916

Searches
52 (incremental* adj2 cost*).tw. 17979
53 ICER.tw. 6297
54 utilities.tw. 9693
55 markov*.tw. 32699
56 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. 55441
57 ((utility or effective*) adj2 analys*).tw. 25775
58 (willing* adj2 pay*).tw. 10210
59 (EQ5D* or EQ-5D*).tw. 14021
60 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. 4066
61 (european* adj2 quality adj3 ("5" or five)).tw. 742
62 or/42-61 515254
63 41 and 62 79

1

Appendix C – Effectiveness evidence study selection



Appendix D – Effectiveness evidence

Systematic reviews

Chun, 2022

Bibliographic Reference	Chun, Magnus J; Saeg, Fouad; Meade, Anna; Kumar, Taruni; Toraih, Eman A; Chaffin, Abigail E; Homsy, Christopher; Immediate Lymphatic Reconstruction for Prevention of Secondary Lymphoedema: A Meta-Analysis.; Journal of plastic, reconstructive & aesthetic surgery : JPRAS; 2022; vol. 75 (no. 3); 1130-1141

Study Characteristics

Study design	Systematic review
Study details	Dates searched January 2009 to June 2020 Databases searched PubMed, Embase, Web of Science
Inclusion criteria	All English-language studies published from January 1, 2009 to June 1, 2020. Studies on immediate lymphatic reconstruction (ILR) interventions, specifically lymphaticovenous anastomoses
Exclusion criteria	Non-ILR interventions (i.e., lymphoedema treatment post-surgery on another date). Literature reviews/letters/commentaries. Non-human or cadaver studies
Intervention(s)	Immediate lymphatic reconstruction (ILR) performed concurrently with ALND
Outcome(s)	Incidence of lymphoedema
Number of studies included in the systematic review	13 studies
Studies from the systematic review that are relevant for use in the current review	Agarwal, 2020 Schwarz, 2019 Johnson, 2019 Hahamoff, 2018 Gomberawalla, 2017 Spiguel, 2016 Feldman, 2015 Boccardo, 2014 Boccardo, 2011 Boccardo, 2009

Studies from the systematic review that are not relevant for use in the current review	Cakmakoglu 2020, Nacchiero 2019, Boccardo 2013 (inguinal lymphadenectomy for melanoma)
Additional comments	10 studies/13 studies relevant to this review question. 3 studies on inguinal lymphadenectomy for melanoma

Critical appraisal - ROBIS checklist

Section	Question	Answer
Overall study ratings	Overall risk of bias	Moderate *(Some limitations due to the lack of randomised trials, incomplete reporting of certain participant and intervention details, and the relatively small evidence base.)*
Overall study ratings	Applicability as a source of data	Fully applicable

Cook, 2022

Bibliographic Reference	Cook, Julia A; Sinha, Mithun; Lester, Mary; Fisher, Carla S; Sen, Chandan K; Hassanein, Aladdin H; Immediate Lymphatic Reconstruction to Prevent Breast Cancer-Related Lymphoedema: A Systematic Review.; Advances in wound care; 2022; vol. 11 (no. 7); 382-391

Study Characteristics

Study design	Systematic review
Study details	Dates searched The systematic review included studies published up to February 16, 2021. Databases searched PubMed Central EBSCO Ovid MEDLINE Sources of funding This manuscript was not specifically supported by any funding sources. Author AHH is supported by grants from the Department of Defense DOD-W81XWH2110135, American Association of Plastic Surgeons, and the Plastic Surgery Foundation.
Inclusion criteria	Original studies describing incidence of lymphoedema after ILR with ALND for breast cancer Human adult studies English language

Exclusion criteria	Delayed lymphatic reconstruction non-breast cancer diagnoses Lymphatic reconstruction for indications other than ALND Lack of defined criteria for lymphoedema diagnosis No follow-up data Duplicate studies, reviews, abstracts, case reports, series <3 patients, commentaries, letters, editorials
Intervention(s)	Immediate lymphatic reconstruction (ILR) performed concurrently with ALND Comparator: ALND without ILR due to inability to find lymphatics, lack of adequate vein, or profound axillary disease.
Outcome(s)	Incidence and severity of lymphoedema, measured by arm circumference, volumetry, bioimpedance, perometry, lymphoscintigraphy and clinical assessment.
Number of studies included in the systematic review	5, Boccardo, 2014; Cook, 2020; Feldman, 2015; Shaffer, 2020; Johnson, 2021
Studies from the systematic review that are relevant for use in the current review	Boccardo, 2014; Cook, 2020; Feldman, 2015; Shaffer, 2020; Johnson, 2021

Study arms

Immediate lymphatic reconstruction (ILR) performed concurrently with ALND (N = 133)

ALND only (N = 23)

Critical appraisal - ROBIS checklist

Section	Question	Answer
Overall study ratings	Overall risk of bias	Moderate *(the observational nature of included studies and some limitations in the review process (e.g. limited search for unpublished studies, unclear if duplicate bias assessment was performed) Some limitations due to the lack of randomised trials, incomplete reporting of certain participant and intervention details, and the relatively small evidence base.)*
Overall study ratings	Applicability as a source of data	Fully applicable

Markkula, 2019

Bibliographic Reference	Markkula, Silja P; Leung, Nelson; Allen, Victoria B; Furniss, Dominic; Surgical interventions for the prevention or treatment of lymphoedema after breast cancer treatment.; The Cochrane database of systematic reviews; 2019; vol. 2; cd011433

Study Characteristics

Study design	Systematic review
Study details	Dates searched Initial search in June 2020 Updated search in February 2021 Databases searched Cochrane Breast Cancer Group's Specialised Register Cochrane Central Register of Controlled Trials (CENTRAL) MEDLINE Embase CINAHL WHO ICTRP ClinicalTrials.gov Sources of funding None reported
Inclusion criteria	RCTs comparing a surgical intervention to standard care, placebo, or another surgical intervention Participants who had treatment for breast cancer Studies with predefined criteria for diagnosing/assessing lymphoedema No date or language restrictions
Exclusion criteria	None specified
Intervention(s)	Comparator: Usual Care Lymphaticovenular anastomosis
Outcome(s)	Primary: Development of lymphoedema (prevention), reduction of lymphoedema (treatment) Secondary: Patient-reported outcomes, discontinuation of further interventions, surgical and long-term complications
Number of studies included in the systematic review	Boccardo 2009 Boccardo 2011 Dionyssiou 2016
Studies from the systematic review that are relevant for use in the current review	Boccardo 2009 Boccardo 2011
Studies from the	Dionyssiou 2016

systematic review that are not relevant for use in the current review	

Study arms

Lymphaticovenular anastomosis (LVA) (N = 48)

Physical therapy + compression garments alone (N = 47)

Critical appraisal - ROBIS checklist

Section	Question	Answer
Overall study ratings	Overall risk of bias	Low
Overall study ratings	Applicability as a source of data	Partially applicable *(included a study for treatment of lymphoedema)*

Rafn, 2022

Bibliographic Reference	Rafn, Bolette S; Christensen, Jan; Larsen, Anders; Bloomquist, Kira; Prospective Surveillance for Breast Cancer-Related Arm Lymphoedema: A Systematic Review and Meta-Analysis.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2022; vol. 40 (no. 9); 1009-1026

Study Characteristics

Study design	Systematic review
Study details	Dates searched Initial search in June 2020 Updated search in February 2021 Databases searched MEDLINE EMBASE CINAHL Cochrane Central Register of Controlled Trials (CENTRAL) Web of Science (Sci-EXPANDED/SSCI) ClinicalTrials.gov ISRCTN Registry (United Kingdom Sources of funding CASTLE Grant No. R192-A11590-17-S59 PROTECT Grant No. 129405
Inclusion criteria	RCTs with a comparator group that received no intervention, another surveillance programmes, or usual care Observational cohort and case-control studies Participants who had received any type of surgery for any

	type of cancer Prospective surveillance programmess to identify lymphoedema that involved a minimum of three planned post-surgery assessments and early management if lymphoedema was identified Reported incidence, prevalence, or severity of lymphoedema after intervention No date or language restrictions
Exclusion criteria	None specified
Intervention(s)	Intervention: Prospective surveillance with early management Comparator: Usual Care
Outcome(s)	Incidence/severity of chronic lymphoedema Health-related quality of life
Number of studies included in the systematic review	23
Studies from the systematic review that are relevant for use in the current review	Box, 2002,Ridner, 2019,Rafn, 2018,Boccardo, 2009
Studies from the systematic review that are not relevant for use in the current review	Blaney, 2015 Soran, 2014 Bundred, 2020 Kaufman, 2017 Whitworth, 2018 Whitworth, 2018 Erdogan, 2015 Yang, 2016 Kilgore, 2018 Johansson, 2010 Stout Gergich, 2008 Cornish, 2000 Berlin, 1999 Akita, 2016 Fu, 2014 Polat, 2017 Laidley, 2016 Darragh, 2018

Study arms

early management (N = 365)

Lymphoedema education Early intervention with monitoring/self-measurements Worn prevention (compression garments) Exercise/movement

usual care (N = 302)

RCTs with a comparator group that received no intervention, another surveillance programmes, or usual care

Critical appraisal - ROBIS checklist

Section	Question	Answer
Overall study ratings	Overall risk of bias	Moderate *(Selection bias: studies did not adequately describe population, only 4 had <20% loss to follow-upConfounding: 10 studies did not adjust for confounders)*
Overall study ratings	Applicability as a source of data	Partially applicable *(only the randomised clinical trials are relevant, the observational studies were either one arm studies or didn't report participant numbers and included other interventions.)*

Stuiver Martijn M, 2015

Bibliographic Reference	Stuiver Martijn M, ten Tusscher Marieke R, Agasi-Idenburg Carla S, Lucas Cees, Aaronson Neil K, Bossuyt Patrick MM; Conservative interventions for preventing clinically detectable upper-limb lymphoedema in patients who are at risk of developing lymphoedema after breast cancer therapy; Cochrane Database of Systematic Reviews: Reviews; 2015; vol. issue2

Study Characteristics

Study design	Systematic review
Study details	Dates searched The review searched for studies published up to May 2013. Databases searched Cochrane Breast Cancer Group's Specialised Register MEDLINE EMBASE CINAHL PEDro PsycINFO CENTRAL WHO ICTRP Sources of funding None reported.
Inclusion criteria	RCTs comparing a conservative intervention to usual care, placebo, or another conservative intervention Participants at risk of developing lymphoedema after treatment for breast cancer Studies that reported lymphoedema as the primary outcome using a predefined objective assessment
Exclusion criteria	None specified
Intervention(s)	Comparator: Usual Care

	Manual lymph drainage (MLD) Exercise (early vs delayed shoulder mobilization, progressive resistance exercise) Compression therapy (in combination with MLD) Comprehensive programmess (education, monitoring, exercise, early intervention)
Outcome(s)	Primary: Incidence of lymphoedema Secondary: Infection, range of motion, pain, health-related quality of life, level of functioning in daily activities, psychosocial morbidity, adverse event
Number of studies included in the systematic review	10 RCTs
Studies from the systematic review that are relevant for use in the current review	Bendz 2002 Box 2002 Castro-Sanchez 2011 Cinar 2008 Devoogdt 2011 Sagen 2009 Schmitz 2010 Todd 2008 Torres 2010 Zimmermann 2012
Studies from the systematic review that are not relevant for use in the current review	0

Study arms

conservative non-pharmacological interventions (N = 595)
Manual lymphatic drainage Exercise and movement Compression therapy

no intervention, usual care, or other conservative interventions (N = 601)

Critical appraisal - ROBIS checklist

Section	Question	Answer
Overall study ratings	Overall risk of bias	Moderate *(lack of blinding, unclear randomization and allocation concealment methods, attrition (in early vs delayed exercise studies),)*
Overall study ratings	Applicability as a source of data	Fully applicable

Randomised controlled trials

Ammitzboll, 2019

Bibliographic Reference	Ammitzboll, Gunn; Johansen, Christoffer; Lanng, Charlotte; Andersen, Elisabeth Wreford; Kroman, Niels; Zerahn, Bo; Hyldegaard, Ole; Wittenkamp, Merete Celano; Dalton, Susanne Oksbjerg; Progressive resistance training to prevent arm lymphoedema in the first year after breast cancer surgery: Results of a randomised controlled trial.; Cancer; 2019; vol. 125 (no. 10); 1683-1692

Study details

Study type	Randomised controlled trial (RCT)
Study location	East Denmark (covering 3 hospitals)
Study setting	Hospital-based
Study dates	August 2015 - January 2018
Sources of funding	Knæk Cancer (2014), TrygFonden (grant to G. Ammitzbøll), Juzo provided compression sleeves
Intervention(s)	Progressive resistance training (PRT) exercise: Supervised group sessions 2x/week for 20 weeks Once weekly self-administered for 30 weeks Exercises for major upper/lower body muscle groups
Comparator	Usual care control group with no exercise intervention
Inclusion criteria	Women aged 18-75 years Primary unilateral breast cancer Underwent axillary lymph node dissection No distant metastases No previous axillary surgery on contralateral side Able to participate in group exercise
Exclusion criteria	Previous history of arm lymphoedema (postsurgical swelling not excluded)
Outcome measures	Arm lymphoedema (interlimb volume difference by water displacement) Patient-reported symptoms (swelling, heaviness, tightness) Clinical examination for lymphoedema criteria Limb strength Range of motion Interlimb soft tissue mass difference (DXA)
Number of participants	Baseline: 158 (82 intervention, 76 control) 12 month follow-up: 158
Duration of follow-up	Not reported
Loss to follow-up	12 months
Methods of analysis	Intention-to-treat using t-tests and regression models Multiple imputation for missing data

Study arms

Progressive resistance training (PRT) exercise (N = 82)

Supervised group sessions 2x/week for 20 weeks Once weekly self-administered for 30 weeks
Exercises for major upper/lower body muscle groups

Usual care control group (N = 76)
Usual care control group with no exercise intervention

Characteristics

Study-level characteristics

Characteristic	Study (N = 158)
% Female Sample size	n = 158 ; % = 100
Mean age (SD) Custom value	Intervention: 53 (10) years Control: 52 (10) years
Location of lymphoedema Custom value	Upper limb/arm lymphoedema

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Bland, 2019

Bibliographic Reference	Bland, Keiva L; Kosir, Mary A; Improving the quality of life in breast cancer survivors at risk for lymphoedema.; Surgery; 2019; vol. 166 (no. 4); 686-690

Study details

Study type	Randomised controlled trial (RCT)
Study location	Detroit, Michigan, USA
Study setting	Karmanos Cancer Institute, Wayne State University
Study dates	Not reported
Sources of funding	Department of Defense Breast Cancer Research Programmes-Idea Grant Department of Surgery, Wayne State University
Intervention(s)	Structured 45-minute preoperative lymphoedema education class by expert plus individual refresher at 6 months
Comparator	Standard preoperative surgical counseling and educational booklet
Inclusion criteria	Breast cancer patients undergoing surgery
Exclusion criteria	Previous breast cancer treatment Stage IV breast cancer Existing upper extremity lymphoedema Surgery not including axillary surgery Postoperative radiation planned
Outcome measures	reported outcomes: Quality of life (FACT-B) Lymphoedema incidence and severity (limb volume measurements)

Number of participants	119
Duration of follow-up	Up to 3 years
Loss to follow-up	90 of 209 consented patients (43%)
Methods of analysis	Univariate and multivariate analysis

Study arms

preoperative lymphoedema education class (N = 64)
Structured 45-minute preoperative lymphoedema education class by expert Individual refresher session at 6 months

Standard preoperative surgical counselling and educational booklet (N = 55)

Characteristics

Study-level characteristics

Characteristic	Study (N = 119)
% Female Sample size	n = 119 ; % = 100
Mean age (SD) Custom value	Intervention: 52.64 years (SD not provided) Control: 52.76 years (SD not provided)
Location of lymphoedema Custom value	Upper extremities

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate (*The lack of blinding and incomplete adherence raises some concerns for bias. There was high attrition rate (43%), which raises some concerns about outcome data.)*
Overall bias and Directness	Overall Directness	Directly applicable

Bloomquist, 2019

Bibliographic Reference	Bloomquist, Kira; Adamsen, Lis; Hayes, Sandra C; Lillelund, Christian; Andersen, Christina; Christensen, Karl Bang; Oturai, Peter; Ejlertsen, Bent; Tuxen, Malgorzata K; Moller, Tom; Heavy-load resistance exercise during chemotherapy in physically inactive breast cancer survivors at risk for lymphoedema: a randomised trial.; Acta oncologica (Stockholm, Sweden); 2019; vol. 58 (no. 12); 1667-1675

Study details

Study type	Randomised controlled trial (RCT)
Study location	Copenhagen, Denmark

Study setting	Hospital (University Hospitals Centre for Health Research, Copenhagen University Hospital, Rigshospitalet)
Study dates	2014 to July 2016
Sources of funding	Danish Cancer Society, Novo Nordic Foundation, Trygfonden Denmark
Intervention(s)	HIGH: 12-week supervised, group-based multimodal exercise including heavy-load resistance training (80-90% 1RM, 3 sets of 5-8 reps)
Comparator	LOW: Home-based walking programmes with pedometer and consultations
Inclusion criteria	Women receiving adjuvant chemotherapy for stage I-III breast cancer WHO performance status 0-1 Physically inactive (<150min moderate or 2x20min vigorous activity/week) pre-diagnosis
Exclusion criteria	Not reported
Outcome measures	Lymphoedema severity (inter-arm volume difference L-Dex, self-reported swelling and symptoms) upper-extremity strength quality of life (EORTC QLQ-BR23)
Number of participants	153 total (HIGH: 75, LOW: 78)
Duration of follow-up	39 weeks
Loss to follow-up	15% at 12 weeks, 21% at 39 weeks
Methods of analysis	Linear mixed models to evaluate equivalence for lymphoedema outcomes, superiority analysis for strength and QOL

Study arms

HIGH (resistance training) (N = 75)
12-week supervised, group-based multimodal exercise including heavy-load resistance training (80-90% 1RM, 3 sets of 5-8 reps)

LOW: Home-based walking programmes (N = 78)
LOW: Home-based walking programmes with pedometer and consultations

Characteristics

Study-level characteristics

Characteristic	Study (N = 153)
% Female Sample size	n = 153 ; % = 100
Mean age (SD) Mean (SD)	51.7 (9.4)
Location of lymphoedema Custom value	Upper limb (including fingers, hand, forearm, upper arm), chest wall, breast
Severity of lymphoedema Custom value	Participants were at risk of developing lymphoedema. 5 participants (3.3%) reported receiving treatme

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(The lack of blinding and incomplete adherence raises some concerns for bias. However, the use of objective measures, blinded outcome assessors, intention-to-treat analysis, and consistency with per-protocol results suggests the risk of bias was not high.)*
Overall bias and Directness	Overall Directness	Directly applicable

Bloomquist, 2021

Bibliographic Reference	Bloomquist, Kira; Krustrup, Peter; Fristrup, Bjorn; Sorensen, Victor; Helge, Jorn Wulff; Helge, Eva Wulff; Soelberg Vadstrup, Eva; Rorth, Mikael; Hayes, Sandra C; Uth, Jacob; Effects of football fitness training on lymphoedema and upper-extremity function in women after treatment for breast cancer: a randomised trial.; Acta oncologica (Stockholm, Sweden); 2021; vol. 60 (no. 3); 392-400

Study details

Study type	Randomised controlled trial (RCT)
Study location	Copenhagen, Denmark
Study setting	University hospital
Study dates	Recruitment from March 2017 to October 2018
Sources of funding	The Preben & Anna Simonsen Foundation and The Lundbeck Foundation
Intervention(s)	Football Fitness group (FFG) participated in supervised group football training twice weekly for 52 weeks.
Comparator	Control group (CON) with no intervention.
Inclusion criteria	Women aged 18-75 years Received surgery for stage I-III breast cancer Completed (neo)adjuvant chemotherapy and/or radiotherapy within 5 years WHO performance status 0-1 Could read and understand Danish
Exclusion criteria	Osteoporosis Serious cardiac morbidity Poorly controlled hypertension Cardiac arrhythmia or pacemaker Ongoing anticoagulant therapy Planned chemotherapy or radiotherapy during intervention period
Outcome measures	Lymphoedema: Inter-arm volume difference from DXA, extracellular fluid (L-Dex) from bioimpedance Patient-reported breast/arm symptoms (EORTC QLQ-BR23) Upper extremity function (DASH)
Number of participants	Baseline: FFG 46, CON 22 6 months: FFG 35, CON 18 12 months: FFG 33, CON 16

Duration of follow-up	12 months
Loss to follow-up	FFG: 13/46 (28%) at 12 months CON: 6/22 (27%) at 12 months
Methods of analysis	Linear mixed models

Study arms

Football Fitness group (FFG) (N = 46)
participated in supervised group football training twice weekly for 52 weeks.

Control group (N = 22)
Control group (CON) with no intervention.

Characteristics

Study-level characteristics

Characteristic	Study (N = 68)
Mean age (SD) Custom value	FFG: 47.4 (9.4) years CON: 50.0 (9.3) years
Location of lymphoedema Custom value	Upper extremity/arm

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(suboptimal adherence to the intervention and risk of attrition bias from missing data, which raise some concerns about the risk of bias.)*
Overall bias and Directness	Overall Directness	Directly applicable

Coriddi, 2023

Bibliographic Reference	Coriddi, Michelle; Dayan, Joseph; Bloomfield, Emily; McGrath, Leslie; Diwan, Richard; Monge, Jasmine; Gutierrez, Julia; Brown, Stav; Boe, Lillian; Mehrara, Babak; Efficacy of Immediate Lymphatic Reconstruction to Decrease Incidence of Breast Cancer-related Lymphoedema: Preliminary Results of Randomised Controlled Trial.; Annals of surgery; 2023; vol. 278 (no. 4); 630-637

Study details

Study location	Memorial Sloan Kettering Cancer Center, New York, NY, USA
Study setting	Tertiary cancer center
Study dates	January 2020 to March 2023
Sources of funding	NIH grants, Memorial Sloan Kettering Cancer Center support grant
Intervention(s)	Immediate lymphatic reconstruction (ILR) group - Underwent microsurgical lymphaticovenous bypass to connect transected arm lymphatics to a nearby vein during axillary lymph node dissection

Comparator	Control group - No lymphatic reconstruction, transected lymphatics were ligated
Exclusion criteria	Men with breast cancer Recurrent disease in the axilla Bilateral axillary surgery Sentinel lymph node biopsy only without axillary dissection
Outcome measures	Incidence of breast cancer-related lymphoedema (primary) Bioimpedance spectroscopy Quality of life (LYMQOL, ULL-27) Compression garment usage
Number of participants	12 months: ILR 50, Control 49 18 months: ILR 39, Control 31 24 months: ILR 21, Control 19
Duration of follow-up	24 months
Loss to follow-up	Up to 12 months: ILR 3/72 (4%), Control 3/72 (4%) Up to 24 months: numbers not provided
Methods of analysis	Cumulative incidence for lymphoedema T-tests, chi-square tests, Fisher's exact test for secondary outcomes

Study arms

immediate lymphatic reconstruction (ILR) (N = 72)
Immediate lymphatic reconstruction (ILR) group underwent microsurgical lymphaticovenous bypass during axillary lymph node dissection to connect transected arm lymphatics to a nearby vein.

no lymphatic reconstruction (control group) (N = 72)
Control group - No lymphatic reconstruction, transected lymphatics were ligated

Characteristics

Study-level characteristics

Characteristic	Study (N = 144)
% Female Sample size	n = 144 ; % = 100
Mean age (SD) Custom value	ILR group: 48.5 (11.3) years Control group: 46.3 (11.4) years
Location of lymphoedema Custom value	Upper extremity/arm lymphoedema after axillary surgery Copy

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(The main limitation is the potential for attrition bias affecting the longer 18 and 24-month follow-up results)*
Overall bias and Directness	Overall Directness	Directly applicable

Donmez, 2017

NG101 Early, locally advanced and advanced breast cancer: evidence reviews for the non-pharmalogical prevention of lymphoedema DRAFT FOR CONSULTATION SEPTEMBER 2024

Bibliographic Reference	Donmez, Ayse Arikan; Kapucu, Sevgisun; The effectiveness of a clinical and home-based physical activity programmes and simple lymphatic drainage in the prevention of breast cancer-related lymphoedema: A prospective randomised controlled study.; European journal of oncology nursing : the official journal of European Oncology Nursing Society; 2017; vol. 31; 12-21

Study details

Study type	Randomised controlled trial (RCT)
Study location	Ankara, Turkey
Study setting	University hospital
Study dates	December 2014 - January 2016
Sources of funding	Hacettepe University Scientific Research Projects Coordination Unit
Intervention(s)	Clinical and home-based programmes: Simple lymphatic drainage (SLD) by investigators and taught to patients, 40 min twice weekly for 6 weeks Physical activity exercises in 2 stages (breathing, ball squeezing, aerobic, stretching)
Comparator	Control group received usual care with no intervention
Inclusion criteria	Diagnosed with breast cancer undergoing surgery Age > 18 years No mental/communication problems BMI ≤ 30 kg/m2 Underwent axillary lymph node dissection No prior cancer or lymphoedema
Exclusion criteria	Underwent total mastectomy or bilateral lymph node dissection Using other complementary/alternative therapies Surgical area infection Lymphangitis or deep venous obstruction
Outcome measures	Upper extremity circumference measurements Lymphoedema symptom severity scores (pain, heaviness, tension, numbness) DASH scores for upper extremity function
Number of participants	Baseline: 52 (25 intervention, 27 control) Follow-up: 52
Duration of follow-up	6 weeks
Loss to follow-up	Not reported
Methods of analysis	Non-parametric tests (Mann-Whitney U, Kruskal-Wallis) General linear models with repeated measures

Study arms

Clinical and home-based programmes: (N = 25)
Simple lymphatic drainage (SLD) by investigators and taught to patients, 40 min twice weekly for 6 weeks Physical activity exercises in 2 stages (breathing, ball squeezing, aerobic, stretching)

Control group (N = 27)
Control group received usual care with no intervention

Characteristics

Study-level characteristics

Characteristic	Study (N = 52)
% Female Sample size	n = 52 ; % = 100
Mean age (SD) Custom value	Intervention: 48.6 (8.3) years Control: 49.5 (11.9) years
Location of lymphoedema Custom value	Upper extremity/arm lymphoedema

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(lack of details on the randomization sequence generation and uncertainties about adherence to the home-based portions of the intervention.)*
Overall bias and Directness	Overall Directness	Directly applicable

Zang , 2016

Bibliographic Reference Fan, A.; Yan, J.; He, Y.; Zhang, H.; Zhong, Q.; Liu, F.; Luo, Q.; Zhang, L.; Tang, H.; Xin, M.; Combining manual lymph drainage with physical exercise after modified radical mastectomy effectively prevents upper limb lymphoedema; Lymphatic Research and Biology; 2016; vol. 14 (no. 2); 104-108

Study details

Study type	Randomised controlled trial (RCT)
Study location	Guangzhou, China
Study setting	Sun Yat-Sen University Cancer Center,
Study dates	May 2012 to October 2014
Sources of funding	National Natural Science Foundation of China, Sun Yat-Sen Excellent Young Teacher Programmes, and CMB Excellent Young Teacher Programmes.
Intervention(s)	Self-manual lymph drainage (MLD) performed 3 times per day for 30 minutes, in addition to physical exercise.
Comparator	Physical exercise only (control group)
Inclusion criteria	Women with breast cancer scheduled for modified radical mastectomy.
Exclusion criteria	Not reported.
Outcome measures	Severity of lymphoedema (measured by upper limb circumference) Scar formation Shoulder abduction
Number of participants	1000

Duration of follow-up	12 months
Loss to follow-up	None reported
Methods of analysis	T-test, Chi-square test, or Fisher's exact test for between-group comparisons

Study arms

MLD group (N = 500)
Self-manual lymph drainage (MLD) performed 3 times per day for 30 minutes, in addition to physical exercise.

Physical exercise only (control group) (N = 500)
Physical exercise only (control group)

Characteristics

Study-level characteristics

Characteristic	Study (N = 1000)
% Female Sample size	n = 1000 ; % = 100

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Hansdorfer-Korzon, 2016

Bibliographic Reference	Hansdorfer-Korzon, R.; Teodorczyk, J.; Gruszecka, A.; Wydra, J.; Lass, P.; Relevance of low-pressure compression corsets in physiotherapeutic treatment of patients after mastectomy and lymphadenectomy; Patient Preference and Adherence; 2016; vol. 10; 1177-1187

Study details

Study type	Randomised controlled trial (RCT)
Study location	Gdansk, Poland
Study setting	University hospital
Study dates	Not reported
Sources of funding	Not reported
Intervention(s)	Low-pressure class I compression corsets worn around the chest/trunk area on the operated side, started 1 month after surgery.
Inclusion criteria	Women undergoing mastectomy and axillary lymph node dissection for breast cancer
Exclusion criteria	Not reported

Outcome measures	Severity of lymphoedema (subcutaneous tissue thickness ratio between operated and non-operated chest wall sides measured by ultrasound) Pain (assessed by visual analog scale)
Number of participants	Baseline: 50 Completed study: 37 (19 intervention, 18 control)
Duration of follow-up	7 months
Loss to follow-up	13 participants excluded during follow-up
Additional comments	Non-parametric tests (Mann-Whitney U, Friedman ANOVA)

Study arms

Low-pressure class I compression corsets (N = 19)
Low-pressure class I compression corsets worn around the chest/trunk area on the operated side, started 1 month after surgery.

Control (N = 18)
Control group received no physiotherapeutic treatment

Characteristics

Study-level characteristics

Characteristic	Study (N = 37)
% Female Sample size	n = 37 ; % = 100
Mean age (SD) Custom value	Intervention: 62.37 (12.94) years Control: 62.50 (11.98) years
Location of lymphoedema Custom value	Trunk/chest wall lymphoedema

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(The main limitations were the lack of details about the randomization method, potential deviations from adherence to wearing compression corsets, and relatively high attrition.)*
Overall bias and Directness	Overall Directness	Directly applicable

Nadal Castells, 2021

Bibliographic Reference	Nadal Castells, Maria J; Ramirez Mirabal, Eliot; Cuartero Archs, Jordi; Perrot Gonzalez, Jean C; Beranuy Rodriguez, Marta; Pintor Ojeda, Alberto; Bascunana Ambros, Helena; Effectiveness of Lymphoedema Prevention Programmess With Compression Garment After Lymphatic Node Dissection in Breast Cancer: A Randomised Controlled Clinical Trial.; Frontiers in rehabilitation sciences; 2021; vol. 2; 727256

Study details

NG101 Early, locally advanced and advanced breast cancer: evidence reviews for the non-pharmalogical prevention of lymphoedema DRAFT FOR CONSULTATION SEPTEMBER 2024

Study type	Randomised controlled trial (RCT)
Study location	Barcelona, Spain
Study setting	Tertiary hospital (Hospital de la Santa Creu i Sant Pau)
Study dates	March 2011 - April 2013 (recruitment)
Sources of funding	Not reported
Intervention(s)	1-hour educational session on lymphoedema + 12-week exercise programmes+ prescribed to use compression garments for ≥8 hours/day for 3 months, then 2 hours/day
Comparator	1-hour educational session on lymphoedema + 12-week exercise programmes
Inclusion criteria	Age 18-85 years Underwent axillary lymph node dissection for primary breast cancer Accepted study conditions
Exclusion criteria	Recurrent or metastatic cancer Open wounds or skin integrity issues Dependency or cognitive impairment Arterial insufficiency, deep vein thrombosis, heart failure Severe neuropathy Existing lymphoedema
Outcome measures	Incidence of lymphoedema (primary outcome)
Number of participants	Baseline: 70 (35 in each arm) Completed 2-year follow-up: 65 (32 conventional, 33 experimental)
Duration of follow-up	2 years
Loss to follow-up	5 out of 70 (7.1%) after baseline
Methods of analysis	Chi-square test Student's t-test Mann-Whitney U test ANOVA of repeated measures

Study arms

compression garments, educational session on lymphoedema + 12-week exercise programmes (N = 35)
1-hour educational session on lymphoedema + 12-week exercise programmes prescribed to use compression garments for ≥8 hours/day for 3 months, then 2 hours/day

1-hour educational session on lymphoedema + 12-week exercise programmes (N = 35)
1-hour educational session on lymphoedema + 12-week exercise programmes

Characteristics

Study-level characteristics

Characteristic	Study (N = 70)
% Female Sample size	n = 70 ; % = 100
Mean age (SD) Custom value	Conventional: 58.86 (12.7) years Experimental: 56.11 (12.7) years

Characteristic	Study (N = 70)
Location of lymphoedema Custom value	Upper limb lymphoedema

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Ochalek, 2017

Bibliographic Reference Ochalek, Katarzyna; Gradalski, Tomasz; Partsch, Hugo; Preventing Early Postoperative Arm Swelling and Lymphoedema Manifestation by Compression Sleeves After Axillary Lymph Node Interventions in Breast Cancer Patients: A Randomised Controlled Trial.; Journal of pain and symptom management; 2017; vol. 54 (no. 3); 346-354

Study details

Study type	Randomised controlled trial (RCT)
Study location	Krakow, Poland
Study setting	Hospice setting (St. Lazarus Hospice)
Study dates	November 2014 - May 2015
Sources of funding	University of Physical Education grant
Intervention(s)	Compression group received circular knit arm compression sleeves (15-21 mmHg) for daily wear, along with a standardised exercise programmes
Comparator	Control group received no compression sleeves, but the same standardised exercise programmes
Inclusion criteria	Women undergoing breast cancer surgery Axillary lymph node dissection or sentinel lymph node biopsy
Exclusion criteria	Symptoms/signs of infection in affected limb Heart, renal, liver or severe pulmonary insufficiency Vein thrombosis Preoperative lymphoedema ≥10% volume difference History of bilateral lymph node dissection
Outcome measures	Incidence of lymphoedema (≥10% increase in arm volume) Health-related quality of life (EORTC QLQ-C30, QLQ-BR23)
Number of participants	Baseline: 45 (23 compression, 22 control) Completed 12-month follow-up: 45
Duration of follow-up	12 months
Loss to follow-up	9 participants resigned at start (1 compression, 8 control)
Methods of analysis	T-tests Wilcoxon tests Chi-square tests

	Linear regression

Study arms

Compression group (N = 23)
Compression group received circular knit arm compression sleeves (15-21 mmHg) for daily wear, along with a standardised exercise programmes

Control group (N = 22)
Control group received no compression sleeves, but the same standardised exercise programmes

Characteristics

Study-level characteristics

Characteristic	Study (N = 45)
% Female Sample size	n = 45 ; % = 100
Mean age (SD) Custom value	Compression group: 52.9 (9.3) years Control group: 64.0 (8.6) years
Location of lymphoedema Custom value	Upper limb/arm lymphoedema

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Ochalek, 2019

Bibliographic Reference	Ochalek, Katarzyna; Partsch, Hugo; Gradalski, Tomasz; Szygula, Zbigniew; Do Compression Sleeves Reduce the Incidence of Arm Lymphoedema and Improve Quality of Life? Two-Year Results from a Prospective Randomised Trial in Breast Cancer Survivors.; Lymphatic research and biology; 2019; vol. 17 (no. 1); 70-77

Study details

Secondary publication of another included study- see primary study for details	Preventing Early Postoperative Arm Swelling and **Lymphoedema** Manifestation by Compression Sleeves After Axillary **Lymph** Node Interventions in **Breast Cancer** Patients: A **Randomised** Controlled Trial. MEDLINE ALL (Ovid) Journal of pain and symptom management; 2017; vol. 54 (no. 3); 346-354
Other publications associated with this study included in review	Ochalek, Katarzyna; Gradalski, Tomasz; Partsch, Hugo

Study arms

Compression group (N = 22)
Compression group received circular knit arm compression sleeves (15-21 mmHg) for daily wear, along with a standardised exercise programmes

Control group (N = 22)
Control group received no compression sleeves, but the same standardised exercise programmes

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Paramanandam, 2022

Bibliographic Reference	Paramanandam, Vincent S; Dylke, Elizabeth; Clark, Gary M; Daptardar, Anuradha A; Kulkarni, Ajeeta M; Nair, Nita S; Badwe, Rajendra A; Kilbreath, Sharon L; Prophylactic Use of Compression Sleeves Reduces the Incidence of Arm Swelling in Women at High Risk of Breast Cancer-Related Lymphoedema: A Randomised Controlled Trial.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2022; vol. 40 (no. 18); 2004-2012

Study details

Study location	Mumbai, India
Study setting	Tertiary cancer center (Tata Memorial Hospital)
Study dates	February 2018 - December 2018 (recruitment)
Sources of funding	Not reported
Intervention(s)	Compression group received two compression sleeves (20-25 mmHg) to wear ≥8 hours/day from first postoperative day until 3 months after adjuvant treatments + usual care
Comparator	Control group received usual care (education and exercises)
Inclusion criteria	Women aged ≥18 years Scheduled for unilateral breast cancer surgery Undergoing axillary lymph node dissection
Exclusion criteria	Preoperative arm swelling on bioimpedance spectroscopy (BIS) Any condition hindering compression sleeve use Unable to complete questionnaires independently
Outcome measures	Incidence of arm swelling (primary outcome) Quality of life (EORTC QLQ-C30, QLQ-BR23)
Number of participants	Compression group: 152 Control group: 149
Duration of follow-up	1 year
Loss to follow-up	Compression group: 3 (2%) Control group: 3 (2%)

Methods of analysis	Kaplan-Meier analysis Cox regression models Log-rank tests

Study arms

Compression group (N = 154)
Compression group received two compression sleeves (20-25 mmHg) to wear ≥8 hours/day from first postoperative day until 3 months after adjuvant treatments + usual care

Control group (N = 152)
Control group received usual care (education and exercises)

Characteristics

Study-level characteristics

Characteristic	Study (N = 301)
% Female Sample size	n = 301 ; % = 100
Mean age (SD) Custom value	Compression group: 46.7 (10.4) years Control group: 47.0 (11.7) years
Location of lymphoedema Custom value	Upper limb/arm lymphoedema

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Paskett, 2021

Bibliographic Reference	Paskett, Electra D; Le-Rademacher, Jennifer; Oliveri, Jill M; Liu, Heshan; Seisler, Drew K; Sloan, Jeffrey A; Armer, Jane M; Naughton, Michelle J; Hock, Karen; Schwartz, Michael; Unzeitig, Gary; Melnik, Marianne; Yee, Lisa D; Fleming, Gini F; Taylor, John R; Loprinzi, Charles; A randomised study to prevent lymphoedema in women treated for breast cancer: CALGB 70305 (Alliance).; Cancer; 2021; vol. 127 (no. 2); 291-299

Study details

Study type	Randomised controlled trial (RCT)
Study location	38 sites across the United States
Study setting	Cooperative group clinical trial setting (CALGB/Alliance)
Study dates	December 2006 - September 2013 (recruitment); follow-up until December 2015
Sources of funding	National Cancer Institute, Susan G Komen, Lance Armstrong Foundation, private donor
Intervention(s)	Education on lymphoedema etiology, symptoms, treatments and self-care+ exercise programmes with breathing, stretching, strengthening; hand weights; elastic compression sleeve; instruction video
Comparator	Education on lymphoedema etiology, symptoms, treatments and self-care

Inclusion criteria	Women aged ≥18 years Newly diagnosed with breast cancer (stage I-III) Underwent sentinel lymph node or axillary lymph node dissection No prior lymphoedema
Exclusion criteria	Undergoing bilateral mastectomy or bilateral lymph node dissection Inflammatory breast cancer Ductal/lobular carcinoma in situ
Outcome measures	Incidence of lymphoedema (primary outcome) Self-reported range of motion Adherence to compression sleeves and exercises (in LEAP group)
Number of participants	EO group: 242 LEAP group: 312 Total: 554
Duration of follow-up	18 months
Loss to follow-up	Around 15% in each group had missing data at 12 and 18 months and were considered treatment failures in the analysis.
Methods of analysis	Cochran-Mantel-Haenszel tests Logistic regression Generalized estimating equations

Study arms

LEAP group (N = 312)
Education on lymphoedema etiology, symptoms, treatments and self-care + exercise programmes with breathing, stretching, strengthening; hand weights; elastic compression sleeve; instruction video

Education Only (EO) group: (N = 242)
Education on lymphoedema etiology, symptoms, treatments and self-care

Characteristics

Study-level characteristics

Characteristic	Study (N = 554)
% Female Sample size	n = 554 ; % = 100
Mean age (SD) Custom value	EO group: 59 years LEAP group: 58 years
Location of lymphoedema Custom value	Upper limb/arm lymphoedema

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(The main potential limitations were the lack of described adherence-enhancing strategies in the LEAP group and the moderate amount of missing data for the primary outcome assessment.)*
Overall bias and Directness	Overall Directness	Directly applicable

Shi, 2023

Bibliographic Reference	Shi, Bohui; Lin, Zihan; Shi, Xiaowei; Guo, Pingli; Wang, Wen; Qi, Xin; Zhou, Can; Zhang, Huifang; Liu, Xiaona; Iv, Aili; Effects of a lymphoedema prevention programmes based on the theory of knowledge-attitude-practice on postoperative breast cancer patients: A randomised clinical trial.; Cancer medicine; 2023; vol. 12 (no. 14); 15468-15481

Study details

Study type	Randomised controlled trial (RCT)
Study location	Xi'an, Shaanxi Province, China
Study setting	tertiary public hospital
Study dates	March 2020 - November 2020 (recruitment)
Sources of funding	Key research and development project of Shaanxi Province
Intervention(s)	Education sessions, guidance on exercises/self-monitoring measures, peer sharing, printed materials, WeChat groups during perioperative period and first 3 chemotherapy cycles
Comparator	Usual care with routine perioperative education, chemotherapy side effects care
Inclusion criteria	Women aged ≥18 years Diagnosed with unilateral breast cancer stage I-III Undergoing surgery and ≥6 cycles of adjuvant chemotherapy Able to communicate
Exclusion criteria	Other cancers besides breast cancer Prior arm/neck trauma, infection or surgery Serious cardiovascular, liver or kidney diseases Preoperative arm disability or lymphoedema Thrombus in affected limb Receiving neoadjuvant chemotherapy
Outcome measures	Incidence of lymphoedema Handgrip strength Range of motion Arm disability (DASH) Quality of life (FACT-B)
Number of participants	Intervention group: 47 Control group: 50
Duration of follow-up	4 months (assessed at 9 and 18 weeks post-surgery)
Loss to follow-up	11 participants (6 control, 5 intervention)
Methods of analysis	T-tests Chi-square tests ANOVA

Study arms

lymphoedema prevention programmes (N = 52)
education sessions, guidance on exercises/self-monitoring measures, peer sharing, printed materials, WeChat groups during perioperative period and first 3 chemotherapy cycles.

Usual care (N = 56)
Usual care with routine perioperative education, chemotherapy side effects care

Characteristics

Study-level characteristics

Characteristic	Study (N = 108)
% Female Sample size	n = 108 ; % = 100
Mean age (SD) Custom value	Intervention: 49.58 (11.03) years Control: 51.02 (8.33) years
Location of lymphoedema Custom value	Upper limb/arm lymphoedema

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Temur, 2019

Bibliographic Reference	Temur, Kubra; Kapucu, Sevgisun; The effectiveness of lymphoedema self-management in the prevention of breast cancer-related lymphoedema and quality of life: A randomised controlled trial.; European journal of oncology nursing : the official journal of European Oncology Nursing Society; 2019; vol. 40; 22-35

Study details

Study type	Randomised controlled trial (RCT)
Study location	Ankara, Turkey.
Study setting	General Surgery Department of a state university hospital
Study dates	November 20, 2015 to November 20, 2016
Sources of funding	Not reported
Intervention(s)	Self-Management of Lymphoedema Programmes (SMLP): Education on lymphoedema symptoms, risk factors, prevention, skin care, arm protection, weight management, and exercise Hand squeezing exercises, active/passive arm exercises Simple lymphatic drainage massage
Comparator	Education on lymphoedema symptoms
Inclusion criteria	Patients aged between 18 and 65 Patients with a body mass index (BMI) ≤ 30 Patients who had undergone a modified radical mastectomy or breast-conserving surgery Patients who had axillary lymph node dissection (at least 2 lymph nodes removed) Willing to participate
Exclusion criteria	Patients with BMI ≥ 30 Patients with bilateral lymph node dissection Pregnant or lactating patients

	Patients with cancer other than breast cancer
Outcome measures	Severity of lymphoedema (arm circumference measurements) Adverse events Quality of life (EORTC QLQ-C30, EORTC QLQ-BR23) Arm disability (DASH questionnaire) Patient-reported symptoms
Duration of follow-up	6 months
Loss to follow-up	11 out of 72 enrolled patients (15.3%)
Methods of analysis	Mann-Whitney U test Kruskal-Wallis H test Wilcoxon test Friedman test

Study arms

Self-Management of Lymphoedema Programmes (SMLP) (N = 30)
Education on lymphoedema symptoms, risk factors, prevention, skin care, arm protection, weight management, and exercise Hand squeezing exercises, active/passive arm exercises Simple lymphatic drainage massage

Usual care (N = 31)
Education on lymphoedema symptoms

Characteristics

Study-level characteristics

Characteristic	Study (N = 72)
% Female Sample size	n = 72 ; % = 100
Mean age (SD) Custom value	Intervention 47.6 (8.96) years, Control 45.6 (9.03) years
Location of lymphoedema Custom value	Upper limb

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Thakur, 2016

Bibliographic Reference	Thakur, R.R.; Bhat, A.; Kaur, A.; Effectiveness of early physiotherapy to prevent lymphoedema after breast cancer related surgery; Indian Journal of Physiotherapy and Occupational Therapy; 2016; vol. 10 (no. 3); 96-101

Study details

Study type	Randomised controlled trial (RCT)

Study location	Not reported
Study setting	Not reported
Study dates	Not reported
Sources of funding	Not reported
Intervention(s)	Early physiotherapy programmes including: Manual lymphatic drainage Stretching exercises Progressive active and active assisted shoulder exercises Proprioceptive neuromuscular facilitation exercises This group also received an educational strategy.
Comparator	Educational strategy only (usual care)
Inclusion criteria	Age above 18 years Women who underwent unilateral breast cancer surgery with axillary lymph node dissection
Exclusion criteria	Recurrence or relapse of breast cancer Bilateral breast cancer Untreated infection, heart disease, renal disease, DVT Any other physiotherapeutic contraindications
Outcome measures	Severity of lymphoedema (measured by volumetric measurements) Quality of life (measured by a quality-of-life questionnaire)
Number of participants	20
Duration of follow-up	3 weeks, with 3 visits per week.
Loss to follow-up	None reported
Methods of analysis	Paired t-test for within-group comparisons Unpaired t-test for between-group comparisons

Study arms.

Early physiotherapy (N = 10)
Manual lymphatic drainage Stretching exercises Progressive active and active assisted shoulder exercises Proprioceptive neuromuscular facilitation exercises This group also received an educational strategy.

Usual care (educational strategy only) (N = 10)

Characteristics

Study-level characteristics.

Characteristic	Study (N = 20)
% Female Sample size	n = 20 ; % = 100
Mean age (SD) Custom value	Not reported

1 **Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

2

Appendix E – Forest plots

No meta-analyses of data were conducted therefore no forest plots were produced.

Appendix F – GRADE tables

Lymphoedema Education

Table 27:Structured training + preoperative counselling vs preoperative counselling

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	education	usual care	Relative (95% CI)	Absolute (95% CI)		
Quality of life												
Quality of life FACT-B scores ±MID 7-8 points (follow-up: mean 1 years)												
1[a]	randomised trials	serious[b]	serious[c]	not serious	serious[e]	none	64	55	-	MD **12.74 lower** (28.86 lower to 3.38 higher)	Very low	CRITICAL
Lymphoedema (incidence)												
Incidence of acute lymphoedema MID 0.8 to 1.25 (follow-up: mean 1 years)												
1[a]	randomised trials	serious[b]	serious[c]	not serious	very serious[e]	none	33/64 (51.6%)	26/55 (47.3%)	**RR 1.09** (0.76 to 1.57)	**43 more per 1,000** (from 113 fewer to 269 more)	Very low	CRITICAL
Incidence of chronic lymphoedema MID 0.8 to 1.25 (follow-up: mean 1 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	education	usual care	Relative (95% CI)	Absolute (95% CI)		
1[a]	randomised trials	serious[b]	serious[c]	not serious	very serious[e]	none	6/64 (9.4%)	7/55 (12.7%)	**RR 0.74** (0.26 to 2.06)	**33 fewer per 1,000** (from 94 fewer to 135 more)	Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio
a. Bland,2019
b. Study at moderate risk of bias. Downgraded once for risk of bias.
c. Single study. Downgraded once for inconsistency
d. 95%CI crosses MID once. Downgraded once for imprecision
e. 95%CI crosses MID twice. Downgraded twice for imprecision

1 **Table 28:Summarised preoperative education vs routine preoperative education**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	education	usual care	Relative (95% CI)	Absolute (95% CI)		
Lymphoedema (incidence)												
Incidence of lymphoedema MID 0.8 to 1.25 (follow-up: 18 weeks)												
1[a]	randomised trials	serious[b]	serious [c]	not serious	not serious	none	2/52 (3.8%)	4/56 (7.1%)	**RR 1.04** (0.95 to 1.13)	**3 more per 1,000** (from 4 fewer to 9 more)	low	CRITICAL
Lymphoedema (arm function)												
Handgrip strength ±MID -2.32 to 2.32 (follow-up: 18 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	education	usual care	Relative (95% CI)	Absolute (95% CI)		
1[a]	randomised trials	not serious	serious [c]	not serious	serious[d]	none	52	56	-	MD **3.58 higher** (1.66 higher to 5.5 higher)	Low	CRITICAL
Arm & shoulder function (DASH scores) ±MID: MD –7 to +7 points (follow-up: 18 weeks)												
1[e]	randomised trials	not serious	serious [c]	not serious	serious [d]	none	52	56	-	MD **6.42 lower** (8.51 lower to 4.33 higher)	Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio
a. Shi, 2023
b. Study at moderate risk of bias. Downgraded once for risk of bias.
c. Single study. Downgraded once for inconsistency
d. 95%CI crosses MID once. Downgraded once for imprecision

Early intervention

Table 29:Prospective surveillance vs usual care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early intervention	usual care	Relative (95% CI)	Absolute (95% CI)		
Lymphoedema (incidence)												
Incidence of chronic breast cancer-related arm lymphoedema MID 0.8 to 1.25 (follow-up: mean 12 months)												
2[a]	randomised trials	very serious[b]	not serious	not serious	serious[c]	none	NR	NR	**RR 0.31** (0.10 to 0.95)	**Not calculable**	Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Rafn,2022

b. More than 33% of studies at high risk of bias. Downgraded twice for risk of bias.

c. 95%CI crosses MID once. Downgraded once for imprecision.

Table 30:Early shoulder mobilising exercises vs delayed shoulder mobilising exercises

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early intervention	usual care	Relative (95% CI)	Absolute (95% CI)		
Lymphoedema (incidence)												
Incidence of lymphoedema MID 0.8 to 1.2 (follow-up: range 6 months to 12 months; assessed with: Volumetry/ Circumference)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early intervention	usual care	Relative (95% CI)	Absolute (95% CI)		
3[a]	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	26/186 (14.0%)	18/192 (9.4%)	**RR 1.69** (0.94 to 3.01)	**65 more per 1,000** (from 6 fewer to 188 more)	Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a Stuiver,2015

b. More than 33% of studies at high risk of bias. Downgraded twice for risk of bias.

c. 95%CI crosses MID once. Downgraded once for imprecision.

Table 31:Progressive resistance exercise vs control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early intervention	usual care	Relative (95% CI)	Absolute (95% CI)		
Lymphoedema (incidence)												
Incidence of lymphoedema MID 0.8 to 1.2 (follow-up: range 12 months to 24 months; assessed with: Volumetry)												
2[a]	randomised trials	very serious [b]	not serious	not serious	serious[c]	none	12/176 (6.8%)	21/175 (12.0%)	**RR 0.58** (0.30 to 1.13)	**50 fewer per 1,000** (from 84 fewer to 16 more)	Vert low	CRITICAL

Explanations
a. Stuiver,2015
b. More than 33% of studies at high risk of bias. Downgraded twice for risk of bias.
c. 95% CI crosses one MID. Downgraded once for imprecision.

Table 32: Early exercise vs delayed exercise

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early intervention	usual care	Relative (95% CI)	Absolute (95% CI)		
Lymphoedema (arm mobility)												
Shoulder range of motion for internal rotation (follow-up: mean 3 months)												
2[a]	randomised trials	very serious[b]	not serious	not serious	very serious [c]	none	128	134	-	MD **0.23 higher** (2.21 lower to 2.67 higher)	Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early intervention	usual care	Relative (95% CI)	Absolute (95% CI)		
Lymphoedema (arm mobility)												
Shoulder range of motion for internal rotation (follow-up: mean 3 months)												
(Early vs delayed exercise) Shoulder range of motion for internal rotation (follow-up: mean 6 months)												
2[a]	randomised trials	very serious[b]	not serious	not serious	very serious[c]	none	128	134	-	MD **2.48 higher** (0.33 lower to 5.29 higher)	Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Stuiver,2015

b. More than 33% of studies at high risk of bias. Downgraded twice for risk of bias.

c. 95% CI crosses the line of no effect and number of people in the analysis <400. Downgraded twice for imprecision

Table 33: Education + Exercise Vs Education Only

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early intervention	usual care	Relative (95% CI)	Absolute (95% CI)		
Lymphoedema (incidence and severity)												
Lymphoedema-free rates MID 0.8 to 1.25 (follow-up: mean 18 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early intervention	usual care	Relative (95% CI)	Absolute (95% CI)		
1[a]	randomised trials	not serious	serious[b]	not serious	serious[c]	none	172/315 (54.6%)	141/253 (55.7%)	**RR 0.88** (0.87 to 1.31)	**67 fewer per 1,000** (from 72 fewer to 173 more)	Low	CRITICAL
severity of lymphoedema (follow-up: mean 12 months; assessed with: as defined by changes in arm circumference at the site of greatest difference)												
1[a]	randomised trials	not serious	serious[b]	not serious	not serious	none		312	242	MD **0.04 lower** (0.97 lower to 0.88 higher)	Moderate	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Paskett,2021

b. single study, downgraded once for inconsistency

c. 95%CI crosses MID once. Downgraded once for imprecision.

Table 34:Early physiotherapy including MLD vs no early physiotherapy or physiotherapy without MLD

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early intervention	usual care	Relative (95% CI)	Absolute (95% CI)		
Lymphoedema (incidence)												
lymphoedema incidence MID 0.8 to 1.2 (follow-up: mean 12 months)												
1[a]	randomised trials	serious[g]	not serious	not serious	very serious[f]	none	18/75 (24.0%)	15/79 (19.0%)	**RR 1.26** (0.69 to 2.32)	**49 more per 1,000** (from 59 fewer to 251 more)	Very low	CRITICAL
lymphoedema incidence MID 0.8 to 1.2 (follow-up: mean 6 months)												
1[b]	randomised trials	very serious[e]	not serious	not serious	Not serious	none	0/33 (0.0%)	24/34 (70.6%)	**RR 0.02** (0.00 to 0.33)	**692 fewer per 1,000** (from 473 fewer to - -)	low	CRITICAL
incidence of lymphoedema MID 0.8 to 1.2 (follow-up: mean 8 months)												
1[c]	randomised trials	serious[g]	not serious	not serious	very serious[f]	none	1/24 (4.2%)	6/24 (25.0%)	**RR 0.17** (0.02 to 1.28)	**208 fewer per 1,000** (from 245 fewer to 70 more)	Very low	CRITICAL
Incidence of lymphoedema MID 0.8 to 1.2 (follow-up: mean 12 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early intervention	usual care	Relative (95% CI)	Absolute (95% CI)		
1[d]	randomised trials	very serious[e]	not serious	not serious	Not serious	none	4/59 (6.8%)	14/57 (24.6%)	**RR 0.28** (0.10 to 0.79)	**177 fewer per 1,000** (from 221 fewer to 52 fewer)	low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Devooght 2011 (in Stuiver 2015 SR)
b. Zimmermann 2012 (In Stuiver 2015 SR)
c. Castro-Sanchez 2011 (in Stuiver 2015 SR)
d. Torres 2010 (in Stuiver 2015 SR)
e. Study at high risk of bias. Downgraded twice for risk of bias.
f. 95%CI crosses MID twice. Downgraded twice for imprecision.
g. Study at moderate risk of bias. Downgraded once for risk of bias.

Worn preventions

Table 35:Low-Pressure Compression Corsets Vs No Physiotherapeutic Treatment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Worn prevention	usual care	Relative (95% CI)	Absolute (95% CI)		
Lymphoedema (incidence)												
Incidence of lymphoedema MID 0.8 to 1.2 (follow-up: mean 7 months)												
1[a]	randomised trials	not serious	serious [b]	not serious	not serious	none	0/19 (0.0%)	11/18 (61.1%)	**RR 0.04** (0.00 to 0.65)	**587 fewer per 1,000** (from 214 fewer to --)	Moderate	CRITICAL
Patient-reported outcomes (pain)												
Pain reduction MID 0.8 to 1.2 (follow-up: mean 7 months; assessed with: based on the Visual Analog Scale (VAS))												
1[a]	randomised trials	not serious	serious [b]	not serious	serious[c]	none	11/19 (57.9%)	6/18 (33.3%)	**RR 1.74** (0.81 to 3.70)	**247 more per 1,000** (from 63 fewer to 900 more)	Low	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a.Hansdorfer-Korzon,2016

b. Single study, downgraded once for inconsistency

c. 95%CI crosses MID once. Downgraded once for imprecision.

.

f.

Table 36:Compression garments vs conventional preventative therapy

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Worn prevention	usual care	Relative (95% CI)	Absolute (95% CI)		
Lymphoedema (incidence)												
Incidence of lymphoedema MID 0.8 to 1.2 (follow-up: mean 2 years)												
1[a]	randomised trials	not serious	serious[b]	not serious	very serious[c]	none	4/32 (12.5%)	4/33 (12.1%)	**RR 1.00** (0.26 to 3.82)	**0 fewer per 1,000** (from 90 fewer to 342 more)	Very low	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Nadal Castells 2021

b. single study, downgraded once for inconsistency

c. 95%CI crosses MID twice. Downgraded twice for imprecision.

Table 37:Compression garments vs no compression sleeves

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Worn prevention	usual care	Relative (95% CI)	Absolute (95% CI)		
Lymphoedema (incidence)												
Incidence of lymphoedema MID 0.8 to 1.25 (follow-up: mean 12 months; assessed with: mean arm volume change)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Worn prevention	usual care	Relative (95% CI)	Absolute (95% CI)		
1[a]	randomised trials	not serious	serious	not serious	very serious[b]	none	1/20 (5.0%)	6/21 (28.6%)	**RR 0.17** (0.02 to 1.33)	**237 fewer per 1,000** (from 280 fewer to 94 more)	Very low	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Ochalek 2019

b. 95%CI crosses MID twice. Downgraded twice for imprecision.

Table 38:Compression sleeves vs Education

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Worn prevention	usual care	Relative (95% CI)	Absolute (95% CI)		
Lymphoedema (incidence)												
Incidence of lymphoedema MID 0.8 to 1.25 (follow-up: mean 1 years; assessed with: based on bioimpedance spectroscopy)												
1[a]	randomised trials	not serious	serious [b]	not serious	serious[c]	none	154	152	**HR 0.61** (0.43 to 0.85)	**Not calculable**	Low	CRITICAL
Incidence of lymphoedema arm volume increase ≥10%, MID 0.8 to 1.2 (follow-up: mean 1 years; assessed with: bioimpedance spectroscopy)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Worn prevention	usual care	Relative (95% CI)	Absolute (95% CI)		
1[a]	randomised trials	not serious	serious [b]	not serious	serious[c]	none	154	152	**HR 0.56** (0.33 to 0.96)	**Not calculable**	Low	CRITICAL
Quality of life												
EORTC-QLQ-C30 Questionnaire and the Breast and Arm Symptom Scales of the BR23 Questionnaire (Global Health Decreased) MID 0.8 to 1.2 (follow-up: mean 12 months)												
1[a]	randomised trials	not serious	serious [b]	not serious	serious[c]	none	50/136 (36.8%)	64/137 (46.7%)	**RR 0.79** (0.59 to 1.05)	**98 fewer per 1,000** (from 192 fewer to 23 more)	Low	CRITICAL
EORTC-QLQ-C30 Questionnaire and the Breast and Arm Symptom Scales of the BR23 Questionnaire (Physical Functioning Decreased) MID 0.8 to 1.2 (follow-up: mean 12 months)												
1[a]	randomised trials	not serious	serious [b]	not serious	serious[c]	none	63/143 (44.1%)	52/142 (36.6%)	**RR 1.20** (0.91 to 1.60)	**73 more per 1,000** (from 33 fewer to 220 more)	Low	CRITICAL
EORTC-QLQ-C30 Questionnaire and the Breast and Arm Symptom Scales of the BR23 Questionnaire (breast symptoms increased) ±MID 0.8 to 1.2 (follow-up: mean 12 months)												
1[a]	randomised trials	not serious	serious [b]	not serious	serious[c]	none	74/142 (52.1%)	71/140 (50.7%)	**RR 1.04** (0.83 to 1.31)	**20 more per 1,000** (from 86 fewer to 157 more)	Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Worn prevention	usual care	Relative (95% CI)	Absolute (95% CI)		
EORTC-QLQ-C30 Questionnaire and the Breast and Arm Symptom Scales of the BR23 Questionnaire (arm symptoms increased) ±MID 0.8 to 1.2 (follow-up: mean 12 months)												
1[a]	randomised trials	not serious	serious [b]	not serious	serious [c]	none	98/141 (69.5%)	85/140 (60.7%)	**RR 1.14** (0.96 to 1.36)	**85 more per 1,000** (from 24 fewer to 219 more)	Low	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio
Explanations
a. Paramanandam,2022
b. single study, downgraded once for inconsistency
c. 95%CI crosses MID once. Downgraded once for imprecision.

Exercise and movement

Table 39:Progressive Resistance Training vs usual care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise	usual care	Relative (95% CI)	Absolute (95% CI)		
Lymphoedema (incidence)												
Incidence of lymphoedema (follow-up: mean 12 months; assessed with: mean change in interlimb volume difference)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise	usual care	Relative (95% CI)	Absolute (95% CI)		
1[a]	randomised trials	not serious	serious [b]	not serious	very serious[c]	none	82	76	-	MD **0.3 higher** (1.7 lower to 2.3 higher)	Very low	CRITICAL
Incidence of lymphoedema MID 0.8 to 1.25 (follow-up: mean 1 years; assessed with: Incidence of >3% increase in interlimb volume difference)												
1[a]	randomised trials	not serious	serious[b]	not serious	very serious[c]	none	82	76	**OR 1.2** (0.5 to 2.8)	**Not calculable**	Very low	CRITICAL
Incidence of clinically relevant lymphoedema MID 0.8 to 1.25 (follow-up: mean 12 months)												
1[a]	randomised trials	not serious	serious [b]	not serious	very serious[c]	none	-/82	-/76	**OR 1.1** (0.5 to 2.8)	**Not calculable**	Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Explanations

a. Ammitzbøll,2019

b. single study, downgraded once for inconsistency

c. 95% CI crosses the line of no effect and number of people in the analysis <400. Downgraded twice for imprecision d.

Table 40:Heavy-load resistance exercise vs home based walking programmes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise	usual care	Relative (95% CI)	Absolute (95% CI)		
Lymphoedema (incidence)												
Incidence of lymphoedema (follow-up: mean 39 weeks; assessed with: L-Dex score - difference in extracellular fluid)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise	usual care	Relative (95% CI)	Absolute (95% CI)		
1[a]	randomised trials	serious[b]	not serious	not serious	very serious[d]	none	41	34	-	MD **0.7 higher** (2.2 lower to 3.6 higher)	Very low	CRITICAL
Lymphoedema (volume)												
Inter-arm volume % difference (follow-up: mean 39 weeks)												
1[a]	randomised trials	serious[b]	not serious	not serious	very serious[d]	none	50	49	-	MD **1.7 lower** (7.7 lower to 4.3 higher)	Very low	CRITICAL
Patient-reported outcomes (pain)												
Pain (follow-up: mean 39 weeks)												
1[a]	randomised trials	serious[b]	not serious	not serious	not serious	none			-	MD **0.8 lower** (1.5 lower to 0.1 lower)	Moderate	CRITICAL
Quality of life												
EORTC QLQ-BR23 scores (follow-up: mean 39 weeks; assessed with: Breast symptoms)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise	usual care	Relative (95% CI)	Absolute (95% CI)		
1[a]	randomised trials	serious[b]	serious [c]	not serious	very serious[d]	none	59	55	-	MD **4 lower** (12 lower to 3 higher)	Very low	CRITICAL
EORTC QLQ-BR23 scores (follow-up: mean 39 weeks; assessed with: Arm symptoms)												
1[a]	randomised trials	serious[b]	serious [c]	not serious	very serious[d]	none	59	56	-	MD **4 lower** (12 lower to 3 higher)	Very low	CRITICAL
EORTC QLQ-BR23 scores (follow-up: mean 39 weeks; assessed with: Body Image)												
1[a]	randomised trials	serious[b]	serious [c]	not serious	very serious[d]	none	61	56	-	MD **1 higher** (6 lower to 8 higher)	Very low	CRITICAL
EORTC QLQ-BR23 (follow-up: mean 39 weeks; assessed with: Systemic therapy)												
1[a]	randomised trials	serious[b]	serious [c]	not serious	very serious[d]	none	61	57	-	MD **1 higher** (5 lower to 7 higher)	Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Explanations

a Bloomquist,2019

b. Study at moderate risk of bias. Downgraded once for risk of bias.

c. single study, downgraded once for inconsistency

d. 95% CI crosses the line of no effect and number of people in the analysis <400. Downgraded twice for imprecision

Table 41:Football Fitness Training Vs Physical Activity

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise	usual care	Relative (95% CI)	Absolute (95% CI)		
Lymphoedema (incidence and severity)												
L-Dex score ±MID -2.76 to 2.76 (follow-up: mean 12 months)												
1[a]	randomised trials	serious[b]	serious [c]	not serious	serious [d]	none	30	16	-	MD **2.5 SD lower** (5.85 lower to 0.85 higher)	Very low	CRITICAL
Inter-arm volume difference ±MID-4.4 to 4.4 (follow-up: mean 12 months)												
1[a]	randomised trials	serious[b]	serious [c]	not serious	serious[d]	none	33	15	-	MD **2 higher** (1.88 lower to 5.88 higher)	Very low	CRITICAL
Lymphoedema (arm function)												
DASH score ±MID-7 to 7 (follow-up: mean 12 months)												
1[a]	randomised trials	serious[b]	serious [c]	not serious	serious[d]	none	31	16	-	MD **3.9 higher** (0.85 lower to 8.65 higher)	Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise	usual care	Relative (95% CI)	Absolute (95% CI)		
Quality of life												
EORTC QLQ BR23 breast symptom score ±MID -7.8 to 7.8 (follow-up: mean 12 months)												
1[a]	randomised trials	serious[b]	serious [c]	not serious	serious[d]	none	31	16	-	MD **2.5 lower** (11.1 lower to 6.01 higher)	Very low	CRITICAL
EORTC QLQ BR23 arm symptom score ±MID-14.5 to 14.5 (follow-up: mean 12 months)												
1[a]	randomised trials	serious [b]	serious [c]	not serious	serious[d]	none	31	16	-	MD **6.6 higher** (3.41 lower to 16.61 higher)	Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Explanations

a. Bloomquist,2021

b. Study at moderate risk of bias. Downgraded once for risk of bias.

c. single study, downgraded once for inconsistency

d.95%CI crosses MID once. Downgraded once for imprecision.

Table 42: Physical exercise with simple lymphatic drainage vs physical exercise

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise	usual care	Relative (95% CI)	Absolute (95% CI)		
Lymphoedema (incidence)												
Incidence of Upper limb lymphoedema ±MID 0.8 to 1.25 (follow-up: mean 3 months)												
1[a]	randomised trials	not serious	serious [b]	not serious	not serious	none	6/500 (1.2%)	23/500 (4.6%)	**RR 0.26** (0.11 to 0.64)	**34 fewer per 1,000** (from 41 fewer to 17 fewer)	Moderate	CRITICAL
Incidence of Upper limb lymphoedema ±MID 0.8 to 1.25 (follow-up: mean 6 months)												
1[a]	randomised trials	not serious	serious [b]	not serious	not serious	none	9/500 (1.8%)	25/500 (5.0%)	**RR 0.36** (0.17 to 0.76)	**32 fewer per 1,000** (from 42 fewer to 12 fewer)	Moderate	CRITICAL
Incidence of Upper limb lymphoedema ±MID 0.8 to 1.25 (follow-up: mean 12 months)												
1[a]	randomised trials	not serious	serious [b]	not serious	not serious	none	8/500 (1.6%)	39/500 (7.8%)	**RR 0.21** (0.10 to 0.43)	**62 fewer per 1,000** (from 70 fewer to 44 fewer)	Moderate	CRITICAL
Scar formation												
scar formation ±MID 0.8 to 1.25 (follow-up: mean 3 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise	usual care	Relative (95% CI)	Absolute (95% CI)		
1[a]	randomised trials	not serious	serious[b]	not serious	serious [c]	none	4/500 (0.8%)	12/500 (2.4%)	**RR 0.33** (0.11 to 1.03)	**16 fewer per 1,000** (from 21 fewer to 1 more)	Low	CRITICAL
scar formation ±MID 0.8 to 1.25 (follow-up: mean 6 months)												
1[a]	randomised trials	not serious	serious [b]	not serious	not serious	none	3/500 (0.6%)	48/500 (9.6%)	**RR 0.06** (0.02 to 0.20)	**90 fewer per 1,000** (from 94 fewer to 77 fewer)	Moderate	CRITICAL
scar formation ±MID 0.8 to 1.25 (follow-up: mean 12 months												
1[a]	randomised trials	not serious	serious [b]	not serious	not serious	none	4/500 (0.8%)	75/500 (15.0%)	**RR 0.05** (0.02 to 0.14)	**143 fewer per 1,000** (from 147 fewer to 129 fewer)	Moderate	CRITICAL

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

Explanations
a. Zhang,2016
b. single study, downgraded once for inconsistency
c. 95%CI crosses MID once. Downgraded once for imprecision.

Surgery

Table 43:Lymphaticovenular anastomosis vs physical and compression therapy

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	usual care	Relative (95% CI)	Absolute (95% CI)		
Lymphoedema (incidence)												
Incidence of lymphoedema MID 0.8 to 1.25 (assessed with: Arm circumference, bioimpedance spectroscopy & Perometry, Bioimpedance spectroscopy)												
2[a]	randomised trials	very serious [b]	not serious	not serious	not serious	none	3/48 (6.3%)	15/47 (31.9%)	**RR 0.20** (0.06 to 0.63)	**255 fewer per 1,000** (from 300 fewer to 118 fewer)	Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Markkula,2019

b. More than 33% of studies at high risk of bias. Downgraded twice for risk of bias.

Table 44:Immediate Lymphatic Reconstruction after axillary lymph node dissection vs axillary lymph node dissection only

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	usual care	Relative (95% CI)	Absolute (95% CI)		
Lymphoedema (limb volume)												
Changes in Bioimpedance Values From Baseline ±MID -5.2 to 5.2 (follow-up: mean 24 months)												
1[a]	randomised trials	not serious	serious[b]	not serious	serious [c]	none	21	19	-	MD **1.2 lower** (7.57 lower to 5.17 higher)	Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Coriddi 2023

b. single study, downgraded once for inconsistency

c. 95%CI crosses MID once. Downgraded once for imprecision.

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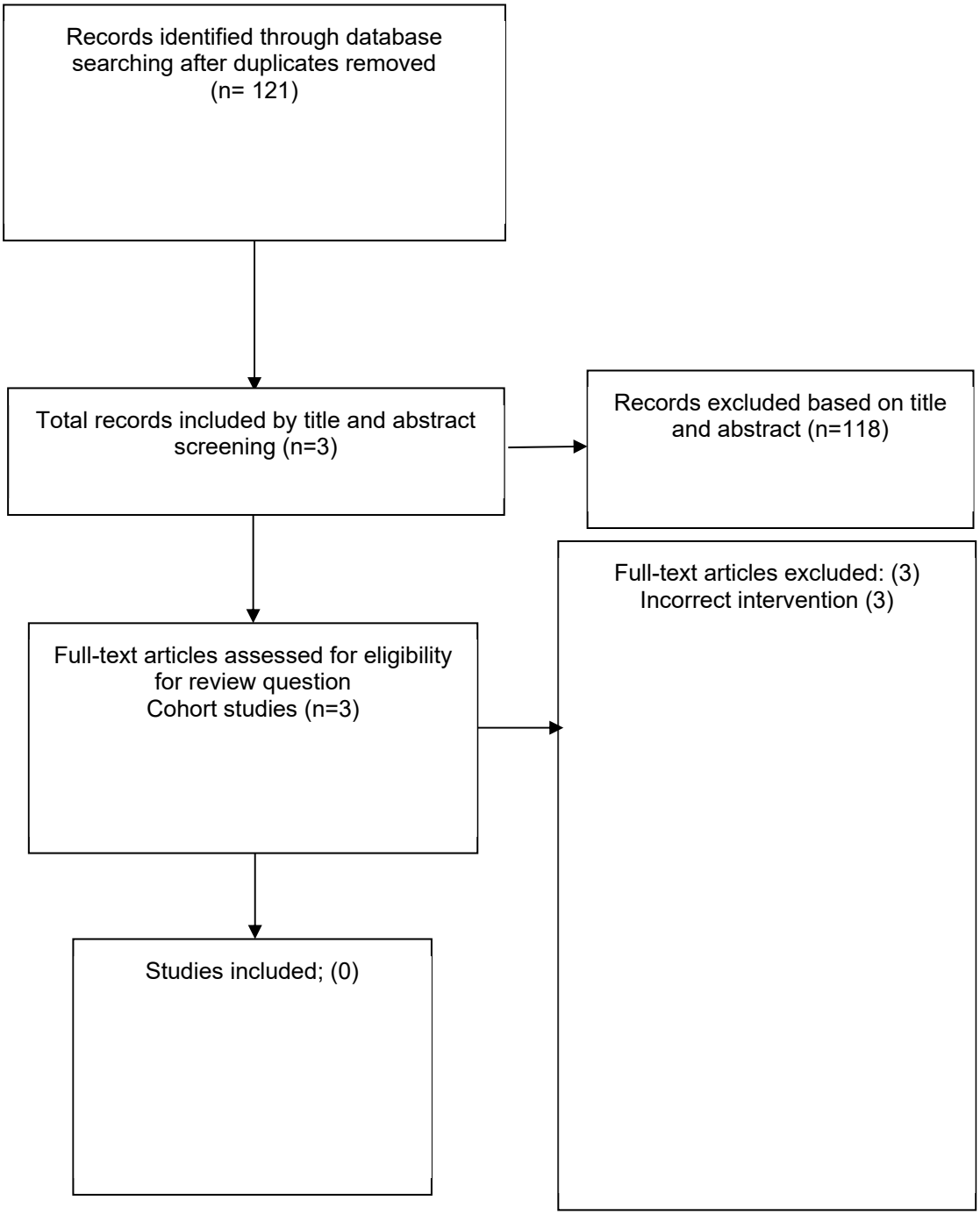
Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

None.

Appendix J – Excluded studies

Randomised controlled trials

Study	Exclusion reason
Ammitzboll, Gunn, Lanng, Charlotte, Kroman, Niels et al. (2017) Progressive strength training to prevent LYmphoedema in the first year after breast CAncer - the LYCA feasibility study. Acta oncologica (Stockholm, Sweden) 56(2): 360-366	- Comparator in study does not match that specified in protocol
Anik, Arifur R, Hasan, Kamrul, Islam, Md Manirul et al. (2023) Non-Invasive Portable Technologies for Monitoring Breast Cancer Related Lymphoedema to Facilitate Telehealth: A Scoping Review. IEEE journal of biomedical and health informatics 27(9): 4524-4535	- Not a relevant study design
Author not, found (2013) Microsurgery for primary prevention of lymphoedema following surgery for breast cancer. Lansdale, PA: HAYES, Inc	- Not a relevant study design
Bergmann, A, da Costa Leite Ferreira, M G, de Aguiar, S S et al. (2014) Physiotherapy in upper limb lymphoedema after breast cancer treatment: a randomized study. Lymphology 47(2): 82-91	- Study looks at treatment of lymphoedema
Bloomquist, Kira, Oturai, Peter, Steele, Megan L et al. (2018) Heavy-Load Lifting: Acute Response in Breast Cancer Survivors at Risk for Lymphoedema. Medicine and science in sports and exercise 50(2): 187-195	- Not a relevant study design
Bozdemir, Havva and Aygin, Dilek (2021) Effect of structured training programmesme on arm dysfunction, lymphoedema and quality of life after breast cancer surgery. JPMA. The Journal of the Pakistan Medical Association 71(5): 1413-1419	- Does not contain a population of people who do not have lymphoedema/are at risk of lymphoedema
Bruce, Julie, Mazuquin, Bruno, Mistry, Pankaj et al. (2022) Exercise to prevent shoulder problems after breast cancer surgery: the PROSPER RCT. Health technology assessment	- Study objectives do not match protocol *Study objectives are to restore the movement in the shoulder, improve strength and increase physical activity and not to evaluate the interventions that*

(Winchester, England) 26(15): 1-124	*aim to reduce the risk of lymphoedema (as per our protocol)*
Cal, Ayse; Bahar, Zuhal; Gorken, Ilknur (2020) Effects of Health Belief Model based nursing interventions offered at home visits on lymphoedema prevention in women with breast cancer: A randomised controlled trial. Journal of clinical nursing 29(1314): 2521-2534	- Not a relevant study design
Devoogdt, Nele, Geraerts, Inge, Van Kampen, Marijke et al. (2018) Manual lymph drainage may not have a preventive effect on the development of breast cancer-related lymphoedema in the long term: a randomised trial. Journal of physiotherapy 64(4): 245-254	- Study does not contain a relevant intervention
Hahamoff, Mandee, Gupta, Nachi, Munoz, Derly et al. (2019) A Lymphoedema Surveillance Programmes for Breast Cancer Patients Reveals the Promise of Surgical Prevention. The Journal of surgical research 244: 604-611	- Not a relevant study design
Kilgore, Lyndsey J, Korentager, Sabrina S, Hangge, Amanda N et al. (2018) Reducing Breast Cancer-Related Lymphoedema (BCRL) Through Prospective Surveillance Monitoring Using Bioimpedance Spectroscopy (BIS) and Patient Directed Self-Interventions. Annals of surgical oncology 25(10): 2948-2952	- Study does not contain a relevant intervention
Kim, S and Ryu, E (2022) Effects of Education Programmes for Combined Management of Lymphoedema with regard to Breast Cancer Patients with Axillary Lymph Node Dissection: a Quasi-Experimental Study. Asian oncology nursing 22(4): 214-224	- Comparator in study does not match that specified in protocol *Non-equivalent control group*
Koelmeyer, Louise A, Moloney, Emma, Boyages, John et al. (2021) Prospective surveillance model in the home for breast cancer-related lymphoedema: a feasibility study. Breast cancer research and treatment 185(2): 401-412	- Not a relevant study design *Single group intervention study*
Naughton, Michelle J, Liu, Heshan, Seisler, Drew K et al. (2021)	- Not a relevant study design

Health-related quality of life outcomes for the LEAP study-CALGB 70305 (Alliance): A lymphoedema prevention intervention trial for newly diagnosed breast cancer patients. Cancer 127(2): 300-309	
Ridner, Sheila H, Dietrich, Mary S, Boyages, John et al. (2022) A Comparison of Bioimpedance Spectroscopy or Tape Measure Triggered Compression Intervention in Chronic Breast Cancer Lymphoedema Prevention. Lymphatic research and biology 20(6): 618-628	- Study does not contain a relevant intervention
Ridner, Sheila H, Dietrich, Mary S, Cowher, Michael S et al. (2019) A Randomized Trial Evaluating Bioimpedance Spectroscopy Versus Tape Measurement for the Prevention of Lymphoedema Following Treatment for Breast Cancer: Interim Analysis. Annals of surgical oncology 26(10): 3250-3259	- Study does not contain a relevant intervention
Torres Lacomba, M., Yuste Sanchez, M.J., Zapico Goni, A. et al. (2010) Effectiveness of early physiotherapy to prevent lymphoedema after surgery for breast cancer: randomised, single blinded, clinical trial. BMJ (Clinical research ed.) 340: b5396	- included in systematic review
Yuan, Qianqian, Wu, Gaosong, Xiao, Shu-Yuan et al. (2019) Identification and Preservation of Arm Lymphatic System in Axillary Dissection for Breast Cancer to Reduce Arm Lymphoedema Events: A Randomized Clinical Trial. Annals of surgical oncology 26(11): 3446-3454	- Study does not contain a relevant intervention
Yuan, QQ, Wu, GS, Hou, JX et al. (2022) Identification and preservation of arm lymphatics in axillary lymph node dissection to prevent arm lymphoedema: a single center randomized controlled trial. Zhonghua zhong liu za zhi [Chinese journal of oncology] 44(5): 430-435	- Study does not contain a relevant intervention
Zhang, L.-F., Chen, J., Zhang, C. et al. (2020) Effect of pbl-based health education on lymphoedema and	- Not a relevant study design

cancer related fatigue and shoulder joint motion in patients underwent modified radical mastectomy. International Journal of Clinical and Experimental Medicine 13(6): 4544-4552	
Zimmermann, A., Wozniewski, M., Szklarska, A. et al. (2012) Efficacy of manual lymphatic drainage in preventing secondary lymphoedema after breast cancer surgery. Lymphology 45(3): 103-112	Included in systematic review

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2 **Systematic reviews**

Study	Exclusion reason
Baumann, Freerk T, Reike, Alexandra, Hallek, Michael et al. (2018) Does Exercise Have a Preventive Effect on Secondary Lymphoedema in Breast Cancer Patients Following Local Treatment? - A Systematic Review. Breast care (Basel, Switzerland) 13(5): 380-385	- Does not contain a population of people who are at risk of lymphoedema/don't have lymphoedema
Jorgensen, M.G.; Toyserkani, N.M.; Sorensen, J.A. (2018) The effect of prophylactic lymphovenous anastomosis and shunts for preventing cancer-related lymphoedema: a systematic review and meta-analysis. Microsurgery 38(5): 576-585	- Only contains 3 studies with people who have breast cancer-related lymphoedema, and they were included in another included systematic review
Naik, M.; Nayak, P.; Kumar, K.U.D. (2021) Effect of physiotherapy in the prevention and relief of secondary lymphoedema in subjects with postoperative breast cancer- a systematic review of randomised controlled trials. Journal of Clinical and Diagnostic Research 15(5): ye01-ye05	- Secondary publication of an included study that does not provide any additional relevant information
Pagliara, Domenico, Grieco, Federica, Rampazzo, Silvia et al. (2024) Prevention of Breast Cancer-Related Lymphoedema: An Up-to-Date Systematic Review of Different Surgical Approaches. Journal of clinical medicine 13(2)	- Data not reported in an extractable format
Perdomo, Marisa, Davies, Claire, Levenhagen, Kimberly et al. (2023) Patient education for breast cancer-related lymphoedema: a systematic review. Journal of cancer survivorship : research and practice 17(2): 384-398	- Secondary publication of an included study that does not provide any additional relevant information
Tantawy, Sayed A, Abdelbasset, Walid K, Nambi, Gopal et al. (2019) Comparative Study Between the Effects of Kinesio Taping and Pressure Garment on Secondary Upper Extremity Lymphoedema and Quality of Life	- Secondary publication of an included study that does not provide any additional relevant information

Following Mastectomy: A Randomized Controlled Trial. Integrative cancer therapies 18: 1534735419847276	
Taradaj, J, Halski, T, Rosinczuk, J et al. (2016) The influence of Kinesiology Taping on the volume of lymphoedema and manual dexterity of the upper limb in women after breast cancer treatment. European journal of cancer care 25(4): 647-60	- Does not contain a population of people who are at risk of lymphoedema
Tendero-Ruiz, Laura, Palomo-Carrion, Rocio, Megia-Garcia-Carpintero, Alvaro et al. (2023) The effect of therapeutic exercise in the prevention of lymphoedema secondary to breast cancer: a systematic review. Archives of medical science : AMS 19(6): 1684-1692	- Secondary publication of an included study that does not provide any additional relevant information
Whitworth, Pat, Vicini, Frank, Valente, Stephanie A et al. (2022) Reducing rates of chronic breast cancer-related lymphoedema with screening and early intervention: an update of recent data. Journal of cancer survivorship : research and practice	- Conference abstract

Cohort studies

Study	Exclusion reason
Blaney, J M, McCollum, G, Lorimer, J et al. (2015) Prospective surveillance of breast cancer-related lymphoedema in the first-year post-surgery: feasibility and comparison of screening measures. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 23(6): 1549-59	- Prospective surveillance
Boccardo, Francesco, Casabona, Federico, De Cian, Franco et al. (2014) Lymphatic microsurgical preventing healing approach (LYMPHA) for primary surgical prevention of breast cancer-related lymphoedema: over 4 years follow-up. Microsurgery 34(6): 421-4	- Primary Study
Chung, Jae-Ho, Kwon, Sang-Ho, Jung, Seung-Pil et al. (2023) Assessing the preventive effect of immediate lymphatic reconstruction on the upper extremity lymphoedema. Gland surgery 12(3): 334-343	- Surgical interventions

Darragh, L.; McGuinness, E.; Kirk, S.J. (2018) Prospective surveillance with bioelectrical impedance to guide early treatment of breast cancer-related lymphoedema. Wounds International 9(4): 39-43	- Prospective surveillance
Feldman, Sheldon, Bansil, Hannah, Ascherman, Jeffrey et al. (2015) Single Institution Experience with Lymphatic Microsurgical Preventive Healing Approach (LYMPHA) for the Primary Prevention of Lymphoedema. Annals of surgical oncology 22(10): 3296-301	- Primary Study
Fu, Mei R, Axelrod, Deborah, Guth, Amber A et al. (2014) Proactive approach to lymphoedema risk reduction: a prospective study. Annals of surgical oncology 21(11): 3481-9	- Prospective surveillance
Granoff, Melisa D, Fleishman, Aaron, Shillue, Kathy et al. (2023) A 4-Year Institutional Experience of Immediate Lymphatic Reconstruction. Plastic and reconstructive surgery 152(5): 773e-778e	- Surgical interventions
Gupta, Sandhya, Gupta, Neerja, Kadayaprath, Geeta et al. (2020) Use of Sentinel Lymph Node Biopsy and Early Physiotherapy to Reduce Incidence of Lymphoedema After Breast Cancer Surgery: an Institutional Experience. Indian journal of surgical oncology 11(1): 15-18	- Primary Study
Herremans, Kelly M, Cribbin, Morgan P, Riner, Andrea N et al. (2021) Five-Year Breast Surgeon Experience in LYMPHA at Time of ALND for Treatment of Clinical T1-4N1-3M0 Breast Cancer. Annals of surgical oncology 28(10): 5775-5787	- Surgical interventions
Iacorossi, Laura, Gambalunga, Francesca, Molinaro, Simona et al. (2019) The Effectiveness of the Sport "Dragon Boat Racing" in Reducing the Risk of Lymphoedema Incidence: An Observational Study. Cancer nursing 42(4): 323-331	- Primary Study
Johnson, Anna Rose, Fleishman, Aaron, Granoff, Melisa D et al. (2021) Evaluating the Impact of	- Surgical interventions

Immediate Lymphatic Reconstruction for the Surgical Prevention of Lymphoedema. Plastic and reconstructive surgery 147(3): 373e-381e	
Kaufman, David I, Shah, Chirag, Vicini, Frank A et al. (2017) Utilization of bioimpedance spectroscopy in the prevention of chronic breast cancer-related lymphoedema. Breast cancer research and treatment 166(3): 809-815	- Intervention not on list
Le, N.K., Liu, L., Jesus Cruz, R. et al. (2023) Efficacy of Immediate Lymphatic Reconstruction in Prevention of Breast Cancer-Related Lymphoedema. Annals of Plastic Surgery 90(6supplement): 363-s365	- Surgical interventions
Levy, Adam S, Murphy, Alexander I, Ishtihar, Sherene et al. (2023) Lymphatic Microsurgical Preventive Healing Approach for the Primary Prevention of Lymphoedema: A 4-Year Follow-Up. Plastic and reconstructive surgery 151(2): 413-420	- Primary Study
Lu, Shiang-Ru, Hong, Rong-Bin, Chou, Willy et al. (2015) Role of physiotherapy and patient education in lymphoedema control following breast cancer surgery. Therapeutics and clinical risk management 11: 319-27	- Early intervention
Ozmen, T., Layton, C., Friedman-Eldar, O. et al. (2022) Evaluation of Simplified Lymphatic Microsurgical Preventing Healing Approach (SLYMPHA) for the prevention of breast cancer-related lymphoedema after axillary lymph node dissection using bioimpedance spectroscopy. European Journal of Surgical Oncology 48(8): 1713-1717	- Primary Study
Ozmen, Tolga, Lazaro, Mesa, Zhou, Yan et al. (2019) Evaluation of Simplified Lymphatic Microsurgical Preventing Healing Approach (S-LYMPHA) for the Prevention of Breast Cancer-Related Clinical Lymphoedema After Axillary Lymph Node Dissection. Annals of surgery 270(6): 1156-1160	- Primary Study

Shaffer, Kristina, Cakmakoglu, Cagri, Schwarz, Graham S et al. (2020) Lymphoedema Prevention Surgery: Improved Operating Efficiency Over Time. Annals of surgical oncology 27(12): 4695-4701	- Outcome to be predicted do not match that specified in the protocol
Singh, Chiara; De Vera, Mary; Campbell, Kristin L (2013) The effect of prospective monitoring and early physiotherapy intervention on arm morbidity following surgery for breast cancer: a pilot study. Physiotherapy Canada. Physiotherapie Canada 65(2): 183-91	- Early intervention
Torralba-Puebla, T.; Ortiz-Fernandez, L.; Zamarripa-Cuesta, M. (2015) Patient education program: School of lymphoedema prevention. European Journal of Lymphology and Related Problems 27(73): 25-27	- Not a relevant study design
Tsuchiya, Miyako, Masujima, Mariko, Mori, Miki et al. (2018) Information-seeking, information sources and ongoing support needs after discharge to prevent cancer-related lymphoedema. Japanese journal of clinical oncology 48(11): 974-981	- Intervention not on list
Weinstein, Brielle, Le, Nicole K, Robertson, Ellen et al. (2022) Reverse Lymphatic Mapping and Immediate Microsurgical Lymphatic Reconstruction Reduces Early Risk of Breast Cancer-Related Lymphoedema. Plastic and reconstructive surgery 149(5): 1061-1069	- Surgical interventions
Whitworth, Pat W and Cooper, Andrea (2018) Reducing chronic breast cancer-related lymphoedema utilizing a program of prospective surveillance with bioimpedance spectroscopy. The breast journal 24(1): 62-65	- Prospective surveillance
Whitworth, Pat W, Shah, Chirag, Vicini, Frank et al. (2018) Preventing Breast Cancer-Related Lymphoedema in High-Risk Patients: The Impact of a Structured Surveillance Protocol Using Bioimpedance	- Prospective surveillance

Spectroscopy. Frontiers in oncology 8: 197	
Yang, Eun Joo, Ahn, Soyeon, Kim, Eun-Kyu et al. (2016) Use of a prospective surveillance model to prevent breast cancer treatment-related lymphoedema: a single-center experience. Breast cancer research and treatment 160(2): 269-276	- Primary Study
Yang, W., Yang, L., Mao, S. et al. (2023) Analysis of the effect of nursing care based on action research method on the prevention of postoperative lymphoedema in breast cancer patients. Medicine (United States) 102(52): e36743	- Primary Study
Zhang, Yue, Li, Na, Chen, Jing et al. (2022) Breast Cancer-Related Lymphoedema Risk-Management Behaviors Among Chinese Breast Cancer Survivors and Relationships with Socio-Demographic and Clinical Characteristics: A Longitudinal Study. Patient preference and adherence 16: 797-808	- Not a relevant study design

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Appendix K– Research recommendations – full details

Research recommendation

What is the effectiveness and cost-effectiveness of lymphovenous anastomosis during axillary or for preventing secondary lymphoedema and what is the acceptability of the intervention for different groups, such as:

- Women, men, trans people and non- binary people
- People from ethnic minority backgrounds
- People with disabilities

Why this is important

Secondary lymphoedema is a common and potentially debilitating complication of lymph node dissection. Finding effective preventive measures could significantly improve patients' quality of life. The committee highlighted that there was a lack of long-term effectiveness of LVA They also noted that lower quality evidence compared LVA during auxiliary node dissection to an auxiliary node dissection alone, showed some signalling of significance in most of the outcomes but without a clear effect. They discussed the importance of investigating outcomes at longer follow-up times (beyond 12 months) to understand how the surgery benefits people in the long term. The committee highlighted that there's a scarcity of well-designed RCTs comparing preventive LVA to standard care, much of the existing research on LVA has focused on its use as a treatment for established lymphoedema rather than as a preventive measure. They also noted that there is limited data on different anatomical sites they noted that the evidence mainly focused on axillary than inguinal making it difficult to generalize results. Also, no studies have rigorously examined the cost-effectiveness of this preventive approach compared to standard care or treatment of established lymphoedema. Results from this research could influence treatment protocols and surgical guidelines for cancer patients undergoing lymph node dissections. Therefore, a research recommendation was developed to cover this gap in the evidence.

Rationale for research recommendation

Importance to ‘patients’ or the population	Little is known about the best way of preventing secondary lymphoedema, new research will help ascertain the effectiveness of surgical intervention in the prevention of secondary lymphoedema.
Relevance to NICE guidance	Current guidance on surgical intervention lymphoedema prevention is under NICE interventional procedure guidance due to limited Low certainty evidence (on 1,969 patients from 4 systematic reviews, 1 prospective cohort study and 6 retrospective cohort studies) None of the included studies were based in the UK and primarily focused on lower limb

	lymphoedema. The average follow-up time in most studies was relatively short, limiting the evaluation of long-term effectiveness. More evidence is likely to influence current NICE guidance.
Relevance to the NHS	The outcome would affect the ways of delivering interventions to prevent lymphoedema. by the NHS. More knowledge on this can also reduce the number of people who experience persistent problems, and the costs associated with additional treatment for those people.
National priorities	Moderate
Current evidence base	2 systematic reviews and 1 RCT
Equality considerations	None known

Modified PICO table

Population	Adults with early or locally advanced breast cancer (18 and over) who have undergone or undergoing axillary or inguinal lymph node dissection for cancer treatment.
Intervention	(Lymph node dissection performed with lymphovenous anastomosis lymph node dissection performed with lymph node dissection VNLT
Comparator	Standard lymph node dissection alone (current standard of care)
Outcome	• Upper limb function: • Disabilities of the Arm, Shoulder and Hand scale (DASH; activity limitations domain should be reported separately) • Range of movement (ROM), for example: shoulder flexion and abduction • Upper limb muscle strength • Pain (validated scales for example: numerical rating scale [NRS], Oxford Shoulder Score) • Incidence of lymphoedema • Quality of life (EQ-5D, FACT-B+4, EORTC-QoL-C30) • Resource use and cost
Study design	• Randomised controlled trial. • Multicentre study to increase generalizability and recruitment. • Parallel group design (1:1 randomisation)
Timeframe	Short term: 6 months Medium term: 12 months

	Long term: 2 years or longer
Additional information	Subgroups: • women, men, trans people, and non-binary people • people from minority ethnic family backgrounds • people with mental or health disabilities • neurodiverse people • Stratified randomization by anatomical site (axillary vs. inguinal) and cancer type

Research recommendation

What is the effectiveness of vascularised lymph node transfer during axillary lymph node dissection for preventing secondary lymphoedema? and what is the acceptability of the intervention for different groups, such as:

- women, men, trans people and non-binary people
- people from ethnic minority backgrounds
- people with disabilities.

Why this is important.

Secondary lymphoedema is a common and potentially debilitating complication of lymph node dissection. Finding effective preventive measures could significantly improve patients' quality of life. The committee highlighted that there was a lack of long-term effectiveness data for VLNT. They also noted that lower quality evidence comparing VLNT during axillary node dissection to axillary node dissection alone showed some signals of significance in most outcomes but without a clear effect. They discussed the importance of investigating outcomes at longer follow-up times (beyond 12 months) to understand how the surgery benefits people in the long term.

The committee highlighted that there's a scarcity of well-designed RCTs comparing preventive VLNT to standard care. Much of the existing research on VLNT has focused on its use as a treatment for established lymphoedema rather than as a preventive measure. They also noted that there is limited data on different anatomical sites, with the evidence mainly focusing on axillary applications, making it difficult to generalize results.

Additionally, no studies have rigorously examined the cost-effectiveness of this preventive approach compared to standard care or treatment of established lymphoedema. Results from this research could influence treatment protocols and surgical guidelines for cancer patients undergoing lymph node dissections. Therefore, a research recommendation was developed to cover this gap in the evidence.

Rationale for research recommendation

Importance to 'patients' or the population	Little is known about the best way of preventing secondary lymphoedema, new research will help ascertain the effectiveness of surgical intervention in the prevention of secondary lymphoedema.
Relevance to NICE guidance	Current guidance on surgical intervention lymphoedema prevention is under NICE interventional procedure guidance due to limited Low certainty evidence None of the included studies were based in the UK and primarily focused on lower limb lymphoedema. The average follow-up time in most studies was relatively short, limiting the evaluation of long-term effectiveness. More evidence is likely to influence current NICE guidance.
Relevance to the NHS	The outcome would affect the ways of delivering interventions to prevent lymphoedema. by the NHS. More knowledge on this can also reduce the number of people who experience persistent problems, and the costs associated with additional treatment for those people.
National priorities	Moderate
Current evidence base	2 systematic reviews and 1 RCT
Equality considerations	• women, men, trans people, and non-binary people • people from minority ethnic family backgrounds • people with mental or health disabilities

Modified PICO table

Population	Adults (18 and over) with early or locally advanced breast cancer who have undergone or are undergoing axillary lymph node dissection for cancer treatment.
Intervention	Standard axillary lymph node dissection plus immediate vascularized lymph node transfer (VLNT)

	VLNT performed in separate surgical session to the lymph node dissection
Comparator	Standard lymph node dissection alone (current standard of care)
Outcome	• Upper limb function: • Disabilities of the Arm, Shoulder and Hand scale (DASH; activity limitations domain should be reported separately) • Range of movement (ROM), for example: shoulder flexion and abduction • Upper limb muscle strength • Pain (validated scales for example: numerical rating scale [NRS], Oxford Shoulder Score) • Incidence of lymphoedema • Quality of life (EQ-5D, FACT-B+4, EORTC-QoL-C30) • Resource use and cost
Study design	• Randomised controlled trial. • Multicentre study to increase generalizability and recruitment. • Parallel group design (1:1 randomisation)
Timeframe	Short term: 6 months Medium term: 12 months Long term: 2 years or longer
Additional information	Subgroups: • women, men, trans people, and non-binary people • people from minority ethnic family backgrounds • people with mental or health disabilities • neurodiverse people • Stratified randomization by anatomical site (axillary vs. inguinal) and cancer type

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