BMJ 2017;357:j2330 doi: 10.1136/bmj.j2330 (Published 2017 June 01)

PRACTICE

UNCERTAINTIES

Which are the best conservative interventions for lymphoedema after breast cancer surgery?

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Lymphoedema is a common complication of breast cancer surgery with or without adjuvant cancer treatments.[1] Fluid accumulates because of damage to the lymphatic system, most commonly after axillary lymph node dissection. Box 1 shows factors associated with lymphoedema. Swelling is commonly in the arm but can involve the chest or back; it can result in pain, dysfunction, and disturbance of body image.[3]

Nearly 1 in 5 women who survive breast cancer develops lymphoedema within two years of diagnosis or surgery, with the incidence increasing with time.[1 3] In recent years, sentinel lymph node biopsy has been implemented as standard care and has greatly reduced the incidence of lymphoedema. This means that women with clinically positive lymph nodes undergo the higher risk axillary lymph node dissection, but others can avoid the procedure.

Lymphoedema cannot be completely cured, although it can be managed and perhaps prevented. Box 2 and figure 1 outline non-surgical strategies to prevent and treat lymphoedema that are commonly employed in clinical practice. These are often used together. This article discusses the uncertainty about the effectiveness of their use following breast cancer treatment.

Decongestive lymphatic therapy, also called complete decongestive therapy, is the mainstay of lymphoedema treatment. The therapy is divided into two phases: a reduction phase to reduce lymphoedema, which might last 2-4 weeks, followed by a maintenance phase to prevent recurrence. Treatment comprises a combination of manual lymph drainage, compression bandaging, exercise, and education for the reduction phase, and use of fitted compression garments in the maintenance phase. Clinically, the combinations of these decongestive lymphatic phase components vary. They are often used together, however uncertainty exists on the relative effectiveness of the interventions.[6-8]

The use of surgical interventions for prevention of lymphoedema is not widespread and as treatments they are usually reserved for severe lymphoedema. We do not discuss these interventions here.[6 9]

What is the evidence of uncertainty?

Three Cochrane systematic reviews examine the efficacy of conservative interventions for prevention or treatment of lymphoedema after breast cancer treatment.[7-10] Strong evidence for which interventions work is lacking because there are few, often small trials, with contradictory results. Further, the effect of some interventions could be dose dependent (eg, compression class of hosiery, frequency of manual lymphatic drainage), and different types of intervention could complement one other (eg, compression and exercise).

Prevention

Conservative treatment to minimise the risk of developing lymphoedema includes education, monitoring, and early intervention, exercise, manual lymphatic drainage, and compression therapy by bandaging or hosiery (box 2, fig 1).

A Cochrane systematic review in 2015 (10 randomised controlled trials, 1205 patients)[10] evaluated effectiveness of these approaches, alone or in combination, in preventing lymphoedema compared with either no intervention or with another conservative approach. The findings are summarised in table 2⇓.

The included trials were heterogeneous and some lacked power to measure whether lymphoedema could be prevented. It was only possible to perform a meta-analysis with two equivalence studies (358 patients) intended to establish safety of progressive resistance exercise training. There was moderate quality evidence that this does not increase the risk of developing lymphoedema compared with no exercise, and might even

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What you need to know

- An estimated 20% of women who have been treated for breast cancer will develop lymphoedema
- Advise patients to watch for early symptoms such as swelling, feelings of heaviness, or tension in the skin of the arm or the breast
- Lymphoedema might be prevented or treated using one or more conservative approaches including patient education, physical exercise, manual lymphatic drainage, and compression therapy
- Evidence for the effectiveness of any of these interventions, alone or in combination, is limited

Box 1: Risk factors for breast cancer related lymphoedema with reported ranges of odds ratios (OR)[1]

Factors related to disease and treatment

- Higher number of metastatic lymph nodes: OR 1.1-2.8
- Axillary lymph node dissection: OR 1.3-6.7
- Greater number of lymph nodes dissected: OR 1.0-2.1
- Mastectomy: OR 2.7-7.4
- Radiotherapy: OR 1.7-3.8
- Chemotherapy: OR 1.6-2.0

Other factors

- High BMI: OR 0.1-5.5 per point increase
- Lack of participation in regular physical activity: OR 2.1-6.1
- Development of an infection in the limb at any time after breast cancer treatment: OR 2.17; 95% confidence interval: 0.93-5.08[2]

Box 2: Strategies to prevent lymphoedema

Discuss with the patient

- the function of the lymphatic system
- awareness of early symptoms such as swelling, feelings of heaviness, or tension in the skin
- avoiding skin puncture and injections in the upper limbs on the affected side
- maintaining a healthy body weight
- wearing compression garments for exercise or travel
- the potential risks associated with long haul air travel
- recognising the signs of infection or cellulitis and skin care practices to avoid infection[4 5]

reduce it (relative risk 0.58, 95% confidence interval 0.30; 1.13, P=0.11).[10]

The small number of studies and their clinical and statistical heterogeneity mean there is insufficient evidence to make recommendations for clinical practice.[10] Further, these interventions might impose discomfort or dependency and have associated costs.

Treatment

A Cochrane systematic review in 2004 (three randomised controlled trials, 150 patients) assessed effectiveness of physical treatments such as manual lymphatic drainage, massage, bandaging, and compression sleeve in reducing or controlling lymphoedema of the limbs.[7] The trials included different combinations of treatments and were too small to draw definitive conclusions.[11-13]

A Cochrane systematic review in 2015 (six randomised controlled trials, 208 patients) considered the effectiveness of combined manual lymph drainage and other treatments compared with other treatments alone for lymphoedema after breast cancer treatment.[8] The findings are summarised in table 3⇓. Findings support the use of an intensive course of compression bandaging to reduce lymphoedema volume. One year follow-up findings suggest better maintenance of reduction in limb volume in those who used compression hosiery. Manual lymph drainage was found to offer additional benefit when added to compression bandaging (mean difference in reduction of arm volume 7%, 95% confidence interval 1.75-12.47, P=0.009). Analyses of combined individual patient data of two studies showed that this benefit occurred in the subgroup of participants with mild to moderate lymphoedema.

However, the trials are small, ranging from 24 to 45 participants, and the wide confidence intervals lead to uncertainty. Information on adverse effects, patient preferences, and costs for these interventions is not available. Authors of both reviews conclude that well designed large randomised trials are needed to provide clear recommendations.

Is ongoing research likely to provide relevant evidence?

Ongoing studies could provide further evidence, in particular on the effectiveness of early interventions for subclinical lymphoedema to prevent clinical lymphoedema. Further studies could address the added value of manual lymphatic drainage both for prevention and treatment, and optimal compression strategies for the treatment of lymphoedema. We searched the World Health Organisation clinical trials registry (http://apps.who.int/trialsearch/) in February 2017 for studies on prevention and treatment of breast cancer related lymphoedema. Table 4⇓ (online) provides details of studies we found.

We identified five records of trials on prevention of lymphoedema. Two studies investigate the effectiveness of resistance exercises and physical therapy compared with usual care. It is not clear whether the remaining studies have started.

We found 16 records of ongoing studies on treatment of breast cancer related lymphoedema, of which two are not yet enrolling patients. For one study it is unclear whether it has commenced. These studies examine the added effectiveness of manual lymphatic drainage, compare different forms of compression therapy or different modalities of exercise, and study the effectiveness of laser treatment, yoga, or traditional Chinese medicine (acupuncture or moxibustion). Although some studies have large target sample sizes, nine of these studies have a target sample size <50, which might limit reliability of findings.

Since publication of the discussed Cochrane reviews, additional studies have been published that address some of the clinical uncertainties discussed in this article. The availability of these new studies, and expected results from ongoing studies, highlight the need for an update of the existing systematic reviews in the near future.

What should we do in light of the uncertainty?

We should educate and help those who wish to change their modifiable risk factors such as high BMI and inactivity, which increase the risk[1] of developing lymphoedema (box 1). There is insufficient evidence on other precautionary behaviours such as avoiding blood draws and injections in the arm on the side of surgery,[2] yet these might have merit, particularly in individuals at higher risk of developing lymphoedema.[14]

Until recently, there was some controversy on the safety of resistance training for patients with and at risk of lymphoedema. Current evidence suggests that resistance training does not increase the risk of lymphoedema, and is also safe and beneficial for patients with existing lymphoedema. Breast cancer survivors should be encouraged to perform such exercises regularly.

Expert consensus guidelines proposed by the American National Lymphedema Network (www.lymphnet.org) advise patients to monitor for early symptoms such as swelling, feelings of heaviness, and tension in the skin, and to consult a health professional if symptoms do not subside.[5]

Once symptoms occur, prompt treatment by a specialised health professional certified in lymphoedema is recommended. Consistent with international best practice recommendations, treatment should at least include compression therapy and exercise.[6] After initial treatment, use of compression hosiery should be offered to prevent recurrence of swelling. Considering the chronic nature, education on the condition and optimisation of self-management practices should be integral parts of treatment.

We have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Accepted: 02 05 2017

How patients were involved in the creation of this article

A breast cancer survivor with arm lymphoedema reviewed the initial manuscript. She emphasised the need for better patient education and we have added this aspect to the article

Recommendations for further research

Population: Women who have been treated for breast cancer (prevention) or women who have lymphoedema after breast cancer treatment (treatment)

Interventions: Control visits and/or self-surveillance; early intervention for subclinical lymphoedema; manual lymphatic drainage, compression, exercise therapy, structured education, alone or in combination (fig 1)

Comparisons: How do different combinations or doses of interventions to prevent or treat lymphoedema compare with each other or with education only?

Outcomes: For prevention studies: cost effectiveness with regard to reduced incidence of lymphoedema and harm. For treatment studies: cost-effectiveness with regard to reduced lymphoedema symptoms (including psychological consequences), resulting disability (treatment) and quality of life, and harm.

A future update of the Cochrane reviews on conservative interventions for prevention of lymphoedema, and of physical therapies for the treatment of lymphoedema is recommended to assess whether findings from new studies are sufficiently robust to inform practice

Education into practice

- In a woman who is at risk of lymphoedema, what signs and symptoms would you ask her to report?
- How would you share uncertainty about the prevention and management of lymphoedema with a patient?
- Can you succinctly describe the range of options available and mechanistically how they might work?

What patients need to know

After surgery for breast cancer, some people develop swelling in the arm and/ or the breast on the treated side

We are unsure about the value of treatments for prevention of lymphoedema, but we do know that it is important to maintain a healthy weight, and to be moderately physically active

If you experience sensations of heaviness or tension, or if swelling occurs, you should see a doctor about this as soon as possible if the symptoms do not subside within a few days. The doctor can refer you to a dedicated health professional for treatment

Tables

Table 2| Summary of evidence for conservative interventions for prevention of lymphoedema after treatment for breast cancer10

Intervention	Type of evidence	Summary of evidence	Evidence of harms
Manual lymph drainage	Systematic review (4 RCTs that combined MLD with other treatments; 395 participants).	Insufficient and very low quality* evidence	Insufficient evidence
Compression therapy	Systematic review; (1 RCT combining compression with MLD; 48 participants)	Insufficient and very low quality* evidence	Insufficient evidence
Early full range shoulder exercises after surgery	Systematic review (3 RCTs with 378 participants)	Insufficient and very low quality* evidence: pooled estimate of RR for lymphoedema after early full range shoulder exercises compared with delayed start of exercises: 1.69 (95%CI 0.94-3.01, P=0.078)	Insufficient and very low quality evidence that delaying full range shoulder exercises might limit range of motion int short term (<6 months). Insufficient and very low quality evidence does not indicate increased risk of wound infection after early start (RR 0.83, 95%CI 0.20 - 3.39, P=0.80)
Patient education	Systematic review (no studies identified)	Insufficient evidence	Insufficient evidence
Comprehensive program: exercises, self-monitoring and regular follow-up with early intervention for subclinical lymphoedema	Systematic review (1 RCT, 65 participants)	Insufficient and very low quality* evidence	None reported, but insufficient evidence

Table 2 (continued)

Intervention	Type of evidence	Summary of evidence	Evidence of harms
Progressive resistance training	Systematic review (2 RCTs; 358 participants)	Moderate quality evidence* that progressive resistance training does not increase the risk of lymphoedema compared to no exercise: RR 0.58 (95%CI 0.30-1.13, P=0.69)	No evidence of harm

*GRADE system applied in this review. RCT: randomised controlled trial. MLD: manual lymphatic drainage. RR: risk ratio. CI: confidence interval.

Table 3| **Summary of evidence for conservative interventions for manifest lymphoedema after treatment for breast cancer78**

Intervention	Comparator	Type of evidence	Summary of evidence	Evidence of harms
Compression therapy: compression bandaging+compression hosiery	Hosiery alone	Systematic review: 1 RCT, 90 participants[7]	15.2% additional percent reduction benefit from compression bandaging sustained over 24-weeks (95% CI: 6.2 to 24.2; P=0.001)	None reported
MLD+compression hosiery+exercise	Compression hosiery+exercise	Systematic review: 1 RCT, 42 participants[8]	No evidence of benefit	None reported
MLD+compression bandaging	Compression bandaging	Systematic review: 2 RCTs, 83 participants[8]	7.11% additional percent reduction benefit from MLD (95% CI: 1.75% to 12.47%; P=0.009)	None reported
MLD plus compression sleeve	Simple lymphatic drainage (self-massage)+compression sleeve	Systematic review: 1 RCT, 31 participants[8]	No evidence of benefit	None reported
MLD+compression sleeve	Intermittent pneumatic pump+compression sleeve	Systematic review: 1 RCT, 24 participants[8]	No evidence of benefit	None reported
MLD+compression Bandaging	Simple lymphatic drainage by therapist+compression bandaging	Systematic review: 1 RCT, 28 participants[8]	No evidence of benefit	None reported

RCT: randomised controlled trial. MLD: manual lymphatic drainage

Table 4| Ongoing randomised controlled trials on prevention or treatment of lymphoedema after breast cancer treatment

Registration date	Country	Intervention	Comparator	Estimated enrolment	Notes
Prevention					
03/2015	Denmark	Progressive resistance training and close monitoring	Usual care (not specified)	158	Recruiting
6/2012	UK	MLD in addition to skin care, compression garments and exercise	Skin care, compression garments and exercise	178	Unclear recruitment status
02/2011	USA	Compression sleeve in patients with subclinical lymphoedema	Observation only	200	Unclear recruitment status
09/2006	USA	Pneumatic compression (flexitouch) in patients with subclinical signs of lymphoedema	Observation only	200	Unclear recruitment status
09/2006	USA	Physical therapy (unspecified)+education	Education alone	877	Active but not recruiting
Treatment					
12/2016	Canada	Resistance exercise+adjustable compression wrap/ resistance exercise+fitted compression sleeve	Home exercise+compression sleeve	24	Pilot study, 3 arms; recruiting
8/2016	New Zealand	Low level laser	Usual care including physical therapy	20	Not yet recruiting
06/2016	China	Acupuncture	Sham acupuncture	150	Not yet recruiting
11/2016	China	Moxibustion	Pneumatic compression	40	Crossover study
07/2015	France	CDT+endermology	CDT	93	Recruiting
02/2015	Spain	Precast adjustable compression wrap (Circaid)	Multilayer bandaging	47	Active, not recruiting
12/2014	China	Laser acupuncture	No treatment	80	Recruiting
07/2014	Canada	Daytime compression+night time compression	Daytime compression	120	Active, not recruiting
07/2014	Malaga	Compression+MLD	MLD	44	Not yet recruiting
07/2014	Japan	Self-care program (exercises, breathing technique and self-MLD)	Standard self care	40	Recruiting Phase II study
5/2014	Canada	Acupuncture+electric stimulation	No treatment	40	Recruiting Phase II study
6/2013	Australia	Aerobic exercise or resistance exercise	Monitoring symptoms	48	Recruiting
12/2013	Denmark	Bandaging+MLD	Bandaging	160	Recruiting
9/2013	Denmark	Accelerated treatment (compression garments, exercise instruction and education)	Standard treatment (compression garments, exercise instruction and education)	84	Recruiting
02/2011	Australia	Yoga	Usual care (self care, exercises, MLD if required)	40	Recruiting
09/2005	Taiwan	CDT+Kinesiotaping	CDT	877	Active, not recruiting. Last verified in 2006

CDT: Complete decongestive therapy. MLD: manual lymphatic drainage

Figure

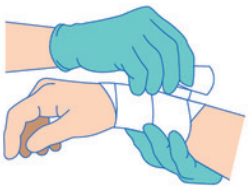
Treatment	Treatment	Proposed mechanism
Compression therapy 	Multilayer bandaging or pneumatic compression (treatment phase 2-4 weeks) or using a graduated hosiery/compression sleeve (prevention and ongoing maintenance phase)	Enhance lymph flow, increase muscle pump function, and prevent further swelling
Exercise 	Specific remedial exercises that involve repetitive, non-resistive motion of the involved body part. The exercise sequence progresses from proximal to distal General exercises such as resistance exercise, yoga, and Nordic walking	Enhance lymph flow, increase muscle pump function, and prevent further swelling
Manual lymph drainage 	Gentle manual massage techniques applied by a specialised health professional (physiotherapist or skin therapist)	Enhance lymph flow to prevent or treat oedema
Decongestive lymphatic (complete decongestive) therapy (treatment only) 	A combination treatment for manifest lymphoedema, usually comprising compression therapy, manual lymph drainage, exercise, and skin care. There is a reduction phase (2-4 weeks) and a maintenance phase which aims at preventing relapse	All of the above combined

Fig 1 Clinical and patient management and treatment of lymphoedema