BMJ Open

Effectiveness of physical exercise programmes in reducing complications associated with secondary lymphoedema to breast cancer: a protocol for an overview of systematic reviews

Raúl Alberto Aguilera-Eguía [1,2] Ruvistay Gutiérrez-Arias [3,4] Carlos Zaror [5] Pamela Seron [6]

To cite: Aguilera-Eguía RA, Gutiérrez-Arias R, Zaror C, *et al*. Effectiveness of physical exercise programmes in reducing complications associated with secondary lymphoedema to breast cancer: a protocol for an overview of systematic reviews. *BMJ Open* 2023;**13**:e071630. doi:10.1136/bmjopen-2023-071630

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-071630).

Received 05 January 2023
Accepted 23 June 2023

For numbered affiliations see end of article.

Correspondence to
Dr Pamela Seron;
pamela.seron@ufrontera.cl

ABSTRACT

Introduction Breast cancer-related lymphoedema (BCRL) is one of the most underestimated and debilitating complications associated with the treatment that women with breast cancer receive. Several systematic reviews (SRs) of different physical exercise programmes have been published, presenting disperse and contradictory clinical results. Therefore, there is a need for access to the best available and summarised evidence to capture and evaluate all the physical exercise programmes that focus on reducing BCRL.

Objective To evaluate the effectiveness of different physical exercise programmes in reducing the volume of lymphoedema, pain intensity and improving quality of life.

Method and analysis The protocol of this overview is reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols, and its methodology is based on Cochrane Handbook for Systematic Reviews of Interventions. Only those SRs involving physical exercise by patients with BCRL will be included, whether on its own or combined with other exercises or other physical therapy interventions.
The outcomes of interest to be considered will be lymphoedema volume, quality of life, pain intensity, grip strength, range of motion, upper limb function and any adverse event. The MEDLINE/PubMed, Lilacs, Cochrane Library, PEDro and Embase databases will be searched for reports published from database inception to April 2023.
Two researchers will perform study selection, data extraction and risk of bias assessment independently. Any discrepancy will be resolved by consensus, or ultimately, by a third-party reviewer. We will use Grading of Recommendations Assessment, Development and Evaluation System to assess the overall quality of the body of evidence.

Ethics and dissemination The results of this overview will be published in peer-reviewed scholarly journals and the scientific dissemination will take place in national or international conferences. This study does not require approval from an ethics committee, as it does not directly collect information from patients.

PROSPERO registration number CRD42022334433.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ In order to provide a clear and concise overview, we will use the PRIOR statement.
⇒ The study will be carried out according to the recommendation of the Cochrane handbook for overviews of systematic reviews of interventions.
⇒ The GROOVE tool will be used to graphically represent the degree of overlap in the primary studies.
⇒ The quality of the evidence will be evaluated by using the Grading of Recommendations Assessment, Development and Evaluation System approach.
⇒ A potential limitation of this study may be the heterogeneity between published studies that prevents meta-analysing de novo.

INTRODUCTION

According to recent statistics, breast cancer was the most common type of cancer diagnosed in 2020.[1] It has been reported that although breast cancer mortality is diminishing in high-income countries,[2–4] its incidence has been constantly increasing.[1 5 6] This could be due to substantial improvements in early detection, diagnosis and advances in the treatments being used.[3 7–12] However, we must also consider that these treatments are not exempt from adverse consequences or effects, including anxiety, alterations in bone health, cardiotoxicity, peripheral neuropathy induced by chemotherapy, alterations in cognitive function, depressive symptoms, falling, fatigue, deterioration in the health-related quality of life, nausea, pain, diminished physical capacity, a decrease of lean mass, an increase of fat mass, altered sexual function, sleep disorders, intolerance of treatment and secondary breast cancer-related lymphoedema (BCRL).[13]

BCRL has been described as one of the most underestimated and debilitating

complications associated with the treatment that women with breast cancer receive.[14] Its reported incidence in the general population varies between 3% and 65%, depending on the type of treatment received and the length of follow-up.[14–16]

There is currently no clarity on lymphoedema's aetiology,[17] however, it is thought to be caused by an interruption of the lymphatic flow together with other factors,[14] including total mastectomy, axillary dissection positive lymph nodes (>quantity of removed lymph nodes), radiotherapy, use of taxanes and obesity.[15–35]

Clinically, patients with lymphoedema tend to present swelling in one limb, with an accompanying feeling of weakness.[36 37] They also refer to a heavy or stiff feeling in the affected limb, restriction of movement in the upper limb, pain or discomfort. In more severe cases, they present a hardening and thickening of the skin (fibrosis).[36 37] There is greater risk of infection and a chronic, progressive course of the condition, which can lead to cases of anxiety and a deterioration in quality of life.[38–40]

Physical therapy for BCRL is based on a multimodal therapy approach[41 42] that includes various interventions such as complete decongestive therapy,[43] manual lymphatic drainage,[44–48] low-level laser therapy,[49–52] pneumatic pumps,[53] kinesio-taping,[54–56] Yoga,[57] Pilates[57] and aquatic therapy,[58] among other. Many of these interventions are combined during sessions. However, exercise programmes, such as aerobic/endurance training[59] and resistance training[59] or a combination of these, are part of physical therapy interventions.[60]

Research reports numerous benefits of different physical exercise programmes in terms of performance, reduction in lymphoedema volume, muscular strength, upper limb function and range of motion, quality of life, pain reduction, cardiovascular function, reduction in body weight and lymphatic circulation,[57 59 61–73] among others.

Currently, it has been demonstrated that physical exercise has a positive impact on the lymphatic system. This is due to its ability to increase blood flow, cardiac output and blood pressure, thereby promoting capillary filtration and entry of fluids and proteins into lymphatic capillaries.[74–76] Furthermore, exercise increases lymph propulsion through lymphatic vessels through intrinsic and extrinsic mechanisms, such as skeletal muscle pumping, respiratory pumping and pulse of nearby blood vessels, facilitating lymph return.[74 76]

Currently, there is a large quantity of systematic reviews (SRs) that evaluates the different physical exercise programmes for the reduction of BCRL. However, different SRs that combine this information have been published, presenting disperse and contradictory clinical results.[57–59 61 63 65–67 69 70 72 77–92]

There are currently no studies that summarise and evaluate the effectiveness of all the SRs that include randomised clinical trials (RCTs) on the different physical exercise programmes focused on the reduction of BCRL.

Overviews of SRs compile information from multiple SRs to provide a comprehensive synthesis of evidence, providing a wider perspective on the heterogeneity, possible sources of bias and methodological quality of SRs that may affect the certainty of evidence. Overviews are designed to be accessible and easy-to-use documents, and tend to present a much broader reach that any single SR.[93–95]

There is a need for access to the best available and summarised evidence to capture and evaluate all the physical exercise programmes that focus on reducing the volume of lymphoedema and complications associated such as poor quality of life, pain intensity, grip strength, range of motion, upper limb function and any adverse events in patients with BCRL.

Therefore, the results that can be obtained by this overview will provide relevant information for clinical decision making for patients, researchers, physical therapists, physicians and stakeholders.

Research question

Are different physical exercise programmes effective and safe in patients diagnosed with BCRL?

Objective

To evaluate the effectiveness of different physical exercise programmes in reducing the volume of lymphoedema and pain intensity and improving quality of life. Secondarily adverse events, grip strength, range of movement and upper limb function will be also evaluated.

METHODS AND ANALYSIS

This research protocol has been reported following the reference items for publishing SRs and Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Protocols[96] (online supplemental appendix A). This overview is registered in the PROSPERO database (CRD42022334433). Any amendments to the protocol will be made through PROSPERO.

We will use a focus that allows us to summarise the evidence from more than one SR of different interventions (all physical exercise programmes) for the same condition or problem (BCRL).[97]

When reporting the overview, we will use the Preferred Reporting items for Overviews of Reviews (PRIOR) statement[98] and the methodology will be conducted based on the Cochrane Handbook for Systematic Reviews of Interventions.[97]

Patient and public involvement

None.

Eligibility criteria for study type

SRs with or without meta-analysis will be included.[95] They must present an explicit methodology that corresponds to an SR[99]: clearly articulated objectives and questions to be addressed, inclusion and exclusion criteria stipulated a priori that determine the eligibility of studies, use a

search strategy in two or more databases (eg, MEDLINE, Lilacs), appraisal of the quality of included studies,[100] and the included primary studies should correspond to RCTs. In addition, SRs that were conducted using a rapid review methodology will be included.[101] If SRs include studies with other primary study designs, they will only be included if the data from the RCTs are reported in a disaggregated manner, allowing for extraction of their information. SRs protocols, scoping review and narrative reviews will be excluded. We will only include studies that are written in English, Spanish or Portuguese.

Eligibility criteria for participants and context

We will include SR where the patients have a diagnosis of BCRL.

Eligibility criteria for the intervention

We will include SRs that incorporate any type of physical exercise programme (eg, resistance training, aerobic exercise, yoga, Pilates), either on its own or in combination with other exercises or other physical therapy interventions (eg, complete decongestive therapy, manual lymphatic drainage, low-level laser therapy).

Eligibility criteria for the comparison

We will include SRs where the comparison group is the usual care without exercise, without treatment or education, or any other type of physical therapy.

Eligibility criteria for the outcomes

The following primary outcomes will be considered:

- Volumetric changes in arm. The volume could be measured in any of the following ways, all of which made a comparison with the unaffected side (lymphoedema volume,[102 103] volume reduction,[102 104 105]; per cent reduction[102 104–106]), which must be measured by any of the following valid methods: water displacement volumetry, measurement of the limb's circumference, bioimpedance spectroscopy, dual X-ray absorptiometry and perometry (online supplemental appendix B).
- Quality of life, which must be evaluated by any validated generic or specific self-report scale (eg, EORTC-QLQ-C30).
- Pain intensity, which must be evaluated by validated generic or specific self-report scale (eg, Numerical Rating Scale or Visual Analogue Scale).

The following secondary outcomes will be considered:

- Adverse events from the physical exercise programmes such as an increase in lymphoedema volume and pain.
- Grip strength in patients undergoing physical therapy interventions, evaluated with dynamometry.
- Range of motion in patients undergoing physical therapy interventions, evaluated with goniometry.
- Upper limb function, which must be evaluated by any validated generic or specific self-report scale (eg, Disabilities of the Arm, Shoulder and Hand (DASH)).

Search strategy

We will perform a search of SRs of RCTs in the following electronic databases: MEDLINE/PubMed, Embase, Cochrane Library, PEDro and Lilacs will be searched for reports published from data base inception to April 2023.

The search strategy will present a highly sensitive focus and the use of controlled language (MeSH, Emtree or DeCS) and natural language.[107] The details of the search strategy used in the databases are described in online supplemental appendix C.

Selection process

The records provided from the different databases will be exported to the Rayyan platform (https://www.rayyan.ai/about.html).[108] After eliminating duplicated articles, two researchers will independently select the studies by reading the titles and abstracts. Then, the same researchers will independently review the full texts of the potentially eligible records. Any discrepancy will be resolved by consensus, or ultimately by a third-party reviewer. A table will descriptively explain which studies are excluded once the full text has been read.

Managing overlapping SRs

We recognise that the SRs to be included in this overview will address very similar research questions. Therefore, it is probable that they will include several of the same primary studies. If we find overlapping SRs, we will avoid double counting data by ensuring that the findings of each primary study are separately extracted one time only.[95]

To evaluate the overlapping of primary studies included in the SRs, we will create a matrix to visually present the amount of overlapping.[109] Then, we will evaluate the degree of overlapping in the primary studies by using the 'corrected covered area' (CCA), as it represents the proportion of repeated occurrence of primary studies in other SRs, divided by the number of unique primary studies. The degree of overlapping of primary studies between SRs will be interpreted and reported as follows: slight (0%–5%), moderate (6%–10%), high (11%–15%) and very high (>15%).[109] The CCA will be calculated and plotted by means of Graphical Representation of Overlap for OVErviews tool (GROOVE tool).[110]

Data extraction

Two researchers will independently compile the information of the data extracted from each one of the included SRs, using a standard Excel worksheet. A third author will check extracted information and will solve discrepancies.

The data to be extracted will consider:

- Details of the SRs publication: authors, year published, research team, associated institutions, involved countries, databases included in the SRs and type of synthesis (qualitative or quantitative).
- Type of participants: number and characteristics.

- Characteristics of the intervention: modality of physical exercise programme, if is a multicomponent exercise programme or a sole intervention, intensity, dosification and duration of the programme.
- Type of comparisons.
- Reported outcomes.
- Derived conclusions.

Assessment of the methodological quality of the included reviews

Two researchers will be responsible for the methodological assessment. Any discrepancy will be resolved by consensus, or ultimately by a third-party reviewer.

According to the Cochrane handbook's requirements, both the methodological quality of the included reviews and the quality of evidence from the individual studies included in the reviews must be assessed.

The methodological quality of the included SRs will be assessed using the ROBIS (Risk of Bias in Systematic Review) tool.[111] This tool has been developed using a rigorous methodology and is focused on four epidemiological categories of SRs: intervention, diagnosis, prognosis and aetiology.[111]

The ROBIS tool has been made for authors that summarise SRs, and that require evaluating the risk of bias in their reviews.[111]

The ROBIS tool is completed in three phases[111]: (1) assess relevance (optional); (2) identify concerns with the review process (study eligibility criteria, identification and selection of studies, data collection and study appraisal, synthesis and findings; (3) judge risk of bias (Concerns with the review process (phase 2), three questions related to the interpretation of the review's findings are answered and global assessment). Answers to the signal questions are categorised as 'yes', 'probably yes', 'no', 'probably no' or 'no information'. The risk of bias is judged as 'high', 'low' or 'unclear'.

Quality of evidence in the primary studies included in reviews

If the SRs included in our overview report the risk of bias through the second version of Cochrane collaboration methodological tool (RoB 2),[112] we will extract this information and it will be used in our evaluation. Meanwhile, is the SRs do not use RoB 2, we will assess the risk of bias of the individual trials included in the SRs using the RoB 2, which include the following domains: bias derived from the randomisation process, bias due to deviations from planned interventions, bias due to lack of results data, bias in the measurement of the result, and bias in the selection of the reported result.

A series of signalling questions that aim to provide a structured approach to obtaining relevant information on bias risk assessment will be included for each domain. For each domain, the possible risk of bias judgements will be reported as: low risk of bias, some concerns and high risk of bias.[59]

The Grading of Recommendations Assessment, Development and Evaluation System (GRADE) will be used to evaluate the overall quality of evidence related to the estimated effects of the different physical exercise programmes, whether on their own or combined with other exercise or physical therapy interventions on the reduction of secondary lymphoedema associated with breast cancer, quality of life, decrease of pain, articular range, grip strength.[113 114] Therefore, if the included SRs report the certainty of evidence through the GRADE methodology, the information will be extracted and used in our overview. But, if the included SRs do not present or evaluate the quality of evidence with the GRADE methodology, we will evaluate and report the certainty of evidence using the GRADE methodology. The criteria evaluated by GRADE are: 'study design', 'risk of bias', 'inconsistency', 'indirectness', 'imprecision', 'suspected publication bias', 'other considerations'.[115 116]

GRADEproGDT software (www.gradepro.org) will be used to generate the 'findings of summary' tables, which will indicate the principal results with their respective quality of evidence evaluation.

We will use four levels of evidence, according to the GRADE working group's recommendations[117] :

- High quality: it is very unlikely that additional studies change our confidence in the estimated effect.
- Moderate quality: it is likely that additional research has an impact on our confidence in the estimated effect and may change the estimation.
- Low quality: it is very likely that additional research has an important impact on our confidence in the estimated effect and will probably change the estimation.
- Very low quality: little confidence in the estimated effect.

Data synthesis

The results will be reported according to recommendations from the Cochrane Handbook for Systematic Reviews of Interventions. We will also use the PRISMA flow chart to indicate the study selection process.

We will summarise the scientific evidence presented on the different exercise programmes and the reduction of secondary lymphoedema associated with breast cancer.

The characteristics of the included SRs (details of the SRs publication; type of participants: number and characteristics; characteristics of the intervention; type of comparisons; reported outcome of interest; derived conclusions), will be reported in tables that summarise all relevant information.

When overlapping SRs are found, we will avoid double counting data. We will ensure that the findings of each primary study are separately extracted one time only. However, assuming that there will be overlapping RCTs in different SRs, we will reanalyse the results, which will mean extracting and reanalysing all information corresponding to primary studies in the included SRs. In order to avoid the inclusion

of indirect evidence, we will verify whether or not the RCTs included in the SRs answer our overview's research question.

Therefore, we propose carrying our new meta-analyses for each comparison and outcome of interest, considering subgroups by exercise modality or programme. We will use relative risk as a measure of effect for the dichotomous outcome data, with its respective 95% CI. When the outcome of interest is measured on the same scales, we will present the continuous interest outcomes as mean differences (MD), with their respective 95% CI. The standardised MDs will be calculated when the outcome of interest are measures on different scales.

Heterogeneity will be evaluated using the inconsistency test (I^2). We will use the following heterogeneity classification values: (1) 0%–40% might not be important; (2) 30%–60%: may represent moderate heterogeneity; (3) 50%–90% may represent substantial heterogeneity and (4) 75%–100% considerable heterogeneity.[118] The data will not be pooled if I^2 was over 75%. If meta-analysis is not plausible or appropriate, the comparable RCT outcomes will be qualitatively described in the text. If a statistical heterogeneity of >75% is presented, other sources of heterogeneity will be explored. The reporting biases will be evaluated if at least 10 RCTs are included in the meta-analyses. We will use the Begg's test to analyse the funnel plot.[119 120] If there are asymmetries, we will examine other causes in addition to reporting bias, such as selective outcome reporting, poor methodological quality in smaller studies and heterogeneity. We will perform a sensitivity analysis only if we are able to find an appropriate number of studies. This analysis will include the following:

- Restricting the analysis to studies that present a low risk of bias.

Ethics and dissemination

This overview's results will be published in peer-reviewed academic journals and the scientific dissemination will take place in national or international conferences relevant in this area of study and/or specialty.

This study does not require approval from an ethics committee, as it does not directly collect information from patients.

Author affiliations
[1]Departamento de Salud Pública, Facultad de Medicina, Universidad Católica de la Santísima Concepción, Concepcion, Chile
[2]Department of Paediatrics, Obstetrics and Gynaecology and Preventive Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain
[3]Departamento de Apoyo en Rehabilitación Cardiopulmonar Integral, Instituto Nacional del Tórax, Santiago, Chile
[4]Exercise and Rehabilitation Sciences Institute, Faculty of Rehabilitation Sciences, Universidad Andres Bello, Santiago 7591538, Santiago, Chile
[5]Pediatric Dentist and Orthodontic, Universidad de La Frontera, Temuco, Chile
[6]CIGES, Universidad de La Frontera, Temuco, Chile

Twitter Ruvistay Gutiérrez-Arias @ruvistay

Acknowledgements RAA-E is a Ph.D. candidate in Methodology of Biomedical Research and Public Health programme, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain.

Contributors RAA-E, CZ, RG-A and PS contributed to the conception and design of the study. RAA-E developed the search strategies. RAA-E, CZ and PS designed the data analysis. All authors drafted the article and made the final approval of the version to be published.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Raúl Alberto Aguilera-Eguía http://orcid.org/0000-0002-4123-4255
Ruvistay Gutiérrez-Arias http://orcid.org/0000-0003-1881-9316
Carlos Zaror http://orcid.org/0000-0001-6942-6956
Pamela Seron http://orcid.org/0000-0003-0190-8988

REFERENCES

1 Sung H, Ferlay J, Siegel RL, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209–49.
2 Narod SA, Iqbal J, Miller AB. Why have breast cancer mortality rates declined?. *J Cancer Policy* 2015;5:8–17.
3 Britt KL, Cuzick J, Phillips K-A. Key steps for effective breast cancer prevention. *Nat Rev Cancer* 2020;20:417–36.
4 Hendrick RE, Helvie MA, Monticciolo DL. Breast cancer mortality rates have stopped declining in U.S. women younger than 40 years. *Radiology* 2021;299:143–9.
5 Parkin DM, Fernández LMG. Use of statistics to assess the global burden of breast cancer. *Breast J* 2006;12 Suppl 1:S70–80.
6 Sun Y-S, Zhao Z, Yang Z-N, *et al*. Risk factors and preventions of breast cancer. *Int J Biol Sci* 2017;13:1387–97.
7 Rossi L, Mazzara C, Pagani O. Diagnosis and treatment of breast cancer in young women. *Curr Treat Options Oncol* 2019;20:86.
8 Waks AG, Winer EP. Breast cancer treatment: a review. *JAMA* 2019;321:288–300.
9 Basu P, Zhang L, Hariprasad R, *et al*. pragmatic approach to tackle the rising burden of breast cancer through prevention & early detection in countries 'in transition' *Indian J Med Res* 2020;152:343–55.
10 Pashayan N, Antoniou AC, Ivanus U, *et al*. Personalized early detection and prevention of breast cancer: ENVISION consensus statement. *Nat Rev Clin Oncol* 2020;17:687–705.
11 Bartelink H. The changing landscape in radiotherapy for breast cancer: lessons from long term follow-up in some European breast cancer trials. *Radiother Oncol* 2016;121:348–56.
12 Whelan TJ, Olivotto IA, Parulekar WR, *et al*. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med* 2015;373:307–16.

13 Campbell KL, Winters-Stone KM, Wiskemann J, *et al*. Exercise guidelines for cancer survivors: consensus statement from international multidisciplinary roundtable. *Med Sci Sports Exerc* 2019;51:2375–90.
14 Pereira C. N, Pons P. G, Masià A. J. Linfedema asociado al cáncer de mama: factores de riesgo, diagnóstico y tratamiento quirúrgico. *Rev Cir* 2019;71:79–87.
15 McLaughlin SA, Brunelle CL, Taghian A. Breast cancer-related lymphedema: risk factors, screening, management, and the impact of locoregional treatment. *J Clin Oncol* 2020;38:2341–50.
16 Leray H, Malloizel-Delaunay J, Lusque A, *et al*. Body mass index as a major risk factor for severe breast cancer-related lymphedema. *Lymphat Res Biol* 2020;18:510–6.
17 He L, Qu H, Wu Q, *et al*. Lymphedema in survivors of breast cancer. *Oncol Lett* 2020;19:2085–96.
18 Hull MM. Lymphedema in women treated for breast cancer. *Semin Oncol Nurs* 2000;16:226–37.
19 Kwan JYY, Famiyeh P, Su J, *et al*. Development and validation of a risk model for breast cancer-related lymphedema. *JAMA Netw Open* 2020;3:e2024373.
20 Wu R, Huang X, Dong X, *et al*. Obese patients have higher risk of breast cancer-related lymphedema than overweight patients after breast cancer: a meta-analysis. *Ann Transl Med* 2019;7:172.
21 Meijer EF, Bouta EM, Mendonca C, *et al*. A retrospective analysis of commonly prescribed medications and the risk of developing breast cancer related lymphedema. *Clin Res Trials* 2020;6.
22 Li F, Lu Q, Jin S, *et al*. A scoring system for predicting the risk of breast cancer-related lymphedema. *Int J Nurs Sci* 2020;7:21–8.
23 Zhang X, Tang B, Zou D, *et al*. Discussion of relationships among changes of pathological indicators, postoperative lymphedema of the upper limb, and prognosis of patients with breast cancer. *Biosci Rep* 2019;39.
24 Rupp J, Hadamitzky C, Henkenberens C, *et al*. Frequency and risk factors for arm lymphedema after multimodal breast-conserving treatment of nodal positive breast cancer - a long-term observation. *Radiat Oncol* 2019;14:14–39.
25 Zou L, Liu F-H, Shen P-P, *et al*. The incidence and risk factors of related lymphedema for breast cancer survivors post-operation: a 2-year follow-up prospective cohort study. *Breast Cancer* 2018;25:309–14.
26 Nguyen TT, Hoskin TL, Habermann EB, *et al*. Breast cancer-related lymphedema risk is related to multidisciplinary treatment and not surgery alone: results from a large cohort study. *Ann Surg Oncol* 2017;24:2972–80.
27 McDuff SGR, Mina AI, Brunelle CL, *et al*. Timing of lymphedema after treatment for breast cancer: when are patients most at risk? *Int J Radiat Oncol Biol Phys* 2019;103:62–70.
28 McLaughlin SA, DeSnyder SM, Klimberg S, *et al*. Considerations for clinicians in the diagnosis, prevention, and treatment of breast cancer-related lymphedema, recommendations from an expert panel: part 2: preventive and therapeutic options. *Ann Surg Oncol* 2017;24:2827–35.
29 Ozcinar B, Guler SA, Kocaman N, *et al*. Breast cancer related lymphedema in patients with different loco-regional treatments. *Breast* 2012;21:361–5.
30 Kilbreath SL, Refshauge KM, Beith JM, *et al*. Risk factors for lymphoedema in women with breast cancer: a large prospective cohort. *Breast* 2016;28:29–36.
31 Shaw C, Mortimer P, Judd PA. A randomized controlled trial of weight reduction as a treatment for breast cancer-related lymphedema. *Cancer* 2007;110:1868–74.
32 J Tsai R, K Dennis L, F Lynch C, *et al*. Lymphedema following breast cancer: the importance of surgical methods and obesity. *Front Womens Healt* 2018;3:1–6.
33 Tsai C-L, Chang W-W, *et al*. Effects of weight reduction on the breast cancer-related lymphedema:a systematic review and meta-analysis. *Breast* 2020;52:116–21.
34 Davies C, Levenhagen K, Ryans K, *et al*. Interventions for breast cancer-related lymphedema: clinical practice guideline from the academy of oncologic physical therapy of APTA. *Phys Ther* 2020;100:1163–79.
35 Gillespie TC, Sayegh HE, Brunelle CL, *et al*. Breast cancer-related lymphedema: risk factors, precautionary measures, and treatments. *Gland Surg* 2018;7:379–403.
36 Kibar S, Dalyan Aras M, Ünsal Delialioğlu S. The risk factors and prevalence of upper extremity impairments and an analysis of effects of lymphoedema and other impairments on the quality of life of breast cancer patients. *Eur J Cancer Care (Engl)* 2017;26.
37 Nesvold I-L, Fosså SD, Holm I, *et al*. Arm/shoulder problems in breast cancer survivors are associated with reduced health and poorer physical quality of life. *Acta Oncol* 2010;49:347–53.
38 Eaton LH, Narkthong N, Hulett JM. Psychosocial issues associated with breast cancer-related lymphedema: a literature review. *Curr Breast Cancer Rep* 2020;12:216–24.
39 Taghian NR, Miller CL, Jammallo LS, *et al*. Lymphedema following breast cancer treatment and impact on quality of life: a review. *Crit Rev Oncol Hematol* 2014;92:227–34.
40 Fu MR, Ridner SH, Hu SH, *et al*. Psychosocial impact of lymphedema: a systematic review of literature from 2004 to 2011. *Psychooncology* 2013;22:1466–84.
41 López Jiménez RM, López CM, López Jiménez S. Tratamiento fisioterápico del linfedema en las pacientes tratadas de cáncer de mama. *Rev Enfermería Docente* 2015;103:55–9.
42 Mella Abarca W, Barraza-Sánchez V, Ramírez-Parada K. Sistema de selección de sistemas elastocompresivos en personas con cáncer de mama de un hospital con recursos limitados. *ARS Med* 2020;45.
43 Cendron SW, Paiva LL, Darski C, *et al*. Fisioterapia complexa descongestiva associada a terapias de compressão no tratamento do linfedema secundário ao câncer de mama: uma revisão sistemática. *Rev Brasileira De Cancerologia* 2015;61:49–58.
44 Eh R, Phd PHD, Pt PT, *et al*. Vodder manual lymphatic drainage versus Casley-Smith manual lymphatic drainage on lymphedema post mastectomy. *J Complement Med Res* 2021;12:178.
45 Huang T-W, Tseng S-H, Lin C-C, *et al*. Effects of manual lymphatic drainage on breast cancer-related lymphedema: a systematic review and meta-analysis of randomized controlled trials. *World J Surg Oncol* 2013;11:15.
46 Thompson B, Gaitatzis K, Janse de Jonge X, *et al*. Manual lymphatic drainage treatment for lymphedema: a systematic review of the literature. *J Cancer Surviv* 2021;15:244–58.
47 Shao Y, Zhong D-S. Manual Lymphatic drainage for breast cancer-related lymphoedema. *Eur J Cancer Care (Engl)* 2017;26.
48 Liang M, Chen Q, Peng K, *et al*. Manual lymphatic drainage for lymphedema in patients after breast cancer surgery: a systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2020;99:e23192.
49 Monteiro SE, Resende LV, Felicíssimo MF, *et al*. Treatment of upper limb lymphedema with low-level laser: a systematic review. *Fisioter Mov* 2014;27:663–74.
50 E Lima M, E Lima JGM, de Andrade MFC, *et al*. Low-level laser therapy in secondary lymphedema after breast cancer: systematic review. *Lasers Med Sci* 2014;29:1289–95.
51 Baxter GD, Liu L, Petrich S, *et al*. Low level laser therapy (Photobiomodulation therapy) for breast cancer-related lymphedema: a systematic review. *BMC Cancer* 2017;17:833.
52 Smoot B, Chiavola-Larson L, Lee J, *et al*. Effect of low-level laser therapy on pain and swelling in women with breast cancer-related lymphedema: a systematic review and meta-analysis. *J Cancer Surviv* 2015;9:287–304.
53 Shao Y, Qi K, Zhou QH, *et al*. Intermittent pneumatic compression pump for breast cancer-related lymphedema: a systematic review and meta-analysis of randomized controlled trials. *Oncol Res Treat* 2014;37:170–4.
54 Thomaz JP, Dias T, de Rezende LF. Effect of taping as treatment to reduce breast cancer lymphedema: literature review. *J Vasc Bras* 2018;17:136–40.
55 Tremback-Ball A, Harding R, Heffner K, *et al*. The efficacy of kinesiology taping in the treatment of women with post–mastectomy lymphedema: a systematic review. *J Womens Health Phys Therap* 2018;42:94–103.
56 Kasawara KT, Mapa JMR, Ferreira V, *et al*. Effects of kinesio taping on breast cancer-related lymphedema: a meta-analysis in clinical trials. *Physiotherapy Theory and Practice* 2018;34:337–45.
57 Keilani M, Hasenoehrl T, Neubauer M, *et al*. Resistance exercise and secondary lymphedema in breast cancer survivors—a systematic review. *Support Care Cancer* 2016;24:1907–16.
58 Yeung W, Semciw AI. Aquatic therapy for people with lymphedema: a systematic review and meta-analysis. *Lymphat Res Biol* 2018;16:9–19.
59 Panchik D, Masco S, Zinnikas P, *et al*. Effect of exercise on breast cancer-related lymphedema: what the lymphatic surgeon needs to know. *J Reconstr Microsurg* 2019;35:37–45.
60 Haque MA, Sultan P, Medical M. Effects of physiotherapy on breast cancer related secondary lymphedema : a systematic review. *Int J Med Sci Diagnosis Res* 2018;2:5–10.
61 Chan DNS, Lui LYY, So WKW. Effectiveness of exercise programmes on shoulder mobility and lymphoedema after axillary

lymph node dissection for breast cancer: systematic review. *J Adv Nurs* 2010;66:1902–14.
62 Kwan ML, Cohn JC, Armer JM, *et al*. Exercise in patients with lymphedema: a systematic review of the contemporary literature. *J Cancer Surviv* 2011;5:320–36.
63 Cheema B, Gaul CA, Lane K, *et al*. Progressive resistance training in breast cancer: a systematic review of clinical trials. *Breast Cancer Res Treat* 2008;109:9–26.
64 Wanchai A, Armer JM. Effects of weight-lifting or resistance exercise on breast cancer-related lymphedema: a systematic review. *Int J Nurs Sci* 2019;6:92–8.
65 Romesberg M, Tucker A, Kuzminski K, *et al*. The effects of resistance exercises on secondary lymphedema due to treatment of breast cancer. *J Womens Health* 2017;41:91–9.
66 Singh B, Disipio T, Peake J, *et al*. Systematic review and meta-analysis of the effects of exercise for those with cancer-related lymphedema. *Arch Phys Med Rehabil* 2016;97:302–15.
67 Tatham B, Smith J, Cheifetz O, *et al*. The efficacy of exercise therapy in reducing shoulder pain related to breast cancer:a systematic review. *Physiother Can* 2013;65:321–30.
68 Baumann FT, Reike A, Reimer V, *et al*. Effects of physical exercise on breast cancer-related secondary lymphedema: a systematic review. *Breast Cancer Res Treat* 2018;170:1–13.
69 Wei C-W, Wu Y-C, Chen P-Y, *et al*. Effectiveness of yoga interventions in breast cancer-related lymphedema: a systematic review. *Complement Ther Clin Pract* 2019;36:49–55.
70 De Groef A, Van Kampen M, Dieltjens E, *et al*. Effectiveness of postoperative physical therapy for upper limb impairments following breast cancer treatment: a systematic review. *Arch Phys Med Rehabil* 2015;96:1140–53.
71 McNeely ML, Campbell K, Ospina M, *et al*. Exercise interventions for upper-limb dysfunction due to breast cancer treatment. *Cochrane Database Syst Rev* 2010.
72 Moseley AL, Carati CJ, Piller NB. A systematic review of common conservative therapies for arm lymphoedema secondary to breast cancer treatment. *Ann Oncol* 2007;18:639–46.
73 Chung C, Lee S, Hwang S, *et al*. Systematic review of exercise effects on health outcomes in women with breast cancer. *Asian Nurs Res (Korean Soc Nurs Sci)* 2013;7:149–59.
74 Lane K, Worsley D, McKenzie D. Exercise and the lymphatic system: implications for breast-cancer survivors. *Sports Med* 2005;35:461–71.
75 Stuiver MM, Tusscher MR, Agasi-Idenburg CS, *et al*. Conventional interventions for preventing clinically detectable upper-limb lymphoedema in patients who are at risk of developing lymphoedema after breast cancer therapy. *Cochrane Database Syst Rev* 2012;2.
76 Aukland K, Reed RK. Interstitial-lymphatic mechanisms in the control of extracellular fluid volume. *Physiol Rev* 1993;73:1–78.
77 Nelson NL. Breast cancer-related lymphedema and resistance exercise: a systematic review. *J Strength Cond Res* 2016;30:2656–65.
78 Stuiver MM, ten Tusscher MR, Agasi-Idenburg CS, *et al*. Conservative interventions for preventing clinically detectable upper-limb lymphoedema in patients who are at risk of developing Lymphoedema after breast cancer therapy. *Cochrane Database Syst Rev* 2015.
79 Baumann FT, Reike A, Hallek M, *et al*. Does exercise have a preventive effect on secondary lymphedema in breast cancer patients following local treatment? - a systematic review. *Breast Care (Basel)* 2018;13:380–5.
80 Tendero-Ruiz L, Palomo-Carrión R, Megía-García-Carpintero Á, *et al*. The effect of therapeutic exercise in the prevention of lymphoedema secondary to breast cancer: a systematic review. *Arch Med Sci* 2020;1–9.
81 Hasenoehrl T, Palma S, Ramazanova D, *et al*. Resistance exercise and breast cancer–related lymphedema—a systematic review update and meta-analysis. *Support Care Cancer* 2020;28:3593–603.
82 McNeely ML, Campbell K, Ospina M, *et al*. Exercise interventions for upper-limb dysfunction due to breast cancer treatment. *Cochrane Database Syst Rev* 2010;6:CD005211.
83 Haque MA, Sultan P, Medical M. Effects of physiotherapy on breast cancer related secondary lymphedema: a systematic review; 2018, Online ISSN : 2581-3935 Print ISSN : 2589-7837.
84 Douglass J, Graves P, Gordon S. Self-care for management of secondary lymphedema: a systematic review. *PLoS Negl Trop Dis* 2016;10:e0004740.
85 Cheifetz O, Haley L, Breast Cancer Action. Management of secondary lymphedema related to breast cancer. *Can Fam Physician* 2010;56:1277–84.
86 Ortega F, Jairo Alejandro D. Efectos de un programa combinado de ejercicios de fuerza y aerobicos de alta intensidad en pacientes supervivientes del cancer de mama. *Apunt Med Esport* 2015;51:3–12.
87 Rogan S, Taeymans J, Luginbuehl H, *et al*. Therapy modalities to reduce lymphoedema in female breast cancer patients: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2016;159:1–14.
88 Wirtz P, Baumann FT. Physical activity, exercise and breast cancer - what is the evidence for rehabilitation, aftercare, and survival? A review. *Breast Care (Basel)* 2018;13:93–101.
89 Cheema BS, Kilbreath SL, Fahey PP, *et al*. Safety and efficacy of progressive resistance training in breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2014;148:249–68.
90 Hasenoehrl T, Keilani M, Palma S, *et al*. Resistance exercise and breast cancer related lymphedema - a systematic review update. *Disabil Rehabil* 2020;42:26–35.
91 Naghibi S, Varshoie Tabrizi F. Exercise training and breast cancer-related lymphedema: a systematic review. *Razavi Int J Med* 2018;6.
92 Riobó García B, Soto González M. Efectos de los ejercicios de resistencia en el linfedema posmas tectomía, una revisión sistemática. *Fisioterapia* 2018;40:199–207.
93 Pollock M, Fernandes RM, Becker LA, *et al*. What guidance is available for researchers conducting overviews of reviews of healthcare interventions? A scoping review and qualitative Metasummary. *Syst Rev* 2016;5:190.
94 Li L, Tian J, Tian H, *et al*. Quality and transparency of overviews of systematic reviews. *J Evid Based Med* 2012;5:166–73.
95 Pollock M, Fernandes RM, Newton AS, *et al*. The impact of different inclusion decisions on the comprehensiveness and complexity of Overviews of reviews of Healthcare interventions. *Syst Rev* 2019;8:18.
96 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Rev Esp Nutr Humana y Diet* 2016;4:1:1.:.
97 Pollock M, Fernandes RM, Becker LA, *et al*. Overviews of reviews. In: Higgins JPT, Thomas J, Chandler J, et al, eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.2*. Cochrane, 2021. Available: www.training.cochrane.org/handbook
98 Gates M, Gates A, Pieper D, *et al*. Reporting guideline for overviews of reviews of healthcare interventions: development of the PRIOR statement. *BMJ* 2022;378:e070849.
99 MacEntee MI. A typology of systematic reviews for synthesising evidence on health care. *Gerodontology* 2019;36:303–12.
100 Aromataris E, Pearson A. The systematic review: an overview. *Am J Nurs* 2014;114:53–8.
101 Tricco AC, Antony J, Zarin W, *et al*. A scoping review of rapid review methods. *BMC Med* 2015;13:224.
102 McNeely ML, Magee DJ, Lees AW, *et al*. The addition of manual lymph drainage to compression therapy for breast cancer related lymphedema: a randomized controlled trial. *Breast Cancer Res Treat* 2004;86:95–106.
103 Williams AF, Vadgama A, Franks PJ, *et al*. A randomized controlled crossover study of manual lymphatic drainage therapy in women with breast cancer-related lymphoedema. *Eur J Cancer Care (Engl)* 2002;11:254–61.
104 Johansson K, Lie E, Ekdahl C, *et al*. A randomized study comparing manual for treatment of postoperative arm lymphedema; 1998. 56–64.
105 Johansson K, Albertsson M, Ingvar C, *et al*. Effects of compression bandaging with or without manual lymph drainage treatment in patients with postoperative arm lymphedema with or without manual lymph drainage treatment in patients with postoperative arm lymphedema; 1999.
106 Sitzia J, Sobrido L, Harlow W. Manual lymphatic drainage compared with simple lymphatic drainage in the treatment of post-mastectomy lymphoedema. *Physiotherapy* 2002;88:99–107.
107 Montori VM, Wilczynski NL, Morgan D, *et al*. Optimal search strategies for retrieving systematic reviews from MEDLINE: analytical survey. *BMJ* 2005;330:68.
108 Ouzzani M, Hammady H, Fedorowicz Z, *et al*. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016;5:210.
109 Pieper D, Antoine S-L, Mathes T, *et al*. Systematic review finds overlapping reviews were not mentioned in every other overview. *J Clin Epidemiol* 2014;67:368–75.
110 Pérez-Bracchiglione J, Meza N, Bangdiwala SI, *et al*. Graphical representation of overlap for overviews: GROOVE tool. *Res Synth Methods* 2022;13:381–8.

111 Singh J, Tugwell P, Wells G, *et al*. ROBIS: a new tool to assess risk of bias in systematic reviews was developed. *Recenti Prog Med* 2018;109:421–31.
112 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343.
113 Guyatt G, Oxman AD, Akl EA, *et al*. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tabless. *J Clin Epidemiol* 2011;64:383–94.
114 Guyatt GH, Oxman AD, Schünemann HJ, *et al*. GRADE guidelines: a new series of articles in the journal of clinical epidemiology. *J Clin Epidemiol* 2011;64:380–2.
115 Balshem H, Helfand M, Schünemann HJ, *et al*. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011;64:401–6.
116 Neumann I, Pantoja T, Peñaloza B, *et al*. El sistema GRADE: un cambio en la forma de evaluar la calidad de la evidencia y la fuerza de recomendaciones. *Rev Méd Chile* 2014;142:630–5.
117 Kirmayr M, Quilodrán C, Valente B, *et al*. Metodología GRADE, parte 1: cómo evaluar la certeza de la evidencia. *Medwave* 2021;21:e8109.
118 Deeks J, JPT H, DG A. Chapter 10: analysing data and undertaking meta-analyses. In: *Cochrane Handbook for Systematic Reviews of Interventions version 62*. 2021. Available: https://training.cochrane.org/handbook/current/chapter-10
119 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088–101.
120 Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.