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Can resistance exercise prevent breast cancer–related lymphoedema? A systematic review and metanalysis protocol

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ABSTRACT

Introduction Evidence shows that resistance training (RT) reduces lymphoedema in patients with breast cancer–related lymphoedema (BRCL), making it a safe and efficient intervention. However, it is uncertain if RT is safe and effective in patients at risk of developing BRCL. This systematic review (SR) protocol aims to describe all methodological aspects in order to evaluate the short-, medium- and long-term effects of RT on the prevention of BCRL.

Materials and methods Throughout 2024, randomised clinical trials (RCTs) will be identified in electronic databases MEDLINE/PubMed, Embase, Cochrane Central Register of Controlled Trials, PEDro and LILACS. Only studies in English, Spanish and Portuguese will be included. Grey literature and clinical trial registration will also be reviewed. The primary outcome will be the occurrence of lymphoedema and quality of life. Second, pain intensity, upper limb function, range of movement, grip strength and adverse events will be considered. The individual studies' risk of bias will be evaluated using the Cochrane Risk of Bias 2.0 tool. Pairwise meta-analyses using a frequentist approach and random effects model will be conducted. The Grading of Recommendations Assessment, Development and Evaluation system will be used to evaluate the certainty of the evidence.

Ethics and dissemination This protocol does not require the approval of an ethics committee, as it is a secondary study. The results will be disseminated through peer-reviewed publications.

PROSPERO registration number CRD42023455720.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will be the first systematic review to evaluate the efficacy of resistance training in the prevention of breast cancer–related lymphedema in people at risk of developing lymphoedema.
⇒ This study will be undertaken according to the recommendations of the Cochrane Handbook for Systematic Review of Interventions.
⇒ Certainty of evidence will be evaluated by using the Grading of Recommendations Assessment, Development and Evaluation approach.
⇒ One potential limitation of this study could be the heterogeneity among the randomised clinical trials due to the characteristics of the intervention (intensity, duration, frequency).

INTRODUCTION

Breast cancer (BC) became the most commonly diagnosed type of cancer in 2020,[1] registering 2.3 million new cases (11.7%). Although it has been established that BC's mortality is decreasing in high-income countries,[2–4] its incidence has been constantly increasing,[1 5 6] which means that there is a better chance of survival after diagnosis. Breast cancer–related lymphoedema (BCRL) is one of the most underestimated and debilitating consequences of the treatment that people with breast cancer receive.[7] Its incidence varies from 3% to 75.4% of the general population, depending on the type of treatment received and the follow-up period evaluated.[7–13] It has been reported that among women treated for BC, 20% were diagnosed with BCRL more than 2 years after their initial diagnosis[14] and that there is a probability between 27% and 49% that they will develop it up to 20 years after treatment.[15–17] This data demonstrates that BCRL can be present months or years after initial treatment and can occur gradually or suddenly.[18 19]

BCRL is caused by the interruption of lymphatic flow and other risk factors, such as mastectomy, axillary dissection, positive lymph nodes, radiotherapy, taxane use and obesity.[8 19–27] Clinically, BCRL is characterised by an increased volume of the affected arm, a heavy or rigid sensation in the limb, limitation of movement, pain or discomfort, and, in more severe cases, hardening and fibrosis, which negatively affect functionality and lead to a decrease in quality of life.[28 29]

Currently, the treatment of BCRL focuses on controlling the limb's volume through

physical therapy together with compression treatments,[30 31] which results in a great financial burden for patients and health systems.[32 33]

For a long time, physicians and physical therapists have advised women under treatment for BC to avoid physical exercise and lifting weights, believing that these activities could cause or exacerbate BCRL.[34–37] However, there are several systematic reviews (SRs) that analyse the effect of resistance training (RT) on the reduction of BCRL, making it a safe and effective intervention for people with BCRL.[38 39]

Currently, it has been shown that physical exercise increases blood flow, cardiac output and blood pressure, which favours capillary filtration, the movement of liquids and proteins in the lymphatic capillaries.[40] Exercise also increases the lymph's propulsion through the lymphatic vessels by intrinsic and extrinsic mechanisms, such as the skeletal muscle pump, respiratory pump and the pulse of the nearby blood vessels in order to facilitate the lymph's return.[40 41]

Due to BCRL's impact on quality of life after BC treatment and associated economic costs, it is fundamental to focus preventative efforts on women at risk of developing BCRL.

The American College of Sports Medicine[42] and Clinical Practice Guideline from the Academy of Oncologic Physical Therapy of APTA 2020[43] recommend progressive, supervised RT as a preventative strategy for BCRL. This recommendation is only based on five clinical trials.[44–48]

However, just one SR[49] evaluating the preventative effect of conservative interventions (non-surgical and non-pharmacological) has been published to date. These interventions include manual lymphatic drainage, early versus late intervention with shoulder mobility exercises, RT, education, and early intervention and follow-up in patients at risk of developing BCRL. This SR[49] included trials published up to May 2013, and only two studies related to RT.[50 51] In addition, the SR did not perform a sensitivity or subgroups analysis, due to the lack of RCTs included. The conclusion was that RT does not increase the risk of developing BCRL, as long as symptoms are monitored and immediately treated should they turn up. As for pain, it was observed that the group of patients treated more frequently with RT reported pain more often in comparison with the control group. As for quality of life, no significant difference was found between groups.

Despite the advancements and efforts made,[52] RT's efficacy and safety in patients at risk of developing BCRL are still uncertain.[53] This may be caused by a series of factors that limit the existing evidence and its quality.

Due to new evidence that has emerged after 2013 that analyses the efficacy of RT in women at risk of developing BCRL,[45 54 55] we believe that it is necessary to carry out this SR to determine if RT is safe and effective in the prevention of BCRL in people at risk of developing lymphoedema. In addition, we will consider if the type of RT impacts the effectiveness and focus our assessment on patient-important outcomes.

Objective

Evaluate the short-, medium- and long-term efficacy and safety of RT in preventing BCRL.

METHODS AND ANALYSIS

This protocol was registered in PROSPERO database (CRD42023455720) and is reported according to the guidelines of the PRISMA-P[56] (online supplemental appendix 1). The SR will be carried out according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.[57]

Criteria for including studies in this review

Types of studies

Randomised clinical trials (RCTs) written in English, Spanish and Portuguese will be included. If we identify abstracts published in congress and poster minutes, we will attempt to reach out to the study's authors to gather further information and validate the methodology and findings shared. Should we not receive a response from the authors, those materials will not be incorporated into our review.[58]

Types of participants

RCTs, including women who have had surgery for BC and are therefore at risk for developing BCRL after treatment, will be eligible. Treatments for BC could include surgical treatment for breast cancer with axillary lymph node dissection, sentinel lymph node biopsy or axillary sampling, with or without radiotherapy to the axilla or the supraclavicular fossa or both, or radiotherapy alone.[49] Trials in people who had been diagnosed with lymphoedema or cancer recurrence will not be eligible for inclusion.[49]

Types of interventions

RCTs that applied any RT after surgery that directly analysed their preventive effects, or not, will be included when the comparison group considers the same other physical therapy interventions so that the difference between the groups is the use of RTE. RT or 'strength training' is a programme of strengthening exercises that require the body to apply force against some type of resistance (eg, lifting weights, elastic bands, working with one's own body weight). This type of training is designed to improve the strength, potency, resistance and size of the skeletal muscle.[59]

Types of comparator(s)/control

RCTs that included a control group without exercise, patient education or forms of exercise other than RT (eg, aerobic exercise or flexibility) will be included.

Follow-up

The follow-up for each outcome will be classified as follows:

- Short term: ≤ 3 weeks.
- Medium-term: > 3 weeks up to 6 weeks.

- Long-term: ≥ 6 weeks.

Types of outcome measures

Primary outcomes

The primary outcome in our review is the occurrence of lymphoedema and quality of life. This occurrence of lymphoedema could be reported as either a dichotomous outcome or a continuous outcome (volume or percentage volume change).[49] Time-to-event data, with lymphoedema as the event, will also be used if reported.[49] Because of the variety of ways in which lymphoedema can be defined and diagnosed, studies will be considered eligible only if they use a predefined criterion for establishing lymphoedema based on an objective assessment.[49] This includes circumference measurements, water displacement methods, bioimpedance measurements, laser scanning, perimetry and dual-energy X-ray absorptiometry scanning. This means we will not include studies that evaluate an intervention based solely on a diagnosis of lymphoedema made by a healthcare professional or on self-reported swelling or complaints of oedema.[49] Meanwhile, quality of life must be evaluated by any validated generic or specific self-report scale, such as EORTC Core Quality of Life questionnaire.

Secondary outcomes

The secondary outcomes will be:

- Pain intensity measured by a validated generic or specific self-report scale, such as a numerical rating scale or visual analogue scale.
- Upper limb function measured by any validated generic or specific self-report scale (eg, Disabilities of the Arm, Shoulder and Hand questionnaire).
- Range of motion evaluated with goniometry.
- Grip strength evaluated with dynamometry.
- Adverse events from the RT alone or as part of a physical therapy programme, such as increased in lymphoedema volume and pain.

Search methods for identification of studies

Electronic searches

A search of RCTs will be conducted in the following databases: MEDLINE/PubMed, Embase, Cochrane Central Register of Controlled Trials, PEDro and LILACS will be searched for reports published from data base inception to October 2024. Details of the search strategy for each database are described in the online supplemental appendix 2. We will perform a search of grey literature in the European grey literature database (http://www.opengrey.eu) and Open Access Theses and Dissertations. In addition, we will examine the reference lists of all relevant articles, including studies and previous SRs.

For RCT protocols, we will search the following registries:

1. Registro de Ensayos (https://www.registroensayosclinicos.org/).
2. ClinicalTrials.gov (https://clinicaltrials.gov/).
3. International Clinical Trials Registry Platform (https://www.who.int/clinical-trials-registry-platform).
4. Public Access Policy (https://publicaccess.nih.gov/).

We will also review the following preprint servers to identify relevant studies.[60] The servers we will consult include:

1. medrXiv (https://www.medrxiv.org/).
2. bioRxiv (https://www.biorxiv.org/).

Data collection and analysis

Selection of studies

All results will be exported to Rayyan software.[61] Once duplicated records are eliminated, two researchers will independently filter by title and abstract. Then, two researchers will independently revise each full text of the potentially eligible articles. Any discrepancy will be resolved by the authors' consensus. If no consensus is reached, the decision will be made by a third author.

Data extraction and management

Two authors will independently perform data extraction using a previously piloted standardised form. Any discrepancy will be resolved by mutual consensus between the authors. If they cannot reach a consensus, a third author will make the final decision.

The following information will be extracted from each included study[62] :

1. Study's characteristics (year published, country, design, setting, sample size, duration of follow-up).
2. Study participants' basal characteristics (age, stage of the disease).
3. Intervention's characteristics (type of RT, dose, frequency).
4. Comparator's characteristics (control group without exercise, education or other type of exercise that is not RT).
5. Outcomes includes.
6. Results of interest (proportion of case incidence per group, relative risk of dichotomous data, or mean and SD per group for continuous data).

Assessment of risk of bias

Two authors will independently evaluate the risk of bias of each included study according to the Revised Cochrane Risk of Bias Tool (RoB 2.0).[57] Any discrepancy will be resolved by mutual consensus between the authors. If they are unable to reach a consensus, a third author will make the final decision.

RoB 2.0 evaluates the following domains: bias derived from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcomes and bias in the selection of the reported results. A series of signalling questions will be included for each domain to provide a structured approach to obtaining relevant information on bias risk assessment. For each domain, the possible risk of bias judgements will be low risk of bias,

some concerns and high risk of bias.[57] We will also graphically summarise the risk of bias.

Addressing missing data

A primary analysis will be done using all available data, followed by a sensitivity analysis. Furthermore, to reduce the risk of bias and increase the study's robustness, should the primary studies have incomplete data, the authors will be contacted.[63] If they do not respond after receiving two requests for data via email, an imputation method will be used for the missing values. This method will consist of a statistical evaluation based on the worst-case scenario, using STATA's 'metamiss' module for missing data.[64] This imputation's impact will be evaluated in the SR manuscript's discussion section.

Estimation of the treatment effect

Relative risk will be used on the dichotomous results.[65] As for the continuous results, when the result of interest is measured with the same scale, we will use the means difference (DM) with its respective 95% CI.[65] When the results of interest are measured with different scales, we will use the standardised means difference (SMD).[57]

Assessment of heterogeneity

Heterogeneity will be measured through the inconsistency test (I^2). An I^2 greater than 75% will be considered significant heterogeneity, between 40% and 75% as moderate heterogeneity and less than 40% as low heterogeneity.[66]

Assessment of publication biases

Publication biases will be evaluated if at least 10 RCTs are included in the meta-analysis. We will use Begg's test to analyse the Funnel plot.[67] 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.

Data synthesis

The results will be reported according to recommendations from the Cochrane Handbook for Systematic Reviews of Interventions.[68] The process of the selection of the studies will be illustrated in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.[68] The reasons for excluding a study in the phase of full-text reading will be described in a table where the reason that the study was excluded will be indicated. The characteristics of the included RCTs (study information, type of participants: age, stage of disease, interventions, comparator type; results of interest and adverse effects), will be reported in tables where all relevant information will be summarised.

For each comparison, we will pool the results of studies with similar characteristics in terms of participants, interventions and outcome measures. The data will be analysed using a frequentist random effects model with the restricted maximum likelihood estimator, as we expected variation in effects due to differences in study populations and methods. Forest plots will be constructed, showing the summary and 95% CI estimated in the meta-analyses.

All analyses will be carried out using Stata 18 (Stata Corp LP, USA).

Subgroup analysis and investigation of heterogeneity

We will consider all types of RT in this SR. In case moderate heterogeneity is found, together with the availability of information, we will perform an analysis of the subgroup according to the type of RT (intensity, frequency) and quality of life scale.[63]

Sensitivity analysis

We will perform a sensitivity analysis only if we include an appropriate number of studies[63] to evaluate the results' strength by repeating the analysis with the following adjustments:

- Restricting the analysis of studies that present low risk of bias.
- Analyse the results as SMD in all scales or individually as MD for each scale.

Summary of finding table

We will use the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) system focus to evaluate the evidence's certainty and the degree of recommendation.[69 70] We will use the GRADEpro GDT Software (https://gdt.gradepro.org/app/) to generate the 'Summary of finding table' for each result of interest. The quality of the evidence according to the GRADE focus will be classified as:[69 70] high, moderate, low or very low, according to the risk of bias, that is, inconsistency, indirectness, imprecision and publication bias.

Patient and public involvement

No patients will be involved.

Ethics and dissemination

This protocol does not require the approval of an ethics committee, as it is a secondary study. Special attention will be given to the relevance of the research question, and rigorous and transparent scientific methods will be employed. Clear criteria will also be established to recognise the contribution of each researcher and ensure respect for authorship rights.[71] The results will be disseminated through peer-reviewed publications.

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Contributors RAAE was responsible for the conception, study design, development of search strategies, data analysis, drafting the manuscript and final approval of the version to be published. PS contributed to the conception, study design, development of search strategies, data analysis, drafting the manuscript and final approval of the version to be published. RGA involved in the conception, study design, development of search strategies, data analysis, drafting the manuscript and final approval of the version to be published. CZ participated in the conception, study design, development of search strategies, data analysis, drafting the manuscript and final approval of the version to be published. RAAE is the guarantor.

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