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Acute and chronic effects of physical exercise on pain in breast cancer survivors during chemotherapy: a systematic review protocol

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ABSTRACT

Background: Pain is a common and clinically relevant symptom during chemotherapy for breast cancer, negatively affecting quality of life. Although physical exercise is recommended and considered safe during chemotherapy, it may acutely exacerbate pain while potentially reducing it in the long term. Therefore, this study aims to systematically review the acute and chronic effects of physical exercise on pain outcomes in breast cancer survivors undergoing chemotherapy.

Methods: This protocol follows PRISMA-P guidelines. Searches will be conducted in PubMed, Embase, Scopus, Web of Science, and CENTRAL. Eligible studies will include randomized controlled trials enrolling adults with breast cancer undergoing chemotherapy who participate in structured exercise interventions and have pain assessed using objective and/or subjective measures. Risk of bias will be assessed using RoB 2, and certainty of evidence using GRADE.

Discussion: By distinguishing short- and long-term effects, the review aims to clarify the role of exercise in pain management during treatment. Anticipated heterogeneity will be addressed through structured risk of bias assessment, subgroup and sensitivity analyses, and evaluation of evidence certainty.

Registration: The protocol is registered in PROSPERO (CRD420251102981).

KEY WORDS

Cancer pain; Breast tumor; Exercise oncology; Supportive care.

INTRODUCTION

Breast cancer (BC) is characterized by the uncontrolled proliferation of abnormal breast cells, leading to tumor formation with the potential to invade other tissues and distant organs, and encompasses a broad spectrum of tumor morphologies with distinct molecular profiles and clinical responses [1]. Globally, BC was the second leading type of cancer incidence in 2022, with an estimated 2.3 million new cases (11.6% of all cancer diagnoses), and the fourth leading cause of cancer mortality, accounting for approximately 666,000 deaths, while among women it remains the most commonly diagnosed cancer and the leading cause of cancer-related mortality worldwide [2].

Cancer treatment typically includes surgery to remove the tumor, chemotherapy, radiotherapy, hormone therapy, and immunobiological agents [3]. Chemotherapy is toxic to normal body cells and typically causes adverse events in patients, such as vomiting, alopecia, anemia, and fatigue [4]. In addition, during cancer treatment, patients may experience a condition known as “chemobrain”, characterized by cognitive dysfunction, general discomfort, and mood disorders [5]. These burdens raise concerns about other patient-reported outcomes, including pain, due to its close association with health-related quality of life [6].

In women with BC, 2 cycles of anthracycline chemotherapy did not alter body pain, as assessed by the Medical Outcome Study Short Form 36 (SF-36) [7], comparing pre- and post-chemotherapy assessments, and compared with a control group of apparently healthy women [8].

In this context, chemotherapy may be associated with a greater pain burden compared with antibody–drug conjugates. Randomized clinical trials comparing chemotherapy treatment of physician’s choice with trastuzumab deruxtecan reported more favorable pain-related outcomes in the trastuzumab deruxtecan groups, whereas chemotherapy alone showed no meaningful improvement in pain [6,9]. Similarly, sacituzumab govitecan was associated with reductions in pain symptoms when compared with chemotherapy [10]. Moreover, taxane-based chemotherapy appears to be associated with a worse pain prognosis than non-taxane regimens [11–14], including a higher frequency of myalgia and arthralgia during treatment [12,13].

Among breast cancer survivors (BCS) during chemotherapy, physical exercise (EX) can improve peak oxygen consumption ($\text{VO}_{2\text{peak}}$) [15], muscle strength [16] and pathological complete response when combined with dietary intervention [17]. Nevertheless, EX may also reduce fatigue [18] and prevent functional disability ($\text{VO}_{2\text{peak}} \leq 18.0 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, as reported by Foulkes et al. (2023)). However, one of the possible acute side effects of EX is pain.

Exercise-induced pain may occur acutely during sessions with high metabolic stress, due to hypoxia and reduced hydrogen potential (pH), as hydrogen ion accumulation leads to acidosis and nociceptor activation. In addition, exercise may lead to delayed-onset muscle soreness (DOMS), a late musculoskeletal pain response associated with exercise-induced microdamage and subsequent inflammatory processes, including edema and the release of mediators such as bradykinin and prostaglandins, which also stimulate nociceptors [19].

In young, untrained, and apparently healthy women, a single session of resistance training (RT) reduces peak torque (PT) and increases delayed-onset muscle soreness (DOMS) and muscle thickness compared with baseline, with these changes persisting for up to four days after the session [20].

The relationships among a session of EX, DOMS and the inflammatory cascade responsible for edema are illustrated in Figure 1.

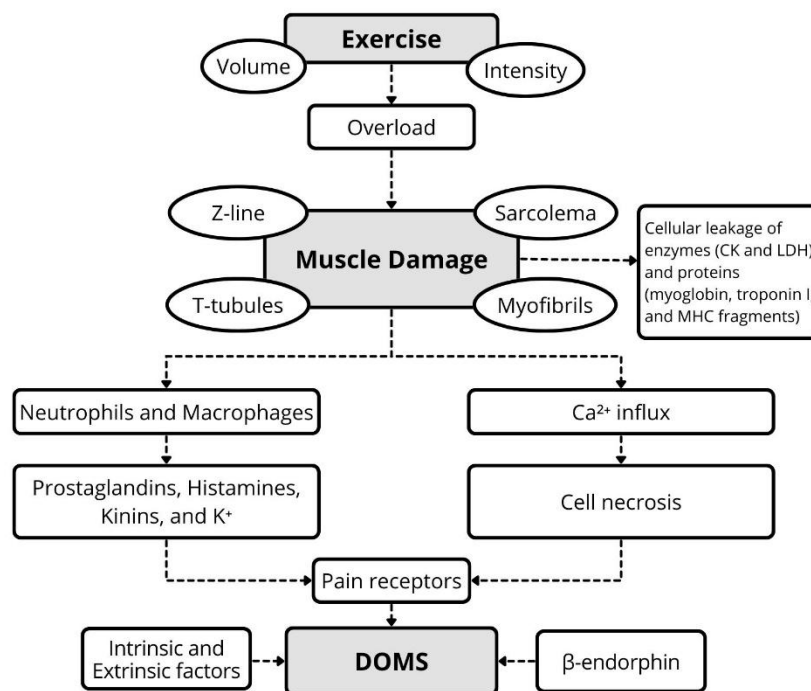


Figure 1. Theoretical representation of the relationships between exercise (EX), muscle damage, and delayed-onset muscle soreness (DOMS). CK = creatine kinase, LDH = lactate dehydrogenase, MHC = myosin heavy chain, Ca²⁺ = calcium, K⁺ = potassium. Adapted from Foschini, Prestes and Charro (2007) [21].

Conversely, exercise interventions have been evaluated for their potential to attenuate pain in breast cancer survivors. [22] found no significant differences in pain outcomes between exercise and usual care following axillary dissection. Similarly, a systematic review with meta-analysis assessed the effects of exercise on aromatase inhibitor-induced musculoskeletal symptoms and reported no significant effects of exercise on overall pain severity, although improvements were observed in bodily pain domain score of the SF-36, favoring exercise [23].

Other systematic reviews have examined the effects of exercise on pain and related patient-reported outcomes in women with breast cancer; however, these reviews predominantly focused on populations undergoing hormone, with some specifically restricted to women experiencing aromatase inhibitor-induced arthralgia, rather than patients receiving chemotherapy [23–26]. Consequently, systematic evidence regarding the chronic effects of exercise on pain during chemotherapy remains limited.

Even so, although EX interventions for BCS undergoing chemotherapy has been demonstrated to be safe, feasible, and effective [15–18,27–29], no systematic

review has examined their acute and chronic effects on pain in this population. Clarifying this issue is important to inform health professionals on the prescription and guidance of exercise for this population, particularly with regard to its potential role in pain in the short and long term.

Therefore, this study aims to systematically review the acute and chronic effects of physical exercise on pain indicators in breast cancer survivors undergoing chemotherapy. The authors hypothesize that exercise may acutely exacerbate pain intensity during exercise sessions while attenuating pain in the long term in breast cancer patients undergoing chemotherapy.

METHODS

This systematic review protocol was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement [30,31].

Registration

The review protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD420251102981). Any important amendments to this protocol will be documented with the date, description, and rationale for the change. Amendments will be reported in the final systematic review and, when applicable, updated in the PROSPERO record.

Bibliographic databases

The searches will be conducted by two independent researchers (N. M. A. D. and V. A. M) in the following electronic databases: PubMed, Excerpta Medica dataBASE (Embase), Scopus, Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL). For CENTRAL, searches will be restricted to records indexed as randomized controlled trials (Trials). The review will only include studies published in English. There will no search date restrictions. Other studies will be identified by: contacting authors or experts and reference list checking.

Search strategy

A simplified version of the PICOS strategy is shown in **Table 1**. The full and detailed search strategy is available in **Supplementary Material 1**.

Table 1. Simplified PICOS search strategy.

Complete strategy	((#1 AND #2) AND #3 AND #4) AND #5	
Population	#1	Breast Cancer
	#2	Chemotherapy
Intervention	#3	Physical Exercise
Comparator	*	*
Outcome	#4	Pain
Study Type	#5	Randomized Controlled Trials

**Comparator-related terms were intentionally omitted from the search strategy, as the review will include studies with any comparator.*

Eligibility criteria

The eligibility criteria are described according to the following participants, interventions, comparators, outcomes and study design (PICOS) framework:

Studies will be included if they (i) are peer-reviewed randomized controlled trials; (ii) enrolling adult (≥ 18 years) diagnosed with breast cancer (at any stage of the disease); and (iii) undergoing chemotherapy. The intervention must consist of (iv) physical exercise programs, such as resistance training, (including modalities using body weight, dumbbells, elastic bands, machines, or other strengthening devices), endurance training, combined training or other alternative exercise modalities (yoga, pilates, nordic walking, dance...).

All types of comparisons will be considered acceptable, such as Exercise \times Usual care, Exercise + Usual care \times Usual care. Exercise \times Any other type of physical exercise, Exercise + Usual care \times Usual care + Any other type of physical exercise. Although, different study designs will be analyzed separately in the results section.

Additionally, will only be included (v) studies that measured pain intensity, assessed using: specific pain intensity questionnaires; quality-of-life, fatigue, neuropathy, lymphedema and/or other types of questionnaires that contain a pain domain score; visual analog scales (VAS); or pain pressure threshold (PPT) measured by pressure algometry at any anatomical site.

Studies will be excluded if data from BCS undergoing chemotherapy cannot be extracted separately from other treatment phases (*e.g.*, radiotherapy or hormone therapy) of cancer types (*e. g.*, colorectal, cervical, or ovarian cancer). Trials in which the intervention does not involve structured physical exercise — such as psychological/behavioral therapies, surgical procedures, pharmacological or hormone therapy alone — will also be excluded.

Randomized controlled trial protocols and pilot studies will not be considered. Studies with multiple intervention arms (*e.g.*, exercise vs usual care vs psychological therapy) will not be excluded, provided that at least one eligible exercise arm and one acceptable comparator are present.

Selection process

All references retrieved from database searches will be imported into Rayyan for automatic followed manual duplicate removal. Study selection will be conducted in two stages by two reviewers independently and in a blinded manner. In the first stage, titles and abstracts will be screened according to the predefined eligibility criteria. Studies considered potentially eligible will proceed to the full-text assessment stage. In the second stage, full texts will be independently assessed for final inclusion. Disagreements at any stage will be resolved through discussion, and a third reviewer will be consulted if consensus cannot be reached. Reasons for exclusion at the full-text stage will be recorded and reported, and all studies assessed in full text but excluded from the review will be properly cited in the main text or supplementary materials. Reasons for exclusion at the full-text stage will be recorded and reported. The overall study selection process will be presented using a PRISMA flow diagram.

Data extraction

Data to be extracted will include participant characteristics, intervention characteristics (type, frequency, intensity, and duration), comparator details, pain-

related outcomes and measurement instruments, study design features, follow-up duration, and funding sources when available. Data will be extracted independently and in duplicate by two reviewers using a standardized and pilot-tested data extraction form. Discrepancies will be resolved through discussion or, when necessary, by consultation with a third reviewer. When required, study authors will be contacted to clarify or confirm missing or unclear information.

Study risk of bias and reporting bias assessment.

Risk of bias will be assessed using the Cochrane risk-of-bias tool for randomized trials, version 2 (RoB 2) [32].

Risk of bias will be assessed independently by at least two reviewers with a process to resolve differences. Additional information will be sought from study investigators if required information is unclear or unavailable in the study publications/reports.

The risk of bias will be assessed for each included study using the RoB 2 tool. Judgements will be made at the outcome level, and the overall certainty of evidence for each outcome will be downgraded in GRADE based on the risk of bias of the studies contributing to that outcome.

Reporting bias will be assessed through a funnel-plot analysis and, if applicable, an Egger's Regression Test.

Certainty of evidence assessment

The certainty of the body of evidence will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Data synthesis

Data synthesis is planned through meta-analysis when studies present comparable outcome assessment tools, allowing the combination of outcomes using either post-intervention scores or mean change values (Δ) from baseline for the intervention and control groups, whenever these data are available. Effect sizes will be expressed as mean difference (MD) when all studies use the same pain scale, or as

standardized mean differences (SMD, i.e., Hedges' g) with corresponding 95% confidence intervals (CI) when two or more different pain scales are used.

If applicable, subgroup analyses will be performed to assess whether exercise type, participant age, sex, comorbidities, tumor subtype, cancer stage, or other relevant characteristics influence pain intensity outcomes.

Several sensitivity analyses (leave-one-out analysis) will be conducted to assess the robustness of the pooled results and to examine the influence of each individual study on the overall effect estimates and heterogeneity.

Statistical heterogeneity will be assessed using τ^2 , H^2 , Q statistic and inconsistency I^2 test. The I^2 statistic estimates the percentage variance between studies and can be roughly interpreted as low (0%–40%), moderate (30%–60%), substantial (50%–90%), or considerable (75%–100%) heterogeneity. Remarkably, I^2 classifications overlap as these are rough guidelines suggested by [33].

Narrative synthesis

When quantitative synthesis is not applicable, a narrative synthesis will be undertaken. Studies will be grouped and summarized according to intervention and sample characteristics, pain assessment tools, and timing of outcome assessment. The direction and magnitude of effects on pain outcomes will be described and compared across studies, supported by structured tables to enhance transparency and interpretability.

DISCUSSION

This systematic review protocol proposes a methodologically rigorous synthesis of the available evidence on the acute and chronic effects of exercise on pain in breast cancer survivors undergoing chemotherapy. Pain was selected as the primary outcome due to its high clinically meaningful impact on quality of life in this population, while the restriction to randomized controlled trials was intended to strengthen causal inference and reduce the influence of confounding factors.

By integrating the current literature, this review may contribute to a clearer understanding of the role of exercise in managing pain during chemotherapy, as well as identify gaps in the existing literature. The findings may also inform future research

designs and support the refinement and optimization of exercise-based lifestyle interventions for breast cancer treatment, focusing on reducing pain.

Despite these strengths, some methodological challenges should be considered when interpreting the results of this review. Restricting inclusion to English-language publications may lead to the exclusion of evidence available in other languages. Furthermore, considerable heterogeneity is expected across studies with respect to participant characteristics (*e.g.*, age, disease stage, and comorbid conditions), exercise modalities (*e.g.*, resistance, aerobic, combined, and mind–body training), and pain-related outcomes (*e.g.*, lymphedema-associated pain, myalgia, arthralgia, and back pain). Such variability may reduce the statistical power of quantitative syntheses and limit the external validity of pooled effect estimates.

To address these limitations, systematic risk of bias assessments, as well as subgroup and sensitivity analyses, will be conducted when applicable, and the certainty of the evidence will be evaluated using established grading frameworks.

Emerging technologies and contemporary healthcare approaches may help address existing clinical and research gaps regarding their potential effects on patient-reported outcomes in breast cancer survivors, such as the effects of eHealth and virtual reality interventions on quality of life and pain management [34–36]. Therefore, future reviews should further investigate these topics.

From a practical perspective, the findings of this review may be relevant to health professionals involved in breast cancer care, clinical decision-making, and the development of exercise-based interventions, while also promoting higher-quality and transparent research, as well as evidence-based practice, aimed to mitigate breast cancer treatment-related side effects.

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Authors' contributions

N.M.A. conceived the research idea, drafted the protocol, and will act as guarantor of the review.

V.A.M. contributed to the planning of the data synthesis and will independently perform study screening, selection, data extraction, and risk of bias assessment.

R.B.V. is a systematic review expert with extensive experience in exercise sciences and biostatistics applied to health sciences and contributed to the overall methodological design of the study.

G.S.V. is also a systematic review expert with experience in physiotherapy, pain, and exercise-based interventions for pain management, and contributed to the methodological design from the conception of the protocol.

A.G.S. and R.R.A. are experts in exercise interventions for breast cancer survivors during chemotherapy and contributed to refining the research question and will support the critical synthesis of the data.

C.A.V. and R.R.A. are experienced breast cancer researchers and supervised N.M.A. throughout the study conception, planning, and writing process.

All authors reviewed and approved the final manuscript.

Data availability

No datasets were generated or analyzed in this study, as it is a protocol for a systematic review. Data generated during the review process will be made available from the corresponding author upon reasonable request.

Competing interests

The authors declare no conflict of interests.

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(CAPES), Brazil. These funding sources had no role in the design of the study, data collection, analysis, interpretation, or manuscript preparation.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the corresponding author used ChatGPT (OpenAI) to review and suggest improvements to text originally drafted by the authors, with the aim of refining language, clarity, and academic style. The AI tool was not used to generate scientific content, interpret data, or make methodological decisions. After using this tool, the corresponding author reviewed and edited the content as needed and take full responsibility for the content of the published article.

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