

*Protocol*

# Exercise as an intervention in preventing and reducing chemotherapy-induced cardiotoxicity among breast cancer survivors: Protocol for a scoping review

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## ABSTRACT

Cardiotoxicity is a serious side effect of chemotherapy in breast cancer survivors. Although the use of anthracyclines and trastuzumab improves the survival rate, it also produces cardiotoxicity over a period of time. Exercises can be a choice of non-pharmacologic interventions in preventing and reducing the cardiotoxicity effects of chemotherapy. Exercise has been recognized as an effective means of preventing cardiovascular disease and has been shown to lower the risk of cardiovascular mortality. Exercise may also protect the heart from the cardiotoxic effects of chemotherapy in breast cancer survivors. The goal of this scoping review is to summarize the evidence on exercise as a treatment to reduce the cardiotoxicity caused by chemotherapy in breast cancer survivors. This scoping review will identify the research gaps and the need for the future research. The frameworks proposed by Arksey and O'Malley, as well as the methodology for conducting scoping reviews published by the Joanna Briggs Institute, will be used. The standards for reporting will be the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews. A search strategy was established using keywords associated with the theme. A structured literature search will be conducted through databases such as PubMed, Ovid Emcare, Embase, Scopus, Web of Science, and the Cochrane Library. The titles, abstracts, and full text will be screened by two independent reviewers using Covidence software. Data will be extracted from included records using a pre-determined data extraction form by two independent reviewers. Extracted data will be evaluated and summarized in tabular and diagrammatic format. A narrative summary will accompany the results in the form of charts or graphs, describing how the results relate to the purpose and questions of the review.

**Keywords:** Breast cancer survivors, Anthracyclines, Trastuzumab, Chemotherapy-induced cardiotoxicity, Exercise

## INTRODUCTION

Breast cancer, accounting for 11.7%, is the most common type of cancer and the leading cause of cancer-related deaths in women. According to the Global Agency for Research on Cancer – GLOBOCAN 2020 – 2.2 million new cases of breast cancer will be diagnosed globally each year.<sup>[1]</sup> Early screening and advanced cancer management strategies improve survival rates significantly.<sup>[2]</sup> Despite the positive, a significant number of breast cancer survivors are dealing with the long-term side effects of chemotherapy changes in their bodies months or years after treatment.<sup>[3]</sup> The most common side effects of chemotherapy in breast cancer survivors are tiredness (fatigue), as well as an increased risk of cardiac dysfunction and functional disability.<sup>[4]</sup> Chemotherapy-induced cardiotoxicity is recognized as a serious clinical

issue, limiting treatment options, and contributing to the risk of cardiovascular morbidity and mortality in breast cancer survivors.<sup>[5]</sup> Cardiotoxicity is commonly associated with cytotoxic therapies, particularly the use of chemotherapeutic agents, in the setting of breast cancer.<sup>[5,6]</sup> Cardiotoxicity is defined as a decrease in the left ventricular ejection fraction of more than 10% to a value of 53%, as proposed by the American Society of Echocardiography and the European Association of Cardiovascular Imaging.<sup>[7,8]</sup> Chemotherapy-induced cardiotoxicity is a continuous and dose-dependent process.<sup>[9,10]</sup> The first sign of cardiotoxicity is acute myocardial damage, which is detected by elevations in circulating cardiac biomarkers.<sup>[11,12]</sup> Decrease in the left ventricular function might eventually lead to heart failure. In addition to the manifestations associated with

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chemotherapy, breast cancer survivors frequently have existing cardiovascular risk factors.<sup>[13]</sup> It is established that exercise reduces cardiovascular disease by reducing the effects of risk factors.<sup>[14]</sup> Exercise training along with routine cancer treatment may reduce cardiotoxicity by improving cardiac function.<sup>[15,16]</sup> It will be worthwhile to identify and analyze evidence pertaining to intervention in preventing or reducing chemotherapy-induced cardiotoxicity in breast cancer survivors.

## RATIONALE

This scoping review will summarize the evidence on how exercise as an intervention can prevent or reduce chemotherapy-induced cardiotoxicity in breast cancer survivors.

### Objectives

This scoping review will find and analyze the evidence pertaining to exercise as an intervention in preventing or reducing chemotherapy-induced cardiotoxicity among breast cancer survivors.

## MATERIALS AND METHODS

In general, this protocol will adopt the methodological framework developed by Arksey and O'Malley.<sup>[17]</sup> Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) will be used to report the studies. Arksey and O'Malley's framework comprises six stages, five of which are required. The phases are as follows:

1. Research question formulation.
2. Identification of appropriate articles.
3. Selecting relevant studies.
4. Documenting the data.
5. Organizing, summarizing, and reporting the results.
6. Consultation exercise (optional).

## RESEARCH QUESTION

This review will map the scope of research on the effects of exercise in preventing chemotherapy-induced cardiotoxicity among the breast cancer population. The primary question for this scoping review is as follows:

- 1) Does exercise as an intervention help to prevent chemotherapy-induced cardiotoxicity among breast cancer survivors?

This scoping review will answer the following secondary questions in addition to the primary question:

What type of exercise interventions are used in breast cancer survivors with chemotherapy-induced cardiotoxicity?

Do the studies have a focus?

- a) On risk factors and the prevention of adverse consequences?
- b) Focuses on factors that support health and wellbeing?

## STUDY IDENTIFICATION

This scoping review will follow a three-stage systematic approach to ensure that all available published and gray literature are considered. As recommended, an initial search was conducted on MEDLINE (PubMed) and Ovid (Embase). The MeSH terms identified from databases will allow us to link previously unidentified terms connected with search components.

The information retrieved was used to develop a complete and inclusive search strategy, which was then adapted to map each database in the second stage. Ovid Emcare, Scopus, Web of Science, the Cochrane Library, and gray literature databases such as ProQuest for Healthcare Research and Quality will be searched. A preliminary full search strategy for MEDLINE (PubMed) is shown in [Table 1].

In third stage, the reference list of all studies will be screened for in-depth research. Studies published from 2016 to December 2021 will be included in the study.

### Inclusion criteria

1. Studies conducted on humans and published in the English language from 2016 (past five years) onward.
2. Research studied the effect of exercise in preventing or reducing cardiotoxicity in breast cancer survivors and managed with chemotherapy.

## PARTICIPANTS

Breast cancer survivors those who developed chemotherapy-induced cardiotoxicity.

## CONCEPT

Exercise used as intervention in preventing chemotherapy-induced cardiotoxicity among breast cancer survivors.

## CONTEXT

Over the years, research on chemotherapy-induced cardiotoxicity and its effects on cardiac health and quality of life have grown. Exercise may aid in the prevention or reduction of cardiotoxicity during and after chemotherapy treatment among breast cancer survivors. As a result, it is preferable to limit this review to recent studies. Studies published before 2016 will be excluded, as stated previously.

## TYPES OF SOURCES

The primary research involving human subjects will only be considered.

### Study selection

Following the preliminary search, all the identified citations will be imported to Covidence software, and duplicate studies will be removed. The review process will be divided into two stages. Two independent reviewers (KR and PB) will assess the studies as per the predetermined criteria. At the

**Table 1:** Preliminary search strategy (MEDLINE)**On August 23, 2021, a full search strategy for MEDLINE was conducted.**

| Search type | Search terms (Using MeSH and all filters)  | Retrieved records/results |
|-------------|--|---------------------------|
| #1          | ((breast cancer) OR (breast neoplasm)) OR (breast carcinoma)   | 451,967                   |
| #2          | 3,957,684  |                           |
| #3          | 32,663   |                           |
| #4          | 5,745,114  |                           |
| #5          | ((exercise) OR (aerobic)) OR (endurance training)) OR (anaerobic)) OR (resistance training)  | 655,545                   |
| #6          | ((((breast cancer) OR (breast neoplasm)) OR (breast carcinoma)) AND (((chemotherapy) OR (cancer therapy)) OR (drug therapy)) OR (chemotherapeutics agents)) OR (anthracyclines)) OR (trastuzumab))) AND (((cardiotoxicity) OR (cardiac toxicity)) OR (chemotherapy-induced cardiotoxicity)) OR (chemotherapy-induced cardiac toxicity)) OR (anthracycline-induced cardiotoxicity)) OR (trastuzumab-induced cardiotoxicity))) AND (((prevention) OR (preventing)) OR (prevent)) OR (reducing)) OR (reduces)) OR (reduction))) AND (((exercise) OR (aerobic)) OR (endurance training)) OR (anaerobic)) OR (resistance training)) | 47                        |
| #7          | Filters: In the past 5 years   | 35                        |

first step, the titles and summaries will be screened. In case of non-consensus between two reviews, inclusion or exclusion of studies based on preliminary screening the abstract the second level of screening will be carried out, if both reviewers come to an agreement to exclude the study, it will be excluded from the study.

The full text of studies based on preliminary screening will be retrieved and assessed to ensure that they meet the inclusion criteria at the second level of the screening process.

The detailed search report will be documented and presented in a PRISMA-ScR flowchart. Details of excluded studies with appropriate reasons will be documented and reported.

## DATA EXTRACTION

A data extraction template with the following criteria will be used.

- Researchers.
- Published year.
- Where the study was published or conducted
- Aims and objectives.
- Research sample.
- Research design.
- Exercise type + details (e.g., aerobic, anaerobic, timings, and dosage).
- Supervised/unsupervised exercise.
- Study aims and outcomes (e.g., cardiotoxicity outcome – cardiac biomarkers) were investigated.
- Key findings related to the scoping review objectives (including any assessment of feasibility of intervention).

This process will be overseen by two independent reviewers.

## Data synthesis and report generation

The extracted data will be organized, documented, and described in accordance with the objectives. Tabular and graphical data representations will be used to demonstrate the findings. Narrative descriptions will be provided wherever required. The significance of the results and their inferences for further research and practice will be deliberated. The findings will be reported using the PRISMA-ScR.

## Patient and public involvement

This study design and conception were not influenced by patients or the general public.

## Ethical considerations

The proposed work does not require ethics clearance as it analyzes the published data. The findings will be submitted to an open-access peer-reviewed journal for publication. This scoping review is registered with Open Science Framework (OSF) with the registration number <https://osf.io/mpqf3>.

## Strengths and limitations of this study

This will be the first scoping review to identify the importance of exercise in preventing chemotherapy-induced cardiotoxicity among breast cancer survivors.

The PRISMA-ScR for scoping reviews will be used, ensuring that findings are reported transparently.

One significant limitation of this review would be inclusion of studies published in only English. Only articles published in peer-reviewed journals and gray literature databases will be included in the study.

**Authors' contributions**

The authors state that each author contributed significantly to the final manuscript and that they all agree on all aspects of it.

**Declaration of patient consent**

Patient's consent not required as there are no patients in this study.

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Nil.

**Conflicts of interest**

One of the authors is an editorial board member.

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