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Effects of combined and resistance training on the inflammatory profile in breast cancer survivors: A systematic review

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ABSTRACT

Objective: The present systematic review aimed to verify the effect of resistance and combined training on the inflammatory profile of breast cancer survivors.
Design: The searches were made on the platforms PsycINFO, PubMed, Cochrane, Science Direct and Scopus, from 1996 to 2017, using the keywords: cancer survivors, cancer treatment, cancer patients, breast cancer, inflammation, inflammatory profile, immune function, resistance training, strength training, weight training, physical activity, concurrent training and combined training. References of selected articles were also considered. Seven studies fulfilled the criteria adopted for analysis.
Results: None of these studies have shown reduced inflammatory markers in breast cancer survivors undergoing combined or isolated resistance training.
Conclusions: It is not yet possible to conclude which resistance and/or combination training protocol is capable of improving the short-term inflammatory profile in this population. Future studies should seek to establish how structural training variables (intensity, volume, density, intra- and inter-series recovery, among others) act on anti-inflammatory processes in breast cancer survivors.

1. Background

The incidence of breast cancer (BC) in the world has progressed alarmingly in recent years. From 2008–2012, the number of new BC cases increased by 20% and in 2012 a total of 1.7 million new cases and 522,000 deaths were recorded[1]. In contrast to this progression of BC, early detection in concomitance with the effectiveness of new cancer treatments in the reduction and elimination of tumor burden has changed the natural course of survival in this population.[2,3]

However, the numerous adverse effects of these treatments, such as fatigue,[4] sarcopenia,[5] osteopenia,[6,7], cardiovascular dysfunction,[8] overweight,[9] immunosuppression,[10] systemic inflammation[11] and sleep disturbance,[4] contribute to worsening health status and lead to poor quality of life in BC survivors[12]. Eventually, the inflammatory process triggered in BC survivors is an underlying pathway both for the triggering or worsening of comorbidities as well as for tumor recurrence.[13]

Several studies have demonstrated that 12–16 week interventions involving aerobic, resistance and combined training are able to reduce proinflammatory cytokines in other chronic non-infectious chronic diseases,[14–16]and that this reduction is associated with improvements in aerobic conditioning[15] and increased muscle mass.[17]

In BC survivors, specifically, the results involving physical training and inflammatory profile are still quite controversial, especially related to which type of intervention is applied. Recent studies have shown that moderate intensity aerobic training (AT) and muscle relaxation techniques, such as yoga, were effective both to decrease markers of inflammation and to improve immune function in BC survivors in the posttreatment period[18–21]. On the other hand, studies that involved isolated intervention from resistance (RT)[22,23]or combined (CT, where CT = AT + RT) training[24–26] did not produce the same results in relation to the reduction of pro-inflammatory markers. These differences in results on inflammatory markers may be related to several other

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factors, such as the baseline levels of physical activity and health conditions of cancer survivors, since the benefits of RT and CT are notorious in other groups.

In healthy individuals, RT and CT have been recognized as efficient in generating the adaptations and physiological stimuli involved in both the decrease of the body fat and the increase of muscle mass[27,28] and the improvement in the inflammatory profile provided by exercise is related to these effects in the body composition.[17] But in BC survivors, there are still questions that need to be answered about the application of these types of training. Is there improvement in the levels of inflammatory markers with the use of RT and CT? What exercises can be recommended? What intensities and training volumes can be safely applied in this population?

Some responses emerged after a recent systematic review with meta-analysis by Meneses-Echávez et al.[21], but their conclusions deserve attention due to the limitations pointed out by the authors themselves. Although that study demonstrated that physical training significantly improves inflammatory mediators in BC survivors, the study does not stratify the results by modality, frequency, and duration of training. In addition, a bibliographical tracking on the subject identifies three studies that were not included in that review.[22,23,29] Thus, the present review aimed to update the information about the subject, considering only data from studies of the effects of RT and CT on inflammation associated with cancer, its treatment and comorbidities, seeking to distinguish the anti-inflammatory effects of physical training in survivors of BC, in order to try to establish a consensus on the impact of resistance and/or combined training on inflammatory cytokines in this type of population.

2. Materials and methods

2.1. Search strategy

The methodological design of the study is characterized by a systematic review of the literature based on a bibliographic research using the databases PsycINFO, PubMed, Cochrane, Science Direct and Scopus.The search was performed by a couple of researchers using the same search method. The papers were considered only when both researchers found the same search results.The keywords and Boolean terms used in the systematic search operation were: ‘cancer survivors’ or ‘cancer treatment’ or ‘cancer patients’ or ‘breast cancer’ and ‘inflammation’ or ‘inflammatory profile’ or ‘immune function’ and ‘resistance training’ or ‘strength training’ or ‘weight training’ or ‘physical activity’ or ‘concurrent training’ or ‘combined training’, including studies from 1996 to 2017. In addition to the search in these databases, manual searches were performed in the reference lists of the selected studies. The searches were conducted in June 2017. No language restrictions were applied.

2.2. Selection of studies

An initial screening in the databases by two of the authors (MAFJL and FJA) of this paper was used to identify potentially relevant studies based on their titles and abstracts. When one or both reviewers disagreed regarding the fulfillment of the inclusion criteria for a particular study and when the information was inadequate to enable the decision-making, complete copies of the texts were analyzed by both researchers. In a second moment, the articles compiled in the initial stage were fully analyzed, having been selected those that met all the following criteria of eligibility: 1) articles with controlled or uncontrolled clinical trials or pilot studies (with robust samplings) that have compared the group that undergone intervention with a control group; 2) articles which included female survivors of BC (after surgery) under 70 years of age; and 3) articles that evaluated the effects of resistance and/or combined exercise on the inflammatory profile (cytokines and/or interleukins) in breast cancer survivors. Studies that included 1) populations of survivors of other cancers; 2) other types of intervention (drugs, dietary supplements, resources and rehabilitation materials); and 3) practice of exercises that did not use the upper limb, were excluded from the present review. Reviewers were not blind to authors, journals or results. Studies that were identified by mutual consent were included in the review. In cases of disagreement between two researchers, a discussion with all authors was held to reach consensus. The entire preparation process of this systematic review followed the guidelines known as PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[30].

2.3. Evaluation of study quality

The methodological quality of the studies was independently assessed by two researchers using the Delphi criteria list,[31] which contains a set of nine criteria for quality assessment of randomized clinical trials. Since it is too possible to have blinded participants and care providers in this kind of intervention study, only the utilization of blinded evaluators was considered. Each criteria item is associated with a question that must be answered with yes (+) or not (−).

2.4. Data extraction

Two of the researchers in this review compiled relevant data from each study into an Excel worksheet: 1) study characteristics (first author, year of publication and sample size); 2) characteristics of the intervention (type of training, exercises applied, frequency, intensity and duration of the intervention); 3) methods of evaluation; and 4) intervention results related to the inflammatory profile. Any disagreements were verified and discussed among all authors until a consensus was reached.

3. Results

Fig. 1 illustrates all steps used in the selection of articles. Based on the strategy defined, the search resulted in 583 articles. After removing duplicates (n = 213), 370 potential articles remained to be evaluated. In a first analysis, through the reading of the title, 302 did not fit the theme, having thus remained 68 articles. After reading the abstracts of these preselected articles, 58 were not related to the proposed theme, with only 10 articles remaining. By means of more in-depth analyzes of these 10 articles, three articles were withdrawn in light of the objectives of the inclusion criteria study. The remaining seven articles constituted the group of publications considered in the proposed analysis.

The seven articles selected were evaluated according to the Delphi criteria list. Nine criteria were examined in each of the studies. The evaluations of these studies are shown in Table 1. In total, one study met four criteria,[32] three studies met five criteria,[24,29,33] and the other studies met more than six criteria.[22,23,26] Two of those studies failed to hide the allocation.[24,32] Just one of those studies was evaluator-blinded.[22]

Table 2 presents a summary of studies selected for this review. Of these, three studies intervened with RT[22,23,29] and four with CT[24,26,32,33] protocols. The intervention time ranged from 12 weeks to 6 months, with intensities of 60–80% of maximal repetition and 70–80% of maximal aerobic capacity, with frequency varying from 2 to 3 times per week. In addition, four studies[22,24,32,33] did not mention progression of intensity throughout the intervention. The most analyzed cytokines were IL-6, IL-8, IL-10 and TNF-α. None of the studies showed statistically significant reduction in blood levels of inflammatory markers after the intervention.

As can be seen in Table 2, there is great heterogeneity in the profile of variables analyzed in the different studies considered here. The most recurrent pattern of analysis involves IL-6 cytokines, considered in six of those studies, IL-10, considered in three of the studies, and TNF-α, considered in four studies. Therefore, Table 3 was constructed with the