



## **Inflammatory biomarkers and Tumoral Growth Factors are Modulated By Exercise In Breast Cancer Survivors**

**Running title:** Growth factor system and exercise in breast cancer survivors

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## Abstract

**Introduction:** Insulin-like growth factors (IGF's) play a crucial role in controlling cancer cell proliferation, differentiation and apoptosis. Exercise has been postulated as an effective intervention in improving cancer-related outcomes and survival, although its effects on IGF's are not well understood. This meta-analysis aimed to determine the effects of exercise in modulating IGF's system in breast cancer survivors.

**Methods:** Databases of PubMed, EMBASE, Cochrane Central Register of Controlled Trials, EMBASE, ClinicalTrials.gov, SPORTdiscus, LILACS and Scopus were systematically searched up to November 2014. Effect estimates were calculated through a random-effects model of meta-analysis according to the DerSimonian and Laird method. Heterogeneity was evaluated with the  $I^2$  test. Risk of bias and methodological quality were evaluated using the PEDro score.

**Keywords:** Breast cancer, Exercise, Insulin-Like Growth Factor Binding Proteins, Tumor Microenvironment

## Introduction

Insulin-like growth factors (IGFs) are mitogens that are involved in regulating cell proliferation, differentiation, and apoptosis [1]. The IGF system includes the single-chain polypeptides IGF-I and IGF-II and six binding proteins (IGFBP-I - IGFBP-6) [2]; the IGFBP proteases may also be considered as part of the IGF system because they indirectly regulate the action of IGFs [3]. Evidence is beginning to accumulate, however, that also implicates the IGF family in several metabolic and disease states, including type 1 diabetes and cancer, especially of the lung, breast,



and prostate [3-6]. Both IGF-I and IGF-II exert mitogenic and antiapoptotic actions and regulate tumor cell proliferation and differentiation [3]; however, IGFBP-3 regulates the mitogenic action of IGFs and inhibits their antiapoptotic effects in breast cancer cells [7]. In addition, high levels of IGFBP-3 can be associated with low concentrations of estrogen receptor (ER) or progesterone receptor and large tumor size, suggesting a poor prognosis and decreased survival [8,9].

Exercise has been proposed as an effective non-pharmacological intervention to promote psychological well-being during and following cancer treatment [10-12]. However, the role of exercise in the modulation of the IGF system remains poorly understood, although some data from experimental studies continue to emerge. At the same time, other researchers have proposed that exercise can be used as a mechanism to decrease IGF levels and aid in cancer prevention [13]. These viewpoints are contradictory, as one suggests that exercise will increase IGF levels, and the other suggests that increased activity will decrease IGF levels [14].

Numerous studies have reported higher levels of circulating IGF associated with physical activity, although many other studies have reported no difference or even a decrease in IGF levels. For example, in 2009, Irwin et al. [15] reported significant reductions in IGF-I and IGFBP-3 in postmenopausal women after a 6-month walking-based intervention compared to non-exercisers. However, Sprod et al. [16] found no significant changes in IGFBP-I and IGFBP-3 after a 12-week intervention of Tai Chi Chuan in twenty-one breast cancer survivors. A limited comprehensive summary has been published that systematically reviews all literature on this topic. In light of this lack of consensus in the literature, the aim of this meta-analysis was to determine the effects of exercise in modulating the IGF system in breast cancer survivors.

## Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement to conduct this review [17]. No funding was received. The PubMed, EMBASE, Cochrane Central Register of Controlled Trials, EMBASE, ClinicalTrials.gov, SPORTDiscus, LILACS and Scopus databases were systematically searched between May and November 2014 by three blinded authors (JFME, JSRV and EGJ) without restrictions on language. The reviewers



were blinded to both the name of the authors and the results of the studies. The following search terms were used: 'breast cancer' and 'exercise' or 'physical activity' and 'insulin' or 'glucose' or 'growth factors' or 'IGF' or 'IGFBP'. The reference lists from retrieved articles were checked to identify additional titles. The authors also examined data from previous reviews published by Ballard-Barbash et al. [18] and Löf and colleagues [19]. Moreover, two authors (MI and RR-V) searched for other relevant trials listed in journals that specialized in oncology (e.g., *Breast Cancer Research, Cancer, Cancer Epidemiology, Biomarkers & Prevention, Journal of Clinical Oncology, Journal of Oncology Practice* and *The Lancet Oncology*). Aiming to provide stronger sensitivity to the search process, the authors contacted high-profile researchers in this area to ask for other possibly relevant trials, published or unpublished.

### ***Selection criteria***

Two authors (JSR-V and JEC-B) independently checked all of the retrieved trials against the eligibility criteria (Box 1). The title and abstract were examined, and full-text was obtained if ambiguity regarding the eligibility of the study was noted. A third author arbitrated the consensus for eligibility (EG-J). Attempts were made to contact authors of trial reports if clarification was necessary.

A cancer survivor was defined as a person who is diagnosed with cancer and survives from the time of diagnosis through the balance of his or her life [20]. Exercise interventions were defined as a form of physical activity that is planned, structured and repetitive and aims to improve fitness, performance or health [21]. Hence, we included randomized controlled trials (RCTs) that compared exercise interventions (aerobic, resistance training and stretching exercises such as Tai Chi Chuan) with a control group (conventional care) in women with breast cancer and that measured the following biomarkers: insulin-like growth factors (IGF-I and IGF-II), insulin-like growth factor-binding protein (IGFBP-I and IGFBP-3), and insulin serum levels as well as insulin resistance and glucose. This set of biomarkers was selected because they play a vital role in the tumoral microenvironment and cancer prognosis [22,23]. Finally, we excluded trials where exercise was combined with another intervention.

### ***Methodological quality assessment***



The methodological quality of the studies including their risk of bias was assessed using the Physiotherapy Evidence Database (PEDro) scale [24]. The PEDro scale scores the methodological quality of randomized trials and has a maximum possible score of 10. Scores were based on all information available from both the published version and from communication with the authors. A score of 5 of 10 was set as the minimum score for inclusion in the review. The score for each included study was determined by two trained authors (JFM-E and MI). Disagreements were solved by consensus or by a third reviewer (JEC-B). We calculated the inter-observer agreement using the *Kappa (k)* statistic [25]; the agreement rate between authors was  $k=0.91$  for methodological quality assessment.

### ***Ethics declarations***

Two investigators (JFM-E and RR-V) confirmed that the studies included had ethics committee approval and that the participants signed consent forms.

### ***Data extraction and analysis***

Relevant data were extracted independently by two reviewers (JFM-E and RR-V) using a standard form; a third author (JEC-B) mediated in cases of disagreement. The reviewers extracted information about the methods (i.e., design, breast cancer staging, participants and interventions) and the outcome data for the experimental and control groups. High agreement was observed between reviewers ( $k=0.89$ ).

Changes in the Insulin-Like Growth Factors were reported as differences between arithmetic means pre and post exercise interventions. Statistical heterogeneity was evaluated using the  $I^2$  statistic ( $I^2 = [(Q - df) / Q] \times 100\%$ , where  $Q$  is the chi-square statistic and  $df$  is its degrees of freedom), which was defined according to the following categories [26]: negligible heterogeneity, 0% to 40%; moderate heterogeneity, 30% to 60%; substantial heterogeneity, 50% to 90%; and considerable heterogeneity, 75% to 100%. Other possible sources of heterogeneity were evaluated via subgroup analysis and a cumulative meta-analysis model if necessary. We conducted a random-effects model of the meta-analysis when substantial heterogeneity ( $I^2 > 50\%$ ) was present. Continuous outcomes were reported as the Mean Difference (MD) with the 95% confidence interval (95% CI), with statistical significance set at a  $P < 0.05$ . Publication bias was



examined using Egger's test ( $P < 0.05$ ) and the funnel plot based on the number of studies included (i.e. if more than 10 trials were included). Based on data availability, we conducted subgroup analysis to explore the particular effects of the modes of exercise separately. All analyses were conducted by JFM-E using Stata (Version 12.0; Stata Corp, College Station, TX).

## Discussion

The most remarkable finding from this meta-analysis was that exercise training improved the serum levels of IGF-I, IGF-II, IGFBP-I and IGFBP-3 in breast cancer survivors after successful anticancer treatment. Similar conclusions have been reported in previous experimental studies [15,26,28]. Moreover, it is important to highlight that this is the first meta-analysis that has summarized the effectiveness of exercise training in modulating the IGF system in breast cancer survivors because a previous systematic review regarding exercise and blood biomarkers in breast cancer survivors was published by Löf and colleagues [19], but the authors did not undertake data synthesis analysis.

IGF-1 exerts both mitogenic and antiapoptotic effects in breast cancer cells that have been linked to a poorer prognosis [30] and increased all-cause mortality [31]. The type of exercise did not appear to affect any putative association; however, it is probable that different exercise modalities cause different responses in IGF-1. Our pooled analysis demonstrated that exercise reduced IGF-I concentrations in women with breast cancer after successful treatment. These findings are consistent with those published by Fahey et al. [26], in which a 15-week aerobic exercise intervention resulted in significant decreases in IGF-I levels (10.9%) in fifty-three postmenopausal breast cancer survivors. Data from a Yale study [15] also confirm our findings; in this study, the authors found an 8.9% significant reduction in IGF -I in an experimental group composed of 38 breast cancer survivors that completed 150 min/wk of moderate intensity aerobic exercise during five weeks compared to a control intervention (i.e., instructions for patients to maintain their current physical activity level). Therefore, based on this evidence, it is possible to confirm that exercise training is associated with long disease-free survival rates in women with breast cancer likely via IGF-1 modulation. This statement requires further well-conducted



prospective studies for total confirmation. Another consideration in assessing studies using an exercise intervention is the timing of blood sampling in relation to exercise. Most studies that have demonstrated a post-exercise increase in IGF-1 found an immediate post-exercise spike followed by a gradual return to baseline or lower than baseline IGF -1 levels over the next 30 min to several hours [13].

It has been demonstrated that IGFBP-3 restricts IGF-1 availability and biological activity [32]. Therefore, low levels of IGFBP-3 have been associated with an increased risk of breast cancer [33] and a poorer prognosis and have been postulated as predictors of distant recurrence of breast carcinoma in postmenopausal women [34]. We found that exercise training increased IGFBP-3 serum levels in breast cancer survivors, although high statistical heterogeneity was observed in the overall effect estimate ( $I^2=84.2\%$ ). We obtained similar results for the aerobic exercise subgroup analysis. These findings are consistent with those published by Fairey et al. [26] and Irwin et al. [15] from the Yale study described above. In addition, when adjusted by exercise mode in the subgroup analysis, we found that Tai Chi was an effective intervention for increasing IGFBP-3 serum levels in breast cancer survivors, although statistical significance was not reached. Similar results were recently published by Janelins et al. [28] in a randomized controlled trial that included 19 breast cancer survivors, in which a 12-week exercise intervention of Tai Chi increased IGFBP-3 serum levels compared to non-exercise. Conversely, non-significant changes in IGFBP-3 were observed by Sprod et al. [16] in a more recent study with a similar intervention using Tai Chi. Interestingly, the authors reported an association between changes in IGFBP-3 and physical functioning, suggesting a link between changes in IGF binding proteins and some domains of quality of life in breast cancer survivors, although these associations warrant additional research. However, several studies that have reported a change in IGFBP-3 following an acute exercise challenge generally found a pattern similar to that found for total IGF-1 [13].

Regarding the secondary outcomes of this meta-analysis, our analyses showed that exercise produces significant increases in insulin and significant decreases in the insulin resistance of breast cancer survivors; reductions in the glucose levels did not reach statistical significance. Subgroup analysis by mode of exercise was limited for insulin and insulin resistance due to the



number of studies included. Similar to our results, Sprod et al. [16] reported slight increases in insulin levels after a Tai Chi intervention. Nonetheless, other studies have reported mixed findings. Schmitz et al. [29] found no changes in insulin or glucose after weight training exercise in 85 breast cancer survivors; Ligibel et al. [35] detected significant reductions in insulin levels after a twice-weekly resistance training intervention for 16 weeks in breast cancer survivors. Lastly, Irwin et al. [15] stated that the lack of changes in insulin and glucose levels can be affected by weight status at baseline measurements (i.e., obese breast cancer survivors have higher insulin levels than participants with normal or lower weight), suggesting that heavier participants can benefit more from exercise compared to leaner participants with respect to changes in glycemic control.

In this sense, several biologically plausible mechanisms could explain the effects of exercise in modulating the IGF and IGFBP systems. It is widely known that exercise has the potential to reduce both hepatic and muscle insulin resistance and to increase glucose availability due to insulin signaling pathways, improvements in capillary density leading to a better delivery of muscle glucose, increases in glucose protein transporters and effects on mRNA [36]. These conditions decrease the insulin concentration, which is reflected by lower concentrations of IGFs via insulin-mediated changes in IGFBP concentrations [14]. However, further research is needed to confirm these mechanisms, especially in breast cancer survivors during and after anticancer treatment regimens, and gain insight regarding the benefits that exercise and multidimensional behavioral change interventions can provide on cancer treatment related outcomes and survival, moving from preventive strategies toward patients facing cancer.

Only one study examined the effects of resistance training alone, and this method was also beneficial [29]. The effects of resistance exercise have not been addressed by the American Cancer Society but have been examined recently in people undergoing cancer treatment [37]. However, the present review indicates that more evidence regarding resistance training alone would be helpful in advising people with cancer who are undergoing cancer therapy whether this type of training is helpful in isolation. To understand the possible mechanisms, more information is required regarding the effects of initial chemotherapy and radiation therapy on muscle satellite (progenitor) cells that are activated to proliferate in response to resistance exercise [10,11].



### *Strengths and limitations*

To our knowledge, this is the first meta-analysis to evaluate the changes on insulin-like growth factors and their binding proteins after exercise training in breast cancer survivors. Our results provide novel insight regarding the role of exercise as a non-pharmacological and non-cytotoxic effective intervention in modulating the tumoral microenvironment as well as in the management of cancer treatment-related side effects (i.e., fatigue, depression and impairments of quality of life). In addition, there were numerous methodological limitations that impacted the generalizability of studies, including a lack of adjustment for confounding factors (e.g., plasma volume, participant age or body composition) and a lack of consideration of effect modification [13]. Furthermore, our findings have crucial implications on cancer recurrence and disease free survival rates. In addition, all studies included exhibited moderate to high methodological quality and low risk of bias, which is an important issue in terms of external validity.

Nevertheless, some limitations with regard to our study exist that are important to state. The overall effects estimates were increased due to different modes of exercise across the studies included, although such differences were approached through models of subgroup analysis according to the mode of exercise. High statistical heterogeneity levels were detected for most of the effect estimates, which suggests some caution when interpreting our findings. This evidence of heterogeneity was counteracted by a random effects model of analysis and can be explained by differences in some characteristics of exercise such as intensity, duration, intervention length, follow up periods and adherence rates across studies. Furthermore, dose-response relationships were not explored due to the number of studies included, and further trials might provide specific details regarding training intensity, duration and length of exercise interventions to strengthen the consensus in this field. Finally, considering that all studies involved women who completed their therapeutic treatments, it is important that further studies include patients during the active treatment stages to elucidate the effects of exercise on IGFs in patients undergoing anti-cancer treatment.

### **Conclusion**



Exercise training is an effective and safe intervention for the improvement of serum levels of the IGF system and its binding proteins (IGFBP-I and IGFBP3) as well as for insulin and glucose control in breast cancer survivors, suggesting a beneficial role of exercise for the tumoral microenvironment and breast cancer recurrence and disease free survival rates in women with breast malignancies. Important components for future research have been identified that should address many of the limitations found in the reviewed studies, which would advance this area of research by answering questions on exercise, IGFs, and human health, an area that is growing in interest and importance. Further high-quality studies are necessary to determine an optimal exercise program and to assess the clinical relevance of the results of available research.

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## **List of abbreviations**

CI: Confidence Interval

ELISA: Enzyme-Linked Immunosorbent Assay

IGF: Insulin-like Growth Factors

IGFBP: Insulin-like Growth Factor Binding Protein

MD: Mean Difference

PEDro: Physiotherapy Evidence Database



RCT: Randomized Controlled Trials

SD: Standard Deviation

## Authors' contributions

JFM-E and RR-V participated in the study design, acquisition of the data, data analysis and interpretation and drafting the manuscript. MI, EG-J and JSR-V participated in the data analysis and interpretation and drafting the manuscript. All authors have read and approved the manuscript. **Competing Interests**

The authors have nothing to disclose.

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