Review Article

# The effect of 1-year tailored exercise training, on according to cytokine levels and immune function at emphasis on IL-6 in breast cancer patients: A meta-analysis

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## Abstract

Physical activity performance of patients during and after breast cancer treatment is common and is associated with increased toxicity from treatment, shorter time to tumor progression, and decreased survival. Exercise is a potential intervention to maintain or increase physical performance. We conducted a meta-analysis review of the 1-year tailored exercise training, according to cytokine levels and immune function with emphasis on IL-6 in breast cancer patients. A comprehensive search was performed in September 2022 for randomized controlled trials reporting the effects of structured exercise training on breast cancer effect with cytokine levels and immune function with an emphasis on IL-6 during or after cancer treatment. A random-effects meta-analysis was completed using the absolute net difference in the change between intervention and control groups as the outcome measure. Sensitivity and subgroup analyses were also performed. Data from 18 studies involving 1833 breast cancer survivors were included in the meta-analysis. Overall, there was a significant benefit of exercise training compared with the control (I2 = 71.3%, 95% CI = 38.4% to 77.6%, P < 0.001). Subgroup analysis showed positive effects for resistance training and aerobic training and for exercise training conducted during or after cancer treatment. Compared with usual care, exercise training has a beneficial effect on in women with breast cancer, both during and after cancer treatment. Given the physiological and functional importance of women with breast cancer, oncologists should encourage their patients to engage in regular exercise training, with particular emphasis on resistance training.

***Key Words:*** **Breast cancer, Exercise training, Immune function, Oncology**

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**Received 19 July 2023; Accepted 21 September 2023**

## Introduction

Breast cancer is the most common cancer among women, with an estimated 2.5 million new cases diagnosed worldwide in 2020 (Bray et al. 2018). Advances in diagnosis and treatment and improved patient performance in recent decades have led to improved survival rates, meaning women are now living longer after diagnosis (American Cancer Society 2018). Because of this, it has led to a growing population of women who may need more care and ongoing prevention due to the common side effects of breast cancer and its treatment.

Physical activity and exercise have been proven to be beneficial in the oncological setting. Observational evidence shows a positive relationship between physical activity and the survival and treatment process of patients, especially in breast, colorectal, and prostate cancer.

Today, breast cancer is an important risk factor for the health of women and men (in general male breast cancer is rare compared with female breast cancer. Female: male incidence ratios vary from 70 to 130 around the world.) worldwide, because it is the most common cancer in women and accounts for approximately one-third of all cancers in women in Western countries (Siegel R et al. 2013, Arabestanino AR et al. 2022).

## Objective

Exercise interventions are renovator and attractive non-pharmacological therapies for treating compromised cellular immunity associated with anti-cancer therapies. This mechanism can randomly reconstruct the desired factors because of the interventions it creates; this can be considered a good outcome.

Primary Objective: To evaluate the effect of the exercise program on changes in after-exercise intervention (after chemotherapy, 12 months after surgery).

Exploratory: To evaluate the effect of the exercise program on changes in Body function, body composition, QOL, patient-reported outcomes, and the diversity and composition of the

level and physical condition after an exercise intervention of patients with breast cancer from the day before surgery to 12 months after surgery.

## Material and Methods

This meta-analysis was reported in accordance with the PRISMA guidelines.

### 1. Search Strategy:

Electronic databases (PubMed/MEDLINE, EMBASE, CENTRAL, CINAHL, LIBRARY GENESIS and PEDro, Academic Search Complete) were searched by three authors. For searches in PubMed/MEDLINE and EMBASE, terms from MeSH and Emtree were used, respectively; for the other two electronic databases, the keywords were adjusted. The selected keywords for the search included "cancer, neoplasm, Breast Cancer, tumor, malignancies, exercise, resistance training, aerobic training, immune function, immune system, innate immunity, humoral immunity, adaptive immunity, mucosal immunity, cellular immunity, cytokines, cytokine receptors, leukocytes, neutrophils, lymphocytes, monocytes, dendritic cells, natural killer cells, killer cells, and IL- 6." Additional resources searched included Scopus (conference papers), American Society of Clinical Oncology, Go-ogle Scholar (130 first results), and the reference lists of all identified trials and relevant reviews. The search was limited to English-language studies published between inception and September 2022.

### 2. Data extraction and quality assessment:

The inclusion criteria for this meta-analysis followed the population, intervention, comparator, outcomes, and study design framework. The following information was extracted for analysis: bibliographic information (author, publication year), baseline participant characteristics, breast cancer, intervention details, immune-related components, immunoassay protocols, and results of reported outcomes. Because it is difficult (if not impossible) to blind participants to an exercise intervention, we considered the blinding of the operator to the outcome assessment as a quality criterion. Data extraction and quality assessment were completed by independent reviewers.

For this meta-analysis, the terms 'article' and 'study' are used synonymously, and 'trial' is the unit included in the meta-analysis. A given article may have resulted in more than one eligible 'trial' if the article included more than one intervention group. Initially, article titles and abstracts were screened for relevance. The full text of potentially eligible articles was obtained to review eligibility

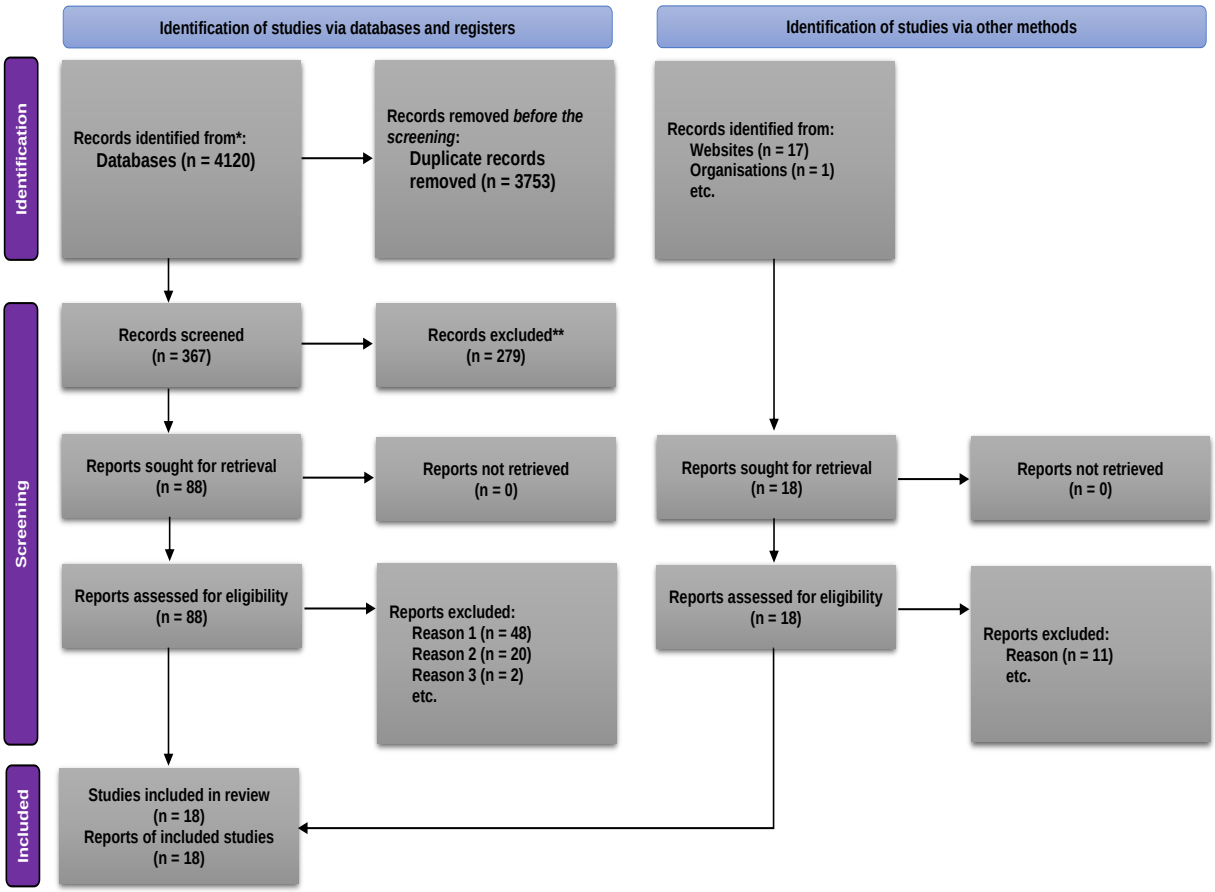


Figure 1. Flow diagram of the study selection process.

for inclusion.

Studies were excluded if (A) they were not published in English in a peer-reviewed journal; (B) they were not full-text articles reporting results of original research (e.g., reviews, letters to the editor, protocol papers, or conference abstracts); (C) study participants included mixed cancer populations, where data from women with breast cancer could not be isolated;(D) interventions involved exercise training in combination with pharmacotherapy or specific dietary manipulation, where the effects of the exercise training intervention could not be isolated; and (E) exercise training interventions were restricted to only one body region (e.g., shoulder mobility exercises).

### 3. Outcome selection:

Desired biomarkers related to the immune system including immune-related cytokines and immune cells were recorded. Subsequently, to determine which outcomes were included in the analyses, two steps were followed. First, cytokines with no clear role in the immune system were excluded. Second, biomarkers that were reported in less than three trials were excluded. The desired biomarker under investigation is [IL-6].

Cytokines were considered but were excluded due to having less than three studies included and the necessary need for IL-2, IL-3, IL-4, IL-5, IL-7, IL-9, IL-12, IL-13, IL-15, IL-16, IL-17, IL-18, IL-1α, INF-α, TNF-ß, IL-2ra, sIL-2R, sTNF-R, sTNF-RII, G-CSF, GM-CSF, CTACK, Eotaxin (CCL11), MIP-1α (CCL3), MIP-1ß (CCL4), IP-10 (CCL10), MIG (CCL9), ENA78 (CXCL5), RANTES (CCL5), PDGF, LIF, MCSF, and MCP-2.

### 4. Data synthesis and data analysis:

Absolute net differences for the change between the intervention and the control groups were used to combine study effect estimates in this meta-analysis. For each outcome of interest, the pre and post-intervention values (mean and standard deviation), as well as mean differences and associated standard deviations, were extracted. When mean differences and associated standard deviations were not published, the study authors were contacted. If an author failed to respond, the values were estimated based on methods from the Cochrane Handbook for Systematic Reviews of Interventions.

All extracted data were entered into software designed specifically for meta-analyses (Open Meta-Analyst, http://www.cebm.brown.edu/openmeta). Random effects modeling was used to account for both within- and between-study variability. Effect sizes were calculated as standardized mean differences (SMD), where < 0.2 was defined as trivial, 0.2 to 0.4 as small, 0.4 to 0.8 as moderate, and > 0.8 as large. The statistical heterogeneity across different trials in the meta-analysis was assessed by the I2 statistic, where < 30% indicates a low risk of heterogeneity, 30% to 80% indicates a moderate risk of heterogeneity, and > 80% indicates a considerable risk of heterogeneity. Sensitivity analyses were carried out by excluding one trial at a time to test the robustness of the pooled results.

## Result and Discussion

The electronic database search yielded 4120 results after the removal of duplicates. After title and abstract screening, 367 full-text articles were obtained, with 18 studies meeting our inclusion criteria All 18 studies reported estimates of total derived from dual-energy absorptiometry. Corresponding authors for 9 studies were contacted to request more information, with additional data obtained for eight studies.

Most patients with breast cancer undergo intense cancer treatments, including surgery, chemotherapy, and hormone therapy, depending on the stage and subtypes of cancer. In general, according to the needs of each patient, the desired exercise was provided to them. Survivors 18 studies enrolling a total of 1930 breast cancer survivors were included in our final analysis. Figure 1 displays a flow diagram of study selection.

Results from the risk of bias assessment are presented in all studies that met criteria for reporting study inclusion criteria, random allocation, group similarity at baseline, and point and variability statistics. No study reported participants or therapists blinded to the intervention, although this is difficult to achieve in exercise intervention studies. There was variability between studies across all other risks of bias criteria.

### 1. Study Characteristics:

Study sample sizes ranged from 20 to 573 participants, with the mean age of participants in each study ranging from 39.6 to 65.9 yr. eight studies enrolled only postmenopausal women, and one study included any women who were premenopausal at study commencement. The characteristics of the included 18 articles are presented in eight articles reported results from case-control studies, and 5 articles reported findings from cohort studies, of which one article reported on two cohort studies and another article reported on three cohort studies within 5 single articles. Therefore, there are a total of 8 case-control studies and 9 cohort studies included in the current meta-analysis. The articles were published between 1995 and 2022. These studies were conducted in North America, South America, Europe, and Asia. Receiving sports programs according to the type of physical performance and coordination of the patients, according to their desired conditions.

Compared a 12-month exercise intervention group with a wait-list

control group that received no intervention from baseline to 6 months, and then the exercise intervention from 6 to 12 months. For our meta-analysis, we included the baseline to 12-month data from this study to compare the intervention with the control.

## 2. Exercise intervention characteristics and associations between Exercise Training and breast cancer:

10 studies provided entirely supervised exercise training, whereas 8 studies had completely unsupervised interventions. had one intervention arm that completed supervised group exercise in a hospital setting, and another that completed an unsupervised walking program at home. The remaining studies (used a combination of supervised and unsupervised exercise training within their interventions. Three studies used solely aerobic training in their exercise interventions, with another involving aerobic training combined with impact-loading exercise. More studies used only resistance training interventions, whereas another study combined resistance training with impact-loading exercise.

The multivariable-adjusted RRs for each study and the combined RR for the highest compared with the lowest categories of Breast Cancer are the pooled results that found a positive association between the exercise training.

## 3. Primary analysis:

The overall pooled analysis demonstrated a significant absolute net difference for the change in favoring exercise training versus control (0.74 kg, 95% CI = 0.31 to 0.78, P < 0.001) (Fig. X). There was significant moderate heterogeneity for the effect of exercise training on (I2 = 71.3%, 95% CI = 38.4% to 77.6%, P < 0.001). Regarding publication bias, the examination of the funnel plot of net differences (Fig. 2) suggests an even distribution of studies, aside from one outlier. Egger's regression asymmetry test approached significance (P = 0.071).

## 4. Sensitivity and Subgroup Analysis:

Intervention effects remained consistent with the overall analysis when sensitivity analysis excluding studies at greater risk of bias (score <6) was performed.

## 5. Analysis of the results and sensitivity analyses:

The model results were summarized by the median as a point estimate and the 95% confidence interval as a measure of uncertainty of the point estimate. Potential publication bias was assessed with funnel plots. The funnel plots assume that studies with high precision will be plotted near the average mean effect, and studies with low precision will be spread evenly on both sides. We also estimated the mean effect considering the missing studies based on the trim-and-fill methodology.

The association between breast cancer, serum inflammatory biomarkers, and physical activity has gained worldwide attention over the past few years, with a growing number of randomized trials evaluating these potential properties. However, to our knowledge, this is the first evidence-based study to evaluate the effect of exercise training on serum inflammatory biomarkers in

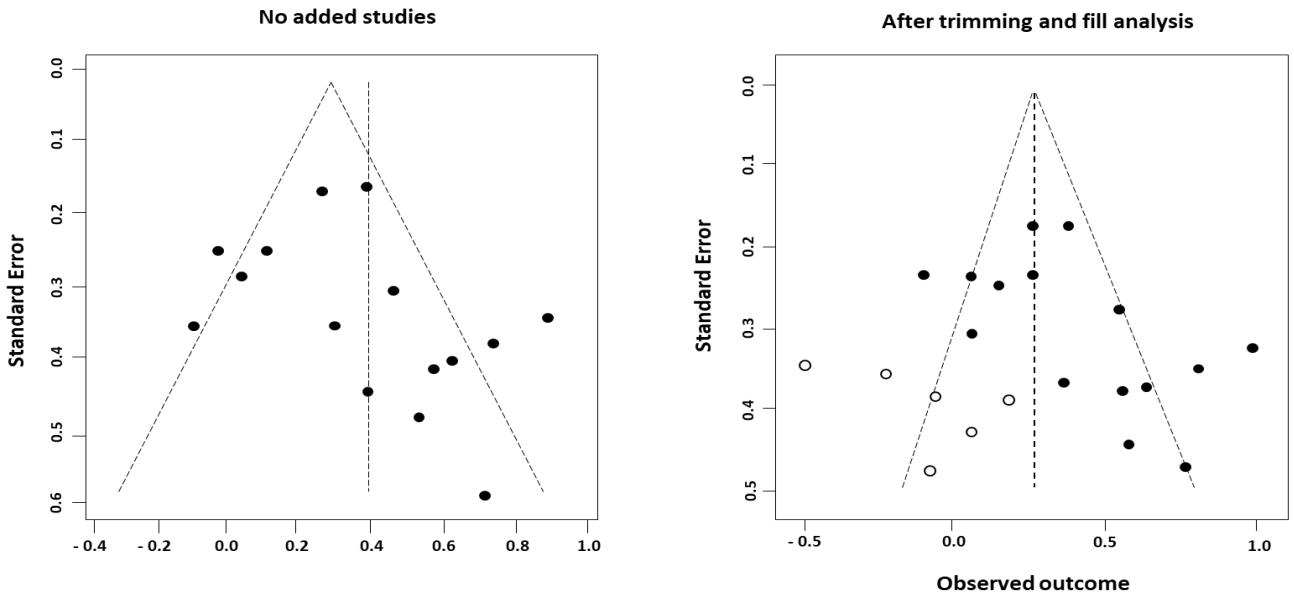


Figure 2. Outputs obtained.

women with breast cancer for a period of 1 year, to the best of our understanding statistically.

## Abnormal pearls in breast cancer

Breast cancer is the most common cancer in women worldwide, and breast cancer accounts for 22% of all women's cancers, which is more than twice the number of cancers in other women (Arabestanino et al. 2022). Returning to life and maintaining health in cancer patients is very important. Treatment of patients makes the treatment process more difficult due to inflammatory and immunological factors that are worrying in patients.

However, according to the progress in the field of treatment, interventional sports are considered one of the best treatment methods for these patients, especially for breast and colorectal cancer patients.

Exercise interventions for patients undergoing curative breast cancer therapy have been well tolerated and have shown positive effects on physical function and CRF (Shaffer and Ginsberg 2017, Furmaniak AC et al. 2016). Patients with breast cancer usually exhibit hypersensitivity to pressure pain compared with healthy control subjects. Chronic aerobic exercise training in healthy individuals has shown positive effects on pain tolerance but not on pressure-pain threshold (PPT). However, the hypoalgesia effect of acute exercise is well-established (Caro-Moran E et al. 2016, Jone MD et al. 2014, Naugle KM et al. 2012).

The physiological effects of circuit resistance exercise have been verified by several studies reported that high-intensity exercise can help prevent Breast cancer by enhancing the secretion and elevating the blood concentration of myokines (Genttman L.R and Pollock ML 1981, Brunelli D.T et al. 2014, Tabata I 2019). Exercise intervention may help to enhance the quality of life and ameliorate some side effects of cancer and its treatments, such as fatigue, peripheral neuropathy, and lymphoedema; moderate evidence is available for bone health.

Moderate physical activity plays an important role (with the release of myokines from skeletal muscles) in the prevention of inflammatory diseases including breast cancer. Exercise can decrease body fat, obesity, and low-grade systemic inflammation. Since each of these factors plays a role in cancer pathogenesis, exercise is potentially involved in the prevention of cancer, in recent years, new research (Pedersen BK 2011, Lee IM 2003).

In many studies, reduced tumor volume has been reported following regular exercise, but the exact mechanism has not been identified so far. Murphy et al reported that tumor volume was also reduced in the exercise group that performed endurance training for 20 weeks. They attributed the reduction in tumor volume to the reduction of inflammatory factors (Jones LW et al. 2012, Zielinski MR et al. 2004).

According to one theory, during physical activity, there is competition between the tumor microenvironment and active muscles for the supply of blood, oxygen, and nutrients. By reducing the blood flow inside the tumor, hypoxia in the middle part of the tumor increases the possibility of apoptosis in it. So far, there has not been much study regarding the evaluation of the factors involved in angiogenesis that can include sufficient and desired evidence (Thompson HJ et al. 2009).

## Sports intervention application and communication mechanism

Currently, studies that test the effects of endurance exercise programs on breast cancer patients show only small beneficial effects, but still, it can be one of the therapeutic applications in cancer patients.

The theory seems to be true that there is a competition between active muscles and tumor tissue in blood and nutrient supply, during which blood flow is directed towards active muscles, and tumor tissue probably undergoes higher necrotic and apoptotic stress by receiving less blood flow and nutrients, as nutrients and tropic factors are consumed in active muscles. Endurance exercise in decreasing the level of inflammatory and angiogenic intra-tumor cytokine levels and subsequent tumor volume.

Early studies, testing the effects of endurance exercise programs on CRCI in breast cancer patients, show small effects. One reason could be that the applied training regimens, with low to moderate exercise intensities, were not intense enough to have meaningful effects on patients' cognition. Moreover, recent research, in patients with breast cancer, shows that high-intensity endurance training is not only safe and feasible, but is also more efficient than low to moderate endurance exercise, in terms of cognitive benefits. The assumption is that higher intense exercise regimens are superior (Knobf MT et al. 2014, Hartman SJ et al. 2018, Mijwel S et al. 2018, Toohey K et al. 2017, Mijwel S et al. 2017). HIIT increases anti-inflammatory markers and neurotrophic factors, in a particularly effective and efficient way (Ramos JS et al. 2015, Cabral Santos C et al. 2016).

The most common side effects that can be reported after surgery are decreased shoulder range of motion (ROM), decreased shoulder strength, chronic pain, and sensory and functional impairment (Lauridsen MC et al. 2005).

The clinical significance of body weight in breast cancer is well-documented, which can convey clinical messages, with obesity at diagnosis, poorer disease prognosis, and weight change (gain or loss) during treatment associated with cancer recurrence and reduced survival predictions (Gaden E et al. 2012, Playdon MC et al. 2015, Rodriguez San Felipe MJ et al. 2013).

Pilot studies present HIIT as a safe training strategy in patients

with breast cancer. In addition, HIIT may induce beneficial neuromuscular adaptations and anti-inflammatory effects. both proposed as mechanisms contributing to fatigue (Schmitt J et al. 2016, Buchheit M and Laursen PB 2013, Stechling FM et al. 2016, LaVoy ECP et al. 2016). HIIT improved cardiovascular fitness in breast cancer patients as well as cardiac vagal activity and sympathetic nervous system responses in subjects with remote baseline values, potentially reducing the risk of diseases such as CVD. High-intensity interval training was safe and effective for breast cancer survivors to participate in with promising results as improved health outcomes were observed (Shaffer and Ginsberg 2017).

High-intensity interval endurance training (HIIT) seems to be an especially promising and time-efficient regimen, as a potential supportive care option for CRCI, among the more intense exercise interventions. High-intensity interval endurance training increases peak aerobic fitness, it alleviates cardiovascular risk and fatigue in cancer patients (Szuhany KL et al. 2015).

Regarding bone health, exercise may be an important tool for improving bone remodeling, matrix mineralization, and marrow health, thus leading to the preservation of bone mineral density (Campbell K.L et al. 2019, Hong A.R and Kim S.W. 2018, Schwab P and Scalupino K 2011).

As endurance exercise has been claimed to act as adjuvant therapy, there seems to be a contradiction between this point and tumor growth in this group. There are two reasons for this: First, the regression of growth was lower in this group, i.e.

This means that the groups that did exercise had smaller tumors during tumor formation, but tumor growth regression was lower in another group after exercise. Another point is that the central part of the tumor usually becomes necrotic because of a low supply of blood and oxygen.

## Combined effects for cytokenin and exiting il-6 biomarkers

One of the desired receptors and the dominant activator in NK cells is NKG2D. In the context of cancer cell surveillance and elimination, NKG2D binds to cellular stress ligands that are often overexpressed on malignantly transformed cells, causing cytokine secretion or direct cytotoxicity (Schmiedel D and Mandelboim O 2018).

For immune surveillance and elimination of transformed cells, it is important for NK cells to be mobilized and cytotoxic. There is a direct relationship between NK cell deployment and catecholamine release during and immediately after exercise. Studies have revealed that acute exercise leads to NK cell mobilization by the release of epinephrine binding to their β adre--nergic receptors. A recent meta-analysis reported a significant and strong increase in NK cell cytotoxic activity after acute exercise. In contrast to the acute effects mentioned above, there exists limited and contradictory literature regarding the effects of chronic exercise training on NK cell mobilization or function (Pedersen L et al. 2016, Rumpf C et al. 2020, Mohamady TM et al. 2013, Fairey AS et al. 2005, Nieman DC et al. 1990 and Nieman DC et al. 1993).

Therefore, we can conclude that acute exercise has a more pronounced effect on all analyzed outcomes in contrast to chronic exercise. Chronic polarized exercise has the potential to downregulate the AhR/IDO axis and activate NK cell cytotoxicity. We can also concur that endurance polarized training might represent a more potent stimulus for AhR/IDO-mediated NK cell receptor changes compared to a standard endurance exercise regime (Metcalfe AJ et al. 2018).

Myokines, which are produced by repetitive muscle contractions, increase cytotoxicity and play an important role in immune cell infiltration into tumors, reported that myokines have anti-inflammatory effects. They regulate NK cell proliferation, maturation, and activation, and increase the production of interleukin by blood monocytes. In particular, the amount of myokines released may depend on exercise intensity, contracted muscle mass, and type of exercise performed by an individual.

In general, there are several major molecular subtypes of breast cancer, grouped into estrogen receptor-dependent and independent breast cancers. Most breast cancers (known as estrogen receptor-α (ER-α positive) are epithelial tumors arising from the cells lining breast ducts or lobules (Hoffman Goetz L 2003).

IL-6 is a pleiotropic cytokine overexpressed in many human diseases such as arthritis, diabetes, obesity, and different cancer types. IL-6 has a pro-inflammatory role in the tumor microenvironment, and it is involved in tumor angiogenesis and metastasis. Evidence suggests that IL-6 is produced in high concentrations in estrogen receptor-dependent human breast cancer cells and breast tumor samples (Hong DS et al. 2007, Sullivan NJ 2011, Honma S et al. 2002).

The results showed that the levels of IL-6 were significantly different between groups performing and not performing exercise. tumor volume in early weeks in ETE and ETR groups compared with the others and the difference in the level of measured cytokines after training protocol, endurance exercise seems to play a preventive role and be an effective adjuvant therapy in estrogen hormone-dependent breast cancer.

In the present study, we observed that the level of IL-6 in tumor tissue was significantly reduced in groups performing endurance

exercises after tumor induction in comparison with other groups. Regular exercise reduces the level of pro-inflammatory cytokines such as IL-6 in tumor tissue. Since this cytokine has an effective role in producing by stimulating the expression of hypoxia-inducible factor- α (HIF-α), reduced levels of IL-6 in groups doing exercise indicated the apparent role of regular physical activity in the reduction of angiogenesis in tumors by suppressing the production of pro-inflammatory cytokines. These results agreed with the tumor growth rate, i.e., regression of tumor growth was lower in exercise groups (Leek et al. 2009).

Some earlier studies reported that exercise training significantly reduced pro-inflammatory biomarkers in breast cancer patients. High-intensity interval training resulted in reduced IL-6 concentrations in breast cancer patients. Concurrent training in another study decreased CRP in older breast cancer survivors undergoing aromatase inhibitor therapy. However, some other studies failed to find a significant effect of exercise training on inflammatory biomarkers. For instance, Kim et al. (2017) found no significant CRP changes following 12-week exercise training in breast cancer survivors. In addition, Ligibel et al. (2019) also failed to find significant changes in CRP and IL-6 after exercise training in women with newly diagnosed breast cancer. Training type and duration might partially explain these inconsistent findings.

Another study reported a reduction in tumor volume after 20 weeks of exercise with cancer, which was attributed to a reduced level of intra-tumor inflammatory cytokines and showed a direct relationship between inflammatory cytokines and tumor volume. Reduced volume of tumors in our study was observed in exercise groups and considering the strong correlation between the level of IL-6 and tumor volume (r= 0.729), the reduction in tumor volume in exercise groups was attributed to decreased level of intra-tumor inflammatory factors. In this regard, the findings of our study can better justify the relationship between inflammatory cytokines and tumor volume changes, since it seems that local cytokine levels in the tumor microenvironment are more effective than systemic and circulating levels of cytokines. Another study evaluated the effect of 6 weeks of endurance exercise on the levels of IL-6, tumor necrotizing factor- α (TNF-α), and IL-10 in tumors. The results showed that IL-6 and TNF-α were decreased in the tumor exercise group compared with control tumor groups. In addition, the level of IL-10 as an antitumor cytokine was higher relative to TNF-α in the exercise group (Murphy EA et al. 2011, Donatto F et al. 2013).

The key strengths of this systematic review and meta-analysis are that it was conducted in accordance with the PRISMA guidelines (Moher D et al. 2015) and that it included only those that used robust, image-derived measurements of the total. However, there are also some limitations. First, imputations were made to include data from four studies in the meta-analysis. Despite this, the results were unchanged when these studies were excluded or if more conservative values were imputed.

## Conclusions

In summary, this meta-analysis of 18-exercise training in breast cancer patients indicates that exercise training has a beneficial effect compared with usual care in women with breast cancer. These effects were observed both during and after treatment, and the largest effects were observed when resistance training was included as part of the exercise intervention. Given that loss is common in this population, clinicians should encourage all patients to participate in regular exercise training and consider referring them to an exercise specialist for assistance with appropriate exercise prescriptions.

## What is already known on this subject?

Physical activity performance of patients during and after breast cancer treatment is common and is associated with increased toxicity from treatment, shorter time to tumor progression, and decreased survival.

## What this study adds?

Exercise training has a beneficial effect compared with usual care in women with breast cancer.

## Acknowledgements

The authors of this study have no financial disclosures to declare.

## Funding

Due to the type of structural process, this work has no financial need and was done by the authors themselves.

## Compliance with ethical standards

**Conflict of interest** The author declare that she has no conflict of interest.

**Ethical approval** Applicable to human studies ethics committees, internal review boards, and guidelines that follow are written and approved.

**Informed consent** Not applicable.

## Author contributions

Conceptualization: A.R.A., A.N.I., F.V., E.R.E.; Methodology: P.A., A.R.A., A.A., B.D.; Software: None; Validation: A.R.A., B.D., F.V., E.R.E.; Formal analysis: None; Investigation: A.R.A., A.N.I., F.V., E.R.E.; Resources: P.A., A.R.A., A.A., B.D.; Data curation:

A.A., P.A., E.R.E, S.N.I.; Writing - original draft: A.R.A., F.V.; Writing - review & editing: S.N.I., A.A., F.V.; Visualization: A.R.A.; Supervision: A.R.A.; Project administration: S.N.I.; Funding acquisition: None.

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