

The Effect of Exercise Training on Mediators of Inflammation in Breast Cancer Survivors: A Systematic Review with Meta-analysis

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Abstract

Several sources of evidence indicate that exercise during and after breast cancer could positively modulate the tumor microenvironment. This meta-analysis aimed to determine the effects of exercise training on mediators of inflammation in breast cancer survivors. We searched for randomized controlled trials published from January 1990 to March 2014. An inverse variance method of meta-analysis was performed using a random effects model in the presence of statistical heterogeneity. Eight high-quality trials ($n = 478$) were included. Exercise improved the serum concentrations of IL6 [weighted mean difference (WMD) = -0.55 pg/mL; 95% confidence interval (CI), -1.02 to -0.09], TNF α (WMD =

-0.64 pg/mL; 95% CI, -1.21 to -0.06), IL8 (MD = -0.49 pg/mL; 95% CI, -0.89 to -0.09), and IL2 (WMD = 1.03 pg/mL; 95% CI, 0.40 to 1.67). No significant differences were found in the serum concentrations of C-reactive protein (WMD = -0.15 ; 95% CI, -0.56 to 0.25) or IL10 (WMD = 0.41 ; 95% CI, -0.18 to 1.02). Exercise training positively modulates chronic low-grade inflammation in women with breast cancer, which may impact upon carcinogenic mechanisms and the tumor microenvironment. These findings align with the other positive effects of exercise for breast cancer survivors, reinforcing the appropriateness of exercise prescription in this population. *Cancer Epidemiol Biomarkers Prev*; 25(7); 1009–17. ©2016 AACR.

Introduction

Breast cancer is the most common cancer among women, with nearly 1.4 million cases worldwide annually (1). Several mechanisms have been postulated regarding the etiology and progression of breast cancer (2). Among these mechanisms, chronic inflammation is widely recognized to play a crucial role in cancer development, progression, and risk of recurrence due to its effects on carcinogenesis and the tumor microenvironment (3). Cytokine signaling and oxidative stress result in DNA damage and genomic changes, enhancing tumor progression, angiogenesis, cell proliferation, invasiveness, metastasis, and tumor-cell resistance against several anticancer treatments

(4, 5). In addition, mediators of inflammation are associated with reduced overall survival in women with breast cancer, even after adjustments for age, tumor stage, race, and body mass index (6).

A strong body of evidence supports exercise training as a therapy for cancer patients during and after anticancer treatment (7, 8) because exercise training reverses some of the detriments that cancer causes in quality of life, fatigue, depression, muscular strength, and body composition (7–10), without adverse side effects (11). Several of these signs and symptoms that occur commonly in cancer have been associated statistically and linked aetiologically with proinflammatory cytokines (12, 13). Therefore, one crucial mechanism by which physical exercise exerts favorable health effects may be its capacity to reduce chronic low-grade inflammation (Fig. 1).

In 2012, Löf and colleagues published a thorough systematic review of randomized trials attempting to establish the effect of exercise on inflammatory mediators in survivors of breast cancer (14). The review found no significant effects on interleukins (IL) among four trials, and some evidence that exercise may decrease C-reactive protein (CRP) levels in one trial. The authors of that review concluded that further data were needed.

Although the systematic review by Löf and colleagues was published relatively recently, further data have already become available. For example, simple citation tracking from the systematic review by Löf and colleagues via Google Scholar identifies two additional trials with further data about the effect of exercise on numerous inflammatory mediators (15, 16). Further trials may be identified by rigorous searching. Furthermore, the review by Löf and colleagues did not undertake any meta-analysis, but this is possible with the currently available data. Therefore, the aim of

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

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doi: 10.1158/1055-9965.EPI-15-1061

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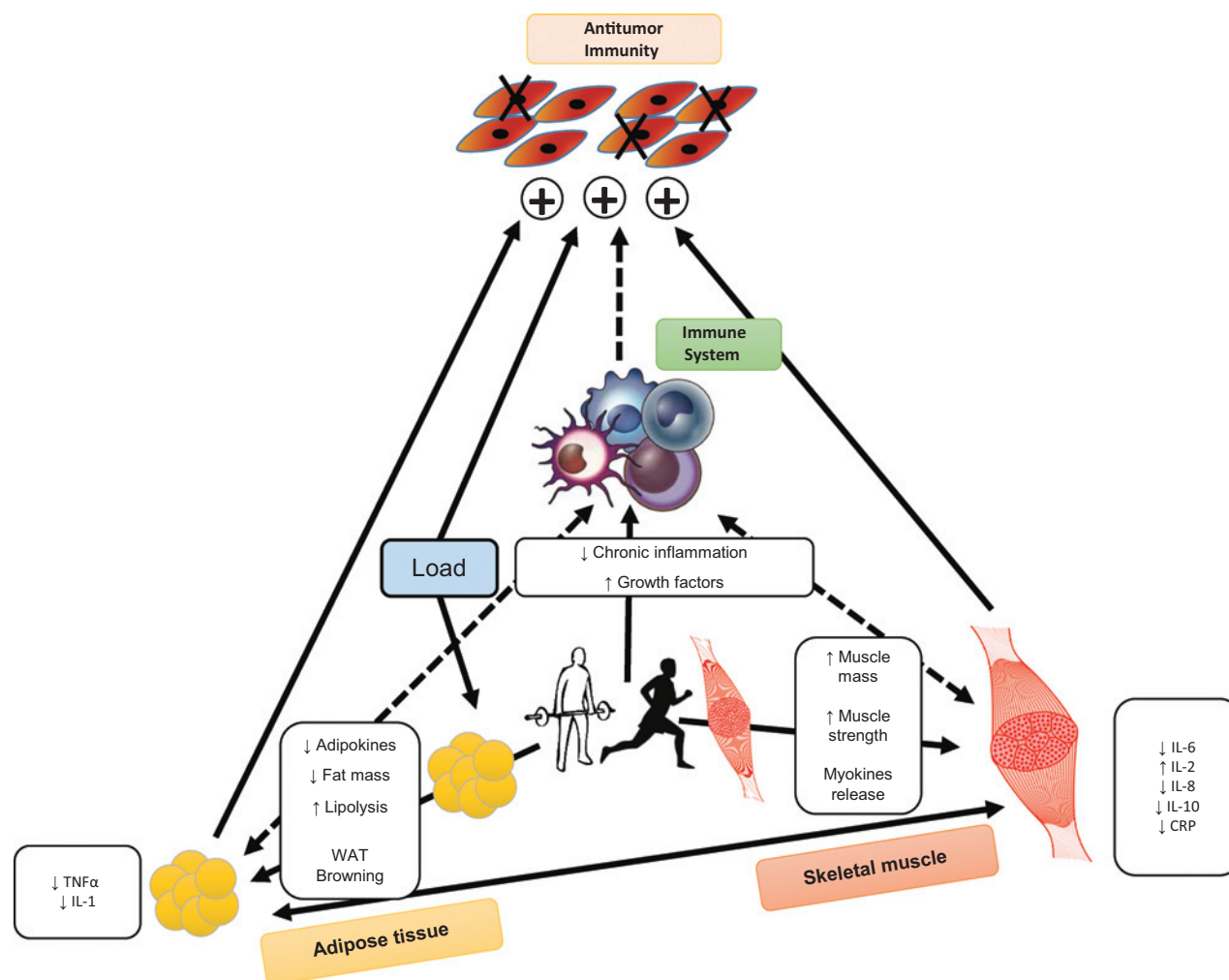


Figure 1. Potential role of exercise-induced inflammatory markers in breast cancer survivors. Combination of aerobic and resistance training stimulates production, secretion, and expression of inflammatory markers or other muscle fiber-derived peptides, i.e., myokines (IL-6, IL-2, IL-8, IL-10, and CRP), which subsequently exert their effects locally within the muscle or their target organs. The fact that the classical proinflammatory cytokines, TNF α and IL-1, in general do not increase with exercise indicates that the cytokine cascade induced by exercise markedly differs from the cytokine cascade induced by infections. These effects reduce the likelihood of tumor reactivation and progression (anti-tumor immunity). Abbreviation: WAT, white adipose tissue.

the following systematic review was to determine the effect of exercise training on mediators of inflammation in breast cancer survivors, including pooling of the data with meta-analysis where possible.

Materials and Methods

Protocol

The protocol for this systematic review was registered in the PROSPERO database (CRD42014009402) and the PRISMA statement was used to guide the reporting of the review (17). No funding was received.

Identification and selection of trials

Three reviewers (J.F. Meneses-Echávez, J.S. Río-Valle, and E. González-Jiménez) independently screened the search results. The reviewers were blinded to both the name of the authors and to the results of the studies. Searches were conducted between January and May 2014. We searched the PubMed, Embase,

Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL) databases using Boolean operators to identify records with terms for the disease (breast cancer, tumor, or carcinoma), the intervention (exercise, physical exercise, or physical training), and the outcomes (inflammation, mediators, anti-inflammatory, cytokines, interleukin*, IL2, IL6, IL8, IL10, CRP, tumor necrosis factor or TNF α). See Supplementary Material S1 for a detailed description of the search strategy. Studies published between 1990 and 2014 were considered for selection. In addition, the reviewers examined the reference lists of the included studies and the conference abstracts of the American Society of Clinical Oncology Annual Meeting on its website from 2004 to 2013, as well as 6 relevant journals: The Lancet Oncology, Journal of Clinical Oncology, Journal of the National Cancer Institute, Journal of Breast Cancer, The Breast Journal, and The Breast. Moreover, the authors contacted high-profile researchers in this area to ask for other possibly relevant trials, published or unpublished. No language restrictions were applied.

Selection criteria

The studies were included if they met the following criteria: (i) a randomized controlled trial involving breast cancer survivors; (ii) included an experimental group performing an exercise training program (categorized as aerobic, resistance, combined aerobic/resistance, yoga or Tai Chi); (iii) included a control group that undertook conventional care only, education only, or no intervention; and (iv) measured serum concentrations of at least one of the following inflammatory mediators: cytokines (IL2, IL6, IL8, IL10), TNF α , and CRP.

Studies were not excluded on the basis of the gender of the participants with breast cancer. Exercise training was defined as any body movement causing an increase in energy expenditure involving a planned or structured movement of the body performed in a systematic manner in terms of frequency, intensity, and duration that was designed to maintain or enhance health-related outcomes (18). Studies were excluded if the exercise intervention included dietary intervention, manual therapy, or psychologic therapeutic approaches. Attempts were made to contact the authors of the trial reports if clarification was necessary. Three reviewers (F. Lobelo, J.E. Correa-Bautista, and M. Elkins) independently screened the studies for eligibility. Disagreements were resolved by discussion and, where necessary, arbitration by a fourth reviewer (E. González-Jiménez).

Outcome measures

The outcome measures evaluated in this systematic review were serum levels of inflammatory mediators (IL2, IL6, IL8, IL10, CRP, and TNF α) after the exercise interventions. The procedures used to measure the serum concentrations of these inflammatory mediators, such as cytokine immunoassay and ELISA kits, were evaluated by one reviewer (R. Ramírez-Vélez) when each study was considered for inclusion.

Ethics declarations

Two investigators (J.F. Meneses-Echávez and R. Ramírez-Vélez) confirmed that the included studies had ethics committee approval and that the participants signed consent forms.

Data extraction

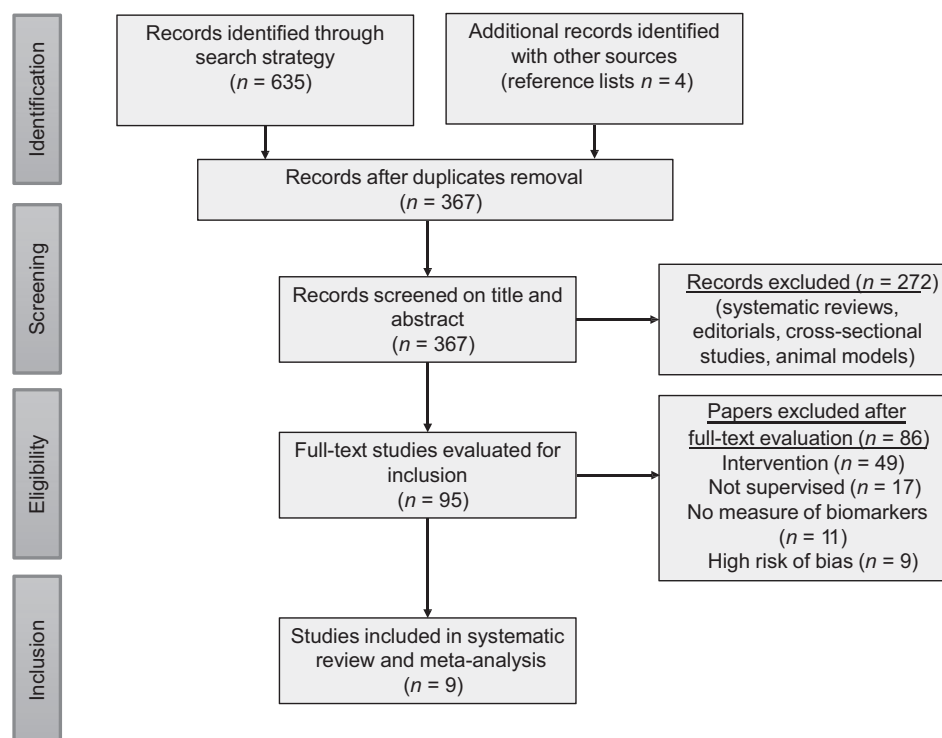
After selecting the studies, the relevant data were extracted by three reviewers (J.F. Meneses-Echávez, M. Elkins, and E. González-Jiménez) blinded to the name of the authors. The following information was extracted: (i) study design: publication year, randomization methods, selection criteria, and intervention groups; (ii) participants: sample size, age, menopausal status, current treatment (yes/no), treatment regimen (chemotherapy, radiotherapy, surgery), stage of disease, and baseline values for outcome measures; (iii) intervention: exercise modality, length (weeks), frequency (sessions/week), duration of training (minutes/session), and intensity of training (maximal heart rate %); (iv) outcome data for each group regarding inflammatory mediators and adverse events.

After data extraction, the data were examined for completeness and accuracy by a third reviewer (J.S. Río-Valle). Disagreements were resolved via review of the trial report and discussion.

Assessment of the risk of bias and completeness of reporting

We used the PEDro scale (19) to assess the risk of bias and the completeness of reporting of the included studies. The PEDro scale is based on the Delphi list (20) and evaluates external validity (criterion 1), internal validity (criteria 2–9), and whether sufficient statistical information is provided to interpret the effect of the intervention (criteria 10–11). Two reviewers (E. González-Jiménez and J.S. Río-Valle) independently performed these assessments, with disagreements resolved by discussion.

Figure 2. Flow diagram for search strategy methods. Flow diagram is reported according to the PRISMA statement.



Statistical analysis

For continuous outcomes, we recorded the group size, the mean values, and the SDs for each group compared in the included studies. If SDs were not reported, they were calculated from SEs, CIs, or *t* values (21). Pooled effects were calculated using an inverse of variance model, and the data were pooled to generate a weighted mean difference (WMD) in the original units with corresponding 95% confidence intervals (CI). All the studies for each outcome reported data in the same units, so we were able to pool all studies regardless of whether they reported change data or final data. Significance was set at *P* < 0.05. Statistical heterogeneity was evaluated using the *I*² statistic, and classified according to the Cochrane Handbook (22): negligible heterogeneity, 0%–40%; moderate heterogeneity, 30%–60%; substantial heterogeneity, 50%–90%; and considerable heterogeneity, 75%–100%. Other possible sources of heterogeneity were evaluated via subgroup analysis and a cumulative meta-analysis model if necessary. Throughout the results, the ± symbol represents SD.

A fixed-effect model was used if heterogeneity was low (*I*² < 50%); otherwise, a random effects model was used. Subject to data availability, we planned to conduct subgroup analyses according to the modality of exercise investigated (resistance, aerobic, mixed, yoga, Tai Chi), the type of cancer treatment (active or not), and the stage of disease. Meta-regression analysis was performed to examine the association between publication year, length of the intervention program (weeks), duration (minutes/session), and frequency (sessions/week) of exercise training with changes in effect size for each inflammatory mediator. Finally, publication bias was examined via Egger linear regression test for funnel plot asymmetry (*P* < 0.05), for each outcome with ≥ 10 trials. If no outcomes reached this threshold, publication bias was assessed for the outcome with the greatest number of trials. All analyses were performed by one reviewer (J.F. Meneses-Echávez) using Comprehensive Meta-Analysis (Version 2.0) and checked against the extracted data by one author (M. Elkins). A sensitivity analysis for quality was conducted by excluding those trials with a quality score less than 5 from the meta-analyses to see whether this affected the overall results of the meta-analyses.

Results

Flow of studies and participants into the review

After the removal of duplicates, 367 studies were screened, with 95 studies being retrieved in full text for detailed evaluation of eligibility. Eight trials (*n* = 478), reported in nine papers, were included in the review (15, 16, 23–29). The results of the search and the reasons for exclusions are presented in Fig. 2. The pooled cohort included 253 women randomized to an exercise training group and 225 women randomized to a control group.

Risk of bias and completeness of reporting

Most of the criteria on the PEDro scale were met by all or most of the included trials. The criteria on the PEDro scale that were met by a minority of the trials were intention-to-treat analysis (38%), concealed allocation (25%), and blinding of participants and therapists (0%). The specific criteria met by each of the trials are presented in Table 1.

Table 1. Assessment of methodologic quality and risk of bias with PEDro scale

Study	Random allocation	Concealed allocation	Groups similar at baseline	Participant blinding	Therapist blinding	Assessor blinding	< 15% dropouts	Intention-to-treat analysis	Between-group difference reported	Point estimate and variability reported	Total (0–10)
Bower et al. 2014 (23)	Y	N	Y	N	N	N	Y	N	Y	Y	5
Ergun et al. 2013 (24)	Y	N	Y	N	N	Y	Y	N	Y	Y	6
Gómez et al. 2011 (16)	Y	N	Y	N	N	N	N	N	Y	Y	4
Hutnick et al. 2005 (25)	N	N	Y	N	N	N	Y	N	Y	Y	4
Janelins et al. 2011 (26)	Y	Y	Y	N	N	N	N	Y	Y	Y	6
Sprod et al. 2012 (29)	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Jones et al. 2013 (15)	Y	N	Y	N	N	Y	Y	N	Y	Y	7
Kiecolt-Glaser et al. 2014 (27)	Y	Y	Y	N	N	Y	Y	Y	Y	Y	7
Rogers et al. 2013 (28)	Y	N	Y	N	N	Y	N	Y	Y	Y	6
	88%	25%	100%	0%	0%	50%	63%	38%	100%	100%	

Abbreviations: N, No; Y, Yes.

Characteristics of the included trials

Table 2 summarizes the characteristics of the participants, interventions, and outcome measures in the eight included trials. All eight trials included in the systematic review provided statistical estimates appropriate for meta-analysis.

Participants. The mean age of the participants in the included trials ranged from 49 to 56 years, with a mean of 54 ± 4. The majority of these trials involved postmenopausal women. Participants exhibiting different stages of disease were recruited (breast cancer type 0–IIIb). The included trials rarely reported time since diagnosis.

Interventions. Four trials tested a combination of aerobic and resistance training (16, 24, 25, 28). Two trials tested aerobic exercise alone (15, 24). Two trials tested yoga (23, 27). One trial, reported in two articles, tested Tai-chi (26, 29). The exercise interventions were performed for a mean length of 19 ± 13 weeks at a frequency of 3 ± 1 sessions per week for 69 ± 34 minutes per exercise session. The majority of interventions were supervised by health care providers.

Effect estimates of exercise on the inflammatory mediators

With respect to the effects of exercise training on the serum levels of cytokines in breast cancer survivors, the results of all the meta-analyses and subgroup analyses are summarized in Supplementary Table S1. The meta-analyses for each individual cytokine are discussed in detail below.

IL6. The most data were obtained for IL6, with all eight trials contributing data. Exercise improved the concentration of IL6, with a WMD of -0.55 pg/mL, which was statistically significant (95% CI, -1.02 to -0.09). The description of subgroup analysis according to the mode of training and the overall estimate are shown in Fig. 3.

TNFα. Six trials provided data about TNFα (15, 16, 23, 24, 27, 28). Again a significant beneficial effect was observed, with a WMD of -0.64 pg/mL (95% CI, -1.21 to -0.06), as shown in Supplementary Fig. S1.

IL8. The interleukin, IL8, also showed a very similar response. The WMD was -0.49 pg/mL, which was statistically significant (95% CI, -0.89 to -0.09), as shown in Supplementary Fig. S2. This was based on the pooled data from four trials (16, 24, 26, 28, 29), one of which was reported in two publications.

IL2. Two trials, one of which was reported in two publications, reported the effect of exercise on IL2 (16, 26, 29). A significant benefit was observed for IL2 with a mean difference of 1.03 pg/mL (95% CI, 0.40 to 1.67), as shown in Supplementary Fig. S3.

CRP. No significant effect was observed for CRP (WMD -0.15; 95% CI, -0.56 to 0.25) based on data from two trials (15, 23), as shown in Supplementary Fig. S4.

IL10. No significant effect was observed for IL10 (WMD 0.41; 95% CI, -0.18 to 1.02) based on data from two trials (16, 28), as shown in Supplementary Fig. S5.

Adverse events

Ergun and colleagues (24) reported an adverse event: one participant was diagnosed with metastases in the exercise group.

Publication bias

A funnel plot was constructed for IL6. Egger linear regression test did not reveal any significant evidence of publication bias ($P = 0.06$). See Supplementary Fig. S6 for the funnel plot.

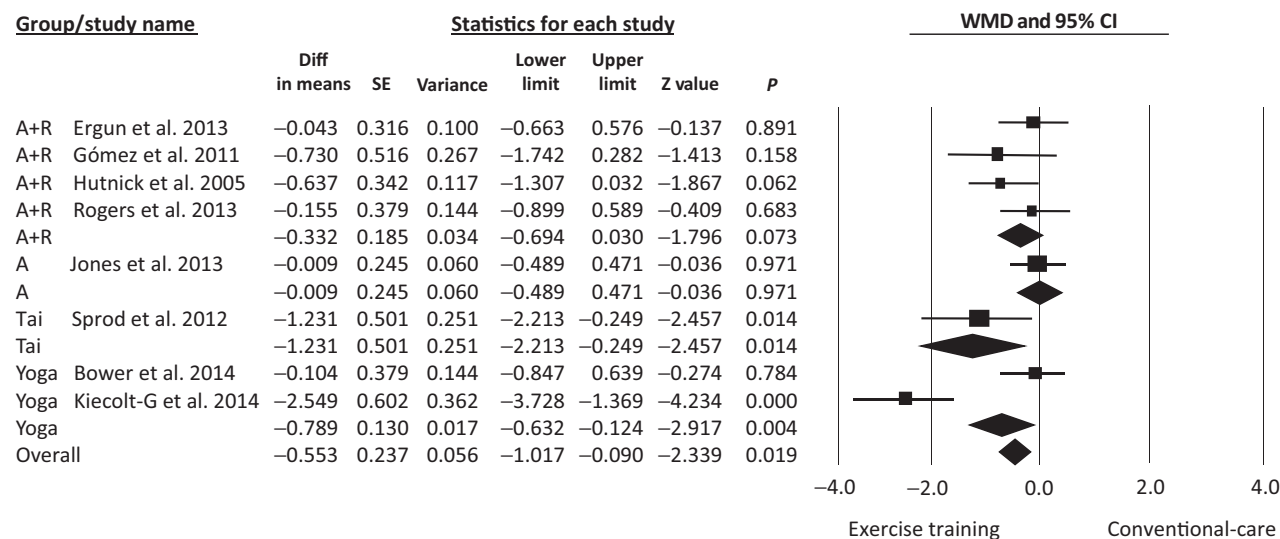


Figure 3. Effects of exercise on IL6 in breast cancer survivors with subgroup analysis according to the mode of training. A, aerobic; A+R, aerobic + resistance training; CI, confidence interval; Tai, Tai Chi.

Changes in inflammatory mediators according to exercise mode

Subgroup analysis by exercise mode was conducted if two or more trials were available. Yoga interventions provided significant benefits in the modulation of IL6 and TNF α ($P < 0.05$). Furthermore, Tai-Chi was effective in reducing IL6. When combined, aerobic and resistance exercise tended to improve IL6, IL8, and TNF α , but these effects did not reach statistical significance. Further details about subgroup analyses are shown in Supplementary Table S1.

Meta-regression analysis

Our meta-regression analysis revealed significant linear interactions between intervention length (> 11 weeks) and duration (> 45 minutes/session) with changes in IL6 levels ($P < 0.05$). No statistically significant dose-response relationships were observed for year of publication, training intensity, or frequency of exercise. Figure 4 shows the dose-response relationship between exercise intervention length and changes in the effect estimate for reductions in the serum levels of IL6 in breast cancer survivors.

Sensitivity analysis

The overall results of the meta-analyses were not substantially affected by the removal of the two trials with low-quality scores (IL-6 WMD = -0.42 pg/mL; 95% CI, 1.10 to 0.17).

Discussion

Within the last decade, an increasing number of studies have demonstrated that exercise training programs are beneficial for breast cancer patients. This systematic review generated novel evidence that regular exercise reduces the serum concentrations of

some proinflammatory mediators, such as IL6, in breast cancer survivors. Similar conclusions were reported in 2012 by Löf and colleagues (14) in a previous systematic review conducted of this topic. In that review, the authors observed weak to moderate evidence that physical activity interventions affect the levels of serum biomarkers (i.e., inflammatory mediators and insulin growth factors) in breast cancer survivors. A key difference between the previous systematic review (14) and our meta-analysis is that we observed significant differences in the levels of IL2, IL8, IL6, and TNF α .

The most data were obtained for the effect of exercise on IL6. Importantly, in breast cancer survivors, IL6 has been associated with symptoms of fatigue, the most common and devastating complaint among cancer survivors (30, 31), and a strong body of evidence has demonstrated that exercise improves fatigue in people with breast cancer specifically (32, 33) and in people with cancer generally (34, 35). Therefore, the results of our meta-analysis lead us to hypothesize that exercise improves fatigue by counteracting key mediators of low-grade inflammation in women with breast cancer. However, acute exposure to exercise training and its effect on the inflammatory profile are short-lived, and it is unlikely that a single bout of exercise causes any adaptive changes; the repetition of exercise appears to be required for its long-term health benefits (36).

In addition to being associated with fatigue, IL6 is also predictive of survival in people with metastatic breast cancer (37). This finding may therefore help in understanding the favorable trend in survival due to exercise in various cancer populations (38, 39). Indeed, the finding of reductions in a range of cytokines (specifically IL2, IL8, IL6, and TNF α) may have similar implications because chronic inflammation is widely recognized to play a

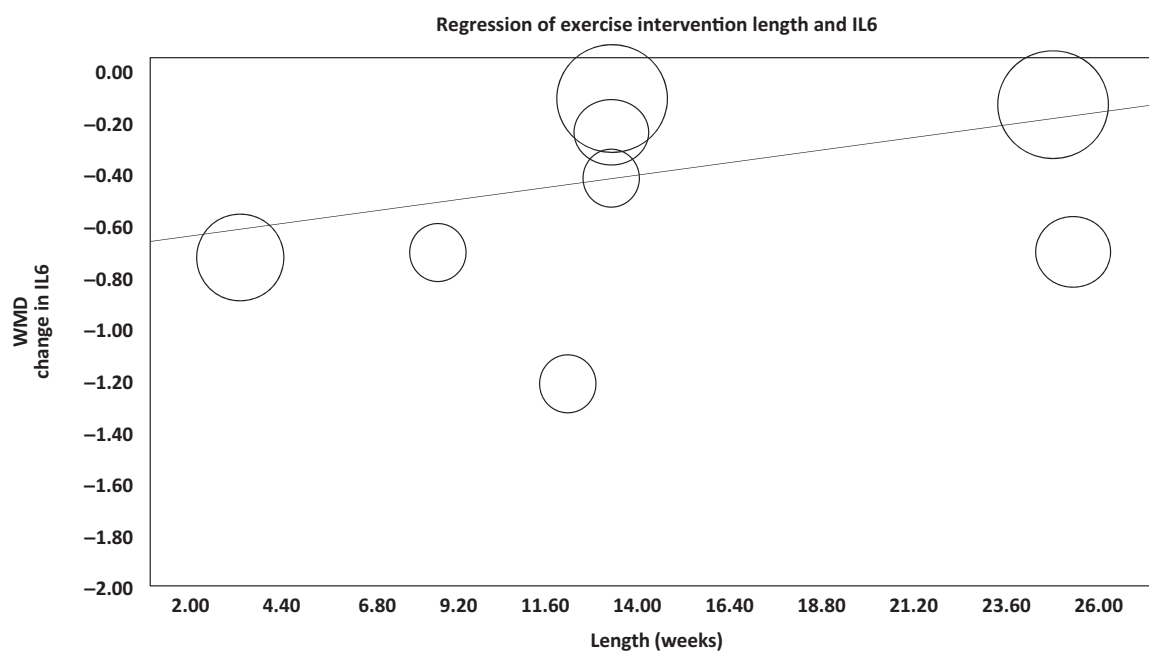


Figure 4.

Meta-regression of exercise intervention length and IL6. Bubble plot for the dose-response relationship between the intervention length (weeks) and effect estimates changes for IL6 from the eight randomized controlled trials included in the meta-regression analysis. WMD, weighted mean difference.

Table 2. Characteristics of the included studies (*n* = 8)

Study	Participants	Intervention	Outcome measures
Bower et al. 2014 (23)	31 female breast cancer patients (stage 0-II) with fatigue after local and/or adjuvant therapy Exp: <i>n</i> = 16, age (yr) = 54 (SD 6) Con: <i>n</i> = 15, age (yr) = 53 (SD 5)	Exp = Yoga (90 min × 2/wk × 12 wk) Con = Education (120 min × 1/wk × 12 wk)	IL6, CRP, TNF α
Ergun et al. 2013 (24)	60 female breast cancer patients (stage I-IIIa) after surgery, radiotherapy, and chemotherapy Exp1: <i>n</i> = 20, age (yr) = 50 (SD 8) Exp2: <i>n</i> = 20, age (yr) = 55 (SD 7) Con: <i>n</i> = 20, age (yr) = 55 (SD 10)	Exp1 = Aerobic/resistance exercise (45 min × 3/wk × 12 wk) + aerobic exercise (30 min × 3/wk × 12 wk) + education (30 min) Exp2 = Aerobic exercise (30 min × 3/wk × 12 wk) + education (30 min) Con = Education (30 min)	IL6, IL8, TNF α
Gómez et al. 2011 (16)	16 female breast cancer patients (stage I-II) after surgery, radiotherapy and chemotherapy Exp: <i>n</i> = 8, age (yr) = 50 (SD 6) Con: <i>n</i> = 8, age (yr) = 49 (SD 6)	Exp = Aerobic/resistance exercise (90 min × 3/wk × 8 wk) Con = Usual care	IL2, IL6, IL8, IL10, TNF α
Hutnick et al. 2005 (25)	49 female breast cancer patients (stage I-III) during or after chemotherapy and after radiotherapy and surgery Exp: <i>n</i> = 28, age (yr) = 49 (SD 11) Con: <i>n</i> = 21, age (yr) = 52 (SD 9)	Exp = Aerobic/resistance exercise (40-90 min × 3/wk × 24 wk) Con = Usual care	IL6
Janelins et al. 2011 (26) and Sprod et al. 2012 (29)	31 female breast cancer patients (stage 0-IIIb) after surgery, radiotherapy, and chemotherapy Exp: <i>n</i> = 9 completers, age (yr) = 54 (SD 11) Con: <i>n</i> = 10 completers, age (yr) = 53 (SD 7)	Exp = Tai Chi (60 min × 3/wk × 12 wk) Con = Education and psychosocial support	IL2, IL6, IL8
Jones et al. 2013 (15)	75 female breast cancer patients (stage 0-IIIa) after adjuvant treatment (except endocrine therapy) Exp: <i>n</i> = 37, age (yr) = 56 (SD 10) Con: <i>n</i> = 38, age (yr) = 55 (SD 8)	Exp = Aerobic exercise (150 min × 3/wk × 24 wk) Con = Usual care	IL6, CRP, TNF α
Kiecolt-Glaser et al. 2014 (27)	200 female breast cancer patients (stage 0-IIIa) after surgery, radiotherapy, and chemotherapy (except tamoxifen / aromatase inhibitors) Exp: <i>n</i> = 100, age (yr) = 52 (SD 10) Con: <i>n</i> = 100, age (yr) = 51 (SD 9)	Exp = Yoga (90 min × 2/wk × 12 wk) Con = Usual care	IL6, TNF α
Rogers et al. 2013 (28)	28 female breast cancer patients (stage I-IIIa) after surgery, radiotherapy, and chemotherapy Exp: <i>n</i> = 15, age (yr) = 58 (SD 6) Con: <i>n</i> = 13, age (yr) = 54 (SD 14)	Exp = Aerobic exercise (150 min/wk × 12 wk) + resistance exercise (2/wk × 12 wk) Con = Educational materials	IL6, IL8, IL10, TNF α

crucial role in cancer development, progression, risk, and survival (3-6).

A novel finding in our meta-analysis was the positive effect of exercise training on the levels of IL2, which is broadly involved in the differentiation and proliferation of natural killer cells, suggesting that exercise impacts the proliferation of T and B cells and immunologic function and ultimately enhances natural killer cell activity (40). In 2008, Kintscher and colleagues (41) reported that exercise reduces body fat and increases the expression of certain inflammatory cytokines, including IL2; the authors concluded that these effects reduce the likelihood of tumor reactivation and progression. In contrast to our results, Janelins and colleagues (26) reported nonsignificant differences in the IL2 levels after a moderately intense 12-week exercise intervention that included Tai Chi in 9 breast cancer survivors compared with nonexercise controls. These discrepancies can likely be explained by the wide range of characteristics of the treatments and disease stages of the breast cancer patients across these studies.

It is well recognized that muscular contractions during exercise induce the release of IL6, which increases the levels of IL10, thereby strengthening systemic inflammatory responses after exercise training (42). Experimental evidence has demonstrated that the circulating levels of IL10, which is released by tumor-associated macrophages, are associated with the regulation of antitumor responses and tumor growth via several pathways, such as angiogenic factors (43, 44). Li and colleagues (45) reported that improvements in the IL10 levels are associated with improved prognosis and life expectancy in breast cancer survivors. Our analysis showed that exercise can improve the serum IL10 levels, although no statistically significant changes were detected, probably due to the fact that only two studies (16, 28) evaluated this cytokine, restricting the strength of this result. Positive changes in the IL10 concentrations highlight the anti-inflammatory and immunoregulatory effects of exercise on the chronic inflammatory status of breast cancer survivors.

We observed significant reductions in the serum levels of IL8 and TNF α after exercise in women with breast cancer. Rotter and colleagues (46) concluded that, by reducing adipose tissue, exercise training reduces the expression of certain proinflammatory cytokines, such as TNF α and IL1 β .

We did not observe any significant differences in the CRP levels due to exercise. This is consistent with the nonsignificant effects of exercise on CRP levels in healthy and obese people (47, 48).

Overall, the results of this review suggest that the effect of exercise training on tumor-competitive immune cells and tumor host-relevant mediators, such as cytokines, is an important mechanism that could be exploited to improve prognosis after cancer. However, further investigation is required to fully characterize the roles of cytokines, including the IL system, CRP, and TNF α , as effectors of cancer patient survival (Fig. 1).

Limitations

Although some differences in the effects of various exercise modalities were observed, these may be confounded by differences in the length, frequency, and duration of training in these studies. These discrepancies presented considerable barriers to particular subgroup analyses, such as those for disease progression, the modality of exercise (such as examining aerobic and resistance training separately), and menopausal status. Therefore, further trials that include clear documentation of these variables are warranted to strengthen the conclusions about exercise modality. The studies included in this meta-analysis recruited women of different social and clinical characteristics, including age, menopausal status, stage of breast cancer progression, and therapeutic regimen (i.e., chemotherapy, radiotherapy, or both).

References

1. Ferlay J, Shin H, Bray F, Forman D, Mathers C, Parkin D. GLOBOCAN 2008, Cancer incidence and mortality worldwide: IARC Cancer Base No 10. Lyon, France: International Agency for Research on Cancer; 2010.
2. Cavalieri E, Rogan E. The etiology and prevention of breast cancer. *Drug Discov Today Dis Mech* 2012;9:e55–e69.
3. Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2002;420:860–67.
4. Korkaya H, Liu S, Wicha MS. Breast cancer stem cells, cytokine networks, and the tumor microenvironment. *J Clin Invest* 2011;121:3804–9.
5. Vendramini-Costa DB, Carvalho JE. Molecular link mechanisms between inflammation and cancer. *Curr Pharm Des* 2012;18:3831–52.
6. Pierce BL, Ballard-Barbash R, Bernstein L, Baumgartner RN, Neuhauser ML, Wener MH, et al. Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. *J Clin Oncol* 2009;27:3437–44.
7. Wolin KY, Schwartz AL, Matthews CE, Courneya KS, Schmitz KH. Implementing the exercise guidelines for cancer survivors. *J Support Oncol* 2012;10:171–7.
8. Buffart LM, Galvão DA, Brug J, Chinapaw MJ, Newton RU. Evidence-based physical activity guidelines for cancer survivors: current guidelines, knowledge gaps and future research directions. *Cancer Treat Rev* 2014;40:327–40.
9. Courneya KS, Segal RJ, Mackey JR, Gelmon K, Reid RD, Friedenreich CM, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *J Clin Oncol* 2007;25:4396–404.
10. Courneya KS, McKenzie DC, Mackey JR, Gelmon K, Friedenreich CM, Yasui Y, et al. Effects of exercise dose and type during breast cancer chemotherapy: multicenter randomized trial. *J Natl Cancer Inst* 2013;105:1821–32.

Conclusion

In summary, this review demonstrated that exercise is an effective intervention for controlling low-grade inflammation, which is closely associated with carcinogenesis and the tumor microenvironment in people with breast cancer. The positive effects generated by the meta-analyses for a range of inflammatory mediators justify investigation into the mechanisms underlying these effects so that exercise training can be more precisely prescribed to optimize the prognosis of people with breast cancer. In the interim, exercise training can be encouraged in people during or after breast cancer treatment: because of its known benefits on the problems that cancer induces in physical fitness, function, fatigue, depression, and quality of life (23, 24, 32, 34, 35, 48–51); because of the favorable trends observed in survival with exercise training (38, 39); and now also, given the results of this review, because of its positive effects on inflammatory mediators in the tumor microenvironment.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The authors thank the Norwegian Knowledge Centre for the Health Services in Oslo, Norway, and the Department of Research at Universidad Santo Tomás in Bogotá, Colombia.

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Received October 12, 2015; revised March 17, 2016; accepted March 30, 2016; published OnlineFirst April 12, 2016.

11. Paramanandam VS, Roberts D. Weight training is not harmful for women with breast cancer-related lymphoedema: a systematic review. *J Physiother* 2014;60:136–43.
12. Schubert C, Hong S, Natarajan L, Mills PJ, Dimsdale JE. The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review. *Brain Behav Immun* 2007;21:413–27.
13. Lee BN, Dantzer R, Langley KE, Bennett GJ, Dougherty PM, Dunn AJ, et al. A cytokine-based neuroimmunologic mechanism of cancer-related symptoms. *Neuroimmunomodulation* 2004;11:279–92.
14. Löf M, Bergström K, Weiderpass E. Physical activity and biomarkers in breast cancer survivors: a systematic review. *Maturitas* 2012;73:134–42.
15. Jones SB, Thomas GA, Hesselsweet SD, Alvarez-Reeves M, Yu H, Irwin ML. Effect of exercise on markers of inflammation in breast cancer survivors: the Yale exercise and survivorship study. *Cancer Prev Res* 2013;6:109–18.
16. Gómez AM, Martínez C, Fiuza-Luces C, Herrero F, Pérez M, Madero L, et al. Exercise training and cytokines in breast cancer survivors. *Int J Sports Med* 2011;32:461–67.
17. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
18. Wolin KY, Schwartz AL, Matthews CE, Courneya KS, Schmitz KH. Implementing the exercise guidelines for cancer survivors. *J Support Oncol* 2012;10:171–7.
19. De Morton N. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. *Aust J Physiother* 2009; 55:129–33.
20. Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, et al. The Delphi list: a criteria list for quality assessment of randomised clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol* 1998;51:1235–41.

21. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
22. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. The Cochrane Collaboration ; 2011 . Available from: <http://handbook.cochrane.org/>.
23. Bower JE, Greendale G, Crosswell AD, Garet D, Sternlieb B, Ganz PA, et al. Yoga reduces inflammatory signaling in fatigued breast cancer survivors: a randomized controlled trial. *Psychoneuroendocrinology* 2014;43:20–9.
24. Ergun M, Eyigor S, Karaca B, Kisim A, Uslu R. Effects of exercise on angiogenesis and apoptosis-related molecules, quality of life, fatigue and depression in breast cancer patients. *Eur J Cancer Care* 2013;22:626–37.
25. Hutnick NA, Williams NI, Kraemer WJ, Orsega-Smith E, Dixon RH, Bleznak AD, et al. Exercise and lymphocyte activation following chemotherapy for breast cancer. *Med Sci Sports Exerc* 2005;37:1827–35.
26. Janelsins MC, Davis PG, Wideman L, Katula JA, Sprod LK, Peppone LJ, et al. Effects of Tai Chi Chuan on insulin and cytokine levels in a randomized controlled pilot study on breast cancer survivors. *Clin Breast Cancer* 2011;11:161–70.
27. Kiecolt-Glaser J, Bennett J, Andridge R, Peng J, Shapiro CL, Malarkey WB, et al. Yoga's impact on inflammation, mood, and fatigue in breast cancer survivors: a randomized controlled trial. *J Clin Oncol* 2014; 32:1040–9.
28. Rogers LQ, Fogleman A, Trammell R, Hopkins-Price P, Vicari S, Rao K, et al. Effects of a physical activity behavior change intervention on inflammation and related health outcomes in breast cancer survivors: pilot randomized trial. *Integr Cancer Ther* 2013;12:323–35.
29. Sprod LK, Janelsins MC, Palesh OG, Carroll JK, Heckler CE, Peppone LJ, et al. Health-related quality of life and biomarkers in breast cancer survivors participating in tai chi chuan. *J Cancer Surviv* 2012;6:146–54.
30. Schubert C, Hong S, Natarajan L, Mills PJ, Dimsdale JE. The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review. *Brain Behav Immun* 2007;21:413–27.
31. Saligan LN, Kim HS. A systematic review of the association between immunogenomic markers and cancer-related fatigue. *Brain Behav Immun* 2012;26:830–48.
32. Battaglini CL, Mills RC, Phillips BL, Lee JT, Story CE, Nascimento MG, et al. Twenty-five years of research on the effects of exercise training in breast cancer survivors: a systematic review of the literature. *World J Clin Oncol* 2014 10;5:177–90.
33. Zou LY, Yang L, He XL, Sun M, Xu JJ. Effects of aerobic exercise on cancer-related fatigue in breast cancer patients receiving chemotherapy: a meta-analysis. *Tumour Biol* 2014;35:5659–67.
34. Meneses-Echávez JF, González-Jiménez E, Ramírez-Vélez R. Effects of supervised exercise on cancer-related fatigue in breast cancer survivors: a systematic review and meta-analysis. *BMC Cancer* 2015;15:77.
35. Meneses-Echavez JF, González-Jiménez E, Ramírez-Vélez R. Supervised exercise reduces cancer-related fatigue: a systematic review. *J Physiother* 2015;61:3–9.
36. Taylor NF, Dodd KJ, Shields N, Bruder A. Therapeutic exercise in physiotherapy practice is beneficial: a summary of systematic reviews 2002-2005. *Aust J Physiother* 2007;53:7–16.
37. Salgado R, Junius S, Benoy I, Van Dam P, Vermeulen P, Van Marck E, et al. Circulating interleukin-6 predicts survival in patients with metastatic breast cancer. *Int J Cancer* 2003;103:642–46.
38. Courneya KS, Friedenreich CM, Franco-Villalobos C, Crawford JJ, Chua N, Basi S, et al. Effects of supervised exercise on progression-free survival in lymphoma patients: an exploratory follow-up of the HELP trial. *Cancer Causes Control* 2015;26:269–76.
39. Barbaric M, Brooks E, Moore L, Cheifetz O. Effects of physical activity on cancer survival: a systematic review. *Physiother Can* 2010;62:25–34.
40. Katano M, Matsuo T, Morisaki T, Naito K, Nagumo F, Kubota E, et al. Increased proliferation of human breast carcinoma cell line by recombinant interleukin-2. *Cancer Immunol Immunother* 1994;39: 161–66.
41. Kintscher U, Hartge M, Hess K, Foryst-Ludwig A, Clemenz M, Wabitsch M, et al. T-lymphocyte infiltration in visceral adipose tissue: a primary event in adipose tissue inflammation and the development of obesity-mediated insulin resistance. *Arterioscler Thromb Vasc Biol* 2008;28:1304–10.
42. Petersen AM, Pedersen BK. The role of IL-6 in mediating the anti-inflammatory effects of exercise. *J Physiol Pharmacol* 2006;57:43–51.
43. Fox SB, Taylor M, Grøndahl-Hansen J, Kakolyris S, Gatter KC, Harris AL. Plasminogen activator inhibitor-1 as a measure of vascular remodelling in breast cancer. *J Pathol* 2001;195:236–43.
44. Bando H, Toi M. Tumor angiogenesis, macrophages, and cytokines. *Adv Exp Med Biol* 2000;476:267–84.
45. Li Y, Yu H, Jiao S, Yang J. Prognostic value of IL-10 expression in tumor tissues of breast cancer patients. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi* 2014;30:517–20.
46. Huffman KM, Slentz CA, Bales CW, Houmard JA, Kraus WE. Relationships between adipose tissue and cytokine responses to a randomized controlled exercise training intervention. *Metab Clin Exp* 2008;57:577–83.
47. Nicklas BJ, Ambrosius W, Messier SP, Miller GD, Penninx BW, Loeser RF, et al. Diet-induced weight loss, exercise, and chronic inflammation in older, obese adults: a randomized controlled clinical trial. *Am J Clin Nutr* 2004;79:544–51.
48. Markes M, Brockow T, Resch KL. Exercise for women receiving adjuvant therapy for breast cancer. *Cochrane Datab Syst Rev* 2006;4:CD005001.
49. Zeng Y, Huang M, Cheng AS, Zhou Y, So WK. Meta-analysis of the effects of exercise intervention on quality of life in breast cancer survivors. *Breast Cancer* 2014;21:262–74.
50. Meneses-Echávez JF, González-Jiménez E, Correa-Bautista JE, Valle JS, Ramírez-Vélez R. Effectiveness of physical exercise on fatigue in cancer patients during active treatment: a systematic review and meta-analysis. *Cad Saude Publica* 2015;31:667–81.
51. Neil-Sztramko SE, Kirkham AA, Hung SH, Niksirat N, Nishikawa K, Campbell KL. Aerobic capacity and upper limb strength are reduced in women diagnosed with breast cancer: a systematic review. *J Physiother* 2014;60:189–200.