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Meta-Analysis

Effects of exercise on inflammation in female survivors of nonmetastatic breast cancer: a systematic review and meta-analysis

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Abstract

Background: Despite advances in breast cancer treatment, recurrence remains common and contributes to higher mortality risk. Among the potential mechanisms, inflammation plays a key role in recurrence by promoting tumor progression. Exercise provides a wide array of health benefits and may reduce inflammation, potentially reducing mortality risk. However, the effects of exercise, including mode (ie, resistance training [RT], aerobic training [AT], and combined RT and AT) and program duration, on inflammatory biomarkers in breast cancer survivors remain to be elucidated.

Methods: A systematic search was undertaken in PubMed, CINAHL, Embase, SPORTDiscus, and CENTRAL in August 2024. Randomized controlled trials examining the effects of exercise on interleukin-1 beta (IL-1β), interleukin 6 (IL-6), IL-8, IL-10, tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP) were included. A random-effects meta-analysis was undertaken to quantify the magnitude of change.

Results: Twenty-two studies were included ($n = 968$). Exercise induced small to large statistically significant reductions in IL-6 (standardized mean difference [SMD] = −0.85; 95% CI = −1.68 to −0.02; $P = .05$) and TNF-α (SMD = −0.40; 95% CI = −0.81 to 0.01; $P = .05$) and a trend for a decrease in CRP. When stratifying by exercise mode, trends toward reduction in IL-6 and TNF-α were observed for combined exercise, while changes were not generally affected by exercise program duration.

Conclusion: Exercise, especially combined RT and AT, can reduce pro-inflammatory biomarkers, and may be a suitable strategy to reduce inflammation in breast cancer survivors. However, further research is needed to investigate the effects of exercise mode and program duration on markers of inflammation in this survivor group.

Introduction

Breast cancer is a major global health concern contributing substantially to both morbidity and mortality.[1] In 2022 alone, 2.3 million new cases of breast cancer were diagnosed worldwide with approximately 660 000 deaths, making breast cancer the most diagnosed and leading cause of cancer-related death in women.[1] Moreover, recurrence rates remain significant even years after treatment completion, leading survivors of breast cancer to a higher mortality risk.[2,3] The increasing incidence and recurrence, coupled with mortality rates, highlights the need for further advancements in prevention, monitoring, and treatment.

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Among the mechanisms underpinning breast cancer development, progression, and recurrence, chronic inflammation plays a pivotal role due to its effects on the tumor microenvironment.[4,5] In particular, inflammatory factors such as interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP) are critically involved in modulating the tumor microenvironment.[6-8] A persistent inflammatory state creates a pro-oncogenic environment by enhancing communication between cancer cells and surrounding stromal cells (eg, fibroblasts and immune cells) and, in turn, promotes tumor progression by influencing processes such as cell proliferation, survival, invasiveness, and metastasis.[4,5,9,10] Additionally, the presence of inflammatory mediators (eg, IL-6, CRP) indirectly promotes tumor progression by inhibiting immune effector cells such as T cells, as summarized in the cancer immunogram.[11] Indeed, several studies reported that elevated levels of inflammatory biomarkers (ie, IL-6, TNF-α, and CRP) are associated with increased risk of breast cancer progression, recurrence, and mortality.[12-14] Given that local (eg, surgery and radiation therapy) and systemic (eg, chemotherapy and hormone therapy) treatments for breast cancer as well as the related side effects (eg, physical deconditioning and changes in body composition) can exacerbate the inflammatory state, survivors of breast cancer may be at increased risk of recurrence due to heightened inflammation during and following treatment.[15,16] This interplay between inflammation and cancer progression emphasizes the need for strategies to reduce the inflammatory status which, in turn, could potentially reduce the risk of recurrence and mortality in breast cancer survivors.

Exercise is acknowledged as a key therapeutic strategy in the management of breast cancer.[17-20] The body of evidence supports exercise as being safe and effective during and after cancer treatment to improve various health-related outcomes such as physical fitness, body composition, and fatigue.[17-21] Importantly, exercise is also associated with a 40% reduced risk of disease recurrence and mortality.[17-20,22-24] The underlying mechanisms are not fully understood; however, it has been postulated that exercise may play a critical role in this process by reducing inflammation.[25-27] Indeed, skeletal muscle is an endocrine organ releasing anti-inflammatory cytokines during muscle contraction, which exert autocrine, paracrine, and endocrine effects.[26,28-30] In several recent systematic reviews, it has been reported that exercise training programs in survivors of breast cancer may result in favorable changes in pro-inflammatory (eg, IL-6, TNF-α) and anti-inflammatory cytokines (eg, IL-10), although the results were not consistent among the studies.[25,31-33] This may be attributed to the researches including multiple forms of exercise training, including yoga and Tai Chi, in addition to traditional exercise training modes which may have obscured findings due to the vastly different physiological effects compared with conventional aerobic and resistance exercise modes.[25,31] Similarly, Abbasi et al.[32] and Zhou et al.[33] included exercise clinical trials with breast cancer patients before or during cancer treatment as well as apparently healthy women which, again, may have altered the reported effects of exercise on inflammation markers. Taken together, these limitations prevent definitive conclusions to be drawn, and further research with rigorous study design is necessary to determine the effects of exercise on inflammation in breast cancer.

While there is evidence that exercise can alter the systemic inflammatory state in patients with breast cancer, it is yet to be determined if there are differential effects of different exercise modes on specific markers of inflammation. When examining exercise interventions used in the breast cancer setting, 2 modes are commonly employed, resistance training (RT) and aerobic training (AT).[19] To date, it remains unclear whether RT, AT, or combined exercise training (ie, RT plus AT) induce different alterations in pro- and anti-inflammatory cytokines. This is of utmost importance for creating more targeted exercise prescription for breast cancer survivors. Indeed, although the implementation of exercise as cancer therapy has dramatically improved over the last 2 decades, the underlying mechanistic understanding for application of precision exercise prescription remains to be determined. To the best of our knowledge, this is the first systematic review with meta-analysis aiming to examine the effects of exercise on biomarkers of inflammation in survivors of breast cancer. In detail, we investigated a selective range of pro-inflammatory markers such IL-1 beta (IL-1β), IL-6, IL-8, TNF-α, and CRP, and anti-inflammatory markers, such as IL-10, to provide a clear overview of the effects of exercise on inflammation in this population. Thus, the aims of the current review are: (1) to examine the effects of exercise on biomarkers of inflammation in breast cancer survivors and (2) to determine if the effects vary by exercise mode (ie, RT, AT, or combined) and exercise program duration.

Methods

All procedures undertaken in the present review were conducted in compliance with the guidelines outlined by the Cochrane Back Review Group,[34] adhering to the reporting standards established in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA),[35,36] and registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42024575738).

Search strategy and study selection procedure

A systematic search was conducted in PubMed, CINAHL, Embase, SPORTDiscus (via EBSCOhost), and Cochrane Library (CENTRAL) from inception to August 27, 2024, by an author with experience in bibliographic searches (S.G.L.). The full search strategies are reported in Table S1. References from all retrieved studies were manually reviewed to identify articles potentially eligible for inclusion. Duplicates were removed using EndNote (version 20.4.1) as described by Bramer et al.[37] During the screening phase, titles and abstracts were first independently evaluated following the eligibility criteria by at least 2 independent authors (A.B., U.C., L.M.), with disagreements resolved by a third author (F.B.). When abstracts did not provide sufficient information, they were selected for full-text evaluation. Full-text articles that met the criteria were then independently examined by at least 2 independent authors (A.B., U.C., L.M.) for final inclusion, with disagreements resolved by a third author (F.B.).

Eligibility criteria

For the current review, we included randomized clinical trials assessing the effects of exercise on inflammatory biomarkers in survivors of breast cancer. Primary outcomes were the effects on IL-1β, IL-6, IL-8, IL-10, TNF-α, and CRP in the blood (ie, serum or plasma) before and after an exercise training program. The inclusion criteria were: (1) adult women (ie, ≥18 years of age) with stages I–III breast cancer; (2) with or without endocrine therapy; (3) completed primary treatment for breast cancer (eg, chemotherapy, radiation therapy, surgery); (4) allocated to any form of RT, AT, or combined; and (5) blood collected before and after the exercise training program (at least 24 h after the last training session). Exclusion criteria were: (1) women with diagnosis of breast cancer undergoing primary cancer treatments (eg, chemotherapy);

(2) studies adopting any other form of exercise not included in the inclusion criteria (eg, yoga, pilates, etc.); (3) studies coupling exercise with diet intervention; (4) studies not reporting data regarding the variables of interest; and (5) studies written in a language other than English.

Data extraction

Data extraction was performed by 2 independent authors (F.B. and S.G.L.), with disagreements resolved by a third author (P.L.). Study information, including sample size, age, body mass index (BMI), cancer stage, time after treatment, exercise training intervention, adherence rate, and time points of blood collection were collected along with the outcomes of interest (ie, IL-1β, IL-6, IL-8, IL-10, TNF-α, and CRP). For the outcomes examined, baseline and postintervention assessments were extracted in their absolute units, inclusive of mean and SD. When graphs were used instead of numerical data, the graphs were analyzed using a specific tool for data extraction (WebPlotDigitizer, San Francisco, CA).[38] Authors were contacted in case of missing data.

Study quality assessment

The quality of the study was assessed using the revised risk of bias tool for randomized controlled trials (RoB 2).[39,40] The study quality assessment for all included studies were performed independently by 2 authors (F.B. and A.A.), with disagreements resolved by a third author (S.G.L.).

Statistical analysis

We originally planned to perform a network meta-analysis; however, there was an insufficient number of studies to run such an analysis based on exercise mode. Therefore, a 3-level mixed-effects meta-analysis with study included as a random effect was performed to examine the effects of exercise training on biomarkers of inflammation. A minimum of 2 studies were required to run a meta-analysis. Given the availability of several dependent outcomes from the same study, a robust variance estimation approach was undertaken to account for the nested structure of the effect sizes calculated from the studies included (ie, effects nested within categories nested within studies).[41] The pooled effect estimated from the outcomes of interest was obtained from within-group mean difference (MD) and expressed as the standardized mean difference (SMD). Cluster robust point estimates and 95% confidence intervals (CI) were reported, weighted by inverse sampling variance to account for the within- and between-study variances (τ^2). In addition, restricted maximal-likelihood estimation was used in all models. The criterion for statistical significance was set at a P value less than 0.05. According to Hedges' g, SMD values of 0.0 to smaller than 0.5 indicate small, 0.51 to 0.79, moderate, and greater than 0.8, large effects.[42] In addition, we considered results approaching statistical significance (P value ranging from 0.05 to 0.10) when SMD was above 0.50, with results reported as trend.

Statistical heterogeneity was assessed using the Cochran Q test. High heterogeneity was defined by a threshold P value of 0.1 or I^2 values greater than 50%. Outliers were examined using sensitivity analysis by omitting one study at a time (leave-one-out method). Publication bias was explored by contour-enhanced funnel plots and Egger's test when more than 10 studies were available.[43] Subgroup analyses were provided for: (1) different exercise modes (ie, RT, AT, and combined) and (2) exercise program duration (<16 and ≥16 weeks). In addition, a meta-regression was also undertaken to quantify the association of age and BMI with changes in outcomes of interest when more than 10 studies were available.[43]

Results

A total of 10 820 studies were retrieved from our search, with 6081 potential records retained for screening after duplicate removals. After excluding 5887 records due to their irrelevance to the research question, 194 were considered eligible for full-text assessment (Figure 1). A total of 22 articles on the effects of exercise training on biomarkers of inflammation in survivors of breast cancer were subsequently included.

Participants and intervention characteristics

A total of 968 survivors of breast cancer participated in the included studies; median age was 53.6 (interquartile range [IQR]: 49.3, 57.0) years and median BMI was 28.2 kg/m^2 (IQR: 26.5, 30.6). The participants in the included studies were diagnosed with breast cancer stages I–III, and time after primary treatment (eg, chemotherapy) ranged from 2 weeks to 36 months.[44-65] In regard to the exercise mode, RT was employed in 4 exercise arms,[53,60-62] AT in 8 arms,[44,49,50,52,54,56,57] and combined RT and AT in 12 exercise arms,[45-49,51,55,58,59,63-65] with a program duration ranging from 8 to 52 weeks, frequency from 1 to 6 days per week, and exercise adherence from 66% to 100%. In addition, fasting blood was collected before the exercise training program and 24 to 48 h after the last training session (Table 1).

For RT, 4-11 resistance exercises (ie, dumbbells, weight-machines, and elastic band) for 8-20 repetitions at an intensity between 55% and 90% 1-repetition maximum (1RM) for 1-4 sets were adopted.[45-49,51,53,55,58-65] For AT, session duration of moderate intensity continuous training (MICT) ranged from 10 to 50 min, at an intensity between 50% and 80% maximal heart rate (HRmax), 60% and 75% maximal oxygen uptake (VO2max), and 35% and 65% heart rate reserve (HRreserve)[45,47-52,54-57,59,63-65]; while session duration of high-intensity interval training (HIIT) ranged from 20 to 38 min, at an intensity between 50% and 95% HRmax and 60% and 90% VO2max.[44,46,54,56]

The study quality assessment is summarized in Figure 2. The overall risk of bias was moderate, with some concerns observed in the randomization process.

Interleukin-1 beta

Main model

Three studies and 3 effect sizes were undertaken for IL-1β (Table 2 and Figure S1).[44,51,61] There was no statistically significant change in IL-1β between exercise and control groups (SMD = 0; 95% CI = −1.84 to 1.84; P = 1.00). The heterogeneity I^2 was 8.8%. There was an insufficient number of studies to examine changes in IL-1β when stratifying by age and BMI, as well as by exercise mode and program duration.

Interleukin 6

Main model

Fifteen studies and 18 effect sizes were undertaken for IL-6 (Table 2 and Figure 3).[44,46-49,51,53-58,61,63,64] There was a statistically significant large decrease in IL-6 in favor of exercise compared with control groups (SMD = −0.85; 95% CI = −1.68 to −0.02; P = .05). The heterogeneity I^2 was 83.2%, with 1 study being the candidate for high heterogeneity[44]; which, after removal, reduced the main effect to −0.56 SMD (95% CI = −1.15 to 0.04; P = .06) and the heterogeneity I^2 to 66%. No effect of publication bias was found (t = −0.8; P = .45). In addition, age (β = 0.09 ± 0.09;

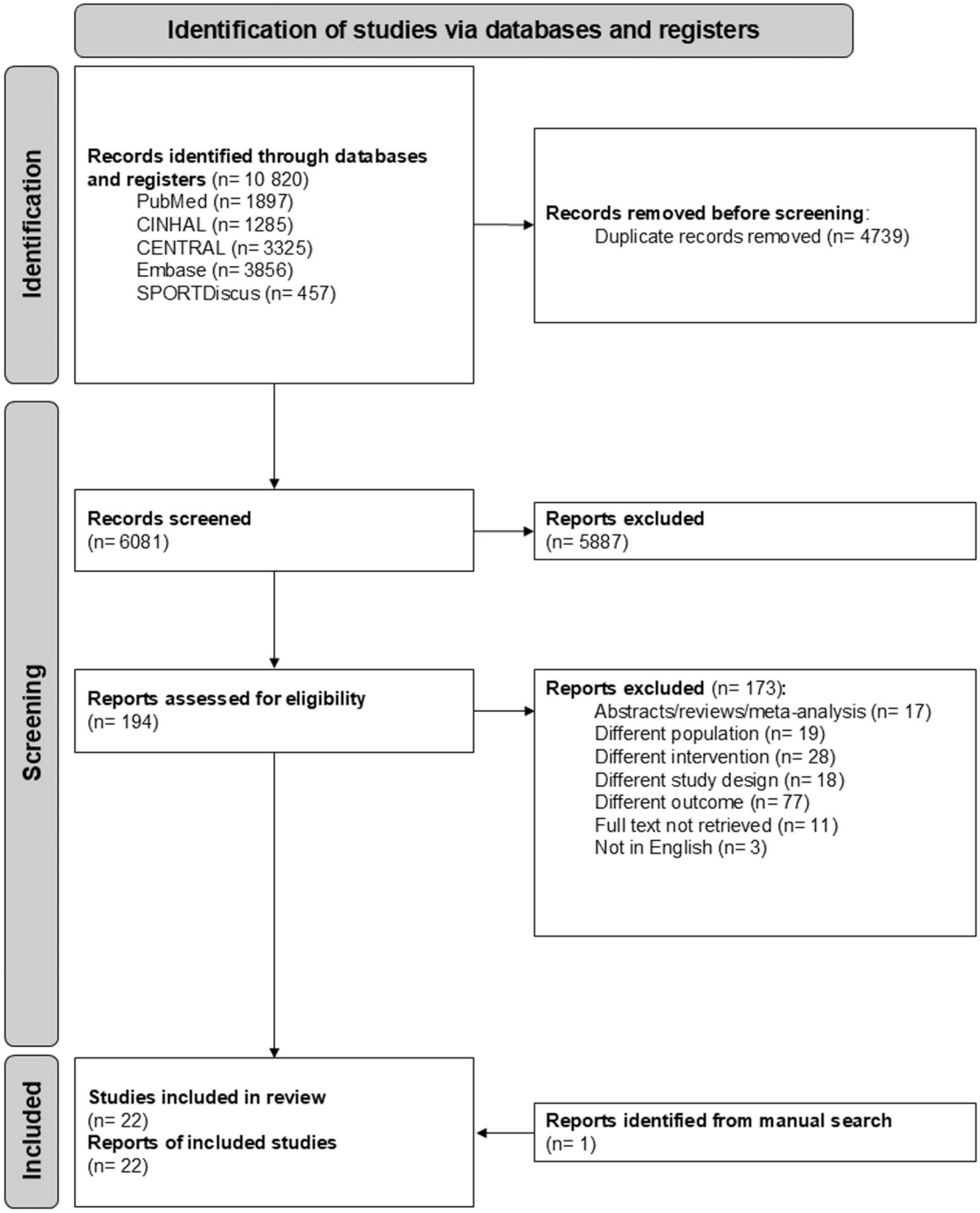

Figure 1. Flow chart of study selection process.

$P = .36$) as well as BMI ($\beta = -0.13 \pm 0.13$; $P = .35$) were not significantly associated with changes in IL-6 (Figure S2).

Exercise mode

There was no statistically significant change between RT (SMD = 0.14; 95% CI = −6.16 to 6.45; $P = .82$)[53,61] as well as AT (SMD = −1.10; 95% CI = −3.74 to 1.54; $P = .31$)[44,49,54,56,57] and control groups. However, a trend toward a decrease was observed in favor of combined exercise compared with control groups (SMD = −0.88; 95% CI = −1.84 to 0.08; $P = .07$).[46-49,51,55,58,63,64]

Exercise program duration

There was no statistically significant change when exercise program duration was shorter than 16 weeks (SMD = −0.54; 95% CI = −1.78 to 0.69; $P = .34$),[44,49,51,54,56,58,61,63,64] while a trend toward decrease was observed when exercise program duration was longer than 16 weeks (SMD = −1.31; 95% CI = −2.70 to 0.08; $P = .06$).[46-48,53,55,57]

Interleukin 8

Main model

Eight studies and 10 effect sizes were undertaken for IL-8 (Table 2 and Figure S3).[46-49,51,54,63,64] There was no statistically significant

Table 1. Summary of included studies measuring the effects of exercise on markers of inflammation.

Study	Population	Study design	Intervention	Control group	Adherence	Blood collection	Markers
Dieli-Conwright et al.[48] B; adipose tissue inflammation in breast cancer survivors: effects of a 16-week combined aerobic and resistance exercise training intervention	BCS I—III, **INT (*n* = 10)**: age = 53 ± 10 y, BMI = 33.5 ± 5.7 kg/m^2, time after treatment = NR; **CON (*n* = 10)**: age = 55 ± 4.5 y, BMI = 33.3 ± 8.7 kg/m^2, time after treatment = NR	Two-arm RCT	**Combined RT and AT—**RT = 8 exercises, 10-15 repetitions at 60%-80% 1RM for 3 sets; MICT = 30-50 min at 65%-80% HRmax; 2-3 d/w for 16 w	Usual care	97%	After 24-h rest and fasting	IL-6, IL-8, CRP
Rogers et al.[64] B; biobehavioral factors mediate exercise effects on fatigue in breast cancer survivors	BCS I—II, **INT (*n* = 20)**: age = 57.2 ± 5.5 y, BMI = 29.8 ± 4.8 kg/m^2, time after treatment ≥4 w; **CON (*n* = 22)**: age = 55.2 ± 9.1 y, BMI = 32.6 ± 6.6 kg/m^2, time after treatment ≥4 w	Two-arm RCT	**Combined RT and AT—**RT = 8 exercises with elastic band, 15 repetitions for 2 sets; MICT = 40 min at 48%-52% HRreserve; 4 d/w for 12 w	Usual care	92%	After 24-h rest and fasting	IL-6, IL-8, IL-10, TNF-α
Isanejad et al.[56]; comparison of the effects of high-intensity interval and moderate-intensity continuous training on inflammatory markers, cardiorespiratory fitness, and quality of life in breast cancer patient	BCS I—III, **INT1 (*n* = 10)**: age = 44 ± 9.14 y, BMI = 26.5 ± 3.5, time after treatment ≥1 m; **INT2 (*n* = 10)**: age = 46.3 ± 6.3 y, BMI = 28.1 ± 5.1, time after treatment ≥1 m; **CON (*n* = 10)**: age = 44.9 ± 5 y, BMI = 27.3 ± 4.9, time after treatment ≥1 m	Three-arm RCT	**INT1: AT—**HIIT = 33 min at 60%-90% VO2max; 3 d/w for 12 w; **INT2: AT—**MICT = 41 min at 60% VO2max; 3 d/w for 12 w	Usual care	92%-98%	After 48-h rest and fasting	IL-6, IL-10, TNF-α
Jones et al.[57]; effect of exercise on markers of inflammation in breast cancer survivors: the Yale exercise and survivorship study	BCS I—IIIA, **INT (*n* = 36)**: age = 56.4 ± 9.6 y, BMI = 30.6 ± 6 kg/m^2, time after treatment ≥6 m; **CON (*n* = 32)**: age = 55.4 ± 7.6 y, BMI = 29.4 ± 7.3 kg/m^2, time after treatment ≥6 m	Two-arm RCT	**AT—**MICT = 15-30 min at 50%-80% HRmax; 5 d/w for 26 w	Usual care	80%	After 24-h rest and fasting	IL-6, TNF-α, CRP
Fairey et al.[50]; effect of exercise training on C-reactive protein in postmenopausal breast cancer survivors: a randomized controlled trial	BCS I—IIIB, **INT (*n* = 24)**: age = 59 ± 5 y, BMI = 29.4 ± 7.4 kg/m^2, time after treatment = NR; **CON (*n* = 28):** age = 58 ± 6 y, BMI = 29.1 ± 6.1 kg/m^2, time after treatment = NR	Two-arm RCT	**AT—**MICT = 15-35 min at 70%-75% VO2max; 3 d/w for 15 w	Usual care	98%	After 48-h rest and fasting	CRP
Rogers et al.[63] A; effects of a physical activity behavior change intervention on inflammation and related health outcomes in breast cancer survivors: pilot randomized trial	BCS I—IIIA, **INT (*n* = 11)**: age = 58 ± 6.1 y, BMI = 33.9 ± 7.4 kg/m^2, time after treatment ≥8 w; **CON (*n* = 9)**: age = 53.7 ± 13.9 y, BMI = 30.3 ± 7.11 kg/m^2, time after treatment ≥8 w	Two-arm RCT	**Combined RT and AT—**RT = 8 exercises, 20 repetitions at moderate intensity; MICT = 150 min at moderate intensity per week; 3 d/w for 12 w	Education	73%-100%	After 24-h rest and fasting	IL-6, IL-8, IL-10, TNF-α
Dieli-Conwright et al.[47] A; effects of aerobic and resistance exercise on metabolic syndrome, sarcopenic obesity, and circulating biomarkers in overweight or obese survivors of breast cancer: a randomized controlled trial	BCS I—III, **INT (*n* = 46)**: age = 52.8 ± 10.6 y, BMI = 33.1 ± 5.7 kg/m^2, time after treatment = 1.8 m; **CON (*n* = 45)**: age = 53.6 ± 10.1 y, BMI = 33.4 ± 5.2 kg/m^2, time after treatment = 1.2 m	Two-arm RCT	**Combined RT and AT—**RT = 10 repetitions for 3 sets; MICT = 50 min at 65%-80% HRmax; 3 d/w for 16 w	Usual care	95%	After 24-h rest and fasting	IL-6, IL-8, TNF-α, CRP

(continued)

Table 1. (continued)

Study	Population	Study design	Intervention	Control group	Adherence	Blood collection	Markers
Ergun et al.[49]; effects of exercise on angiogenesis and apoptosis-related molecules, quality of life, fatigue and depression in breast cancer patients	BCS I—IIIA, **INT1 (*n* = 20)**: age = 49.7 ± 8.3 y, BMI = 26.6 ± 4.4 kg/m^2, time after treatment = NR; **INT2 (*n* = 20)**: age = 55.1 ± 6.9 y, BMI = 28.6 ± 5.2 kg/m^2, time after treatment = NR; **CON (*n* = 20)**: age = 50.3 ± 10.4 y, BMI = 28.6 ± 5.1 kg/m^2, time after treatment = NR	Three-arm RCT	**INT1: Combined RT and AT—**RT = 7 exercises with elastic band at moderate intensity; MICT = 30 min; 6 d/w for 12 w; **INT2**: **AT—**MICT = 30 min; 3 d/w for 12 w	Education	NR	After 24-h rest and fasting	IL-6, IL-8, TNF-α
Kim et al.[59] A; effects of exercise training on circulating levels of Dickkpof-1 and secreted frizzled-related protein-1 in breast cancer survivors: a pilot single-blind randomized controlled trial	BCS I—III, **INT (*n* = 11)**: age = 56 ± 6.5 y, BMI = 23.9 ± 2.7 kg/m^2, time after treatment ≥6 m; **CON (*n* = 13)**: age = 49.3 ± 4.8 y, BMI = 25 ± 4.7 kg/m^2, time after treatment ≥6 m	Two-arm RCT	**Combined RT and AT—**RT = 8 exercises with body weight and elastic band, 12-16 repetitions for 1 to 3 sets; MICT = 20 min at RPE 11-15; 3 d/w for 12 w	Usual care	NR	After 24-h rest and fasting	CRP
Moghadam et al.[54]; the effects of high-intensity interval training vs moderate-intensity continuous training on inflammatory markers, body composition, and physical fitness in overweight/obese survivors of breast cancer: a randomized controlled clinical trial	BCS I—III, **INT1 (*n* = 13)**: age = 57 ± 1 y, BMI = 28.2 ± 2.2, time after treatment ≥ 6 m; **INT2 (*n* = 13)**: age = 57 ± 1 y, BMI = 28.2 ± 2.2, time after treatment ≥6 m; **CON (*n* = 14)**: age = 57 ± 1 y, BMI = 28.2 ± 2.2, time after treatment ≥6 m	Three-arm RCT	**INT1: AT—**HIIT = 20-30 min at 90% HRmax; 3 d/w for 12 w; **INT2: AT—**MICT = 20-30 min at 55%-65% HRmax; 3 d/w for 12 w	Usual care	87%	After 48-h rest and fasting	IL-6, IL-8, IL-10, TNF-α
de Paulo et al.[45]; effects of resistance plus aerobic training on body composition and metabolic markers in older breast cancer survivors undergoing aromatase inhibitor therapy	BCS I—IIIA undergoing hormone therapy, **INT (*n* = 18)**: age = 63.2 ± 7.1 y, BMI = 28.9 ± 5.2 kg/m^2, time after treatment = NR; **CON (*n* = 18)**: age = 66.6 ± 9.6 y, BMI = 31.5 ± 6.2 kg/m^2, time after treatment = NR	Two-arm RCT	**Combined RT and AT—**RT = 8 exercises, 8-20 repetitions at 55%-75% 1RM for 1 to 3 sets; MICT = 20-30 min at 50%-80% HRmax; 3 d/w for 36 w	Stretching	78%-94%	After 24-h rest and fasting	CRP
Hutnick et al.[55]; exercise and lymphocyte activation following chemotherapy for breast cancer	BCS I—III, **INT (*n* = 16)**: age = 48.5 ± 10.6 y, BMI = 26.67 ± 5.35 kg/m^2, time after treatment ≥2 w; **CON (*n* = 12)**: age = 52.3 ± 9.2 y, BMI = 26.63 ± 4.13 kg/m^2, time after treatment ≥2 w	Two-arm RCT	**Combined RT and AT—**RT = 4 exercises with elastic bands, 8-12 repetitions for 1 to 3 sets; MICT = 10-20 min at 60%-75% functional capacity; 3 d/w for 26 w	Usual care	76%	After 48-h rest and fasting	IL-6
Dethlefsen et al.[46]; exercise regulates breast cancer cell viability: systemic training adaptations vs acute exercise responses	BCS I—III, **INT (*n* = 37)**: age = 46 ± 9.6 y, BMI = 24 ± 3.8, time after treatment = 2 m; **CON (*n* = 37)**: age = 48.2 ± 7.8 y, BMI = 24.8 ± 3.7, time after treatment = 2 m	Two-arm RCT	**Combined RT and AT—**RT = 8-10 repetitions at 70%-90% 1RM for 3 sets; HIIT = 30 min at 80%-90% HRmax; 1 d/w for 26 w	Education	66%	After 24-h rest and fasting	IL-6, IL-8, IL-10, TNF-α
Gómez et al.[51]; exercise training and cytokines in breast cancer survivors	BCS I—II, **INT (*n* = 8)**: age = 50 ± 5.6 y, BMI = 24 ± 3.03 kg/m^2, time after treatment = 36.4 ± 12.4 m; **CON (*n* = 8)**: age = 48.8 ± 5.4 y, BMI = 25.2 ± 3.4 kg/m^2, time after treatment = 35.4 ± 11.3 m	Two-arm RCT	**Combined RT and AT—**RT = 11 exercises, 8-15 RM for 2-3 sets; MICT = 20-30 min at 70%-80% HRmax; 3 d/w for 8 w	Usual care	91%	After 24-h rest and fasting	IL-1β, IL-6, IL-8, IL-10, TNF-α
Alizadeh et al.[44]; high-intensity interval training can modulate the systemic inflammation and HSP70 in the breast cancer: a randomized control trial	BCS I—III undergoing hormone therapy, **INT (*n* = 24)**: age = 49.2 ± 9.7 y, BMI = 27.9 ± 4 kg/m^2, time after treatment = ≥ 1 m; **CON (*n* = 24)**: age = 48.4 ± 7.5 y, BMI = 27.9 ± 3.9 kg/m^2, time after treatment ≥1 m	Two-arm RCT	**AT—**HIIT = 38 min at 50%-95% HRmax; 3 d/w for 12 w	Usual care	85%	After 48-h rest and fasting	IL-1β, IL-6, IL-10

(continued)

Table 1. (continued)

Study	Population	Study design	Intervention	Control group	Adherence	Blood collection	Markers
Lee and An[60]; impact of high-intensity circuit resistance exercise on physical fitness, inflammation, and immune cells in female breast cancer survivors: a randomized control trial	BCS I—IIIA, **INT (*n* = 15)**: age = 54.7 ± 5.1 y, BMI = 23.6, time after treatment ≥24 m; **CON (*n* = 15)**: age = 55.4 ± 4.3 y, BMI = 22.8, time after treatment ≥24 m	Two-arm RCT	**RT—**RT = 8 exercises, 8-16 repetitions at 40%-80% 1 RM for 3-4 sets; 2-3 d/w for 12 w	Usual care	NR	After 24-h rest and fasting	CRP
Robbins et al.[62]; kynurenine metabolism as a mechanism to improve fatigue and physical function in postmenopausal breast cancer survivors following resistance training	BCS I—III, **INT (*n* = 22)**: age = 61.6 ± 1.5 y, BMI = 32.7 ± 1.4, time after treatment ≥6 m; **CON (*n* = 10)**: age = 67.2 ± 1.2 y, BMI = 28.9 ± 4.5, time after treatment ≥ 6 m	Two-arm RCT	**RT—**RT = 7 exercises, 15-20 repetitions to exhaustion for 3 sets; 3 d/w for 12 w	Cognitive training	86%	After 48-h rest and fasting	CRP
Martins et al.[61]; lower-body resistance training reduces interleukin-1b and transforming growth factor-b1 levels and fatigue and increases physical performance in breast cancer survivors	BCS I—III, **INT (*n* = 11)**: age = 52.1 ± 10.1 y, BMI = 26.2 ± 3.3, time after treatment = NR; **CON (*n* = 11)**: age = 57.7 ± 8.8 y, BMI = 26.2 ± 6.4, time after treatment = NR	Two-arm RCT	**RT—**RT = 4 exercises, 8-20 repetitions at 60%-80% 1RM for 1-3 sets; 3 d/w for 12 w	Stretching	100%	After 24-h rest and fasting	IL-1β, IL-6, IL-10, TNF-α
Kim et al.[58] B; pro-inflammatory cytokine levels and cancer-related fatigue in breast cancer survivors: effects of an exercise adherence program	BCS I—III, **INT (*n* = 12)**: age = 49.9 ± 8.1 y, BMI = NR, time after treatment = NR; **CON (*n* = 6)**: age = 48.1 ± 6.7 y, BMI = NR, time after treatment = NR	Two-arm RCT	**Combined RT and AT—**8 exercises at light to vigorous intensity; 1 d/w for 12 w	Usual care	90%	After 24-h rest and fasting	IL-6, TNF-α
Guinan et al.[52]; the effect of aerobic exercise on metabolic and inflammatory markers in breast cancer survivors—a pilot study	BCS I—III, **INT (*n* = 14)**: age = 50 ± 8.3 y, BMI = NR, time after treatment = 3.8 ± 0.9 m; **CON (*n* = 8)**: age = 45 ± 9 y, BMI = NR, time after treatment = 3.6 ± 1.2 m	Two-arm RCT	**AT—**MICT = 21-42 min at 35 65% HRreserve; 3 d/w for 8 w	Usual care	NR	After 24-h rest and fasting	CRP
Hagstrom et al.[53]; the effect of resistance training on markers of immune function and inflammation in previously sedentary women recovering from breast cancer: a randomized controlled trial	BCS I—IIIA, **INT (*n* = 19)**: age = 51.2 ± 8.5 y, BMI = 27.6 ± 4.2 kg/m^2, time after treatment = NR; **CON (*n* = 15)**: age = 52.7 ± 9.4 y, BMI = 29.9 ± 6.5 kg/m^2, time after treatment = NR	Two-arm RCT	**RT—**RT = 8 exercises, 8-10 repetitions at 80% 1 RM for 3 sets; 3 d/w for 16 w	Usual care	85%	After 24-h rest and fasting	IL-6, IL-10, TNF-α, CRP
Sturgeon et al.[65]; WISER survivor trial: combined effect of exercise and weight loss interventions on inflammation in breast cancer survivors	BCS I—III, **INT (*n* = 80)**: age = 59.2 ± 8.2 y, BMI = 34.1 ± 6.3, time after treatment ≥6 m; **CON (*n* = 81)**: age = 58.7 ± 8.4 y, BMI = 34.1 ± 5.8, time after treatment ≥ 6 m	Two-arm RCT	**Combined AT and RT—**RT = 9 exercises, 10 repetitions for 2-3 sets; MICT = 180 min per week; 2 d/w for 52 w	Usual care	84%	After 24-h rest and fasting	CRP

Abbreviations: AT = aerobic training; BCS = breast cancer stage; BMI = body mass index; CON = control; d/w = days per week; h = hours; HIIT = high-intensity interval training; HRmax = maximal heart rate; HRreserve = heart rate in reserve; INT = intervention; kg = kilograms; m = months; MICT = moderate-intensity continuous training; min = minutes; NR = not reported; RCT = randomized controlled trials; RM = repetition maximum; RT = resistance training; VO2max = maximal oxygen uptake; w = weeks; y = years.

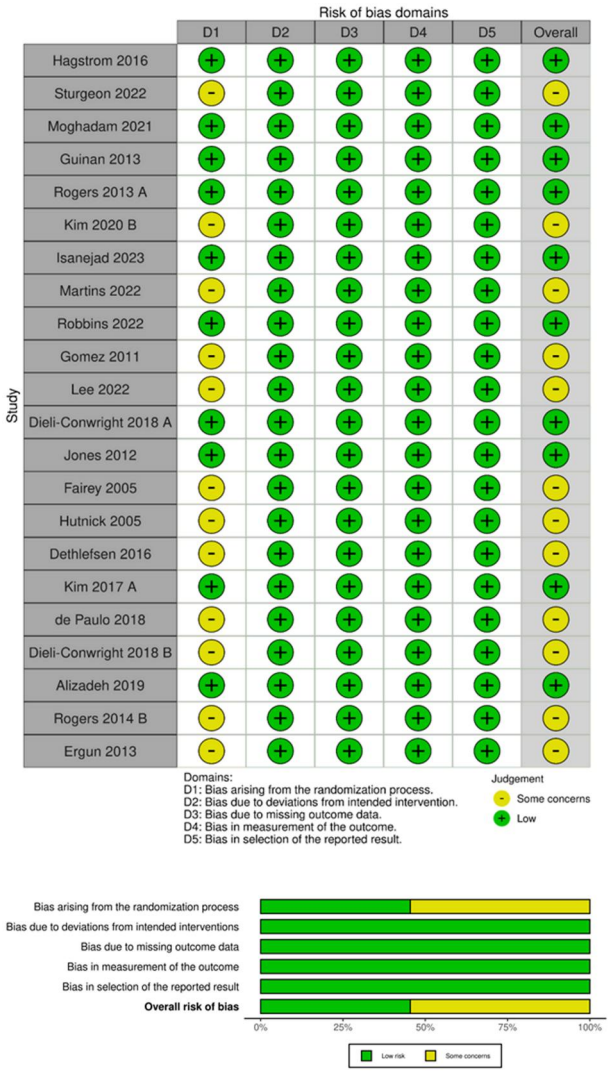

Figure 2. The risk of bias assessment according to RoB 2.

change in IL-8 between exercise and control groups (SMD = −0.69; 95% CI = −1.92 to 0.55; $P = .23$). The heterogeneity I^2 was 83.4%, with 1 study being the candidate for high heterogeneity[47]; which, after removal, reduced the main effect to −0.23 SMD (95% CI = −1.10 to 0.64; $P = .54$) and the heterogeneity I^2 to 60.1%. There was an insufficient number of studies to examine changes in IL-8 when stratifying by age and BMI.

Exercise mode

There was no statistically significant change between AT (SMD = −0.19; 95% CI = −1.97 to 1.60; $P = .41$)[49,54] as well as combined exercise (SMD = −0.76; 95% CI = −2.26 to 0.74; $P = .26$)[46-49,51,63,64] and control groups. There was an insufficient number of studies to examine changes when stratifying by RT.

Exercise program duration

There was a statistically significant small change in IL-8 when exercise program duration was shorter than 16 weeks (SMD = −0.19; 95% CI = −0.35 to −0.02; $P = .03$),[49,51,54,63,64] while no significant change was observed when exercise program duration was longer than 16 weeks (SMD = −1.54; 95% CI = −7.77 to 4.68; $P = .40$).[46-48]

Interleukin 10

Main model

Nine studies and 11 effect sizes were undertaken for IL-10 (Table 2 and Figure S4).[44,46,51,53,54,56,61,63,64] There was no statistically significant change in IL-10 between exercise and control groups (SMD = 0.03; 95% CI = −0.34 to 0.39; $P = .87$). The heterogeneity I^2 was 0%. There was an insufficient number of studies to examine change in IL-10 when stratifying by age and BMI.

Exercise mode

There was no statistically significant change between RT (SMD = 0.26; 95% CI = −1.19 to 1.71; $P = .26$),[53,61] AT (SMD = 0.27; 95% CI = −0.83 to 1.37; $P = .39$),[44,54,56] as well as combined exercise (SMD = −0.36; 95% CI = −1.00 to 0.29; $P = .17$)[46,51,63,64] compared with control groups.

Exercise program duration

There was no statistically significant change when exercise program duration was shorter than 16 weeks (SMD = 0.12; 95% CI = −0.28 to 0.53; $P = .48$)[44,51,54,56,61,63,64] as well as longer than 16 weeks (SMD = −0.28; 95% CI = −4.85 to 4.30; $P = .58$).[46,53]

Tumor necrosis factor alpha

Main model

Twelve studies and 15 effect sizes were undertaken for TNF-α (Table 2 and Figure 4).[46,47,49,51,53,54,56-58,61,63,64] There was a small decrease in TNF-α that approached statistical significance in favor of exercise compared with control groups (SMD = −0.40; 95% CI = −0.81 to 0.01; $P = .05$). The heterogeneity I^2 was 23.7%, and an effect of publication bias was found ($t = 2.2$; $P = .047$). In addition, age ($\beta = 0.03 \pm 0.05$; $P = .50$) as well as BMI ($\beta = -0.01 \pm 0.13$; $P = .91$) were not significantly associated with changes in TNF-α (Figure S5).

Exercise mode

There was no statistically significant change between RT (SMD = 0.08; 95% CI = −2.96 to 2.80; $P = .78$)[53,61] as well as AT (SMD = −0.13; 95% CI = −0.30 to 0.03; $P = .08$)[49,54,56,57] and control group. However, a trend toward decrease was observed in favor of combined exercise (SMD = −0.65; 95% CI = −1.40 to 0.09; $P = .08$)[46,47,49,51,58,63,64] compared with control groups.

Exercise program duration

There was no statistically significant change when exercise program duration was shorter than 16 weeks (SMD = −0.13; 95% CI = −0.27 to 0.01; $P = .06$)[49,51,54,56,58,61,63,64] as well as longer than 16 weeks (SMD = −0.91; 95% CI = −2.23 to 0.42; $P = .12$).[46,47,53,57]

C-reactive protein

Main model

Eleven studies and 11 effect sizes were undertaken for CRP (Table 2 and Figure 5).[45,47,48,50,52,53,57,59,60,62,65] A trend toward decrease in CRP was observed in favor of exercise compared with control groups (SMD = −0.67; 95% CI = −1.43 to 0.08; $P = .07$). The heterogeneity I^2 was 36.8%, and no effect of publication bias was found ($t = -1.6$; $P = .13$). In addition, age ($\beta = 0.11 \pm 0.04$; $P = .06$) as well as BMI ($\beta = -0.08 \pm 0.10$; $P = .48$) were not significantly associated with changes in CRP (Figure S6).

Exercise mode

There was no statistically significant change between RT (SMD = −0.31; 95% CI = −1.41 to 0.78; $P = .34$),[53,60,62] AT (SMD = −0.45; 95% CI = −2.06 to 1.17; $P = .34$),[50,52,57] as well as

Table 2. Effect of exercise training on biomarkers of inflammation.

					Random-effect meta-analysis		Heterogeneity		
			K	No. of ES	SMD (95% CI)	P	Q	I^2	P
IL-1β	**Main model**	Overall effect	3	3	0 (−1.84 to 1.84)	1.00	2.2	8.8	.32
	Exercise mode	RT			NA				
		AT			NA				
		Combined training			NA				
	Exercise duration	<16 w			NA				
		≥16 w			NA				
IL-6	**Main model**	Overall effect	15	18	−0.85 (−1.68 to −0.02)	.05	74.6	83.2	0
	Exercise mode	RT	2	2	0.14 (−6.16 to 6.45)	.82	1.3	10.3	.26
		AT	5	7	−1.10 (−3.74 to 1.54)	.31	37.1	91.7	.26
		Combined training	9	9	−0.88 (−1.84 to 0.08)	.07	31.9	37.6	0
	Exercise duration	<16 w	9	12	−0.54 (−1.78 to 0.69)	.34	42.0	84.4	0
		≥16 w	6	6	−1.31 (−2.70 to 0.08)	.06	24.7	40.2	0
IL-8	**Main model**	Overall effect	8	10	−0.69 (−1.92 to 0.55)	.23	46.1	83.4	0
	Exercise mode	RT			NA				
		AT	2	3	−0.19 (−1.97 to 1.60)	.41	0.2	0	.92
		Combined training	7	7	−0.76 (−2.26 to 0.74)	.26	44.9	42.9	0
	Exercise duration	<16 w	5	7	−0.19 (−0.35 to −0.02)	.03	0.5	0	.99
		≥16 w	3	3	−1.54 (−7.77 to 4.68)	.40	40.5	47	.99
IL-10	**Main model**	Overall effect	9	11	0.03 (−0.34 to 0.39)	.87	6.1	0	.80
	Exercise mode	RT	2	2	0.26 (−1.19 to 1.71)	.26	0.1	0	.79
		AT	3	5	0.27 (−0.83 to 1.37)	.39	2.1	0	.79
		Combined training	4	4	−0.36 (−1.00 to 0.29)	.17	1.3	0	.74
	Exercise duration	<16 w	7	9	0.12 (−0.28 to 0.53)	.48	4.4	0	.82
		≥16 w	2	2	−0.28 (−4.85 to 4.30)	.58	0.9	0	.31
TNF-α	**Main model**	Overall effect	12	15	−0.40 (−0.81 to 0.01)	.05	14.8	23.7	.39
	Exercise mode	RT	2	2	−0.08 (−2.96 to 2.80)	.78	0.3	0	.60
		AT	4	6	−0.13 (−0.30 to 0.03)	.08	0.2	0	.60
		Combined training	7	7	−0.65 (−1.40 to 0.09)	.08	10.5	22	.10
	Exercise duration	<16 w	8	11	−0.13 (−0.27 to 0.01)	.06	1	0	1
		≥16 w	4	4	−0.91 (−2.23 to 0.42)	.12	7.7	30.3	1
CRP	**Main model**	Overall effect	11	11	−0.67 (−1.43 to 0.08)	.07	37.4	36.8	0
	Exercise mode	RT	3	3	−0.31 (−1.41 to 0.78)	.34	1.1	0	.58
		AT	3	3	−0.45 (−2.06 to 1.17)	.34	2.6	8.4	.58
		Combined training	5	5	−1.00 (−2.99 to 0.98)	.23	32.4	43.7	0
	Exercise duration	<16 w	5	5	−0.41 (−1.02 to 0.19)	.13	3	0	.56
		≥16 w	6	6	−0.89 (−2.41 to 0.64)	.19	33.9	42.9	.56

Abbreviations: AT = aerobic training; CI = confidence interval; combined training = RT plus AT; ES = effect size; I^2 = percentage of variation across studies that is due to heterogeneity; K = number of studies; ; NA = not available; P = P-value; Q = Cochran's Q test of heterogeneity; RT = resistance training; SMD = standardized mean difference; w = weeks.

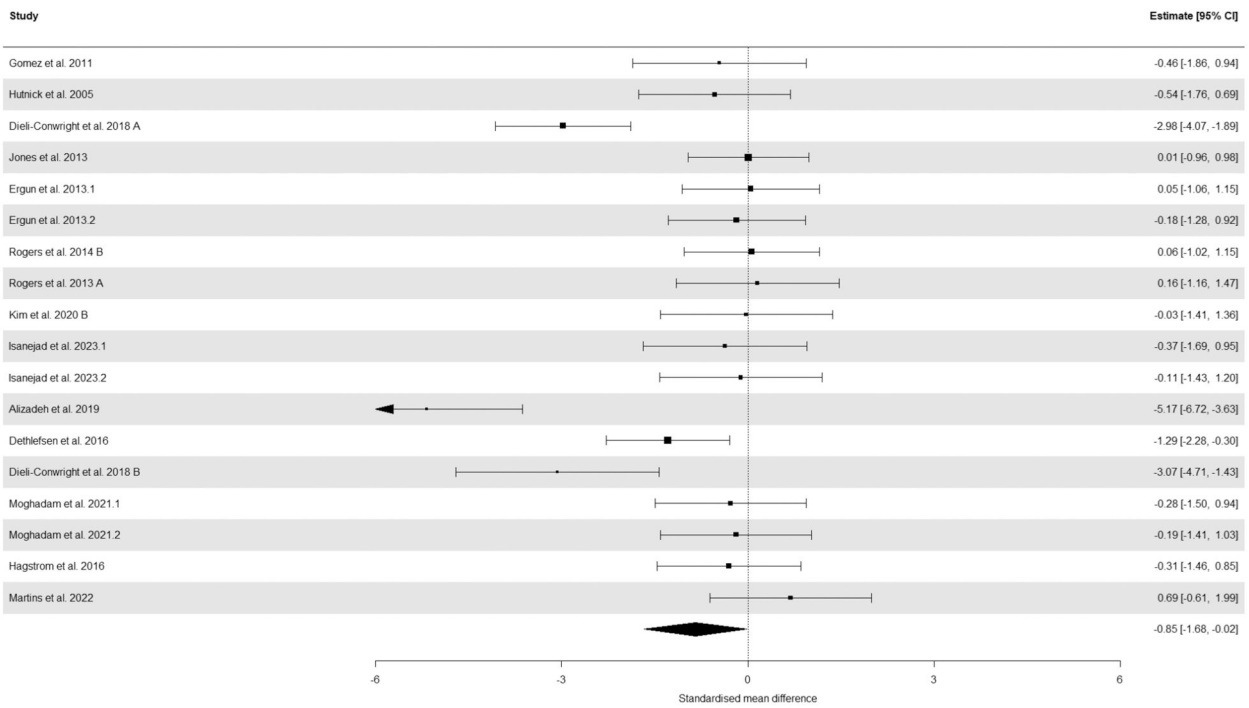

Figure 3. Forest plot of overall effects of exercise on IL-6 in breast cancer survivors. Abbreviation: CI = confidence interval; IL-6 = interleukin 6.

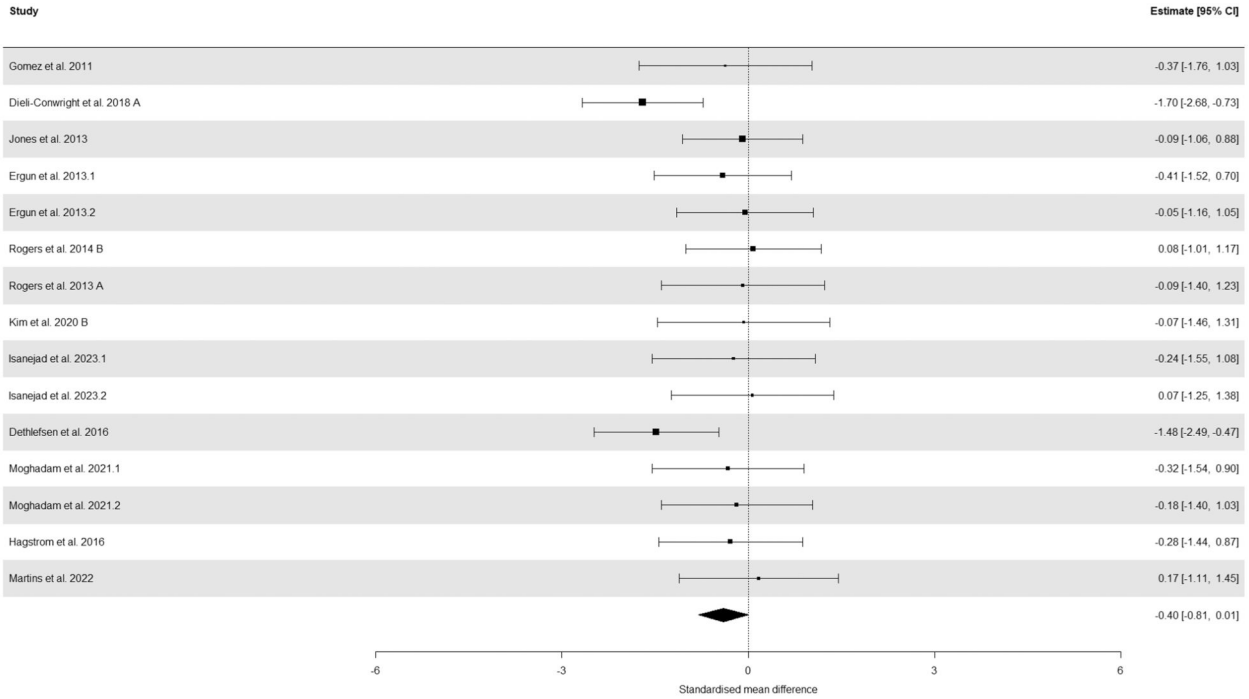

Figure 4. Forest plot of overall effects of exercise on TNF-α in breast cancer survivors. Abbreviation: CI = confidence interval; TNF-α = tumor necrosis factor alpha.

combined exercise (SMD = −1.00; 95% CI = −2.99 to 0.98; $P = .23$)[45,47,48,59,65] and control groups.

Exercise program duration

There was no statistically significant change when exercise program duration was shorter than 16 weeks (SMD = −0.41; 95% CI = −1.02 to 0.19; $P = .13$)[50,52,59,60,62] as well as longer than 16 weeks (SMD = −0.89; 95% CI = −2.41 to 0.64; $P = .19$).[45,47,48,53,57,65]

Discussion

In this systematic review and meta-analysis, we examined the overall effects of exercise, as well as mode and program duration, on pro-inflammatory (ie, IL-1β, IL-6, IL-8, TNF-α, and CRP) and

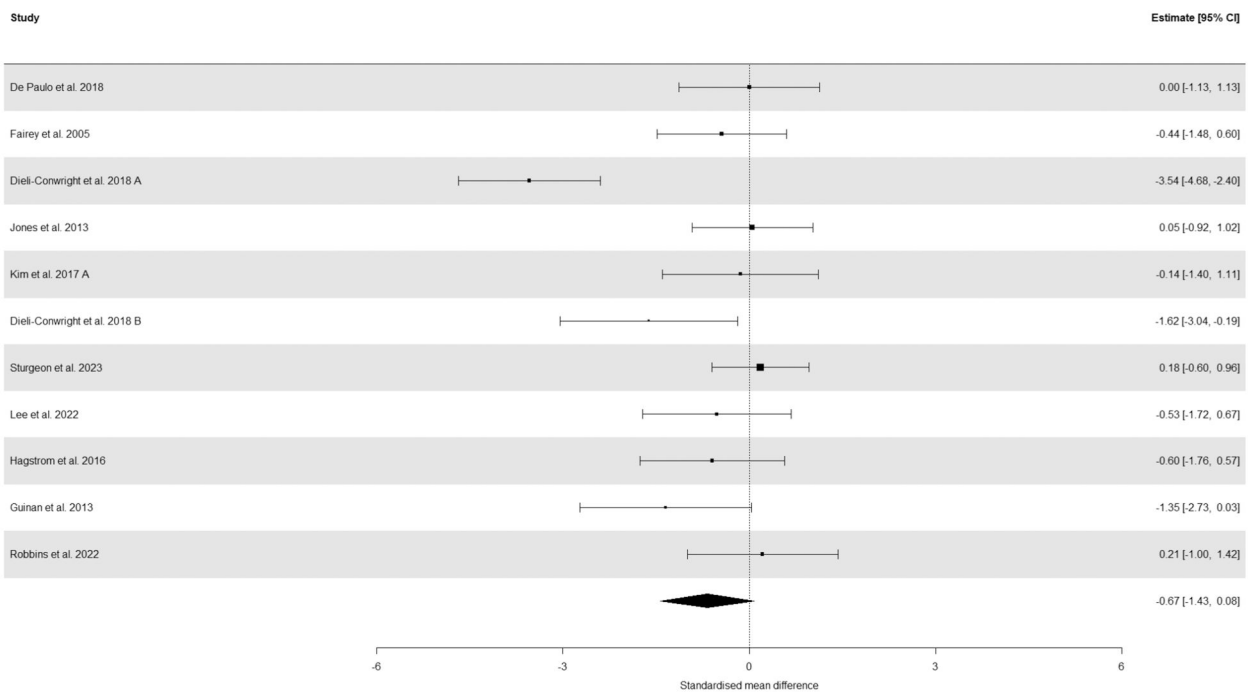

Figure 5. Forest plot of overall effects of exercise on CRP in breast cancer survivors. Abbreviation: CI = confidence interval; CRP = C-reactive protein.

anti-inflammatory (ie, IL-10) biomarkers in survivors of breast cancer. There were 3 important findings. First, exercise training induced small to large significant reductions in IL-6 and TNF-α and a trend for a decrease in CRP compared with controls. Second, when stratifying by exercise mode, although not statistically significant, it appears that combined exercise (ie, RT plus AT) elicited greater reductions in IL-6 and TNF-α compared with controls. Third, changes in markers of inflammation did not appear to be significantly affected when stratifying by exercise program duration, except for IL-8, which showed a significant reduction when exercise program was shorter than 16 weeks. Our findings is that a program of exercise, especially combined exercise, may be a suitable strategy to reduce selective markers of inflammation in survivors of breast cancer.

Regarding the pro-inflammatory biomarkers, it appears that exercise can reduce inflammation, as highlighted by the significant changes observed for IL-6 and TNF-α. Furthermore, although IL-1β and IL-8 did not reveal any significant change, other pro-inflammatory markers (ie, CRP) trended toward decrease, supporting the potential anti-inflammatory effects of exercise. By contrast, no change was found in the anti-inflammatory marker assessed (ie, IL-10). Our findings are a novel perspective for survivors of breast cancer, as previous systematic reviews included breast cancer patients during cancer treatments and interventions such as yoga and Tai Chi, which we deliberately excluded as they differ in structural and physiological responses and adaptations from conventional forms of exercise training.[25,31-33] Our findings are of importance as pro-inflammatory biomarkers are involved in tumorigenesis, directly promoting tumor progression by influencing cell proliferation, survival, invasiveness, and metastasis,[4,5,9,10] and indirectly promoting tumorigenesis by inhibiting immune effector cells.[11] Specifically for breast cancer, IL-6 promotes with tumor cell survival, metastasis, and immune evasion,[13] TNF-α contributes to tumor progression by enhancing the inflammatory microenvironment and suppressing antitumor immunity,[66] while elevated CRP levels indicate systemic inflammation, correlating with poor prognosis and increased tumor recurrence risk.[67] By favorably modulating these markers, exercise may reorder the communication between cancer cells and surrounding stromal cells (eg, fibroblasts, immune cells, etc.), with the potential to reduce the risk of breast cancer recurrence.[4,5,9,10] In addition, it is well known that elevated pro-inflammatory biomarkers are also associated with higher risks of developing cardiovascular diseases, diabetes, and obesity in survivors of breast cancer[68-70] which, in turn, lead to a poorer quality of life and higher risk of mortality.[71] Thus, given that augmented levels of pro-inflammatory factors are associated with an increased risk of cancer recurrence and mortality in breast cancer survivors,[15] our findings may partially explain the underlying reasons for the association between higher levels of exercise and lower risks of cancer recurrence and mortality.[24,26,27,72,73] In addition, although speculative, differences in the biological half-lives of the cytokines, specific regulatory mechanisms, and potential for exercise-induced signals to interact differently with each cytokine pathway may have accounted for the lack of significant changes in some markers (eg, IL-1β and IL-10)[74,75]; however, more research is needed to clearly elucidate the underlying biological reasons. Interestingly, high heterogeneity (ie, ≈80%) was observed only in 2 markers (ie, IL-6 and IL-8) which, in turn, reduced to ≈60% after the removal of such sources of heterogeneity,[44,47] increasing the confidence in our results.

Although we focused on AT and RT and their combination, various exercise prescriptions were adopted in the trials evaluated in this review. It should be acknowledged that exercise for patients with cancer needs to adhere to current guidelines[19] and that a certain threshold for exercise intensity, volume, and frequency is required to derive physical and physiological benefit.[18-20] The prescription of exercise that is insufficient in regards to volume, intensity, duration, or frequency may constrain physiological changes (ie, inflammatory markers),[26] and this may be a limitation in some studies undertaken to date in survivors of breast cancer. For example, in the current review, the intensity

(eg, % 1RM) of some RT interventions was not clearly specified,[47,58,63] or elastic bands were employed,[49,55,59] making it difficult to accurately determine the exercise intensity. Additionally, the volume (eg, low number of exercises, repetitions, and sets)[55,58,61] as well as frequency (eg, 1 day per week)[46] used by some RT studies were quite modest compared with current guidelines (ie, 8-15 repetitions for 2 sets at 60%-80% 1 RM, at least 2 days per week).[19] Similarly, regarding AT, intensity (eg, poorly reported),[49,58,63] session duration (eg, 10-15 min),[49,55,59] and frequency (eg, 1 day per week)[46] adopted in some studies were relatively low in comparison to intensity (ie, 60%-80% HRmax), session duration (75-150 min per week), and frequency (ie, at least 3 days per week) recommended in current guidelines.[19]

When performing the subgroup analysis by exercise mode and program duration in survivors of breast cancer, no statistically significant changes were noted in favor of RT, AT, or combined training compared with the control group. Nevertheless, a trend toward a decrease was found for IL-6 and TNF-α for survivors of breast cancer undertaking combined exercise training. As expected, the combination of both RT and AT appears to elicit greater response in markers of inflammation, likely due to the involvement of both anaerobic and aerobic pathways[76] and potentially higher overall exercise dosage. Resistance training promotes muscle growth and glucose uptake, by releasing anti-inflammatory cytokines, which, in turn, reduces systemic inflammation.[77] In contrast, AT has been shown to reduce systemic inflammation through improved circulation, increasing the delivery of immune cells and enhancing their function.[78,79] The synergistic effects of RT and AT may, therefore, result in greater changes in inflammatory biomarkers compared with single mode exercise. However, it should be noted that few studies investigated the effects of isolated AT and, especially, RT on markers of inflammation in breast cancer survivors, meaning that more research is needed to clearly elucidate the potential impact of each exercise mode. Furthermore, we also examined whether different exercise program duration, shorter than 16 or longer than 16 weeks, influenced pro- and anti-inflammatory factors. A statistically significant reduction was found only for IL-8 when exercise program duration was shorther than 16 weeks. Nevertheless, it appears that greater effects were observed in favor of an exercise program duration longer than 16 weeks for IL-6, given by the trend noted. Indeed, although it is plausible to assume that changes in physiological outcomes may benefit more from longer exercise training interventions, it is yet to be determined as to the optimal program duration to induce such changes in survivors of breast cancer.[80,81] Taken together, the precise role of exercise mode and program duration on pro- and anti-inflammatory biomarkers is yet to be determined, and more research exploring these variables is required. Furthermore, it should be noted that the adherence rate was considered acceptable (ie, ≥75%) in most trials, with only 1 exception reporting a lower rate of 66%.[46] Lastly, the risk of bias was moderate, owing to some concerns in the randomization process. However, this should not have impacted the findings of this systematic review.

Strength and limitations

The strengths of the current study are: (1) a large number of RCTs ($n = 22$) with inclusion of only survivors of breast cancer who have completed primary treatment; (2) blood collected at least 24 h after the last training session to avoid the arousal effect of exercise; and (3) subgroup analyses (ie, exercise mode and program duration) and meta-regression (ie, age and BMI). However, some limitations are worthy of comment. First, our study is limited by the inclusion of exclusively English language publications, potentially leading to language bias. Second, heterogeneity in disease stage (eg, stages I and III), the type of cancer treatment received (eg, chemotherapy and hormone therapy) as well as time after treatment (ie, ranging from 2 weeks to 36 months) lead to substantial variability in the population included. Third, some studies may have not adequately controlled for confounding factors, such as diet and physical activity outside of the exercise training programs, which could have influenced inflammatory biomarkers.

Directions for future research

Future research should examine survivors of breast cancer based on cancer stage (eg, early stage vs advanced) and treatment modalities (eg, chemotherapy, radiation therapy, hormone therapy, immunotherapy, targeted agents), to better understand how exercise interacts with tumor biology, immune profile, and treatment-induced inflammation. Indeed, given that both systemic and local treatments for breast cancer may elevate levels of systemic inflammation,[82] it is important to consider whether exercise interventions might yield more pronounced benefits when pro-inflammatory stimuli are heightened due to cancer treatments. Studies should adopt precise exercise prescriptions that align with established guidelines,[19] in terms of volume, intensity, frequency, and duration. Standardizing these variables will enhance reproducibility and comparability among trials, enabling clearer conclusions regarding the optimal exercise dosage for reducing inflammation in breast cancer survivors. Furthermore, future research should also aim to elucidate the mechanistic pathways through which exercise influences inflammatory biomarkers in survivors of breast cancer. In this regard, correlative studies using advanced techniques (eg, multiomics[83,84]) are warranted to identify key molecular targets modulated by exercise. Additionally, mechanistic studies could explore how exercise impacts systemic inflammation by examining interactions between inflammatory cytokines and the social determinants of health (eg, socioeconomic status, health-care access, chronic stress).[85,86] Indeed, these factors may influence baseline inflammation and biological aging processes, leading to individual responses to exercise. Thus, stratifying survivors of breast cancer based on these factors could provide insights into how different subgroups respond to exercise, supporting the development of tailored exercise prescriptions. Lastly, future exercise trials should be designed with a specific focus on assessing the mediating role of inflammation modulation in survival outcomes. By systematically investigating how exercise-induced changes in inflammatory biomarkers correlate with cancer recurrence and mortality, the causal pathways through which exercise may impact long-term prognosis in survivors of breast cancer may be established.

Conclusion

Exercise training can potentially reduce pro-inflammatory biomarkers in survivors of breast cancer, especially IL-6 and TNF-α, while changes in anti-inflammatory factors were not observed. In addition, although comparatively few studies investigated the isolated effects of RT and AT, it appears that combined exercise training (ie, RT plus AT) may induce greater effects on inflammatory factors, while changes were not generally affected by exercise program duration. Nevertheless, additional research is needed to clearly elucidate the effects of exercise on biomarkers

of inflammation in survivors of breast cancer, especially the effects of isolated AT and RT.

Author contributions

Francesco Bettariga (Conceptualization, Data curation, Formal analysis, Methodology, Writing—original draft), Dennis Taaffe (Conceptualization, Writing—review & editing), Anita Borsati (Data curation, Formal analysis, Writing—review & editing), Alice Avancini (Data curation, Writing—review & editing), Sara Pilotto (Data curation, Writing—review & editing), Stefano Lazzarini (Data curation, Formal analysis, Writing—review & editing), Pedro Lopez (Conceptualization, Data curation, Formal analysis, Methodology, Writing—review & editing), Luca Maestroni (Data curation, Writing—review & editing), Umberto Crainich (Data curation, Writing—review & editing), John Campbell (Data curation, Writing—review & editing), Timothy Clay (Data curation, Writing—review & editing), Daniel Galvao (Conceptualization, Data curation, Writing—review & editing), and Robert Newton (Conceptualization, Data curation, Supervision, Writing—review & editing).

Supplementary material

Supplementary material is available at *JNCI: Journal of the National Cancer Institute* online.

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Conflicts of interest

All authors declare that they have no conflicts of interest relevant to the content of this study.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Meta-Analysis