Brain, Behavior, and Immunity 81 (2019) 92–104

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Exercise training, circulating cytokine levels and immune function in cancer survivors: A meta-analysis

Nasim Khosravi[a,b,1], Lee Stoner[a,2], Vahid Farajivafa[a,b,3], Erik D. Hanson[a,*,4]

[a] Department of Exercise and Sport Science, Exercise Oncology Research Laboratory, University of North Carolina at Chapel Hill, NC, USA
[b] Physical Education & Sport Sciences Department, Faculty of Humanities, Tarbiat Modares University, Tehran, Iran

ARTICLE INFO

Keywords:
Aerobic training
Resistance training
Exercise oncology
Immune system
Inflammation

ABSTRACT

Background: Anti-cancer therapies lead to chronic non-resolving inflammation and reduced immune function. One potential therapy is exercise training, but the effectiveness of these interventions to improve immune-related outcomes, the gaps in the literature, and recommendations to progress the field need to be determined.
Objectives: (1) to conduct separate meta-analyses in cancer survivors to determine the effects of exercise training on pro- and anti-inflammatory markers, and immune cell proportions and function; and (2) to perform subgroup analyses to determine whether exercise modality, cancer type, and specific markers help to explain heterogeneity in each meta-analysis.
Data sources: Electronic databases (PubMed/MEDLINE, EMBASE, CENTRAL, and CINAHL) from inception to March 2018. The reference lists of eligible articles and relevant reviews were also checked.
Study selection: Inclusion criteria were adult cancer survivors from randomized controlled trials performing structured exercise intervention (aerobic, resistance or combined training or Tai Chi/yoga) compared to usual care control group and included pro-inflammatory, anti-inflammatory, and/or immune cell outcomes.
Appraisal and synthesis methods: A total of 5349 potentially eligible articles were identified, of which 26 articles (27 trials) met the inclusion criteria. Effect sizes were calculated as standardized mean differences (SMD), where < 0.2 was defined as trivial, 0.2–0.3 as small, 0.4–0.8 as moderate, and > 0.8 as a large effect.
Results: Exercise training decreased pro-inflammatory markers (SMD: −0.2, 95% CI: −0.4, −0.1, $p < 0.001$). Sub-group analysis for the pro-inflammatory markers indicated that combined aerobic and resistance training had the greatest effect (SMD: −0.3, 95% CI: −0.5, −1.9, $p < 0.001$), that prostate (SMD: −0.5, 95% CI: −0.8, 0.1, $p = 0.004$) and breast cancer populations were most responsive (SMD: −0.2, 95% CI: −0.3, –0.1, $p = 0.001$), and that C-reactive protein (SMD: −0.5, 95% CI: −0.9, −0.06, $p = 0.025$) and tumor necrosis factor (SMD: −0.3, 95% CI: −0.5, –0.06, $p = 0.004$) were the most sensitive to change. Exercise training tended to decrease anti-inflammatory markers ($p = 0.072$) but had no effect on natural killer or natural killer T cell proportions or cytotoxic activity.
Conclusions: Exercise training reduces pro-inflammatory markers in cancer survivors, with the strongest evidence for combined training and for prostate and breast cancer survivors. Further research is warranted to determine if these changes are clinically relevant or are associated with improvements in symptoms. To strengthen future research, focusing on novel immune populations that include functional parameters and standardized reporting of key immune outcomes is recommended.

1. Introduction

Cancer is widespread and costly, with an estimated 1.7 million new cases and ~600,000 deaths this year in the US alone with annual treatment costs estimated to exceed $75 billion (Chang et al., 2004). Cancer mortality is in decline (Siegel et al., 2019), likely owing to

* Corresponding author at: Department of Exercise and Sport Science, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599 USA.
E-mail address: edhanson@email.unc.edu (E.D. Hanson).
[1] ORCID numbers: 0000-0001-6679-9335.
[2] ORCID numbers: 0000-0002-0682-2270.
[3] ORCID numbers: 0000-0001-9709-1575.
[4] ORCID numbers: 0000-0002-7744-5652.

https://doi.org/10.1016/j.bbi.2019.08.187
Received 28 April 2019; Received in revised form 6 August 2019; Accepted 21 August 2019
Available online 24 August 2019
0889-1591/

earlier diagnosis and advanced treatments. However, numerous adverse side effects, including chronic non-resolving inflammation (Crusz and Balkwill, 2015; Marelli et al., 2017; Roxburgh and McMillan, 2014; Siegel et al., 2019) and reduced immune function (Copelan, 2006; Zitvogel et al., 2008), often accompany anti-cancer therapies and decrease overall quality of life (Bower, 2007, 2014; Schag et al., 1994). Chronic inflammation and compromised cellular immunity are major concerns, as both promote a pro-tumor environment that may contribute to disease progression (Aggarwal and Gehlot, 2009; Balkwill and Mantovani, 2001; Mantovani et al., 2008; Tan and Coussens, 2007). As such, there remains a need to identify options to manage inflammation while maximizing immune function in cancer survivorship. Exercise is potentially an attractive option. However, the role of exercise training on immune function and inflammatory markers is not well-addressed in current exercise oncology guidelines (Hayes et al., 2019; Schmitz et al., 2010). To assist with the development of future guidelines, a meta-analysis of the available exercise immunology and inflammatory literature is warranted to address the influx of new literature, to examine sources of heterogeneity (e.g., cancer type, exercise mode, specific biomarker) within key outcomes, to identify gaps in the current literature, and to provide recommendations to improve the field.

Exercise training is a non-pharmacological, complementary therapy that assists with symptom management by systematically targeting specific adverse effects of treatment, including inflammation (Ballard-Barbash et al., 2012; Courneya et al., 2014; Galvao and Newton, 2005; Hanson et al., 2016). Exercise may also favorably manipulate immune system parameters (Fairey et al., 2002; Koelwyn et al., 2015), as animal model show reduced tumor growth via immune cell infiltration and redistribution (Pedersen et al., 2016). Immune function has a critical role in cancer progression and recurrence (Finn, 2008), with exercise potentially improving immune surveillance (Koelwyn et al., 2015), such that both innate and adaptive immunity have clinical relevance and potential survival implications.

Immune cell proportions and function provide direct evidence of immunity in cancer survivors, but this approach is less common. Alternatively, circulating biomarkers are commonly assessed (Fairey et al., 2002; Kruijsen-Jaarsma et al., 2013), because of the relative ease of obtaining them during clinic visits. Cytokines are generally categorized as either pro- or anti-inflammatory, with some, e.g., interleukin (IL)-6, functioning as both (Opal and DePalo, 2000; Scheller et al., 2011; Stoner et al., 2013). While a dichotomous classification of biomarkers is an oversimplification (Cavaillon, 2001), markers are often grouped and analyzed together to provide insight into the overall inflammatory state of the body. Higher circulating levels of pro-inflammatory cytokines are linked to cancer-related outcomes. For example, breast cancer patients with advanced tumors had higher circulating levels of tumor necrosis factor (TNF) compared to healthy individuals (Ma et al., 2017; Sheen-Chen et al., 1997). Similarly, higher TNF levels are correlated with the extent and progression of prostate cancer (Michalaki et al., 2004), and increased levels of C-reactive protein (CRP) are associated with higher mortality in cancer patients (Allin et al., 2009; Crusz and Balkwill, 2015; Shrotriya et al., 2018). Previously, systematic reviews concluded that exercise training had no effects on circulating cytokines in cancer survivors in general (Kruijsen-Jaarsma et al., 2013; Lof et al., 2012). However, favorable effects were reported for TNF, IL-6, IL-8, and IL-2 in breast cancer by a recent meta-analysis using a more homogenous population (Meneses-Echavez et al., 2016). Despite the role of inflammatory status in several cancers (Balkwill and Mantovani, 2001; Michalaki et al., 2004) and the growing body of literature examining cytokines in exercise oncology (Christensen et al., 2014; Dethlefsen et al., 2016; Dieli-Conwright et al., 2018; Glass et al., 2015; Hagstrom et al., 2016; Hojan et al., 2017; Hojan et al., 2015; Hvid et al., 2016; Lee et al., 2017; Liu et al., 2015; Rogers et al., 2014; Schmidt et al., 2016), it remains unclear if exercise benefits extend beyond breast cancer.

In addition to inflammatory status, immune function is important as these cells recognize and eliminate malignant tumors (Bui and Schreiber, 2007; Finn, 2008). Natural killer (NK) cells are one of the most widely studied components of the immune system with exercise (Pedersen, 1991; Walsh et al., 2011). In healthy individuals, circulating NK cell number rapidly increases following acute exercise, with evidence of increased cytotoxicity (Pedersen and Ullum, 1994; Timmons and Cieslak, 2008; Walsh et al., 2011). Exercise training may also enhance immune function (Nieman, 1994) but this is not conclusive (Walsh et al., 2011). Within cancer populations, exercise training has been hypothesized to improve immune function (Kruijsen-Jaarsma et al., 2013; McTiernan, 2008), with increases in NK cell activity and lymphocyte proliferation as supporting evidence (Fairey et al., 2002; Kruijsen-Jaarsma et al., 2013). Animal models demonstrate that exercise training reduces the incidence and growth of cancer through pathways related to NK cell mobilization (Pedersen et al., 2016). The movement of NK cells into the tumor may help activate the adaptive immune system, with T cell infiltration having beneficial impacts on survival outcomes (Fridman et al., 2012). While human studies show that circulating immune cell numbers appear stable following training, a consensus on enhanced function is lacking, particularly in subsets beyond NK cells. Moreover, the magnitude and potential clinical significance of any training-induced effects have not been defined.

Previous reviews on inflammation and exercise training report mixed findings (Kruijsen-Jaarsma et al., 2013; Lof et al., 2012; Meneses-Echavez et al., 2016), with several possible reasons existing within oncology populations. Immune and inflammatory marker effects are likely influenced by the common use of multiple exercise modalities and different exercise intensities and volumes that produce different endocrine and immune responses (Nieman et al., 2012; Wells et al., 2016). Cancer types also vary substantially based on several factors (e.g., origin site, treatment protocols). For instance, chemotherapy is widely used for some cancers (e.g., breast, leukemia) but less so in others (prostate), whereas endocrine treatments are commonly used in hormone-dependent cancers. As such, different cancer types are likely to affect the immune and inflammatory responses via decreases in circulating cell number (Geinitz et al., 2001; Lerner et al., 1976; Moertel et al., 1994) or altered cytokine levels (Collado-Hidalgo et al., 2006; Dehqanzada et al., 2007). Consequently, exercise modality and specific cancer type are important factors to consider when assessing immunity and inflammatory profiles in cancer survivors, such that exercise and public health organizations may consider the effects of exercise training on inflammatory profiles and immune function when issuing future guidelines.

1.1. Objective

Exercise interventions are attractive non-pharmacological therapies for treating chronic inflammation and compromised cellular immunity associated with anti-cancer therapies. There is a need to consolidate the literature to determine the effectiveness of exercise training, guide the extension of exercise guidelines, highlight gaps in the literature, and determine specific areas of need for progressing the field. Therefore, the objectives were (1) to conduct separate meta-analyses to identify and quantitatively review randomized controlled trials assessing the effects of exercise training on pro- and anti-inflammatory markers, and immune cell proportions function and; and (2) to perform subgroup analyses to determine whether exercise modality, cancer type, and specific markers help to explain heterogeneity in each meta-analysis.

2. Methods

This meta-analysis is reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher et al., 2015) and is reported in supplementary Table 1.

2.1. Data sources and searches

Electronic databases (PubMed/MEDLINE, EMBASE, CENTRAL, and CINAHL) were searched by two authors (NK, VF). For searches in PubMed/MEDLINE and EMBASE, terms from MeSH and Emtree were used, respectively; for the other two electronic databases, the keywords were adjusted. To permit a comprehensive search, Boolean operators and wild cards were used. The selected keywords for the search included "cancer, neoplasm, tumor, tumour, malignancies, exercise, resistance training, aerobic training, immune function, immunity, immune system, immun*, innate immunity, humoral immunity, adaptive immunity, mucosal immunity, cellular immunity, cytokines, cytokine receptors, leukocytes, neutrophils, lymphocytes, monocytes, dendritic cells, natural killer cells, killer cells, immunoglobulins, and T lymphocytes." Additional resources searched included Scopus (conference papers), American Society of Clinical Oncology, Google Scholar (200 first results) (Bramer et al., 2017), and the reference lists of all identified trials and relevant reviews. The search was limited to English-language studies published between inception and March 2018.

2.2. Article selection

For the purpose of this meta-analysis, the terms 'article' and 'study' are used synonymously, and 'trial' is the unit included in the meta-analysis. A given article may have resulted in more than one eligible 'trial' if the article included more than one intervention group. Initially, article titles and abstracts were screened for relevance. The full text of potentially eligible articles was obtained to review eligibility for inclusion. The following criteria were used for inclusion in the review: (1) the study was a randomized controlled trial; (2) the intervention was exercise training alone (i.e., not in combination with other non-exercise interventions); (3) the control group comprised of non-exercising cancer survivors; (4) participants were adults; and (5) immune-related outcomes (i.e., direct immune markers or cytokines/markers associated with immune function) were reported. In trials with multiple treatment arms and a single control group, the sample size of the control group was divided by the number of treatment groups to avoid over-inflation of the sample size (Higgins and Green, 2008). Two researchers (NK and VF) completed the study selection independently. If there was disagreement, a third reviewer (EH) was consulted.

2.3. Data extraction and quality assessment

The following information was extracted for analysis: bibliographic information (author, publication year), baseline participant characteristics, intervention details, immune-related components, immunoassay protocols, and results of reported outcomes. The methodological quality of studies was assessed using a modified Physiotherapy Evidence Database (PEDro) scale (range 1–8). Because it is difficult (if not impossible) to blind participants to an exercise intervention, we considered the blinding of the operator to the outcome assessment as a quality criterion. Data extraction and quality assessment were completed by two independent reviewers (NK and VF).

2.4. Outcome selection

All biomarkers related to the immune system including immune-related cytokines and immune cells were recorded. Subsequently, to determine which outcomes were included in the analyses, two steps were followed. First, cytokines with no clear role in the immune system were excluded. Second, biomarkers that were reported in less than three trials were excluded. Cytokines were classified as pro-inflammatory (IL-1β, IL-6, IL-8, TNF, interferon [IFN]-γ, monocyte chemoattractant protein [MCP]-1 and MCP-3, along with the acute phase protein CRP) or anti-inflammatory (interleukin 1 receptor antagonist [IL-1ra] and IL-10) by two authors (EH, LS), based on previous studies (Opal and DePalo, 2000; Scheller et al., 2011; Stoner et al., 2013). Cytokines that were considered but were excluded due to having less than three studies included IL-2, IL-3, IL-4, IL-5, IL-7, IL-9, IL-12, IL-13, IL-15, IL-16, IL-17, IL-18, IL-1α, INF-α, TNF-ß, IL-2ra, sIL-2R, sTNF-R, sTNF-RII, G-CSF, GM-CSF, CTACK, Eotaxin (CCL11), MIP-1α (CCL3), MIP-1ß (CCL4), IP-10 (CCL10), MIG (CCL9), ENA78 (CXCL5), RANTES (CCL5), PDGF, LIF, MCSF, and MCP-2.

2.5. Data Synthesis

For each outcome of interest, the pre- and post-intervention values (mean and standard deviation), as well as mean differences and associated standard deviations, were extracted. When mean differences and associated standard deviations were not published, the study authors were contacted. If an author failed to respond, the values were estimated based on methods from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins and Green, 2008). For studies reporting multiple time points, only the immediate post-intervention value was used in analyses. Aggregation and calculation of final results were conducted by two authors (NK and VF).

2.6. Data analysis

All extracted data were entered into software designed specifically for meta-analyses (Open Meta-Analyst, http://www.cebm.brown.edu/openmeta). Random effects modeling, with the DerSimonian-Laird method, was used to account for both within- and between-study variability (Borenstein et al., 2010). Effect sizes were calculated as standardized mean differences (SMD), where < 0.2 was defined as trivial, 0.2 to 0.4 as small, 0.4 to 0.8 as moderate, and > 0.8 as large (Borenstein et al., 2010; Cohen, 1992). The statistical heterogeneity across different trials in the meta-analysis was assessed by the I^2 statistic (Higgins et al., 2003), where $< 25\%$ indicates a low risk of heterogeneity, 25% to 75% indicates a moderate risk of heterogeneity, and $> 75\%$ indicates a considerable risk of heterogeneity. Sensitivity analyses were carried out by excluding one trial at a time to test the robustness of the pooled results. Publication bias was evaluated by visual inspection of the Begg's funnel plot when (1) at least 10 trials were included in the meta-analysis, and (2) there was substantial variation in sample size for the included trials (Higgins and Green, 2008). One author (LS) conducted the data analysis.

3. Results

3.1. Literature search and trial selection

A total of 5349 potentially eligible articles were identified. After duplicates were removed, 4952 articles remained for screening. Screening based on study title and abstract review excluded 4906 papers. The remaining 46 papers underwent a full-text screening and 20 papers were excluded (Fig. 1). The final analysis included 26 articles (27 trials) (Bower et al., 2014; Christensen et al., 2014; Dethlefsen et al., 2016; Dieli-Conwright et al., 2018; Ergun et al., 2013; Fairey et al., 2005a; Fairey et al., 2005b; Galvao et al., 2010; Glass et al., 2015; Gomez et al., 2011; Hagstrom et al., 2016; Hojan et al., 2017; Hojan et al., 2015; Hvid et al., 2016; Janelsins et al., 2011; Jones et al., 2013; Lee et al., 2017; Liu et al., 2015; Na et al., 2000; Nieman et al., 1995; Rao et al., 2008; Rogers et al., 2013; Rogers et al., 2014; Schmidt et al., 2016; Sprod et al., 2012; Sprod et al., 2010).

3.2. Description of the included trials

3.2.1. Trial Setting and participants

The trial characteristics are summarized in Table 1.The number of participants in each trial ranged from 12 (Liu et al., 2015) to 123 (Lee et al., 2017). Seventeen trials included only female participants (Bower

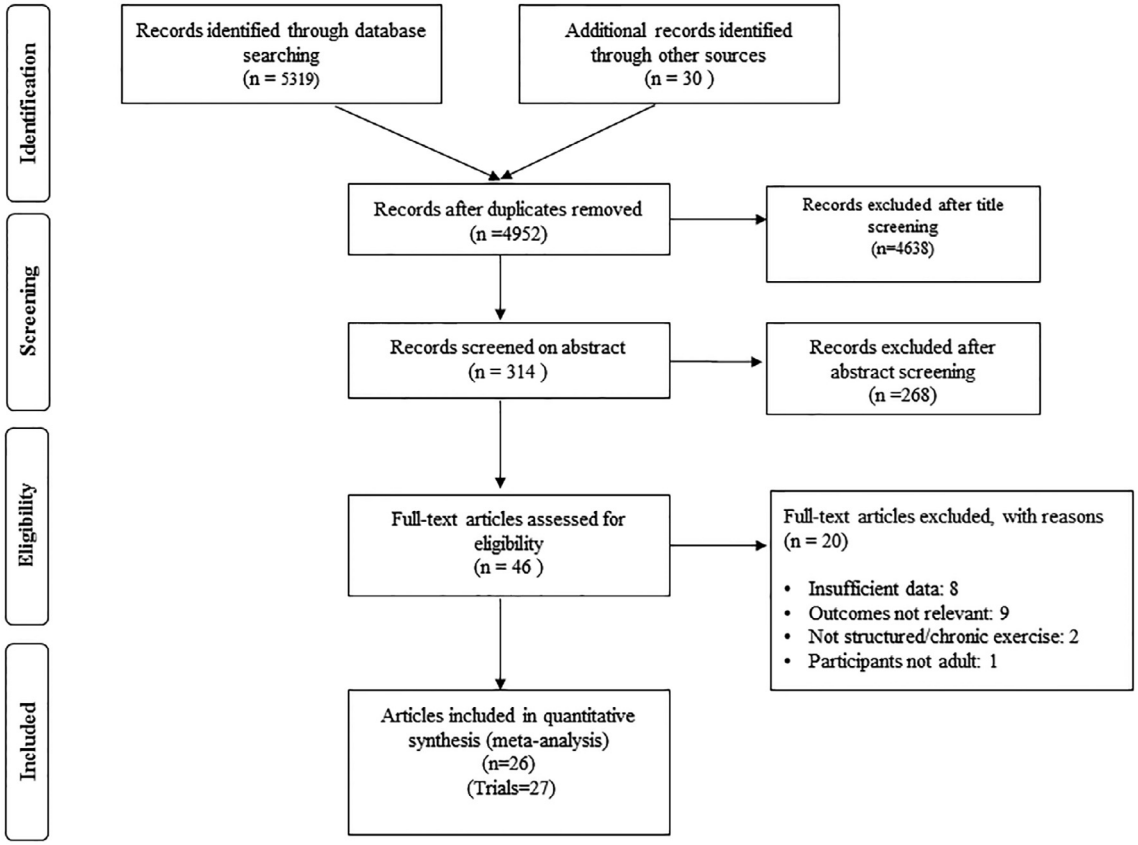

Fig. 1. Flow chart of the study selection process.

et al., 2014; Dethlefsen et al., 2016; Dieli-Conwright et al., 2018; Ergun et al., 2013; Fairey et al., 2005a; Fairey et al., 2005b; Gomez et al., 2011; Hagstrom et al., 2016; Janelsins et al., 2011; Jones et al., 2013; Nieman et al., 1995; Rao et al., 2008; Rogers et al., 2013; Rogers et al., 2014; Schmidt et al., 2016; Sprod et al., 2012), five trials studied only male participants (Christensen et al., 2014; Galvao et al., 2010; Hojan et al., 2017; Hojan et al., 2015; Hvid et al., 2016), and four trials examined both sexes (Glass et al., 2015; Lee et al., 2017; Liu et al., 2015; Sprod et al., 2010). The control groups consisted of usual care (n = 17) (Christensen et al., 2014; Fairey et al., 2005a; Fairey et al., 2005b;

Table 1
Study Characteristics.

Reference	PEDro Score	Cancer Type	Setting	Sample Size	Female (n)	Age (SD) Exercisers	Age (SD) Controls
Hojan et al. (2017) [59]	8	Prostate	Supervised	72	0	65.7 (6.2)	67.9 (4.9)
Dieli-Conwright et al. (2018) [61]	5	Breast	Supervised	21	21	53 (10)	55 (4.5)
Lee et al. (2017) [60]	5	Colorectal	Home-based	123	64	56.3 (9.7)	56.3 (9.9)
Dethlefsen et al. (2016) [55]	5	Breast	Supervised	74	74	46 (9.6)	48.2 (7.8)
Hagstrom et al. (2016) [56]	8	Breast	Supervised	39	39	51.2 (9.4)	52.7 (9.4)
Schmidt et al. (2016) [58]	5	Breast	Supervised	103	103	57.2 (8.8)	57.1 (8.9)
Hvid et al. (2016) [57]	4	Prostate	Home-based	19	0	69.8 (2.9)	68 (6.1)
Glass et al. (2015) [52]	7	Solid tumors	Supervised	44	36	56 (10)	54 (11)
Hojan et al. (2017) [53]	6	Prostate	Supervised	54	0	67.4 (8.3)	69.9 (7.2)
Liu et al. (2015) [54]	5	Lung	Supervised	27	12	62.6 (8.4)	60.5 (7.1)
Christensen et al. (2014) [50]	6	Germ cell	Supervised, Hospital-based	19	0	34.4 (7.6)	35.8 (8.9)
Bower (2014) [75]	5	Breast	Supervised	31	31	54 (5.4)	54 (5.4)
Rogers et al. (2014) [51]	8	Breast	Supervised + Home-based	46	46	57.2 (5.5)	55.2 (9.1)
Ergun et al. (2013) [76]	6	Breast	1) Supervised; 2) Home-based	60	60	49.7 (8.3)	50.3 (10.4)
Jones et al. (2013) [82]	7	Breast	Supervised + Home-based	75	75	56.4 (9.6)	55.4 (7.6)
Rogers et al. (2013) [86]	6	Breast	Supervised + Home-based	28	28	58 (6.1)	53.7 (13.9)
Sprod et al. (2012) [87]	6	Breast	Supervised	19	19	54.3 (3.5)	52.7 (2.1)
Gomez et al. (2011) [80]	4	Breast	Supervised	16	16	50 (5)	50 (5)
Janelsins et al. (2011) [81]	5	Breast	Supervised	19	19	54.3 (10.6)	52.7 (6.7)
Sprod et al. (2010) [88]	6	Breast & Prostate	Home-based	38	27	56.6 (13.7)	63.3 (9.4)
Galvao et al. (2010) [79]	7	Prostate	Supervised	57	0	69.5 (7.3)	70.1 (7.3)
Rao et al. (2008) [85]	6	Breast	Supervised + Home-based	69	69	49.2 (9.6)	49.2 (9.6)
Fairey et al. (2005a,b) [77]	8	Breast	Supervised	53	53	59 (5)	58 (6)
Fairey et al. (2005a,b) [78]	8	Breast	Supervised	53	53	59 (5)	58 (6)
Na et al. (2000) [83]	3	Stomach	Supervised	35	NA	57.8 (12.1)	52.2 (10.3)
Nieman et al. (1995) [84]	4	Breast	Supervised	12	12	60.8 (4)	51.2 (4.7)

Galvao et al., 2010; Glass et al., 2015; Gomez et al., 2011; Hagstrom et al., 2016; Hojan et al., 2017; Hojan et al., 2015; Hvid et al., 2016; Jones et al., 2013; Lee et al., 2017; Liu et al., 2015; Nieman et al., 1995; Rogers et al., 2013; Rogers et al., 2014; Sprod et al., 2010), educational interventions (n = 3) (Bower et al., 2014; Ergun et al., 2013), support therapy (n = 2) (Janelsins et al., 2011; Sprod et al., 2012), health evaluation (n = 1) (Dethlefsen et al., 2016), support counselling plus shoulder rehabilitation movements (n = 1) (Rao et al., 2008), relaxation (n = 1) (Schmidt et al., 2016), and delayed intervention (n = 1) (Dieli-Conwright et al., 2018). Seventeen trials studied breast cancer (Bower et al., 2014; Dethlefsen et al., 2016; Dieli-Conwright et al., 2018; Ergun et al., 2013; Fairey et al., 2005a; Fairey et al., 2005b; Gomez et al., 2011; Hagstrom et al., 2016; Janelsins et al., 2011; Jones et al., 2013; Nieman et al., 1995; Rao et al., 2008; Rogers et al., 2013; Rogers et al., 2014; Schmidt et al., 2016; Sprod et al., 2012), with the remaining trials including prostate (n = 4) (Hojan et al., 2017; Hojan et al., 2015; Hvid et al., 2016), germ cells (n = 1) (Christensen et al., 2014), lung (n = 1) (Liu et al., 2015), colorectal (n = 1) (Lee et al., 2017), and mixed cancers (n = 2) (Glass et al., 2015; Sprod et al., 2010). The majority of studies were conducted after treatment (n = 19) (Bower et al., 2014; Dethlefsen et al., 2016; Dieli-Conwright et al., 2018; Ergun et al., 2013; Fairey et al., 2005a; Fairey et al., 2005b; Galvao et al., 2010; Gomez et al., 2011; Hagstrom et al., 2016; Hvid et al., 2016; Janelsins et al., 2011; Jones et al., 2013; Lee et al., 2017; Liu et al., 2015; Na et al., 2000; Nieman et al., 1995; Rogers et al., 2013; Rogers et al., 2014; Schmidt et al., 2016; Sprod et al., 2012), 6 during treatment (Christensen et al., 2014; Galvao et al., 2010; Glass et al., 2015; Hojan et al., 2015; Rao et al., 2008; Sprod et al., 2010), and 1 study during and after treatment (Hojan et al., 2017).

3.2.2. Interventions

A brief description of the exercise interventions is provided in Table 2. Intervention duration varied from 2 to 104 weeks, with a median of 12 weeks. Thirteen trials used a combination of aerobic training (AE) and resistance training (RT) (Dethlefsen et al., 2016; Dieli-Conwright et al., 2018; Ergun et al., 2013; Galvao et al., 2010; Gomez et al., 2011; Hojan et al., 2017; Hojan et al., 2015; Lee et al., 2017; Nieman et al., 1995; Rogers et al., 2013; Rogers et al., 2014; Sprod et al., 2010), five trials used AE only (Fairey et al., 2005a; Fairey et al., 2005b; Glass et al., 2015; Hvid et al., 2016; Jones et al., 2013), three trials used RT only (Christensen et al., 2014; Hagstrom et al., 2016; Schmidt et al., 2016), and five trials included yoga (n = 2) (Bower et al., 2014; Rao et al., 2008) or Tai Chi (n = 3) (Janelsins et al., 2011; Liu et al., 2015; Sprod et al., 2012).

3.2.3. Immunoassays

Details of immune-related outcomes and immunoassays are presented in Table 2. Circulating biomarker levels were reported in 24 trials (Bower et al., 2014; Christensen et al., 2014; Dethlefsen et al., 2016; Dieli-Conwright et al., 2018; Ergun et al., 2013; Fairey et al., 2005b; Galvao et al., 2010; Glass et al., 2015; Gomez et al., 2011; Hagstrom et al., 2016; Hojan et al., 2017; Hojan et al., 2015; Hvid et al., 2016; Janelsins et al., 2011; Jones et al., 2013; Lee et al., 2017; Rao et al., 2008; Rogers et al., 2013; Rogers et al., 2014; Schmidt et al., 2016; Sprod et al., 2012; Sprod et al., 2010), immune cell number in 3 trials (Glass et al., 2015; Hagstrom et al., 2016; Liu et al., 2015), and immune cell activity in three trials (Fairey et al., 2005a; Na et al., 2000; Nieman et al., 1995). The immunoassays used to determine circulating cytokine and CRP levels included enzyme-linked immunosorbent assay (ELISA) (n = 13) (Bower et al., 2014; Ergun et al., 2013; Fairey et al., 2005b; Glass et al., 2015; Hvid et al., 2016; Janelsins et al., 2011; Jones et al., 2013; Rao et al., 2008; Rogers et al., 2013; Schmidt et al., 2016; Sprod et al., 2012; Sprod et al., 2010), bead-based arrays (n = 5) (Gomez et al., 2011; Hagstrom et al., 2016; Hojan et al., 2017; Hojan et al., 2015; Rogers et al., 2014), chromium release assay (n = 3) (Fairey et al., 2005a; Na et al., 2000; Nieman et al., 1995), Meso Scale Discovery (n = 2) (Christensen et al., 2014; Dethlefsen et al., 2016), flow cytometry (n = 2) (Hagstrom et al., 2016; Liu et al., 2015), immunoturbidimetric assay (n = 2) (Hagstrom et al., 2016; Lee et al., 2017), MicroSlide Technology (Dieli-Conwright et al., 2018), and one trial did not report the methods used (Galvao et al., 2010).

3.3. Methodological quality assessment

The methodological assessment details are presented in supplementary Table 2. Of the 27 trials, five had maximal scores on the modified 8-point PEDro scale (Fairey et al., 2005a; Fairey et al., 2005b; Hagstrom et al., 2016; Hojan et al., 2017; Rogers et al., 2014), three scored below 5 (Gomez et al., 2011; Hvid et al., 2016; Nieman et al., 1995), and the remaining 16 trials fell between these values (Bower et al., 2014; Christensen et al., 2014; Dethlefsen et al., 2016; Dieli-Conwright et al., 2018; Ergun et al., 2013; Galvao et al., 2010; Glass et al., 2015; Hojan et al., 2015; Janelsins et al., 2011; Jones et al., 2013; Lee et al., 2017; Liu et al., 2015; Rao et al., 2008; Rogers et al., 2013; Schmidt et al., 2016; Sprod et al., 2012; Sprod et al., 2010), with a mean of 6.33. Random allocation, group similarity at baseline, between-group differences, point estimates, and variability were reported in all trials (Bower et al., 2014; Christensen et al., 2014; Dethlefsen et al., 2016; Dieli-Conwright et al., 2018; Ergun et al., 2013; Fairey et al., 2005a; Fairey et al., 2005b; Galvao et al., 2010; Glass et al., 2015; Gomez et al., 2011; Hagstrom et al., 2016; Hojan et al., 2017; Hojan et al., 2015; Hvid et al., 2016; Janelsins et al., 2011; Jones et al., 2013; Lee et al., 2017; Liu et al., 2015; Nieman et al., 1995; Rao et al., 2008; Rogers et al., 2013; Rogers et al., 2014; Schmidt et al., 2016; Sprod et al., 2012; Sprod et al., 2010). Concealed allocation was reported only in 11 trials (Fairey et al., 2005a; Fairey et al., 2005b; Galvao et al., 2010; Hagstrom et al., 2016; Hojan et al., 2017; Hojan et al., 2015; Janelsins et al., 2011; Liu et al., 2015; Rao et al., 2008; Rogers et al., 2014; Sprod et al., 2012). In 11 trials, assessors were blinded (Christensen et al., 2014; Ergun et al., 2013; Fairey et al., 2005a; Fairey et al., 2005b; Glass et al., 2015; Hagstrom et al., 2016; Hojan et al., 2017; Jones et al., 2013; Rao et al., 2008; Rogers et al., 2013; Rogers et al., 2014). Outcomes reported from > 85% of the participants initially allocated to groups was met by 15 trials (Bower et al., 2014; Christensen et al., 2014; Dethlefsen et al., 2016; Dieli-Conwright et al., 2018; Ergun et al., 2013; Fairey et al., 2005a; Fairey et al., 2005b; Galvao et al., 2010; Glass et al., 2015; Hagstrom et al., 2016; Hojan et al., 2017; Hojan et al., 2015; Jones et al., 2013; Rogers et al., 2014; Sprod et al., 2010). Intention-to-treat analyses were reported by 13 trials (Fairey et al., 2005a; Fairey et al., 2005b; Galvao et al., 2010; Glass et al., 2015; Hagstrom et al., 2016; Hojan et al., 2017; Jones et al., 2013; Lee et al., 2017; Rogers et al., 2013; Rogers et al., 2014; Schmidt et al., 2016; Sprod et al., 2012; Sprod et al., 2010).

3.4. Synthesis of the results

The effects of exercise interventions on the selected immune outcomes are reported in the subsequent sections. Numerical values are presented as SMD (95% CI) unless otherwise stated. Summary text is provided to consolidate the findings for each meta-analysis.

3.5. Pro-inflammatory cytokines

The results are shown in Table 3. There was a small [effect size] decrease in the pro-inflammatory markers (SMD: −0.253, 95% CI: −0.370 to −0.137, $p = 0.001$); however, there was moderate heterogeneity ($I^2 = 43\%$, $p < 0.001$). None of the trials unduly influenced the outcome, and inspection of the funnel plots indicated no evidence of publication bias. The influence of each individual study is presented for cancer type, exercise mode, and marker in supplementary Figs. 1–3, respectively.

Table 2
Summary of exercise interventions and immunoassay protocols.

Reference	Intervention	Duration (wks)	Control Group	Immune components
Hojan et al. (2017) [59]	AE + RT; F: 3x/wk; I: AE: 65–70% of HRR; RT: 70–75% of 1RM; V: 65–85 min	48	Usual care	IL-6, IL-1ß, TNF
Dieli-Conwright et al. (2018) [61]	AE + RT; F: AE: 3x/wk, RT: 2x/wk; I: AE: 65–85% of MHR, RT: 60–80% of 1RM; V: AE: 50 min, RT: 8 exercise/15 Reps	16	Delayed intervention	CRP, IL-6, IL-8
Lee et al. (2017) [60]	AE + RT; F: RT: 2x/wk, AE: NA; I: AE: > 18METs, RT: NA; V: AE: 10,000 steps/day, RT:30 min	12	Usual care	CRP, TNF
Dethlefsen et al. (2016) [55]	AE + RT; F: 2x/wk; I: AE: 80–100% MHR, RT: 70–90% 1-RM; V: AE: NR, RT: 6 exercise, 3 sets, 8–10 reps	26	Health evaluation group	IL-6, IL-8, IL-10, TNF
Hagstrom et al. (2016) [56]	RT; F: 3x/wk; I: 8 RM; V: 60 min, 3 sets, 8–10 reps of 8 RM	16	Usual care	NK %, NKT %
Schmidt et al. (2016) [58]	RT; F: 2x/wk; I: 60–80% of 1Rm; V: 8 exercises, 3 sets, 8–12 reps	12	Relaxation	IL-6, IL-1ra
Hvid et al. (2016) [57]	AE; F: 3x/wk; I: 60–65% of $VO2_{max}$; V: 35 min	104	Usual care	IL-6, TNF
Glass et al. (2015) [52]	AE; F: 3x/wk; I: 55–100% of $VO2_{peak}$; V: 20–45 min	12	Usual care	NK%, NKT%
Hojan et al. (2017) [53]	AE + RT; F: 5x/wk; I: AE: 65–75% of MHR, RT: 70–75% of 1RM; V: AE: 30 min, RT: 8 reps, 2 sets	8	Usual care	IL-6, IL-1ß, TNF
Liu et al. (2015) [54]	Tai chi; F: 3x/wk; I: NR; V: 60 min	16	Usual care	NK %, NKT %
Christensen et al. (2014) [50]	RT; F: 3x/wk; I: 10–12-RM load; V: 4 exercise, 10 reps, 4 sets	9	Usual care	IFN-γ, IL-1ß, IL-6, IL-8, IL-10, TNF
Bower (2014) [75]	Yoga; F: 2x/wk; I: NR; V: 90 min	12	Health education	IL-6, IL-1ra, CRP
Rogers et al. (2014) [51]	RT + AE; F: 4x/wk; I: AE: 48%-52% of HRR, RT: NR; V: AT: 40 min, RT: 15 reps, 2 sets	12	Usual care	IL-6, IL-8, IL-10, TNF
Ergun et al. (2013) [76]	1) RT + AE; F: 6x/wk; I: NR; V: AE: 30–45 min, RT: NR 2) T: AE; F: 3x/wk; I: NR; V: 30 min	9	Educational group	IL-6, IL-8, TNF, MCP1, MCP3
Jones et al. (2013) [82]	AE; F: 5x/wk; I: 60–80% of predicted MHR; V: 30 min	26	Usual care	IL-6, CRP, TNF
Rogers et al. (2013) [86]	AE + RT; F: 2x/wk; I: NR; V: AE: 75 min, RT: 8 exercises, 20 reps	12	Usual care	IL-6, IL-8, IL-10, TNF
Sprod et al. (2012) [87]	Tai chi; F: 3x/wk; I: NR; V: 60 min	12	Support therapy	IL-6, IL-8
Gomez et al. (2011) [80]	AE + RT; F: 3x/wk; I: AE: 80% of MHR, RT: NR; V: AE: 30 min, RT: NR	8	Usual care	IFN-γ, IL-1ß, IL-1ra, IL-6, IL-8, IL-10, MCP-1, MCP-3, TNF,
Janelsins et al. (2011) [81]	Tai chi; F: 3x/wk; I: moderate; V: 60 min	12	Psychological support therapy	IIL-6, IL-2, INF-γ
Sprod et al. (2010) [88]	AE + RT; F: 7x/wk; I: moderate; V: A: NR, RT: 15 reps, 4sets	4	Usual care	IL-6, TNF
Galvao et al. (2010) [79]	AE + RT; F: 2x/wk; I: AE: 65–80% MHR, RT: 12–6 RM; V: AE: 15–20 min, RT: 8 exercises, 2–4 sets 6–12 reps	12	Usual care	CRP
Rao et al. (2008) [85]	Yoga; F: 4-7x/wk; I: NR; V: 30 min	4	Counselling & rehabilitation	TNF, INF-γ
Fairey et al. (2005a,b) [77]	AE; F: 3x/wk; I: 70–75% of $VO2_{peak}$; V: 35 min	15	Usual care	NKCA
Fairey et al. (2005a,b) [78]	AE; F: 3x/wk; I: 70–75% of $VO2_{peak}$; V: 35 min	15	Usual care	CRP
Na et al. (2000) [83]	AE; F: 5x/wk; I: 60% of MHR; V: 60–90 min	2	Usual care	NKCA
Nieman et al. (1995) [84]	RT + AE; F: 3x/wk; I: AE: 75% of MHR, RE: NR; V: AE: 30 min, RT: 12 reps-2 sets	8	Usual care	NKCA

Abbreviations: F = exercise frequency; I = exercise intensity; V = exercise volume; RT = resistance training; AE = aerobic training; RM = repetition maximum; HRR = heart rate reserve; reps = repetitions; MHR = maximum heart rate; METs = metabolic equivalents; NR = not reported; IL = interleukin; TNF = tumor necrosis factor; IF = interferon; MCP = monocyte chemoattractant protein; VO2peak = peak oxygen uptake; NKCA = natural killer cell cytotoxic activity; CRP = C-reactive protein; IL-1ra = interleukin 1 receptor antagonist; NK = natural killer; NKT = natural killer T; wk = week.

Table 3
Changes in Pro-inflammatory Cytokines with Training.

	Intervention N	Control N	Weight %	SMD 95% CI		P value	I^2	Heterogeneity P value
Overall	1183	1152	100	−0.253	−0.370, −0.137	***0.001***	43%	< 0.001
Cancer Type								
Breast	768	762	77.5	−0.224	−0.358, −0.090	***0.001***	34%	0.018
Germ Cell	36	40	3.8	−0.089	−0.750, 0.571	0.791	52%	0.103
Mixed	38	38	2.7	0.118	−0.239, 0.475	0.468	0%	0.687
Prostate	239	216	12.5	−0.481	−0.808, −0.150	***0.004***	65%	0.004
Colorectal	102	96	3.5	−0.224	−0.503, 0.056	0.117	0%	0.462
Exercise Mode								
Tai Chi/Yoga	97	106	10.5	−0.039	−0.321, 0.242	0.785	2%	0.409
RT	85	85	5	−0.119	−0.699, 0.461	0.688	37%	0.175
AE + RT	745	726	62.8	−0.352	−0.518, −0.186	< ***0.001***	57%	< 0.001
AE	256	235	21.7	−0.152	−0.330, 0.027	0.095	0%	0.897
Marker								
IL-6	349	331	27.3	−0.159	−0.379, 0.061	0.156	38%	0.055
CRP	164	160	12.4	−0.465	−0.872, −0.060	***0.025***	67%	0.011
IL-8	144	146	14	−0.298	−0.709, 0.113	0.156	64%	0.005
INFgamma	26	28	3.4	0.130	−0.509, 0.770	0.419	28%	0.249
TNF	338	325	27.3	−0.297	−0.530, −0.060	***0.004***	52%	0.013
MCP-1	48	48	4.9	−0.381	−0.785, 0.023	0.064	0%	0.845
MCP-3	48	48	4.9	−0.222	−0.624, 0.179	0.278	0%	0.981
IL-1b	70	66	5.8	−0.239	−0.577, 0.100	0.167	0%	0.429

Abbreviations: RT = resistance training; AE + RT = combined training; AE = aerobic training; IL = interleukin; CRP = C-reactive protein; TNF = tumor necrosis factor; MCP = monocyte chemoattractant protein.

3.5.1. Subgroup analysis: cancer type

There was a moderate decrease for the prostate group (SMD: −0.481, 95% CI −0.808 to −0.150, $p = 0.004$) and a small decrease for the breast cancer group (SMD: −0.224, 95% CI −0.358 to −0.090, $p = 0.001$). There was no effect of training on germ cell ($p = 0.791$), colorectal ($p = 0.117$), and mixed cancer ($p = 0.468$) groups.

3.5.2. Subgroup analysis: exercise mode

There was a small decrease for the AE + RT group (SMD: −0.352, 95% CI −0.518 to −0.186, $p < 0.001$), a trivial trend to decrease for the AE group (SMD: −0.152, 95% CI −0.330–0.027, $p = 0.095$), with no changes in the RT ($p = 0.688$) or Tai Chi/Yoga ($p = 0.785$) groups.

3.5.3. Subgroup analysis: marker

There was a moderate decrease in CRP (SMD: −0.465, 95% CI −0.872 to −0.060, $p < 0.025$), and a small decrease in TNF (SMD: −0.297, 95% CI −0.530 to −0.060, $p = 0.004$). There was a trivial-small decreasing trend in MCP-1 (SMD: −0.381, 95% CI −0.785–0.023, $p = 0.064$) with no changes in IL-8 ($p = 0.156$), IL-6 ($p = 0.156$), IL-1β ($p = 0.167$), MCP-3 ($p = 0.278$), or INF-γ ($p = 0.419$).

3.5.4. Pro-inflammatory cytokines summary

Overall, exercise appeared to decrease pro-inflammatory markers. The effects of training were largest in the prostate (moderate ES) and breast (small ES) cancer groups; AE + RT was the most effective exercise modality (small ES), and CRP (moderate ES) and TNF (small ES) were the markers most sensitive to change.

3.6. Anti-inflammatory

The results are shown in Table 4. The meta-analysis indicated a small decrease (SMD: −0.207, 95% CI: −0.432–0.018, $p = 0.072$) in anti-inflammatory markers, which approached significance. There was insufficient data to calculate heterogeneity, but a leave-one-out analysis indicated that none of the trials influenced the outcome. The influence of each individual study is presented for cancer type, exercise mode, and marker in supplementary Figs. 4–6, respectively.

3.6.1. Subgroup analysis: cancer type

Only two cancer types were included, breast and germ cell cancers. There was a trend for a trivial decrease in anti-inflammatory markers for the breast cancer group (SMD: −0.196, 95% CI −0.428–0.038, $p = 0.100$). Only one study for germ cell cancer was available.

3.6.2. Subgroup analysis: exercise mode

There was no change in anti-inflammatory markers with the AE + RT ($p = 0.222$) and RT ($p = 0.275$) groups. Only one study for Tai Chi/Yoga exercise was available.

3.6.3. Subgroup analysis: marker

Only two anti-inflammatory markers were included, with no effects observed in IL–1ra ($p = 0.151$) and IL-10 ($p = 0.257$).

3.6.4. Anti-inflammatory cytokines summary

Overall, exercise was associated with a trend towards decreasing anti-inflammatory levels, but the effect was small. The findings were not influenced by exercise mode or by marker, and there was insufficient data to explore cancer type.

3.7. Immune cells

The results are shown in Table 5. There was a trivial effect on the immune markers (SMD: 0.183, 95% CI: –0.212–0.529, $p = 0.364$); however, there was also moderate heterogeneity ($I^2 = 55\%$, $p = 0.004$). One trial (Nieman et al., 1995) influenced the outcomes and its removal increased the SMD to a small ES (SMD: 0.303, 95% CI: −0.021–0.628, $p = 0.067$) that approached significance. The influence of each individual study is presented for cancer type, exercise mode, and marker in supplementary Figs. 7–9, respectively.

3.7.1. Subgroup analysis: cancer type

There was a small decrease (SMD: −0.256, 95% CI −1.049–0.537, $p = 0.527$) for the breast cancer group; however, the effect size became trivial with the removal of Neiman et al., (1995) (SMD: 0.081, 95% CI −0.548–0.711, $p = 0.800$). There was a moderate increase for the lung cancer group (SMD: 0.560, 95% CI 0.015–1.104, $p = 0.044$) but no effect in the mixed-cancer group ($p = 0.730$). Only one trial was available for the stomach cancer group.

Table 4
Change in Anti-inflammatory Cytokines with Training.

	Intervention N	Control N	Weight %	SMD	95% CI	P value	I^2	Heterogeneity P value
Overall	153	154	100	−0.207	−0.432, 0.018	0.072	0%	0.807
Cancer Type								
Breast	144	144	93.9	−0.195	−0.428, 0.038	0.100	0%	0.732
Germ Cell	9	10	6.1	−0.389	−1.298, 0.52	N/A	N/A	N/A
Exercise type								
Tai Chi/Yoga	14	15	9.5	−0.295	−1.027, 0.437	N/A	N/A	N/A
RT	53	55	35.4	−0.211	−0.589, 0.168	0.275	0%	0.672
AE + RT	86	84	55.1	−0.189	−0.493, 0.114	0.222	0%	0.476
Marker								
IL-1ra	66	68	43.8	−0.249	−0.590, 0.091	0.151	0%	0.73
IL-10	87	86	56.2	−0.174	−0.474, 0.127	0.257	0%	0.554

Abbreviations: RT = resistance training; AE + RT = combined training; IL = interleukin.

3.7.2. Subgroup analysis: exercise type

There were moderate increases for the Tai Chi/yoga (SMD: 0.560, 95% CI 0.015–1.104, $p = 0.044$) and AE groups (SMD: 0.448, 95% CI −0.007–0.903, $p = 0.054$), with the latter showing a trend for statistical significance. There was no effect in the RT group ($p = 0.329$), and only one AE + RT trial was available.

3.7.3. Subgroup analysis: marker

There was no effect on natural killer cell activity (NKCA) ($p = 0.840$) following training. With the removal of Nieman et al., (1995), there was a large increase in NKCA (SMD: 0.817, 95% CI 0.377–1.256, $p < 0.001$). There were no effects of training on NK cell ($p = 0.435$) and natural killer T (NKT) cell Proportions ($p = 0.876$).

3.7.4. Immune cells summary

Overall, exercise training had a trivial effect on immune function markers; however, the findings were moderately heterogeneous. Training induced moderate increases in immune function for lung cancer and AE and Tai Chi/Yoga intervention and immune markers were restricted to NK and NKT populations only.

4. Discussion

The main finding of this meta-analysis is that exercise training decreases circulating pro-inflammatory markers, notably CRP and TNF. Prostate and breast cancer survivors experienced the greatest training-induced reductions in pro-inflammatory markers compared to the other cancer types analyzed. Combined aerobic and resistance exercise was the most widely studied training modality and was associated with the largest reductions in pro-inflammatory marker levels. Exercise training did not statistically change circulating anti-inflammatory cytokines or immune cell markers, although overall trends were present for both groups of markers. However, it should be considered that the available data for anti-inflammatory cytokines and immune cell markers were limited, highlighting the need for additional research in these areas. Collectively, based on the results of this study, regular participation in a combination of RT and AT training in prostate and breast cancer survivors appears to be associated with a decrease in low-grade inflammation with the implications for anti-inflammatory and immune function still being unclear.

4.1. Limitations and strengths

There were several limitations in the existing literature that affected the conclusions and implications of this study. First, for some outcomes, there was a low number of studies and high heterogeneity, which made interpretation and generalization of the results challenging. Moreover, 12 out of 27 studies had low quality (scoring ≤5 out of 8 in the modified PEDro scale). Second, unsupervised exercise was used in 8 out of 27 trials, which may have led to imprecise reporting of exercise characteristics. Third, all inflammatory markers were obtained from circulating blood samples, such that the source of each cannot be determined, as immune cells (Dranoff, 2004), endothelial cells (Mai et al., 2013), fibroblasts (Pang et al., 1994), and skeletal muscle (Pedersen and Febbraio, 2012) all secrete cytokines. Fourth, CRP, IL-6, and IL-10 have both pro- and anti-inflammatory roles (Del Giudice and

Table 5
Changes in Immune Cells with Training.

	Intervention N	Control N	Weight %	SMD	95% CI	P value	I^2	Heterogeneity P value
Overall	155	154	100	0.183	−0.212, 0.579	0.364	65%	0.004
Cancer Type								
Breast	68	64	42.2	−0.256	−1.049, 0.537	0.527	78%	0.004
Mixed	42	46	25.4	0.074	−0.345, 0.492	0.730	0%	0.995
Lung	28	26	21.3	0.560	0.015, 1.104	***0.044***	0%	0.742
Stomach	17	18	11.3	1.091	0.381, 1.802	N/A	N/A	N/A
Exercise Mode								
AE	83	92	49.8	0.448	−0.007, 0.903	0.054	55%	0.082
RT	38	30	23.3	−0.239	−0.720, 0.242	0.329	0%	0.591
Tai Chi/Yoga	28	26	21.3	0.560	0.015, 1.104	***0.044***	0%	0.742
AE + RT	6	6	5.8	−1.831	−3.180, −0.484	N/A	N/A	N/A
Marker								
NKCA	47	52	30	0.128	−1.115, 1.372	0.840	86%	0.001
NK%	54	51	35	0.163	−0.246, 0.573	0.435	10%	0.327
NKT%	54	51	35	0.036	−0.409, 0.480	0.876	24%	0.270

Abbreviations: AE = aerobic training; RT = resistance training; AE + RT = combined training; NKCA = Natural killer cell activity; NK% = natural killer cell proportion; NKT% = natural killer T cell proportions.

Gangestad, 2018; Dennis et al., 2013; Hanriot et al., 2008; Scheller et al., 2011), which complicates the interpretation of these findings. Finally, other factors also may have influenced the results, including age, sex, exercise intensity and duration, and intervention length that were beyond the scope of this analysis, although these details are reported in Tables 1 and 2.

This study also had several strengths. First, to our knowledge, this is the first meta-analysis examining the exercise training effects on several aspects of the immune system in all cancer types. Second, this comprehensive study allows us to create a "big picture" on possible training effects within the inflammation-immune axis in cancer patients. Previous studies have been limited to systematic reviews (Kruijsen-Jaarsma et al., 2013; Lof et al., 2012) or meta-analyses on certain pro-inflammatory markers only in breast cancer survivors (Meneses-Echavez et al., 2016). Last, an a priori subgroup analysis allowed examination of the available data based on different cancer types, exercise modalities, and specific biomarkers as sources of heterogeneity within the analysis.

4.2. Pro-inflammatory cytokines

The link between cancer and inflammation was first suggested by Rudolf Virchow in 1863 (Balkwill and Mantovani, 2001). Inflammation has a crucial role in cancer development and progression (Balkwill and Mantovani, 2001; Mantovani et al., 2008). Conversely, exercise training is assumed to improve the inflammatory profile in cancer survivors (Koelwyn et al., 2015; McTiernan, 2008), albeit with limited evidence to support that hypothesis. In this meta-analysis, exercise training was associated with a small decrease in circulating pro-inflammatory markers in cancer survivors. Among the specific cytokines analyzed, IL-6 was the most-studied cytokine. Despite a prominent role within several metabolic pathways during physical exertion (Pedersen et al., 2004; Steensberg, 2003), IL-6 did not change with exercise training and was consistent with previous reports in cancer populations (Kruijsen-Jaarsma et al., 2013; Lof et al., 2012). Exercise training was also associated with moderate decreases in CRP levels, which is consistent with previous work in cancer survivors (Ballard-Barbash et al., 2012; Betof et al., 2013; Winters-Stone et al., 2018). This finding may be important clinically, as elevated CRP levels are associated with poor prognosis and early death in cancer survivors (Allin et al., 2009; Li et al., 2017; Nikiteas et al., 2005). TNF is another key mediator of inflammation in cancer, regulating a cascade of inflammatory responses via activating a various range of cytokines, chemokines, adhesions, and angiogenic factors (Balkwill and Mantovani, 2001; Coussens and Werb, 2002). The current study also indicated small decreases in TNF with exercise training, which is consistent with a previous meta-analysis in breast cancer (Meneses-Echavez et al., 2016). Collectively, the current study reports small-moderate reductions in CRP and TNF levels following exercise training. Presently, there is a lack of data to determine the clinical importance of these changes.

Exercise training appears to reduce inflammation in prostate and breast cancers, although the number of trials for prostate cancer was limited (n = 4). Other included cancer types with no changes in inflammation were germ cell, colorectal, and mixed cancers. Physiological and treatment differences in cancer types exist and may influence the exercise response; however, a more likely explanation is the greater statistical power of breast and prostate cancer studies owing to their higher relative frequency within exercise oncology (Jones and Alfano, 2013). While prostate and breast cancer survivors appear to have greater inflammation reduction with exercise training, more studies are needed to be conducted in other cancer sites to determine if these benefits extend to other populations.

Combined aerobic and resistance training was the only exercise mode that reduced pro-inflammatory levels; however, this exercise mode was also the most studied intervention. Interestingly, the effect sizes for AE and RT were both small (-0.15 and −0.11, respectively), whereas AE + RT had a small to moderate effect size (-0.35). Although the number of studies using RT or AE was not equal to AE + RT, it is possible that the larger effect size observed for AE + RT intervention may be attributed to larger cumulative exercise dose relative to RT or AE only interventions. Currently, AE + RT is recommended for cancer survivors by several exercise and cancer organizations (Hayes et al., 2019; Rock et al., 2012; Schmitz et al., 2010), and the results of this meta-analysis and others (Meneses-Echavez et al., 2016) lend support to those guidelines.

4.3. Anti-inflammatory cytokines

The current study revealed a small, marginally significant ($p = 0.072$) decrease in anti-inflammatory cytokines. At first glance, this may seem detrimental, as higher physical activity levels are linked to elevated IL-10 in healthy men (Jankord and Jemiolo, 2004), and training tended to increase IL-10 in individuals with impaired glucose handling (Oberbach et al., 2006). However, anti-inflammatory cytokines are modulatory molecules that have a dynamic interaction with pro-inflammatory cytokines (Opal and DePalo, 2000), such that decreased pro-inflammatory cytokines may potentially lower anti-inflammatory levels by reducing the stimulus for release. A functional and available receptor (Turner et al., 2014), along with the receptor density which is influenced by exercise training (Flynn and McFarlin, 2006; Shephard et al., 1994), are also important considerations regarding circulating cytokine levels. Examination of the ratio of pro- and anti-inflammatory markers may partially address these issues but both marker-types need to originate from the same study for valid comparisons.

The anti-inflammatory analysis in the current study was limited to only IL-10 and IL-1ra, as these markers appeared frequently enough in the literature to allow for an analysis to be performed. IL-1ra has a therapeutic role in cancer by blocking pro-inflammatory IL-1 functions and inhibiting tumor angiogenesis (Mantovani et al., 2008; Voronov et al., 2003). IL-10 is generally considered anti-inflammatory but has a paradoxical role within tumor function (Ahmad et al., 2018; Dennis et al., 2013; Galizia et al., 2002; Mannino et al., 2015; Stoner et al., 2013). The subgroup analyses showed no changes in either marker, nor were there any effects of cancer type and exercise mode. Although consistent with previous works in breast cancer (Meneses-Echavez et al., 2016; van Vulpen et al., 2018), limited data of low quality (4 out of 6 scored ≤5 in the PEDro scale) limited the strength of the evidence. The anti-inflammatory effects of exercise training in cancer survivors appear to primarily arise from decreases in pro-inflammatory markers only, as seen in aging and other chronic diseases (Flynn et al., 2007; Petersen and Pedersen, 2005).

4.4. Immune cell markers

Immune cells play a critical role in the recognition and elimination of tumor cells (Bui and Schreiber, 2007; Finn, 2008). Various immune cells are involved, but NK cells as part of innate immunity are considered the first line of defense against malignant cells (Bui and Schreiber, 2007; Waldhauer and Steinle, 2008). NKT cells, a small population within T cells that are similar to NK cells, also participate in the defense against cancer and act as a bridge between innate and adaptive immunity (Nair and Dhodapkar, 2017; Terabe and Berzofsky, 2008). NK cells play an important role in the training-related reduction in tumor growth and incidence in animal models (Pedersen et al., 2016). In the current study, exercise training was not associated with significant changes in immune cell proportion or function. However, this finding needs to be interpreted cautiously because the number of studies and cell populations analyzed were limited, and overall study quality was poor (50% were ≤5 in the PEDro scale). Additionally, circulating cell proportions do not necessarily reflect the levels at the tissues or the tumor (Campbell and Turner, 2018; Dhabhar et al., 2012;

Kruijsen-Jaarsma et al., 2013; Pedersen and Hoffman-Goetz, 2000). Leukocyte redeployment from circulation into the tissues following stress is well established and varies based on the type of stress (short vs. long term) and time since the stimuli (Campbell and Turner, 2018; Dhabhar, 2014). Obesity and diabetes, which are relatively common in cancer survivors, also reduce circulating T cell numbers with higher accumulation within adipose tissue (Carolan et al., 2015; Magalhaes et al., 2015) while acute (Krüger et al., 2008) and chronic exercise (Pedersen et al., 2016) also increase immune cell accumulation within tissues in animal models. As immune cell pools are highly responsive to stress stimuli (Dhabhar, 2014), blood-derived samples from cancer survivors must consider these factors when interpreting these results.

Subgroup analyses on specific immune markers found that exercise training was not associated with a change in NKCA or NK and NKT cell proportions. However, the removal of one study (Nieman et al., 1995) led to a large, significant increase in NKCA. NKCA was also reported to increase in another non-randomized study in a cancer population (Peters et al., 1994), providing indirect support for this finding. Moreover, improved NKCA along with unchanged NK cell numbers were reported in healthy individuals (Nieman et al., 1990). When assessing NK function, cytotoxic capacity is assessed by different methods, with chromium release assays considered the gold standard (Whiteside and Herberman, 1994). However, a lack of standardized effector to target cell (E:T) ratios used in these assays limits the ability to pool data and may lead to fundamental interpretation errors. Reporting the lytic units reduces the arbitrary selection error of different E:T ratio (Bryant et al., 1992) but was only performed in a single trial (Fairey et al., 2005a). To obtain sufficient data for our analysis, the highest reported E:T ratio for NKCA from each study was used. For future studies, we recommend reporting the lytic activity in future studies so results may be pooled and more easily analyzed together. Collectively, this meta-analysis suggests exercise training has the potential to improve NKCA in cancer survivors. Enhanced immune cell function may represent a key clinical outcome in cancer survivors by partially offsetting treatment-induced leukopenia while possibly contributing to a reduced frequency of general illness but needs corroboration. Future work should also include exploring other immune populations along with functional outcomes (e.g., proliferation, phagocytosis, tumor infiltration capacity) to develop a greater understanding of the influence exercise training has on this system.

Subgroup analyses based on cancer type revealed that exercise training has moderate effects on lung cancer but was based on a single study with no other cancer types showing similar findings. AE and Tai Chi/Yoga were also associated with a moderate effect on immune system biomarkers. The lack of data does not permit firm conclusions at this stage in either subgroup analyses.

4.5. Implications

In the American College of Sports Medicine (ACSM) exercise guidelines for cancer survivors released in 2010 (Schmitz et al., 2010), the immune system and inflammation were not discussed as a category A, B or C evidence-based outcomes, due to a lack of data. The updated Exercise and Sports Science (ESSA) position stand provides comprehensive exercise prescriptions for a wide range of symptom management but also fails to address inflammation or immune function (Hayes et al., 2019). Literature in this area, inflammatory markers, in particular, has grown rapidly in recent years as the majority of the analyzed studies (21 out of 26) in the current meta-analysis were published after 2010. Future exercise oncology guidelines should consider reduced inflammation as an evidence-based outcome of exercise training, based on our and other recent analyses (Kruijsen-Jaarsma et al., 2013; Meneses-Echavez et al., 2016). A summary of the implications is provided in Table 6.

Combination training (AE + RT) is a beneficial mode of exercise for cancer survivors to reduce the pro-inflammatory cytokine levels, particularly in prostate and breast cancers. Performing 150 min of exercise per week, including two days of resistance exercise, is recommended for cancer survivors (Demark-Wahnefried et al., 2015; Schmitz et al., 2010). Our results lend support to this recommendation. Cancer survivors should be encouraged to engage in a regular combination training to improve their inflammatory profile, as chronic low-level inflammation may influence the development of secondary cancers (Donin et al., 2016) and cardiovascular disease (Okwuosa et al., 2017) while contributing to the overall health of cancer survivors.

Table 6
Summary of Key Findings.

Previous Gaps in the Literature
- Conflicting results on the effects of exercise training on pro-inflammatory markers.
- Limited data for immune and anti-inflammatory markers, the magnitude of effects not previously defined.
- Influence of cancer type, exercise mode, and specific biomarkers are unknown.

What Have We Learned from this Study?
- Pro-inflammatory markers appear to decrease with exercise training.
- Largest changes occur with AE + RT in prostate and breast cancer for CRP and TNF.
- No clear effect of training on immune cell populations or anti-inflammatory cytokines, but limited data permits only tentative conclusions.

How to Use this New Information?
- Inflammation merits consideration as an evidence-based outcome in exercise oncology guidelines.
- Analysis supports current guidelines recommending combined exercise training in oncology populations.
- Enhanced NKCA in conjunction with lower pro-inflammatory cytokines create a better anti-tumor environment.

What Needs to Happen Next?
- Focus on specific immune populations with functional outcomes, and standardized reporting of data.
- Comparing changes in the ratios of pro- and anti-inflammatory markers.
- Determine if changes are clinically relevant or are associated with improvements in symptoms.

Abbreviations: AE + RT = combined training; CRP = C-reactive protein; TNF = tumor necrosis factor; NKCA = Natural killer cell activity.

While this meta-analysis found that pro-inflammatory markers decreased, it is not clear if this change is clinically significant or leads to improvements in symptoms (Kazdin, 1999). There are several inflammation-related symptoms reported in cancer survivors such as fatigue, depression, and cognition impairment (Bower, 2014; Seruga et al., 2008) which could be used as an evaluation tool for clinical significance of inflammatory changes with exercise training. Despite the decrease in pro-inflammatory cytokines following exercise, there was no improvement in anti-inflammatory markers which needs to be considered within the context of the pro-inflammatory response as the balance between these markers that dictates overall inflammation.

Considering the dynamic balance between pro- and anti-inflammatory cytokines (Coussens and Werb, 2002; Opal and DePalo, 2000), further studies are needed 1) to examine this relationship as small changes in both markers may alter the inflammatory profile and 2) in light of the fact that only two markers (IL-10 and IL-1ra) were available for the current analysis. Similarly, insufficient immune cell data left us unable to reach firm conclusions. A reasonable number of immune-related studies exist, examining lymphocytes (Na et al., 2000; Nieman et al., 1995), T cells (Glass et al., 2015; Nieman et al., 1995; Wang and Joyce, 2010), B cells (Glass et al., 2015), dendritic cells (Liu et al., 2015), monocytes (Glass et al., 2015), neutrophils (Nieman et al., 1995), and complete blood cells counts (Karvinen et al., 2014) following exercise training. However, data were inconsistently reported, and the criterion of ≥ 3 studies necessary for inclusion in the analyses was not met for most markers. Moving forward, we recommend including 1) complete blood counts with differential, 2) reporting both cell counts and proportions for all populations of interest, 3) clearly indicating the time since the last exercise session, and 4) presenting functional assays on a per cell basis (i.e. lytic units). The adoption of

these standard procedures when evaluating immune outcomes will allow for more thorough analyses in future meta-analyses while also address limitations within the current literature.

5. Conclusion

Previous reports present conflicting evidence on the effects of exercise training on pro- and anti-inflammatory markers in cancer survivors, and no meta-analyses have examined specific immune outcomes. In the current meta-analysis, exercise training is associated with small decreases in pro-inflammatory markers. Specifically, TNF and CRP were lower after training, which may have clinical relevance as both are considered as prognostic biomarkers in cancer (Ma et al., 2017; Michalaki et al., 2004; Shrotriya et al., 2018). Prostate and breast cancer survivors are most likely to experience these benefits when using combined aerobic and resistance training, which is consistent with current exercise oncology guidelines (Hayes et al., 2019; Rock et al., 2012; Schmitz et al., 2010). Exercise training produced only a trend for decreased anti-inflammatory cytokines. However, when considered with the decrease in pro-inflammatory levels, a potential change in these cytokine ratios may produce a more optimal anti-tumor environment. The possible increase in NKCA also contributes to an anti-tumor environment but the low quantity and quality of data diminish the impact of this conclusion. Additional high-quality studies are necessary to examine if exercise training alters anti-inflammatory cytokines and innate and adaptive immune cell proportion and function during and after cancer treatment. Further research is also warranted to determine if changes in these biomarkers are clinically significant and translate to improvements in symptoms and ultimately survivorship.

Acknowledgments

The authors wish to thank Mohamdod Alzer for his critical review of this work and to acknowledge key feedback provided by the reviewers which helped to improve the overall quality of the final manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2019.08.187.

References

Aggarwal, B.B., Gehlot, P., 2009. Inflammation and cancer: how friendly is the relationship for cancer patients? Curr. Opin. Pharmacol. 9, 351–369.
Ahmad, N., Ammar, A., Storr, S.J., Green, A.R., Rakha, E., Ellis, I.O., Martin, S.G., 2018. IL-6 and IL-10 are associated with good prognosis in early stage invasive breast cancer patients. Cancer Immunol. Immunother. 67, 537–549.
Allin, K.H., Bojesen, S.E., Nordestgaard, B.G., 2009. Baseline C-reactive protein is associated with incident cancer and survival in patients with cancer. J. Clin. Oncol. 27, 2217–2224.
Balkwill, F., Mantovani, A., 2001. Inflammation and cancer: back to Virchow? Lancet 357, 539–545.
Ballard-Barbash, R., Friedenreich, C.M., Courneya, K.S., Siddiqi, S.M., McTiernan, A., Alfano, C.M., 2012. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. J. Natl Cancer Inst. 104, 815–840.
Betof, A.S., Dewhirst, M.W., Jones, L.W., 2013. Effects and potential mechanisms of exercise training on cancer progression: a translational perspective. Brain Behav. Immun. 30, S75–S87.
Borenstein, M., Hedges, L.V., Higgins, J.P., Rothstein, H.R., 2010. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res. Synth. Methods 1, 97–111.
Bower, J.E., 2007. Cancer-related fatigue: links with inflammation in cancer patients and survivors. Brain Behav. Immun. 21, 863–871.
Bower, J.E., 2014. Cancer-related fatigue—mechanisms, risk factors, and treatments. Nat. Rev. Clin. Oncol. 11, 597.
Bower, J.E., Greendale, G., Crosswell, A.D., Garet, D., Sternlieb, B., Ganz, P.A., Irwin, M.R., Olmstead, R., Arevalo, J., Cole, S.W., 2014. Yoga reduces inflammatory signaling in fatigued breast cancer survivors: a randomized controlled trial. Psychoneuroendocrinology 43, 20–29.
Bramer, W.M., Rethlefsen, M.L., Kleijnen, J., Franco, O.H., 2017. Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. System. Rev. 6 245-245.
Bryant, J., Day, R., Whiteside, T.L., Herberman, R.B., 1992. Calculation of lytic units for the expression of cell-mediated cytotoxicity. J. Immunol. Methods 146, 91–103.
Bui, J.D., Schreiber, R.D., 2007. Cancer immunosurveillance, immunoediting and inflammation: independent or interdependent processes? Curr. Opin. Immunol. 19, 203–208.
Campbell, J.P., Turner, J.E., 2018. Debunking the myth of exercise-induced immune suppression: redefining the impact of exercise on immunological health across the lifespan. Front. Immunol. 9, 648.
Carolan, E., Tobin, L.M., Mangan, B.A., Corrigan, M., Gaoatswe, G., Byrne, G., Geoghegan, J., Cody, D., O'Connell, J., Winter, D.C., 2015. Altered distribution and increased IL-17 production by mucosal-associated invariant T cells in adult and childhood obesity. J. Immunol. 194, 5775–5780.
Cavaillon, J.M., 2001. Pro- versus anti-inflammatory cytokines: myth or reality. Cell Mol. Biol. (Noisy-le-grand) 47, 695–702.
Chang, S., Long, S.R., Kutikova, L., Bowman, L., Finley, D., Crown, W.H., Bennett, C.L., 2004. Estimating the cost of cancer: results on the basis of claims data analyses for cancer patients diagnosed with seven types of cancer during 1999 to 2000. J. Clin. Oncol. 22, 3524–3530.
Christensen, J.F., Tolver, A., Andersen, J.L., Rorth, M., Daugaard, G., Hojman, P., 2014. Resistance training does not protect against increases in plasma cytokine levels among germ cell cancer patients during and after chemotherapy. J. Clin. Endocrinol. Metabol. 99, 2967–2976.
Cohen, J., 1992. A power primer. Psychol. Bull. 112, 155–159.
Collado-Hidalgo, A., Bower, J.E., Ganz, P.A., Cole, S.W., Irwin, M.R., 2006. Inflammatory biomarkers for persistent fatigue in breast cancer survivors. Clin. Cancer Res. 12, 2759–2766.
Copelan, E.A., 2006. Hematopoietic stem-cell transplantation. N. Engl. J. Med. 354, 1813–1826.
Courneya, K.S., Segal, R.J., McKenzie, D.C., Dong, H., Gelmon, K., Friedenreich, C.M., Yasui, Y., Reid, R.D., Crawford, J.J., Mackey, J.R., 2014. Effects of exercise during adjuvant chemotherapy on breast cancer outcomes. Med. Sci. Sports Exerc. 46, 1744–1751.
Coussens, L.M., Werb, Z., 2002. Inflammation and cancer. Nature 420, 860.
Crusz, S.M., Balkwill, F.R., 2015. Inflammation and cancer: advances and new agents. Nat. Rev. Clin. Oncol. 12, 584.
Dehqanzada, Z.A., Storrer, C.E., Hueman, M.T., Foley, R.J., Harris, K.A., Jama, Y.H., Shriver, C.D., Ponniah, S., Peoples, G.E., 2007. Assessing serum cytokine profiles in breast cancer patients receiving a HER2/neu vaccine using Luminex® technology. Oncol. Rep. 17, 687–694.
Del Giudice, M., Gangestad, S.W., 2018. Rethinking IL-6 and CRP: Why they are more than inflammatory biomarkers, and why it matters. Brain Behav. Immun. 70, 61–75.
Demark-Wahnefried, W., Rogers, L.Q., Alfano, C.M., Thomson, C.A., Courneya, K.S., Meyerhardt, J.A., Stout, N.L., Kvale, E., Ganzer, H., Ligibel, J.A., 2015. Practical clinical interventions for diet, physical activity, and weight control in cancer survivors. CA Cancer J. Clin. 65, 167–189.
Dennis, K.L., Blatner, N.R., Gounari, F., Khazaie, K., 2013. Current status of IL-10 and regulatory T-cells in cancer. Curr. Opin. Oncol. 25, 637–645.
Dethlefsen, C., Lillelund, C., Midtgaard, J., Andersen, C., Pedersen, B.K., Christensen, J.F., Hojman, P., 2016. Exercise regulates breast cancer cell viability: systemic training adaptations versus acute exercise responses. Breast Cancer Res Treat. 159, 469–479.
Dhabhar, F.S., 2014. Effects of stress on immune function: the good, the bad, and the beautiful. Immunol. Res. 58, 193–210.
Dhabhar, F.S., Malarkey, W.B., Neri, E., McEwen, B.S., 2012. Stress-induced redistribution of immune cells–from barracks to boulevards to battlefields: a tale of three hormones–Curt Richter Award winner. Psychoneuroendocrinology 37, 1345–1368.
Dieli-Conwright, C.M., Parmentier, J.-H., Sami, N., Lee, K., Spicer, D., Mack, W.J., Sattler, F., Mittelman, S.D., 2018. Adipose tissue inflammation in breast cancer survivors: effects of a 16-week combined aerobic and resistance exercise training intervention. Breast Cancer Res. Treat. 168, 147–157.
Donin, N., Filson, C., Drakaki, A., Tan, H.J., Castillo, A., Kwan, L., Litwin, M., Chamie, K., 2016. Risk of second primary malignancies among cancer survivors in the United States, 1992 through 2008. Cancer 122, 3075–3086.
Dranoff, G., 2004. Cytokines in cancer pathogenesis and cancer therapy. Nat. Rev. Cancer 4, 11.
Ergun, M., Eyigor, S., Karaca, B., Kisim, A., Uslu, R., 2013. Effects of exercise on angiogenesis and apoptosis-related molecules, quality of life, fatigue and depression in breast cancer patients. Euro. J. Cancer Care 22, 626–637.
Fairey, A.S., Courneya, K.S., Field, C.J., Bell, G.J., Jones, L.W., Mackey, J.R., 2005a. Randomized controlled trial of exercise and blood immune function in postmenopausal breast cancer survivors. J. Appl. Physiol. (Bethesda, Md. 1985) 98, 1534–1540.
Fairey, A.S., Courneya, K.S., Field, C.J., Bell, G.J., Jones, L.W., Martin, B.S., Mackey, J.R., 2005b. Effect of exercise training on C-reactive protein in postmenopausal breast cancer survivors: a randomized controlled trial. Brain Behav. Immun. 19, 381–388.

Fairey, A.S., Courneya, K.S., Field, C.J., Mackey, J.R., 2002. Physical exercise and immune system function in cancer survivors: a comprehensive review and future directions. Cancer 94, 539–551.
Finn, O.J., 2008. Cancer immunology. N. Engl. J. Med. 358, 2704–2715.
Flynn, M.G., McFarlin, B.K., 2006. Toll-like receptor 4: link to the anti-inflammatory effects of exercise? Exerc. Sport Sci. Rev. 34, 176–181.
Flynn, M.G., McFarlin, B.K., Markofski, M.M., 2007. The anti-inflammatory actions of exercise training. Am. J. Lifestyle Med. 1, 220–235.
Fridman, W.H., Pages, F., Sautes-Fridman, C., Galon, J., 2012. The immune contexture in human tumours: impact on clinical outcome. Nat. Rev. Cancer 12, 298–306.
Galizia, G., Orditura, M., Romano, C., Lieto, E., Castellano, P., Pelosio, L., Imperatore, V., Catalano, G., Pignatelli, C., De Vita, F., 2002. Prognostic significance of circulating IL-10 and IL-6 serum levels in colon cancer patients undergoing surgery. Clin. Immun. 102, 169–178.
Galvao, D.A., Newton, R.U., 2005. Review of exercise intervention studies in cancer patients. J. Clin. Oncol. 23, 899–909.
Galvao, D.A., Taaffe, D.R., Spry, N., Joseph, D., Newton, R.U., 2010. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. J. Clin. Oncol. 28, 340–347.
Geinitz, H., Zimmermann, F.B., Stoll, P., Thamm, R., Kaffenberger, W., Ansorg, K., Keller, M., Busch, R., van Beuningen, D., Molls, M., 2001. Fatigue, serum cytokine levels, and blood cell counts during radiotherapy of patients with breast cancer. International Journal of Radiation Oncology* Biology*. Physics 51, 691–698.
Glass, O.K., Inman, B.A., Broadwater, G., Courneya, K.S., Mackey, J.R., Goruk, S., Nelson, E.R., Jasper, J., Field, C.J., Bain, J.R., Muehlbauer, M., Stevens, R.D., Hirschey, M.D., Jones, L.W., 2015. Effect of aerobic training on the host systemic milieu in patients with solid tumours: an exploratory correlative study. Br. J. Cancer 112, 825–831.
Gomez, A.M., Martinez, C., Fiuza-Luces, C., Herrero, F., Perez, M., Madero, L., Ruiz, J.R., Lucia, A., Ramirez, M., 2011. Exercise training and cytokines in breast cancer survivors. Int. J. Sports Med. 32, 461–467.
Hagstrom, A.D., Marshall, P.W., Lonsdale, C., Papalia, S., Cheema, B.S., Toben, C., Baune, B.T., Fiatarone Singh, M.A., Green, S., 2016. The effect of resistance training on markers of immune function and inflammation in previously sedentary women recovering from breast cancer: a randomized controlled trial. Breast Cancer Res. Treat. 155, 471–482.
Hanriot, D., Bello, G., Ropars, A., Seguin-Devaux, C., Poitevin, G., Grosjean, S., Latger-Cannard, V., Devaux, Y., Zannad, F., Regnault, V., Lacolley, P., Mertes, P.-M., Hess, K., Longrois, D., 2008. C-reactive protein induces pro- and anti-inflammatory effects, including activation of the liver X receptor alpha, on human monocytes. Thromb. Haemost. 99, 558–569.
Hanson, E.D., Wagoner, C.W., Anderson, T., Battaglini, C.L., 2016. The independent effects of strength training in cancer survivors: a systematic review. Curr Oncol Rep 18, 31.
Hayes, S.C., Newton, R.U., Spence, R.R., Galvão, D.A., 2019. The Exercise and Sports Science Australia position statement: Exercise medicine in cancer management. J. Sci. Med. Sport in press.
Higgins, J., Green, S., 2008. Cochrane Handbook for Systematic Reviews of Intereventions. John Wiley & Sons, Hoboken, NJ.
Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ 327, 557–560.
Hojan, K., Borowczyk, E.K., Leporowska, E., Milecki, P., 2017. Inflammation, cardiometabolic markers, and functional changes in men with prostate cancer. A randomized controlled trial of a 12month exercise program. Pol Arch Intern Med 127, 25–35.
Hojan, K., Milecki, P., Kwiatkowska-Borowczyk, E., Leporowska, E., 2015. Physical exercises, inflammation, fatigue and aerobic fitness in prostate cancer patients undergoing antiandrogen-and radiotherapy. Arch. Phys. Med. Rehabil. 10, e5.
Hvid, T., Lindegaard, B., Winding, K., Iversen, P., Brasso, K., Solomon, T.P., Pedersen, B.K., Hojman, P., 2016. Effect of a 2-year home-based endurance training intervention on physiological function and PSA doubling time in prostate cancer patients. Cancer Causes Control : CCC 27, 165–174.
Janelsins, M.C., Davis, P.G., Wideman, L., Katula, J.A., Sprod, L.K., Peppone, L.J., Palesh, O.G., Heckler, C.E., Williams, J.P., Morrow, G.R., Mustian, K.M., 2011. Effects of Tai Chi Chuan on insulin and cytokine levels in a randomized controlled pilot study on breast cancer survivors. Clin. Breast Cancer 11, 161–170.
Jankord, R., Jemiolo, B., 2004. Influence of physical activity on serum IL-6 and IL-10 levels in healthy older men. Med. Sci. Sports Exerc. 36, 960–964.
Jones, L.W., Alfano, C.M., 2013. Exercise-oncology research: past, present, and future. Acta Oncol. 52, 195–215.
Jones, S.B., Thomas, G.A., Hesselsweet, S.D., Alvarez-Reeves, M., Yu, H., Irwin, M.L., 2013. Effect of exercise on markers of inflammation in breast cancer survivors: the Yale exercise and survivorship study. Cancer Prev. Res. (Philadelphia, Pa.) 6, 109–118.
Karvinen, K.H., Esposito, D., Raedeke, T.D., Vick, J., Walker, P.R., 2014. Effect of an exercise training intervention with resistance bands on blood cell counts during chemotherapy for lung cancer: a pilot randomized controlled trial. SpringerPlus 3, 15.
Kazdin, A.E., 1999. The meanings and measurement of clinical significance. J. Consult. Clin. Psychol. 67, 332–339.
Koelwyn, G.J., Wennerberg, E., Demaria, S., Jones, L.W., 2015. Exercise in regulation of inflammation-immune axis function in cancer initiation and progression. Oncology (Williston Park, N.Y.) 29, 908–920, 922.
Krüger, K., Lechtermann, A., Fobker, M., Völker, K., Mooren, F., 2008. Exercise-induced redistribution of T lymphocytes is regulated by adrenergic mechanisms. Brain Behav. Immun. 22, 324–338.
Kruijsen-Jaarsma, M., Révész, D., Bierings, M.B., Buffart, L.M., Takken, T., 2013. Effects of exercise on immune function in patients with cancer: a systematic review. Exercise immunology review 19.
Lee, M.K., Kim, J.-Y., Kim, D.-I., Kang, D.-W., Park, J.-H., Ahn, K.-Y., Yang, H.I., Lee, D.H., Roh, Y.H., Lee, J.-W., 2017. Effect of home-based exercise intervention on fasting insulin and Adipocytokines in colorectal cancer survivors: a randomized controlled trial. Metabolism 76, 23–31.
Lerner, H., Band, P., Israel, L., Leung, B., 1976. Phase II study of tamoxifen: report of 74 patients with stage IV breast cancer. Cancer Treat. Rep. 60, 1431–1435.
Li, C., Xu, Q., Chen, L., Luo, C., Ying, J., Liu, J., 2017. C-reactive protein (CRP) as a prognostic factor for colorectal cancer after surgical resection of pulmonary metastases. Bull. Cancer 104, 232–236.
Liu, J., Chen, P., Wang, R., Yuan, Y., Wang, X., Li, C., 2015. Effect of Tai Chi on mononuclear cell functions in patients with non-small cell lung cancer. BMC Complementary Altern. Med. 15, 3.
Lof, M., Bergstrom, K., Weiderpass, E., 2012. Physical activity and biomarkers in breast cancer survivors: a systematic review. Maturitas 73, 134–142.
Ma, Y., Ren, Y., Dai, Z.-J., Wu, C.-J., Ji, Y.-H., Xu, J., 2017. IL-6, IL-8 and TNF-α levels correlate with disease stage in breast cancer patients. Adv Clin Exp Med 26, 421–426.
Magalhaes, I., Pingris, K., Poitou, C., Bessoles, S., Venteclef, N., Kiaf, B., Beaudoin, L., Da Silva, J., Allatif, O., Rossjohn, J., Kjer-Nielsen, L., McCluskey, J., Ledoux, S., Genser, L., Torcivia, A., Soudais, C., Lantz, O., Boitard, C., Aron-Wisnewsky, J., Larger, E., Clement, K., Lehuen, A., 2015. Mucosal-associated invariant T cell alterations in obese and type 2 diabetic patients. J. Clin. Investig. 125, 1752–1762.
Mai, J., Virtue, A., Shen, J., Wang, H., Yang, X.-F., 2013. An evolving new paradigm: endothelial cells–conditional innate immune cells. J. Hematol. Oncol. 6, 61.
Mannino, M.H., Zhu, Z., Xiao, H., Bai, Q., Wakefield, M.R., Fang, Y., 2015. The paradoxical role of IL-10 in immunity and cancer. Cancer Lett. 367, 103–107.
Mantovani, A., Allavena, P., Sica, A., Balkwill, F., 2008. Cancer-related inflammation. Nature 454, 436.
Marelli, G., Sica, A., Vannucci, L., Allavena, P., 2017. Inflammation as target in cancer therapy. Curr. Opin. Pharmacol. 35, 57–65.
McTiernan, A., 2008. Mechanisms linking physical activity with cancer. Nat. Rev. Cancer 8, 205.
Meneses-Echavez, J.F., Correa-Bautista, J.E., Gonzalez-Jimenez, E., Schmidt Rio-Valle, J., Elkins, M.R., Lobelo, F., Ramirez-Velez, R., 2016. The effect of exercise training on mediators of inflammation in breast cancer survivors: a systematic review with meta-analysis. Cancer Epidemiol. Biomarkers Prev. 25, 1009–1017.
Michalaki, V., Syrigos, K., Charles, P., Waxman, J., 2004. Serum levels of IL-6 and TNF-α correlate with clinicopathological features and patient survival in patients with prostate cancer. Br. J. Cancer 90, 2312.
Moertel, C.G., Gunderson, L.L., Mailliard, J.A., McKenna, P.J., Martenson Jr, J.A., Burch, P.A., Cha, S.S., 1994. Early evaluation of combined fluorouracil and leucovorin as a radiation enhancer for locally unresectable, residual, or recurrent gastrointestinal carcinoma. The North Central Cancer Treatment Group. J. Clin. Oncol. 12, 21–27.
Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A., Group, P.-P, 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 4, 1.
Na, Y.M., Kim, M.Y., Kim, Y.K., Ha, Y.R., Yoon, D.S., 2000. Exercise therapy effect on natural killer cell cytotoxic activity in stomach cancer patients after curative surgery. Arch. Phys. Med. Rehabil. 81, 777–779.
Nair, S., Dhodapkar, M.V., Natural Killer, T., 2017. Cells in cancer immunotherapy. Front. Immunol. 8, 1178.
Nieman, D., Nehlsen-Cannarella, S., Markoff, P., Balk-Lamberton, A., Yang, H., Chritton, D., Lee, J., Arabatzis, K., 1990. The effects of moderate exercise training on natural killer cells and acute upper respiratory tract infections. Int. J. Sports Med. 11, 467–473.
Nieman, D.C., 1994. Exercise, infection, and immunity. Int. J. Sports Med. 15 (Suppl. 3), S131–141.
Nieman, D.C., Cook, V.D., Henson, D.A., Suttles, J., Rejeski, W.J., Ribisl, P.M., Fagoaga, O.R., Nehlsen-Cannarella, S.L., 1995. Moderate exercise training and natural killer cell cytotoxic activity in breast cancer patients. Int. J. Sports Med. 16, 334–337.
Nieman, D.C., Konrad, M., Henson, D.A., Kennerly, K., Shanely, R.A., Wallner-Liebmann, S.J., 2012. Variance in the acute inflammatory response to prolonged cycling is linked to exercise intensity. J. Interferon Cytokine Res. 32, 12–17.
Nikiteas, N.I., Tzanakis, N., Gazouli, M., Rallis, G., Daniilidis, K., Theodoropoulos, G., Kostakis, A., Peros, G., 2005. Serum IL-6, TNFalpha and CRP levels in Greek colorectal cancer patients: prognostic implications. World J. Gastroenterol. 11, 1639–1643.
Oberbach, A., Tonjes, A., Kloting, N., Fasshauer, M., Kratzsch, J., Busse, M.W., Paschke, R., Stumvoll, M., Bluher, M., 2006. Effect of a 4 week physical training program on plasma concentrations of inflammatory markers in patients with abnormal glucose tolerance. Eur. J. Endocrinol. 154, 577–585.
Okwuosa, T.M., Anzevino, S., Rao, R., 2017. Cardiovascular disease in cancer survivors. Postgrad. Med. J. 93, 82–90.
Opal, S.M., DePalo, V.A., 2000. Anti-inflammatory cytokines. Chest 117, 1162–1172.
Pang, G., Couch, L., Batey, R., Clancy, R., Cripps, A., 1994. GM-CSF, IL-1α, IL-β, IL-6, IL-8, IL-10, ICAM-1 and VCAM-1 gene expression and cytokine production in human duodenal fibroblasts stimulated with lipopolysaccharide, IL-1α and TNF-α. Clin. Exp. Immunol. 96, 437–443.
Pedersen, B., 1991. Influence of physical activity on the cellular immune system: mechanisms of action. Int. J. Sports Med. 12, S23–S29.
Pedersen, B., Steensberg, A., Fischer, C., Keller, C., Keller, P., Plomgaard, P., Wolsk-Petersen, E., Febbraio, M., 2004. The metabolic role of IL-6 produced during exercise: is IL-6 an exercise factor? Proc. Nutr. Soc. 63, 263–267.
Pedersen, B.K., Febbraio, M.A., 2012. Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nat. Rev. Endocrinol. 8, 457.

Pedersen, B.K., Hoffman-Goetz, L., 2000. Exercise and the immune system: regulation, integration, and adaptation. Physiol. Rev. 80, 1055–1081.
Pedersen, B.K., Ullum, H., 1994. NK cell response to physical activity: possible mechanisms of action. Med. Sci. Sports Exerc. 26, 140–146.
Pedersen, L., Idorn, M., Olofsson, G.H., Lauenborg, B., Nookaew, I., Hansen, R.H., Johannesen, H.H., Becker, J.C., Pedersen, K.S., Dethlefsen, C., Nielsen, J., Gehl, J., Pedersen, B.K., Thor Straten, P., Hojman, P., 2016. Voluntary running suppresses tumor growth through epinephrine- and IL-6-dependent NK cell mobilization and redistribution. Cell Metab. 23, 554–562.
Peters, C., Lotzerich, H., Niemeier, B., Schule, K., Uhlenbruck, G., 1994. Influence of a moderate exercise training on natural killer cytotoxicity and personality traits in cancer patients. Anticancer Res. 14, 1033–1036.
Petersen, A.M., Pedersen, B.K., 2005. The anti-inflammatory effect of exercise. J. Appl. Physiol. (Bethesda, Md. 1985) 98, 1154–1162.
Rao, R.M., Nagendra, H.R., Raghuram, N., Vinay, C., Chandrashekara, S., Gopinath, K.S., Srinath, B.S., 2008. Influence of yoga on postoperative outcomes and wound healing in early operable breast cancer patients undergoing surgery. Int. J. Yoga 1, 33–41.
Rock, C.L., Doyle, C., Demark-Wahnefried, W., Meyerhardt, J., Courneya, K.S., Schwartz, A.L., Bandera, E.V., Hamilton, K.K., Grant, B., McCullough, M., Byers, T., Gansler, T., 2012. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J. Clin. 62, 243–274.
Rogers, L.Q., Fogleman, A., Trammell, R., Hopkins-Price, P., Vicari, S., Rao, K., Edson, B., Verhulst, S., Courneya, K.S., Hoelzer, K., 2013. Effects of a physical activity behavior change intervention on inflammation and related health outcomes in breast cancer survivors: pilot randomized trial. Integr Cancer Ther 12, 323–335.
Rogers, L.Q., Vicari, S., Trammell, R., Hopkins-Price, P., Fogleman, A., Spenner, A., Rao, K., Courneya, K.S., Hoelzer, K.S., Robbs, R., Verhulst, S., 2014. Biobehavioral factors mediate exercise effects on fatigue in breast cancer survivors. Med. Sci. Sports Exerc. 46, 1077–1088.
Roxburgh, C., McMillan, D.C., 2014. Cancer and systemic inflammation: treat the tumour and treat the host. Br. J. Cancer 110, 1409.
Schag, C., Ganz, P., Wing, D., Sim, M.-S., Lee, J., 1994. Quality of life in adult survivors of lung, colon and prostate cancer. Qual. Life Res. 3, 127–141.
Scheller, J., Chalaris, A., Schmidt-Arras, D., Rose-John, S., 2011. The pro- and anti-inflammatory properties of the cytokine interleukin-6. BBA 1813, 878–888.
Schmidt, M.E., Meynkohn, A., Habermann, N., Wiskemann, J., Oelmann, J., Hof, H., Wessels, S., Klassen, O., Debus, J., Potthoff, K., Steindorf, K., Ulrich, C.M., 2016. Resistance exercise and inflammation in breast cancer patients undergoing adjuvant radiation therapy: mediation analysis from a randomized, controlled intervention trial. Int. J. Radiat. Oncol. Biol. Phys. 94, 329–337.
Schmitz, K.H., Courneya, K.S., Matthews, C., Demark-Wahnefried, W., Galvao, D.A., Pinto, B.M., Irwin, M.L., Wolin, K.Y., Segal, R.J., Lucia, A., Schneider, C.M., von Gruenigen, V.E., Schwartz, A.L., 2010. American college of sports medicine american college of sports medicine roundtable on exercise guidelines for cancer survivors. Med. Sci. Sports Exerc. 42, 1409–1426.
Seruga, B., Zhang, H., Bernstein, L.J., Tannock, I.F., 2008. Cytokines and their relationship to the symptoms and outcome of cancer. Nat. Rev. Cancer 8, 887–899.
Sheen-Chen, S.-M., Chen, W.-J., Eng, H.-L., Chou, F.-F., 1997. Serum concentration of tumor necrosis factor in patients with breast cancer. Breast Cancer Res. Treat. 43, 211–215.
Shephard, R.J., Rhind, S., Shek, P.N., 1994. Exercise and training: influences on cytotoxicity, interleukin-1, interleukin-2 and receptor structures. Int. J. Sports Med. 15 (Suppl. 3), S154–166.
Shrotriya, S., Walsh, D., Nowacki, A.S., Lorton, C., Aktas, A., Hullihen, B., Benanni-Baiti, N., Hauser, K., Ayvaz, S., Estfan, B., 2018. Serum C-reactive protein is an important and powerful prognostic biomarker in most adult solid tumors. PLoS ONE 13 e0202555-e0202555.
Siegel, R.L., Miller, K.D., Jemal, A., 2019. Cancer statistics, 2019. CA Cancer J. Clin. 69, 7–34.
Sprod, L.K., Janelsins, M.C., Palesh, O.G., Carroll, J.K., Heckler, C.E., Peppone, L.J., Mohile, S.G., Morrow, G.R., Mustian, K.M., 2012. Health-related quality of life and biomarkers in breast cancer survivors participating in tai chi chuan. J. Cancer Surviv. 6, 146–154.
Sprod, L.K., Palesh, O.G., Janelsins, M.C., Peppone, L.J., Heckler, C.E., Adams, M.J., Morrow, G.R., Mustian, K.M., 2010. Exercise, sleep quality, and mediators of sleep in breast and prostate cancer patients receiving radiation therapy. Commun. Oncol. 7, 463–471.
Steensberg, A., 2003. The role of IL-6 in exercise-induced immune changes and metabolism. Exerc. Immunol. Rev. 9, 40–47.
Stoner, L., Lucero, A.A., Palmer, B.R., Jones, L.M., Young, J.M., Faulkner, J., 2013. Inflammatory biomarkers for predicting cardiovascular disease. Clin. Biochem. 46, 1353–1371.
Tan, T.-T., Coussens, L.M., 2007. Humoral immunity, inflammation and cancer. Curr. Opin. Immunol. 19, 209–216.
Terabe, M., Berzofsky, J.A., 2008. The role of NKT cells in tumor immunity. Adv. Cancer Res. 101, 277–348.
Timmons, B.W., Cieslak, T., 2008. Human natural killer cell subsets and acute exercise: a brief review. Exerc Immunol Rev 14, 8–23.
Turner, M.D., Nedjai, B., Hurst, T., Pennington, D.J., 2014. Cytokines and chemokines: at the crossroads of cell signalling and inflammatory disease. BBA 1843, 2563–2582.
van Vulpen, J.K., Schmidt, M.E., Velthuis, M.J., Wiskemann, J., Schneeweiss, A., Vermeulen, R.C., Habermann, N., Ulrich, C.M., Peeters, P.H., van der Wall, E., 2018. Effects of physical exercise on markers of inflammation in breast cancer patients during adjuvant chemotherapy. Breast Cancer Res. Treat. 168, 421–431.
Voronov, E., Shouval, D.S., Krelin, Y., Cagnano, E., Benharroch, D., Iwakura, Y., Dinarello, C.A., Apte, R.N., 2003. IL-1 is required for tumor invasiveness and angiogenesis. Proc. Natl. Acad. Sci. 100, 2645–2650.
Waldhauer, I., Steinle, A., 2008. NK cells and cancer immunosurveillance. Oncogene 27, 5932.
Walsh, N.P., Gleeson, M., Shephard, R.J., Gleeson, M., Woods, J.A., Bishop, N.C., Fleshner, M., Green, C., Pedersen, B.K., Hoffman-Goetz, L., Rogers, C.J., Northoff, H., Abbasi, A., Simon, P., 2011. Position statement. Part one: immune function and exercise. Exerc Immunol Rev 17, 6–63.
Wang, H.-W., Joyce, J.A., 2010. Alternative activation of tumor-associated macrophages by IL-4: priming for protumoral functions. Cell Cycle 9, 4824–4835.
Wells, A.J., Hoffman, J.R., Jajtner, A.R., Varanoske, A.N., Church, D.D., Gonzalez, A.M., Townsend, J.R., Boone, C.H., Baker, K.M., Beyer, K.S., Mangine, G.T., Oliveira, L.P., Fukuda, D.H., Stout, J.R., 2016. Monocyte recruitment after high-intensity and high-volume resistance exercise. Med. Sci. Sports Exerc. 48, 1169–1178.
Whiteside, T.L., Herberman, R.B., 1994. Role of human natural killer cells in health and disease. Clin. Diagn. Lab. Immunol. 1, 125–133.
Winters-Stone, K.M., Wood, L.J., Stoyles, S., Dieckmann, N.F., 2018. The effects of resistance exercise on biomarkers of breast cancer prognosis: a pooled analysis of three randomized trials. Cancer Epidemiol. Prev. Biomarkers 27, 146–153.
Zitvogel, L., Apetoh, L., Ghiringhelli, F., Kroemer, G., 2008. Immunological aspects of cancer chemotherapy. Nat. Rev. Immunol. 8, 59.