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Review article

Effect of Exercise on Immune System Markers in Cancer Patients and Survivors: A Systematic Review

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Abstract

This systematic review aimed to analyze the impact of aerobic, resistance, combined, and mind-body exercise on the cellular markers of the immune system in cancer patients and survivors. Pubmed, Web of Science, the Cochrane Library, and Scopus databases were searched to identify pertinent randomized controlled trials that looked at the effect of exercise interventions on cellular markers of immune system. Risk of Bias 2 (RoB2) Tool was used to evaluate the methodological quality of each study. Of the 20 investigations included, 8 observed beneficial results on the effect of aerobic, resistance, combined, and mind-body exercise on immune cells in cancer patients and survivors when compared to control groups. Observed changes included increases in natural killer (NK) cells, peripheral blood mononuclear cells (PBMCs) and dendritic cell marker $DC11c^{+}$ cytotoxicity, immunoglobulin A, total white blood cells, lymphocytes, NK cell percentages, and NK cell receptor expression ($NKG2D^{+}$ and $KIR2DL3^{+}$). Additionally, NK cell infiltration into healthy prostatic tissue and platelet counts were modulated in some studies. Risk of bias was rated as low in 35% of studies, with 45% classified as high risk, mainly due to randomization and intervention deviations. Exercise, particularly aerobic and mind-body modalities, may improve innate and adaptive immune responses in cancer patients and survivors, although effects were not consistent across all interventions or immune outcomes. More high-quality studies involving diverse types, intensities, and durations of physical exercise are needed during different cancer phases and stages of treatment. *Registration Number:* CRD42022370010

Key words: Aerobic Exercise, Resistance Training, Combined Exercise, Mind-Body Therapies, Acquired Immunity, Innate Immunity.

Introduction

According to the International Agency for Research on Cancer, the burden of cancer death and incidence is quickly rising worldwide (Bray et al., 2024). In 2022, about 20.0 million new cases of cancer were detected worldwide, with breast cancer, lung cancer, and colorectal cancer accounting for the majority of new cases (Bray et al., 2024).

It is widely recognized that cancer patients can benefit from exercise training since it not only improves physical fitness and body composition, attenuates treatment-related symptoms, and enhances quality of life (Idorn and Hojman, 2016; Pedersen and Saltin, 2015), but also emerges as an auspicious ally of anti-cancer treatments, contributing to a reduction in the proliferative capacity and growth of the tumor (Hojman et al., 2017). Further, the immune system adaptations derived from exercise also play an important role in tackling tumor cell proliferation. Exercise, both in the short- and long-term, affects the number and functionality of several innate and adaptive immune cell types (Koelwyn et al., 2017). While much of the evidence stems from animal models (Hojman et al., 2017; Lin et al., 1993; Pedersen et al., 2016), humans studies on healthy adults also underscore the regulatory effects of exercise on the cellular immune system (Goncalves et al., 2019; Thomas et al., 2017; Nieman and Wentz, 2019). In contrast, emerging research in clinical populations, including cancer, suggests that treatment-related immune suppression may attenuate or modify these responses (Gustafson et al., 2021; Lee et al., 2022).

Despite increasing interest in the immunological effects of exercise, the number of studies specifically investigating this topic in cancer populations remains limited, and results appear to vary depending on the type, timing, and intensity of the exercise intervention. Systematic reviews conducted in those with cancer disease have reported that different types of exercise are associated with beneficial changes in both number and activity of multiple immune cell populations (Khosravi et al., 2019; Kruijsen-Jaarsma et al., 2013; Lyu, 2023). Further, previous reviews have primarily focused on pro- and anti-inflammatory cytokines or general health outcomes, while limited attention has been given to specific immune cell markers such as natural killer (NK) cells or T cell subsets (Khosravi et al., 2019).

Given the growing recognition of the immune system's role in cancer progression, treatment response, and survivorship, there is a pressing need to synthesize the evidence on how different forms of exercise influence both innate and adaptive immunity. Therefore, the purpose of this investigation was to perform a systematic review of randomized controlled trials (RCTs) that assessed the impact of aerobic, resistance, combined, and mind-body exercise on alterations in outcomes related to cellular markers of the innate immune system (e.g., NK cells, monocytes, neutrophils, macrophages) and adaptive immune system (e.g., T-cells and B-cells) in cancer patients and survivors.

Methods

The present systematic review was registered on PROSPERO (CRD42022370010) and was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive literature search was conducted using four databases (i.e., Pubmed, Web of Science, Scopus, and

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Cochrane), for the eligible articles until July 31, 2024 (Table 1). Relevant Boolean words used to perform the search were related to cancer, immune system, and exercise (Table 1).

Table 1. Database keywords.

Databases	Keywords
PubMed	((Exercise) OR (Physical Activity)) AND ((cancer) OR (tumour) OR (tumor)) AND ((NK cells) OR (Lymphocytes) OR (Immune) OR (Macrophages) OR (T Cells) OR (CD4) OR (CD8) OR (CD3) OR (CD56)) with randomized controlled trial and clinical trial filter
Web of Science	TS=(Exercise OR Physical Activity) AND TS=(cancer OR tumour OR tumor) AND TS=(NK cells OR Lymphocytes OR Immune OR Macrophages OR T Cells OR CD4 OR CD8 OR CD3 OR CD56)
Scopus	ALL ((exercise OR physical AND activity) AND (cancer OR tumour OR tumor) AND (nk AND cells OR lymphocytes OR immune OR macrophages OR t AND cells OR cd4 OR cd8 OR cd3 OR cd56)) AND (LIMIT-TO (DOCTYPE , "ar")) with article filter
Cochrane	(Exercise OR Physical Activity) AND (Cancer OR Tumour OR Tumor) AND (NK cells OR Lymphocytes OR Immune OR Macrophages OR T Cells OR CD4 OR CD8 OR CD3 OR CD56)

Inclusion and exclusion criteria

For the inclusion and exclusion criteria, the PICOS structure was adopted: **Population (P):** cancer patients or survivors; **Intervention (I):** investigations involving exercise interventions; those including multiple component interventions (e.g. exercise and diet) were excluded; **Comparison (C):** non-exercise control group; **Outcome (O):** cellular markers of the immune system (CD4, CD8, CD56, NK cells, monocytes and granulocyte counts, peripheral blood mononuclear cell (PBMC) function); **Study design (S):** RCTs written in English.

Study selection and data extraction

The eligible studies were independently assessed by two authors (EO and IRC) according to inclusion and exclusion criteria by evaluating the titles and abstracts of each paper after duplicate removal. Any disagreements were decided by dialogue with a third reviewer (AB). In cases where there was insufficient data in the title and/or abstract regarding the population or intervention, the full-text version was retrieved to evaluate the article. The reference lists of each eligible study were manually checked for additional papers. Details from each eligible article, including article identification, type of cancer, treatment, the number of participants, age, exercise intervention/duration, and results were extracted.

The primary outcomes were related to the immune system, categorized into innate (e.g., NK cells, monocytes, neutrophils, macrophages) and adaptive (e.g., T-cells and B-cells) immunity. Humoral markers such as immunoglobulin levels were included only if reported alongside cellular outcomes but were not a specific focus of the search strategy. Data was sought from all reported results within eligible studies, with prioritization given to validated measures and those identified as primary outcomes by study authors. For studies reporting outcomes at multiple time points, data from the final follow-up period were included to assess sustained effects. Any changes to predefined outcomes were minimal and supported by their relevance to the review's objectives. Effect measures reported in the included studies were extracted as presented. No meta-analysis was performed as the extracted data were summarized qualitatively to highlight trends and variability across studies.

Data synthesis

Studies were grouped by intervention type (aerobic, resistance, combined, mind-body) and by treatment status (survivors or active treatment). Data extracted from included studies were synthesized narratively. If studies reported outcomes in different formats (e.g., percentages vs. absolute counts), these were presented as-is without conversion to maintain the integrity of the original data. Results were synthesized narratively by identifying patterns and trends across studies within each intervention type and outcome domain.

Risk of bias assessment

The methodological quality of the included randomized controlled trials was assessed using the revised Cochrane Risk of Bias tool (RoB 2) (Sterne et al., 2019). This tool evaluates potential sources of bias across five domains: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result. Each domain was rated as "low risk of bias," "some concerns," or "high risk of bias," and an overall judgment for each study was derived following the RoB 2 guidelines (Sterne et al., 2019). The risk of bias assessments is presented in Table 2.

Results

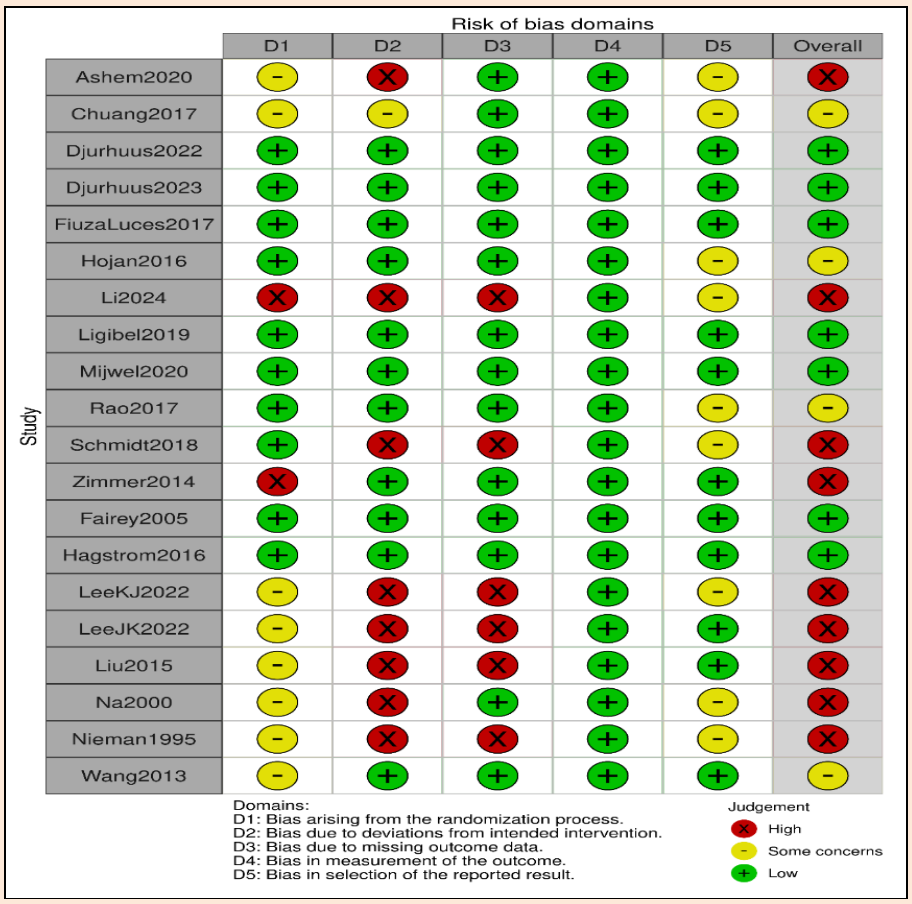
Study Process

The initial literature search identified 15,386 articles through the database search in PubMed (n = 242), Scopus (n = 7823), Web of Science (n = 6133), and Cochrane Library (n = 1188). All articles were verified for duplicates. After duplicate removal (n = 979), 14,407 articles were screened by title and/or abstract, and 13,924 studies were excluded due to not being about cancer or solely exercise intervention. The remaining 483 articles were assessed for eligibility, and 463 were excluded for not meeting the inclusion/exclusion criteria. A total of 20 investigations were included in this review, accounting for a total of 996 cancer patients and survivors. A PRISMA diagram is shown in Figure 1.

Characteristics of included investigations

Of the 20 investigations, 9 included breast cancer, 2 included non-Hodgkin lymphoma, 2 non-small cells lung cancer (NSCLC), 3 prostate carcinoma, 1 stomach cancer, 1 ovarian cancer, 1 lung cancer and 1 synovial sarcoma, ewing sarcoma, osteosarcoma, burkitt lymphoma, neuroblastoma, hodgkin lymphoma, diffuse large B-cell lymphoma, T-cell lymphoblastic lymphoma, and ganglioneuroblastoma.

Table 2. **Risk of bias assessment of the included investigations.**



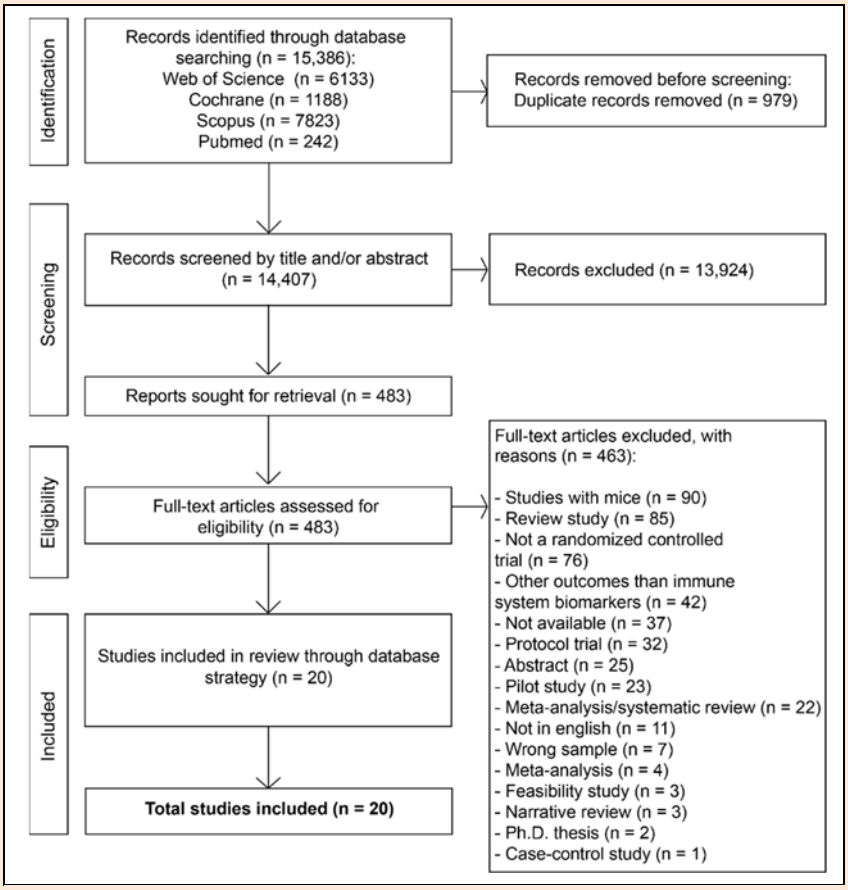


Figure 1. **PRISMA flow diagram. Flow chart of the methodology for the identification and inclusion of investigations.**

Risk of bias in included investigations

The risk of bias assessments across the 20 included studies are presented in Table 2. Overall, 9 studies (45%) were rated as having "high risk of bias," 4 studies (20%) as having "some concerns," and 7 studies (35%) as having "low risk of bias." Most studies showed low risk of bias regarding missing outcome data (Domain 3), measurement of outcomes (Domain 4), and selection of the reported result (Domain 5). However, bias arising from the randomization process (Domain 1) and deviations from intended interventions (Domain 2) were more frequent sources of concern or high risk. These findings suggest that while a substantial proportion of included studies were methodologically rigorous, some sources of bias may have contributed to the observed heterogeneity in immune outcomes.

Results of individual investigations

Studies including aerobic, resistance, and/or combined training protocols were the most common interventions (16 out of the 20 investigations included) (Ashem et al., 2020; Djurhuus et al., 2022; 2023; Fairey et al., 2005; Fiuza-Luces et al., 2017; Hagstrom et al., 2016; Hojan et al., 2016; Lee et al., 2022; Lee and An, 2022; Ligibel et al., 2019; Mijwel et al., 2020; Na et al., 2000; Nieman et al., 1995; Schmidt et al., 2018; Zimmer et al., 2014; Li et al., 2024). In general, these interventions included activities such as walking, running, and cycling, as well as machine-based and free-weight exercises. These study characteristics (e.g., type of cancer, intervention types, sample size, treatment, collection methods and endpoints, and outcomes) and results (e.g., mean differences, percentages) are summarized in Table 3 for survivors and Table 4 for patients undergoing active treatment.

The duration of each intervention varied across the studies, ranging from an acute exercise protocol (30 minutes) (Zimmer et al., 2014) to a long-term intervention lasting 18 weeks (Ashem et al., 2020). Also, the treatment protocol differed between investigations; nine studies were conducted in participants undergoing active treatment at the time of the exercise intervention, including chemotherapy (Ashem et al., 2020; Chuang et al., 2017; Fiuza-Luces et al., 2017; Li et al., 2024; Mijwel et al., 2020; Schmidt et al., 2018; Zimmer et al., 2014), radiotherapy (Rao et al., 2017) or androgen deprivation therapy (Hojan et al., 2016). Three additional studies included patients in the pre-surgical phase (Djurhuus et al., 2022; 2023; Ligibel et al., 2019). The remaining eight studies were conducted in cancer survivors, defined as individuals who had completed active treatment prior to the exercise intervention (Fairey et al., 2005; Hagstrom et al., 2016; Lee et al., 2022; Lee and An, 2022; Liu et al., 2015; Na et al., 2000, Nieman et al., 1995; Wang et al., 2013).

Aerobic training interventions

Considering the interventions with an aerobic approach (Ashem et al., 2020; Djurhuus et al., 2022; 2023; Fairey et al., 2005; Mijwel et al., 2020; Na et al., 2000; Schmidt et al., 2018; Zimmer et al., 2014), six studies implemented a multi-week aerobic training program (Ashem et al., 2020; Djurhuus et al., 2023; Fairey et al., 2005; Mijwel et al., 2020; Na et al., 2000; Schmidt et al., 2018), while two studies assessed acute responses following a single bout of aerobic exercise (Djurhuus et al., 2022; Zimmer et al., 2014).

Among the long-term interventions, three studies reported significant between-group effects favoring the exercise group (Ashem et al., 2020; Djurhuus et al., 2023; Fairey et al., 2005), including enhanced NK cell cytotoxicity, immunoglobulin A levels, and NK cell infiltration. The acute studies assessing transient immune responses to a single exercise session reported a within-group increase in histone acetylation (H3K9ac) in $CD8^+$ T cells following aerobic stimulus (Zimmer et al., 2014), while another investigation observed an acute increase in lymphocyte count during the exercise bout (Djurhuus et al., 2022).

Resistance training interventions

Only 3 interventions included resistance training in their protocol (Hagstrom et al., 2016; Lee and An, 2022; Schmidt et al., 2018). Only within-groups differences were found, while no between groups changes were reported on NK and NKT cells, NK cell activity, T cell receptor (TCR), $CD3^+$, $CD4^+$, $CD8^+$, and B cells.

Combined training interventions

In this systematic review, 7 investigations used combined training as the intervention (Fiuza-Luces et al., 2017; Hojan et al., 2016; Lee et al., 2022; Ligibel et al., 2019; Mijwel et al., 2020; Nieman et al., 1995; Li et al., 2024). Three of the studies did not demonstrate any significant results (Fiuza-Luces et al., 2017; Nieman et al., 1995; Li et al., 2024); one showed between-group results (Mijwel et al., 2020) regarding the concentration of thrombocytes (platelets), which may play a modulatory role in immune function, one showed between-group results concerning several immune cells (leucocytes, neutrophils, lymphocytes, NK cells, NKT cells, and cytotoxicity) (Lee et al., 2022), favoring the exercise group; and the remaining two studies did not report any between-groups differences (Hojan et al., 2016; Ligibel et al., 2019).

Mind-body interventions

Four studies included a mind-body intervention (Chuang et al., 2017; Liu et al., 2015; Rao et al., 2017; Wang et al., 2013); two articles included Tai Chi as the exercise intervention (Liu et al., 2015; Wang et al., 2013); one included yoga (Rao et al., 2017); and one involved Chan-Chuang Qigong (Chuang et al., 2017). Wang et al. (2013) assessed T-helper (TH1/TH2), T-cytotoxic (Tc1/Tc2), and T1/T2 immune profiles and did not report between-group results for Tai Chi, whereas Liu et al. (2015) measured NK cells, NKT cells, $DC11c^+$ dendritic cells, and PBMC proliferation and cytotoxicity against lung cancer cell lines and demonstrated between and within-group improvements favoring the intervention group. The other two studies including yoga (Rao et al., 2017), which measured NK cell percentage and absolute lymphocyte count, and Chan-Chuang Qigong (Chuang et al., 2017), that assessed total white blood cell and platelet counts, observed significant increases in NK cells and white blood cell counts, respectively.

Table 3. **Results of the included studies with participants that completed treatment (survivors).**

First Author, Year	Cancer	Intervention	Sample size (age, years)	Treatment	Collection Methods and Endpoints	Outcomes	
						Within-groups	Between-groups
Na, Y et al., (2000)	Stomach cancer (survivors)	• **2 weeks** • **G1:** 30min; active ROM exercise, pelvic tilting exercise, and isometric quadriceps-setting exercise while in bed, 3x/day or when ambulatory, supervised aerobic activity using arm and bicycle ergometers, 2x/day, 5x/wk. • **G2:** Usual Care	• **N:** 35 • **G1:** 17 (57.8y) • **G2:** 18 (52.2y)	Treatment completed (underwent surgery)	**Time points:** • Postoperative day (POD) 1 at 10 AM • POD 7 at 10 AM • POD 14 at 10 AM **Collection methods:** • Ficoll-Hypaque gradients • Chromium release Cytotoxicity assay	**Mean NKCA:** **G1 -** Pre: 16.2%; Mid: 14.6%; Post: 27.9%; **G2 -** Pre: 19.7%; Mid: 17.9%; Post: 13.3%;	**Mean NKCA:** Pre: Ø ($p > 0.05$); Mid: Ø ($p > 0.05$); • Post: G1 > G2 ($p < 0.05$);
Liu, J., et al. (2015)	Non-small cell lung cancer (survivors)	**16 weeks** • **G1:** 60 min, 3x/wk, Tai Chi exercise • **G2:** Usual care	**N:** 27 • **G1:** 14 (8M and 6F) (62.6y) • **G2:** 13 (7M and 6F) (60.5y)	Treatment completed (underwent surgery)	**Time points:** • Baseline • End of the intervention **Collection methods:** • Density gradient centrifugation • MTT cell proliferation kit Flow cytometric analysis	**PBMC proliferative capacity 0.5 × (10^6) cell density –** G1 - Pre: 0.70 ± 0.28; Post: 0.92 ± 0.24; $p < 0.05$ G2 - Pre: 0.89 ± 0.26; Post: 0.99 ± 0.25; $p = 0.284$ **PBMC proliferative capacity 1 × (10^6) cell density –** G1 - Pre: 1.21 ± 0.23; Post: 1.66 ± 0.37; $p < 0.001$ G2 - Pre: 1.33 ± 0.26; Post: 1.39 ± 0.18; $p = 0.537$) **PBMC cytolytic/oncolytic activity against lung cancer cells A549 -** • 50:1 E:T Ratio: G1 - Pre: 1.04 ± 0.19; Post: 0.51 ± 0.15; $p < 0.001$ G2 - Pre: 1.04 ± 0.33; Post: 0.99 ± 0.25; • 25:1 E:T Ratio: G1 - Pre: 0.85 ± 0.16; Post: 0.51 ± 0.13; $p < 0.001$ G2 - Pre: 0.85 ± 0.39 ; Post: 0.76 ± 0.22; • 12.5:1 E:T Ratio: G1 - Pre: 0.53 ± 0.15; Post: 0.52 ± 0.20; G2 - Pre: 0.66 ± 0.20; Post: 0.63 ± 0.20;	**PBMC proliferation capacity:** Ø Cytotoxicity of PBMCs at 25:1 and 50:1 E:T cell ratio: G1 > G2 ($p < 0.05$) **Percentage of NK cells:** G1 - Pre: 22.66 ± 8.23; Post: 27.94 ± 10.3; G2 - Pre: 20.49 ± 6.82; Post: 20.17 ± 7.35; $p < 0.05$ **NKT:** G1 - Pre: 3.58 ± 2.97; Post: 3.83 ± 3.03; G2 - Pre: 3.89 ± 2.59; Post: 2.87 ± 1.71; $p < 0.05$ **DC11c:** G1 - Pre: 2.37 ± 1; Post: 3.09 ± 1.57; G2 - Pre: 1.63 ± 0.80; Post: 1.47 ± 0.61; $p < 0.01$

NK cells, Natural killer cells; PBMCs, Peripheral blood mononuclear cells; Th1/Th2 ratio, CD3+ T lymphocyte subset helper cell type 1/CD3+ T lymphocyte subset helper cell type 2; NSCLC, non-small cells lung cancer; CTx, chemotherapy; TCR, T-cell receptor; RCT, randomized controlled trial.

Table 3. Continue….

First Author, Year	Cancer	Intervention	Sample size (age, years)	Treatment	Collection Methods and Endpoints	Outcomes	
						Within-groups	Between-groups
Wang, R. et al. (2013)	Non-small cell lung cancer (survivors)	**16 weeks** **G1:** 60 min, 3x/wk guided Tai Chi exercise. **G2:** Usual care	**N**: 27 **G1:** 13 (7 M and 6 W) (63.1y) **G2:** 14 (8 M and 6 W) (59.3y)	Treatment completed (underwent surgery)	**Time points:** Baseline End of the intervention **Collection methods:** Flow cytometry	**T1/T2 –** G1 - Pre: 1.90 ± 0.63; Post: 2.06 ± 0.62; p = 0.204; G2 - Pre: 1.98 ± 0.38; Post: 1.64 ± 0.46; p = 0.002 **T1 –** G1 - Pre: 42.53 ± 11.07; Post: 40.58 ± 13.16; p = 0.470; G2 - Pre: 37.90 ± 11.99; Post: 34.43 ± 9.49; p = 0.048 **T2 –** G1 - Pre: 23.95 ± 8.80; Post: 20.61 ± 7.13; p = 0.037; G2 - Pre: 19.08 ± 6.45; Post: 21.69 ± 6.41; p = 0.005 **Tc1/Tc2 –** G1 - Pre: 1.20 ± 0.27; Post: 1.31 ± 0.20; p = 0.221; G2 - Pre: 1.35 ± 0.23; Post: 1.08 ± 0.17; p = 0.000 **Tc1 –**G1 - Pre: 25.90 ± 9.31; Post: 24.4 ± 8.63; p = 0.455 G2 - Pre: 24.20 ± 10.43; Post: 20.74 ± 7.74; p = 0.008 **Tc2 –**G1 - Pre: 22.41 ± 8.94; Post: 18.82 ± 6.87; p = 0.036; G2 - Pre: 17.65 ± 6.10; Post: 19.13 ± 5.78; p = 0.010 **TH1/TH2 –**G1 - Pre: 11.76 ± 6.11; Post: 10.12 ± 5.85; p = 0.295; G2 - Pre: 10.26 ± 5.16; Post: 5.73 ± 4.46; p = 0.030 **TH1 –** G1 - Pre: 16.63 ± 7.37; Post: 16.18 ± 8.69; p = 0.750; G2 - Pre: 13.70 ± 3.57; Post: 13.69 ± 4.55; p = 0.989 **TH2 –** G1 - Pre: 1.55 ± 0.47; Post: 1.79 ± 0.89; p = 0.284; G2 - Pre: 1.61 ± 0.75; Post: 2.92 ± 1.26; p = 0.010	Not reported
Nieman, (1995)	Breast (survivors)	**8 weeks** **G1:** 60 min; 3x/wk; resistance training: 2 sets of 12 reps; aerobic training: 75% HRmax, walking on an indoor track for 30 min a session; **G2:** Usual care	**N:** 12 **G1:** 6 (60.8y) **G2:** 6 (51.2y)	Treatment completed (underwent surgery, CTx, and/or radiation treatment within the previous four years)	**Time points:** Baseline End of the intervention **Collection methods:** Coulter STKS instrument	Not reported	**NKCA and concentrations of circulating immune cells: Ø** **Total leukocytes** – G1 - Pre: 5.7 ± 0.3; Post: 4.9 ± 0.4; G2 - Pre: 5.9 ± 0.9; Post: 6.1 ± 0.9; p = 0.07 **Neutrophils –** G1 - Pre: 3.7 ± 0.3; Post: 3.0 ± 0.4; G2 - Pre: 3.8 ± 0.7; Post: 3.9 ± 0.8; p = 0.10 **Lymphocytes –** G1 - Pre: 1.4 ± 0.2; Post: 1.1 ± 0.2; G2 - Pre: 1.4 ± 0.2; Post: 1.6 ± 0.3; p = 0.19 **T cells –** G1 - Pre: 0.9 ± 0.1; Post: 0.9 ± 0.1; G2 - Pre: 1.0 ± 0.2; Post: 1.2 ± 0.2; p = 0.14 **NK cells –**G1 - Pre: 0.3 ± 0.1; Post: 0.3 ± 0.1; G2 - Pre: 0.2 ± 0.1; Post: 0.2 ± 0.1; p = 0.99

NK cells, Natural killer cells; PBMCs, Peripheral blood mononuclear cells; Th1/Th2 ratio, CD3+ T lymphocyte subset helper cell type 1/CD3+ T lymphocyte subset helper cell type 2; NSCLC, non-small cells lung cancer; CTx, chemotherapy; TCR, T-cell receptor; RCT, randomized controlled trial.

Table 3. Continue….

First Author, Year	Cancer	Intervention	Sample size (age, years)	Treatment	Collection Methods and Endpoints	Outcomes	
						Within-groups	Between-groups
Hagstrom, et al. (2016)	Breast (survivors)	**16-week** **G1:** 60 min; 3x/wk; resistance training: 3 sets of 8-10 reps at 8RM/80% of the 1RM; **G2:** Usual care	**N:** 39 (51.9y) **G1:** 20 (52.7y) **G2:** 19 (51.2y)	Treatment completed (underwent surgery, radiotherapy, and/or CTx)	**Time points:** Baseline End of the intervention **Collection methods:** Fluorescence-activated cell sorting (FACS) Multiparametric flow cytometry	Not reported	**NK (%):** G1 - Pre: 10.4 ± 4.9; Post: -1.0 ± 3.3; G2 - Pre: 9.5 ± 6.2; Post: 1.1 ± 3.7; p = 0.94 **Expression of TNF-α on their NK cells:** G1 - Pre: 13.8 ± 4.7; Post: -1.4 ± 5.1; G2 - Pre: 13.5 ± 4.0; Post: 4.3 ± 6.2; p = 0.005 **NKT (%):** G1 - Pre: 6.9 ± 5.1; Post: -1.5 ± 4.4; G2 - Pre: 5.5 ± 3.6; Post: -0.1 ± 3.5; p = 0.55 **Expression of TNF-α on their NKT cells:** G1 - Pre: 9.9 ± 5.9; Post: -3.0 ± 5.0; G2 - Pre: 13.6 ± 7.0; Post: 0.1 ± 8.5; p = 0.038
Fairey et al. (2005)	Breast (survivors)	**15-weeks** **G1:** 3x/wk; weeks 1-3: 15 min; increase 5 min every 3 wk; weeks 13-15: 35 min; recumbent or upright cycle ergometers; ~70–75% of peak oxygen consumption. **G2:** Usual care	**N:** 52 (59y) **G1:** 24 (59y) **G2:** 28 (58y)	Treatment completed (underwent surgery, radiotherapy, and/or CTx with or without current tamoxifen or anastrozole therapy use)	**Time points:** Baseline 15 weeks **Collection methods:** Hemocytometer Coulter STKS instrument Flow cytometry Immunofluorescence assay ELISA kits	Not reported	**NK cell cytotoxic activity** **3.125:1 effector-to-target ratio:** G1 - Pre: 7.2 ± 5.1; Post: 12.4 ± 6.6; G2 - Pre: 5.8 ± 4.5; Post: 5.7 ± 4.2; p < 0.0016.25:1 effector-to-target ratio: G1 - Pre: 21.7 ± 9.0; Post: 27.7 ± 10.1; G2 - Pre: 18.9 ± 9.4; Post: 19.8 ± 9.2; p = 0.022 **12.5:1 effector-to-target ratio:** G1 - Pre: 36.2 ± 10.6; Post: 41.2 ± 8.4; G2 - Pre: 32.2 ± 10.1; Post: 33.8 ± 10.7; p = 0.041 **25:1 effector-to-target ratio:** G1 - Pre: 44.2 ± 12.8; Post: 49.8 ± 8.3; G2 - Pre: 45.3 ± 12.1; Post: 44.0 ± 11.3; p = 0.024 **50:1 effector-to-target ratio:** G1 - Pre: 55.5 ± 12.1; Post: 61.4 ± 9.8; G2 - Pre: 58.0 ± 12.9; Post: 56.4 ± 10.5; p = 0.039 **Total lytic units** – G1 - Pre: 11.98 ± 6.76; Post: 8.60 ± 3.40; G2 - Pre: 12.72 ± 8.19; Post: 11.68 ± 6.00; p = 0.035
Lee, K-J., et al. (2022)	Breast Cancer (survivors)	**12 weeks, 2–3x/wk** **G1:** 50 min; warm-up (walking and stretching, 10 min), main exercise (8 exercises; week 1: 16 reps, 3 set, 1RM 40%; week 2: 12 rep, 4 set, 1 RM 60%; week 3-12: 8rep, 4 set, 1RM 80%; 30 min), and cool-down (stretching, 10 min). **G2:** Activities of daily living	**N:** 30 **G1:** 15 (54.7y) **G2:** 15 (55.4y)	Treatment completed (underwent surgery, radiation, and CTx)	**Time points:** Baseline End of intervention **Collection methods:** Vacutainer tube NK Vue kit Turbidimetric immunoassay using a Cobas 8000 C702 Artificially activated using a ELx808 reader Enzyme-linked immunosorbent assay	NKCA: G1 ↑ G1 - Pre: 773.0 ± 668.6; Post: 1092.7 ± 816.2; p = G2 - Pre: 809.4 ± 784.6; Post: 801.3 ± 786.3; p = Difference between time points, a significant difference was found in NKCA(F = 6.815, p = 0.016)	NKCA (F = 0.180, p = 0.657)

NK cells, Natural killer cells; PBMCs, Peripheral blood mononuclear cells; Th1/Th2 ratio, CD3+ T lymphocyte subset helper cell type 1/CD3+ T lymphocyte subset helper cell type 2; NSCLC, non-small cells lung cancer; CTx, chemotherapy; TCR, T-cell receptor; RCT, randomized controlled trial.

Table 3. Continue….

First Author, Year	Cancer	Intervention	Sample size (age, years)	Treatment	Collection Methods and Endpoints	Outcomes	
						Within-groups	Between-groups
Lee, J-K., et al., (2022)	Ovarian Cancer (survivors)	**12 wks** **G1:** 6x/wk; warm-up (10 min), scheduled workout (Aerobic exercise - 3x/wk, walking or running at 40–70% VO2peak, 50-35min; Resistance exercise – 3x/wk, weight machines, 12RM-6RM x 3 sets, 30-40min) **G2:** Usual Care	**N:** 27 (51.07y) **G1:** 12 (51.67y) **G2:** 15 (50.60y)	Treatment completed (underwent surgery, radiation therapy, or CTx)	**Time points:** Baseline End of intervention **Collection methods:** Automated differential blood cell counts Fluorescence- activated cell sorting (FACS) analysis EDTA-anticoagulant blood samples for automated leucocyte differential tests Flow cytometry Antibody staining	**Leucocytes:** G1 - Pre: 4.74 ± 0.74 x 10^2; Post: 5.69 ± 0.85 x 10^2; p = 0.031; G2 - Pre: 4.68 ± 0.71 x 10^2; Post: 4.43 ± 0.59 x 10^2; p = 0.131 **Neutrophil percentage for leucocytes:** G1 - Pre: 49.77 ± 5.23; Post: 57.48 ± 7.28; p = 0.006 G2 - Pre: 47.33 ± 4.57; Post: 43.72 ± 2.58; p = 0.020 **Lymphocyte percentage for leucocytes:** G1 - Pre: 39.76 ± 3.59; Post: 50.08 ± 5.91; p = 0.004 G2 - Pre: 38.61 ± 6.69; Post: 35.03 ± 4.07; p = 0.044 **Lymphocytes:** G1 - Pre: 15.00 ± 2.26 x 10^2; Post: 20.42 ± 2.11 x 10^2; p = 0.003; G2 - Pre: 15.13 ± 3.36 x 10^2; Post: 13.13 ± 2.67 x 10^2; p = 0.152 **NK cell percentage for lymphocytes:** G1 - Pre: 8.65 ± 2.09; Post: 12.85 ± 3.44; p = 0.005 G2 - Pre: 7.99 ± 2.41; Post: 6.55 ± 2.05; p = 0.348 **NKT cell percentage for lymphocytes:** G1 - Pre: 3.92 ± 1.82; Post: 5.46 ± 2.27; p = 0.059 G2 - Pre: 4.11 ± 2.64; Post: 3.03 ± 1.92; p = 0.093 **Total NK cells:** G1 - Pre: 133.58 ± 34.10; Post: 193.42 ± 70.80; p = 0.019; G2 - Pre: 133.10 ± 28.65; Post: 103.10 ± 47.74; p = 0.023 **NKG2D+ NK:** G1 - Pre: 54.86 ± 11.40; Post: 66.72 ± 14.23; p = 0.010; G2 - Pre: 55.17 ± 12.06; Post: 46.36 ± 16.79; p = 0.073 **KIR2DL3+NK:** G1 - Pre: 34.96 ± 12.55; Post: 24.18 ± 9.30; p = 0.023 G2 - Pre: 34.35 ± 6.68; Post: 41.68 ± 5.35; p = 0.001 **Cytotoxicity:** G1 - Pre: 2.98 ± 1.67; Post: 6.08 ± 2.49; p = 0.008 G2 - Pre: 2.70 ± 2.11; Post: 1.85 ± 1.17; p = 0.006	**Leucocytes** – G1 > G2 (p = 0.001) **Neutrophil percentage for leucocytes**– G1 > G2 (p = 0.001) **Lymphocyte percentage for leucocytes** - G1 > G2 (p = 0.001) **Lymphocytes** – G1 > G2 (p = 0.001) **NK cell percentage for lymphocytes** – G1 > G2 (p = 0.001) **NKT cell percentage for lymphocytes**– G1 > G2 (p = 0.003) **Total NK cells** - G1 > G2 (p = 0.001) **NKG2D + NK** - G1 > G2 (p = 0.002) **KIR2DL3+NK** - G1 > G2 (p = 0.001) **Cytotoxicity** - G1 > G2 (p = 0.001)

NK cells, Natural killer cells; PBMCs, Peripheral blood mononuclear cells; Th1/Th2 ratio, CD3+ T lymphocyte subset helper cell type 1/CD3+ T lymphocyte subset helper cell type 2; NSCLC, non-small cells lung cancer; CTx, chemotherapy; TCR, T-cell receptor; RCT, randomized controlled trial.

Table 4. **Results of the included studies with participants in active treatment.**

First Author, Year	Cancer	Intervention	Sample size (age, years)	Treatment	Collection Methods and Endpoints	Outcomes	
						Within-groups	Between-groups
Schmidt et al. (2018)	Breast cancer	**12-week** • **G1**: 60 min, 2x/wk; 1 set of 20 reps with a hypothetical 50% of the maximum weight • **G2**: 60 min, 2x/wk; indoor bike, 10 min warm-up, 25-30 min, and 5 min cool-down; level 11-14 on Borg scale • **G3**: Usual care	**N**: 67 • **G1**: 21 (53y) • **G2**: 20 (56y) • **G3**: 26 (54y)	Adjuvant CTx	**Time points:** • Baseline • 12 weeks • End of the intervention **Collection methods** • Flow cytometry • BD Multitest 6-color TBNK (M6T) Reagent with BD Trucount Beads	**CD3+ T:** G1 - Pre: 1252.82 ± 422.86; Post: 1010.81 ± 484.96; p = 0.46 G2 - Pre: 1153.40 ± 365.05; Post: 856.00 ± 379.00; p = 0.001 G3 - Pre: 1255.48 ± 340.32; Post: 985.00 ± 323.98; p = 0.001 **TCR αβ:** G1 - Pre: 1209.76 ± 411.78; Post: 969.38 ± 473.59; p = 0.04 G2 - Pre: 1112.35 ± 355.27; Post: 820.70 ± 358.57; p = 0.00 G3 - Pre: 1203.64 ± 328.85; Post: 940.48 ± 308.83; p = 0.00 **TCR γδ:** G1 - Pre: 42.67 ± 25.96; Post: 43.05 ± 29.74; p = 0.95 G2 - Pre: 41.75 ± 47.66; Post: 35.00 ± 52.45; p = 0.14 G3 - Pre: 53.84 ± 66.48; Post: 45.80 ± 48.65; p = 0.12 **CD8+ T:** G1 - Pre: 359.67 ± 156.92; Post: 320.33 ± 208.24; p = 0.13 G2 - Pre: 339.40 ± 173.98; Post: 282.05 ± 152.28; p = 0.04 G3 - Pre: 369.84 ± 150.37; Post: 355.00 ± 170.71; p = 0.41 **CD4+ T:** G1 - Pre: 827.33 ± 317.86; Post: 562.86 ± 210.31; p = 0.001 G2 - Pre: 753.60 ± 259.90; Post: 488.75 ± 192.85; p = 0.001 G3 - Pre: 788.60 ± 199.43; Post: 558.60 ± 159.44; p = 0.001 **NK:** G1 - Pre: 230.14 ± 118.26; Post: 177.48 ± 118.05; p = 0.53 G2 - Pre: 182.65 ± 82.44; Post: 109.30 ± 42.30; p = 0.001 G3 - Pre: 188.76 ± 79.30; Post: 152.16 ± 99.20; p = 0.05 **B cells:** G1 - Pre: 191.81 ± 78.78; Post: 25.71 ± 33.09; p = 0.001 G2 - Pre: 172.70 ± 71.93; Post: 12.80 ± 11.07; p = 0.001 G3 - Pre: 183.20 ± 79.71; Post: 20.6 ± 20.08; p = 0.001	Not significant
Li et al. (2024)	Stage II–IV lung cancer patients	**12 weeks** • **G1:** exercise health education and exercise guidance (30 min daily brisk walking at RPE 13, 5 day/wk, and two resistance training sessions per week, each lasting 20 min • **G2:** general health education materials	• **N:** 38 • **G1:** 21 (14 ≤ 65y; 7 > 65y) • **G2:** 17 (8 ≤ 65y; 9 > 65y)	Adjuvant CTx	**Time points:** • Baseline • Mid-intervention • End of intervention	Eosinophil percentage (p = 0.668): Ø, Neutrophil to-lymphocyte ratio (NLR) (p = 0.543): Ø; Platelet-to-lymphocyte ratio (PLR) (p = 0.430): Ø	Eosinophil percentage (p = 0.985): Ø NLR (p = 0.167): Ø PLR (p =0.668): Ø

NK cells, Natural killer cells; PBMCs, Peripheral blood mononuclear cells; Th1/Th2 ratio, CD3+ T lymphocyte subset helper cell type 1/CD3+ T lymphocyte subset helper cell type 2; NSCLC, non-small cells lung cancer; CTx, chemotherapy; TCR, T-cell receptor; RCT, randomized controlled trial.

Table 4. Continue….

First Author, Year	Cancer	Intervention	Sample size (age, years)	Treatment	Collection Methods and Endpoints	Outcomes	
						Within-groups	Between-groups
Mijwel et al. (2020)	Breast cancer	• **16 weeks** • **G1**: 2x/wk, 60 minutes; 2-3 sets of 8–12 reps at @70-80% 1-RM; HIIT: 3x 3 min/1 min bouts at RPE 16 to 18 on a cycle ergometer. • **G2**: 2x/wk, 60 minutes; 20 min of MICT, 13-15 RPE; same HIIT as in G1 • **G3:** Usual care	• **N:** 206 • **G1:** 74 (52.7y) • **G2:** 72 (54.4y) • **G3:** 60 (52.6y)	Adjuvant CTx	**Time points:** • Baseline • End of intervention **Collection methods:** • Not described.	Not reported	**Thrombocyte concentration** • G1 > G3 (prior to 3rd CTx session) - 95% CI, 0.84 to 54.47 × 109/L; p = .04) • G1 > G3 (prior to the 5th session) - 95% CI, 3.78 to 57.62 × 109/L; p = .019 • G1 > G2 (prior to the 5th session) - 95% CI, 0.09 to 52.95 × 109/L; p = .05) **Concentrations** of: • Hemoglobin: Ø • Lymphocyte: Ø • Neutrophil: Ø **Incidence of thrombocytopenia** • G1 < G3 – G1 vs. G3: OR, 0.27; p = 0.03; G2 < G3 - G2 vs. G3: OR, 0.24; p = 0.01)
Chuang et al., (2017)	Non-Hodgkin Lymphoma	• **21-day, 2-3x/day** • **G1:** Chan-Chuang qigong intervention; 5min warm up, 15min main course and a 5min cool-down. • **G2:** Usual Care	• **N:** 96 • **G1:** 48 (55.85y) • **G2:** 48 (64.54y)	CTx	**Time points:** • Baseline • End of intervention **Collection methods:** • Beckman automatic blood analyser	Not reported	**White blood cell counts:** G1 - Pre: 4731.46 ± 2074.34; Post: 6478.33 ± 4222.05 G2 - Pre: 5482.29 ± 3460.63; Post: 4150.42 ± 2142.67 G1 vs G2 - t = 5.14, p < 0.001 **Platelet counts:** Ø
Zimmer et al. (2014)	Non-Hodgkin Lymphoma	• **30 min** • **G1 and G3:** 30 min on a bicycle ergometer at moderate intensity (13–14 RPE) immediately after t1. • **G2 and G4:** Usual care	• **N:** 36 (26 patients and 10 healthy controls) • **G1:** 14 • **G2:** 12 • **G3:** 5 • **G4:** 5 • **G1 and G2** (62.2y) • **G3 and G4** (56.6y)	CTx	**Time points:** • Baseline • Baseline plus 1h **Collection methods:** • Ficoll-based density-gradient centrifugation protocol • Magnetic-activated cell sorting.	ΔCD8H4K5: G1: ↑ (p = 0.041)	Not reported

NK cells, Natural killer cells; PBMCs, Peripheral blood mononuclear cells; Th1/Th2 ratio, CD3+ T lymphocyte subset helper cell type 1/CD3+ T lymphocyte subset helper cell type 2; NSCLC, non-small cells lung cancer; CTx, chemotherapy; TCR, T-cell receptor; RCT, randomized controlled trial.

Table 4. Continue….

First Author, Year	Cancer	Intervention	Sample size (age, years)	Treatment	Collection Methods and Endpoints	Outcomes	
						Within-groups	**Between-groups**
Fiuza-Luces et al. (2017)	Synovial sarcoma Ewing sarcoma Osteosarcoma Burkitt lymphoma Neuroblastoma Hodgkin lymphoma Diffuse large B-cell lymphoma T-cell lymphoblastic lymphoma Ganglioneuroblastoma	• **The mean duration of the exercise intervention: 17 (5) wks** • **G1:** 3x/wk; 60- to 70-min; inhospital; Aerobic training: 30 mins (60 to 70% max HR); resistance training: 30 mins (2 to 3 sets of 8-15 reps) • **G2:** Physiotherapy	• **N:** 20 • **G1:** 9 (11y) • **G2:** 11 (12y)	Neoadjuvant CTx	**Time points:** • Baseline • End of the treatment • 2 months after the end of the treatment **Collection methods:** • Multiparametric flow cytometry • Polymerase chain reaction	**Leukocytes -** G1 - Pre: 8.6 ± 1.3; Post: 5.8 ± 1.9; Detraining: 6.0 ± 3.5; G2 - Pre: 8.5 ± 1.6; Post: 6.2 ± 1.8; Detraining: 4.7 ± 1.2; p = 0.756 **T cells (%)** G1 - Pre: 67.4 ± 4.1; Post: 55.2 ± 5.5; Detraining: 53.4 ± 5.7; G2 - Pre: 50.5 ± 6.3; Post: 56.2 ± 7.7; Detraining: 57.2 ± 4.0; p = 0.933 **B cells (%):** G1 - Pre: 14.8 ± 2.9; Post: 8.1 ± 3.9; Detraining: 13.1 ± 4.5; G2 - Pre: 13.1 ± 2.4; Post: 3.5 ± 1.0; Detraining: 4.1 ± 1.5; p = 0.013 **NK cells (%):** G1 - Pre: 7.1 ± 2.0; Post: 16.9 ± 2.6; Detraining: 16.4 ± 3.5; G2 - Pre: 11.3 ± 2.5; Post: 14.5 ± 2.2; Detraining: 17.6 ± 2.2; p = 0.007 **NK cell cytotoxicity:** - **Ratio 8:1** G1 - Pre: 31.8 ± 5.0; Post: 22.6 ± 4.7; Detraining: 21.3 ± 4.3; G2 - Pre: 19.4 ± 4.0; Post: 9.7 ± 3.6; Detraining: 12.7 ± 5.4; p = 0.144 - **Ratio 4:1** G1 - Pre: 21.9 ± 4.0; Post: 17.5 ± 4.0; Detraining: 23.4 ± 2.3; G2 - Pre: 15.4 ± 3.1; Post: 13.0 ± 3.2; Detraining: 19.6 ± 5.9; p = 0.482 - **Ratio 2:1** G1 - Pre: 17.9 ± 3.9; Post: 14.0 ± 3.1; Detraining: 19.9 ± 2.7; G2 - Pre: 12.5 ± 2.4; Post: 11.2 ± 3.2; Detraining: 17.2 ± 5.0; p = 0.326 - **Ratio 1:1** G1 - Pre: 16.1 ± 4.0; Post: 11.1 ± 2.7; Detraining: 16.8 ± 2.7; G2 - Pre: 10.5 ± 1.3; Post: 10.5 ± 3.3; Detraining: 14.2 ± 4.7; p = 0.386	**Leukocytes:** Ø; p = 0.842 **T cells (%):** Ø; p = 0.611 **B cells (%):** Ø; p = 0.185 **NK cells (%):** Ø; p = 0.398 **NK cell cytotoxicity:** - Ratio 8:1 p = 0.038 - Ratio 4:1– p = 0.814 - Ratio 2:1 – p = 0.763 - Ratio 1:1 p = 0.717

NK cells, Natural killer cells; PBMCs, Peripheral blood mononuclear cells; Th1/Th2 ratio, CD3+ T lymphocyte subset helper cell type 1/CD3+ T lymphocyte subset helper cell type 2; NSCLC, non-small cells lung cancer; CTx, chemotherapy; T-cell receptor; RCT, randomized controlled trial.

Table 4. Continue….

First Author, Year	Cancer	Intervention	Sample size (age, years)	Treatment	Collection Methods and Endpoints	Outcomes	
						Within-groups	Between-groups
Ashem et al., (2020)	Breast Cancer (stage 1)	• **18 weeks, 3x/wk** • **G1:** Aerobic exercises (treadmill, cycle ergometer, or elliptical machine). 1st-6th wks, 60%VO_{2max}; 7-12wk, 70% VO_{2max}; 12th wk 80% VO_{2max}. 1st-3rd wks: 15min, increase 5min every 3 wk; 18th wk – 45min • **G2:** Usual Care	• **N:** 30 women • **G1:** 15 (45y) • **G2:** 15 (45.06y)	CTx	**Time points:** • Baseline • End of intervention Collection methods: • Phlebotomy	**Immunoglobulins IgA** G1 - Pre: 230.69 ± 7.33; Post: 255.74 ± 11.27; p = 0.0001 G2: Pre: 230.76 ± 7.31; Post: 225.38 ± 12.26; p = 0.112	**Immunoglobulin IgA** Pre: .98; Post: .0001
Ligibel et al. (2019)	Breast cancer	• **Meantime: 29.3 days** • **G1:** 60-90 min, 2x/wk; 30-45 min of at least moderate-intensity aerobic training; 20 min of resistance training; 10 min cool down and stretching. Total (supervised and unsupervised): 220 min/wk, 40 min of strength, and 180 min of MICT • **G2:** Mind-body control	• **N:** 48 (52y)/ 46 • **G1:** 26 (52.3y)/ 25 • **G2:** 22 (53.1y)/ 21	Scheduled for primary breast surgery	**Time points:** • Baseline • End of intervention **Collection methods:** • Radioimmunoassay • Automated chemistry analyzer • ELISA		**FOXP3+ cells** G1 - Pre: 0.44 ± 0.53; Post: 0.76 ± 1.42; G2 - Pre: 0.45 ± 0.77; Post: 2.68 ± 3.57; p = 0.08 **CD4+** G1 - Pre: 0.04 ± 0.05; Post: 36.57 ± 133.42; G2 - Pre: 0.36 ± 0.90; Post: 0.80 ± 0.82; p = 0.64 **CD56+: Ø** G1 - Pre: 1.86 ± 2.15; Post: 1.33 ± 2.34; p = G2 - Pre: 2.14 ± 3.94; Post: 0.90 ± 0.81; p = 0.53 **CD8+** G1 - Pre: 1.36 ± 1.38; Post: 1.60 ± 2.51; G2 - Pre: 1.43 ± 1.13; Post: 1.44 ± 2.08; p = 0.89 **CD163+** G1 - Pre: 5.85 ± 5.40; Post: 1.40 ± 1.32; G2 - Pre: 6.01 ± 7.85; Post: 1.14 ± 1.27; p = 0.85

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Table 4. Continue….

First Author, Year	Cancer	Intervention	Sample size (age, years)	Treatment	Collection Methods and Endpoints	Outcomes	
						Within-groups	Between-groups
Djurhuus et al. (2023)	Prostate cancer	• **2 to 8 weeks** • **G1:** 4x/wk; warm-up: 20-25 min of aerobic HIIT; stationary bicycle ergometer; 4-6 cycles of high-intensity intervals for 1 min at 100-120% Wpeak, followed by 3 min of active recovery at 30% Wpeak • **G2:** Usual care	• **N:** 30 • **G1:** 20 (63y) • **G2:** 10 (68y)	Undergoing radical prostatectomy	**Time points:** • Baseline • Follow up (before surgery) **Collection methods:** Immunohistochemical analysis	**Tumour NK cells** – G1 - Pre: 0.47 ± 0.48; Post: 2.07 ± 1.65; p = 0.004 G2 - Pre: 1.05 ± 1.37; Post: 1.49 ± 1.17; p = 0.396 **Healthy NK cells** – G1 - Pre: 0.62 ± 0.78; Post: 1.95 ± 1.48; p = 0.210 G2 - Pre: 4.15 ± 4.50; Post: 2.26 ± 1.59; p = 0.102	**Tumour NK-cell infiltration:** Ø (p = 0.114) **NK-cell infiltration in the healthy prostatic tissue:** G1 > G2 (p = 0.046)
Djurhuus et al. (2022)	Prostate cancer	• **Acute (one bout)** • **G1:** Peak power output (Wpeak) test followed by an HIIT bout; bicycle ergometer; warm-up 3 min at 70 W, increase of 20 W/min until exhaustion. 10 min active recovery at 30% of Wpeak; four HIIT cycles - 1 min at 100% Wpeak, and 3 min of active recovery at 30% of Wpeak. • **G2:** Usual Care	• **N:** 30 • **G1:** 20 (64y) • **G2:** 10 (65y)	Scheduled for radical prostatectomy	**Time points:** • Baseline • Immediately after the Wpeak test • Immediately after the last HI • 1h into the resting period Collection methods: • Immunohistochemistry **PT Link**	**Total blood lymphocyte count:** G1 - Pre: 1.6 ± 0.4; Post-W_{peak}: 3.7 ± 1.0; Post-exercise: 3.4 ± 1.1; Post-1h rest: 1.3 ± 0.3; p (Pre vs Post-W_{peak}) < 0.001 p (Pre vs Post-exercise) < 0.001 p (Pre vs Post-1h rest) < 0.001	**Tumor NK cell infiltration:** Ø (p = 0.328)
Hojan, (2016)	Prostate cancer	• **8 weeks** • **G1:** 5x/wk MICT; 50-55 min: 30 min aerobic exercise (brisk walking, running indoors or on a treadmill, or cycling); 15 min resistance exercises, 2 sets of 8 reps at 70-75% RM • **G2:** Usual care	• **N:** 55 (68.5y) • **G1:** 27 (67.4y) • **G2:** 28 (69.9y)	Scheduled ADT	**Time points:** • Baseline • End of the intervention **Collection methods:** • BD Cytometric Bead Array (CBA) Enhanced Sensitivity Flex Set • Flow Cytometer	**White blood cells** G1 - Pre: 7.09 ± 1.70; Post: 5.35 ± 1.43; G2 - Pre: 7.61 ± 1.70; Post: 5.68 ± 1.68; **Lymphocytes** G1 - Pre: 1.84 ± 0.58; Post: 1.17 ± 0.94; G2 - Pre: 2.10 ± 0.58; Post: 1.11 ± 0.43; **Platelets** G1 - Pre: 218.00 ± 55.71; Post: 208.30 ± 40.20) G2 - Pre: 237.29 ± 39.58; Post: 211.79 ± 42.99;	**Peripheral blood cell parameters:** Ø

NK cells, Natural killer cells; PBMCs, Peripheral blood mononuclear cells; Th1/Th2 ratio, CD3+ T lymphocyte subset helper cell type 1/CD3+ T lymphocyte subset helper cell type 2; NSCLC, non-small cells lung cancer; CTx, chemotherapy; TCR, T-cell receptor; RCT, randomized controlled trial.

Table 4. Continue….

First Author, Year	Cancer	Intervention	Sample size (age, years)	Treatment	Collection Methods and Endpoints	Outcomes	
						Within-groups	Between-groups
Rao et al. (2017)	Breast Cancer (stage IV)	• **12 wks** • **G1:** 60min, at least 2x/wk; integrated yoga-based stress: a set of asanas (postures done with awareness) breathing exercises, pranayama (voluntarily regulated nostril breathing), meditation, and yogic relaxation techniques with imagery reduction program. • **G2:** Education and supportive therapy sessions	• **N:** 91 (49.6y) • **G1:** 45 (48.9y) • **G2:** 46 (50.2y)	Undergoing radiotherapy	**Time points:** • Baseline • End of intervention **Collection methods:** Flow cytometer	**NK cell % -** G1 - Pre: 9.68 ± 4.28; Post: 11.32 ± 4.92; $p < 0.01$ G2 - Pre: 10.33 ± 5.61; Post: 8.73 ± 5.55; $p = 0.32$ **Absolute lymphocyte count** – G1 - Pre: 2016.05 ± 768.18; Post: 2041.26 ± 853.73 G2 - Pre: 1792.93 ± 997.22; Post: 1829.93 ± 797.73	**NK cell % -** G1 > G2: [F (1, 31) = 5.43, $p = 0.03$ **Absolute lymphocyte count:** Ø

NK cells, Natural killer cells; PBMCs, Peripheral blood mononuclear cells; Th1/Th2 ratio, CD3+ T lymphocyte subset helper cell type 1/CD3+ T lymphocyte subset helper cell type 2; NSCLC, non-small cells lung cancer; CTx, chemotherapy; TCR, T-cell receptor; RCT, randomized controlled trial.

Discussion

This systematic review provides an overview of the effect of different forms of exercise (i.e. aerobic, resistance, combined, and mind-body) on the cellular markers of the immune system in cancer patients and survivors. Overall, 8 out of 20 identified investigations reported that either aerobic, combined, or mind-body exercise can promote noticeable alterations in immune system markers when compared to the control group (Ashem et al., 2020; Chuang et al., 2017; Djurhuus et al., 2023; Fairey et al., 2005; Lee et al., 2022; Liu et al., 2015; Mijwel et al., 2020; Rao et al., 2017). Observed changes included increases in NK cell cytotoxicity, PBMC cytotoxicity, immunoglobulin A, white blood cell and lymphocyte counts, NK cell percentages, and NK-cell infiltration in healthy prostatic tissue. Some studies also showed differences in NK cell receptor expression, reporting increases in NKG2D+, an activating receptor that promotes cytotoxicity, and decreases in KIR2DL3, an inhibitory receptor that suppresses NK cell activity. NKT cells - a subset of T cells that express NK cell markers and mediate rapid immune responses - were also modulated in some interventions. Additionally, increases in DC11c+ cell expression were observed, likely representing dendritic cells involved in antigen presentation and immune activation. Increases in thrombocyte (platelet) counts were also observed; while not immune cells per se, platelets can influence inflammatory and immune processes. These findings suggest that exercise may modulate both innate and adaptive immune functions through multiple mechanisms.

The overall findings across all studies encompassed within this systematic review align harmoniously with existing scientific literature in adults with cancer, suggesting that each bout of exercise induces a transient increase in circulating immune cells and other components of the innate immune system when performed regularly (Nieman and Wentz, 2019). These changes are followed by systemic adaptations - including cytokine signaling, improved oxidative metabolism, and reductions in visceral fat - that collectively contribute to an anti-inflammatory and antioxidant effect over time, with the potential to modulate tumorigenesis (Nieman and Wentz, 2019). However, the extent and nature of this beneficial influence may vary depending on several key factors, including the type of cancer, timing of the intervention (before, during, or after treatment), the specific immune markers measured, participant characteristics, and exercise intervention (i.e., type of exercise, duration of the exercise intervention, whether the exercise was home-based or supervised). Understanding these moderating factors is essential for designing targeted exercise interventions that can more consistently enhance immune function in cancer patients.

Type of cancer

Among the studies reviewed, several different types of cancer were represented, including breast, prostate, colorectal, and lung cancer, which can significantly influence how the immune system responds to exercise. The immune system's response to exercise in these

different cancers can be quite variable, as the underlying pathology and treatment regimen differ widely. For example, patients with hematologic malignancies might respond differently to exercise interventions compared to those with solid tumors due to differences in baseline immune function and the impact of the disease on immune cell populations (Montironi et al., 2021). In studies focused on breast (Ashem et al., 2020; Fairey et al., 2005; Hagstrom et al., 2016; Lee and An, 2022; Ligibel et al., 2019; Mijwel et al., 2020; Nieman et al., 1995; Rao et al., 2017; Schmidt et al., 2018) and prostate cancer (Djurhuus et al., 2022; Djurhuus et al., 2023; Hojan et al., 2016), the exercise interventions showed mixed effects on immune markers, suggesting that the type of cancer could modulate the immune response to exercise. Patients with prostate cancer (Djurhuus et al., 2022, Djurhuus et al., 2023; Hojan et al., 2016) showed more consistent improvements in immune markers - particularly NK cell infiltration and immune cell recovery post-surgery - whereas studies in breast cancer (Fairey et al., 2005; Mijwel et al., 2020; Schmidt et al., 2018) reported more variable or blunted responses, especially during chemotherapy. One possible explanation is that prostate cancer patients were often studied in the pre- or post-surgical phase, when treatment-induced immunosuppression may be less severe (Tang et al., 2020), whereas many breast cancer trials involved concurrent chemotherapy or endocrine therapy, which are known to suppress lymphocyte function and alter immune recovery (Dixon-Douglas et al., 2024). Additionally, prostate cancer is more commonly associated with older male populations who may have greater capacity for thymic rebound after surgery or hormone therapy (Polesso et al., 2023), whereas chemotherapy-related toxicity in breast cancer may blunt immune cell function even when exercise is applied (Mackall et al., 1994).

In contrast, participants with lung or hematological cancers may present more pronounced treatment-related immunosuppression or systemic inflammation (Luo et al., 2023; Dhodapkar and Dhodapkar, 2015), potentially blunting the immune system's responsiveness to exercise. For instance, in hematologic malignancies, both the disease and its treatments can significantly impair immune function (Dhodapkar and Dhodapkar, 2015; Tang et al., 2023). However, exercise has been shown to favorably influence immune parameters in these patients, suggesting potential benefits (Sitlinger et al., 2020). Similarly, in lung cancer, exercise can modulate the tumor immune microenvironment by affecting inflammatory factors and immune cell activity, which may enhance anti-tumor immunity (Luo et al., 2023). Additionally, tumor-specific characteristics - such as immune cell infiltration, the metabolic and inflammatory tumor microenvironment, and the timing and type of immunosuppressive therapies - likely modulate how different cancer types respond to physical activity (Xia et al., 2021; Lim et al., 2020; Feng et al., 2024). Nonetheless, due to the limited number of studies focusing on each cancer type, definitive conclusions remain premature and warrant further investigation in larger, cancer-specific trials.

Timing of the intervention (before, during, or after treatment)

As shown in previous literature, exercise has the capacity to improve the function of the immune system by inducing favorable changes in both the innate (i.e., increased activity and mobilization of NK cells and neutrophils) and adaptive immune system (i.e., enhanced T lymphocyte function and proliferation, particularly CD4+ and CD8+ subsets) (Gustafson et al., 2021). However, certain cancer treatments may be responsible for a temporarily weakened immune system (Fairey et al., 2002), such as those who undergo radiotherapy (Wargo et al., 2015; Wasserman et al., 1989) or chemotherapy (Larsson et al., 2019). Chemotherapy suppresses immune function by reducing and inhibiting T-lymphocytes and NK cells, decreasing NK cell cytotoxicity, and promoting apoptosis (Gajewski et al., 2006; Schirrmacher, 2019; Sharma et al., 2023). Radiotherapy similarly disrupts immunity through inflammation, immune cell damage, and cytokine alterations (Wargo et al., 2015). Hormone therapy, such as androgen deprivation used in prostate cancer, can affect immune homeostasis but may promote thymic regeneration and naïve T cell production (Ben-Batalla et al., 2020; Hawley et al., 2023). Collectively, these immunosuppressive mechanisms may blunt the benefits of exercise during active treatment. Indeed, several studies included in this review involving participants undergoing chemotherapy (Ashem et al., 2020; Chuang et al., 2017; Fairey et al., 2005; Fiuza-Luces et al., 2017; Hagstrom et al., 2016; Lee et al., 2022; Lee and An, 2022; Mijwel et al., 2020; Schmidt et al., 2018; Zimmer et al., 2014) found that immune responses to exercise were often less pronounced (Fiuza-Luces et al., 2017, Schmidt et al., 2018; Zimmer et al., 2014), suggesting that although exercise may help attenuate certain treatment-related adverse effects, its impact on immune function may be limited during chemotherapy. By contrast, studies where exercise was performed before or after chemotherapy more consistently reported improvements in immune markers, suggesting that the timing of exercise in relation to treatment plays a crucial role, with post-treatment exercise showing the most robust immune-enhancing effects. In Hojan et al. (2016), despite the known immune-altering effects of androgen deprivation therapy (ADT), such as increased regulatory T cells and reduced effector T cell function, no significant improvements in immune markers were reported in this study. This may be due to the immunosuppressive effects of ADT counteracting the potential benefits of exercise, though the limited immune outcomes assessed also constrain interpretation.

Specific immune markers

The reviewed studies report a wide range of immune markers, including NK cell activity, white blood cell counts, and various lymphocyte subtypes. Among all immune cell types assessed in the included studies, NK cells emerged as prominently featured (Djurhuus et al., 2023; Fairey et al., 2005; Lee et al., 2022; Liu et al., 2015; Rao et al., 2017). Existing literature has demonstrated that the concentration of immune system cells in the circulation increases following an acute bout of exercise, with a more pronounced increment of NK cells than T and B cells (Idorn and Hojman, 2016). This differential response has been attributed to the higher density of β-adrenergic receptors present on the NK

cell membrane surface than on T and B cells, making them more sensible to the increased catecholamine levels seen during exercise (Idorn and Hojman, 2016). Catecholamine-induced signaling also facilitates the mobilization of other leukocyte populations - such as neutrophils, monocytes, and lymphocytes - into the bloodstream (Thomas et al., 2017). In the current review, studies by Chuang et al. (2017) and Lee and An (2022) reported increases in white blood cell and lymphocyte counts within the intervention group following exercise, while no changes were found against the controls. Given that transient immune cell mobilization is a well-established response to exercise, particularly mediated by catecholamine release, such within-group changes should be interpreted cautiously. Only a few studies in this review (e.g., Lee et al., 2022; Fairey et al., 2005) reported significant between-group improvements in immune markers, underscoring the need to evaluate exercise effects relative to usual care. This distinction is critical in RCTs, where between-group comparisons provide the most robust evidence of exercise-induced immune modulation (Mijwel et al., 2020; Rao et al., 2017).

To clarify the immune outcomes investigated, the most frequently assessed innate immune markers included NK cells ($CD16^+/CD56^+$), NKT cells, monocytes, neutrophils, and dendritic cells (e.g., $DC11c^+$). The adaptive immune markers most measured were $CD3^+$ T cells, $CD4^+$ helper T cells, $CD8^+$ cytotoxic T cells, T cell receptor (TCR) αβ and γδ subsets, and B cells. In addition to specific cell phenotypes, several studies evaluated broader functional immune endpoints, such as lymphocyte cytotoxicity or PBMC-mediated activity. Across studies, immune responses were assessed using different outcome types, which further contributes to variability. These included: (1) increases in immune cell counts in peripheral blood (e.g., NK cells, lymphocytes, monocytes); (2) changes in functional immune activity, such as NK cell cytotoxicity or PBMC-mediated lysis; and (3) immune cell infiltration into tumor tissue, as assessed in a smaller subset of studies (e.g., NK cell infiltration in healthy or cancer-affected tissue). This diversity in immune outcomes adds another layer of complexity when comparing studies and may partially explain the heterogeneity in reported effects.

Participant characteristics

The variability in immune outcomes across studies may also reflect differences in participant characteristics. Most studies identified primarily involved older adults. Older adults may experience age-related immunosenescence that could dampen the effects of exercise on immune markers (Weyand and Goronzy, 2016). In particular, the atrophy of the thymus, that is the organ responsible for producing new T lymphocytes, the loss of regulatory T and B lymphocytes, which are essential to help prevent autoimmunity, and an increase in systemic inflammation are key features of the aging immune system that can affect changes in PBMCs following exercise (Lazarus et al., 2019). However, it should be noted that none of the included studies directly assessed classical markers of immunosenescence, such as CD57 expression, $KLRG1^+$, or the loss of CD27/CD28 on T cells. Thus, any interpretation of immunosenescence is inferred based on participant age rather than on measured biomarkers. Furthermore, as discussed earlier, regular exercise has been shown to counteract some aspects of age-related immune decline (Lazarus et al., 2019), suggesting that older adults may still benefit from exercise interventions depending on individual characteristics and the prescription used.

Type of exercise

Across included RCTs, aerobic exercise interventions were associated with increases in NK cell cytotoxicity, NK cell infiltration, immunoglobulin A, and total leukocyte and lymphocyte counts (Ashem et al., 2020, Djurhuus et al., 2023; Fairey et al., 2005; Na et al., 2000). These effects were typically more pronounced in studies conducted post-treatment. Out of the different aerobic studies included, three did not demonstrate significant immune changes between-groups (Djurhuus et al., 2022; Mijwel et al., 2020; Schmidt et al., 2018). To understand the mechanisms underlying these differential effects, existing literature from healthy populations and preclinical models can be informative. These studies suggest that aerobic exercise positively influences several immune markers by enhancing both innate and adaptive immune cell responses (Goncalves et al., 2019), including increased NK cell mobilization, greater lymphocyte circulation, and elevated anti-inflammatory cytokine production, effects likely mediated through activation of the hypothalamic-pituitary-adrenal axis (Goncalves et al., 2019; Gustafson et al., 2021). When looking at animal models of cancer, mice that voluntarily wheel run experience favorable effects on tumor onset and development, which is accomplished by direct modulation of NK cells (Pedersen et al., 2016). This direct modulation of NK cells includes epinephrine-dependent mobilization of NK cells into the circulation and IL-6-dependent redistribution to tumors (Pedersen et al., 2016).

Resistance training has shown less consistent effects on immune markers compared to aerobic exercise. While some studies showed within-group improvements in $CD4^+$ and $CD8^+$ T cells or NK cell activity (Hagstrom et al., 2016), others found no between-group differences (Lee and An, 2022; Schmidt et al., 2018). Nonetheless, resistance exercise may have an impact on the immune system by increasing Th1, Th2, Th1/Th2 ratio, CD4+, and CD8+ (Lee and Jee, 2021). The limited number of studies may reflect challenges in standardizing resistance protocols in animal models, as they are more difficult to replicate and typically involve higher physical stress (Hornberger and Farrar, 2004), unlike aerobic training, which remains the more commonly studied modality (Koelwyn et al., 2017; Pedersen et al., 2016). The immunological impact of resistance exercise may depend on training load, intensity, and timing relative to treatment.

Combined exercise did not demonstrate clear additive effects beyond aerobic training alone. Some studies found improvements in thrombocyte and leukocytes count or NK-related outcomes (Lee et al., 2022; Mijwel et al., 2020), while others reported no significant changes (Fiuza-Luces et al., 2017; Hojan et al., 2016; Ligibel et al., 2019; Nieman et al., 1995).

Mind-body interventions such as Tai Chi, Qigong, and Yoga were generally implemented in the post-treatment phase and were associated with improvements in NK cell percentages, PBMC cytotoxicity, and white blood

cell counts (Rao et al., 2017; Liu et al., 2015; Chuang et al., 2017). Out of all investigations, there was one yoga intervention, one Qigong, and two Tai Chi interventions. Rao et al. (2017) demonstrated that a yoga-based intervention increased the percentage of NK cells in the intervention group, when compared to the control group, but both groups had no significant differences in absolute lymphocyte count. According to a pilot study, yoga may increase the number of CD4+ and CD8+ T cells, increase anti-tumor activity, and promote a better immune response (Kaushik et al., 2022). The Qigong intervention observed only a significant increase in white blood cell counts in the intervention group when compared with the control group, and no significant difference in platelet counts (Chuang et al., 2017). When looking at the two Tai Chi investigations, one analyzed the effect of Tai Chi on the balance between humoral and cellular immunity by measuring changes in immune cell populations and cytokine levels, with results suggesting only within-group results (Wang et al., 2013). The other Tai Chi investigation assessed the effect on the immune function, with data reporting that Tai Chi did not have significant alterations on the proliferation capacity of PBMC, but did demonstrate a significant impact in the cytotoxicity of PBMCs, the percentage of NK cells, and pre-post changes of NKT and DC11c between the exercise and control group (Liu et al., 2015). Previous evidence showed that, in a variety of cancers, the cytotoxicity of PBMCs is significantly reduced, when compared to non-cancer controls (Steinhauer et al., 1982; Imai et al., 2000). Physical exercise and Tai Chi may have the potential to stimulate PBMC cytotoxicity and thus, improve anti-tumor cellular function (Peters et al., 1994; Fairey et al., 2002). On this topic, evidence on PBMC proliferation is somewhat conflicting, with some studies reporting that exercise (and/or weight loss) causes a decrease (Lin et al., 1993; Nieman et al., 1998), no effect (Mitchell et al., 1996; Hayes et al., 2003) or an increase (Liu et al., 2015). In line with our findings, a systematic review on Tai Chi and Qigong on immune responses demonstrated that these interventions had a small effect on increasing the levels of innate and adaptive immune cells in both healthy adults and adults with different diseases (Oh et al., 2020).

Duration of intervention

The duration of exercise interventions varied widely across the included studies, ranging from a single acute session to 18 weeks of training. This heterogeneity in intervention length may explain some of the variability in immune outcomes. When looking at the current body of evidence, much of the acute effects of exercise on the immune system stem from healthy individuals (Kurowski et al., 2022). Short bouts of exercise induce a rapid, but transient effect on the immune system, including increased circulating neutrophils, monocytes, dendritic cells, CD4+ and CD8+ T lymphocytes, NK cells and CD3+ T cells (Campbell et al., 2009; Goncalves et al., 2019; Kurowski et al., 2022; Nieman and Wentz, 2019). Our systematic review only identified two studies with acute exercise (Djurhuus et al., 2022; Zimmer et al., 2014). In Zimmer et al. (2014), results suggested an increase in histone acetylation levels of H3K9 in CD8+ T cells in the intervention group. This epigenetic modification is associated with increased chromatin accessibility and transcriptional activity, potentially supporting enhanced expression of genes related to immune function and cytotoxicity (Araki et al., 2008). While this finding suggests a possible mechanism of immune activation at the molecular level, the present review focuses on cellular immune markers, and such molecular outcomes fall outside its primary scope. In the other study (Djurhuus et al., 2022), the results showed an increase in total blood lymphocyte count during the exercise bout, which decreased below the baseline value after 1h of rest in the intervention group. Furthermore, no significant differences were found in tumor NK cell infiltration in the intervention group when compared with the control group (Djurhuus et al., 2022). Thus, the results from the two studies in this systematic review are in line with previous studies in healthy individuals, yet not all expected outcomes previously identified were demonstrated.

The contrast between acute and chronic interventions also reflects important biological differences. Acute exercise can trigger transient changes in circulating immune cells, such as mobilization of NK cells and lymphocytes, largely mediated by catecholamine release (Idorn and Hojman, 2016; Nieman and Wentz, 2019). However, these effects are short-lived and may not reflect sustained immune adaptation. In contrast, longer-term interventions allow for the accumulation of physiological adaptations - such as improved cardiorespiratory fitness, anti-inflammatory effects, and changes in immune cell function - that may be necessary to observe meaningful shifts in immune markers (Gustafson et al., 2021; Lazarus et al., 2019). For example, aerobic training over several weeks has been associated with enhanced NK cell function and reduced chronic inflammation in both clinical and healthy populations (Gustafson et al., 2021; Idorn and Hojman, 2016). Without sufficient length, some interventions may not allow time for measurable or lasting immune responses to develop. Future trials should more clearly distinguish between acute and chronic exercise effects and consider intervention duration as a key factor in study design and interpretation.

Supervised vs home-based interventions

Additionally, the distinction between home-based and supervised exercise interventions is significant. Supervised exercise, often conducted in clinical or gym settings, typically offers better adherence and intensity control (Gómez-Redondo et al., 2024; Lacroix et al., 2017), while home-based approaches, though more accessible and sustainable for patients, may also suffer from lower adherence and variable intensity (Gómez-Redondo et al., 2024; Lacroix et al., 2017). These differences may potentially explain the mixed outcomes observed in studies utilizing these interventions. Supervised interventions demonstrated more robust immune responses compared to some of the home-based interventions or interventions with an unsupervised exercise component (Ligibel et al., 2019), where adherence and intensity were less rigorously monitored. In this review, nine studies explicitly reported supervised interventions (Djurhuus et al., 2023; Fairey et al., 2005; Fiuza-Luces et al., 2017; Hagstrom et al., 2016; Lee et al., 2022;

Liu et al., 2015; Mijwel et al., 2020; Schmidt et al., 2018; Zimmer et al., 2014), while several others were home-based or partially unsupervised (e.g., (Chuang et al., 2017; Na et al., 2000; Rao et al., 2017)). The different degrees of supervision across studies may have influenced both adherence and the magnitude of immune outcomes observed.

Study quality and risk of bias considerations

In this systematic review, the risk of bias across the included randomized controlled trials was generally low to moderate. Nearly half of the studies were rated at low risk of bias across domains related to outcome measurement, missing data, and reporting. However, concerns were more frequent in the domains of randomization and deviations from intended interventions, which are known challenges in exercise oncology trials. Approximately one-third of the studies were judged at high overall risk of bias, often driven by issues with randomization procedures or intervention adherence. These methodological issues could have contributed to variability in immune outcomes observed across studies. While most studies demonstrated robust outcome assessment and minimal missing data, future trials should prioritize transparent randomization methods and detailed intervention reporting to minimize potential biases and strengthen the reliability of findings in exercise-oncology research.

Strengths and Limitations

To the best of our knowledge, this is the first systematic review to comprehensively assess the effects of exercise on immune system markers in cancer patients and survivors. A major strength of this review was the exclusive inclusion of RCTs, since this type of investigation is the most scientifically rigorous way of testing hypotheses and is the gold standard trial for assessing the efficacy of interventions. Moreover, this review looked at more than just the conventional forms of exercise (aerobic, resistance, or combined), we also assessed the effect of mind-body interventions on immune system markers, which is a growing trend when it comes to exercise interventions in cancer patients. Nevertheless, this study is not without limitations. First, there was considerable heterogeneity across studies in terms of cancer types, treatment stages, exercise modalities and duration, and immune markers assessed. This variability limits the comparability of results and precludes drawing firm conclusions about the effects of exercise on immune function across all cancer populations. Lastly, interventions that did not consist solely of exercise (e.g., exercise plus diet) were excluded to focus solely on the effect of exercise on this population. However, it is possible that important data and information is missing by not including these other investigations. Although the last point may be a limitation, it can also be a strength in this study since diet can have an impact on the immune system and, thus, would confound our ability to understand if alterations in the immune system were derived from the exercise, from the diet or a combination of the two.

Conclusion

Evidence on the impact of aerobic, resistance, combined, and mind-body exercise on the immune system in cancer patients and survivors remains limited, with only 8 out of 20 studies reporting significant between-group effects, most notably in response to aerobic and mind-body interventions. Future high-quality studies are needed involving diverse types, intensities, and durations of physical exercise in patients with different cancer types during distinct cancer phases and stages of treatment.

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Key points

- Exercise interventions, including aerobic, combined, and mind-body exercises, appear to have positive effects on immune system markers in cancer patients and survivors, such as increases in NK cells and other immune parameters.
- Only 8 out of 20 studies demonstrated significant effects of exercise on immune system, highlighting the variability and limited nature of the evidence.
- Factors such as exercise type, intensity, timing relative to cancer treatment, and the type of cancer influence immune outcomes.
- The review underscores the need for more high-quality RCTs exploring diverse exercise modalities and their effects on immunity in different cancer phases.

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