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Effects of Exercise during Chemo- or Radiotherapy on Immune Markers: A Systematic Review

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Abstract

Introduction: Patients with cancer receiving radio- or chemotherapy undergo many immunological stressors. Chronic regular exercise has been shown to positively influence the immune system in several populations, while exercise overload may have negative effects. Exercise is currently recommended for all patients with cancer. However, knowledge regarding the effects of exercise on immune markers in patients undergoing chemo- or radiotherapy is limited. The aim of this study is to systematically review the effects of moderate- and high-intensity exercise interventions in patients with cancer during chemotherapy or radiotherapy on immune markers. ***Methods:*** For this review, a search was performed in PubMed and EMBASE, until March 2023. Methodological quality was assessed with the PEDro tool and best-evidence syntheses were performed both per immune marker and for the inflammatory profile. ***Results:*** Methodological quality of the 15 included articles was rated fair to good. The majority of markers were unaltered, but observed effects included a suppressive effect of exercise during radiotherapy on some pro-inflammatory markers, a preserving effect of exercise during chemotherapy on NK cell degranulation and cytotoxicity, a protective effect on the decrease in thrombocytes during chemotherapy, and a positive effect of exercise during chemotherapy on IgA. ***Conclusion:*** Although exercise only influenced a few markers, the results are promising. Exercise did not negatively influence immune markers, and some were positively affected since suppressed inflammation might have positive clinical implications. For future research, consensus is needed regarding a set of markers that are most responsive to exercise. Next, differential effects of training types and intensities on these markers should be further investigated, as well as their clinical implications.

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Introduction

Yearly, millions of people are diagnosed with cancer worldwide; in 2020, over 18 million new cases were reported [1]. Both the disease and common treatments such as chemotherapy and radiotherapy can have significant negative impact on daily functioning and quality of life [2, 3]. People with cancer undergo many immunological stresses during their treatment trajectory. These include immunosuppressive effects induced by malignant cells in the tumor microenvironment, cancer-related systemic inflammation, and immunosuppressive effects of cancer treatments such as chemotherapy- or radiotherapy-induced leukopenia or neutropenia [4, 5]. At the same time, a well-functioning immune system is important both for physical recovery and prevention of cancer cell proliferation and metastasis [6].

In healthy people, regular exercise is associated with better immune functioning, shown by lower risk of infections or development of malignant tumors [7, 8]. Possible underlying mechanisms include improved glycemic and lipid profiles, which could counteract systemic inflammation [9, 10]. At the same time, it is expected that high exercise workloads may have a negative effect on immune parameters [11]. Immunological effects of exercise during cancer treatment are of special interest because the right type and dose of exercise are expected to improve health outcomes after cancer treatment [12].

Exercise during cancer treatment is recommended because this can improve cardiorespiratory fitness and muscle strength, which in turn are associated with faster recovery after major surgery, shorter hospital stay, longer survival, and smaller chance for tumor recurrence [12–14]. Knowledge regarding the effects of exercise during cancer treatment on immunological markers is limited.

A systematic review in 2013 found no effect of exercise on various immune cell types such as leukocytes and leukocyte subsets, although some studies did report increases in cell numbers [15]. Furthermore, pro- and anti-inflammatory cytokines were generally unaltered by exercise. It should be noted that the number of studies assessing each parameter was limited and results were not consistent, which indicates that an updated review is needed. A recent review on the effects of exercise on inflammatory markers in survivors of breast cancer showed that exercise reduced several pro-inflammatory markers [16]. It is not known to what extent these results can be translated to patients undergoing immunosuppressive therapies such as chemotherapy and radiotherapy. Therefore, the goal of the current systematic review is to investigate the effects of exercise interventions during chemotherapy or radiotherapy on immune markers.

Methods

A systematic literature search was conducted in the electronic databases of PubMed and EMBASE, until March 2023. PRISMA guidelines and reporting guidelines for synthesis without meta-analyses (SWiM) were adhered [17, 18]. Publications were included when they met the following inclusion criteria:

- Participants aged ≥18 years and diagnosed with cancer
- Intervention study, including a period (at least 2 weeks) of exercise training
- Exercise intervention of moderate intensity or higher because the relationship between exercise and immune function was shown to be intensity-dependent [11]. This way, studies will be more comparable. If intensity was not defined in terms of "moderate," "high" or "strenuous" by the authors, the following definition was used:
  - Aerobic exercise above 46% of VO2max, or above 64% maximum heart rate (HR) or BORG ≥12 on a scale of 6–20 or a similar measure [19]
  - Resistance exercise: ≥50% of one repetition maximum (1RM) [19]
- Exercise intervention took place during chemotherapy or radiotherapy
- Effects of the intervention on one or more immune markers were assessed. Based on most common markers in the current literature, the following selection of immune markers was made: absolute and relative cell counts of leukocytes, neutrophils, lymphocytes, thrombocytes, CD3+, CD4+, CD8+, CD16+/CD56+, and CD4+/CD69+ cells, immune cell functioning (cell cytotoxicity, degranulation or proliferation) immunoregulatory cytokines IL-1β, IL-6, IL-8, IFN-γ, TNF-α, leptin, CRP, IL-1ra, IL-10, and immunoglobulin A (IgA) [15, 20, 21]
- Full text available in English

Studies were excluded when analyses were conducted on animal models or when they involved caloric restriction or dietary interventions targeting specific essential nutrients because these might influence immune markers.

Search strings included the key terms "immune marker," "exercise," "cancer," and synonyms and corresponding MeSH Terms in PubMed (online suppl. Material 1; for all online suppl. material, see https://doi.org/10.1159/000534390). Articles were first screened on title and abstract; thereafter, duplicates were removed from this first selection. A second screening on eligibility criteria was performed based on full texts. Reference lists of related articles were checked for additional studies that met the eligibility criteria. Two authors (R.H.H.P. and A.M.S.H.) independently performed the literature search and article selection, and afterward, differences in the selection were discussed until consensus was reached on a final selection. In case of disagreement, a third author (J.J.D. or K.V.) screened the publication in question, and the three authors discussed until consensus was reached.

Data Extraction

From all included full texts, the following information was extracted: participant characteristics (sex, mean age, cancer type), timing of intervention with regard to treatment, type of intervention, and results regarding immune markers.

Assessment of Methodological Quality

A.H. and R.P. independently assessed the risk of bias of all included articles. Differences were discussed until consensus was reached. In case of a persisting disagreement, a third researcher was consulted (J.J.D. or K.V.) in order to reach consensus.

Risk-of-bias studies with a randomized controlled trial (RCT) design were assessed using the PEDro tool [22, 23]. This tool comprises eleven questions regarding possible risk of bias, which were answered by "+" (criterium satisfied; low risk of bias), "–" (criterium not satisfied; increased risk of bias), or "?" (unknown risk of bias/information not given in article). A total score is calculated by taking the sum of satisfied criteria. Following the guidelines of the tool, the item "eligibility criteria" is not taken into account in this calculation. Scores of 0–3 are considered "poor," 4–5 "fair," 6–8 "good," and 9–10 "excellent."

Risk of bias of other studies was reviewed using the NIH Quality Assessment Tool for Before-After Studies with No Control Group [24]. This tool comprises twelve items questions, which were also answered with a "+", "–," or "?". The overall quality of the study (good/fair/poor) was assessed subjectively by both assessors based on the number of possible risk-of-bias factors and the severity of risk of bias. Next, the two assessors discussed until consensus was reached on a final rating.

Synthesis of Results

The heterogeneity in study characteristics and outcome measures did not allow for a meta-analysis. Therefore, SWiM guidelines were adhered for synthesis without meta-analysis [17]. Since chemotherapy and radiotherapy may differentially affect immune markers, the studies were first grouped by the type of treatment that participants received, and evidence was reviewed per subgroup.

Strength of evidence for an effect of the intervention was assessed via a best-evidence synthesis as proposed by van Tulder et al. [25] for each immune parameter. This synthesis takes into account methodological quality, consistency of findings, and statistical significance of findings. Strength of evidence was classified as follows:

- Strong evidence: consistent findings among multiple high-quality randomized controlled trials
- Moderate evidence: consistent findings among multiple low-quality RCT and/or clinical controlled trials (CCTs) and/or one high-quality RCT
- Limited evidence: one low-quality RCT and/or CCT
- No evidence: no RCTs or CCTs

Effects with a p level <0.05 were deemed significant. Similar to earlier systematic reviews, results were considered consistent when at least 75% of the studies showed results in the same direction [26].

Furthermore, a best-evidence synthesis was performed on the inflammatory profile, i.e., taking into account all measured pro- and anti-inflammatory cytokines per study. This synthesis was performed because inflammation does not depend on a single cytokine but can be affected by any disbalance in cytokine levels. For this synthesis, an effect on the inflammatory profile was assumed when the authors of the study concluded that exercise significantly affected inflammation.

Results

Selection Procedure

Figure 1 shows the selection procedure. The initial search in PubMed and EMBASE resulted in 4,661 hits. Screening of titles and abstracts on inclusion and exclusion criteria resulted in a selection of 148 articles, of which 61 duplicates were removed. 87 full-text articles were screened for eligibility. Of these, 5 reports were not retrieved, and 67 were excluded for not meeting the inclusion criteria. The most common reason for exclusion was timing of the intervention (n = 38). In all of these cases, the onset of the exercise intervention was after completion of the cancer treatment. Screening of reference lists of these articles did not yield additional results, and a final selection of 15 articles was included in the review.

Study Characteristics

Characteristics of the selected studies are presented in Table 1. Eight studies included patients with breast cancer [27–34]. Other study populations were patients with prostate cancer [35, 36], testicular germ cell cancer [37], leukemia [38], or different solid tumors [39–41]. In total, our selection contained eleven randomized controlled trials [27–33, 35–37, 42], two pilot RCTs [34, 39], one pre-post noncontrolled experimental study [38], and one randomized trial with a 2 × 2 factorial design [40].

Exercise interventions comprised either a resistance exercise training [31, 33, 37] or aerobic training [27, 30, 31, 34, 41] or a combination of the two [28, 29, 35, 36, 38–40]. One study combined data from a resistance training intervention and a combined resistance and aerobic training intervention [32]. Exercise intensity of six interventions was moderate-to-high [27, 32–34, 39, 41] and three studies performed high-intensity exercise interventions [28, 29, 40]. Six studies performed moderate-intensity exercise interventions [30, 31, 35, 36, 41, 37].

Seven studies compared one exercise intervention with usual care/no intervention [27, 30, 34–37, 39, 41]. Three studies compared two different exercise interventions with a control group [28, 29, 31], and one compared an intervention group with a healthy reference intervention group and a control group [37]. In some cases, the authors explicitly stated that usual care did involve exercise

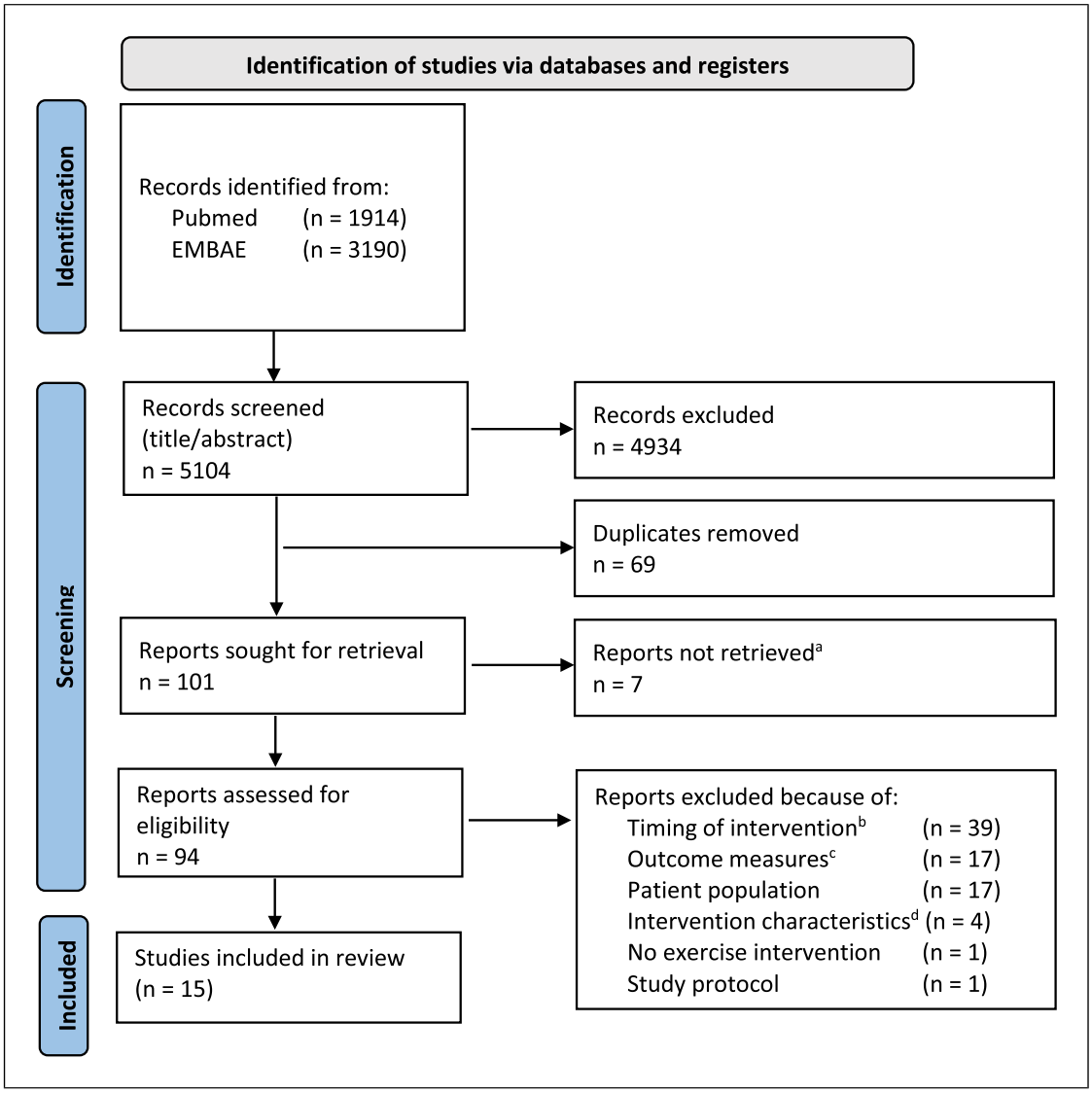

Fig. 1. Flowchart indicating article selection procedure [22]. [a]In all of these cases, only congress abstract was available. [b]The exercise intervention started >6 months after completion of cancer treatment. [c]No outcome measures of interest. [d]For example, no moderate- or high-intensity exercise or exercise was combined with dietary intervention such as caloric restriction.

recommendations [28, 29, 31, 36]. Two studies offered a muscle relaxation program to the control group [32, 33], and in one study, the effects of a light-intensity exercise program were compared with those of a moderate-to-high-intensity program [40].

The assessed immune markers in the studies that were taken into account in the synthesis were the following: absolute and relative (in %) amounts of several cell subsets, e.g., leukocytes, thrombocytes, CD3+, CD4+, CD8+, CD16+/CD56+, cell functioning in terms of NK cell degranulation levels and cytotoxicity, cytokines IL-1β, IL-6, IL-6/IL-1ra ratio, IL-8, IFN-γ, TNF-α, leptin, CRP, IL-1ra, IL-10, and immunoglobulin A (IgA).

Methodological Quality

Methodological quality of the studies was judged as good [27, 29, 31, 33–37, 40, 41] or fair [28, 30, 32, 38, 39] (Table 2, 3). In none of the studies, it was possible to blind

Table 1. Study characteristics

Author (year)	Design	*N*	Cancer type(s)	Timing and duration of intervention	Group	Mean age, years	Intervention and control characteristics	Supervised training	Exercise intensity of intervention
Toffoli et al. [39] (2021)	Pilot RCT	14	Breast or colon cancer	During chemotherapy	Intervention, *n = 8*	55.1 (14.8)	Resistance and aerobic training	Yes	MOD-to-HI
				9–12 weeks	Control, *n = 6*	60.7 (7.6)	Usual care (delayed intervention)	–	–
				2x/week					
Febvey-Combes et al. [27] (2021)	RCT	58	Breast cancer	During chemotherapy	Intervention, *n = 40*	53.8 (10.9)	Aerobic training and nutritional counseling	Yes	MOD-to-HI
				2x/week and after chemotherapy 3x/week	Control, *n = 18*	48.9 (11.1)	Nutritional counseling and exercise recommendations	–	–
Schauer et al. [40] (2021)	Randomized trial	394[a]	Breast, prostate, and colorectal cancer	During primary adjuvant cancer treatment	Intervention 1, *n = 189*	59 (12)	Aerobic training and resistance training	No	HI
					Intervention 2, *n = 188*	59 (12)	Aerobic training and resistance training	No	LO-to-MOD
Hiensch et al. [28] (2020)	RCT	240	Breast cancer	During chemotherapy	Intervention 1, *n = 79*	52.2±10.1	Resistance training & HIIT	Yes	HI
Mijwel et al. [29] (2020)				16 weeks	Intervention 2, *n = 80*	53.9±7.4	Moderate-intensity aerobic training & HIIT	Yes	MOD + HI
				2x/week	Control, *n = 81*	52.9±10.1	Usual care: Information about PA	–	–
Ashem et al. [30] (2020)	RCT	30	Breast cancer	During chemotherapy	Intervention, *n* = 15		Aerobic exercise training	Yes	MOD
				5 months 3x/week	Control, *n* = 15		No exercise intervention	–	–
Schmidt et al. [31] (2018)	RCT	81	Breast cancer	During chemotherapy	Intervention 1, *n* = 21	53.0±12.5	Resistance training	Yes	LO
				12 weeks	Intervention 2, *n* = 20	56.0±10.2	Endurance training	Yes	MOD
				2x/week	Control, *n* = 26	54.0±11.2	Usual care: Information about feasibility and impact of physical activity	–	–
van Vulpen et al. [32] (2018)	RCT	130	Breast cancer	During chemotherapy (+radiotherapy)	Intervention, *n* = 64	50.8±9.1	Pooled data of PACT: resistance and aerobic training + unsupervised PA	Yes	MOD-to-HI
							BEATE: resistance training	Yes	MOD-to-HI
				18 weeks, 2x/week supervised + 3x/week unsupervised (PACT) or 12 weeks, 2x/week (BEATE)	Control, *n* = 66	52.3±9.3	Progressive muscle relaxation	–	–

Table 1 (continued)

Author (year)	Design	*N*	Cancer type(s)	Timing and duration of intervention	Group	Mean age, years	Intervention and control characteristics	Supervised training	Exercise intensity of intervention
Hojan et al. [35] (2017)	RCT	72	Prostate cancer	During radiotherapy and ADT 12 months 5x/week during RT 3x/week after RT	Intervention, *n* = 36	65.7±6.3	Aerobic and resistance exercise training	Yes	MOD
					Control, *n* = 36	67.9±4.9	Usual care	–	–
Hojan et al. [36] (2016)	RCT	54	Prostate cancer	During radiotherapy (start 1 week before) 8 weeks 5x/week	Intervention, *n* = 27	65.7±6.2	Aerobic and resistance training	Yes	MOD (aerobic) + HI (resistance)
					Control, *n* = 27	67.9±4.9	Usual care: standard advice regarding daily PA. Instructed not to start any formal exercise programs while during the study	–	–
Glass et al. [41] (2015)	RCT	44	Solid tumors	During cytotoxic therapy and synthetic erythropoietin 12 weeks 3x/week	Intervention, *n* = 21	56±10	Aerobic training	Yes	MOD-to-HI
					Control, *n* = 23	54±11	Usual care	–	–
Schmidt et al. [33] (2016)	RCT	103	Breast cancer	During adjuvant radiation therapy 12 weeks 2x/week	Intervention, *n* = 80	57.1±8.9	Group-based resistance exercise training (BEST study)	Yes	MOD-to-HI
					Control, *n* = 49	57.3±8.8	Relaxation training	–	–
Christensen et al. [37] (2014)	RCT	49	Testicular germ cell cancer	During chemotherapy 9 weeks 3x/week	Intervention, *n* = 15	35.8±8.9	Resistance training	Yes	MOD
					Control, *n* = 15	34.4±7.6	Usual care[b]	–	–
					Healthy reference, *n* = 19	31.5±6.0	Resistance training	Yes	MOD
Jones et al. [34] (2013)	Pilot RCT	20	Breast cancer	During neoadjuvant chemotherapy 12 weeks 3x/week	Intervention, *n* = 10	51.0±6.0	Aerobic exercise training	Yes	MOD-to-HI
					Control, *n* = 10	46.0±11.0	No exercise program	–	–
Battaglini et al. [38] (2009)	Clinical trial, pre-post design	10	Leukemia	During chemotherapy 5–7 weeks 3–4x/week	Intervention, *n* = 10	35.7±8.9	Resistance and aerobic training	Yes	MOD

RCT, randomized clinical trial; CCT, controlled clinical trial; LO, low intensity; MOD, moderate intensity; HI, high intensity; MOD-to-HI, moderate-to-high intensity; MOD + HI, combined intervention of moderate and high intensity; –, not applicable; ?, not specified. [a]From this initial group, eventually 377 included. [b]Usual care group was allowed to participate in usual care exercise programs.

all participants or therapists due to the nature of the intervention. Blinding of assessors was the least reported: 9 out of 18 used blinded assessors [28, 29, 31, 34–37, 40, 41]. The variability in reporting of methodological aspects was large; for example, one study was judged to be of fair quality because of five items that were not met, though all methodological aspects were described in detail [28]. Another study was judged to be of fair quality because five items were not reported at all and two items were not met [30]. In four studies, all items on the PEDro checklist were reported [28, 31, 35, 36].

Synthesis of Results

Effects on the inflammatory mediators are shown in Table 4 and effects on leukocytes, leukocyte subsets, and lymphocyte subsets are shown in Table 5. More detailed information regarding the effect sizes can be found in online supplementary Material 2.

Effects of Interventions during Chemotherapy

Eleven studies assessed the effects of an intervention during chemotherapy [27–32, 34, 37–39, 41]. Two of these conducted analyses based on data from the same clinical trial [28, 29]. One study included patients undergoing chemotherapy, radiotherapy, and endocrine treatment and performed a subgroup analysis on patients undergoing chemotherapy [40]. The results of the subgroup analyses were included in the current synthesis because endocrine treatment was an exclusion criterium.

Inflammatory Cytokines

Nine of our selected studies investigated the effect of exercise on plasma inflammatory cytokines during chemotherapy treatment [27, 28, 32, 34, 37–41]. Pro-inflammatory markers generally increased over the course of radiotherapy and chemotherapy treatment in all patients. Anti-inflammatory markers either increased, decreased, or remained stable. There was no effect of exercise on most markers, shown with strong evidence (IL-6, IL-8, IFN-γ, TNF-α, CRP, IL-10), moderate evidence (IL-1ra), or limited evidence (IL-6/IL-1ra ratio). Conflicting evidence was found for an effect of exercise on IL-1β and leptin.

Cell Numbers

Three studies investigated the effect of exercise on immune cell counts or percentages during chemotherapy [29, 31, 41]. Immune cell numbers generally decreased over the course of chemoradiotherapy in all patients. Moderate evidence was found for a suppressive effect of exercise on the decrease of thrombocytes. Furthermore, moderate evidence was found for no effect on other leukocyte subtypes (CD3, CD4, CD8, CD16/CD56, % CD4, %CD8, CD16/56).

Cell Functioning

One study found preserved NK cell degranulation levels and cytotoxicity in the exercise group versus decreased degranulation and cytotoxicity in the control group [39] (data not shown in the table). Since this study was of fair quality and the authors stated the results should be interpreted as hypothesis-generating instead of hypothesis-testing, the evidence for this effect was limited.

Immunoglobulins

One study assessed immunoglobulin A (IgA) [30] (data not shown in the table). After the intervention, IgA was significantly higher in the AT group compared to the control group ($p < 0.001$), indicating a positive effect of the aerobic exercise intervention on IgA. This single study of fair quality provides limited evidence for a positive effect of exercise on IgA.

Effect on Inflammatory Profile during Chemotherapy

From the nine studies investigating the effect of exercise on plasma inflammatory cytokines during chemotherapy treatment, four studies concluded that exercise significantly influenced inflammation [28, 34, 40, 41]. This was shown by a suppressive effect of exercise on the increase of pro-inflammatory cytokines IL-6 [28], TNF-α [40, 41], IL-1b [34], or CRP [40]. The conclusion regarding an effect on inflammatory cytokines by Schauer et al. [40] was based on a p value >0.05 ($p = 0.053$ for TNF-a and $p = 0.101$ for CRP) and therefore not identified in our synthesis per individual marker. Four studies concluded that exercise does not significantly affect inflammation [27, 32, 37, 39]. One study observed a marginally significant decrease ($p = 0.059$) in IL-6 over time in the exercise group but did not compare with a control group [38]. Overall, conflicting evidence exists for the effect of an exercise intervention during chemotherapy on the inflammatory profile.

Effects of Interventions during Radiotherapy

Inflammatory Cytokines

Three studies investigated the effect of exercise on inflammatory cytokines during radiotherapy [33, 35, 36]. Moderate evidence was found for no effect on TNF-α

Table 2. Assessment of methodological quality by the PEDro quality assessment tool (for controlled trials and randomized controlled trials)

	1. Eligibility criteria	2. Random allocation	3. Allocation concealment	4. Similar groups at baseline	5. Blinding subjects[a]	6. Blinding therapists[a]	7. Blinding assessors	8. Measures assessed >85% of initial group	9. Treatment as allocated, or intention to treat analyses	10. Between-group comparison	11. Point measures and measures of variability	Overall rating
Toffoli et al. [39] 2021	+	+	?	+	–	–	?	–	+	+	+	Fair
Schauer et al. [40] 2021	+	+	+	+	–	–	+	+	+	+	+	Good
Febvey-Combes et al. [27] 2021	+	+	+	+	–	–	?	+	+	+	+	Good
Hiensch et al. [28] 2020	+	+	+	–[b]	–	–	+	–[c]	–[c]	+	+	Fair
Mijwel et al. [29] 2020	+	+	+	?	–	–	+	–	+	+	+	Good
Ashem et al. [30] 2020	+	+	?	?	–	–	?	?	?	+	+	Fair
Schmidt et al. [31] 2018	+	+	+	+	–	–	+	–	–	+	+	Good
van Vulpen et al. [32] 2018	+	+	?	+	–	–	?	–	+	+	+	Fair
Hojan et al. [35] 2017	+	+	+	+	–	–	+	+	+	+	+	Good
Hojan et al. [36] 2016	+	+	+	+	–	–	+	+	+	+	+	Good
Glass et al. [41] 2015	+	+	?	+	–	–	+	+	+	+	+	Good
Schmidt et al. [33] 2016	+	+	+	?	–	–	?	+	+	+	+	Good
Christensen et al. [37] 2014	+	+	?	+	–	–	+	+	?	+	+	Good
Jones et al. [34] 2013	+	+	+	?	–	–	+	+	+	+	+	Good

[a]Blinding of participants and therapists was not possible in any of the studies due to the nature of the intervention. [b]Women in the RT-HIIT group were significantly more physically active at baseline compared to the UC group. [c]Only blood samples from participants who attended ≥60% of exercise sessions were analyzed; this was less than 50% of the participants at baseline.

and IL-1ra, and strong evidence was found for no effect on IL-1β. Strong evidence was found for a suppressive effect of exercise on the increase of IL-6 during radiotherapy because two high-quality studies identified a significant suppressive effect [33, 35] and the third high-quality study identified a difference in a similar direction, although this was not significant. Lastly, based on one high-quality study, moderate evidence was found for a suppressive effect of exercise on the increase in IL-6/IL-1ra ratio [33].

Cell Counts

One good-quality study investigated the effects of an exercise intervention during radiotherapy, on white blood cells and lymphocyte counts [36]. Leukocyte and lymphocyte counts decreased significantly both in the exercise group and in the control group ($p < 0.05$) [36]. No significant differences between groups were identified, resulting in moderate evidence for no effect of exercise during radiotherapy on white blood cell counts.

Effect on Inflammatory Profile during Radiotherapy

Three good-quality studies concluded that exercise had a suppressive effect on inflammation. This was indicated by a smaller increase in pro-inflammatory cytokine IL-6 [33, 35, 36] and IL-6/IL-1ra ratio [33], although the between-group effect was not significant in one study [36]. This provides strong evidence for a suppressive effect of exercise during radiotherapy on inflammation.

Discussion

This systematic review investigated the evidence for the effects of exercise on immune markers in patients undergoing chemo- or radiotherapy. Results show that exercise had no effect on most inflammatory cytokines, although for some cytokines, the evidence was conflicting. Treatment-dependent differences were seen since exercise during radiotherapy had a suppressive effect on pro-inflammatory cytokines (strong and moderate evidence), while this was not shown during chemotherapy. There was limited evidence for a preserving effect of exercise during chemotherapy on NK cell degranulation levels and cytotoxicity. Exercise during radiotherapy had no effect on total leukocyte count and leukocyte subsets (moderate evidence), while a suppressive effect of exercise during chemotherapy on the decrease in thrombocytes was seen (moderate evidence). Lastly, limited evidence was found for a positive effect of exercise during chemotherapy on IgA.

Table 3. Quality assessment by the NIH Quality Assessment Tool for before-after (pre-post) studies with no control group [28]

	1. Study objective	2. Eligibility criteria	3. Participants representative for population of interest	4. All eligible participants enrolled	5. Sufficient sample size	6. Intervention clearly described and delivered consistently	7. Outcome measures prespecified, clearly defined, valid, reliable and assessed consistently	8. Assessors blinded to intervention	9. <20% loss to follow-up, accounted for lost to follow-up in analyses	10. Pre-post changes statistically examined and *p* values provided	11. Interrupted time-series design	12. In case of intervention at group level; individual-level data taken into account	Overall rating[a]
Battaglini et al. 2009 [38]	+	+	+	?	?[b]	+[c]	+	?[d]	–	+	+	NA	fair[e]

[a]Following the NIH guideline, the researchers provide a rating (good, fair, or poor) based on all items and the severity of risk of bias. [b]Assessing effects on cytokines was not the primary aim of the study, and therefore no sample size calculation was performed for this analysis. Small sample size was opted by the authors as reason for absence of significant effects. [c]Intervention is clearly described, although adherence is not mentioned. [d]An oncology nurse, who was a member of the research team, collected the samples. It is not mentioned whether the laboratory personnel were blinded. [e]There were some serious risks of bias because of missing information in the research article and high percentage of loss to follow-up.

Table 4. Effect of exercise interventions on inflammatory mediators

Author (year)	Effect measure	Group	Pro-inflammatory soluble cytokines							Anti-inflammatory soluble cytokines		
			IL-1β	IL-6	IL-6/IL-1ra	IL-8	IFN-γ	TNF-α	leptin	CRP	IL-1ra	IL-10
Interventions during chemotherapy												
Toffoli et al. [39] (2021)	Pre-post change	RT&AT		↑								
		Control		–								
Febvey-Combes et al. [27] (2021)	Pre-post change	AT		↑				↑	↓			
		Control		↑				↑	↓			
Schauer et al. [40] (2021)	Pre-mid TER	RT & AT HI	–	↑		↑		↑[a]		–[a]		–
		RT & AT LMI	–	↑		↑		↑		↑		–
	Mid-post TER	RT & AT HI	–	↓		–		↓		↓		–
		RT & AT LMI	–	↓		–		↓		↓		–
	Pre-post TER	RT & AT HI	–	–		–				–		–
		RT & AT LMI	–	–		↑		↑		–		–
Hiensch et al. [28] (2021)	Pre-post ES	RT&HIIT	–	–[b]			–	↑				–
		AT&HIIT	–	–			–	↑				↓
		Control	–	↑			–	↑				↓ –
van Vulpen et al. [32] (2018)	Pre-mid TER	RT & AT		–	–			–	–	–	–	
		Control		–	–			–	–	–	↑	
	Pre-post TER	RT & AT		↑	↑			–	–[b]	–	–	
		Control		↑	–			–	–	–	–	
	Pre-follow-up TER	RT & AT		↓	↓			–	–	↓	–	
		Control		–	–			–	–	–	–	
Glass et al. [41] (2015)	Pre-post change	AT	–	–		–	–	–[b]			–	–
		Control	–	–		–	–	↑			–	–
Christensen et al. [37] (2014)	Pre-wk3 change	RT		↑		–	–	–				–
		Control		↑		↑	–	–				↑
	Pre-wk6 change	RT		–		↑	–	–				–
		Control		–		↑	–	–				↑
	Pre-wk9 (post) change	RT		↑		↑	–	–				↑
		Control		↑		↑	–	–				↑
	Pre-wk21 change	RT		–		–	↑	–			–	
		Control		–		-	–	–				–
Jones et al. [34] (2013)[d,e]	Pre-wk6 change	AT	↓[c]	–		-	–	–				–
		Control	↑	–		–	–	–				–
	Pre-wk12 (post) change	AT	↓[c]	–		–	–	–				–
		Control	↓	–		–	–	–				–
Battaglini et al. [38] (2009)	Pre-mid change	AT & RT		–			–					–
	Mid-post change	AT & RT		–			–					–

Author (year)	Effect measure	Group	Best-evidence synthesis									
			conflicting evidence	strong evidence for no effect	limited evidence for no effect	strong evidence for no effect	strong evidence for no effect	strong evidence for no effect	conflicting evidence	strong evidence for no effect	moderate evidence for no effect	strong evidence for no effect
Interventions during radiotherapy												
Hojan et al. [35] (2017)	Pre-post mean change	AT & RT	↑	↑[c]				↑				
		Control	↑	↑				↑				
	Post-follow-up mean change	AT & RT	–	–[c]								
		Control	–	–								
Hojan et al. [36] (2016)	Pre-post mean change	AT & RT	↓	↑				↑				
		Control	↑	↑				↑				
Schmidt et al. [33] (2016)	Adj. mean change pre-post	RT		↑[b]	↑[b]						↓	
		Control		↑	↑						↓	
Best-evidence synthesis			Strong evidence for no effect	Strong evidence suppressive effect of exercise	Moderate evidence suppressive effect of exercise	–	–	Moderate evidence for no effect	–	–	Moderate evidence for no effect	–

Gray areas indicate between-group differences. IL, interleukin; IL-1ra, IL-1 receptor antagonist; IFN, interferon; CRP, C-reactive protein; RT, resistance training; AT, aerobic training; HIIT, high intensity interval training; ES, effect size; TER, treatment-effect ratio; AT-mod, aerobic training moderate intensity; AT-low, aerobic training low intensity. ↑: within-group increase, but significance not assessed (only mixed group-time effects assessed); ↓: within-group decrease, but significance not assessed (only mixed group-time effects assessed); ↑: significant within-group increase ($p < 0.05$); ↓: significant within-group decrease ($p < 0.05$); –: not significant. [a]Authors indicate significant between-group difference; change over time is different compared to the control group. It is not indicated as significant difference here because $p > 0.05$. [b]Significant between-group difference; change over time is different compared to control group. [c]Group-interaction effect between exercise and control group regarding multiple measures over time.

Inflammatory Cytokines

Our results were only partly in line with an earlier review, where strong evidence was found for no effect of exercise on inflammatory markers in patients with cancer [15]. The current review confirmed that exercise did not have an effect on the majority of inflammatory markers. However, exercise during radiotherapy suppressed some pro-inflammatory cytokines. In another recent review (2021), strong evidence was found for a reduction in pro-inflammatory markers in breast cancer survivors [43]. A possible explanation for these differences could be the interfering effect of ongoing systemic cancer treatments. For example, the review in 2013 included a more heterogenous population, including patients receiving hormone therapy or stem cell transplantation. In the current study, we focused on patients receiving chemotherapy or radiotherapy and mainly found effects in patients undergoing radiotherapy. Possibly, chemotherapy treatment induces such severe systemic effects, where the effects of exercise are insufficient to counteract these.

Since increased inflammation has been linked to various comorbidities and worse clinical outcomes, it is relevant to further investigate a potential suppressive effect of exercise on inflammation. Generally, pro-inflammatory markers increased over the course of chemo- and radiotherapy [28, 32, 33, 35–37, 39–41]. This review showed that moderate- and high-intensity exercises did not further increase inflammation, and interventions during radiotherapy had a suppressive effect on pro-inflammatory markers. While acute inflammation is a functional response to counteract internal or external stressors and induce recovery, chronic inflammation can be harmful: inflammation plays a role in initiation, promotion, and progression of cancer [44]. Furthermore, higher levels of pro-inflammatory cytokines have been associated with several symptoms such as cancer-related fatigue [45]. Therefore, exercise-induced suppression of inflammation could be a promising treatment strategy to counteract morbidity and mortality in patients undergoing radiotherapy.

Effects on Cell Counts – A Dose-Response Relationship?

The finding that leukocytes and leukocyte subsets were mostly unaltered by exercise is in line with an earlier review [15], although a recent study investigating the effect of resistance training during radiotherapy found a significant protective effect of exercise on the decrease in total leukocytes [46]. The latter study was excluded from the current review because exercise intensity was not specified. Since reviews of the literature have described a dose- and type-dependent effect of exercise on the immune system, a possible explanation for the discrepancies might be that only specific combinations of intensity and type of training may affect cell counts [47]. It was not possible to compare the effects of different exercise intensities because the number of studies assessing this was too small. This should be further investigated by future studies comparing different exercise protocols.

The current review did show a protective effect of exercise during chemotherapy on the decrease in thrombocytes. Besides their role in clot formation, thrombocytes have important immunoregulatory functions, both via pro- and anti-inflammatory pathways. Activated platelets can stimulate dendritic cells to secrete IL-10 and stimulate monocytes to secrete IL-8. Furthermore, thrombocytes can secrete IL-1, which stimulates acute-phase reactants, fever, and adhesion molecules. Since the effect of exercise on thrombocytes was only assessed in a single study, this effect and its clinical implications should be further investigated.

Effect on Cell Functioning

In line with the earlier review by Kruijsen-Jaarsma et al. [15], a preserving effect of exercise during chemotherapy on NK cell degranulation levels and cytotoxicity was found, although evidence was limited [15]. Improved NK cell degranulation and cytotoxicity may be clinically relevant for patients with cancer since NK cells participate in the early defense against both virally infected cells and tumor cells [48]. Assessment of cell functioning has been less common in previous research compared to the assessment of cell counts or cytokine levels. However, the results until now have been promising. A recent review underlined the potential role of exercise as a prophylactic strategy in the management of neutropenia during chemotherapy [49]. They argued that exercise training rather resulted in enhanced neutrophil functions such as augmented phagocytic and migration capacity and reactive oxygen production, instead of an increase in cell numbers. Since the immune system is a responsive system, the capacity of the immune system might be shown best in response to stressors or other stimuli [50].

No Negative Effects of Exercise

Earlier research concluded that too high workloads might negatively impact the immune system [11, 51]. Although it is difficult to define negative impact based on immune parameters, examples of possible negative effects could be increased inflammation or decreased cell functioning compared to the control group. Interestingly, this review shows that in none of the studies, negative effects were seen. This suggests that in studies concerning moderate exercise intensity as well as high-intensity

Table 5. Effect of exercise on cell counts and percentages

Author (year)	Effect measure	Group	Leuko	Thrombo	CD3	CD4	CD8	CD16/56	%CD4	%CD8	%CD16/56
Interventions during chemotherapy											
Mijwel et al. [29] (2020)	Between-group difference Week 3 of chemo	RT & HIIT versus control		RT & HIIT > control							
	Between-group difference Week 5 of chemo			RT & HIIT > control							
	Thrombocytopenia incidence	RT&HIIT AT&HIIT Control		11%[a] 10%[a] 30%							
Schmidt et al. [31] (2018)	Mean pre-post change	RT AT Control			– ↓ ↓	↓ ↓ ↓	– ↓ –	– ↓ –			
Glass et al. [41] (2015)	Mean pre-post change	AT Control							– –	– –	– –
Best-evidence synthesis			–	Limited evidence for suppressive effect of exercise on decrease	Moderate evidence for no effect	Moderate evidence for no effect	Moderate evidence for no effect	Moderate evidence for no effect	Moderate evidence for no effect	Moderate evidence for no effect	Moderate evidence for no effect
Interventions during radiotherapy											
Hojan et al. [36] (2016)	Mean pre-post change	AT & RT Control	↓ ↓	– –							
best-evidence synthesis			Moderate evidence for no effect	Moderate evidence for no effect							

Leuko: leukocytes; thrombo: thrombocytes. Gray areas indicate between-group differences. ↑: significant within-group difference (increase); ↓ significant within-group difference (decrease); –: not significant. [a]Significant between-group difference compared to the control group.

exercise, the total workload was not too high to induce negative effects; for example, because frequency and duration of the training were correctly tuned (NB total workload is a combination of intensity, frequency, and duration of exercise).

Limitations

Some limitations of the current review should be addressed. First, it could not provide a complete overview of all supposedly relevant immune markers responsive to exercise. The immune system is a complex interplay of cells, tissues, and signaling molecules, and, to date, there is no consensus on the most suitable set of markers. In order to be able to compare the results between studies, a selection of the most common markers was chosen for this review. This has improved the interpretability of the data, although it has also limited the richness of data. A challenge for future research is to determine the right set of markers to detect functionally or clinically relevant immune changes. Second, immune functioning is the result of the interaction between many signaling molecules and cells working in functional pathways. Perhaps studying cells or signaling molecules that are functionally connected in an immunological pathway could provide more information in future research.

Third, in order to select a broader range of articles, the type of control group was not specified in the eligibility criteria, and we did not select based on type of cancer or physical fitness of the participants. This increased heterogeneity in study characteristics, which limits comparability between studies. Studies had different control interventions; some compared with usual care, some with a relaxation intervention, and some compared different exercise intensities. Furthermore, some studies explicitly stated that people in the usual care group were allowed to participate in usual care exercise. It can be expected that exercise recommendations have been part of usual care in other studies as well since the beneficial effects of exercise during cancer treatment are well known. Since patients cannot be blinded for group allocation in an exercise intervention study, this could have motivated control group patients to be more physically active, leading to an underestimation of the effect of the exercise intervention.

Conclusion

This review showed that moderate- and high-intensity exercise during cancer treatment only influenced a few of the assessed immune markers. Still, the assessed effects are promising: exercise during radiotherapy had a suppressive effect on the increase of some pro-inflammatory markers and a preserving effect on thrombocytes and on natural killer cell degranulation and cytotoxicity. These effects may indicate improved immune functioning. Interestingly, no negative effects of exercise on immune markers were assessed, both after moderate-intensity exercise as well as high-intensity exercise. For many immune markers, evidence is still conflicting or limited. For future research, consensus is needed regarding a set of markers that are most responsive to exercise, and these could perhaps be assessed in the context of their functional pathways. Second, more research is needed regarding the differential relationship of various types of exercise and different exercise workloads on immune markers in patients undergoing cancer treatment. This knowledge is needed to optimize exercise guidelines during chemo- or radiotherapy with the ultimate goal to improve clinical outcomes after treatment.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

All authors declare no conflict of interest.

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Author Contributions

All authors (A.M.S.H., K.V., J.J.D., C.A.M.K., J.P.R., R.V., and R.H.H.P.) have substantially contributed to this research article, were involved in the study design and interpretation of the results, contributed to revisions of the article, approved the final version to be published, and all authors agree to be accountable for all aspects of the work. A.H. and R.P. performed the data collection and initial analysis. A.M.S.H., R.H.H.P., K.V., and J.J.D. were involved in discussions until consensus was reached regarding the data collection and analysis. A.M.S.H. wrote the draft article.

Data Availability Statement

For original data of the studies included in this review, we kindly refer to the corresponding authors of the studies. All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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