Effects of Exercise on Immune Function in Patients with Cancer: a Systematic Review

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Abstract

Background *The role of exercise therapy in the rehabilitation of cancer patients and survivors is becoming increasingly important as it is thought to modulate immunity and inflammation. More knowledge about the effects of exercise on immune function in these patients is needed. Our aim is to systematically review changes in immune parameters after acute and chronic exercise in cancer patients.*

Results *Of the 3586 retrieved articles, 21 met the inclusion criteria, and were included in this systematic review. The systematic search yielded 18 articles in adults, and three in children. Six were of low methodological quality, mainly due to lack of blinding of the assessor and high drop-out rates. The effect of chronic exercise on immune function was examined in 18 studies, while two studies evaluated the effects of acute exercise, and one study combined acute and chronic exercise. Following exercise, increases were seen in Natural Killer cytotoxic activity, as well as lymphocyte proliferation and the number of granulocytes. The number of leukocytes, lymphocytes, Natural Killer cells, T lymphocytes, C-reactive protein, and pro- and anti-inflammatory mediators remained stable.*

Limitations *Of the 21 included studies, only three were conducted in the pediatric population, and many studies have included small and heterogeneous samples. Due to the large variety in exercise training protocols and immune parameters, no meta-analysis has been performed.*

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Conclusions *Various immune parameters improved after exercise; however, knowledge of the effects of exercise on immune function in cancer patients is still limited. Additional research is needed to gain insight into the mechanism underlying the effects of exercise on immune function in different populations, and to link these immune parameters to clinical outcomes.*

Key words: Neoplasms, Exercise training, Immune system, Inflammation

Background

In 2008, approximately 3.2 million new cases of cancer have been reported in Europe (18), and currently there are more than 11 million cancer survivors in the US alone (28). Due to improving survival rates, more focus is now placed on post-treatment care as it relates to the adverse short- and long-term effects of cancer and its treatment, including increased fatigue, increased susceptibility to infections due to immunosuppression, reduced physical fitness and lower quality of life (21, 58, 64). Pediatric cancer survivors are also exposed to adverse consequences of treatment on growth and development, including diminished neurological function, altered endocrine function, osteoporosis and obesity (65). Moreover, both pediatric and adult cancer survivors are at an increased risk of disease recurrence or development of a secondary malignancy (17).

In the more recent field of 'exercise – oncology' studies have shown that moderate intensity exercise (e.g. 60% VO_{2peak}) is associated with increased survival rates in breast cancer patients, and/or a reduced risk of postmenopausal breast cancer as a result of favorable changes in body-fat and sex hormone profiles (28, 43, 45). As cancer is a complex disease, multiple mechanisms are operative. The individual characteristics, type of exercise, as well as the cancer diagnosis and stage determine which mechanisms may play a role. Possible beneficial effects of exercise on cancer outcomes are the reduced obesity and adipokine concentrations, reduced levels of insulin, glucose, and sex hormones, increased intestinal motility, decreased inflammation (22), and immunostimulation (5, 22, 41, 42, 47, 58). However, the clinically relevant cut-off points of the exercise-induced immuno-inflammatory response are still largely unknown within cancer. Various factors mediate the relationship between exercise, inflammation and immune function, such as catecholamines and cortisol (22, 45, 51, 52, 60, 63). Both the incidence of cancer and the impairment of the immune system also show negative age-related changes that can partially be counteracted with exercise (6, 31). Furthermore, weight loss by dietary and exercise interventions can partially reverse obesity-related metabolic, endocrinal and inflammatory alterations (14, 45, 47, 51).

These effects, however, will often depend on the type of exercise and its duration. Several authors have proposed an 'Inverted J Hypothesis', where an enhanced immune function and low susceptibility to cancer occur with regular moderate exercise, whereas sedentariness and exhaustive exercise suppress immune func-

tion, and elevate susceptibility to infections (7, 17, 40-42, 52, 60). This is supported by results of animal studies, where exercise-trained animals exhibited a lower inflammatory state compared with the sedentary animals (11, 54). On the other end of the spectrum, it has been reported that, compared with low intensity exercise, high intensity exercise can induce a pro-inflammatory state and higher oxidative DNA damage, both of which are hypothesised to be markers of infection and cancer recurrence (22, 56, 58, 63).

It is indicated that chronic exercise training reduces inflammation in patients with chronic inflammatory diseases, whereas single bouts of exercise elicit a worsened inflammatory response, especially in the more severely affected patients (50). Although exercise-induced alterations in immune function are generally short-lived, changes may accumulate over time (60), making it crucial to identify the optimal 'exercise dose' since the main objective in treating patients with chronic inflammatory disease or cancer is either to suppress inflammation when it is elevated (50) or to boost the immune surveillance when it is compromised (17). Exercise seems to have the most beneficial effects on host defence and disease susceptibility or severity if the individual has a compromised immune function (63).

Potentially relevant immunological biomarkers are the number of neutrophils, Natural Killer (NK) cells, T lymphocytes, and/or their regulating cytokines. Also NK cytotoxic activity (NKCA) and the function of neutrophils, lymphocytes and monocytes represent innate and acquired immune components that play an important role in the defense against tumor cells. The aims of this review are to 1) evaluate the changes in immune parameters after acute and chronic exercise in cancer patients, 2) provide a systematic and comprehensive review of the existing literature examining exercise training and immune function in cancer survivors, and 3) offer a critical analysis of this literature and outline directions for future research.

Methods

Literature search

A systematic literature search was performed in Pubmed (Medline), Embase, Cochrane Library and CINAHL (until April 2011). Titles and abstracts were retrieved and screened by two independent reviewers (MKJ, DR). Additionally, the reference lists of all identified reviews were scanned manually. The search strategy used consisted of a combination of database-specific MeSH terms, free text, 'wild cards' (words truncated by using ''*'') and Boolean operators (''AND'', ''OR'', ''NOT''). The detailed search strategy was performed with the following words: Exercise, Motor activity, Sports, Immunity, Leukocytes, Natural killer cells, C-Reactive protein, Interleukins, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, Macrophages, Neoplasms, Immunoproliferative disorders, Tumours, Malignancies.

Inclusion criteria of studies

- Study design: randomized and non-randomized controlled and uncontrolled interventions.

- Participants: cancer patients without any age restriction.
- Interventions: acute or chronic aerobic and/or resistance exercise.
- Outcome measures: all parameters of immune function (e.g. cytokines, mediating proteins, cell counts and functions).

Articles were excluded when multiple interventions were described, if they were case reports, or if they were written in a language other than English.

Definitions

In this review a distinction was made between acute and chronic exercise interventions. Acute exercise was defined as a single bout of exercise followed by assessment of immunological parameters. Chronic exercise was repeatedly performed in the form of an exercise training programme. Aerobic training exercise was defined as exercise that requires the heart and lungs to work harder to meet the increased demand of the body's oxygen needs. Examples include running, cycling and swimming. Other studies described resistance training that works to increase muscle strength and endurance by doing repetitive isometric, isotonic, or isokinetic exercises to strengthen or develop the muscles.

Studies were defined as being either randomized controlled trials (RCT), nonrandomized controlled trials (NCT), and other designs (OD), i.e. pre-post tests without controls.

Quality assessment

Two independent reviewers (MKJ, DR) assessed the methodological quality of the articles using a modified PEDro scale based on the scale utilized by Ploeger et al. (8, 50). Nine criteria were evaluated and scored as either yes, no, not applicable or unclear. Among these were: 1) Blinding of the assessor(s); 2) less than 15% drop-out during the study; 3) between group comparison; 4) proper description of the exercise protocol, defined as reporting of the frequency, intensity and duration of the exercise; 5) sufficient exercise training intensity, defined as a training program in which exercise was performed at ≥40% of the patient's VO_{2peak}, for at least two sessions per week, and at least 30 minutes per session, or at least 50% of their maximum voluntary contraction for resistance training exercise; 6) sufficient acute exercise intensity, defined as exercise at ≥40% of their VO_{2peak} for at least 10 minutes, or at least 50% of their maximum voluntary contraction; 7) reliable measurement methods, defined by proper description of methodology, and no microbead immunoassay to detect cytokines; 8) blood sampling was considered sufficient when samples were taken at least before and after exercise; 9) result reporting was sufficient when means and standard deviations were reported in the studies. Studies were considered to be of high quality if at least 75% of the criteria were scored positively.

Data analysis

Study and patient characteristics, and baseline, post-test, and follow-up data of outcome measures were extracted from the studies. Data analysis was performed separately for studies performed in the pediatric and adult populations, as well as for acute and chronic exercise interventions. A large degree of heterogeneity was expected with regard to patient population (e.g. disease characteristics, age cate-

gories, treatment severity), interventions (e.g. timing, duration, intensity, frequency), and outcome assessments (e.g. methods, timing, presentation of results), making it impossible to perform quantitative meta-analyses. As such, we have formulated a best-evidence synthesis – as proposed by Van Tulder et al. (62) – by assigning different levels of evidence to the effects of exercise on immune parameters, while taking into account the methodological quality and the statistical significance of the findings. Evidence was classified as being:

- Strong; defined as consistent, statistically significant findings in outcome measures in at least two high quality RCTs.
- Moderate; defined as statistically significant findings in outcome measures in at least one high quality RCT, and at least one low quality RCT, or high quality NCT.
- Limited; defined as statistically significant findings in outcome measures in at least one high quality RCT, or at least two high quality NCTs.
- Indicative; defined as statistically significant findings in at least one high quality NCT or low quality RCT, or at least two high quality ODs.
- No evidence; defined as study results that do not meet the criteria for one of the above-mentioned levels of evidence.

Outcome measures

Immune parameters were divided into four categories: leukocyte types, lymphocyte subsets, immune cells functions and the soluble inflammatory mediators (Table 1).

Table 1: Overview of immune parameters divided into four categories

1. Leukocyte types	
Leukocytes, lymphocytes, monocytes, granulocytes, neutrophils, basophils, eosinophils, dendritic cells	
2. Lymphocyte subsets	
CD 3^+ T lymphocytes, $CD4^+$ or $CD8^+$ T lymphocytes, $CD4^+/CD8^+$ ratio, $CD19^+$ or $CD20^+$ B lymphocytes, $CD25^+$ or $CD122^+$ T lymphocytes, $CD56^+$ NK, NK T lymphocytes	
3. Immune cell functions	
NK cytotoxic activity, neutrophil oxidative burst, lymphocyte proliferation or cytolytic activity, lymphocyte activation ($CD69^+$)	
4. Soluble inflammatory mediators	
Pro-inflammatory cytokines	Intercellular Adhesion Molecule 1, IL-1α, IL-1β, IL-6, sIL-6R, IL-8, Interferon-γ, Monocyte chemotactic protein-1, Macrophage Inflammatory Protein-1α, TNF-α, soluble glycoprotein 130 (IL-6 receptor)
Anti-inflammatory cytokines	IL-1ra, IL-1ra/IL-1β ratio, IL-1ra/IL-6 ratio, IL-1ra/TNF-α ratio, IL-4, IL-10, sTNF I/II, Transforming growth factor-β1
C-reactive protein	

CD = Cluster of differentiation; IL = Interleukin; NK = Natural Killer cells; R = Receptor; RA = Receptor antagonist; sIL = soluble interleukin; TNF = Tumor necrosis factor

Results

Retrieved articles and screening

In total, 3586 articles were identified during the systematic search. After screening of titles, abstracts and full texts, 21 relevant articles were included in this review (Figure1).

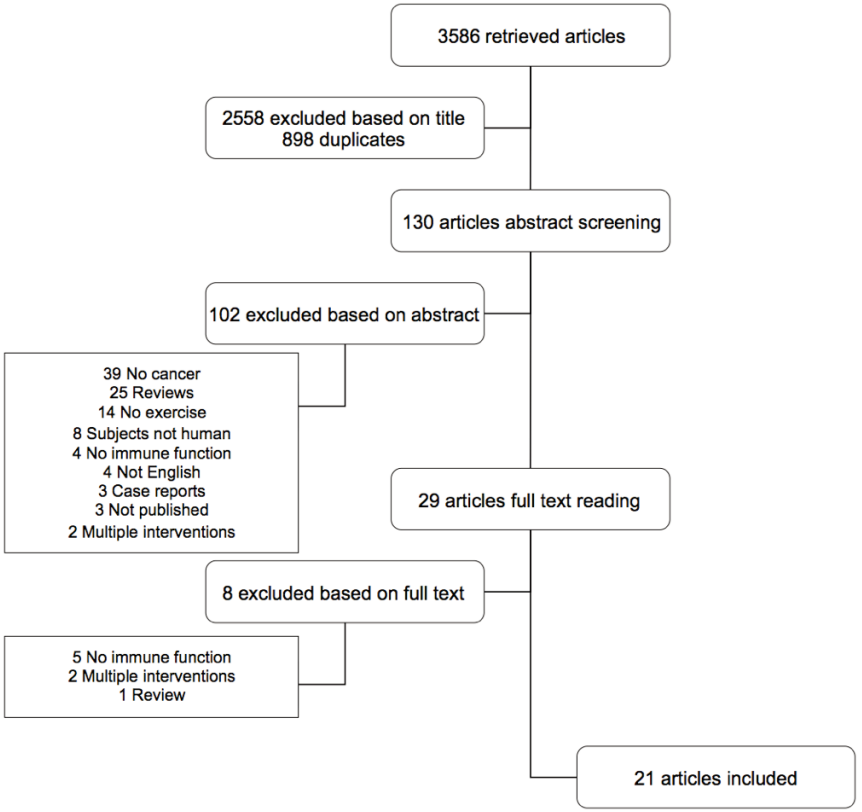

Figure 1: This flowchart shows the in- and exclusion of studies in this systematic review.

Characteristics of the included studies

A total of 10 RCTs, six NCTs and five ODs were identified. Three of the 21 included studies were focused on the pediatric population (9, 37, 57), and 18 on adult cancer patients (1, 4, 13, 15, 16, 19, 20, 25, 26, 30, 32, 35, 36, 44, 46, 48, 49, 59). Only three studies measured the effects of an acute bout of exercise (19, 32, 37), whereas the majority of studies reported the effects of chronic exercise. Only one study has applied resistance training (19), whereas aerobic training has been applied by 11 studies (1, 13, 15, 16, 30, 32, 35-37, 44, 48, 49), and a combination of resistance and aerobic training by eight studies (4, 9, 20, 25, 26, 46, 57, 59).

Table 2: Patient and disease characteristics of the included studies

Primary author	N	Sex	Cancer diagnoses	Disease stage	Age (Mean±SD, or Median;range)	Current treatment protocol	Timing of intervention
Acute exercise in children							
Ladha et al. 2006	E=4 C=6	M	E=Pre-B ALL C=Healthy	ns	E=11.3±5.3y C=10.8±4.6y	Antimetabolites, MTX, 6-MP	During maintenance treatment ALL
Acute exercise in adults							
Galvão et al. 2008[b]	E=10	M	E=PC	ns	?	ADT: LHRHa or CA treatment	More than 2 months after starting with ADT
Jönsson	E=6 C=5	M+F	E=CML C=Healthy	CCgR	E=59; 42-17y C=29; 22-44y	Imatinib	During Imatinib treatment
Chronic exercise in children							
Chamorro-Viña et al. 2010	E=7 C=13	M+F	E=RMS, B-ALL, T-ALL, AML, NB C=Historical	High Risk	E=8±4y C=7±3y	GVHD Prophylaxis: ACV, CsA, MTX, Conditioning therapy: T, F, DXM, BU alHSCT	During hospitalization for alHSCT, from conditioning phase until end of neutropenic phase (± 15 days post-HSCT)
Shore et al. 1999	E=6 C=11	M+F	E=ALL, other C=Historical healthy	ns	E completed (3)=14±0.6y E not completed (3)=13±3.1y C=?	ns	Max 4 weeks after completion of induction phase
Chronic exercise in adults							
Allgayer et al. 2004	E_1=13 E_2=10	M+F	RC, CC	UICC stage II or III	E_1=49, 36-60y E_2=60, 59-67y	No current treatment	At least 4 weeks after completion of primary therapy (e.g. surgery, CT, and/or RT)
Battaglini et al. 2009	E=10	M+F	AML	ns	E=35.7±8.9y	ns	Newly diagnosed or relapsed, receiving (re)induction therapy
Dimeo et al. 1997	E=33 C=37	M+F	E= AC, BC, GCC, MBC, NB, , NSCLC Sarc, SCLC C=Usual care	ECOG score 0-2	E=39±10y C=40±11y	1-4 CT-cycles: ETO, IFF, CIS, (EPI), G-CSF auPBST	Week after first high-dose CT and after auPBST, during hospitalization
Fairey et al. 2005/2005[a]	E=25 C=28	F	E=BC C=BC	I - IIIB	E=59±6y C=58±6y	46% TMX or ANA, 54% no current treatment	After surgery, radiotherapy and/or CT
Galvão et al. 2008[b]	E=10	M	E=PC	ns	?	ADT: LHRHa or CA treatment	More than 2 months after starting with ADT
Galvão et al. 2010	E=29 C=28	M	E=PC C=PC	ns	E=69.5±7.3y C=70.1±7.3y	ADT: LHRHa or CA treatment, 25% RT	More than 2 months after starting with ADT
Hayes et al. 2003	E=6 C_1=6 C_2=?	M+F	E= ALL, BC, NHL, RMS C_1=Matched AML, BC, MM, NHL C_2=Normative healthy	2 high risk stage II +1 stage IV BC	E=39.5y C_1=54.5y C_2=32±8y	CT-cycles, auPBST	During high-dose CT, after auPBST
Hutnick et al. 2005	E=28 C=21	F	E=BC C=BC	I–III (5 not staged)	E=48.5±10.6y C=52.3±9.2y	No current treatment	At least 2 weeks after

							completion of treatment (CT or RT)
Jones et al. 2009	E=12	M+F	E= NSCLC, SCLC, other	stage I-IIIA	E=67±8y	ns	Before primary surgery, until surgical resection
Kim et al. 2005/2006[a]	E=18 C=17	M+F	E=ALL, AML, SAA C=ALL, AML, SAA	ns	E=32.9±7.0y C=34.3±7.8y	alHSCT	During hospitalization with alHSCT
Na et al. 2000	E=17 C=18	M+F	E=SC C=Usual care	ns	E=57.8±12.1y C=52.2±10.3y	ns	From post-operative day 2, after curative surgery
Nieman et al. 1995	E=6 C=6	F	E=BC C=Usual care	ns	E=60.8±4.0y C=51.2±4.7y	No current treatment	After surgery, CT and/or RT (within 4 previous years)
Peters et al. 1994/1995[a]	E=24	F	E=BC	I-II	E=49.3±6.4y	No current treatment	More than 6 months after surgery
Sprod et al. 2010	E=19 C=19	M+F	E=BC, PC C=BC, PC	Mean Karnofsky status: 95.0 ± 8.6	E=56.6±13.7y C=63.3±9.4y	RT, 8% hormone therapy	After primary diagnosis, starting RT of at least 6 weeks

[a] = Patients described in two articles; [b] = Author has investigated both acute and chronic exercise effects E= Exercise group; E_1, E_2= Different exercise protocols; C= Control group; M= Males; F= Females; ns= Not specified

Diseases: AC= Adenocarcinoma; ALL= Acute lymphoblastic leukemia; AML= Acute myelogenous leukemia; B-ALL= B-cell ALL; BC= Breast cancer; CC= Colon carcinoma; CT= Colorectal tumor; ET= Esophagus tumor; GCC= Germ cell cancer; LC= Lung cancer; MBC= Metastatic breast cancer; NB= Neuroblastoma; NHL= Non-Hodgkin's lymphoma; NSCLC= Non-small cell lung carcinoma; PC= Prostate cancer; Pre-B ALL= Precursor B-cell ALL; PT= Pancreas tumor; RC= Rectal carcinoma; RMS= Rhabdomyosarcoma; SAA= Severe aplastic anaemia; Sarc= Sarcoma; SC= Stomach cancer; SCLC= Small cell lung carcinoma; T-ALL= T-cell ALL; VT= Ventriculum tumor

Treatment-related: ACV= Acyclovir; ADT= Androgen deprivation therapy; alHSCT= Allogeneic hematopoietic stem cell transplantation; ANA= Anastrozole; auPBST= Autologous peripheral blood stem cell transplantation; BU= Busulphan; CA= Cyproterone acetate; CCgR= Complete cytogenetic response; CIS= Cisplatinum; CsA= Cyclosporine A; CT= Chemotherapy; DXM= Dexamethasone; ECOG= Eastern Cooperative Oncology Group; EPI= Epirubicine; ETO= Etoposide; F= Fludarabine; GVHD= Graft-versus-Host Disease; IFF= Ifosfamide; LHRHa= Lutenizing hormone-releasing hormone agonist; 6-MP= 6-Mercaptopurine; MTX= Methotrexate; RT= Radiation therapy; T= Thiotepa; TMX= Tamoxifen; UICC= Union for International Cancer Control

Table 3: Description of exercise interventions in the included studies

Primary author	Design	Study duration	Frequency	Aerobic/Resistance exercise	Duration, sets, reps	Intensity
Acute exercise in children with cancer						
Ladha et al. 2006	NCT: Pre-ex Post-ex 1hr post-ex 2hr post-ex	-	-	Aer: intermittent run-walk on treadmill with warming-up and cooling-down	30 min: Aer: 5 min warm 5 min run, 10 min walk, 10 min run, 5 min cool	Run: 85% HR_{peak} Walk: 70% HR_{peak}
Acute exercise in adults with cancer						
Galvão et al. 2008[b]	Pretest-posttest Pre-ex Post-ex	-	-	Res1: hydraulic ex bout Res2: Isotonic ex bout	Res: 4 sets, 8 reps	Res: 6 RM
Jönsson et al. 2011	NCT 3mth pre-ex Pre-ex Post-ex 15min post-ex 45min post-ex 75min post-ex 120min post-ex 180min post-ex 240min post-ex 3mth post-ex	-	-	Aer: Maximal ex test on cycle ergometer (±60 RPM)	-	Aer: Until maximal exhaustion
Chronic exercise in children with cancer						
Chamorro-Viña et al. 2009	NCT Pre-tr 15d post-tr 30d post-tr and Post-ex	ns	Aer: 3x/wk Aer+Res: 2x/wk	In-hospital ex training program: Aer: Cycle ergometer Res: Each muscle group Stretch: Start and end	50 min: Aer: 25-30 min Res: 12-15 reps per ex	Aer: 50-70% HR_{peak}
Shore et al. 1999	NCT Pre-ex Post-ex 7d post-ex	12 wk	Aer: 3x/wk	Aer: Cycling, soccer, skating, skiing, swimming or combination Stretch: Before ex	Aer: 30 min Stretch: 2-3 min	Aer: 70-85% HR_{peak}
Chronic exercise in adults with cancer						
Allgayer et al. 2004	RCT Pre-ex Post-ex	2 wk	Aer: Daily	Maximal Aer ex test on cycle ergometer Mod.Aer group or Low Aer group	Aer: 40 min	Mod.Aer: 55-65% IAP Low Aer: 30-40% IAP
Battaglini et al. 2009	Pretest-posttest Pre-ex 3-4wk ex Post-ex	Hospitalization + 2 wk recovery	Aer+Res: 3-4x/wk 2x/d Recovery: 3x/wk	Baseline and post-ex: Cycle ergometer and squat and biceps curl ex In-hospital ex training: Stretch Aer: Cycle or walk Res: upper and lower body Recovery: Walk	30 min: Stretch: 3-5 min Aer: 5-10 min Res: 5-15 min + 5-10 min core ex Recovery: 10-30 min	Aer: 40-50% HRR Res: RPE 5
Dimeo et al. 1997	RCT Pre-ex Post-ex	Hospitalization	Aer: daily	Baseline and post-ex: treadmill stress-test Aer: Bed cycle ergometer	Aer: 30 min: 15 reps, 1 min, 1 min pause	Aer: 50% CR at 32±5W
Fairey et al. 2005/2005[a]	RCT Pre-ex Post-ex	15 wk	Aer: 3x/wk	Aer: Cycle ergometer with warming-up and cooling-down	Aer: 5 min warm, 15 min (+5 min each 3 wk → 35 min at end), 5 min cool	Aer: 70-75% VO_{2peak} Start + end: 50% VO_{2peak}
Galvão 2008[b]	Pretest-posttest Pre-ex Post-ex	Res1: 10 wk Res2: 10 wk	Res1/2: 2x/wk	Res1: hydraulic ex training Res2: isotonic ex training	Wk 1-2: 2 reps Wk 3-4: 3 reps Wk 5-7: 3 reps Wk 8-10: 4 reps	Wk 1-2: 12RM Wk 3-4: 10RM Wk 5-7: 8RM Wk 8-10: 6RM
Galvão et al. 2010	RCT Pre-ex Post-ex	12 wk	Aer+Res: 2x/wk	Aer: Progressive cycling and walking Res: Progressive upper and lower body ex	Aer: 15-20 min Res: 8 ex, 2-4 sets	Aer: 65-80% HR_{peak} and 11-13 RPE Res: 12-6RM
Hayes et al. 2003	NCT PI=pre-tr PII=post-tr, and pre-ex I1=1mth ex I2=2mth ex PIII=3mth post-tr and post-ex	12 wk	Aer: 3x/wk Res: 2x/wk Con: 3x/wk	Maximal graded ex treadmill test (PII) Aer: treadmill walk and cycle ergometer Res: machine and free weight Con: stretch major muscle groups	Aer: 20-40 min Res: 3-6 ex,15-20 reps (start) and 8-12 reps (end) until failure Con: 20-30 reps, 15-30 sec per stretch	Aer: 70-90% HR_{peak}
Hutnick et al. 2005	NCT T1=pre-tr T2=post-tr and pre-ex	24 wk	Aer+Res: 3x/wk	Aer+Res: First 12 wk: one-on-one sessions (N=28); Second 12 wk: with trainer (N=10); at home (N=6); quit training	40-90 min: Aer: 5 min warm + 10-20 min Res: 4 ex, 1-4 sets (start-end), 8-12	Aer: 60-75% FC

	T3=12wk ex T4=post-ex			(N=12) Aer: Warming-up + treadmill for outdoor running and walking Res: flexbands	reps	
Jones et al. 2009	Pretest-posttest Pre-ex Post-ex	4-6 wk	Aer: 5x/wk	Aer: cycle ergometry with warming-up and cooling-down Wk 1-3: Progressive cycling Wk 4-6: Progressive cycling and interval training	Aer: 20-30 min: Wk 1: 20-30 min Wk 2-3: 4 sessions 25-30 min and 5th session 20-25 min Wk 4-6: 3 sessions 30 min, 4th session 20-30 min, and 5th session 10-15 reps of 30 sec + 60 sec recovery 5 min warm and cool	Aer: Wk 1: 5x 60-65% VO_{2peak} Wk 2-3: 4x 60-65% VO_{2peak} + 1x VT Wk 4-6: 3x 60-65% VO_{2peak} + 1x VT + 1x VO_{2peak}
Kim et al. 2005/2006[a]	RCT Pre-ex Post-ex	6 wk	Aer: Daily	Relaxation breathing bed ex: preliminary ex, relaxation breathing, finish ex	30 min: preliminary ex 10 min, relaxation breathing 10 min, finish ex 10 min	-
Na et al. 2000	RCT 1d post-tr 7d post-tr, ex 14d post-tr and post-ex	2 wk	Bed: 3x/d Aer: 5x/wk 2x/d	Bed: 'Active range of motion' ex Aer: When ambulatory: arm and cycle ergometers	Bed: 30 min Aer: 30 min	Bed: Moderate Aer: 60% HR_{peak}
Nieman et al. 1995	RCT Pre-ex Post-ex	8 wk	Aer+Res: 3x/wk	Maximal ex test on treadmill, 6-min walking test, leg extension strength test Aer: Walking Res: Weights	Aer: 30 min Res: 7 ex, 2 sets, 12 reps	Aer: 75% HR_{peak} Res: Weight increasing
Peters et al. 1994/1995[a]	Pretest-posttest Pre-ex Post-ex 6mth post-ex	5 wk	Aer: 5x/wk Self-report: 2-3x/wk	Aer: Cycle ergometer during hospitalization Self-reported cycling after hospitalization	Aer: 30-40 min	Aer: 60% HR_{peak} Self-report: Moderate
Sprod et al. 2010	RCT Pre-ex Post-ex 3mth post-ex	4 wk	Aer+Res: daily	Aer: Walking Res: Upper body ex	Aer: daily increasing with 5-20% of steps Res: 11 ex, increasing towards 4 sets 15 reps	Aer: 3-5 RPE Res: Low-moderate

[a] = Patients described in two articles; [b] = Author has investigated both acute and chronic exercise effects; Aer= Aerobic exercise; Bed= Bed exercise; Con= Controls; CR= Cardiac reserve; D= Days; Ex= Exercise; FC= Functional capacity; HRR= Heart rate reserve; HR_{peak}= Peak Heart Rate; IAP= Individual aerobic power; Mth= Month; NCT= Nonrandomized Controlled Trial; RCT= Randomized Controlled Trial; Reps= Repetitions; Res= Resistance exercise; RM= Repetition maximum; RPE= Rating of perceived exertion; Tr= Treatment; VO_2= Oxygen uptake; VT= Ventilatory threshold; Wk= Week(s)

Table 2 depicts the patient and disease characteristics of the included studies, while Table 3 describes the exercise interventions of the studies.

Methodological quality

Full consensus was reached when assessing the methodological quality of the included studies (Table 4). In total, 15 studies were identified as having high methodological quality, and six studies were deemed to be of low methodological quality. Strengths of the studies were the adequate description of exercise protocols (100% scored positively), sufficient cell measurement techniques (100%), blood sampling time points (100%) and statistical result reporting (95%). Weaknesses of these studies were the lack of a blinded assessor (24%), and the high drop-out rates (43%). Fairey et al. (15, 16), Kim et al. (35, 36) and Peters et al. (48, 49) have published more than one article about their patient population. For these studies, the methodological quality and the populations were only described once.

Exercise in children

Three high methodological quality NCTs (9, 37, 57) were conducted in children. Each study included four to seven patients, and six to 13 historical (9, 57) or healthy controls (37). Tables 5 and 6 summarize the effects of acute and chronic exercise interventions, respectively.

Table 4: Quality assessment of the studies with a modified PEDro scale[a]

Included studies		Design[b]	Blinding of assessors	Drop-outs <15%	Between group comparison	Exercise protocol described	Exercise intensity sufficient	Measuring methods sufficient	Blood sampling sufficient	Result reporting sufficient	Methodological quality[c]
Acute exercise performed in children											
1	Ladha et al. (2006)	NCT	?	N	Y	Y	Y	Y	Y	Y	High (75%)
Chronic exercise performed in children											
2	Chamorro-Viña et al. (2010)(10)	NCT	Y	Y	Y	Y	Y	Y	Y	Y	High (100%)
3	Shore & Shephard (1999)	NCT	?	N	Y	Y	Y	Y	Y	Y	High (75%)
Acute exercise performed in adults											
4[d]	Galvão et al. (2008)	OD	?	?	N	Y	Y	Y	Y	Y	Low (67%)
5	Jönsson et al. (2011)	NCT	?	Y	Y	Y	Y	Y	Y	Y	High (88%)
Chronic exercise performed in adults											
6	Allgayer et al. (2004)	RCT	N	?	Y	Y	Y	Y	Y	N	Low (63%)
7	Battaglini et al. (2009)	OD	?	N	N	Y	Y	Y	Y	Y	Low (63%)
8	Dimeo et al. (1997)	RCT	Y	Y	Y	Y	Y	Y	Y	Y	High (100%)
9/10	Fairey et al. (2005/2005)*	2 RCT	Y	Y	Y	Y	N	Y	Y	Y	2 High (88%)
4[d]	Galvão et al. (2008)	OD	?	?	N	Y	Y	Y	Y	Y	Low (67%)
11	Galvão et al. (2010)	RCT	Y	Y	Y	Y	Y	Y	Y	Y	High (100%)
12	Hayes et al. (2003)	NCT	?	?	Y	Y	Y	Y	Y	Y	High (75%)
13	Hutnick et al. (2005)	NCT	?	N	Y	Y	Y	Y	Y	Y	High (75%)
14	Jones et al. (2009)	OD	?	N	N	Y	Y	Y	Y	Y	Low (63%)
15/16	Kim et al. (2005/2006)*	2 RCT	?	N	Y	Y	N	Y	Y	Y	2 Low (63%)
17	Na et al. (2000)	RCT	?	?	Y	Y	Y	Y	Y	Y	High (75%)
18	Nieman et al. (1995)	RCT	?	N	Y	Y	Y	Y	Y	Y	High (75%)
19/20	Peters et al. (1994/1995)*	2 OD	?	Y	N	Y	Y	Y	Y	Y	2 High (75%)
21	Sprod et al. (2010)	RCT	?	Y	Y	Y	N	Y	Y	Y	High (75%)

[a] Y = Yes; N = No; ? = Unclear; n/a = not applicable
[b] RCT = Randomized controlled trial; NCT = Nonrandomized controlled trial; OD = Other design
[c] Methodological quality high when ≥ 75% answered Yes
[d] = Galvão et al. (2008) have performed both acute and chronic exercise interventions
[e] = Same patient population

Leukocytes
All three studies in the pediatric population measured the effects of exercise on leukocytes. There is limited evidence that leukocyte numbers increase after acute (37) and chronic exercise (9), although one study reported decreases after chronic exercise (57), and there is limited evidence that the number of lymphocytes and monocytes remain constant (9, 37, 57). We found indicative evidence of an increase in the number of neutrophils (37) after an acute exercise bout, whereas the number of DC (9) and eosinophils (37) decreased after chronic and acute exercise, respectively. The number of basophils (37) and granulocytes (57) remained constant after acute and chronic exercise, respectively.

Lymphocyte subsets
Two studies (9, 57) focused on the lymphocyte subsets in children after chronic exercise. Based on these results, there is limited evidence that $CD8^+$ T lymphocyte and NK numbers remain stable after exercise (9, 57), whereas the number of $CD3^+$ T lymphocytes was reported to either increase (57) or decrease (9) with exercise. One study found that $CD4^+$ and NK T lymphocyte numbers decreased after hematopoietic stem cell transplantation and normalized after 30 days of chronic exercise (9), whereas another study found that $CD4^+$ lymphocyte numbers decreased after chronic exercise (57). Shore et al. reported that chronic exercise did not affect the $CD4^+/CD8^+$ ratio, $CD19^+$ B and $CD122^+$ T lymphocyte numbers, whereas $CD25^+$ T lymphocyte numbers decreased (57).

Cell functions
Two studies have measured immune cell function (37, 57). Acute exercise did not change the oxidative capacity of neutrophils (37), and the proliferative and cytolytic activity of lymphocytes (57) were found to be unaffected by chronic exercise.

Inflammatory mediators
No study has investigated changes in soluble inflammatory mediators in children with cancer.

Exercise in adults
In adults, 12 high quality studies (13, 15, 16, 20, 25, 26, 32, 44, 46, 48, 49, 59) and six low quality studies (1, 4, 19, 30, 35, 36) have been performed. These studies included six to 33 patients and five to 37 controls. Three were identified as being NCTs (25, 26, 32) and 10 were RCTs (1, 13, 15, 16, 20, 35, 36, 44, 46, 59) with either usual care controls (13, 15, 16, 20, 26, 35, 36, 44, 46, 59), healthy matched controls (25, 32), or a low intensity exercise control group (1). The remaining five studies were ODs without controls (4, 19, 30, 48, 49). Tables 4 and 5 summarize the effects of acute and chronic exercise interventions, respectively.

Leukocytes
Six high quality studies (25, 32, 46, 48, 49) and three low quality studies (19, 35, 36) have investigated leukocyte responses in adults. Based on these trials, there is moderate evidence that the number of granulocytes increases after acute (32) and

Table 5: Effects of acute exercise interventions on immune parameters in children and adults with cancer

Primary author	Immune parameters + units	Patients				Controls			
		Pre-bout	Post-bout	Follow-up1	Follow-up2	Pre-ex bout	Post-bout	Follow-up1	Follow-up2
Exercise interventions in children with cancer									
Ladha et al. 2006		**Pre**	**Post**	**1-hr post**	**2-hrs post**	**Pre**	**Post**	**1-hr post**	**2-hrs post**
$\times 10^9$/L	Basophils	0.05 (0.03)	0.08 (0.08)	0.04 (0.02)	0.05 (0.04)	0.07 (0.03)	0.13 (0.07)	0.09 (0.04)	0.11 (0.07)
$\times 10^9$/L	Eosinophils	0.23 (0.08)[d]	0.24 (0.09)	0.13 (0.04)[e]	0.15 (0.09)	0.37 (0.08)[d]	0.40 (0.10)[e]	0.33 (0.08)	0.32 (0.07)
$\times 10^9$/L	Leukocytes	4.70 (2.00)	6.10 (2.30)[e]	4.50 (1.40)[e]	5.00 (1.60)[e]	5.00 (1.50)	6.80 (1.70)[e]	5.70 (1.40)[e]	6.20 (1.80)[e]
$\times 10^9$/L	Lymphocytes	0.82 (0.15)[d]	1.20 (0.37)[e]	0.78 (0.18)[e]	0.89 (0.20)	2.09 (0.48)[d]	2.74 (0.42)[e]	2.09 (0.31)[e]	2.28 (0.14)
$\times 10^9$/L	Monocytes	0.30 (0.06)	0.46 (0.17)	0.32 (0.12)	0.39 (0.12)	0.37 (0.08)	0.54 (0.12)	0.45 (0.10)	0.46 (0.10)
$\times 10^9$/L	Neutrophils[b]	3.3	4.2[e]	3.1[e]	3.4[e]	2.1	3[e]	2.7[e]	2.9[e]
Ratio	Active neutrophils 5 min	33.8 (25.7)[d]	27.3 (18.8)[e]	24.4 (13.1)[e]	18.9 (20.1)[e]	6.0 (5.9)[d]	4.4 (3.9)[e]	7.4 (4.1)[e]	7.2 (4.6)[e]
Ratio	Active neutrophils 10 min	94.4 (81.1)	55.3 (38.9)	49.8 (33.9)	35.2 (30.7)	10.7 (11.0)	4.8 (3.4)	13.1 (8.1)	13.0 (11.6)
Ratio	Active neutrophils 15 min	82.6 (59.1)[d]	63.2 (47.6)[e]	54.8 (36.9)[e]	44.2 (29.4)[e f]	8.5 (9.1)[d]	4.7 (2.6)[e]	13.8 (6.2)[e]	14.6 (10.5)[e f]
RF	Neutrophil function[b]	14[d]	18[e]	20[e]	20[e]	45[d]	52[e]	39[e]	47[e]
Exercise interventions in adults with cancer									
Galvâo et al. 2008[a]		**Pre-bout1**	**Post-bout1**			**Pre-bout2**	**Post-bout2**		
$\times 10^9$/L	Leukocytes	6.7 (0.7)[d]	7.7 (0.9)[e]			6.0 (0.5)[d]	7.3 (0.7)[e]		
$\times 10^9$/L	Lymphocytes	2.0 (0.3)[d]	2.2 (0.3)			1.7 (0.2)	2.2 (0.3)[e]		
$\times 10^9$/L	Monocytes	0.65 (0.09)	0.71 (0.10)			0.56 (0.06)	0.72 (0.07)[e]		
$\times 10^9$/L	Neutrophils	4.0 (0.5)	4.5 (0.6)[e]			3.5 (0.4)	4.2 (0.5)[e]		
Pg/mL	Serum CRP	1.0 (0.55)	0.71 (0.25)			0.63 (0.25)	0.64 (0.24)		
Pg/mL	Serum IL-1ra	301.8 (41.8)	344.8 (47.8)			286.2 (41.6)	307.1 (39.1)		
Pg/mL	Serum IL-6	1.5 (0.2)	1.8 (0.2)			1.6 (0.5)	2.6 (0.5)[e]		
Pg/mL	Serum IL-8	7.6 (1.1)[d]	10.2 (1.9)			10.6 (1.7)[d]	11.4 (1.8)		
Pg/mL	Serum TNF-α	1.7 (0.2)	1.9 (0.4)			1.6 (0.2)	1.8 (0.2)[e]		
Jönsson et al. 2011		**Pre-bout**	**15 min**	**45 min**	**75 min**	**120 min**	**180 min**	**240 min**	
$\times 10^9$/L	Granulocytes Patients[b]	2.5	3.2[e]	2.5	3	3.4[e]	3.6	3.2	
$\times 10^9$/L	Controls[b]	2.5	3.5[e]	2.8	3.5	5.2[e]	5.2	5	
$\times 10^9$/L	Lymphocytes Patients[b]	1.2	2.6[e]	1.2	1	1	1.2	1.4	
$\times 10^9$/L	Controls[b]	2	4[e]	1.6	1.4	1.5	1.6	1.9	

[a] = Author has investigated both acute and chronic exercise effects; [b] = Estimated from graphs and figures; [d] Significant difference between patients and controls (at baseline); [e] Significant difference over time; [f] Significant difference between patients and controls;
Bout1= Hydraulic resistance exercise bout; Bout2= Isotonic resistance exercise bout; CRP = C-reactive Protein; Ex = Exercise; Hrs= Hours; IL = Interleukin; Ra = Receptor antagonist; RF = Relative fluorescence; TNF = Tumor Necrosis Factor

chronic exercise (49), although Fairey et al. did not report any changes after chronic exercise (15). There is also moderate evidence that the number of leukocytes remained stable (25, 46, 49), although some studies reported increases in leukocyte numbers after acute (19) and chronic exercise (19, 36). Similarly, there is moderate evidence that the number of lymphocytes remained stable after acute (19) and chronic exercise (35, 46); however, select studies reported increased numbers after acute (32) and chronic exercise (19, 25), while one study showed a decreased lymphocyte count after chronic exercise (49). There is limited evidence that the number of monocytes remained stable after acute (19) and chronic exercise (15, 19), with only one study reporting a decrease in monocytes (49). Similarly, there is limited evidence that the number of neutrophils remained stable after chronic exercise (19, 46), with one study reporting an increase in neutrophil counts after acute exercise (19), and the duration of neutropenia is reported to be shorter after chronic exercise (13).

Table 6: Effects of chronic exercise interventions on immune parameters in children and adults with cancer

Primary author	Immune parameters + units	Patients			Controls		
		Pre-train	Post-train	Follow-up	Pre-train	Post-train	Follow-up
Exercise interventions in children with cancer							
Chamorro-Viña et al. 2010		**Pre-HSCT**	**15d Post-HSCT**	**30d Post-HSCT**	**Pre-HSCT**	**15d Post-HSCT**	**30d Post-HSCT**
Cells/μL	Dendritic cells	5.4 (2.4)	2.0 (2.2)	2.6 (1.6)	10.6 (8.7)	1.4 (2.3)	1.7 (4.1)
$\times10^9$/L	Leukocytes	2.39 (2.52)	1.27 (1.85)	5.16 (4.08)	2.31 (2.40)	0.86 (1.16)	2.15 (2.85)
$\times10^9$/L	Lymphocytes	1.91 (2.48)	0.23 (0.31)	0.57 (0.28)	1.19 (0.82)	0.16 (0.22)	0.78 (8.60)
$\times10^9$/L	Monocytes	0.63 (0.19)	0.62 (0.31)	0.86 (0.60)	0.42 (0.31)	0.52 (0.51)	0.73 (1.10)
$\times10^9$/L	NK	0.20 (0.18)	0.22 (0.17)	0.37 (0.23)	0.20 (0.15)	0.10 (0.13)	0.33 (0.36)
Cells/μL	NK T lymphocytes	12.7 (17.3)	2.4 (3.2)	4.6 (6.6)	9.3 (11.0)	1.9 (2.7)	7.7 (16.1)
$\times10^9$/L	T lymphocytes	1.27 (1.59)	0.09 (0.12)	0.31 (0.21)	0.93 (0.70)	0.08 (0.10)	0.40 (0.33)
$\times10^9$/L	$CD4^+$	0.64 (0.89)	0.04 (0.05)	0.08 (0.03)	0.40 (0.37)	0.05 (0.07)	0.18 (0.17)
$\times10^9$/L	$CD8^+$	0.53 (0.65)	0.05 (0.07)	0.15 (0.16)	0.53 (0.55)	0.03 (0.04)	0.20 (0.18)
Shore et al. 2010		**Pre-train**	**Post-train**		**Pre-train**	**Post-train**	
$\times10^9$/L	Granulocytes	2.0	1.17 (0.09)		3.0 (0.2)	2.5 (0.2)	
$\times10^9$/L	Leukocytes	2.7 (0.6)[d]	2.4 (0.7)[f]		5.9 (0.5)[d]	5.0 (0.4)[f]	
$\times10^9$/L	Lymphocytes	1.06 (0.43)[d]	0.6 (0.13)		2.6 (0.2)[d]	2.1 (0.2)	
$\times10^9$/L	Monocytes	0.21	0.14 (0.05)		0.33 (0.06)	0.42 (0.06)	
$\times10^9$/L	$CD3^+$	0.51 (0.17)[d]	0.28 (0.07)[f]		1.8 (0.2)[d]	1.4 (0.2)[f]	
$\times10^9$/L	$CD4^+$	0.31 (0.12)[d]	0.13 (0.03)		0.90 (0.01)[d]	0.95 (0.30)	
$\times10^9$/L	$CD8^+$	0.27 (0.07)[d]	0.20 (0.19)		0.85 (0.10)[d]	0.73 (0.10)	
Ratio	$CD4^+/CD8^+$	1.1 (0.2)	0.9 (0.3)		1.3 (0.1)	1.4 (0.1)	
$\times10^9$/L	$CD19^+$	0.01 (0.0)	0.07 (0.06)		0.23 (0.03)	0.25 (0.05)	
$\times10^9$/L	$CD56^+$	0.13 (0.08)	0.10 (0.06)		0.29 (0.03)	0.27 (0.03)	
$\times10^9$/L	$CD25^+$	0.08 (0.03)[d]	0.02 (0.00)[f]		0.15 (0.02)[d]	0.09 (0.02)[f]	
$\times10^9$/L	$CD122^+$	0.08 (0.06)	0.10 (0.08)		0.22 (0.04)	0.17 (0.04)	
$\times10^9$/min	LP (PHA-induced)	12.2 (5.1)[d]	6.2 (2.2)		32.0 (4.7)[d]	35.6 (5.1)	
$\times10^9$/min	LP (PWM-induced)	6.8 (2.4)	3.8 (2.5)		10.9 (1.8)	11.1 (2.6)	
Units/10^6	Cytolytic activity (spontaneous)	2.2 (1.5)	5.1 (3.7)		8.1 (3.4)	4.6 (1.6)	
Units/10^6	Cytolytic activity (IL-2 induced)	3.9 (3.2)	5.0 (2.4)		10.6 (3.7)	6.9 (1.7)	
Exercise interventions in adults with cancer							
Allgayer et al. 2004		**Pre-ME D**	**1 wk**	**2 wk**	**Pre-LE D**	**1 wk**	**2 wk**
Ng/mL	WB IL-1β (LPS)	6.94 (0.82–18.52)	NS/UC	NS/UC	2.23 (1.32–9.81)	NS/UC	NS/UC
Ng/mL	WB IL-1ra (LPS)	28.60 (1.60–30.03)	18.03 (5.04-52.57)[e]	22.89 (6.38-34.73)[e]	27.22 (20.88–29.07)	NS/UC	24[c]
Ratio	WB IL-1ra/IL-1β (LPS)	4.1 (0.09-37.0)	NS/UC	3.7 (0.84-10.3)[e]	9.3 (3.5-21.0)	NS/UC	NS/UC
Ratio	WB IL-1ra/IL-6 (LPS)	2.51 (0.59-6.50)	NS/UC	1.41 (0.29-2.60)[e]	3.3 (3.2-4.3)	NS/UC	NS/UC
Ratio	WB IL-1ra/TNF-α (LPS)	NS/UC	NS/UC	NS/UC	NS/UC	NS/UC	NS/UC
Ng/mL	WB IL-6 (LPS)	12.64 (5.80–30.79)[d]	NS/UC	NS/UC	8.34 (4.83–8.66)[d]	NS/UC	NS/UC
Ng/mL	WB sTNFRI (LPS)	1.30 (0.82–2.51)	NS/UC	NS/UC	1.35 (1.24–1.43)	NS/UC	NS/UC
Ng/mL	WB sTNFRII (LPS)	3.69 (2.42–7.17)	NS/UC	NS/UC	3.28 (3.27–4.17)	NS/UC	NS/UC
Ng/mL	WB TNF-α (LPS)	4.55 (1.94–32.79)	NS/UC	NS/UC	3.64 (2.62–8.06)	NS/UC	NS/UC
Battaglini et al. 2009		**Pre-ex**	**Mid-Ex**	**Post-Ex**			
Pg/mL	WB IFN-γ[c]	33	35	37			
Pg/mL	WB IL-6[c]	58	46	18			
Pg/mL	WB IL-10[c]	28	66	91			
Dimeo et al. 1997							
Days	Duration neutropenia	6.6 (1.5)[f]			7.6 (1.6)[f]		
Fairey et al. 2005[a]		**Pre-train**	**Post-train**		**Pre-train**	**Post-train**	
Mg/L	Serum CRP	5.19 (3.56)	3.79 (2.30)		4.28 (3.05)	4.39 (3.87)	
Fairey et al. 2005[a]		**Pre-train**	**Post-train**		**Pre-train**	**Post-train**	
	Granulocytes	NS/ND	NS/ND		NS/ND	NS/ND	
	$CD3^+$	NS/ND	NS/ND		NS/ND	NS/ND	
	$CD4^+$	NS/ND	NS/ND		NS/ND	NS/ND	
	$CD8^+$	NS/ND	NS/ND		NS/ND	NS/ND	

	$CD14^+$	NS/ND	NS/ND		NS/ND	NS/ND	
	$CD20^+$	NS/ND	NS/ND		NS/ND	NS/ND	
	$CD25^+$	NS/ND	NS/ND		NS/ND	NS/ND	
	$CD56^+$	NS/ND	NS/ND		NS/ND	NS/ND	
RF	Neutrophil function	NS/ND	NS/ND		NS/ND	NS/ND	
%	NKCA (3.125:1 E/T)	7.2 (5.1)	12.4 (6.6)[f]		5.8 (4.5)	5.7 (4.2)[f]	
$/10^3$ cells	Total LU	11.98 (6.76)	8.60 (3.40)[f]		12.72 (8.19)	11.68 (6.00)[f]	
$\times10^9$/min	Spontaneous LP	863 (425)	1042 (290)[f]		776 (417)	811 (247)[f]	
$\times10^9$/min	PHA-induced LP	90098 (49890)	79500 (32218)		91279 (54302)	69487 (31540)	
	PBMC-produced IL-1α	NS/ND	NS/ND		NS/ND	NS/ND	
	PBMC-produced IL-4	NS/ND	NS/ND		NS/ND	NS/ND	
	PBMC-produced IL-6	NS/ND	NS/ND		NS/ND	NS/ND	
	PBMC-produced IL-10	NS/ND	NS/ND		NS/ND	NS/ND	
	PBMC-produced TGF-β1	NS/ND	NS/ND		NS/ND	NS/ND	
	PBMC-produced TNF-α	NS/ND	NS/ND		NS/ND	NS/ND	
Galvão et al. 2008[b]		**Pre-ex**	**10 wk**	**20 wk (post-ex)**			
$\times10^9$/L	Leukocytes	6.4 (0.7)	6.7 (0.7)[e]	6.0 (0.5)[e]			
$\times10^9$/L	Lymphocytes	1.7 (0.2)	2.0 (0.3)[e]	1.7 (0.2)			
$\times10^9$/L	Monocytes	0.56 (0.73)	0.65 (0.09)	0.56 (0.06)			
$\times10^9$/L	Neutrophils	3.9 (0.5)	4.0 (0.5)	3.5 (0.4)			
Pg/mL	Serum CRP	0.91 (0.31)	1.0 (0.55)	0.63 (0.25)			
Pg/mL	Serum IL-1ra	286.5 (39.2)	301.8 (41.8)	286.2 (41.6)			
Pg/mL	Serum IL-6	1.8 (0.3)	1.5 (0.2)	1.6 (0.5)			
Pg/mL	Serum IL-8	8.2 (0.8)	7.6 (1.1)[e]	10.6 (1.7)[e]			
Pg/mL	Serum TNF-α	1.8 (0.2)	1.7 (0.2)	1.6 (0.2)			
Galvão et al. 2010		**Pre-train**	**Post-train**		**Pre-train**	**Post-train**	
Mg/L	Serum CRP	2.7 (3.2)	1.8 (1.1)[f]		2.3 (2.6)	4.5 (6.9)[f]	
Hayes et al. 2003		**PI (pre-Tr)**	**PII (post-Tr)**	**I1 (1mth ex)**	**I2 (2mth ex)**	**PIII (3 mth ex)**	**Norm values**
$\times10^9$/L	Leukocytes	5.46 (0.90)	3.47 (0.78)	5.99 (0.57)	4.70 (0.68)	5.43 (0.47)	5.91 (0.03)
$\times10^9$/L	Lymphocytes	1.14 (0.29)	0.38 (0.14)	1.72 (0.43)[e]	1.49 (0.39)[e]	1.17 (0.17)[e]	2.13 (0.09)
$\times10^9$/L	$CD3^+$	0.65 (0.16)	0.32 (0.15)	1.31 (0.39)[e]	1.10 (0.36)[e]	0.68 (0.16)	1.43 (0.11)
$\times10^9$/L	$CD4^+$	0.37 (0.10)	0.16 (0.08)	0.22 (0.07)[e]	0.24 (0.08)	0.16 (0.03)[e]	0.80 (0.03)
$\times10^9$/L	$CD8^+$	0.28 (0.09)	0.15 (0.07)	1.08 (0.32)[e]	0.87 (0.28)[e]	0.52 (0.15)	0.71 (0.03)
Ratio	$CD4^+/CD8^+$	1.88 (0.54)	1.13 (0.32)	0.29 (0.06)[e]	0.32 (0.03)[e]	0.47 (0.09)[e]	1.21 (0.03)
Ratio	Prolif. Index[c]	1.25	1.0	1.2	1.25	1.1	2.0
Ratio/%	Prolif. Index/$CD3^+$ [c]	2.25	1.35	2.0	2.0	2.8[e]	3.25
Hutnick et al. 2005		**Post-Tr (T2)**	**T3 (3mth)**	**T4 (6mth)**	**Post-Tr (T2)**	**T3 (3mth)**	**T4 (6mth)**
	B lymphocytes	NS/ND	NS/ND	NS/ND	NS/ND	NS/ND	NS/ND
	NK	NS/ND	NS/ND	NS/ND	NS/ND	NS/ND	NS/ND
	$CD3^+$	NS/ND	NS/ND	NS/ND	NS/ND	NS/ND	NS/ND
	$CD4^+$	NS/ND	NS/ND	NS/ND	NS/ND	NS/ND	NS/ND
%	$CD4^+CD69^+$ activation	1.40 (4.00)	0.37 (0.29)	0.51 (0.46)[f]	0.63 (0.82)	0.41 (0.61)[e]	0.34 (0.61)[e f]
	$CD8^+$	NS/ND	NS/ND	NS/ND	NS/ND	NS/ND	NS/ND
CPM	LP 25mg/mL Con-A	14128 (10437)	16352 (16079)	17445 (9587)[f]	10289 (8038)	12771 (14661)	9669 (6274)[f]
CPM	LP 50mg/mL PHA	34600 (27277)	39285 (30853)	39321 (21207)[f]	23694 (17630)	28770 (23537)	26444 (18296)[f]
CPM	LP 5mg/mL PWM	4345 (3077)	5213 (3872)	6754 (5426)[f]	5501 (10184)	4581 (4097)	4192 (2741)[f]
Ng/mL	Lymphocyte-produced IFN-γ (PHA)	24.5 (48.2)	6.6 (11.0)	6.0 (11.0)	15.4 (18.6)	19.3 (44.3)	13.4 (16.6)
Ratio	Lymphocyte-produced IFN-γ/ IL-6 (PHA)	0.2 (0.6)	7.8 (35.5)	0.2 (0.7)	0.3 (0.4)	1.2 (3.6)	0.5 (0.5)
Pg/mL	Lymphocyte-produced IL-6 (PHA)	339.8 (1060.9)	72.5 (114.4)	49.8 (71.3)	72.8 (179.7)	53.8 (87.3)	886.2 (2918.4)
Ng/mL	Plasma IFN-γ	215.4 (490.5)	202.7 (481.6)	279.2 (546.2)	133.2 (236.1)	331.1 (561.6)	239.6 (596.8)
Pg/mL	Plasma IL-6	384.4 (1103.8)	495.2 (1948.8)	690.9 (2333.5)	204.4 (321.6)	176.1 (312.9)	227.9 (388.5)
Ng/mL	Plasma sIL6-R	22.2 (10.7)	26.8 (15.5)	23.9 (20.5)	23.5 (8.0)	21.6 (6.2)	18.3 (12.4)
Ng/mL	Plasma sgp-130	234.5 (118.9)	280.4 (91.5)	309.8 (93.5)	276.0 (74.7)	264.9 (89.3)	282.8 (93.8)
Pg/mL	Plasma BAIL-6	14.7 (34.6)	87.4 (361.4)	133.4 (461.0)	15.3 (28.2)	9.5 (14.6)	18.4 (29.3)
Ratio	Plasma IFN-γ/IL-6	1.31 (0.85)[f]	1.19 (1.09)	1.59 (1.69)	0.70 (0.45)[f]	1.29 (0.90)	3.74 (9.69)

Jones et al. 2009		**Pre-train**	**Post-train**				
Mg/L	Plasma CRP	8.2 (9.3)	6.9 (9.0)				
Ng/mL	Plasma ICAM-1	132.2 (34.9)	120.6 (30.7)[e]				
Pg/mL	Plasma IL-6	6.5 (5.7)	6.3 (4.2)				
Pg/mL	Plasma IL-8	22.9 (22.3)	16.5 (12.7)				
Pg/mL	Plasma MCP-1	214.5 (52.2)	205.2 (36.5)				
Pg/mL	Plasma MIP-1α	35.6 (3.9)	34.4 (3.9)				
Pg/mL	Plasma TNF-α	3.7 (4.8)	4.3 (6.0)				
Kim et al. 2005[a]		**Pre-train**	**Post-train**		**Pre-train**	**Post-train**	
$\times 10^9$/L	Leukocytes	3.92 (1.37)	7.16 (4.18)[e]		4.35 (2.00)	4.64 (2.34)	
Kim et al. 2006[a]		**Pre-train**	**Post-train**		**Pre-train**	**Post-train**	
$\times 10^9$/L	Lymphocytes	1.05 (0.45)	1.09 (0.64)		1.42 (0.62)	0.78 (0.61)[e]	
%	$CD3^+$	50.6 (18.0)	45.0 (29.6)		49.6 (21.3)	47.2 (28.1)	
%	$CD4^+$	20.9 (13.3)	8.9 (8.9)[e]		20.5 (12.9)	8.0 (5.6)[e]	
Ratio	$CD4^+/CD8^+$	0.9 (0.6)	0.6 (1.2)		0.8 (0.4)	0.3 (0.2)	
%	$CD8^+$	24.7 (9.4)	33.0 (25.1)[e]		29.3 (13.2)	40.4 (22.6)[e]	
Na et al. 2000		**Post-Tr d1**	**Post-Tr d7**	**Post-Tr d14**	**Post-Tr d1**	**Post-Tr d7**	**Post-Tr d14**
%	NKCA 50:1 E/T	16.2 (11.4)	14.6	27.9[f]	19.7 (19.6)	17.9	13.3[f]
Nieman et al. 1995		**Pre-train**	**Post-train**		**Pre-train**	**Post-train**	
$\times 10^9$/L	Leukocytes	5.7 (0.3)	4.9 (0.4)		5.9 (0.9)	6.1 (0.9)	
$\times 10^9$/L	Lymphocytes	1.4 (0.2)	1.1 (0.2)		1.4 (0.2)	1.6 (0.3)	
$\times 10^9$/L	Neutrophils	3.7 (0.3)	3.0 (0.4)		3.8 (0.7)	3.9 (0.8)	
$\times 10^9$/L	NK cells	0.3 (0.1)	0.3 (0.1)		0.2 (0.1)	0.2 (0.1)	
$\times 10^9$/L	T lymphocytes	0.9 (0.1)	0.9 (0.1)		1.0 (0.2)	1.2 (0.2)	
%	NKCA 40:1 E/T	39.7 (6.3)	44.3 (4.6)		24.6 (2.6)	38.0 (3.3)	
%	NKCA 20:1 E/T	28.9 (5.8)	41.3 (4.8)		16.0 (2.0)	30.7 (3.4)	
Peters et al. 1994[a]		**Start**	**5 wk**	**7mth**			
$\times 10^9$/L	NK	0.14 (0.12)	0.16 (0.10)	0.16 (0.07)			
%	NK	10.4 (8.7)	12.6 (11.3)	12.9 (5.2)			
%	NKCA 25:1 E/T	18.5 (15.1)	22.4 (18.2)	28.3 (16.0)[e]			
Peters et al. 1995[a]		**Start**	**5 wk**	**7mth**			
$\times 10^9$/L	Granulocytes	3.24 (1.56)	3.21 (1.33)	3.44 (1.60)			
%	Granulocytes	61.3 (7.9)	60.0 (9.7)[e]	65.4 (6.8)[e]			
$\times 10^9$/L	Leukocytes	5.25 (2.08)	5.28 (1.78)	5.19 (2.09)			
$\times 10^9$/L	Lymphocytes	1.49 (0.69)	1.60 (0.73)[e]	1.33 (0.53)[e]			
%	Lymphocytes	28.8 (8.2)	30.6 (9.9)[e]	26.7 (6.6)[e]			
$\times 10^9$/L	Monocytes	0.37 (0.16)	0.35 (0.12)	0.31 (0.17)			
%	Monocytes	7.2 (2.2)	6.8 (1.6)[e]	6.1 (2.2)[e]			
%	PC sheep erythro	44.9 (18.4)	58.3 (18.6)[e]	67.0 (17.5)[e]			
Ratio	PI sheep erythro	1.71 (0.3)	1.91 (0.4)[e]	2.19 (0.4)[e]			
%	PC human erythro	76.6 (8.8)	76.6 (10.3)	78.8 (9.2)			
Ratio	PI human erythro	1.98 (0.3)	1.92 (0.3)	2.02 (0.3)			
Sprod et al. 2010		**Pre-train**	**Post-train**		**Pre-train**	**Post-train**	
Pg/mL	Plasma IL-6	5.74 (0.83–48.10)	6.33 (0.61–24.05)		6.28 (0.08–12.47)	9.26 (1.79–16.74)	
Pg/mL	Serum IL-6	1.08 (0.06–2.97)	1.38 (0.29–6.41)		3.60 (0.00–8.81)	3.75 (0.00–7.76)	
Pg/mL	Serum sTNF-R	760.62 (448.64–1476.21)	680.52 (361.68–1319.53)		766.30 (598.72–933.87)	783.98 (600.99–966.97)	
Pg/mL	Serum TNF-α	0.57 (0.00–4.18)	2.82 (0.00–35.99)		9.43 (0.00–28.84)	9.58 (0.00–29.18)	

[a] = Patients described in two articles; [b] = Author has investigated both acute and chronic exercise effects; [c] = Estimated from graphs and figures; [d] Significant difference between patients and controls (at baseline); [e] Significant difference over time; [f] Significant difference between patients and controls;

CD = Cluster of differentiation; Con-A= Concanavalin A; CPM= Counts per minute; CRP= C-reactive Protein; D= Day(s); E/T= Effector/Target cell ratio; HSCT= Hematopoietic stem cell transplantation; ICAM= Intercellular Adhesion Molecule; IFN= Interferon; IL= Interleukin; LED= Light-intensity exercise; LP= Lymphocyte proliferation; LPS= Lipopolysaccharide stimulation; LU= Lytic Units represent the number of effector cells required to cause 30% lysis of target cells; MCP= Monocyte chemotactic protein; MED= Moderate-intensity exercise; MIP= Macrophage Inflammatory Protein; Mth= Month(s); ND= No difference between groups; NK(CA)= Natural Killer cell cytotoxic activity; NS= Not shown; PBMC= Peripheral Blood Mononuclear Cells; PC= Phagocytosis; PHA= Phytohemagglutin; PI= Phagocytosis Index; Prolif. Index= Proliferation Index; PWM= Pokeweed mitogen; R= Receptor; RF= Relative fluorescence; sgp= soluble glycoprotein; (s)TNF= (soluble) Tumor Necrosis Factor; TGF= Transforming growth factor; Tr= Treatment; UC= Unchanged over time; WB= Whole blood; Wk= Week(s)

Lymphocyte subsets

Five high quality (15, 25, 26, 46, 48) and one low quality study (35) have examined lymphocyte subsets. Strong evidence was found that chronic exercise did not alter $CD3^+$ T lymphocyte (15, 25, 26, 35, 46) and $CD56^+$ NK cell numbers (15, 26, 46, 48). Furthermore, there is moderate evidence that $CD4^+$ T (15, 25, 26),

$CD8^+$ T (15, 25, 26), and $CD20^+$ B lymphocyte numbers (15, 26) are also not altered by chronic exercise, although one study reported that the number of $CD4^+$ T lymphocytes decreased and the number of $CD8^+$ T lymphocytes increased (35). The $CD4^+/CD8^+$ ratio was reported to be constant in one study (35), and decreased in another study (25). We also found that the number of $CD25^+$ T lymphocytes was stable after chronic exercise, but the level of evidence was limited (15).

Cell functions
Seven high quality studies (15, 25, 26, 44, 46, 48, 49) have investigated the function of immune cells. There is strong evidence that NKCA increases as a result of chronic exercise (15, 44, 46, 48), and the total number of lytic units required to cause 30% lysis of target cells decreased (15). There is also moderate evidence that the proliferation of lymphocytes increased due to exercise (15, 26), although one study did not see any changes after chronic exercise (25). Furthermore, there is limited evidence that exercise did not alter neutrophil oxidative burst (15). One high quality NCT analysed the activation marker CD69 on T lymphocytes, and found that the number of $CD4^+$ $CD69^+$ cells did not change after exercise, although the percentage of $CD4^+$ cells expressing CD69 was higher in the exercising group, combined with a significant decrease in the controls (26). Lastly, one study found increased phagocytic activity in monocytes after chronic exercise (49).

Inflammatory mediators
Six high (15, 16, 19, 20, 26, 59) and three low quality studies (1, 4, 30) have examined soluble inflammatory mediators in the adult population. Strong evidence is available that both pro-inflammatory (1, 4, 15, 19, 26, 30, 59) and anti-inflammatory cytokines (1, 4, 15, 19, 30) are unaltered. There is also strong evidence that CRP remains unaltered after acute (19) and chronic exercise (16, 19, 30).

Discussion

The primary aim of this review was to summarize the changes in specific immune parameters after acute and chronic exercise in pediatric and adult cancer patients and survivors. Exercise showed either an increase or no change in the majority of examined immune parameters. For example, the number of leukocytes, lymphocytes and neutrophils increased after acute bouts of exercise in both children and adults. Cytokines, however, did not show a shift towards either a pro- or anti-inflammatory profile in adults. The amount of $CD4^+$ seemingly decreases with exercise, while $CD8^+$ T lymphocytes increase, ultimately resulting in no visible shift in the $CD4^+/CD8^+$ ratio.

We found strong evidence to support an increase in the cytotoxicity of NK cells, and that the number of NK cells and T lymphocytes remained stable, along with the cytokine profile, after exercise. These findings are in line with results from studies in well-trained subjects (34), and asthma patients (40). However, a study in healthy individuals showed an increase after acute bouts of exercise due to higher NK counts (60). These discrepancies across studies may be related to the

different types of exercise performed by participants. More specifically, the increased number of NK cells and NK cytotoxicity seen in healthy participants were reported after acute exercise (53, 55, 61), while the studies in cancer patients have only examined these cells after chronic exercise interventions. Unfortunately, some studies have not reported the exact timing of blood sampling after the exercise session, making it difficult to separate immediate versus longer-term effects of exercise on immune function.

The exact mechanism underlying the effect of exercise on the immune function in cancer patients requires further study. It has been suggested that exercise has anti-inflammatory effects, and therefore, in the long term, regular physical activity can protect against the development of chronic inflammation-associated diseases (22, 33). Exercise may exert its anti-inflammatory effects through systemic mechanisms (such as reduced body fat and a reduced inflammatory status (14, 47) or site-specific mechanisms (release of anti-inflammatory cytokines from contracting muscles, catecholamines, and the inhibition of pro-inflammatory cytokine production). Hereby, a clear distinction has to be made between the role of chronic low-grade inflammation (2, 23, 27), and low numbers of immune components in the increased cancer risk (29). A shift towards an anti-inflammatory state may be favorable for cancer prevention, but may also result in a hampered response of immune cells in the tumor microenvironment. Moreover, the boundaries are still unknown between the beneficial anti-inflammatory effects and the beneficial immune boosting effects of exercise. Immune cells in the tumor microenvironment respond to different signals, such as cytokines, causing them to either display tumor-promoting or tumor-suppressing phenotypes. These cytokines are responsive to acute or chronic bouts of exercise, and may represent an "immune" signature for exercise-induced immunomodulation in the cancer microenvironment. In other words, the balance of these cytokines may indirectly reflect changes in the immune cell phenotype in the tumor microenvironment (24).

Previous studies have also reported that the effects of exercise might be dependent on the intensity, duration and type of exercise (22). We could not confirm this due to the large variety of intervention programmes. We have identified studies that have applied multiple types of exercise interventions, ranging from two to 24 weeks of duration, consisting of different intensities of exercise, and resistance, aerobic as well as combined interventions. Although it is easier to explain the beneficial effects of longer exercise duration, no clear conclusions could be drawn from our findings regarding resistance or aerobic exercise. Previous studies have reported that aerobic exercise had a stronger effect on energy balance than resistance training (3), although the latter might have a stronger effect on bone mineral density (12), and the combination of the two positively influences cardiovascular fitness, body composition, and body fat (38, 39). Future studies could apply a cross-over design in which patients receive both aerobic and resistance training separately in order to compare the effects of these training types on biomarkers and clinical outcomes.

This review highlights the current knowledge of exercise immunology in cancer patients, although a few limitations need to be considered. It is important to

acknowledge that first, only three studies were performed in children, and 18 studies in adult patients. Second, the studies examined consisted primarily of small and heterogeneous samples. Third, there was a large variability in exercise training protocols between studies, making comparison and pooling of data very difficult. Furthermore, it remains unclear whether circulating immune cells and inflammatory mediators reflect the levels at the local microenvironment. Finally, six out of 21 studies were classified as low quality studies due to high drop-out rates, and the lack of assessor blinding. Despite these limitations, this review is strengthened by the systematic and thorough search in various large databases, as well as the independent quality assessment by two reviewers. The study of immunological effects of exercise in humans is a growing area of research (22). We believe that an overview of the studies in exercise immunology in cancer patients is helpful for clinicians and researchers, especially since the last review in this area was carried out a decade ago (17), and 16 additional studies have been published since the time of this original review.

Recommendations for future studies

Based on the currently available literature, future studies should involve more homogeneous populations, preferably including a control group. The interpretation of exercise effects can be improved by detailed reporting of baseline physical fitness characteristics, as well as reports of adherence to the intervention, subject behaviour before blood collection (i.e. medications, dietary intake, and smoking status), the exact timing of blood collection, and the naturally occurring fluctuations in immune parameters. It is also important to monitor and report physical fitness after chronic exercise training.

To gain more insight into exercise-induced alterations in immune function, mediating mechanisms should be examined, outcomes should be measured at more time points during and following exercise, and they should be related to cancer outcomes (i.e. toxicity of treatments, risk of recurrence, and onset of late effects). Ultimately, the aim of research in this area should be to establish the mode, intensity and duration of exercise required to optimize the anti-inflammatory effects in cancer patients (22). Moving into an epoch focused on the practice of personalized cancer care, the study of exercise immunology might help with the development of a personalized training protocol for each cancer patient in order to diminish the side effects of the cancer treatment and to reduce the added risk of cancer recurrence. Our systematic review has focussed on the effects of a wide variety of exercise interventions on inflammation and immune function, but future studies could also look at the (long-term) clinical outcomes in these patients.

Conclusion

Many of the health benefits of regular exercise are thought to be related to its short-term boost of the immune system and long-term anti-inflammatory effects. In this systematic review, we found that Natural Killer cytotoxic activity increased after exercise in cancer patients, along with lymphocyte proliferation and granulocyte cell counts. The number of leukocytes, lymphocytes, Natural Killer cells, T lymphocytes, C-reactive protein, and pro- and anti-inflammatory mediators remained stable in response to exercise. Additional research is needed to gain insight into the mechanism linking exercise and immune function in different populations, as well as to better understand the association between these immune parameters and clinical outcomes.

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