Brain, Behavior, & Immunity - Health 2 (2020) 100016

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Full Length Article

Effects of combined exercise training on the inflammatory profile of older cancer patients treated with systemic therapy

Hugo Parent-Roberge [a,b], Adeline Fontvieille [a,b], René Maréchal [a,b], Richard Wagner [c,d], Tamàs Fülöp [b,c,d], Michel Pavic [c,d], Eléonor Riesco [a,b,*]

[a] University of Sherbrooke, Faculty of Physical Activity Sciences, 2500, boul. de l'Université, Sherbrooke, QC, J1K 2R1, Canada
[b] Research Centre on Aging, affiliated with CIUSSS de l'Estrie - CHUS, 1036, rue Belvédère sud, Sherbrooke, QC, J1H 4C4, Canada
[c] University of Sherbrooke, Faculty of Medicine and Health Sciences, 3001, 12e avenue Nord, Sherbrooke, QC, J1H 5N4, Canada
[d] Centre de recherche du CHUS, Sherbrooke, QC, J1H 5N4, Canada

ARTICLE INFO

Keywords:
Chemotherapy
Cancer related fatigue
Exercise
Inflammation
Indoleamine 2,3 dioxygenase
Oncogeriatric

ABSTRACT

Cancer-related fatigue (CRF) is a major issue in older cancer patients as it is associated with functional decline and a lower quality of life, and an increased inflammatory activity during cancer therapy is suspected to play a key role in CRF etiology. Combined aerobic and resistance exercise training is known to reduce CRF, and this could be mediated by a protective effect against this increased inflammatory activity. Hence, the main objective was to measure the effect of a 12-week combined exercise training on the inflammatory profile of older cancer patients undergoing systemic therapy. A secondary objective was to verify if there was an association between inflammatory profile and CRF.

Methods: Twenty older non-metastatic cancer patients initiating chemotherapy and/or hormone therapy were randomly assigned to 12 weeks of supervised, combined exercise or a control group (static stretching). Primary outcomes were the inflammatory profile, Indoleamine 2,3-deoxygenase activity (KYN/TRP ratio), and CRF (FACIT-F questionnaire). Control outcomes were the fasting nutritional and hormonal blood profiles, body composition (iDXA), physical activity habits (PASE questionnaire), nutritional habits (3-day log), and treatment-related variables.

Results: No worsening of the inflammatory profile was observed in both arms of the study after the intervention. No significant change in CRF was observed, although there was a trend for a reduction in the experimental group ($p = 0.10$). Significant correlations were found at both timepoints between the KYN/TRP ratio and the delay with the previous treatment received ($p \leq 0.03$).

Conclusion: These results suggest that exercise might have elicited a positive effect on CRF, which was not mediated by the modulation of the pro-inflammatory cytokine profile. However, the decrease in IL-6/IL-10 ratio in the exercise group might reflect a possible anti-inflammatory effect of exercise. Moreover, exploratory analyses suggest that an acute effect of chemotherapy treatments influenced the inflammatory profile measurements, which could explain the absence of change in the fasting inflammatory profile.

1. Introduction

Older adults represent almost 65% of the annual cancer incidence, and this proportion is expected to rise up to around 70% in the upcoming twenty years due to the world population aging (Garner et al., 2019). An important issue that has been raised in older cancer patients and survivors (oncogeriatrics) is the fact that disease and treatment-related side effects, mainly cancer-related fatigue (CRF), may accelerate the development of age-associated changes in body composition and comorbidities (Balducci and Fossa, 2013), and affect functional autonomy and quality of life (Luciani et al., 2012).

Many evidences suggest that an increased systemic inflammatory activity during cancer treatments play a key role in the etiology of CRF. Several observational and prospective studies have reported associations between CRF severity and higher blood levels of pro-inflammatory factors such as Interleukin-6 (IL-6), IL-1β and C-reactive protein (CRP) (Saligan et al., 2015). Direct evidence for a causal link was provided by data from melanoma patients receiving interferons therapies (IFN; a

* Corresponding author. University of Sherbrooke, Faculty of Physical Activity Sciences, 2500, boul. de l'Université, Sherbrooke, QC, J1K 2R1, Canada.
E-mail address: E.Riesco@USherbrooke.ca (E. Riesco).

https://doi.org/10.1016/j.bbih.2019.100016
Received 25 October 2019; Accepted 23 November 2019
Available online 20 December 2019

pro-inflammatory cytokine family), where CRF gradually developed in the weeks following therapy initiation (Capuron et al., 2002). Mechanistic insights from neuroimaging studies (Capuron et al., 2007, 2012) and animal models (Mauriño et al., 2010; Qin et al., 2007) showed that administration of IFN-α or lipopolysaccharide (LPS; *which induces a systemic inflammatory response*) upregulates the neuroinflammatory activity and dysregulates the dopaminergic metabolism of the basal ganglia, leading to fatigue or anhedonic behaviors (*reviewed in* Felger and Miller, 2012). One suspected mechanism linking systemic inflammation to CRF is the inflammatory-induced upregulation of indoleamine 2,3 dioxygenase (IDO) activity. IDO catalyzes tryptophan breakdown into kynurenine, which then participates in the CNS disruptions leading to CRF. Indeed, associations were found between CRF and the kynurenine (KYN) to tryptophan (TRP) blood levels ratio (KYN/TRP) in various cancer types (Kim et al., 2015). The KYN/TRP ratio might thus represent a good marker of the inflammatory-induced CNS disruptions that increase CRF. Interestingly, an increased KYN/TRP blood ratio was also found to be related to low-grade chronic inflammation and chronic fatigue in older adults (Capuron et al., 2011), suggesting that cancer- and aging-related inflammatory activity might both contribute to fatigue in oncogeriatrics.

In this context, moderate to vigorous combined exercise training (combining aerobic and resistance exercise) seems a promising approach in oncogeriatrics. Combined and aerobic exercise were shown to be strong non-pharmacological intervention against CRF (Segal et al., 2017). This effect has been attributed to the well-demonstrated protective effect on the fitness level during anticancer therapy (Dimeo, 2001). Based on findings in healthy middle-aged and older adults, it was proposed that this could also be mediated by the anti-inflammatory effect of exercise training (Bower and Lamkin, 2013; LaVoy et al., 2016). Both Aerobic and combined exercise can both elicit a decrease in the blood levels of pro-inflammatory markers such as IL-6 and CRP in middle-aged (Zheng et al., 2019) and older adults (Monteiro Junior et al., 2017; Zheng et al., 2019), as well as in cancer survivors (Khosravi et al., 2019).

However, less is known on the effects of combined exercise training on the inflammatory profile of older cancer patients. A protective effect against an increase of pro-inflammatory cytokines levels has been reported in older prostate cancer patients treated by radiotherapy and antiandrogenic hormone therapies (Galvão et al., 2010; Hojan et al., 2016), and was associated with lower CRF. Not much is known in older patients receiving systemic anticancer therapy (chemotherapy and hormone therapy), and conflicting results were reported in middle-aged patients. Some results suggest a protective effect of exercise against an increase in pro-inflammatory activity and CRF (Glass et al., 2015), while others showed no protective effect against inflammation but a positive impact on CRF (Christensen et al., 2014; van Vulpen et al., 2017). Finally, one study reported no protective effect of exercise against an increase of pro-inflammatory cytokines, but a parallel increase in anti-inflammatory cytokines, thereby suggesting an anti-inflammatory effect (Kleckner et al., 2019).

Therefore, the main objective of this study was to verify the effect of combined exercise training on the inflammatory profile of older cancer patients undergoing systemic anticancer treatments (chemotherapy and/or hormone therapy). It was hypothesized that the systemic therapy regimen would be accompanied by an increased level of pro-inflammatory molecules and that combined exercise would mitigate this inflammatory response. A secondary objective was to explore if changes in the inflammatory profile would be associated with expected changes in CRF.

2. Methods

2.1. Study design

This is an analysis of secondary variables from the CANEX (CANcer and EXercise) pilot study, a single-blind, two arms randomized controlled study. The main objective of the CANEX study was to evaluate the effect of a 12-week progressive and supervised mixed exercise training on CRF and health-related quality of life (HRQoL) in older non-metastatic cancer patients beginning a first-line systemic anti-cancer therapy (chemotherapy and/or hormone therapy), all cancer types being included. Baseline and post-intervention assessments were performed during two separate visits, with at least 48 h between both evaluations. The first visit included detailed presentation of the study and completion of the informed consent form, as well as resting measurement: fasting blood metabolic profile (lipids, glucose, hormonal and inflammatory profiles and nutritional status), anthropometric measures (weight, height, waist circumference), body composition (fat mass, lean mass), and CRF (FACIT-Fatigue questionnaire). Control variables were also considered: dietary habits (3-day dietary record) and physical activity levels (*self-reported past-week Physical Activity Scale for the Elderly*; PASE questionnaire). Both pre- and post-intervention assessments were identical. To control the potential effect of chemotherapy treatments on the study outcomes, post-intervention measurements were performed the same number of days after the last chemotherapy treatment than baseline measurements. Moreover, post-intervention resting measurements were performed at least 48 h after the last intervention session. Ethical approbation was obtained from the Ethics Committee of the Research Center on Aging of the *Center intégré universitaire de santé et services sociaux* (CIUSSS) de l'Estrie – CHUS.

2.2. Participants

Twenty-five men and women were recruited and randomized in the CANEX study, and twenty completed the 12-week experimental or control intervention. Inclusion criteria were: 1) Age between 65 and 85 years old; 2) ECOG (*Eastern Cooperative Oncology Group*) functional status: 0–2; 3) diagnosis of a curable, non-metastatic cancer (all cancer types included); 4) having initiated a first-line systemic anti-cancer therapy (chemotherapy and/or hormone therapy) less than 12 weeks prior to inclusion; and 5) being physically inactive at the time of inclusion (less than 75 min of structured exercise per week). Exclusion criteria were: 1) life expectancy less than 12 months at inclusion or planned surgery within 6 months following inclusion; 2) any orthopedic, musculoskeletal, or other medical contraindication to moderate to vigorous exercise, 3) severe hypertension ($\geq$160/95 mmHg, treated or not), 4) alcohol consumption of more than 2 consumptions per day; 5) smoking; and 6) any heart rate altering medication (i.e., Beta-blockers), as heart rate was used to monitor exercise intensity. Pre-screening and medical clearance to exercise were obtained during an inpatient oncogeriatric consultation at the CIUSSS de l'Estrie - CHUS. Medically eligible patients were contacted by phone for screening and presentation of the study. Interested and eligible patients were then invited for baseline assessments. Random allocation was performed using Excel software (Microsoft® 2016, CA, USA), and the allocation sequence was concealed from the exercise physiologists who performed pre- and post-intervention assessments and supervised both the experimental and control interventions.

2.3. Experimental and control interventions

The experimental intervention consisted of 12 weeks of mixed exercise training (combined aerobic and resistance training within the same session), based on the *American College of Sport's Medicine* guidelines (American College of Sports Medicine, 2017). Aerobic exercise training duration progressed from 20 to 40 min (plus 5 min of warm-up and 5 min of cool-down) and intensity progressed from 40-50% to 70–75% estimated heart rate reserve (maximal heart rate estimated using the Tanaka et al. (2001) equation: 208 – 0.7 × age). Resistance training was composed of five compound multi-joint exercises targeting lower limb, upper limb and one core exercise. As most of the participants had a totally implantable venous access device, exercises involving shoulder hyper-extension (behind the trunk) or abduction were avoided to reduce shear stress on the catheter. Volume and intensity progressed from 1 set

of 12–15 repetitions to 2–3 sets of 10–15 maximal repetitions (repetitions to failure). The progression rate was the same for every participant, and maximal duration/volume and intensity were attained in the first month of the intervention. However, a certain range of intensity and duration was allowed in the session following each chemotherapy administration, to account for the fact that exercise capacity may fluctuate in the days following a treatment. The participants realised 3 sessions per week, with 2 sessions supervised by exercise physiologists. The third weekly session was home-based, for convenience purposes, considering the burden of the many appointments of patients undergoing chemotherapy. To monitor the training load parameters and adherence of home-based sessions, a training log was used to monitor intensity and duration parameters (heart rate, rate of perceived exertion and duration of the session).

The control group also performed two weekly group sessions of supervised static stretching (30–45 min per session). The control intervention had two purposes: 1) static stretching in this population does not have an impact on physical capacity and CRF (Winters-Stone et al., 2015), and therefore served as a placebo intervention, allowing to discern between the physiological effects of exercise training and placebo effects of the supervised and group settings of the intervention; 2) this was used to minimize dropouts in the control intervention that could have resulted from the absence of contact between baseline and post-intervention assessments. To protect participants' blinding during the 3-month intervention, experimental exercise sessions and control static stretching sessions were never held at the same time, ensuring that no experimental and control participant would be present in the exercise room at the same time. All the experimental and control sessions were conducted at the Research Center on Aging (CIUSSS de l'Estrie – CHUS, QC, Canada), in a research-dedicated training facility.

2.4. Inflammatory profile

Fasting inflammatory variables were measured at baseline and post-intervention from 12-h fasting blood draws performed in the antecubital veins by an experimented nurse. Whole blood was centrifuged, and plasma frozen at −80 °C until analysis. The inflammatory profile was established by measuring pro-inflammatory cytokines (IL-6 and IL-1β), anti-inflammatory cytokines (IL-10, IL-1ra and IL-15), the acute phase C-reactive protein (CRP) and inflammatory-associated adipokines (leptin and adiponectin). The IL-6/IL-1ra ratio, IL-6/IL-10 ratio, IL-1β/IL-1ra ratio and leptin/adiponectin ratio were also computed as pro-inflammatory markers. Pro- and anti-inflammatory cytokines and CRP levels were measured by multiplex (Luminex 200, Millipore Sigma, MA, USA) using a single kit for the 5 cytokines (HCYTOMAG-60K, Millipore Sigma, MA, USA), and a separate kit for high sensitivity CRP (hsCRP) (HNDG2MAG-36K, Millipore Sigma, MA, USA). Leptin and adiponectin were measured by ELISA kits (Millipore Sigma, MA, USA), and analyzed using a spectrophotometer (Victor V, PerkinElmer, Woodbridge, ON, Canada). For each analysis, pre- and post-intervention measurements were performed in the same plate for each participant, in duplicate. Duplicates with a coefficient of variability higher than 15% were performed a second time. For CRP assays, some measurements were higher than the upper bound of the assay, and thus performed a second time after a 10-fold dilution of the samples (HCVD3MAG-67K kit, Millipore Sigma, MA, USA), and 3 correctly measured samples (randomly chosen) of the first plate were measured in the second plate to compute an inter-assays CV (Table 1).

2.5. Tryptophan to kynurenine ratio

TRP and KYN blood levels were measured using ultra high performance liquid chromatography with tandem mass spectrometry (LC-MS/MS), as described in Miller et al. (2018). The LC system was a Nexera X2 (Shimadzu, Kyoto, Japan), and the products were separated with a Luna Omega 1.6 µm Polar C18 100 A LC Column 100 × 2.1 mm (Phenomenex, Torrance, CA, USA). This method has been shown to provide high sensitivity to small variations in TRP and KYN blood levels, and a high specificity by detecting transient fluctuations in the KYN/TRP ratio induced by variations in the activity of IDO after administration of an IDO inhibitor.

2.6. Cancer-related fatigue

Cancer-related fatigue was measured using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire (Cella et al., 1993). This questionnaire comprises 13 items meant to quantify specific preoccupations linked to the physical dimension of CRF on 5-point Likert scale. The maximal score of 52 means the absence of CRF. The FACIT-F has been validated against diagnosis criterions of CRF in cancer patients undergoing anti-cancer therapies, and a threshold score of 34/52 was proposed to identify clinically significant CRF in cancer patients (Van Belle et al., 2005).

2.7. Control variables

2.7.1. Fasting metabolic blood profile

Fasting glucose, insulin and lipids (triglycerides, HDL and LDL cholesterol) levels were measured at baseline and post-intervention from 12-h fasting blood draws and used to characterize the baseline and post-intervention metabolic blood profile of the participants. Insulin level was measured by chemiluminescent immunometric assay (IMMULITE 2000 Immunoassay System, Siemens Healthineers, Erlangen, Germany), using an IMMULITE insulin kit. Glucose and lipids levels were measured at the biochemistry laboratory of the CIUSSS de l'Estrie - CHUS by enzymatic colorimetric assays (COBAS 8000 modular analyzer series, Roche Diagnostics, Bale, Switzerland).

2.7.2. Body composition and anthropometric variables

Total fat mass and total lean mass were measured using dual-energy X-ray absorptiometry (iDXA, GE Healthcare, Madison, WI, USA). Weight was measured using an electronic scale (SECA707, Hamburg, Germany) and height was measured with a stadiometer (Takei, Japan). Waist circumference was measured twice with a measuring tape, two centimeters over the iliac crest, and in case of a difference of at least 1 cm, a third measurement was taken, with the final circumference being the average of the two closest measurements.

2.7.3. Physical activity level and dietary habits

The physical activity level was estimated using the *self-reported past-week Physical Activity Scale for the Elderly* (PASE) questionnaire, that is an auto-administered, 7-day retrospective questionnaire. The PASE evaluates leisure, occupational and domestic physical activity levels. This questionnaire is correlated to the energy expenditure measured by accelerometry in community-dwelling older adults (Washburn and Ficker, 1999) and to the moderate-to-vigorous total physical activity weekly duration measured by accelerometry in older lung cancer patients (Granger et al., 2015). A 3-day dietary record (3 non-consecutive days, including two weekdays and one week-end day) was used to evaluate baseline and post-intervention dietary habits. *Nutrific* software (Université Laval, Sainte-Foy, QC, Canada) was used to estimate macronutrients intake and total caloric intake. This tool was shown to be valid and reliable to estimate total caloric intake in community-dwelling older adults without cognitive impairments (Lührmann et al., 1999). It is recognized that self-report of physical activity level and dietary habits might present systematic bias, underestimating the total caloric intake (Lührmann et al., 1999) and overestimating physical activity level in comparison of accelerometry measurement (Prince et al., 2008). However, the assessment of intra-individual change between the two measurement timepoints allows to control for potential behavioral changes between baseline and post-intervention assessments.

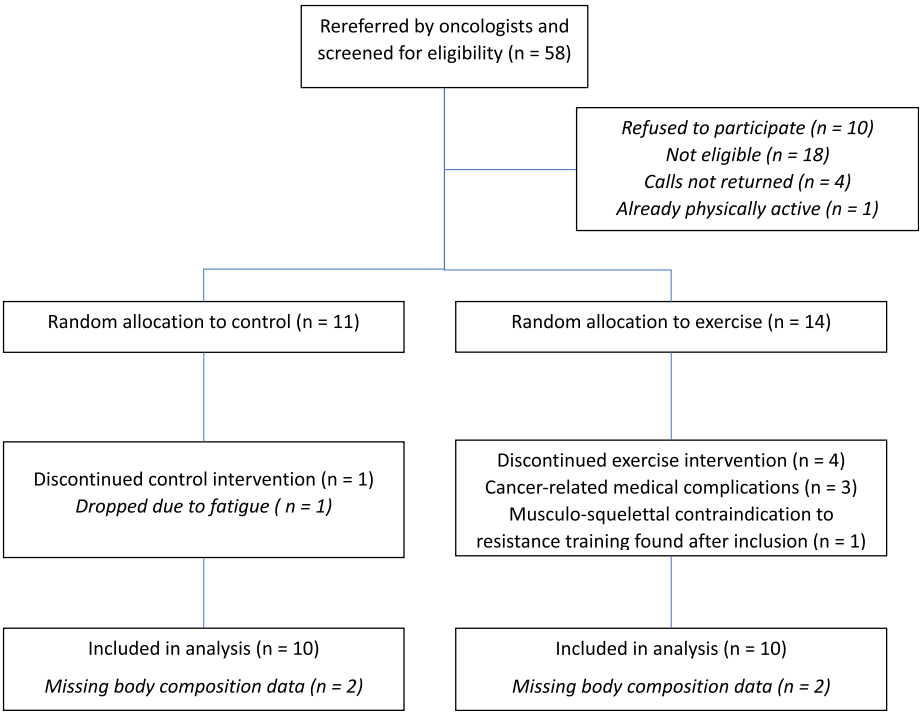

Fig. 1. Participants Flow diagram.

2.7.4. Treatment and disease-related variables

The delay (days) between systemic treatments initiation and baseline assessments could vary between 0 and 60 days. To control for this potential bias, this delay was considered as a confounding factor. In the same vein, the number of chemotherapy treatments that had been administered before each assessment was considered. Finally, the delay (in days) between each assessment and the previous chemotherapy treatment administered was also considered. The baseline delay was reproduced at post-intervention for each participant but could vary between participants. Other treatment- and disease-related control variables included treatment type and cancer type.

2.8. Statistical analysis

Data were analyzed using R version 3.6 and RStudio version 1.1.463 (Boston, MA, USA) statistical softwares. Normality of the distributions was verified using the Shapiro-Wilk test. However, some of the main outcome variables (inflammatory markers) remained significantly left-skewed after different transformation procedures. Considering this and the sample size of this pilot study (n = 20), non-parametric procedures were retained. Post-hoc sensitivity analyses were made by running 2-way factorial ANOVAs on log-transformed inflammatory variables (*data not shown*) and comparing the test results for the main effects of time and group to the corresponding non-parametric test results. This analysis revealed no significant difference that could change our conclusions, and thus, the results presented here are from non-parametric analyses. All descriptive statistics reported are shown as median (1st quartile – 3rd quartile). Between-group comparisons were made with Mann-Whitney U tests and Chi-Squared (χ^2) tests, and within-group pre-post changes were analyzed using pairwise Wilcoxon signed-rank tests. Associations between main, secondary and control variables at baseline and after the intervention were verified with Spearman rank biserial correlation coefficients, and significance level was set at alpha = 0.05, and significant results appear in bold in the tables. Considering the sample size and the exploratory aim of this pilot study, no correction for multiple testing was applied. All tests results are reported and discussed considering the hypothesis-generating goal of this analysis and the expected number of false positives.

3. Results

3.1. Recruitment and participants' characteristics

The recruitment period lasted from January 2016 to February 2019. A total of 58 potentially eligible patients were referred and screened for eligibility, and a total of 25 participants were randomized to one of the two study groups. The trial was ended when 10 participants completed both arms of the study. Baseline or post-intervention blood samples were missing for two participants of the control group and body composition data were missing for two participants in each group. Details concerning participants recruitment, experimental mortality and final sample sizes for analysis are available in Fig. 1.

Baseline characteristics of the study sample are presented in Table 2. Most of the participants were women (16/20), almost exclusively undergoing chemotherapy treatments (with or without combined hormone therapy). Only one participant in the control group of the study was undergoing hormone therapy alone at the time of her participation in the study (aromatase inhibitors). At the time of their baseline assessment, control participants had undergone significantly more chemotherapy treatments than their experimental counterparts (4 *versus* 1.5, $p = 0.05$), and the delay between their assessment and the previous chemotherapy

Table 1
Detection limits and intra-assay coefficient of variability (CV) of enzyme immunoassays.

Variable	Detection limit	Intra-assay CV	Inter-assay CV
IL-6	0.9 pg/mL	7.2%	–
IL-10	1.1 pg/mL	7.1%	–
IL-15	1.2 pg/mL	7.1%	–
IL-1β	0.8 pg/mL	8.1%	–
IL-1Ra	8.3 pg/mL	8.1%	–
hsCRP	0.001 ng/mL	7.2%	5.0%
Leptin	7.8 pg/mL	2.3%	–
Adiponectin	0.891 ng/mL	3.8%	–

Table 2
Baseline participants characteristics and treatment-related variables.

	EXP (n = 10)	CON (n = 10)	*P*
	Median (IQ range)	Median (IQ range)	
Demographic and treatment characteristics			
Age	67.5 (67.0–69.8)	69.5 (68.2–73.5)	0.20
Women (%)	9 (90%)	7 (70%)	0.57[a]
Delay before inclusion (days)	25.5 (17.8–52.0)	54.5 (38.8–60.5)	0.29
Number of chemotherapy treatments at baseline (N = 19) [b]	1.5 (1.0–2.8)	4.0 (3.0–6.0)	**0.05**
Delay between baseline assessment and the previous treatment (N = 19) [b]	14.0 (11.0–15.0)	6.0 (5.0–6.5)	**0.02**
Cancer type			
Breast	5	8	0.4[a]
Colorectal	3	2	
Non-Hodgkin Lymphoma	1	0	
Bile duct cancer	1	0	
Treatment			
Chemotherapy (%)	10	9	1.0[a]
Aromatase inhibitors therapy (%)	0	1	

[a] Between-group comparisons of proportions were performed using chi-square tests.
[b] One participant in the control group was only undergoing hormonal therapy (aromatase inhibitors) and was therefore excluded from every comparison regarding chemotherapy treatments.

treatment received had been significantly shorter (6 *versus* 14 days, $p = 0.02$).

3.2. Inflammatory profile and TRP/KYN ratio

Inflammatory variables are presented in Table 3. At baseline, significant or tendencies toward significance for between-group differences were found for the pro-inflammatory markers IL-1β and CRP levels and anti-inflammatory markers IL-1ra, IL-10 and IL-15 showing higher levels in the control group. After the 12-week intervention, the median values of these inflammatory markers were lower in the control group with CRP being the only between-group difference reaching significance. No statistically significant between-group difference was found after the intervention.

At baseline, a tendency for a higher IL-6/IL-10 ratio (a pro-inflammatory marker) in the experimental group was found ($p = 0.08$). After the 12-week intervention, a significant pre-post difference was found for the IL-6/IL-10 ratios in the experimental group ($p = 0.03$), as well as a tendency for a lower IL-6/IL-10 ratio in the experimental group ($p = 0.08$). The KYN/TRP ratios are presented in Table 3. No between-group difference was found both at baseline and after the intervention, and no pre-post change was found in both groups.

3.3. Cancer-related fatigue

At baseline, the median FACIT-F scores of the experimental and control group were respectively of 36 (33.5–43.2) and 40.5 (35.2–47), which was not significantly different ($p = 0.31$). After the intervention, the median scores of the experimental and control group were respectively of 40.5 (36.5–44) and 45 (27.8–47), which was also not statistically significant ($p = 0.50$). However, there was a trend for a significant increase in the experimental group scores after the intervention group ($p = 0.10$), with the median difference (delta) corresponding in an increase of 4 points on the FACIT-F scale. There was no significant change in CRF level of the control group (p = 0,81), with the median *delta* corresponding to a decrease of 0.5.

3.4. Control variables

3.4.1. Body composition and metabolic profile

Body composition, anthropometric variables and fasting metabolic blood profile are reported in Table 4. The between-group difference reached significance for BMI at post-intervention ($p = 0.05$), although no statistically significant pre-post change was found. Finally, there was a significant increase in total lean mass in the experimental group ($p = 0.02$).

Table 3
Baseline and post-intervention inflammatory variables.

	Baseline			Post-intervention			Pre-Post Change	
	EXP (n = 10)	CON (n = 8)	*P*	EXP (n = 10)	CON (n = 8)	*P*	EXP	CON
	Median (IQ range)	Median (IQ range)		Median (IQ range)	Median (IQ range)		p-value	p-value
IL-1β (pg/mL)	0.9 (0.4–1.1)	4.1 (2.8–9.1)	**0.04**	1 (0.4–1.6)	0.5 (0.4–4.4)	0.89	0.62	0.11
IL-1ra (pg/mL)	28.8 (11.7–43)	104.5 (65–199.8)	0.07	45.4 (7.4–129.7)	11.4 (6.7–105.2)	0.76	0.85	0.31
IL-10 (pg/mL)	1.7 (0.5–9.2)	16.6 (12.2–33.1)	**0.01**	8.2 (4.5–16.4)	8.5 (0.5–14.4)	0.69	0.41	0.25
IL-15 (pg/mL)	2.0 (1.8–4.6)	8.1 (5.8–12.9)	**0.04**	2.5 (1.8–6.6)	1.2 (0.4–11.2)	0.40	0.85	0.20
IL-6 (pg/mL)	0.7 (0.2–3.7)	4.3 (1.3–7.7)	0.23	0.5 (0.1–3.3)	2 (1.1–6.2)	0.19	0.93	0.27
IL-6/IL-10	0.47 (0.3–0.67)	0.15 (0.07–0.35)	0.08	0.17 (0.05–0.24)	0.73 (0.18–3.2)	0.08	**0.03**	0.46
IL-6/IL-1ra	0.02 (0.00–0.30)	0.04 (0.02–0.06)	0.57	0.02 (0.01–0.3)	0.2 (0.0–1.4)	0.17	1.00	0.38
IL-1β/IL-1ra	0.02 (0.01–0.3)	0.05 (0.03–0.07)	0.56	0.02 (0.00–0.27)	0.05 (0.04–0.44)	0.56	0.92	0.38
CRP (mg/L)	4.7 (3.8–5.8)	24.2 (12.1–46.7)	**> 0.0001**	3.1 (2.0–8.1)	10.4 (5.2–20.6)	0.08	0.73	**0.02**
Leptin (ng/mL)	16.2 (9.5–36)	25.1 (20.3–36.5)	0.36	13.4 (8.4–30.9)	31.2 (20.3–50.2)	0.12	0.85	0.46
Adiponectin (μg/ml)	13.8 (9.3–21.3)	17.5 (14.8–24.8)	0.27	15.6 (7.8–24.8)	25.1 (15.4–33.2)	0.10	1.00	0.27
LAR	1.3 (0.5–3.1)	1.2 (0.9–2.5)	0.79	0.8 (0.4–3.5)	1.9 (0.6–2.5)	0.90	0.38	0.74
KYN/TRP	0.05 (0.04–0.05)	0.04 (0.03–0.05)	0.32	0.04 (0.03–0.05)	0.03 (0.03–0.05)	0.76	0.32	0.46

LAR: Leptin to adiponectin ratio.
KYN/TRP: Kynurenine to Tryptophan ratio.

Table 4
Baseline and post-intervention body composition and metabolic profile.

	Baseline		*P*	Post-intervention		*P*	Pre-Post Change	
	EXP (n = 10)	CON (n = 10)		EXP (n = 10)	CON (n = 10)		EXP	CON
	Median (IQ range)	Median (IQ range)		Median (IQ range)	Median (IQ range)		*P*	*P*
Body composition and anthropometrics								
Weight (kg)	61.4 (58.2–72.7)	70.2 (64.2–76.4)	0.40	61 (58.4–71.9)	71.3 (63.9–77)	0.18	0.73	0.43
BMI (kg/m^2)	23.4 (21.7–28.8)	27.5 (25.6–29.7)	0.16	23.3 (22.1–26.1)	26.6 (24.7–30.5)	**0.05**	1.0	0.95
WC (cm)	89.2 (87.4–99.9)	96 (92.9–109.4)	0.48	91.2 (87.5–95.6)	96 (92.5–101.5)	0.25	0.91	0.83
Fat mass (kg)	21.7 (15.5–29)	30.3 (24.9–32.5)	0.28	20.8 (17.5–24.1)	29.4 (24.5–32.9)	0.08	0.94	0.64
Lean mass (kg)	37 (35.3–45.6)	35.8 (35–40.1)	0.69	38.4 (34.1–47.2)	37.1 (35.7–39.9)	1.00	**0.02**	0.74
Fasting metabolic profile								
Resting SBP (mmHg)	128 (119–134)	133 (118–144)	0.60	127 (120–129)	124 (110–147)	0.77	0.55	0.89
Resting DBP (mmHg)	81 (75–85)	79 (71–82)	0.40	75 (68–78)	78 (70–82)	0.41	**0.01**	0.83
Glucose (mmol/L)	4.8 (4.3–5)	4.7 (4.3–5.1)	0.79	4.7 (4.6–4.9)	4.7 (4.2–4.7)	0.93	0.63	1
Insulin (μUI/L)	75 (44.2–93.8)	80 (69–91.2)	0.74	66 (29–104)	65 (36–80)	1.00	0.57	0.82
Total cholesterol (mmol/L)	4.2 (3.6–5.4)	5.1 (4.6–5.9)	0.22	4.5 (3.8–5.3)	5.5 (4.9–6.3)	0.22	0.3	0.36
HDL-C (mmol/L)	1.4 (1.2–1.7)	1.4 (1.3–1.5)	0.79	1.6 (1–1.9)	1.4 (1.4–1.5)	1.00	0.5	0.63
LDL-C (mmol/L)	2.4 (2–2.9)	2.9 (2.4–4)	0.14	2.6 (2.1–3)	3.1 (2.3–3.9)	0.22	0.1	0.36
Triglycerides (mmol/L)	1.2 (0.8–1.5)	1.5 (1.2–1.8)	0.12	1.2 (1.1–1.5)	1.3 (1.1–2.1)	0.39	0.29	0.3
Albuminemia (g/L)	43 (42–44.4)	42.3 (40.9–43.1)	0.13	42.2 (41.9–43.3)	43.1 (42.1–44.6)	0.67	0.77	0.17
Prealbuminemia (g/L)	0.3 (0.2–0.3)	0.2 (0.2–0.3)	0.52	0.2 (0.2–0.3)	0.2 (0.2–0.3)	0.69	0.57	0.25
Physical activity level	86.5 (60.4–127.9)	55 (38.2–63)	0.18	97.7 (82.3–114.5)	72.2 (55.2–119)	0.48	1.00	0.62
Total energy intake (kcal)	1657 (1486–2527)	1714 (1578–1936)	0.72	1989 (1624–2240)	1468 (1377–1792)	**0.02**	0.82	0.25

WC: Waist circumference.

Considering the fasting metabolic blood profile, no between-group difference was found at baseline or after the intervention. Only resting diastolic blood pressure decreased in the experimental group ($p = 0.01$).

3.4.2. *Nutritional and physical activity habits*

No significant difference was observed at baseline. However, there was a difference in the estimated total energy intake ($p = 0.02$) after the 12-week intervention, with a lower total caloric intake in the control group.

3.5. *Associations between the inflammatory profile, CRF and treatment-related variables*

No significant correlation was found between any inflammatory markers and CRF at baseline (all $p > 0.12$) nor after the intervention (all $p > 0.56$). Correlations were also verified between the inflammatory markers and the treatment- and disease-related variables, for exploratory purposes. After the intervention, correlations reaching significance were found for the delay (in days) between the first chemotherapy treatment and post-intervention assessment, and IL-1β ($r = -0.62, p = 0.006$), IL-15 ($r = -0.68, p = 0.001$) and leptin ($r = 0.48, p = 0.045$). Similarly, there was a correlation between the delay separating post-intervention assessment and the previous chemotherapy treatment received, and the KYN/TRP ($r = 0.51, p = 0.03$) and IL-1β/IL-1ra ($r = -0.62, p = 0.006$) ratios. Interestingly, most of the individuals with a low KYN/TRP and all the individuals with an increased IL-1β/IL-1ra had their blood drawn the week following their previous chemotherapy (Supplementary Figs. 1 and 2). No other correlation reaching significance was found between inflammatory markers and treatment- and disease-related variables.

4. Discussion

The main objective of this study was to verify the effect of a 12-week supervised combined exercise training on the inflammatory profile of older cancer patients beginning a systemic anti-cancer therapy. It was hypothesized that the systemic treatments period would be accompanied by an increase of pro-inflammatory markers levels, and that exercise training would blunt this response, in comparison to an increase in the control group. A secondary objective was to verify if changes in the plasma concentration of pro- or anti-inflammatory markers would show associations with CRF changes. Contrary to our hypotheses, no increase in the inflammatory markers was observed in both groups, and no association with CRF were found, both before and after the intervention.

The significant IL-6/IL-10 ratio decrease in the experimental group might reflect a modulatory effect of exercise on the systemic inflammatory activity. Kleckner et al. (2019) also reported that combined exercise training seemed to mitigate the pro-inflammatory effect of chemotherapy by strengthening the correlations between blood levels of IL-6 and IL-10 levels, and IL-1β and IL-10. Nevertheless, when considering all the other inflammatory markers and the KYN/TRP ratio, this hypothesis must be taken cautiously. Regarding CRF, although our results suggest that exercise might have elicited a positive effect on this outcome, no correlation was found between any inflammatory markers and CRF at baseline or after the intervention.

It should be noticed that no worsening of both fasting inflammatory profile and CRF level were observed in the control group after the 12-week intervention. Moreover, the post-intervention inflammatory profile of both groups was comparable to what was previously reported in middle-aged and older adults without cancer (Kim et al., 2011; Stowe et al., 2010; Wyczalkowska-Tomasik et al., 2016). Similarly, the median post-intervention FACIT-F score was also similar to what has been measured in healthy older adults (Montan et al., 2018) and higher than the proposed threshold of 34/52 representing a clinically significant CRF (Van Belle et al., 2005). Overall, the chemotherapy treatments *per se* did not seem to worsen the inflammatory profile and CRF level, which could explain the absence of protective effect of exercise on the pro-inflammatory profile in this study. This might be explained by the fact that the study sample included early stage cancer patients (TNM stage I or II) with high functional status (ECOG score = 0 or 1). No increase in pro-inflammatory markers, both with or without exercise, was also reported in a sample of early stage breast cancer patients undergoing chemotherapy, although exercise elicited a positive effect on CRF (Al-Majid et al., 2015). However, such increases in pro-inflammatory activity has been reported in the control groups of studies including chemotherapy-treated patients for advanced and metastatic cancers with a poorer baseline functional status (Glass et al., 2015; Kleckner et al., 2019; van Vulpen et al., 2017). Accordingly, the TNM cancer stage and functional status were shown to be associated with higher systemic inflammatory activity in colorectal cancer patients (Kersten et al., 2013). Moreover, one prospective study in chemotherapy-treated patients found

significant correlations between increases in fasting inflammatory markers and CRF, but only in patients with higher CRF levels (Cruz et al., 2015). Another possible explanation might rely on the type of cancer treatment. To our knowledge, all studies involving exercise during radiotherapy showed an increased inflammatory activity in their control groups and a protective effect of aerobic or combined exercise (Galvão et al., 2010; Hojan et al., 2016; Schmidt et al., 2016; Sprod et al., 2010). Therefore, considering our results at the light of these studies tend to confirm that the effect of exercise training on the systemic inflammatory profile in cancer patients could be treatment-dependant. Taken altogether, these data suggest that the effect of exercise on CRF during chemotherapy does not seem mediated by a protective effect against increases in blood levels of pro-inflammatory markers, at least in non-metastatic cancer patients with a great baseline functional status.

Nevertheless, in regard of the proposed key-role of inflammation in CRF etiology, another hypothesis should be discussed to explain these discrepancies. The correlations found between the KYN/TRP ratio, the IL-1β/IL-1ra ratio and the delay with the previous treatment received suggests that the inflammatory activity could be acutely influenced by chemotherapy. In that respect, previous studies have shown that a single chemotherapy dose can induce acute and transient peaks of IL-6, TNF-α (Raudonis et al., 2016) and CRP (Milroy et al., 1989) levels in the days following administration in breast and lung cancers, followed by decreases in these levels. Considering the pre-post measurements design of the present study, this could explain why no worsening of the inflammatory profile was observed in both groups after the 12-week intervention. On the opposite, progressive weekly increases were observed in IL-6, IL-1β, CRP and sTNF-RI blood levels in patients receiving daily radiotherapy (Bower et al., 2009) or advanced cancer patients receiving chemoradiotherapy (Wang et al., 2012). This could explain why control groups of exercise studies in radiotherapy patients consistently report a worsening of the inflammatory profile without exercise.

Importantly, these chemotherapy-induced inflammatory peaks also match peaks in CRF in the days following treatment administration (Raudonis et al., 2016). Considering what is already known about inflammation-induced CRF, these peaks might be causally linked. Therefore, it remains possible that the cumulative acute inflammatory peaks caused by successive chemotherapy treatments could induce the CNS disruptions that were previously linked with CRF initiation and progression. In accordance with this hypothesis, animal models of LPS administration, inducing transient systemic inflammation, can induce a prolonged neuroinflammatory activity and dopaminergic alterations (Bodea et al., 2014; Qin et al., 2007, 2013). If this hypothesis is true, it remains possible that exercise could modulate this acute inflammatory response to every single dose of chemotherapy, thereby blunting the peak of CRF that follows treatment administration. The acute immune-inflammatory response to a single aerobic exercise session is well documented. It is known that a transient increase in inflammatory molecules (mainly IL-6) during exercise is followed by an increase in anti-inflammatory molecules IL-1ra and IL-10 in the hours following exercise cessation (Peake et al., 2015). Similarly, exercise acutely interferes with the KYN metabolism and seems to acutely reduce its availability, which could represent a protective mechanism against the KYN-induced CNS disruptions (*reviewed in* Metcalfe et al., 2018). Thus, the timing of exercise could represent an important factor to consider in patients undergoing chemotherapeutic treatments and struggling with CRF. In this regard, future studies should investigate the acute inflammatory and CRF response to a single exercise session in the days following a chemotherapy treatment administration. Moreover, this effect should be specifically verified in older cancer patients, as in healthy older adults, this acute inflammatory response to aerobic exercise is blunted (Windsor et al., 2018).

The reported results and hypothesis discussed here should be weighted against the study limitations. The small sample size, unbalanced baseline groups despite randomization and the non-parametric analyses employed all significantly limit the generalization of these findings. In this regard, it is noteworthy that the between-group differences at baseline and the pre-post observed changes could also be explained by a regression to the mean phenomenon due to randomness, and thus the aim of this exploratory analysis should be seen as an hypotheses-generating rather than a confirmatory one. Still, these results agree with previous studies reporting that exercise in chemotherapy-treated cancer patients can increase levels of IL-10 without significantly altering the fasting blood levels of most pro-inflammatory markers (Al-Majid et al., 2015; Kleckner et al., 2019). Another important limitation is the variability in cancer type and treatment protocol within the sample. However, treatment- and disease-related variables were documented, and the delay between baseline assessment and the last chemotherapy treatment was reproduced at post-intervention assessment, to minimize the effect of this confounding factor. In this regard, an important strength of this study is the rigorous control of many potential confounding biological and behavioral variables and the fact that exercise training in clinical setting is usually prescribed regardless of cancer type.

5. Conclusion

This pilot study suggests that mixed exercise training could elicit a positive effect on CRF without modulating the fasting systemic pro-inflammatory profile in early stage older cancer patients undergoing chemotherapeutic treatments. Based on the reported results and previous findings, we propose that future studies are needed to differentiate the acute and chronic effects of exercise in older adults undergoing chemotherapy.

Declaration of competing interest

The authors declare no conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2019.100016.

References

Al-Majid, S., Wilson, L.D., Rakovski, C., Coburn, J.W., 2015. Effects of exercise on biobehavioral outcomes of fatigue during cancer treatment: results of a feasibility study. Biol. Res. Nurs. 17 (1) https://doi.org/10.1177/1099800414523489.

American College of Sports Medicine, 2017. In: Williams, Lippincott, Wilkins (Eds.), ACSM'S Guidelines for Exercise Testing and Prescription, tenth ed.

Balducci, L., Fossa, S.D., 2013. Rehabilitation of older cancer patients. Acta Oncol. 52 (2), 233–238. https://doi.org/10.3109/0284186X.2012.744142.

Bodea, L.G., Wang, Y., Linnartz-Gerlach, B., Kopatz, J., Sinkkonen, L., Musgrove, R., et al., 2014. Neurodegeneration by activation of the microglial complement-phagosome pathway. J. Neurosci. 34 (25), 8546–8556. https://doi.org/10.1523/JNEUROSCI.5002-13.2014.

Bower, J.E., Ganz, P.A., Tao, M.L., Hu, W., Belin, T.R., Sepah, S., et al., 2009. Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. Clin. Cancer Res.: Off. J. Am. Assoc. Canc. Res. 15 (17), 5534–5540. https://doi.org/10.1158/1078-0432.CCR-08-2584.

Bower, J.E., Lamkin, D.M., 2013. Inflammation and cancer-related fatigue : mechanisms , contributing factors , and treatment implications. Brain Behav. Immun. 30, S48–S57. https://doi.org/10.1016/j.bbi.2012.06.011.

Capuron, L., Gumnick, J.F., Musselman, D.L., Lawson, D.H., Reemsnyder, A., Nemeroff, C.B., Miller, A.H., 2002. Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 26 (01), 643–652. https://doi.org/10.1016/S0893-133X(01)00407-9.

Capuron, L., Pagnoni, G., Demetrashvili, M.F., Lawson, D.H., Fornwalt, F.B., Woolwine, B., et al., 2007. Basal ganglia hypermetabolism and symptoms of fatigue during interferon-α therapy. Neuropsychopharmacology 32 (11), 2384–2392. https://doi.org/10.1038/sj.npp.1301362.

Capuron, L., Pagnoni, G., Drake, D.F., Woolwine, B.J., Spivey, J.R., Crowe, R.J., et al., 2012. Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration. Arch. Gen. Psychiatr. 69 (10), 1044–1053. https://doi.org/10.1001/archgenpsychiatry.2011.2094.

Capuron, L., Schroecksnadel, S., Féart, C., Aubert, A., Higueret, D., Barberger-Gateau, P., et al., 2011. Chronic low-grade inflammation in elderly persons is associated with

altered tryptophan and tyrosine metabolism: role in neuropsychiatric symptoms. Biol. Psychiatry 70 (2), 175–182. https://doi.org/10.1016/j.biopsych.2010.12.006.
Cella, D.F., Tulsky, D.S., Gray, G., Sarafian, B., Linn, E., Bonomi, A., et al., 1993. The functional assessment of cancer therapy scale: development and validation of the general measure. J. Clin. Oncol. https://doi.org/10.1200/JCO.1993.11.3.570.
Christensen, J.F., Tolver, A., Andersen, J.L., Rørth, M., Daugaard, G., Hojman, P., 2014. Resistance training does not protect against increases in plasma cytokine levels among germ cell cancer patients during and after chemotherapy. J. Clin. Endocrinol. Metab. 99 (8), 2967–2976. https://doi.org/10.1210/jc.2013-4495.
Cruz, F.M., Munhoz, B.A., Ca Alves, B., Gehrke, F.S., La Fonseca, F., Kuniyoshi, R.K., et al., 2015. Biomarkers of fatigue related to adjuvant chemotherapy for breast cancer: evaluation of plasma and lymphocyte expression. Clin. Transl. Med. 4 (4), 1–9. https://doi.org/10.1186/s40169-015-0051-8.
Dimeo, F.C., 2001. Effects of exercise on cancer-related fatigue. Cancer 92 (6 Suppl. l), 1689–1693. https://doi.org/10.1002/1097-0142(20010915)92:6+<1689::AID-CNCR1498>3.0.CO;2-H.
Felger, J.C., Miller, A.H., 2012. Cytokine effects on the basal ganglia and dopamine function: the subcortical source of inflammatory malaise. Front. Neuroendocrinol. 33 (3), 315–327. https://doi.org/10.1016/j.yfrne.2012.09.003.
Galvão, D.A., Taaffe, D.R., Spry, N., Joseph, D., Newton, R.U., 2010. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. J. Clin. Oncol. 28 (2), 340–347. https://doi.org/10.1200/JCO.2009.23.2488.
Garner, W.B., Smith, B.D., Shabason, J.E., Williams, G.R., Martin, M.Y., Ballo, M.T., VanderWalde, N.A., 2019. Predicting future cancer incidence by age and gender. J. Clin. Oncol. 37 (15_Suppl. l), 1559. https://doi.org/10.1200/JCO.2019.37.15_suppl.1559.
Glass, O.K., Inman, B.A., Broadwater, G., Courneya, K.S., Mackey, J.R., Goruk, S., et al., 2015. Effect of aerobic training on the host systemic milieu in patients with solid tumours: an exploratory correlative study. Br. J. Canc. 112 (5), 825–831. https://doi.org/10.1038/bjc.2014.662.
Granger, C.L., Parry, S.M., Denehy, L., 2015. The self-reported Physical Activity Scale for the Elderly (PASE) is a valid and clinically applicable measure in lung cancer. Support. Care Cancer 23 (11), 3211–3218. https://doi.org/10.1007/s00520-015-2707-8.
Hojan, Katarzyna, Kwiatkowska-Borowczyk, E., Leporowska, E., Gorecki, M., Ozga-Majchrzak, O., Milecki, T., Milecki, P., 2016. Physical exercise for functional capacity, blood immune function, fatigue, and quality of life in high-risk prostate cancer patients during radiotherapy: a prospective, randomized clinical study. Eur. J. Phys. Rehabil. Med. 52 (4), 489–501.
Kersten, C., Louhimo, J., Ålgars, A., Lahdesmaki, A., Cvancerova, M., Stenstedt, K., et al., 2013. Increased C-reactive protein implies a poorer stage-specific prognosis in colon cancer. Acta Oncol. 52 (8), 1691–1698. https://doi.org/10.3109/0284186X.2013.835494.
Khosravi, N., Stoner, L., Farajivafa, V., Hanson, E.D., 2019. Exercise training, circulating cytokine levels and immune function in cancer survivors: a meta-analysis. Brain Behav. Immun. (August) https://doi.org/10.1016/j.bbi.2019.08.187, 0–1.
Kim, H., Kim, H.-S., Youn, J.-C., Shin, E.-C., Park, S., 2011. Serum cytokine profiles in healthy young and elderly population assessed using multiplexed bead-based immunoassays. J. Transl. Med. 9 (1), 113. https://doi.org/10.1186/1479-5876-9-113.
Kim, S., Miller, B.J., Stefanek, M.E., Miller, A.H., 2015. Inflammation-induced activation of the indoleamine 2,3-dioxygenase pathway: relevance to cancer-related fatigue. Cancer 121 (13), 2129–2136. https://doi.org/10.1002/cncr.29302.
Kleckner, I.R., Kamen, C., Cole, C., Fung, C., Heckler, C.E., Guido, J.J., et al., 2019. Effects of exercise on inflammation in patients receiving chemotherapy: a nationwide NCORP randomized clinical trial. Support. Care Cancer. https://doi.org/10.1007/s00520-019-04772-7.
LaVoy, E.C.P., Fagundes, C.P., Dantzer, R., 2016. Exercise, inflammation, and fatigue in cancer survivors. Exerc. Immunol. Rev. 22 (713), 82–93.
Luciani, A., Jacobsen, P.B., Extermann, M., Foa, P., Marussi, D., Ferrari, D., et al., 2012. The impact of fatigue and anemia on functional status in older cancer patients treated with chemotherapy. J. Geriatr. Oncol. 3 (3), 182–188. https://doi.org/10.1016/j.jgo.2012.02.004.
Lührmann, P.M., Herbert, B.M., Gaster, C., Neuhäuser-Berthold, M., 1999. Validation of a self-administered 3-day estimated dietary record for use in the elderly. Eur. J. Nutr. 38 (5), 235–240. https://doi.org/10.1007/s003940050066.
Mauriño, R., Machado, A., Santiago, M., 2010. Effect of in vivo striatal perfusion of lipopolysaccharide on dopamine metabolites. Neurosci. Lett. 475 (3), 121–123. https://doi.org/10.1016/j.neulet.2010.03.050.
Metcalfe, A.J., Koliamitra, C., Javelle, F., Bloch, W., Zimmer, P., 2018. Acute and chronic effects of exercise on the kynurenine pathway in humans – a brief review and future perspectives. Physiol. Behav. 194 (July), 583–587. https://doi.org/10.1016/j.physbeh.2018.07.015.
Miller, D., Tan, L., Dorshorst, D., Morrissey, K., Mahrus, S., Milanowski, D., et al., 2018. A validated surrogate analyte LC-MS/MS assay for quantitation of endogenous kynurenine and tryptophan in human plasma. Bioanalysis 10 (16), 1307–1317. https://doi.org/10.4155/bio-2018-0044.
Milroy, R., Shapiro, D., Shenkin, A., Banham, S.W., 1989. Acute phase reaction during chemotherapy in small cell lung cancer. Br. J. Canc. 59 (6), 933–935. https://doi.org/10.1038/bjc.1989.197.
Montan, I., Löwe, B., Cella, D., Mehnert, A., Hinz, A., 2018. General population norms for the functional assessment of chronic illness therapy (FACIT)-Fatigue scale. Value Health 21 (11), 1313–1321. https://doi.org/10.1016/j.jval.2018.03.013.
Monteiro Junior, R.S., De Tarso Maciel-Pinheiro, P., Matta M Portugal, E., da Silva Figueiredo, L.F., Terra, R., Carneiro, L.S.F., et al., 2017. Effect of exercise on inflammatory profile of older persons: systematic review and meta-analyses. J. Phys. Act. Health 1–8. https://doi.org/10.1123/ijspp.2015-0012. Oct 26.
Peake, J.M., Della Gatta, P., Suzuki, K., Nieman, D.C., 2015. Cytokine expression and secretion by skeletal muscle cells: regulatory mechanisms and exercise effects. Exerc. Immunol. Rev. 21 (32), 8–25.
Prince, S.A., Adamo, K.B., Hamel, M.E., Hardt, J., Connor Gorber, S., Tremblay, M., 2008. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. Int. J. Behav. Nutr. Phys. Act. 5 https://doi.org/10.1186/1479-5868-5-56.
Qin, L., Liu, Y., Hong, J.S., Crews, F.T., 2013. NADPH oxidase and aging drive microglial activation, oxidative stress, and dopaminergic neurodegeneration following systemic LPS administration. Glia 61 (6), 855–868. https://doi.org/10.1002/glia.22479.
Qin, L., Wu, X., Block, M.L., Liu, Y., Breese, G.R., Knapp, D.J., et al., 2007. Systemic LPS causes chronic Neuroinflammation and progressive neurodegeneration, 55, pp. 453–462. https://doi.org/10.1002/glia.20467.Systemic, 5.
Raudonis, B.M., Kelley, I.H.I.H., Rowe, N., Ellis, J., 2016. A pilot study of proinflammatory cytokines and fatigue in women with breast cancer during chemotherapy. Cancer Nurs. 40 (4), 323–331. https://doi.org/10.1097/NCC.0000000000000406.
Saligan, L.N., Olson, K., Filler, K., Larkin, D., Cramp, F., Sriram, Y., et al., 2015. The biology of cancer-related fatigue: a review of the literature. Support. Care Cancer 23 (8), 2461–2478. https://doi.org/10.1007/s00520-015-2763-0.
Schmidt, M.E., Meynköhn, A., Habermann, N., Wiskemann, J., Oelmann, J., Hof, H., et al., 2016. Resistance exercise and inflammation in breast cancer patients undergoing adjuvant radiation therapy: mediation analysis from a randomized, controlled intervention trial. Int. J. Radiat. Oncol. Biol. Phys. 94 (2), 329–337. https://doi.org/10.1016/j.ijrobp.2015.10.058.
Segal, R., Zwaal, C., Green, E., Tomasone, J.R., Loblaw, A., Petrella, T., Exercise for People with Cancer Guideline Development Group, 2017. Exercise for people with cancer: a systematic review. Curr. Oncol. 24 (4), e290–e315. https://doi.org/10.3747/co.24.3619.
Sprod, L.K., Palesh, O.G., Janelsins, M.C., Peppone, L.J., Heckler, C.E., Adams, M.J., Mustian, K.M., 2010. Exercise, sleep quality, and mediators of sleep in breast and prostate cancer patients receiving radiation therapy. Community Oncology 7 (10), 463–471.
Stowe, R.P., Peek, M.K., Cutchin, M.P., Goodwin, J.S., 2010. Plasma cytokine levels in a population-based study: relation to age and ethnicity. J. Gerontol. Ser. A: Biol. Sci. Med. Sci. 65A (4), 429–433. https://doi.org/10.1093/gerona/glp198.
Tanaka, H., Monahan, K.D., Seals, D.R., 2001. Age-predicted maximal heart rate revisited. J. Am. Coll. Cardiol. https://doi.org/10.1016/S0735-1097(00)01054-8.
Van Belle, S., Paridaens, R., Evers, G., Kerger, J., Bron, D., Foubert, J., et al., 2005. Comparison of proposed diagnostic criteria with FACT-F and VAS for cancer-related fatigue: proposal for use as a screening tool. Support. Care Cancer 13 (4), 246–254. https://doi.org/10.1007/s00520-004-0734-y.
van Vulpen, J.K., Schmidt, M.E., Velthuis, M.J., Wiskemann, J., Schneeweiss, A., Vermeulen, R.C.H., et al., 2017. Effects of physical exercise on markers of inflammation in breast cancer patients during adjuvant chemotherapy. Breast Canc. Res. Treat. 1–11.
Wang, X.S., Williams, L.A., Krishnan, S., Liao, Z., Liu, P., Mao, L., et al., 2012. Serum sTNF-R1, IL-6, and the development of fatigue in patients with gastrointestinal cancer undergoing chemoradiation therapy. Brain Behav. Immun. 26 (5), 699–705. https://doi.org/10.1016/j.bbi.2011.12.007.
Washburn, R.A., Ficker, J.L., 1999. Physical Activity Scale for the Elderly (PASE): the relationship with activity measured by a portable accelerometer. The Journal of Sports Medicine and Physical Fitness 39 (4), 336–340. https://doi.org/10.1177/1010539515590179.
Windsor, M.T., Bailey, T.G., Perissiou, M., Meital, L., Golledge, J., Russell, F.D., Askew, C.D., 2018. Cytokine responses to acute exercise in healthy older adults: the effect of cardiorespiratory fitness. Front. Physiol. 9 (MAR), 1–8. https://doi.org/10.3389/fphys.2018.00203.
Winters-Stone, K.M., Dobek, J.C., Bennett, J.A., Dieckmann, N.F., Maddalozzo, G.F., Ryan, C.W., Beer, T.M., 2015. Resistance training reduces disability in prostate cancer survivors on androgen deprivation therapy: Evidence from a randomized controlled trial. Archives of Physical Medicine and Rehabilitation 96 (1), 7–14. https://doi.org/10.1016/j.apmr.2014.08.010.
Wyczalkowska-Tomasik, A., Czarkowska-Paczek, B., Zielenkiewicz, M., Paczek, L., 2016. Inflammatory markers change with age, but do not fall beyond reported normal ranges. Arch. Immunol. Ther. Exp. 64 (3), 249–254. https://doi.org/10.1007/s00005-015-0357-7.
Zheng, G., Qiu, P., Xia, R., Lin, H., Ye, B., Tao, J., Chen, L., 2019. Effect of aerobic exercise on inflammatory markers in healthy middle-aged and older adults: a systematic review and meta-analysis of randomized controlled trials. Front. Aging Neurosci. 11 (APR) https://doi.org/10.3389/fnagi.2019.00098.