The Journal of Physiology

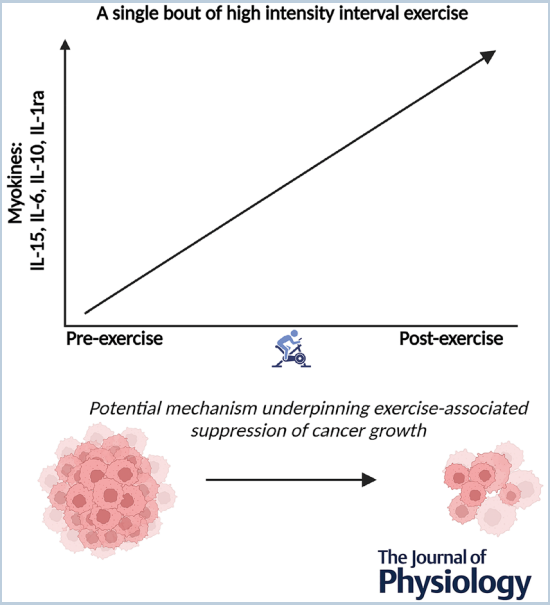
Interleukin-15 and high-intensity exercise: relationship with inflammation, body composition and fitness in cancer survivors

Morgan J. Farley[1,2,3], Alexander N. Boytar[2], Kirsten N. Adlard[2], Chloe E. Salisbury[2], Nicolas H. Hart[1,3,4,5,6], Mia A. Schaumberg[2,7,8,9], David G. Jenkins[2,7,8,10] and Tina L. Skinner[1,2,7,11]

[1]*Human Performance Research Centre, INSIGHT Research Institute, Faculty of Health, University of Technology Sydney (UTS), Sydney, New South Wales, Australia*
[2]*School of Human Movement and Nutrition Sciences, The University of Queensland, Brisbane, Queensland, Australia*
[3]*Cancer and Palliative Care Outcomes Centre, Faculty of Health, Queensland University of Technology (QUT), Brisbane, Queensland, Australia*
[4]*Caring Futures Institute, College of Nursing and Health Sciences, Flinders University, Adelaide, South Australia, Australia*
[5]*Exercise Medicine Research Institute, School of Medical and Health Sciences, Edith Cowan University, Perth, Western Australia, Australia*
[6]*Institute for Health Research, University of Notre Dame Australia, Perth, Western Australia, Australia*
[7]*School of Health, University of the Sunshine Coast, Sunshine Coast, Queensland, Australia*
[8]*Sunshine Coast Health Institute, Sunshine Coast Hospital and Health Service, Birtinya, Queensland, Australia*
[9]*Manna Institute, University of New England, Armidale, New South Wales, Australia*
[10]*Applied Sports Science Technology and Medicine Research Centre, Swansea University, Swansea, UK*
[11]*School of Health Sciences, University of New South Wales, Sydney, Australia*

Handling Editors: Karyn Hamilton & Nathan Winn

The peer review history is available in the Supporting Information section of this article (https://doi.org/10.1113/JP286043#support-information-section).



Abstract figure legend This study demonstrated that high-intensity interval exercise is a sufficient dose of exercise to significantly increase IL-15, IL-6, IL-10 and IL-1ra concentrations immediately after exercise. However, there was no significant influence of training on this response. Myokines including IL-15 and IL-6 have been previously associated with the suppression of cancer growth in pre-clinical and *in vitro* models. Therefore, it can be postulated that repeated bouts of high-intensity exercise may, at least in part, be a key mechanism behind the anti-oncogenic effect of exercise and 4×4 high-intensity interval exercise is sufficient stimulus to elicit this myokine response.

 DOI: 10.1113/JP286043

Abstract Pre-clinical murine and *in vitro* models have demonstrated that exercise suppresses tumour and cancer cell growth. These anti-oncogenic effects of exercise were associated with the exercise-mediated release of myokines such as interleukin (IL)-15. However, no study has quantified the acute IL-15 response in human cancer survivors, and whether physiological adaptations to exercise training (i.e. body composition and cardiorespiratory fitness) influence this response. In the present study breast, prostate and colorectal cancer survivors ($n = 14$) completed a single bout of high-intensity interval exercise (HIIE) [4×4 min at 85–95% heart rate (HR) peak, 3 min at 50–70% HR peak] before and after 7 months of three times weekly high-intensity interval training (HIIT) on a cycle ergometer. At each time point venous blood was sampled before and immediately after HIIE to assess the acute myokine (IL-15, IL-6, IL-10, IL-1ra) responses. Markers of inflammation, cardiorespiratory fitness and measures of body composition were obtained at baseline and 7 months. An acute bout of HIIE resulted in a significant increase in IL-15 concentrations (pre-intervention: 113%; $P = 0.013$, post-intervention: 102%; $P = 0.005$). Post-exercise IL-15 concentrations were associated with all other post-exercise myokine concentrations, lean mass ($P = 0.031$), visceral adipose tissue ($P = 0.039$) and absolute $\dot{V}_{O_2}$ peak ($P = 0.032$). There was no significant effect of 7 months of HIIT on pre- or post-HIIE IL-15 concentrations ($P > 0.05$). This study demonstrates HIIE is a sufficient stimulus to increase circulating IL-15 and other myokines including IL-6, IL-10 and IL-1ra which may be clinically relevant in the anti-oncogenic effect of exercise and repetitive exposure to these effects may contribute to the positive relationship between exercise and cancer recurrence.

(Received 27 November 2023; accepted after revision 27 August 2024; first published online 20 September 2024)
Corresponding author M. Farley: Cancer and Palliative Care Outcomes Centre, Faculty of Health, Queensland University of Technology, Brisbane, Australia. Email: m.farley@qut.edu.au

Key points

- Exercise has been demonstrated to reduce the risk of cancer recurrence.
- Pre-clinical murine and *in vitro* models have demonstrated that exercise suppresses tumour and cancer cell growth, mediated by exercise-induced myokines (IL-6 and IL-15).
- High-intensity interval exercise significantly increased myokines associated with the anti-oncogenic effect of exercise and the magnitude of response was associated with lean mass, but training did not appear to influence this response.
- Given IL-15 has been implicated in the anti-oncogenic effect of exercise and is being explored as an immunotherapy agent, high-intensity interval exercise may improve outcomes for people living beyond cancer through IL-15-mediated pathways.
- Interventions that increase lean mass may also enhance this response.

Introduction

Breast, prostate and colorectal cancers represent the largest proportion of cancer survivors in Australia (Australian Institute of Health & Welfare, 2019), who as a result of their disease- and treatment-related side effects are living with a heightened risk of cancer recurrence and the development of comorbidities (Ng et al., 2018). Physical activity is associated with a reduction in recurrence of these cancers (Friedenreich et al., 2016; Holmes et al., 2005; Meyerhardt et al., 2006), with exercise also demonstrating reductions in cancer cell growth in *in vitro* and pre-clinical models (Kurz et al., 2022; Orange et al., 2020; Pedersen et al., 2016). It is thought that the interplay between transient systemic perturbations in immune cells in response to acute exercise and the chronic adaptations in immune function to exercise training contribute to the anti-oncogenic effect of exercise (Farley et al., 2023).

Interleukin-15 (IL-15) is a pleiotropic cytokine with demonstrated potential as an effective immunotherapy agent (Hu et al., 2018). The binding of IL-15 to its receptor complex activates an 'immune enhancing' signalling cascade with multiple effects including

T-cell proliferation, upregulation of natural killer cell (NK-cell)-derived cytokines, stimulation and proliferation of β-cells, and enhanced NK-cell cytotoxicity (Argiles et al., 2009; Fehniger & Caligiuri, 2001; Mishra et al., 2014). As one of the most abundant myokines (i.e. cytokines produced by working skeletal muscle) found in skeletal muscle (Quinn et al., 1995), IL-15 may play a key role in the anti-oncogenic potency of exercise. Indeed, a recent pre-clinical trial observed an exercise-induced increase in tumour infiltrating lymphocytes (CD8+ T-cells), mediated by IL-15/IL-15Rα (receptor subunit alpha), and resulting in tumour suppression (Kurz et al., 2022). Despite this, very few studies have explored the IL-15 response to exercise in human cancer populations.

Only one study to date has investigated acute changes in IL-15 concentrations in response to exercise in a cancer population (Kim et al., 2023). Kim et al. (2023) recently reported a significant increase (7.8%) in post-exercise IL-15 concentrations in response to a 34 min high-intensity interval cycling session in nine men with metastatic castrate-resistant prostate cancer. This coincided with a 17% reduction in cancer cell growth *in vitro* compared to pre-exercise serum (Kim et al., 2023). However, the variation among participants' IL-15 concentrations immediately following exercise were approximately twice as large as the pre- to post-exercise mean response. The variation in IL-15 response may be explained by other factors that are also influenced by exercise. For example, markers of inflammation such as C-reactive protein (CRP), IL-6, IL-10 and IL-1ra, body composition, and cardiorespiratory fitness, which are all responsive to exercise (Dethlefsen et al., 2016; Devin et al., 2016; Devin et al., 2019), are implicated in cancer progression, yet their association with IL-15 is yet to be explored (Ekblom-Bak et al., 2023; Pati et al., 2023; Zhao et al., 2021). Furthermore, the acute post-exercise IL-15 response is speculated to be either blunted following exercise training due to improved myokine clearance or heightened due to improvements in lean mass (Farley et al., 2023). Whether exercise training influences the IL-15 response and/or its relationship with factors implicated in cancer progression remains to be elucidated.

The primary aim of this study was to investigate the acute response of IL-15 to a single bout of high-intensity interval exercise (HIIE) in breast, prostate and colorectal cancer survivors. The secondary aims were to (1) explore relationships between acute IL-15 response to exercise, and markers of systemic inflammation [CRP, IL-6, tumour necrosis factor alpha (TNF-α) and IL-10], other myokines (IL-6, IL-10 and IL-1ra), body composition and cardiorespiratory fitness, and (2) determine the effect of 7 months of high-intensity interval training (HIIT) on these outcomes.

Methods

Participants

Male and female breast, prostate and colorectal cancer survivors were recruited. Participants included had a confirmed diagnosis of breast, prostate or colorectal cancer, completed their primary cancer treatment (e.g. radiation therapy, chemotherapy or surgical treatment) $\geq$1 month previously and were $\geq$18 years old (mean age: 59.7 $\pm$ 8.0 years). Participants were excluded if they currently performed high-intensity exercise, were pregnant, or presented with any musculoskeletal, neurological, respiratory, metabolic, or cardiovascular conditions that would prevent safe completion of HIIE and HIIT. Participants were required to obtain physician consent for participation in the programme and were individually screened via a medical history form and interview with the investigators to determine eligibility. All participants provided written informed consent and the present study was approved by the Human Research Ethics Committee of Bellberry Ltd (#2015−12-840). This is a secondary analysis of data collected for the 'Peer support for the maintenance of physical activity and health in cancer survivors: the PEER trial' (Australian New Zealand Clinical Trial Registry 12618001855213). The study was conducted according to the guidelines of the Declaration of Helsinki and Good Clinical Practice and analyses were conducted by a blinded investigator. No participants died before the experiments were concluded.

Study design

Participants completed an initial familiarisation session and returned to the laboratory within 1 week to complete baseline testing where measures of cardiorespiratory fitness and body composition, and resting markers of inflammation were obtained. Participants then completed an HIIE testing session within 1 week of their baseline and 7 month assessments. The first month of the intervention was supervised by an Accredited Exercise Physiologist (AEP; Exercise and Sport Science Australia) and the following 6 months was completed unsupervised in a community-based setting. Participants underwent testing at baseline and 7 months for other physiological measures (body composition, cardiorespiratory fitness and systemic inflammation).

Testing procedures

Familiarisation. Participants completed a familiarisation session 1 week prior to baseline testing. During this session participants' medical histories were obtained prior to completing a peak oxygen uptake ($\dot{V}_{O_2}$ peak) test to familiarise the participants with testing procedures.

Pre-testing requirements. For each testing session, participants were asked to maintain a hydrated state in the 24 h prior to testing, abstain from caffeine and alcohol intake for 12 h prior to testing, and avoid any vigorous, high- or unaccustomed moderate-intensity exercise or physical activity for the 48 h prior to testing which was confirmed via a checklist prior to commencing the session. Participants were also required to keep a 24 h food diary prior to baseline testing and 7 month testing to control for dietary changes. For follow-up testing sessions participants were given a copy of their food diary and asked to maintain a similar diet.

Testing session 1

Participants returned to the laboratory 1 week after their familiarisation sessions and after the 7 month exercise intervention where blood samples were obtained, and body composition and cardiorespiratory fitness tests were completed.

Systemic inflammation. Fasted blood samples were obtained at baseline and after 7 months of HIIT. Samples were obtained at rest and analysed for markers of systemic inflammation (i.e. CRP, IL-6, IL-15 and TNF-α). Plasma samples were immediately stored on ice and centrifuged for 10 min at 900 *g*. Samples were stored at −80°C prior to analysis.

Body composition. Body composition was assessed at baseline and following the intervention through dual-energy X-ray absorptiometry (DXA; Horizon A; Hologic, Washington, DC, USA). Values derived were whole-body lean mass, lower body lean mass, whole-body fat mass, body fat percent and visceral adipose tissue (VAT) mass.

Cardiorespiratory fitness. $\dot{V}_{O_2}$ peak testing was completed using a cycle ergometer (Lode Excalibur Sport; Lode B.V., Groningen, Netherlands) and a portable metabolic cart system (ParvoMedics TrueOne 2400, Sandy, Murray, UT, USA), in accordance with the protocol outlined by Devin et al. (2016).

Testing session 2

High intensity interval exercise testing session. At baseline, and following 7 months of HIIT, participants completed a single HIIE testing bout, where blood was sampled before and immediately after exercise. Participants arrived fasted and consumed a meal replacement of 0.5 g/kg of Sustagen Sport (Nestle Australia, Sydney, Australia) mixed with 300 mL of water and then rested for 30 min. After this time, resting venous blood (30–40 mL) was sampled from an antecubital vein. An HIIE session was then completed as per the sessions prescribed within the exercise intervention and is depicted in Fig. 1. Blood was then sampled immediately following HIIE. Plasma samples were immediately stored on ice and centrifuged for 10 min at 900 *g*. Samples were stored at −80°C prior to analysis.

Exercise intervention

The 4×4 HIIE protocol included a 38 min session which comprised a 10 minute warm up at 50–70% heart rate (HR) peak followed by 4×4 minute bouts of cycling at 85–95% HRpeak, separated with 4×3 minute bouts of recovery at 50–70% HRpeak. The HIIE protocol is depicted in Fig. 1. Participants wore a heart rate monitor during all sessions, and power and heart rate data were collected from wattbike data and attendance via a logbook. Adherence to the testing protocol and intervention was measured as adherence to the prescribed intensity measured as the mean heart rate achieved within the high-intensity intervals relative to the measured heart rate peak and expressed as a percentage, attendance to the intervention was measured as the number of completed sessions divided by the prescribed number, and expressed as a percentage, and duration as the average time of the completed sessions.

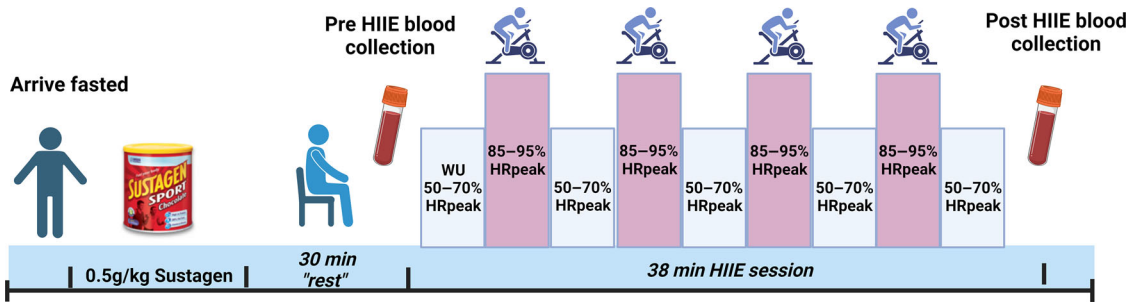


Figure 1. High-intensity exercise testing protocol
HIIE: high-intensity interval exercise, HR: heart rate. [Colour figure can be viewed at wileyonlinelibrary.com]

Plasma analysis

Plasma samples were analysed for an array of cytokines/myokines (IL-1ra, IL-6, IL-10, IL-15) using an electrochemiluminescent multiplex Magpix system (MILLIPLEX, Merck Millipore, Billerica, MA, USA). Resting CRP concentrations were measured using a Randox RX Daytona+ system (Randox Laboratories Ltd, Crumlin, UK). All samples were analysed in duplicate as per the manufacturer's instructions; the technical coefficient of variation for IL-1ra, IL-6, IL-10, IL-15 and CRP was 6.5, 6.8, 7.9, 9.4 and 1.0% respectively. The biological variation added 0.00–0.17 pg/mL to the technical variation when samples collected from the same participant on different days were analysed (Rose et al., 2022). Where samples fell below the limits of detection (IL-15: <0.25, IL-1ra: <0.46, IL-6: <0.12, IL-10: <0.37), the sample was assigned to the minimal detectable limit. Of the 104 measures of myokines, seven (6.7%) fell below the detectable limits of our assay.

Statistical analysis

A priori sample size determinations were calculated using Statistical Considerations Software (Harvard University, MGH). Using data from Riechman et al. (2004), a total of seven participants would be required to determine possible differences in IL-15 (mean = 0.8 pg/mL and an SD of 0.06 pg/mL) at an alpha = 0.05 and power = 0.9. Data were assessed for normality using a Shapiro–Wilk test; for data that were not normally distributed, non-parametric tests and median (interquartile range) were used and reported. To account for the individual change scores, change scores were calculated for each participant and then the mean and SD or median and interquartile range of these values were reported for all physiological outcomes.

The influence of HIIE on IL-15, IL-6, IL-10 and IL-1ra concentrations was assessed using a paired-samples *t* test or a Wilcoxon signed rank test as appropriate. Effect sizes (ES) were calculated using Cohen's *d* and Bonferroni adjustments were made to account for multiple comparisons with each analysis. To assess the change in acute inflammatory response following the 7 month exercise intervention, the delta change (acute pre- to post-exercise) was computed at each time point and analysed by ANOVA. Relationships between IL-15 response to HIIE and other outcomes were assessed using Pearson's product moment or Spearman rank correlation coefficients as appropriate. Where correlations were significant, partial correlations were performed to determine the influence of pre-exercise IL-15 concentrations on the relationship. Change in physiological outcomes (fasted markers of inflammation, body composition and cardiorespiratory fitness) were analysed using a paired-samples *t* test or the Wilcoxon signed rank test as appropriate. Data are presented as mean ± SD unless otherwise stated. Change scores are presented as the mean or median of participants' individual change scores. Alpha was set at <0.05.

Table 1. Participant characteristics

n	14
Age (years)	59.7 ± 8.0
Body mass (kg)	69.1 ± 17.7
Body mass index (kg/m^2)	23.8 ± 3.5
Women [*n* (%)]	8 (57)
Cancer history	
Breast cancer [*n* (%)]	5 (36)
Prostate cancer [*n* (%)]	4 (28)
Colorectal cancer [*n* (%)]	5 (36)
Time since diagnosis (years)	3.9 ± 3.6
Time since treatment (years)	3.0 ± 3.7
Cancer treatment [*n* (%)]	
Surgery	6 (43)
Surgery & radiation	1 (7)
Surgery, chemotherapy & radiation	1 (7)
Surgery, chemotherapy, radiation & hormone therapy	2 (14)
Surgery, radiation & hormone therapy	3 (21)
Surgery, chemotherapy & hormone therapy	1 (7)
Medications (SD)	2.5 ± 4.1
Ethnicity [*n* (%)]	
Caucasian	13 (93)
Asian	1 (7)
Education [*n* (%)]	
Grade 10	1 (7)
Grade 11/12	1 (7)
Certificate/Diploma	3 (21)
University degree	9 (64)
Marital status [*n* (%)]	
Physiological measures	
Systolic blood pressure (mmHg)	115 ± 16
Diastolic blood pressure (mmHg)	76 ± 11
Resting heart rate (b.p.m.)	68 ± 11

SD: standard deviation, b.p.m.: beats per minute.

Results

Participants

Fourteen participants completed baseline HIIE testing, while 12 participants completed post-training HIIE testing. One participant had a recurrence of their cancer during the first 4 weeks of training and withdrew from the study. During the post-training HIIE testing session blood was unable to be sampled from one participant. Participant characteristics for age, sex, body composition, cancer history and psychosocial characteristics are shown in Table 1. Participants were predominantly women (57%), with an average age of 59.7 ± 8.0 years and

Table 2. Participant adherence to pre-testing requirements, high-intensity interval exercise testing protocol and high-intensity interval training intervention

	Baseline Mean ± SD	7 months Mean ± SD
Duration of blood draw		
Start (min, following the final exercise bout)	2.5 ± 2.3	2.3 ± 1.5
End (min, following the final exercise bout)	4.6 ± 3.3	4.1 ± 2.3
Pre-testing requirements (%)	100	100
HIIE testing session adherence*		
Time to heart rate zone (s)	40.5 ± 37.1	35.05 ± 30.7
Heart rate maximum (%)	94.2 ± 5.7	95.6 ± 6.7
HIIT intervention adherence†	**Supervised**	**Unsupervised**
Attendance (%)	100 ± 8	62 ± 16
Intensity (% HRmax)	92 ± 6	94 ± 9
Duration (min)	38 ± 0.1	37 ± 0.8

*HIIE testing session adherence data include time to zone, expressed as time taken to reach the high-intensity zone, and heart rate maximum, expressed as a percentage of heart rate maximum achieved in the $\dot{V}_{O_2}$ peak test.
†Intervention adherence data include attendance expressed as a percentage of prescribed sessions completed, intensity expressed as mean percentage of heart rate maximum for completed sessions, and duration expressed as mean time (min) of exercise completed.
SD: standard deviation, HIIE: high-intensity interval exercise, HIIT: high-intensity interval training, HR: heart rate.

had a body mass index of 23.8 ± 3.5 kg/m^2. Of the 14 participants enrolled in the study, five women had been treated for breast cancer, five men and women had been treated for colorectal cancer, and four men had been treated for prostate cancer. Participants were on average 3.0 ± 3.7 years post-treatment.

Adherence to protocol

All participants adhered to the pre-testing requirements (i.e. fasted and no vigorous exercise or caffeine 24 h previously). There was no significant difference in dietary recall between testing time points for total energy (P = 0.678), protein (P = 0.173), fats (P = 0.314) or carbohydrates P = 0.374). Post-exercise venous blood was sampled 2.5–4.6 ± 2.3–3.3 minutes following the pre-training high-intensity exercise bout and 2.3–4.1 ± 1.5–2.3 minutes following the post-training HIIE bout. Adherence to the testing and exercise training intervention is presented in Table 2. All participants adhered to the acute testing (HIIE) session and to the exercise intervention during the supervised phase. Whilst adherence was met for intensity (94 ± 9% HRmax) and duration (37 ± 0.8 min) during the unsupervised phase, 62% of prescribed sessions were attended.

Myokines

Pre-intervention acute exercise response. There was a significant (113%) increase in acute IL-15 concentrations from pre- to post-exercise before training (ES = 0.58; P = 0.013); post-exercise IL-6, IL-10 and IL-1ra were also higher than pre-exercise concentrations by 96% (P = 0.004), 68% (P = 0.022) and 48% (P = 0.004), respectively, with moderate to large effect sizes (ES = 0.91, 0.74 and 0.63, respectively) before the HIIT intervention (data are presented in Table 3). Individual responses to HIIE before intervention are presented in Fig. 2.

When the acute exercise bout was repeated following 7 months of HIIT, there was a large increase (102%) in acute IL-15 concentrations from pre-exercise values (ES = 1.33; P = 0.005). Post-exercise acute concentrations of IL-6, IL-10 and IL-1ra were also higher than pre-exercise concentrations (by 68, 36 and 60%; P = 0.017, P = 0.004 and P = 0.012, respectively) following 7 months of HIIT and presented in Table 3. Individual post-exercise responses after a 7 month HIIT intervention can be seen in Fig. 2.

Comparison of the acute responses to exercise, before and after 7 months of HIIT. When comparing pre-exercise to post-exercise changes in myokines before and after a 7 month HIIT intervention, there were no significant differences in any of the myokines (data presented in Table 3).

Associations

Pre-training. Post-exercise IL-15 concentrations were strongly associated with all post-exercise myokine concentrations (IL-6, IL-10, IL-1ra) (all = P < 0.001) after adjustment for multiple comparisons. Whilst post-exercise IL-15 concentrations were strongly associated with lean mass (r_s = 0.622, P = 0.031),

VAT mass (r_s = 0.601, P = 0.039) and absolute $\dot{V}_{O_2}$ peak (r_s = 0.574, P = 0.032) pre-HIIT intervention, they did not remain significant after correction for multiple comparisons (data presented in Table 4). No associations were observed between post-exercise IL-15 concentrations and relative $\dot{V}_{O_2}$ peak, leg lean mass, body fat percentage and fat mass before intervention. When controlling for baseline IL-15 concentrations, the only association that remained significant was between post-HIIE IL-15 concentrations and post-HIIE IL-10 concentrations (r = 0.675, P = 0.011).

Changes to baseline markers in response to HIIT

Physiological changes in response to 7 months of HIIT are presented in Table 5.

Chronic inflammation. In response to the 7 month HIIT intervention, there was a non-significant (P = 0.173) moderate reduction (ES = 0.51) in fasted resting concentrations of IL-15 (Table 5). There was a significant reduction in fasted resting concentrations of IL-6 after 7 months of HIIT (ES = 0.46; P = 0.012). Both IL-10 and TNF-α also showed a reduction in fasted resting concentrations in response to the exercise intervention (IL-10: ES = 0.76; P = 0.008, TNF-α: ES = 1.23; P = 0.012).

Body composition. Following the 7-month HIIT intervention there was a moderate decrease in total fat mass (−1.0 ± 1.5 kg; ES = 0.69; P = 0.036) compared to pre-training values. There was a large increase in leg lean mass (+0.5 ± 0.6 kg; ES = 0.83; P = 0.015) post-exercise intervention compared to pre-training. There were no significant differences observed in VAT mass (ES: 0.18; P = 0.555) or total lean mass (ES: 0.11; P = 0.814) from baseline to 7 months post-HIIT. Additionally, there was no significant change in body fat percentage (−1.5 ± 2.3%; 95% CI = −0.03 to 3.02; ES = 0.62; P = 0.054) (Table 5).

Cardiorespiratory fitness. There was a moderate 7.2% increase in relative $\dot{V}_{O_2}$ peak (1.9 ± 2.4 mL/kg/min; ES = 0.74; P = 0.035), but there was no change in absolute $\dot{V}_{O_2}$ peak (P = 0.145) after 7 months of HIIT (Table 5).

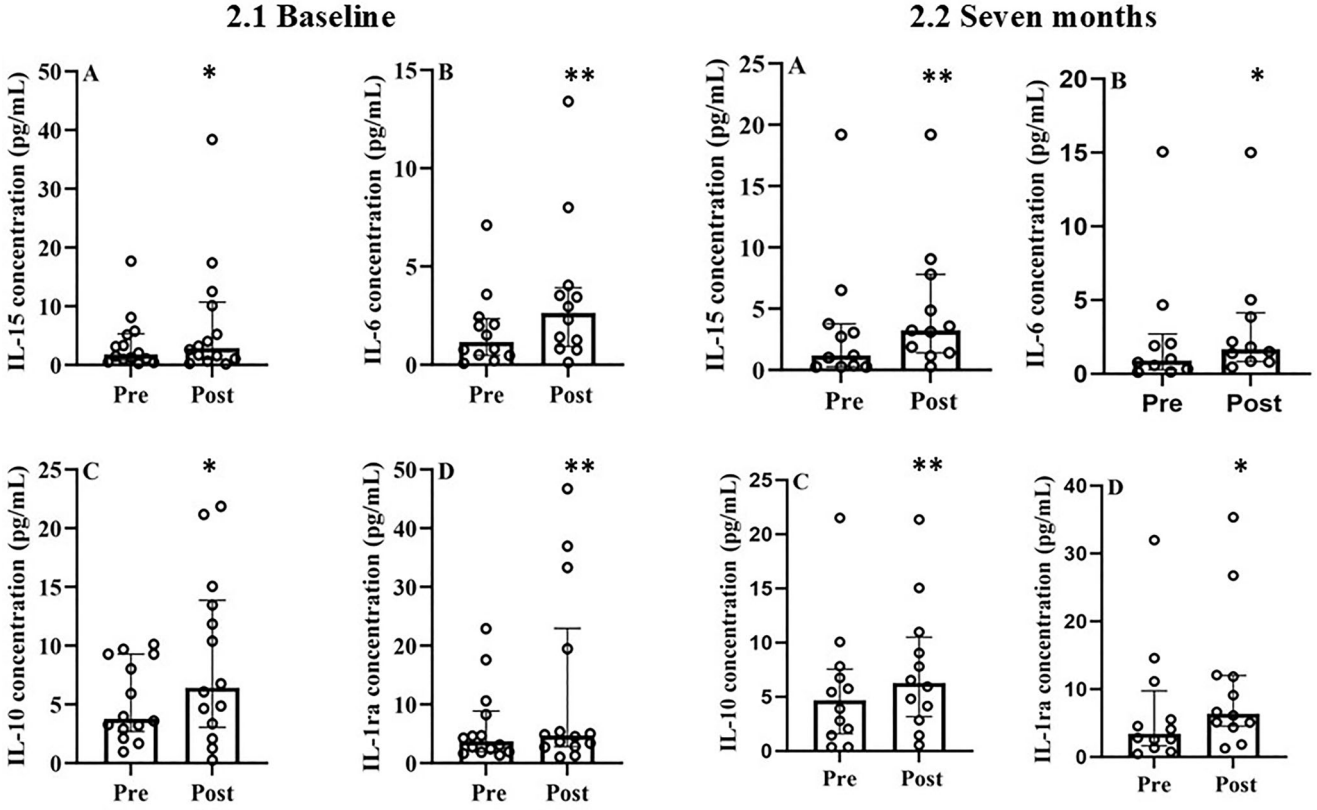


Figure 2. Pre-training and. individual post-training responses
2.1: pre-training responses of (*A*) IL-15, (*B*) IL-6, (*C*) IL-10 and (*D*) IL-1ra to acute high-intensity exercise; and 2.2: individual post-training responses of (*A*) IL-15, (*B*) IL-6, (*C*) IL-10 and (*D*) IL-1ra to high-intensity interval exercise after 7 months of high-intensity interval training. Data are presented as median and interquartile range and analysed using a paired-samples *t* test except where data were not normally distributed, and a Wilcoxon signed rank test was used. $^*P < 0.05$; $^{**}P < 0.01$. IL: interleukin, ra: receptor alpha.

Table 3. Acute inflammatory responses of breast, prostate and colorectal cancer survivors to HIIE before training and after 7 months of HIIT

	Baseline					7 months					Baseline *vs.* 7 months		
	Pre-HIIE (pg/mL)		Post-HIIE (pg/mL)		*P*-value	ES	Pre-HIIE (pg/mL)		Post-HIIE (pg/mL)		*P*-value	ES	Change (pg/mL)	*P*-value	ES
	Median (IQR)	95% CI	Median (IQR)	95% CI			Median (IQR)	95% CI	Median (IQR)	95% CI			Median (IQR)		
IL-15 (pg/mL)	1.80 (4.44)	0.97–6.35	2.92 (9.75)	1.07–13.07	**0.013**	0.58	1.20 (3.52)	−0.58 to 5.98	3.23 (6.40)	1.41–8.70	**0.005**	1.33	−0.5 (4.4)	0.091	0.28
IL-6 (pg/mL)	1.16 (1.86)	0.53–3.05	2.63 (2.99)	1.11–5.90	**0.004**	0.91	0.89 (2.53)	−0.58 to 5.98	1.66 (3.22)	0.15–6.36	**0.017**	0.95	−0.5 (2.3)	0.293	0.42
IL-10 (pg/mL)	3.78 (6.57)	3.37–7.20	6.43 (10.82)	3.37–7.20	**0.022**	0.74	4.68 (5.97)	1.98–9.40	6.25 (7.34)	3.75–11.34	**0.004**	0.88	−1.2 (7.5)	0.061	0.23
IL-1ra (pg/mL)	3.68 (6.94)	2.50–10.07	4.68 (20.10)	3.33–21.12	**0.004**	0.63	3.45 (8.10)	1.18–12.57	6.38 (7.45)	3.90–17.03	**0.012**	0.75	−0.5 (17.1)	0.104	0.13

HIIE: high-intensity interval exercise, HIIT: high-intensity interval training, IQR: interquartile range, ES: effect size, CI: confidence interval, IL: interleukin, ra: receptor alpha. Where data are not normally distributed, pre- to post-exercise myokine change was analysed via a Wilcoxon signed rank test at each time point and data are displayed as median (IQR). Change scores were calculated at each time point as the average of each participant's change scores and reported as median (IQR). The change of the pre- to post-exercise score between baseline and 7 months was analysed by an ANOVA. Bold text indicates *p*-values.

Discussion

Acute responses of IL-15 to a single bout of HIIE before and after an HIIT intervention in breast, prostate and colorectal cancer survivors were investigated, demonstrating a 113% increase in IL-15 concentrations immediately after HIIE with a strong effect size ($P = 0.013$, ES = 0.58). After 7 months of HIIT we also observed an 102% ($P = 0.005$, ES = 1.33) increase in post-exercise IL-15 concentrations. However, there was no significant influence of training on the response of IL-15 to a bout of high-intensity exercise.

Acute bouts of high-intensity exercise elicited large increases (102–113%) in IL-15 concentrations immediately following exercise for cancer survivors, consistent with the majority of the literature among other healthy and clinical populations. Of the seven studies exploring the acute response of IL-15 to exercise in predominantly healthy or overweight and obese populations, five observed significant increases (6–142%) in IL-15 following exercise (Christiansen et al., 2013; Hingorjo et al., 2018; Kim et al., 2023; Pierce et al., 2015; Tamura et al., 2011). Of the two studies (He et al., 2018; Rinnov et al., 2014) that did not observe a significant effect of exercise on IL-15 concentrations, both included young healthy populations and did not report baseline concentrations of IL-15, which may have influenced the response to exercise. Furthermore, the exercise bout prescribed by Rinnov et al. (2014) was longer in duration and performed at a much lower power output (3 h of cycling at ∼60% of $\dot{V}_{O_2}$ max) than was performed in the present study. Additionally, He et al. (2018) failed to perform statistical analyses on their pre-/immediately post-exercise samples, despite appearing potentially different, and this may have contributed to their non-significant findings. A larger fold increase in post-exercise IL-15 concentrations appeared to be observed when studies prescribed higher intensity exercise (Hingorjo et al., 2018; Pierce et al., 2015; Tamura et al., 2011). This is unsurprising given the exercise-induced secretion of myokines is closely associated with muscle glycogen content, and higher intensity exercise triggers greater intramuscular glycogen depletion (Keller et al., 2001). Furthermore, exercise at higher intensities is associated with greater catecholamine release, which has been associated with rapid mobilisation of immune cells, leading to the suppression of cancer growth in pre-clinical models (Pedersen et al., 2016). Thus, future studies exploring the IL-15 response to exercise should consider the population, baseline IL-15 concentrations and prescribed exercise intensity utilised.

The only previous study (Kim et al., 2023) to explore the acute response of IL-15 to high-intensity exercise in a cancer population (metastatic castrate-resistant prostate cancer) also observed a significant increase

Table 4. Associations between post-exercise IL-15 concentrations and post-exercise myokine concentrations, baseline CRP, baseline measures of body composition and cardiorespiratory fitness pre-training

Pre-training	Correlation coefficient	*P*-value
Post-exercise IL-15 concentration		
Post-IL-6 concentration (pg/mL)	0.902[a,b]	**<0.001**
Post-IL-10 concentration (pg/mL)	0.902[a,b]	**<0.001**
Post-IL-1ra concentration (pg/mL)	0.895[a,b]	<0.001
Baseline CRP (mg/L)	0.554[a]	0.050
Fat mass (kg)	0.378	0.226
Body fat percentage (%)	−0.245	0.443
Lean mass (kg)	0.622[a]	0.031
Leg lean mass (kg)	0.566	0.055
VAT mass (g)	0.601[a]	**0.039**
Absolute $\dot{V}_{O_2}$ peak (L/min)	0.574[a]	0.032
Relative $\dot{V}_{O_2}$ peak (mL/kg/min)	−0.095	0.748

Data are presented as Spearman correlation coefficients. IL: interleukin, ra: receptor alpha, CRP: C-reactive protein, VAT: visceral adipose tissue.
[a] $P < 0.05$.
[b] $P < 0.05$ after adjustment for multiple comparisons.

Table 5. Changes in body composition, chronic inflammation and cardiovascular fitness in response to 7 months of high-intensity interval training

	Baseline (n = 14)		7 months (n = 13)		*P*-value	ES
	Mean ± SD/median (IQR)	95% CI	Mean ± SD/median (IQR)	95% CI		
Body mass (kg)	69.1 ± 17.7	55.7–82.4	67.6 ± 18.8	52.3–82.9	0.089	0.49
Fat mass (kg)	26.9 ± 10.1	20.4–33.3	25.7 ± 9.4	19.8–31.6	**0.036**	0.69
Body fat percentage (%)	35.9 ± 6.4	31.7–40.1	35.0 ± 6.4	30.1–39.1	0.054	0.62
VAT (g)	609.8 ± 260.3	437.0–782.5	577.2 ± 2.3	400.6–753.9	0.555	0.18
Lean mass (kg)	43.4 (0.2)	39.3–54.9	40.6 (1.9)	39.5–54.0	0.814	0.11
Leg lean mass (kg)	14.8 ± 3.5	12.4–17.2	15.1 ± 3.8	12.7–17.5	**0.015**	0.83
Chronic IL-15 (pg/mL)	4.3 (2.5)	2.7–6.1	2.5 (3.2)	1.6–5.4	0.173	0.51
Chronic IL-6 (pg/mL)	1.7 (1.9)	−4.0 to 24.2	0.3 (7.7)	−1.5 to 10.1	**0.012**	0.46
Chronic IL-10 (pg/mL)	15.1 (27.2)	6.7–63.7	7.9 (28.6)	0.6–34.1	**0.008**	0.76
Chronic TNF-α (pg/mL)	5.2 (3.5)	4.6–8.2	3.1 (1.2)	2.0–4.2	**0.012**	1.23
CRP (pg/mL)	0.4 (1.5)	−0.8 to 4.8	0.4 (0.7)	0.1–1.4	0.640	0.14
$\dot{V}_{O_2}$ peak (L/min)	1.9 (0.6)	1.6–2.3	2.0 (0.7)	1.5–2.5	0.145	0.48
$\dot{V}_{O_2}$ peak (mL/kg/min)	25.7 ± 6.9	21.6–29.9	28.7 ± 7.3	23.6–33.8	**0.035**	0.74

ES: effect size, VAT: visceral adipose tissue, TNF: tumour necrosis factor, CRP: C-reactive protein, IQR: interquartile range
Where data are normally distributed, a paired-samples t test was performed and data displayed as mean ± SD. Where data are not normally distributed, a Wilcoxon signed rank test was performed and data displayed as median (IQR). Bold text indicates p-values.

(7.8%) in IL-15 concentrations after exercise. However, the post-exercise response of IL-15 in the study by Kim et al. (2023) was lower than was observed in the present study. The blunted IL-15 response may, at least in part, be explained by the concurrent anti-cancer therapies in the men with metastatic prostate cancer and their advanced stage disease compared to the participants in this study who were off-treatment and early-stage survivors of cancer. Secondly, this may be explained by a lower exercise intensity (70–85% heart rate maximum) utilised by the authors in comparison to the present study (85–95% heart rate maximum). Interestingly, the magnitude of change in IL-15 concentrations observed in this study was associated with significant reductions in prostate cancer cell growth *in vitro* when incubated with post-exercise sera compared to pre-exercise sera (Kim et al., 2023). Therefore, one would expect that the larger magnitude of change observed after the present study following higher intensity exercise may result in a similar if not greater suppression of cancer cell growth *in vitro*. Collectively this supports the potential role of exercise intensity in influencing the myokine response.

The potential importance of IL-15 in the anti-oncogenic effect of exercise is supported by a recent pre-clinical trial demonstrating the potential clinical utility of the exercise-induced IL-15 response. This pre-clinical model demonstrated an exercise-induced suppression of cancer growth and enhanced efficacy of immunotherapy in a pancreatic cancer murine model, which was mediated by the IL-15 axis (Kurz et al., 2022). Indeed, IL-15 is also being trialled as an immunotherapy agent in combination with immune checkpoint inhibitors in humans (Waldmann et al., 2020). Preliminary results demonstrate enhanced anti-cancer efficacy, further highlighting the potential clinical relevance of exercise-mediated repeated spikes of IL-15 concentrations. Collectively, this supports the role IL-15 may play in the anti-oncogenic effect of exercise. Thus, future research is required to confirm whether the acute post-exercise IL-15 response in humans is clinically meaningful and the utility of high-intensity exercise as an effective adjuvant therapy during immunotherapy in humans.

Post-exercise IL-15 concentrations were associated with body composition (i.e. lean mass and VAT mass), cardiorespiratory fitness (i.e. absolute $\dot{V}_{O_2}$ peak), CRP and post-exercise concentrations of other myokines (i.e. IL-6, IL-10 and IL-1ra). Strong relationships among post-exercise IL-15 concentrations and post-exercise IL-6, IL-10 and IL-1ra concentrations are inherently due to the fact these are all myokines released from exercising muscles. The positive relationship between post-exercise IL-15 concentrations and lean mass is unsurprising given IL-15 is one of the most abundant myokines found in skeletal muscle and skeletal muscle synthesis influences fat oxidation (Quinn, 2008; Quinn et al., 1995; Quinn et al., 2002; Quinn et al., 2009). However, the positive relationship with VAT mass was somewhat surprising. This relationship may at least in part be due to adipocyte-mediated inflammation, resulting in elevated pre-exercise IL-15 concentrations and thus a higher IL-15 response to exercise. Furthermore, the absolute power output during exercise likely to be achieved by those with higher levels of fat and lean mass may have contributed to a greater IL-15 release. It may also be that whilst DXA-derived VAT reliability is <5% (Rose et al., 2021), DXA is not the gold standard measurement of VAT mass. The positive relationship between cardiorespiratory fitness and post-exercise IL-15 levels may have resulted from a greater absolute intensity and subsequent recruitment of type II muscle fibres achieved by people with higher fitness during the HIIE session (Nielsen et al., 2007; Kristensen et al., 2015). This increased recruitment of type II muscle fibres may also be associated with an increased catecholamine release and subsequent immune cell mobilisation, resulting in the suppression of cancer growth (Pedersen et al., 2016). Importantly, these associations were not significant after controlling for baseline IL-15 concentrations, suggesting the importance of baseline IL-15 in the post-HIIE IL-15 response. This demonstrates a complex interplay between fitness, body composition and myokines.

Three previous studies have explored the effect of resistance training on acute IL-15 responses to exercise, but to our knowledge ours is the first to explore the effect of an aerobic training intervention (Micielska et al., 2019; Prestes et al., 2009; Riechman et al., 2004). Despite the reduction in fat mass and resting IL-6, IL-10 and TNF-α, and increases in leg lean mass and cardiorespiratory fitness being of a moderate to large effect, the acute response of IL-15 to HIIE did not change following 7 months of HIIT. This finding contradicts our hypothesis that the acute IL-15 response to exercise would heighten following training due to training-induced increases in leg lean mass and cardiorespiratory fitness. It may be that the magnitude of change in leg lean mass and cardiorespiratory fitness was not sufficient to influence the acute myokine response to exercise following the training intervention. Interventions targeting whole body lean mass and greater improvements in cardiorespiratory fitness may be required to influence the acute IL-15 response to exercise.

Interestingly, this study observed significant reductions in markers of chronic inflammation in response to 7 months of HIIT. Given the relationships between systemic markers of inflammation and cancer incidence and recurrence, and responsiveness to treatment, this may be of clinical importance to this population (Coussens & Werb, 2002; Dranoff, 2004; Schauer et al., 2023; Wesselink et al., 2021). This systemic reduction in chronic inflammation may, at least in part, result from

repeated perturbations in myokines associated with the anti-inflammatory effect of exercise (Petersen & Pedersen, 2005). This study demonstrates the ability of HIIT to elicit changes in markers of inflammation in response to training, but it would seem that the acute response to exercise is not responsive to training in this population. Therefore, future research should focus on optimising this acute myokine response for the potential to concurrently improve markers of systemic inflammation.

There are several limitations worthy of consideration. First, the present study was only able to analyse post-exercise blood at one time point; additional time points would have allowed greater insight into the time course of the IL-15 response to HIIE and to capture the peak concentrations of other myokines included within the present study. Second, whilst the sample size was sufficient to address the primary aim of the study, the secondary and tertiary outcomes would have benefited from a larger sample size to ensure the robustness of the findings and allow for sub-analysis of other factors that may influence the post-exercise myokine response (e.g. sex and adherence). Whilst there are biological (0.00–0.17 pg/mL) and technical (1.0–9.4%) variations in the inflammatory analyses, our previous work has demonstrated this to be small relative to the magnitude of change observed in this study. Furthermore, other studies that have included a control group have observed no difference in myokine concentrations (>0.05) (Rose et al., 2022). Therefore, we are confident despite a lack of a control group that the differences observed are real. In total, 6.7% of pre-exercise myokine concentrations fell below the detectable limits for analysis and were assigned the minimum detectable value, which may have led to an underestimation of the overall magnitude of change identified within this study. Given the immunomodulatory role of IL-15 (Farley et al., 2023), the present study did not quantify the relationship between exercise-mediated changes in IL-15 concentrations and relationships with immune function. Future research should aim to elucidate these relationships. Whilst this study observed high attendance (100%) to the intervention during the supervised phase, attendance reduced to 62% during the unsupervised phased. Whilst this is in line with other homebased exercise interventions (Neil-Sztramko et al., 2022; Taylor et al., 2020) whether a change in myokine response to HIIE after training would have been observed with higher attendance rates remains to be elucidated and warrants further research.

In conclusion, the present study demonstrated that IL-15 concentrations increased in response to an acute bout of HIIE in breast, prostate and colorectal cancer survivors. The acute post-HIIE increases in IL-15 were associated with myokines (i.e. IL-6, IL-10 and IL-1ra), body composition and cardiorespiratory fitness. Seven months of HIIT did not affect the IL-15 response to HIIE, nor the baseline concentration of IL-15, despite significant improvements in other markers of systemic inflammation, body composition and cardiorespiratory fitness. Given IL-15 has been implicated in the tumour suppressive effect of exercise and improvement in immunotherapy efficacy, and is being explored as an immunotherapy agent, transient exercise-induced increases in IL-15 may be clinically meaningful. This research identifies the potential ability of repeated bouts of HIIE to improve outcomes for people living with and beyond cancer via pathways, probably mediated, at least in part, through IL-15, highlighting the importance of frequent exercise bouts. Future research is required to explore whether the HIIE-induced IL-15 response results in favourable changes in immune function and cytotoxicity.

References

Argiles, J. M., Lopez-Soriano, F. J., & Busquets, S. (2009). Therapeutic potential of interleukin-15: A myokine involved in muscle wasting and adiposity. *Drug Discovery Today*, **14**(3–4), 208–213.

Australian Institute of Health and Welfare (2019). Cancer in Australia: In brief. AHIW, Canberra.

Christiansen, T., Bruun, J. M., Paulsen, S. K., Olholm, J., Overgaard, K., Pedersen, S. B., & Richelsen, B. (2013). Acute exercise increases circulating inflammatory markers in overweight and obese compared with lean subjects. *European Journal of Applied Physiology*, **113**(6), 1635–1642.

Coussens, L. M., & Werb, Z. (2002). Inflammation and cancer. *Nature*, **420**(6917), 860–867.

Dethlefsen, C., Lillelund, C., Midtgaard, J., Andersen, C., Pedersen, B. K., Christensen, J. F., & Hojman, P. (2016). Exercise regulates breast cancer cell viability: systemic training adaptations versus acute exercise responses. *Breast Cancer Research and Treatment*, **159**(3), 469–479.

Devin, J. L., Hill, M. M., Mourtzakis, M., Quadrilatero, J., Jenkins, D. G., & Skinner, T. L. (2019). Acute high intensity interval exercise reduces colon cancer cell growth. *The Journal of Physiology*, **597**(8), 2177–2184.

Devin, J. L., Sax, A. T., Hughes, G. I., Jenkins, D. G., Aitken, J. F., Chambers, S. K., Dunn, J. C., Bolam, K. A., & Skinner, T. L. (2016). The influence of high-intensity compared with moderate-intensity exercise training on cardiorespiratory fitness and body composition in colorectal cancer survivors: A randomised controlled trial. *Journal of Cancer Survivorship*, **10**(3), 467–479.

Dranoff, G. (2004). Cytokines in cancer pathogenesis and cancer therapy. *Nature Reviews Cancer*, **4**(1), 11–22.

Ekblom-Bak, E., Bojsen-Møller, E., Wallin, P., Paulsson, S., Lindwall, M., Rundqvist, H., & Bolam, K. A. (2023). Association between cardiorespiratory fitness and cancer incidence and cancer-specific mortality of colon, lung, and prostate cancer among swedish men. *Journal of the American Medical Association Network Open*, **6**(6), e2321102–e2321102.

Farley, M. J., Bartlett, D. B., Skinner, T. L., Schaumberg, M. A., & Jenkins, D. G. (2023). Immunomodulatory function of interleukin-15 and its role in exercise, immunotherapy, and cancer outcomes. *Medicine, & Science in Sports, & Exercise*, **55**(3), 558–568.

Fehniger, T. A., & Caligiuri, M. A. (2001). Interleukin 15: Biology and relevance to human disease. *Blood*, **97**(1), 14–32.

Friedenreich, C. M., Neilson, H. K., Farris, M. S., & Courneya, K. S. (2016). Physical activity and cancer outcomes: A precision medicine approach. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research*, **22**(19), 4766–4775.

He, Z., Tian, Y., Valenzuela, P. L., Huang, C., Zhao, J., Hong, P., He, Z., Yin, S., & Lucia, A. (2018). Myokine response to high-intensity interval vs. resistance exercise: An individual approach. *Frontiers in Physiology*, **9**, 1735.

Hingorjo, M. R., Zehra, S., Saleem, S., & Qureshi, M. A. (2018). Serum Interleukin-15 and its relationship with adiposity Indices before and after short-term endurance exercise. *Pakistan Journal of Medical Sciences*, **34**(5), 1125–1131.

Holmes, M. D., Chen, W. Y., Feskanich, D., Kroenke, C. H., & Colditz, G. A. (2005). Physical activity and survival after breast cancer diagnosis. *Journal of the American Medical Association Internal Medicine*, **293**(20), 2479–2486.

Hu, Q., Ye, X., Qu, X., Cui, D., Zhang, L., Xu, Z., Wan, H., Zhang, L., & Tao, W. (2018). Discovery of a novel IL-15 based protein with improved developability and efficacy for cancer immunotherapy. *Scientific Reports*, **8**(1), 7675.

Keller, C., Steensberg, A., Pilegaard, H., Osada, T., Saltin, B., Pedersen, B. K., & Neufer, P. D. (2001). Transcriptional activation of the IL-6 gene in human contracting skeletal muscle: Influence of muscle glycogen content. *Federation of American Societies for Experimental Biology Journal*, **15**(14), 2748–2750.

Kim, J. S., Taaffe, D. R., Galvão, D. A., Clay, T. D., Redfern, A. D., Hart, N. H., Gray, E. S., Ryan, C. J., Kenfield, S. A., Saad, F., & Newton, R. U. (2023). Acute effect of high-intensity interval aerobic exercise on serum myokine levels and resulting tumour-suppressive effect in trained patients with advanced prostate cancer. *Prostate Cancer, & Prostatic Diseases*, **26**(4), 795–801.

Kristensen, D. E., Albers, P. H., Prats, C., Baba, O., Birk, J. B., & Wojtaszewski, J. F. (2015). Human muscle fibre type-specific regulation of AMPK and downstream targets by exercise. *The Journal of Physiology*, **593**(8), 2053–2069.

Kurz, E., Hirsch, C. A., Dalton, T., Shadaloey, S. A., Khodadadi-Jamayran, A., Miller, G., Pareek, S., Rajaei, H., Mohindroo, C., Baydogan, S., Ngo-Huang, A., Parker, N., Katz, M. H. G., Petzel, M., Vucic, E., McAllister, F., Schadler, K., Winograd, R., & Bar-Sagi, D. (2022). Exercise-induced engagement of the IL-15/IL-15Rα axis promotes anti-tumor immunity in pancreatic cancer. *Cancer Cell*, **40**(7), 720–737.e725.

Meyerhardt, J. A., Giovannucci, E. L., Holmes, M. D., Chan, A. T., Chan, J. A., Colditz, G. A., & Fuchs, C. S. (2006). Physical activity and survival after colorectal cancer diagnosis. *Journal of Clinical Oncology*, **24**(22), 3527–3534.

Micielska, K., Gmiat, A., Zychowska, M., Kozlowska, M., Walentukiewicz, A., Lysak-Radomska, A., Jaworska, J., Rodziewicz, E., Duda-Biernacka, B., & Ziemann, E. (2019). The beneficial effects of 15 units of high-intensity circuit training in women is modified by age, baseline insulin resistance and physical capacity. *Diabetes Research and Clinical Practice*, **152**, 156–165.

Mishra, A., Sullivan, L., & Caligiuri, M. A. (2014). Molecular pathways: Interleukin-15 signaling in health and in cancer. *Clinical Cancer Research*, **20**(8), 2044–2050.

Nielsen, A. R., Mounier, R., Plomgaard, P., Mortensen, O. H., Penkowa, M., Speerschneider, T., Pilegaard, H., & Pedersen, B. K. (2007). Expression of interleukin-15 in human skeletal muscle effect of exercise and muscle fibre type composition. *The Journal of Physiology*, **584**(Pt 1), 305–312.

Neil-Sztramko, S. E., Smith-Turchyn, J., Fong, A., Kauffeldt, K., & Tomasone, J. R. (2022). Community-based exercise programs for cancer survivors: A scoping review of program characteristics using the consolidated framework for implementation research. *Archives of Physical Medicine and Rehabilitation*, **103**(3), 542–558.e510.

Ng, H. S., Roder, D., Koczwara, B., & Vitry, A. (2018). Comorbidity, physical and mental health among cancer patients and survivors: An Australian population-based study. *Asia-Pacific Journal of Clinical Oncology*, **14**(2), e181–e192.

Orange, S. T., Jordan, A. R., & Saxton, J. M. (2020). The serological responses to acute exercise in humans reduce cancer cell growth in vitro: A systematic review and meta-analysis. *Physiological Reports*, **8**(22), e14635.

Pati, S., Irfan, W., Jameel, A., Ahmed, S., & Shahid, R. K. (2023). Obesity and cancer: A current overview of epidemiology, pathogenesis, outcomes, and management. *Cancers (Basel)*, **15**(2), 485.

Pedersen, L., Idorn, M., Olofsson, G. H., Lauenborg, B., Nookaew, I., Hansen, R. H., Johannesen, H. H., Becker, J. C., Pedersen, K. S., Dethlefsen, C., Nielsen, J., Gehl, J., Pedersen, B. K., Thor Straten, P., & Hojman, P. (2016). Voluntary running suppresses tumor growth through epinephrine- and IL-6 dependent NK cell mobilization and redistribution. *Cell Metabolism*, **23**(3), 554–562.

Petersen, A. M., & Pedersen, B. K. (2005). The anti-inflammatory effect of exercise. *Journal of Applied Physiology*, **98**(4), 1154–1162.

Pierce, J. R., Maples, J. M., & Hickner, R. C. (2015). IL-15 concentrations in skeletal muscle and subcutaneous adipose tissue in lean and obese humans: Local effects of IL-15 on adipose tissue lipolysis. *American Journal of Physiology-Endocrinology and Metabolism*, **308**(12), E1131–E1139.

Prestes, J., Shiguemoto, G., Botero, J. P., Frollini, A., Dias, R., Leite, R., Pereira, G., Magosso, R., Baldissera, V., & Cavaglieri, C. (2009). Effects of resistance training on resistin, leptin, cytokines, and muscle force in elderly post-menopausal women. *Journal of Sports Sciences*, **27**(14), 1607–1615.

Quinn, L. S. (2008). Interleukin-15: A muscle-derived cytokine regulating fat-to-lean body composition. *Journal of Animal Science*, **86**(14 Suppl), E75–83.

Quinn, L. S., Anderson, B. G., Drivdahl, R. H., Alvarez, B., & Argilés, J. M. (2002). Overexpression of interleukin-15 induces skeletal muscle hypertrophy in vitro: implications for treatment of muscle wasting disorders. *Experimental Cell Research*, **280**(1), 55–63.

Quinn, L. S., Anderson, B. G., Strait-Bodey, L., Stroud, A. M., & Argilés, J. M. (2009). Oversecretion of interleukin-15 from skeletal muscle reduces adiposity. *American Journal of Physiology-Endocrinology and Metabolism*, **296**(1), E191–E202.

Quinn, L. S., Haugk, K. L., & Grabstein, K. H. (1995). Interleukin-15: A novel anabolic cytokine for skeletal muscle. *Endocrinology*, **136**(8), 3669–3672.

Riechman, S. E., Balasekaran, G., Roth, S. M., & Ferrell, R. E. (2004). Association of interleukin-15 protein and interleukin-15 receptor genetic variation with resistance exercise training responses. *Journal of Applied Physiology*, **97**(6), 2214–2219.

Rinnov, A., Yfanti, C., Nielsen, S., Akerstrom, T. C., Peijs, L., Zankari, A., Fischer, C. P., & Pedersen, B. K. (2014). Endurance training enhances skeletal muscle interleukin-15 in human male subjects. *Endocrine*, **45**(2), 271–278.

Rose, G. L., Farley, M. J., Flemming, N. B., Skinner, T. L., & Schaumberg, M. A. (2022). Between-day reliability of cytokines and adipokines for application in research and practice. *Frontiers Physiology*, **13**, 967169.

Rose, G. L., Farley, M. J., Slater, G. J., Ward, L. C., Skinner, T. L., Keating, S. E., & Schaumberg, M. A. (2021). How body composition techniques measure up for reliability across the age-span. *The American Journal of Clinical Nutrition*, **114**(1), 281–294.

Schauer, T., Henriksson, A., Strandberg, E., Lindman, H., Berntsen, S., Demmelmaier, I., Raastad, T., Nordin, K., & Christensen, J. F. (2023). Pre-treatment levels of inflammatory markers and chemotherapy completion rates in patients with early-stage breast cancer. *International Journal of Clinical Oncology*, **28**(1), 89–98.

Tamura, Y., Watanabe, K., Kantani, T., Hayashi, J., Ishida, N., & Kaneki, M. (2011). Upregulation of circulating IL-15 by treadmill running in healthy individuals: Is IL-15 an endocrine mediator of the beneficial effects of endurance exercise? *Endocrine*, **58**(3), 211–215.

Taylor, J. L., Holland, D. J., Keating, S. E., Leveritt, M. D., Gomersall, S. R., Rowlands, A. V., Bailey, T. G., & Coombes, J. S. (2020). Short-term and long-term feasibility, safety, and efficacy of high-intensity interval training in cardiac rehabilitation: The FITR heart study randomized clinical trial. *Journal of the American Medical Association Cardiology*, **5**(12), 1382–1389.

Waldmann, T. A., Dubois, S., Miljkovic, M. D., & Conlon, K. C. (2020). IL-15 in the combination immunotherapy of cancer. *Frontiers Immunology*, **11**, 868.

Wesselink, E., Balvers, M. G. J., Kok, D. E., Winkels, R. M., van Zutphen, M., Schrauwen, R. W. M., Keulen, E. T. P., Kouwenhoven, E. A., Breukink, S. O., Witkamp, R. F., de Wilt, J. H. W., Bours, M. J. L., Weijenberg, M. P., Kampman, E., & van Duijnhoven, F. J. B. (2021). Levels of inflammation markers are associated with the risk of recurrence and all-cause mortality in patients with colorectal cancer. *Cancer Epidemiology, Biomarkers, & Prevention*, **30**(6), 1089–1099.

Zhao, H., Wu, L., Yan, G., Chen, Y., Zhou, M., Wu, Y., & Li, Y. (2021). Inflammation and tumor progression: Signaling pathways and targeted intervention. *Signal Transduction and Targeted Therapy*, **6**(1), 263.

Additional information

Data availability statement

The data are available from the authors on request.

Competing interests

The authors have no competing interests to disclose.

Author contributions

All authors contributed to the conception and design of the work; acquisition, analysis or interpretation of the data; and drafting or revising the work critically for important intellectual content. All authors have approved the final version of the manuscript submitted for publication and agree to be accountable for its content.

Funding

This study was funded by a Tour de Cure PhD scholarship (RSP-284-FY2023) and the National Health and Medical Research Council (NHMRC) (APP1132361) and Cancer Council Queensland (CCQ). N.H.H. receives salary support as an NHMRC Investigator Fellow (APP2018070). M.A.S. receives salary support from NHMRC (APP1171759).

Acknowledgements

The authors would like to acknowledge Marika Carr and Gary Wilson for their biochemistry laboratory support and the YMCA Queensland for the use of their facilities.

Open access publishing facilitated by Queensland University of Technology, as part of the Wiley - Queensland University of Technology agreement via the Council of Australian University Librarians.

Keywords

exercise, high-intensity interval training, immunology, interleukins, myokines, neoplasm

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

Peer Review History