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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

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Abstract

Purpose Following colorectal cancer diagnosis and anti-cancer therapy, declines in cardiorespiratory fitness and body composition lead to significant increases in morbidity and mortality. There is increasing interest within the field of exercise oncology surrounding potential strategies to remediate these adverse outcomes. This study compared 4 weeks of moderate-intensity exercise (MIE) and high-intensity exercise (HIE) training on peak oxygen consumption (VO_2peak) and body composition in colorectal cancer survivors.

Methods Forty seven post-treatment colorectal cancer survivors (HIE=27 months post-treatment; MIE=38 months post-treatment) were randomised to either HIE [85–95 % peak heart rate (HR_{peak})] or MIE (70 % HR_{peak}) in equivalence with current physical activity guidelines and completed 12 training sessions over 4 weeks.

Results HIE was superior to MIE in improving absolute ($p=0.016$) and relative ($p=0.021$) VO_2peak. Absolute (+0.28 $L.min^{-1}$, $p<0.001$) and relative (+3.5 $ml.kg^{-1}.min^{-1}$, $p<0.001$) VO_2 peak were increased in the HIE group but not the MIE group following training. HIE led to significant increases in lean mass (+0.72 kg, $p=0.002$) and decreases in fat mass (−0.74 kg, $p<0.001$) and fat percentage (−1.0 %, $p<0.001$), whereas no changes were observed for the MIE group. There were no severe adverse events.

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Conclusions In response to short-term training, HIE is a safe, feasible and efficacious intervention that offers clinically meaningful improvements in cardiorespiratory fitness and body composition for colorectal cancer survivors.
Implications for Cancer Survivors HIE appears to offer superior improvements in cardiorespiratory fitness and body composition in comparison to current physical activity recommendations for colorectal cancer survivors and therefore may be an effective clinical utility following treatment.

Keywords Colorectal cancer [MESH] · Exercise [MESH] · Exercise oncology · High-intensity exercise · Cardiorespiratory fitness · Body composition [MESH]

Introduction

Colorectal cancer is one of the most prevalent cancers worldwide; with the second and third highest mortality rates for men and women, respectively, it represents a significant proportion of the health burden attributable to cancer [1]. Following diagnosis and anti-cancer therapy (locoregional and systemic), many cancer survivors experience acute and chronic toxicities that increase morbidity and mortality [2, 3]. There is increasing interest in the clinical utility of exercise oncology as an adjunctive therapy for improving prognosis following colorectal cancer diagnosis via remediation of adverse clinical outcomes [3].

Cardiorespiratory fitness appears to be a critical prognostic factor across the oncology continuum [4]. Compared with low cardiorespiratory fitness (measured by peak oxygen consumption [VO_2peak]), moderate and high cardiorespiratory fitness has been associated with a 33 and 44 % reduction in colorectal cancer incidence, respectively [4]. Following a cancer diagnosis, cardiorespiratory fitness has been shown to predict cancer mortality in men [5] and women [6]. Indeed, meta-analytical conclusions indicate that compared with lower cardiorespiratory fitness levels, higher cardiorespiratory fitness is associated with a 45 % reduction in cancer-specific mortality [7]. In addition to the strong relationship between cardiorespiratory fitness and mortality, cardiorespiratory fitness has also been shown to be an important predictor of morbidity following major colonic [8] and rectal [9] cancer surgery. Recent data have shown that in pre-operative rectal cancer patients, neoadjuvant chemotherapy leads to a decrease in VO_2peak of between 1.4 and 4.0 $ml.kg^{-1}.min^{-1}$ [10, 11]. These decrements following anti-cancer therapy in conjunction with the poor prognostic relationship between low cardiorespiratory fitness and cancer morbidity and mortality demonstrate the clinical importance of improving cardiorespiratory fitness within the oncology setting.

Mechanistic underpinnings of the reduction in cardiorespiratory fitness following anti-cancer therapy appear to be determined by a multitude of central factors such as cardiac and pulmonary function, as well as peripheral factors including haematological, vascular and skeletal muscle function [3]. Recent pilot data strengthens the mechanistic relationship between reductions in cardiorespiratory fitness and skeletal muscle function, with significant reductions in mitochondrial function following neoadjuvant chemotherapy observed in rectal cancer patients [11]. This reduction in mitochondrial function and subsequent impairment of oxidative phosphorylative capacity may be further compounded by a reduction in skeletal muscle mass. Skeletal muscle atrophy or cachexia is a common comorbidity following diagnosis and anti-cancer treatment characterised by ongoing loss of muscle mass, with or without loss of fat mass, leading to progressive impairment in function [12–14]. The presence of cachexia has been shown to increase premature mortality rates in patients with advanced colorectal carcinoma [15]. Whilst the clinical presentation of advanced cancer cachexia is physically distinguishable, less obvious or 'hidden' conditions such as pre-cachexia or sarcopenic obesity (muscle mass loss masked by adipose tissue hypertrophy) are of perhaps greater clinical importance as these stages may be more responsive and amenable to therapeutic interventions as compared with advanced states of cachexia [12, 14]. Alluding to the clinical importance of body composition following cancer diagnosis, the presence of sarcopenic obesity in colorectal cancer survivors is associated with impaired physical function as well as an increase in premature mortality [16].

Collectively, reductions in cardiorespiratory fitness, skeletal muscle mass and an increase in adipose tissue present a series of adverse comorbidities for colorectal cancer survivors that can severely impair prognosis following treatment. Aerobic exercise training has been suggested to be one of the most effective therapeutic strategies to combat cancer cachexia through remediation of mitochondrial and oxidative phosphorylation dysfunction [17]. Additionally, aerobic exercise training is arguably the most effective method of facilitating improvements in cardiorespiratory fitness and thereby presents itself as a potentially effective therapy to combat the aforementioned adverse clinical outcomes associated with colorectal cancer survivorship. Within the scope of aerobic exercise, a recent meta-analysis demonstrated high-intensity exercise (HIE) to be more efficacious in improving cardiorespiratory fitness compared with moderate-intensity exercise (MIE) in patients with cardio-metabolic disease [18]. Whilst one previous trial has utilised an intervention that included HIE in colorectal cancer survivors [19], no study to date has investigated the comparative effectiveness of HIE and MIE to determine the most effective aerobic intensity prescription for improvements in cardiorespiratory fitness and body composition. The aim of this randomised controlled trial was to compare the effect of a short-term HIE or MIE aerobic exercise intervention as a potential clinical utility to promote

improvements in cardiorespiratory fitness and body composition in colorectal cancer survivors. It was hypothesised that HIE would result in greater improvements in cardiorespiratory fitness and body composition compared to MIE.

Methods

Participants

Men and women previously diagnosed with histologically confirmed colorectal cancer were recruited from Brisbane (Queensland, Australia) for this randomised controlled trial. Participants recruited for this intervention are included as part of the first phase of a larger ongoing trial. Inclusion criteria were as follows: (1) aged ≥18 years, (2) ≥1 month post-treatment for colorectal cancer and not anticipating undergoing treatment during the study period, and (3) free of any musculoskeletal, neurological, respiratory, metabolic or cardiovascular conditions that may have prevented safe completion of the exercise demands of the study. Potential participants were contacted either through access to the population based Queensland Cancer Registry according to previously described procedures [20] or from an existing cohort of colorectal cancer survivors [21]. Participants were required to obtain physician consent for participation in the program and were individually screened via a medical history form and interview with the investigators to determine eligibility.

Study protocol

This study was granted ethical approval by the Human Ethics Committee of The University of Queensland, and written informed consent was obtained from all subjects prior to commencing the study. Date of diagnosis and cancer stage information was extracted from pathology reports. Following recruitment, participants completed a familiarisation session consisting of a test of peak oxygen consumption ($\dot{V}O_2$peak) to assess cardiorespiratory fitness (detailed below). Following familiarisation (≥7 days), participants completed a baseline testing session consisting of an assessment of body composition (detailed below) and a $\dot{V}O_2$peak test. Following baseline testing, a researcher independent to the study stratified the participants according to age (<55 or ≥55 years) and sex and then randomised them via a random number generating process to either HIE or MIE (detailed below) at a ratio of 2:1, respectively. This randomisation ratio was implemented for two reasons: firstly, to account for a potentially inflated drop-out rate as the feasibility of a HIE intervention in this population has not been reported; and secondly, to allow for appropriate sample sizes for future phases of this ongoing trial. Both HIE and MIE groups trained three times per week for 4 weeks. Between 3 and 7 days following the final exercise session, participants completed endpoint testing involving identical procedures to those used at baseline testing.

Physiological performance

$\dot{V}O_2$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, USA). Expired air was analysed for oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$); the fraction of oxygen and carbon dioxide in expired air (FEO_2 and $FECO_2$) were sampled every 15 s during exercise from a mixing chamber, whilst total ventilation (V_E) was recorded every 15 s using a turbine ventilometer (Morgan, Model 096, Kent, England). The gas analysers were calibrated immediately prior to testing and validated after each test using a certified beta gas mixture (BOC, Brisbane, Australia). The ventilometer was calibrated before each test using a 3 L syringe (Hans Rudolph Inc., Shawnee, USA) in accordance with the manufacturer's instructions. Blood pressure was measured against contraindications to exercise testing [22]. The $\dot{V}O_2$peak testing protocol, modified from Wasserman et al. [23], began with 3 min of rest for respiratory normalisation, followed by 4 min of warm-up at a resistance of 50 W. Thereafter, the electronic resistance provided by the cycle ergometer increased incrementally by 20–30 $W.min^{-1}$. Participants cycled at a cadence between 60 and 70 revolutions per minute throughout the test. Heart rate was continuously recorded throughout exercise using a heart rate monitor (Polar FT1; Polar, Kempele, Finland) and blood pressure (DuraShock Sphygmomanometer; Welch Allyn, New York, USA) was recorded every 2 min throughout the test. At the conclusion of each minute, participants indicated their rating of perceived exertion (RPE) on the Borg 6–20 scale [24]. The test was terminated when participants reached volitional fatigue or at the discretion of the researcher in accordance with the indications for exercise test termination as outlined by the American College of Sports Medicine [22]. $\dot{V}O_2$peak was recorded as the mean of the two highest 15-s $\dot{V}O_2$ epochs. Peak power output (PPO) was determined by the addition of the highest completed power level and the fraction of time spent in the incomplete stage multiplied by the stage wattage increments:

$$\text{PPO} = \text{final completed workload} + (\text{workload increment} \times \text{seconds in final stage} \times 60^{-1}) \quad (1)$$

Body composition

Fat mass, percentage body fat and lean mass were derived by dual energy x-ray absorptiometry (DEXA; Hologic Discovery A, Waltham, MA). The coefficients of variation values in our laboratory for whole body fat and lean masses are <1.1 %. All

scans were conducted and analysed by two accredited DEXA technicians. All fat and lean mass results are subtotal values (whole body minus the head) rather than whole body totals. Height and body mass were measured using a stadiometer (Seca, Birmingham, UK) and electronic scales (A & D Mercury, Pty Ltd, Thebarton, Australia), respectively.

Control measures

For each testing session participants were asked to (1) maintain a hydrated state in the 24 h prior to testing, (2) abstain from caffeine and alcohol intake for 12 h prior to testing and (3) avoid any vigorous, high or unaccustomed moderate intensity exercise or physical activity for the 48 h prior to testing which were confirmed via checklist prior to commencing the session. All participants were asked to maintain their current diet and level of physical activity outside of the training sessions for the duration of the study (i.e. not commencing any unaccustomed dietary or physical activity behaviours throughout the duration of the intervention). To quantify and track the weekly physical activity behaviours of participants, the Godin leisure-time exercise questionnaire [25] was completed at both testing time points. The Godin questionnaire has been shown to have a modest correlation compared with accelerometry-derived measures of physical activity (r=0.45) [26] but demonstrates high test-retest reliability (r=0.75) [27].

Exercise intervention

An Accredited Exercise Physiologist (Exercise and Sports Science Australia) supervised all testing and exercise training sessions. Both the HIE and MIE sessions were conducted on air- and magnetically braked cycle ergometers (Wattbike Pro; Wattbike Ltd., Nottingham, England) with heart rate continuously measured throughout each session (Sunnto Ambit2 S; Suunto Oy, Vantaa, Finland). The HIE training sessions commenced with a 10-min warm-up at 50–70 % HR_{peak} before commencing 4×4 min bouts of cycling at 85–95 % $HR_{peak.}$ Each 4-min interval was interspersed with a 3-min period of active recovery at 50–70 % HR_{peak}, totalling 38 min for the session. The MIE training protocol consisted of 50 min of cycling at 50–70 % HR_{peak}. The frequency and volume of MIE was established according to current physical activity guidelines recommended for cancer survivors [28, 29] and for adults by the American College of Sports Medicine for adults (≥150 min of moderate-intensity physical activity per week) [24]. RPE was measured at the conclusion of each 4-min interval in the HIE session and at similarly regular intervals during the MIE session (15, 30, 40 and 50 min). Power output and cadence were continuously measured throughout the sessions and analysed using specialised software (Wattbike Expert; Wattbike Ltd., Nottingham, England).

Rates of completion, adverse events, attendance and adherence

Completion rates were calculated as the number of participants that completed baseline testing divided by the number that were randomised at the beginning of the intervention. Adverse events were defined as 'any untoward medical occurrence in a participant subject to the intervention'. A severe adverse event was defined as any event requiring hospitalisation or causing an inability to carry out usual activities. Adverse events were assessed by monitoring and recording during all exercise sessions by the supervising Exercise Physiologist. Attendance to the intervention was measured as the number of sessions attended ($n_{attended}$) divided by the number of sessions prescribed ($n_{prescribed}$):

$$\text{attendance} = n_{\text{attended}} \times n_{\text{prescribed}}{}^{-1} \times 100 \quad (2)$$

Adherence to the intervention was assessed within the prescriptive domains of duration and intensity. Duration adherence was measured as the duration of the completed session divided by the prescribed duration in minutes:

$$\text{duration adherence} = n_{\text{completed}} \times n_{\text{prescribed}}{}^{-1} \times 100 \quad (3)$$

Adherence to the prescribed intensity for both the HIE and MIE groups was measured as the mean heart rate (HR_{mean}) achieved within the 12 sessions relative to the recorded HR_{peak}:

$$\text{intensity adherence} = \left(\sum \text{HR}_{\text{mean}} \times 12^{-1}\right) \times \text{HR}_{\text{peak}}{}^{-1} \times 100 \quad (4)$$

The MIE HR_{mean} was calculated as the mean HR recorded at four time points (15, 30, 40 and 50 min) throughout the 50-min session, whereas the HIE HR mean was calculated as the mean of the peak HRs recorded during each of the four intervals. Intensity was also concurrently assessed as the mean session RPE recorded throughout the intervention, with session RPE calculated as the mean of RPE recorded at four time points during both sessions.

Statistical analysis

All data were analysed using SPSS (version 22.0; Chicago, IL). Data were assessed for normality of distribution using the Shapiro–Wilk test. Analyses included standard descriptive statistics, independent t tests, Mann–Whitney U tests or chi-squared tests, as appropriate to test for differences between the groups at baseline. Non-parametric data were log-transformed and re-checked for normality prior to univariate within- and between-groups analyses. Differences within groups were assessed using paired samples t tests or the Wilcoxon signed-rank non-parametric test, as appropriate. Differences between groups were assessed using independent t tests and

the non-parametric equivalent Mann–Whitney *U* test where necessary. Statistical significance was accepted at an alpha of $p < 0.05$. Normally distributed data are presented as mean and standard deviation (SD), whereas data-requiring log-transformation were re-transformed and are reported as the geometric mean and 95 % confidence intervals (CI). Data unable to be normally distributed using log-transformation were analysed non-parametrically and presented as median, interquartile range and 95 % CI.

Results

Participant recruitment and baseline characteristics

A consort diagram of participant flow throughout the study is detailed in Fig. 1. Following recruitment and baseline testing, 47 colorectal cancer survivors were randomised. The characteristics of participants included within the analyses are shown in Table 1. There were no significant differences ($p > 0.05$) between groups for any of the measured baseline characteristics. A previous diagnosis of colon cancer was more prevalent than rectal cancer within both the HIE (colon=70.0 %; rectal=30.0 %) and MIE (colon=82.4 %; rectal=17.6 %). Only 30.0 % of participants in the HIE and 41.2 % of MIE participants underwent surgical treatment without any adjunctive therapy, whereas the prevalence of treatment with a chemotherapeutic agent was high with 66.6 % of HIE and 58.6 % of MIE participants undergoing adjunctive chemotherapy. Participants in the HIE intervention were at a median 27.0 months post-treatment, whereas participants in the MIE training were 38.0 months post-treatment. Cancer staging was unable to be determined for 13 participants, 9 due to insufficient pathology report information, and 4 sets of data were unable to be accessed due to consent reasons.

Rates of completion, adverse events, attendance and adherence

Study completion rates for the MIE and HIE were 94.1 and 96.7 %, respectively, with only one participant dropping out in either group (MIE—discontinued the intervention due to personal reasons prior to commencing training, HIE—discontinued after six sessions due to ongoing interruptions resulting from additional medical diagnostic testing for an unrelated condition). No severe adverse events occurred during any exercise testing or training throughout this study. In terms of non-severe adverse events during the study, on three occasions for separate participants (two following a HIE session and one following exercise testing), participants

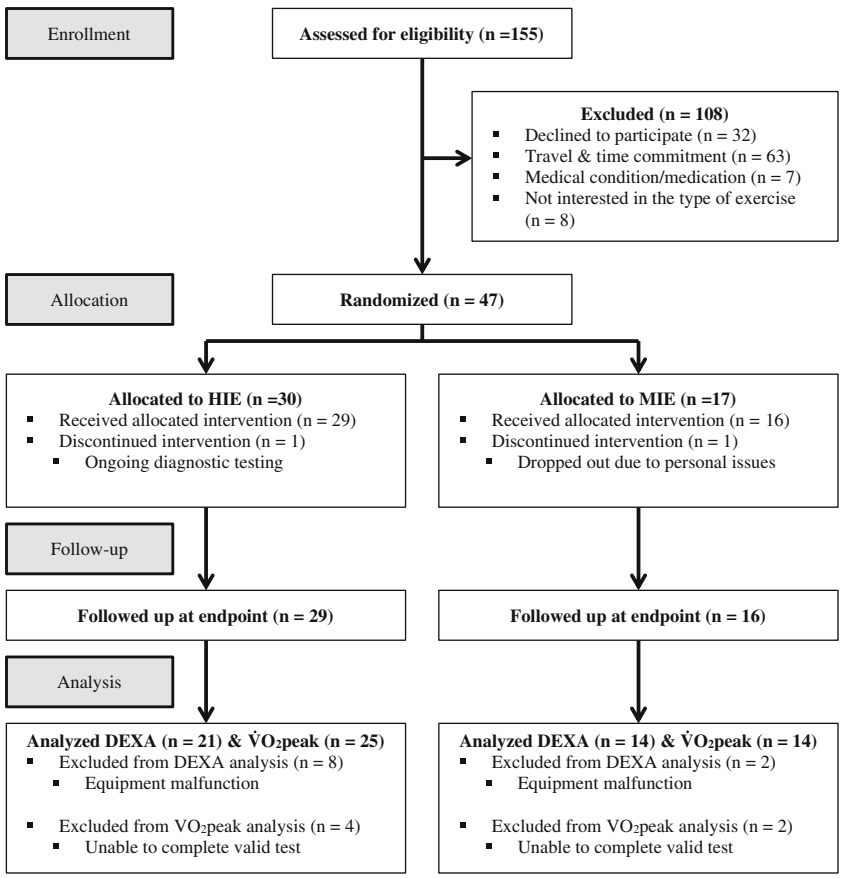

Fig. 1 CONSORT diagram illustrating participant flow through the intervention. *DEXA* dual-energy x-ray absorptiometry, *HIE* high-intensity exercise, *MIE* moderate-intensity exercise, *$\dot{V}O_2peak$* peak oxygen uptake

Table 1 Baseline participant characteristics

n	All 47		HIE 30		MIE 17		*p* value
Age (years)	61.5	(10.9)	61.4	(11.1)	61.5	(10.8)	0.977[a]
Height (cm)	171.9	(9.5)	172.7	(8.0)	170.3	(11.8)	0.405[a]
Body mass (kg)	79.8	(15.6)	81.1	(15.4)	77.2	(16.2)	0.418[a]
Body Mass Index ($kg.m^{-2}$)	26.9	(4.3)	27.1	(4.8)	26.4	(3.4)	0.605[a]
Women [*n* (%)]	21	(44.7)	12	(40.0)	9	(52.9)	0.391[b]
Cancer history							
Colon cancer [*n* (%)]	35	(74.5)	21	(70.0)	14	(82.4)	0.351[b]
Rectal cancer [*n* (%)]	12	(25.5)	9	(30.0)	3	(17.6)	0.351[b]
Time since diagnosis (months)[c]	41.0	(29.0)	31.0	(30.3)	46.0	(30.5)	0.324[d]
Time since treatment (months)[c]	29.0	(29.0)	27.0	(25.8)	38.0	(33.0)	0.521[d]
Cancer stage [*n* (%)]							
I	8	(17.0)	4	(13.3)	4	(23.5)	0.844[b]
II A	7	(14.9)	4	(13.3)	3	(17.6)	0.844[b]
II B	0	(0.0)	0	(0.0)	0	(0.0)	0.844[b]
III A	5	(10.6)	3	(10.0)	2	(11.8)	0.844[b]
III B	8	(17.0)	5	(16.7)	3	(17.6)	0.844[b]
III C	3	(6.4)	3	(10.0)	0	(0.0)	0.844[b]
IV	3	(6.4)	2	(6.7)	1	(5.9)	0.844[b]
Unable to be staged	13	(27.7)	9	(30.0)	4	(23.5)	0.844[b]
Cancer treatment [*n* (%)]							
Surgery	16	(34.0)	9	(30.0)	7	(41.2)	0.764[b]
Surgery and chemotherapy	22	(46.8)	15	(50.0)	7	(41.2)	0.764[b]
Surgery and radiation	1	(2.1)	1	(3.3)	0	(0)	0.764[b]
Surgery, chemotherapy and radiation	7	(14.9)	4	(13.3)	3	(17.6)	0.764[b]
Radiation and chemotherapy	1	(2.1)	1	(3.3)	0	(0)	0.764[b]
Ethnicity [*n* (%)]							
Caucasian	44	(93.6)	28	(93.3)	16	(94.1)	0.693[b]
Asian	2	(4.3)	1	(3.3)	1	(5.9)	0.693[b]
African	1	(2.1)	1	(3.3)	0	(0)	0.693[b]
Smoking history [*n* (%)]							
Never	25	(53.2)	17	(56.7)	8	(47.1)	0.526[b]
Former	22	(46.8)	13	(43.3)	9	(52.9)	0.526[b]
Current	0	(0)	0	(0)	0	(0)	0.526[b]
Education [*n* (%)]							
Primary	4	(8.5)	3	(10.0)	1	(5.9)	0.067[b]
Secondary	15	(31.9)	6	(20.0)	9	(52.9)	0.067[b]
Tertiary	28	(57.6)	21	(70.0)	7	(41.2)	0.067[b]
Marital status [*n* (%)]							
Not married	1	(2.1)	1	(3.3)	0	(0)	0.637[b]
Married	42	(89.4)	27	(90.0)	15	(88.2)	0.637[b]
Divorced/separated	4	(8.5)	2	(6.7)	2	(11.8)	0.637[b]
Employment [*n* (%)]							
Working	23	(49.3)	13	(43.3)	10	(58.8)	0.307[b]
Retired	24	(51.1)	17	(56.7)	7	(41.2)	0.307[b]

Unless stated otherwise, values are presented as mean (SD)

HIE high-intensity exercise, *IQR* interquartile range, *MIE* moderate-intensity exercise, *n* number of participants, *SD* standard deviation

[a] Variables compared using standard independent *t* test

[b] Nominal variables compared using chi-squared analysis

[c] Data presented as median (IQR)

[d] Variables compared using Mann–Whitney *U* test

experienced a symptomatic episode of post-exercise hypotension, which was resolved following active recovery, consumption of fluids and recovery in the supine position if necessary. On one occasion, a participant experienced an

aggravation of pre-existing sciatica following a HIE session. Two participants also experienced an acute exacerbation of knee pain during a HIE interval related to pre-existing osteoarthritis. In both instances, the respective sessions were terminated and the issue did not impact subsequent sessions. The number of non-severe adverse events between HIE and MIE groups were not statistically significantly different (p=0.082). Additionally, following the completion of HIE intervals, two participants occasionally reported brief feelings of nausea, which were resolved following active and passive recovery as well as fluid intake. Attendance rates at sessions across the intervention were 100 % in both MIE and HIE groups for the 16 and 29 participants who completed the intervention in either group (including all participants—MIE=97.1 %; HIE=97.0 %), respectively. The mean±SD duration of the MIE sessions was 50±0 min, indicating a 100 % adherence rate to the prescribed duration. MIE training was completed at a mean±SD intensity of 73.4 ±8.4 % HR_{peak} (prescribed, 70 % HR_{peak}) and a RPE of 12.0±1.7. The mean±SD duration of the HIE intervals completed during each session was 15.95±0.1 min, representing 99.7 % of the prescribed duration. HIE intervals were completed at an intensity of 91.9± 4.2 % HR_{peak} (prescribed, 85–95 % HR_{peak}) at a RPE of 14.6±1.2.

Physical activity levels of participants are displayed in Table 2. There were no significant differences between groups at baseline. No significant changes were observed within groups across the intervention, nor between groups following the intervention (p>0.05).

Physiological performance

Changes in cardiorespiratory fitness and power output are shown in Table 2. There were no significant differences between the HIE and MIE groups for any variables at baseline. HIE training was associated with a mean increase of 0.28± 0.28 $L.min^{-1}$ and 3.5±3.5 $ml.kg^{-1}.min^{-1}$ in absolute and relative $\dot{V}O_2$peak, respectively. Improvements in both absolute $\dot{V}O_2$peak (p<0.001) and relative $\dot{V}O_2$peak (p<0.001) in the HIE group were significant from baseline to endpoint, whereas no significant within-group changes were observed in the MIE group. Mean changes in absolute (p=0.016) and relative (p=0.021) $\dot{V}O_2$peak were significantly higher in the HIE group than the MIE group. PPO significantly increased following the intervention in both the HIE (p<0.001) and MIE (p=0.030) groups. The mean increase of 29.3±20.7 W in response to HIE training was significantly greater than the 11.7±19.3 W MIE group increase (p=0.018). Similar trends in relative PPO were observed with both groups improving from baseline to endpoint (p<0.05), with the mean increase in the HIE group being significantly greater than the HIE group (p=0.043).

Body composition

Body composition data are shown in Table 2. A subset of DEXA data from 10 consecutive participants (8 HIE and 2 MIE) was unable to be analysed due to equipment malfunction, which consequently reduced the sample size for all body composition analyses (excluding body mass) within each group. No significant differences were found between HIE and MIE groups at baseline for any of the body composition variables. For the HIE group, body mass significantly decreased from baseline to endpoint (p=0.005), with mean changes in the HIE group being significantly different compared to MIE (p=0.005). Within the HIE group, lean mass significantly increased by a mean (SD) change of 0.72± 0.80 kg from baseline to endpoint (p=0.002). In the HIE group, both fat mass (p<0.001) and body fat percentage (<0.001) significantly decreased from baseline to endpoint by a mean (SD) change of 0.74±0.65 kg and 1.0±1.0 %, respectively. No significant within-group changes in body composition were observed for the MIE group. No significant differences were observed across the intervention between groups for measures of lean mass, fat mass or fat percentage; however, whilst the mean decrease in fat mass in the HIE group was greater than the MIE group, the difference was not statistically significant (p=0.060).

Discussion

This study compared the influence of HIE training with MIE training on cardiorespiratory fitness and body composition in colorectal cancer survivors. The findings show that 12 sessions of HIE completed over 4 weeks is significantly more effective than MIE in improving absolute and relative $\dot{V}O_2$peak and PPO. Furthermore, HIE was found to elicit increases in lean mass and decreased body mass, fat mass and fat percentage, with no changes associated with MIE in colorectal cancer survivors.

To assess the feasibility of the intervention and the subsequent influence on program efficacy, we assessed the rates of completion, adverse events, adherence and attendance. We found excellent completion rates (MIE=94.1 %; HIE=96.7 %) for participants enrolled in this trial, comparable to rates reported in other interventions in colorectal cancer survivors [19, 30, 31]. Data regarding program safety and adverse events are severely underreported in the current colorectal cancer-exercise literature [32]. Only one study to date has reported these data in colorectal cancer survivors [19], with which our data compares well. Post-exercise hypotension was the most common adverse event and is a well-known post-exercise phenomenon thought to be resultant from a peripheral vasodilatory response in the active musculature coupled with a relative decrease in sympathetic vasoconstrictive

Table 2 Outcome measures

Outcome		Baseline				Endpoint					Change (Δ)		
	n	Mean	SD	95 % CI	p^c	Mean	SD	95 % CI	p^d	p^e	Mean	SD	p^f
Cardiorespiratory fitness													
$\dot{V}O_2$peak (L.min^{-1})													
HIE	25	1.9 [a]	1.3	1.7–2.1	0.362	2.2	1.3	1.9–2.4	<0.001	0.046	0.28	0.28	0.016
MIE	14	1.7 [a]	1.3	1.5–2.0		1.8	1.3	1.5–2.1	0.199		0.07	0.19	
$\dot{V}O_2$peak (ml.kg^{-1} .min^{-1})													
HIE	25	22.8[b]	6.0	21.3–28.0	0.897[g]	27.4	7.5	23.9–32.4	<0.001[h]	0.071[g]	3.5	3.5	0.021
MIE	14	21.5[b]	8.0	20.2–26.4		21.8	6.4	19.4–28.8	0.245[h]		0.9	2.8	
PPO (W)													
HIE	25	161.0[a]	1.4	142.0–182.5	0.651	191.2	1.3	171.4–213.4	<0.001	0.135	29.3	20.7	0.018
MIE	12	153.6[a]	1.3	128.9–183.0		167.2	1.2	145.9–191.6	0.032		11.7	19.3	
Relative PPO (W.kg^{-1})													
HIE	25	2.0[a]	1.3	1.8–2.3	0.928	2.4	1.3	2.2–2.7	<0.001	0.303	0.38	0.26	0.043
MIE	12	2.0[a]	1.4	1.7–2.4		2.2	1.3	1.8–2.7	0.030		0.19	0.28	
Body composition													
Body mass (kg)													
HIE	29	80.6	15.3	74.8–86.4	0.408	80.0	15.1	74.3–85.8	0.005	0.516	−0.3[b]	1.2	0.005[g]
MIE	16	76.5	16.9	67.5–85.5		76.8	17.3	67.6–86.1	0.142		0.3[b]	1.2	
Lean mass (kg)													
HIE	21	44.1[a]	1.3	39.6–49.1	0.227	44.7	1.3	40.1–49.9	0.002	0.210	0.72	0.80	0.363
MIE	14	39.7[a]	1.3	34.3–46.1		40.0	1.3	34.3–46.7	0.299		0.43	1.06	
Fat mass (kg)													
HIE	21	25.1	8.5	21.2–29.0	0.467	24.3	8.6	20.4–28.3	<0.001	0.372	−0.74	0.65	0.060
MIE	14	27.3	9.3	22.0–32.7		27.1	9.4	21.7–32.6	0.448		−0.21	0.99	
Body fat percentage (%)													
HIE	21	34.3	7.4	31.0–37.7	0.094	33.3	7.9	29.8–36.9	<0.001	0.073	−1.00	1.00	0.123
MIE	14	38.9	7.8	34.4–43.4		38.5	8.3	33.7–43.3	0.308		−0.38	1.34	
Physical activity													
Godin index													
HIE	28	32.3	21.1	24.1–40.4	0.495	33.0	25.6	23.0–42.9	0.862	0.997	1.0[b]	23.8	0.932[g]
MIE	16	28.1	15.9	19.6–36.6		32.9	29.5	17.2–48.6	0.450		−1.5[b]	19.5	

HIE high-intensity exercise, *MIE* moderate-intensity exercise, *n* number of participants, *PPO* peak power output, $\dot{V}O_2peak$ peak oxygen uptake, *Δ* change

[a] Data presented as geometric mean, standard deviation and 95 % CI

[b] Data presented as median and IQR

[c] Independent *t* test between groups at baseline

[d] Dependent *t* test within groups from baseline to endpoint

[e] Independent *t* test between groups at endpoint

[f] Independent *t* test between groups

[g] Independent samples Mann–Whitney *U* test

[h] Related samples Wilcoxon signed-rank test

signals to restore homeostasis following exercise cessation [33]. As compared with moderate intensity, high-intensity resistance training has been shown to induce greater reductions in post-exercise blood pressure, which may be due to an increased vasodilatory response of the working musculature due to the increased muscle volume recruited and metabolic demand of higher intensity exercise [34]. To assist in the maintenance of blood pressure, activation of a skeletal muscle-pump mechanism, which augments venous return from the periphery to central circulation, is a critical process to prevent post-exercise hypotension [33]. As such, it is strongly recommended that all HIE sessions and $\dot{V}O_2$peak tests are concluded with a period of active recovery to promote activation of this muscle-pump mechanism, as abrupt cessation of exercise and withdrawal of this muscle-pump can lead to significant decreases in venous return and blood pressure [33]. As an

additional prospective countermeasure, we recommend that participants undertaking HIE maintain adequate fluid intake prior to, during the session and during recovery. Water ingestion is known to induce an acute pressor response, leading to increases in sympathetic drive and increases in blood pressure [35], a response that has been shown to effectively maintain post-exercise blood pressure and prevent hypotension [36]. Exercise-induced gastrointestinal discomfort and nausea are also known to occur with greater frequency following high-intensity exercise when compared with light exercise [37]. The precise causes of this remain to be determined; however, it has been suggested that dehydration, consumption of foods that delay gastric emptying as well as splanchnic hypoperfusion resulting from sympathetic splanchnic vasoconstriction to shunt blood to the working musculature and organs (inverse of the post-exercise hypotension mechanism) may all contribute to symptoms [37]. This further illustrates the importance of appropriate nutritional and hydration-monitoring prior to HIE. Given the small number and nature of the adverse events from this study and coupled with previous reports [19], HIE training appears safe in the clinical setting with appropriate supervision for colorectal cancer survivors.

Our attendance rate of 100 % for participants in both the HIE and MIE groups who completed the intervention (when including all randomised participants—MIE=97.1 %; HIE=97.0 %) was higher than previous trials in colorectal cancer survivor populations, which have reported attendance rates ranging from 75.8 to 91.0 % [19, 30, 38]. Throughout this intervention, we also report excellent adherence to the duration of both the MIE (100 %) and HIE (99.7 %) sessions which again is higher than previous measures of duration adherence (87.3 %) [19]. When considered in conjunction with strong rates of adherence to the prescribed exercise intensity, these outcomes suggest that aerobic MIE and HIE are highly feasible within a supervised clinical environment for colorectal cancer survivors. The median time since treatment for participants undertaking HIE was 27.0 months. Whilst HIE was highly feasible at this time point along the post-treatment continuum, more research is needed to establish the feasibility of HIE at more proximal post-treatment time points. It is the view of the authors that establishing the suitability of a patient for HIE at a point along the post-treatment continuum should not follow a 'one size fits all' approach. Rather, decisions regarding a patient's suitability to undertake HIE should be made with consideration of their overall clinical presentation and comorbidities, which therefore necessitates consideration on an individual-by-individual basis with input from the patient's primary healthcare physician. Given the relatively brief duration of our intervention, these feasibility outcomes may be inflated compared to longer duration interventions (≥12 weeks); however, given our results pertaining to the efficacy of the intervention on cardiorespiratory fitness and body composition, these data provide novel considerations for the design of shorter, highly feasible and efficacious clinical exercise programs for colorectal cancer survivors.

The present study demonstrates HIE to be significantly more efficacious than MIE in improving absolute (0.28 $L.min^{-1}$, $p=0.016$) and relative (3.5 $ml.kg^{-1}.min^{-1}$, $p=0.021$) $\dot{V}O_2$peak as well as PPO (29.3 W, $p=0.018$). Only one previous study has measured changes in $\dot{V}O_2$peak in response to exercise in colorectal cancer utilising a maximal graded exercise test with direct ventilatory measurement similar to the present study. Sellar et al. [19] implemented a longer intervention than the current study (12 weeks) and utilised a combination aerobic and resistance training program (aerobic—three sessions/week, interval training, moderate to high intensity progressively increasing from 60 to 75 % PPO to 110 % PPO; resistance training—2 sessions/week, 2–3 sets, 6–15 repetitions at 65–85 %, 1 repetition maximum) and reported significant increases in absolute (0.24 $L.min^{-1}$, $p<0.001$) and relative (3.0 $ml.kg^{-1}.min^{-1}$, $p<0.001$) $\dot{V}O_2$peak as well as PPO (24.0 W), similar to the present results. A meta-analysis including three other studies in colorectal cancer survivors demonstrated evidence for increases in physical fitness in response to exercise and physical activity interventions; however, submaximal treadmill tests were used to predict physical fitness, which rely on extrapolation of values (e.g. heart rate) to estimate maximal capacity and are therefore less accurate than direct measurement at maximal exercise [30–32, 38]. Meta-analytical data of interventions of all cancer patients suggest mean (95 % CI) improvements in relative $\dot{V}O_2$peak of 2.9 $ml.kg^{-1}.min^{-1}$ (1.16–4.64) following supervised exercise training [39]. Whilst our results are of a similar magnitude and provide further support for the efficacy of exercise interventions to improve cardiorespiratory fitness in oncology populations, previous trials have been of a substantially longer duration than the present study, ranging from 8 to 24 weeks of predominantly MIE. As no studies have previously used an intervention of such a short duration, it is not possible to conclude that similar cardiorespiratory fitness changes similar to the present study were not also observed at 4 weeks in other studies. However, our data provide evidence that short-term exercise training of a higher intensity offers greater physiological adaptations when compared to moderate intensity training of the same duration. This discrepancy between our intervention duration (4 weeks) and others (≥8 weeks) may also explain the lack of $\dot{V}O_2$peak improvement in response to MIE in the present study. Cardiorespiratory fitness improvements in response to MIE may require longer interventions when compared to HIE, which is largely supported by previous studies in cancer survivors of longer durations that are predominantly of a moderate intensity [19, 39]. The present data strongly suggest that exercise intensity is a key prescriptive variable in short-term exercise interventions, with HIE offering significant increases in cardiorespiratory fitness compared with MIE.

In the present study, HIE training led to significant increases in lean mass (0.72±0.80 kg; p=0.005) and reductions in fat mass (−0.74±0.65 kg; p<0.001) and body fat percentage (−1.0±1.0 %; p<0.001), whereas no significant changes were observed in response to training for the MIE group. Comparably, of the seven exercise-intervention studies conducted exclusively in colorectal cancer survivors [19, 30, 31, 38, 40–42], only two incorporated discrete measurement of separate tissues in body composition analysis similar to the present study. Lee et al. [42] used bioelectrical impedance analysis in response to a 12-week home-based physical activity program, whereas Sellar et al. [19] utilised air displacement plethysmography. No changes in fat percentage, lean or fat mass were observed in response to either intervention. Recent meta-analytical data demonstrate that in cancer survivors, resistance training interventions conducted over 12 to 52 weeks are associated with mean (95 % CI) increases in lean mass of 1.1 kg (0.8 to 1.4) and decreases in body fat percentage of −2.1 % (−3.5 to −0.7 %) with non-significant changes in fat mass [43]. Whilst the magnitude of these changes is greater than in the current study, it is promising that improvements in lean mass were seen at all, given that the intervention in the current study did not involve resistance training and was shorter in duration than those in the meta-analyses. These findings, however, are limited by our reduced sample size due to the unavailability of 10 data sets and should be interpreted with caution.

To our knowledge, this is the first trial to demonstrate improvements in both physiological performance and body composition following aerobic HIE in cancer survivors. These increases with HIE but not MIE provide novel insight into the importance of exercise intensity prescription. The HIE prescription within the current study utilised four sets of a 4-min interval duration followed by 3 min of active recovery. Within the breadth of high-intensity interval training literature, a 4-min interval is considered a 'long-interval' (>60 s) and is associated with a high physiological demand, incorporating both anaerobic (phosphocreatine system and anaerobic glycolysis) and aerobic (oxidative phosphorylation) energetics [44]. The physiological demands in terms of energy systems lead to both central and peripheral fatigue in response to long-interval training [45]. Within this study, the use of an air-braked, high-intensity interval cycle ergometer training regime specifically targets the hip and knee extensor musculature, which has been previously shown to increase the activity of various oxidative and glycolytic enzymes (citrate synthase, succinate dehydrogenase and phosphofructokinase) concurrently with PPO and $\dot{V}O_2$max [46–48]. Whilst specific enzymatic measures were not included in the current study, significant improvements in PPO in response to HIE (29.3 W; p<0.001) suggest an increase in peripheral oxidative and glycolytic capacity to offset peripheral muscular fatigue of the lower limb musculature. Increases in mitochondrial biogenesis have been suggested as a primary mechanism underlying the HIE-induced peripheral adaptions leading to increases in oxidative capacity [49]. Specifically, increases in peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α), which is considered the 'master regulator' of mitochondrial biogenesis, has been shown to increase in response to HIE [49–52]. In patients with heart failure, HIE of the same prescription used in the present study increased PGC-1α, whereas no changes were observed in response to MIE [53]. Increases in muscular PGC-1α content have been reported to occur through cellular activation of both the 5′-adenosine monophosphate-activated protein kinase and the p38 mitogen-activated protein kinase (MAPK) as a result of HIE [49, 51]. The latter is a downstream target of the MAPK pathway, which in addition to other key pathways [akt/mammalian target of rapamycin, calcium (Ca^{2+})-dependent pathways], is concurrently an important cellular pathway leading to muscular hypertrophy and anabolic development; however, this is generally only considered in response to resistance training [54, 55]. Evidence to date suggests that HIE is capable of promoting MAPK activation and subsequent cellular signalling which can induce both increases in mitochondrial content as well as muscular hypertrophy which may explain the increases in lean mass observed in HIE but not MIE. Furthermore, HIE has been suggested to be more effective than MIE in reducing fat mass, hypothesised to occur as a result of exercise-induced increases in fat oxidation, catecholamine-mediated fat metabolism or appetite suppression [56]. This presents a mechanistic hypothesis for the interpretation of the current results that is capable of explaining increases in aerobic and anaerobic performance ($\dot{V}O_2$peak and PPO) as well as simultaneous increases in lean tissue and decreases in fat mass in response to aerobic HIE but not MIE. Future cellular analysis of these pathways is required to provide greater mechanistic scope for the interpretation of these findings.

These results have important clinical implications for the therapeutic use of targeted HIE programs within the oncology setting. Cardiorespiratory fitness is strongly and inversely associated with both mortality following cancer diagnosis [4–7] and morbidity following major colonic and rectal surgery [8, 9]. Recent data in male cancer survivors suggest that an increase of 1-metabolic equivalent (MET; 3.5 $ml.kg^{-1}.min^{-1}$) leads to a concurrent 10 % decrease in cancer-specific mortality risk [4]. The present 4-week HIE intervention observed a mean increase in $\dot{V}O_2$peak of 3.5 $ml.kg^{-1}.min^{-1}$ (p<0.001), demonstrating the potentially clinically meaningful improvements of HIE on cancer prognosis following diagnosis and adjuvant therapy. The prevalence of adjuvant chemotherapy was high in the current cohort (HIE=66.6 %; MIE=58.8 %), and given the known decrements in $\dot{V}O_2$peak (1.4–4.0 $ml.kg^{-1}.min^{-1}$) following treatment, the clinical importance of the rapid improvements in $\dot{V}O_2$peak observed in the

present study is further illustrated [10, 11]. The decrease in cardiorespiratory fitness following chemotherapy is thought to be determined primarily by a decrease in mitochondrial content and function [11], the amelioration of which is an important component of this high intensity prescription as improvements in mitochondrial density and function have been reported in response to HIE [57]. Sarcopenic obesity has been associated with impaired functional status and increased mortality risk following colorectal cancer diagnosis [16]. The present increases in lean mass (0.72 kg; $p=0.002$) and decreases in fat mass (−0.74 kg; $p<0.001$) in response to HIE but not MIE may present HIE as an effective intervention to assist in remediating reductions in skeletal muscle and increases in adipose tissue following colorectal cancer treatment. With the observed improvements in cardiorespiratory fitness and body composition, combined with the short-term accrual of these changes, aerobic HIE appears to offer clinically meaningful improvements in colorectal cancer prognosis following diagnosis and treatment, superior to that of MIE.

This study has several limitations that are worthy of comment. Firstly, we did not implement any restrictions on inclusion criteria relating to age, cancer stage, treatment received or time since diagnosis or treatment. Given the known effects of adjuvant chemotherapy on cardiorespiratory fitness, participants who underwent this treatment may be more receptive to cardiorespiratory fitness improvements as a result of lower baseline values when compared to participants who did not receive chemotherapy. Furthermore, this relationship may extend to differences in time since treatment, whereby participants more proximal to final treatment may be more receptive to improvements in cardiorespiratory fitness and body composition. Additional sub-analysis according to these variables was not possible in the present study due to sample size restrictions; however, future trials should endeavour to make these considerations wherever possible. Within this study, we used the MIE group as a 'usual care' condition as this aligns with current physical activity guidelines for cancer survivors and as such there was no true 'control group'. Following from this, our comparison with current physical activity guidelines for cancer survivors meant that controlling for total metabolic expenditure in each intervention was not possible. This may limit the conclusions that can be drawn regarding the isolated effect of exercise intensity between non-isoenergetic protocols. Whilst we did not directly compare the exercise volumes of the HIE and MIE protocols, a previous study estimated that the same HIE protocol implemented in the present study was approximately isoenergetic with 47 min of MIE (at 70 % HR_{peak}) in a group of patients with the metabolic syndrome [58]. This data provides basic support that the volume of exercise completed between the HIE and MIE protocols was somewhat similar; however, the non-isoenergetic nature of these protocols should be acknowledged as a limitation when drawing conclusions from these results. In the present study, we found no increases in leisure-time exercise across either HIE or MIE groups, providing support for the observed changes being resultant from the exercise intervention rather than external participation in exercise or physical activity. Whilst self-reported levels of physical activity using the Godin questionnaire have been shown to be sufficiently reliable [27], recent data has questioned the validity of this method when compared with objectively measured levels of physical activity such as tri-axial accelerometry [59]. Whilst discrepancies between methods may originate from the focus of self-report data on recreational exercise, whereas objective measures capture total physical activity, future research should endeavour to use more accurate measures to quantify external exercise and physical activity so as to strengthen conclusions made as being resultant of the intervention rather than external factors. This extends to changes in dietary patterns also; in the present study, we did not collect dietary records expansive enough to validly assess and track changes in dietary habits across the intervention. Finally, we only assessed outcomes following 4 weeks of exercise training and therefore whether this intervention resulted in clinically meaningful long-term changes is yet to be determined.

The present study is the first to compare the differential effects of moderate- and high-intensity exercise in any cancer survivorship population. Our results demonstrate HIE to be superior to MIE in promoting improvements in VO_2peak, PPO and in body composition, which were not evident in response to MIE. Current guidelines for cancer survivors recommend exercise in accordance with general physical activity guidelines (i.e. 150 min of moderate intensity or 75 min of vigorous intensity exercise per week) [29]. Our results indicate that HIE appears to be significantly more efficacious than MIE to facilitate improvements in cardiorespiratory fitness and body composition for colorectal cancer survivors in the short term. Given the clinical importance of improving cardiorespiratory fitness and body composition in oncology, our results present HIE as a time-effective therapeutic utility, which may lead to clinically meaningful improvements in colorectal cancer prognosis.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no competing interests.

Statement of human rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the Human Ethics Committee of the University of Queensland and with the 1964 Helsinki declaration and its later amendments.

Informed consent Written and informed consent was obtained from all individual participants included in the study.

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