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Case Control Study

Does low volume high-intensity interval training elicit superior benefits to continuous low to moderate-intensity training in cancer survivors?

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Abstract

AIM

To determine the impact of low volume high-intensity interval training (LVHIIT) and continuous low to moderate-

intensity exercise training (CLMIT) on cardiovascular disease (CVD) risk and health outcomes in cancer survivors.

METHODS

Sedentary cancer survivors ($n = 75$, aged 51 ± 12 year) within 24 months of diagnosis, were randomised into three groups for 12 wk of LVHIIT ($n = 25$), CLMIT ($n = 25$) or control group ($n = 25$). The exercise intervention involved 36 sessions (three sessions per week). The LVHIIT group performed 7 x 30 s intervals ($\geq 85\%$ predicted maximal heart rate) with a 60 s rest between intervals, and the CLMIT group performed continuous aerobic training for 20 min ($\leq 55\%$ predicted maximal heart rate) on a stationary bike. Outcome variables were measured at baseline and at 12 weeks and analysed using a 3 x 2 (group x time) repeated measures ANCOVA to evaluate main and interaction effects.

RESULTS

Significant improvements (time) were observed for seven of the 22 variables (ES 0.35-0.97, $P \leq 0.05$). There was an interaction effect ($P < 0.01$) after 12 wk in the LVHIIT group for six-minute walk test ($P < 0.01$; $d = 0.97$; 95%CI: 0.36, 1.56; large), sit to stand test ($P < 0.01$; $d = -0.83$; 95%CI: -1.40, -0.22; large) and waist circumference reduction ($P = 0.01$; $d = -0.48$; 95%CI: -1.10, 0.10; medium). An interaction effect ($P < 0.01$) was also observed for quality of life in both the LVHIIT ($d = 1.11$; 95%CI: 0.50, 1.72; large) and CLMIT ($d = 0.57$; 95%CI: -0.00, 1.20; moderate) compared with the control group ($d = -0.15$; 95%CI: -0.95, 0.65; trivial).

CONCLUSION

Low-volume high-intensity training shows promise as an effective exercise prescription within the cancer population, showing greater improvements in cardio-respiratory fitness, lower body strength and waist circumference compared with traditional CLMIT and control groups. Both LVHIIT and CLMIT improved quality of life. A proposed benefit of LVHIIT is the short duration (3 min) of exercise required, which may entice more cancer survivors to participate in exercise, improving health outcomes and lowering the risk of CVD.

Key words: High-intensity exercise; Health; Oncology; Exercise prescription

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Core tip: Low-volume high-intensity training is not commonly used in the rehabilitation of Cancer Survivors. In this study it shows promise as an effective exercise prescription, with greater improvements in cardio-respiratory fitness, lower body strength and waist circumference compared with traditional continuous low to moderate-intensity exercise training (CLMIT) and control groups. Low volume high-intensity interval

training (LVHIIT) and CLMIT improved quality of life. A proposed benefit of LVHIIT is the short duration (3 min) of exercise required, which may entice more cancer survivors to participate in exercise, improving health outcomes and lowering the risk of cardiovascular disease.

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INTRODUCTION

Worldwide there is an increase in cancer survival rates^[1]. This potentially raises the risk of cancer recurrence and other non-communicable diseases (NCDs) such as type II diabetes and cardiovascular disease (CVD)^[2]. These increased health risks may be due to the effects of cancer treatments and reductions in healthy lifestyle habits, such as physical activity (PA)^[3,4]. Physical activity decreases NCD risk in apparently healthy people^[5], though it is not conclusive if the same trends are evident in individuals with cancer. Exercise during and after cancer treatment has been shown to be safe, improve fitness levels, and quality of life (QoL)^[6,7]. Because of this, there is significant interest in the clinical use of exercise as an adjunctive therapy for improving cancer-related health outcomes.

Evidence is rapidly increasing regarding the benefits of exercise concurrent to treatment in the remediation of adverse clinical outcomes for cancer survivors^[8]. It is uncommon for cancer survivors to be advised by clinicians to participate in an exercise program, despite the existence of exercise guidelines^[9,10]. This may be due to the generic nature of the guidelines, limited practitioner expertise or the costs associated with some programs^[11,12]. The present exercise guidelines lack detail on the type, mode, duration and intensity of exercise necessary to achieve the best outcomes for cancer survivors. Additional research is required to fill the gaps in our current knowledge to further improve exercise recommendations, the evidence-based knowledge and exercise education for cancer survivors and their treating practitioners.

Low volume high-intensity interval training (LVHIIT) is the use of small doses of high-intensity exercise to elicit physiological responses such as improved VO₂ max and positive metabolic changes in skeletal muscle. The physiological changes could potentially be much higher or different to those currently being obtained with participation in other doses of activity, such as continuous, moderate-intensity exercise^[13]. LVHIIT has been shown to improve VO₂ peak and insulin sensitivity in apparently healthy individuals in as little as

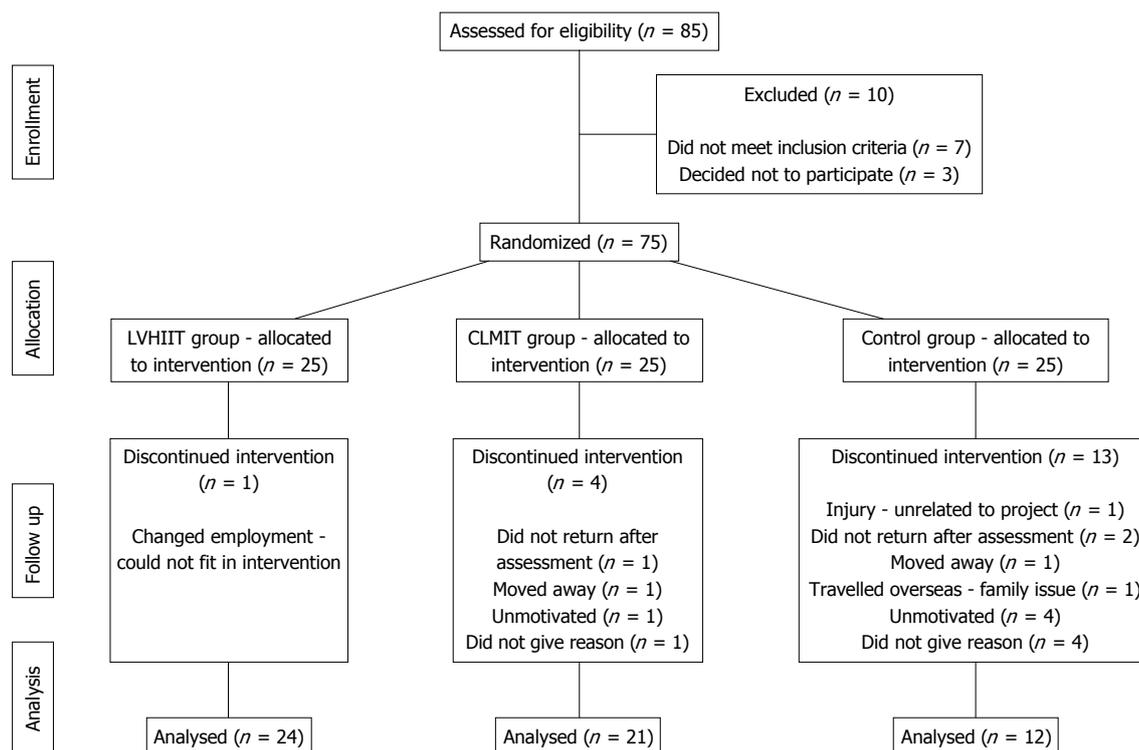


Figure 1 Consort diagram. LVHIIT: Low volume high-intensity interval training; CLMIT: Continuous low to moderate-intensity training.

four weeks^[14,15]. There is limited research examining the effects of LVHIIT in improving health outcomes for cancer survivors. Its application as a modality for use with other chronic disease populations is evolving^[14,16,17], potentially due to its ability to elicit positive physiological improvements in a short period. The current study aimed to investigate and compare the effects of LVHIIT and the more commonly prescribed continuous low to moderate-intensity training (CLMIT) on improving health outcomes and reducing cardiovascular disease (CVD) risk in cancer survivors.

MATERIALS AND METHODS

Participants

Eighty-five cancer survivors (83 female and 2 male, 51.48 ± 12.45 years) were recruited for the 12-wk study. Recruitment was conducted between September 2014 and June 2016 *via* email, pamphlet distribution, word of mouth and online social media. Referrals were obtained from the medical community and community organisations. The inclusion criteria included: (1) Participants within the first 24 mo of diagnosis; (2) in the post-treatment phase of the “physical activity across the cancer experience” (PEACE) organisational model, once the acute effects of medical treatments had dissipated^[18], and (3) sedentary, as described by the American College of Sports Medicine^[19]. Participants were excluded if they had: (1) Brain or metastatic bone cancers; (2) bone pain; (3) resting blood pressure > 180/110 mmHg; (4) were pregnant; (5) undergoing psychotherapy treatment; (6) had musculoskeletal

injuries or disabilities restricting their ability to participate in exercise.

Randomisation

Of the 85 participants, seven participants did not meet the inclusion criteria, and three decided not to participate due to the timing of exercise sessions. The 75 remaining participants were randomly assigned *via* an online randomisation tool into either LVHIIT ($n = 25$) or CLMIT ($n = 25$) or control ($n = 25$) group (Figure 1). A person independent of the research team used the research randomizer computer software^[20] to allocate participant codes into the three groups (LVHIIT, CLMIT, and control).

Of the 75 participants, 57 completed the study (76%). In the LVHIIT group ($n = 24$), one participant changed employment and could not complete the intervention. In the CLMIT group ($n = 21$), one participant did not return after baseline assessment, one moved interstate, one was not motivated to continue, and one failed to provide a reason. In the control group ($n = 12$) one participant sustained an injury (unrelated to the project), two did not return after baseline assessment, one moved interstate, one traveled overseas, four failed to respond to the final evaluation and four did not provide a reason (Figure 1).

Quality of life

The Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire (version 4) was used to measure quality of life (QoL) and functional capacity^[21]. The FACT-G is a validated survey containing 27 items. The questions are in four categories: (1) physical well-

being; (2) social/family well-being; (3) emotional well-being; and (4) functional well-being. The questionnaire is regularly used to measure QoL in cancer survivors^[22] and was completed at baseline and then after the 12-wk intervention.

Anthropometrics

The Dual X-Ray Absorptiometry (DXA) scan (GE Healthcare, Sydney, NSW, Australia) was used to measure total body composition, including; lean mass, body weight and body fat percentage^[23]. The DXA scanner was calibrated each day, using a phantom spine. The manufacturers' guidelines were followed to carry out daily quality control checks. All scans were carried out by trained densitometrists. Participants were asked to fast overnight and wear no jewellery, while being scanned. Hip and waist circumferences were measured using a standard anthropometric tape measure^[24,25]. The same individual measured the circumferences at baseline and post-intervention using WHO STEPwise approach measurement protocols^[25,26].

Cardiovascular functioning

Pulse wave velocity (PWV) and pulse wave analysis (PWA) were measured using the SphygmoCor XCEL system (SphygmoCor; At-Cor Medical Pty Ltd., Sydney, Australia). Carotid-femoral PWV is the recognised gold standard measure of aortic stiffness, a strong independent predictor of cardiovascular risk^[27,28]. PWA, which included measures of resting heart rate (RHR), augmentation index (AIx), central systolic blood pressure (CSP), central diastolic blood pressure (CDP), central pulse pressure (CPP), augmentation pressure (AP), mean arterial pressure (MAP), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were assessed at baseline and upon completion of the intervention. The pulse pressure (PP) waveform of the left carotid artery was measured with an applanation tonometer. Participants rested supine for 10 min before the measurements were obtained. Twenty continuous waveforms were essential for results to be considered valid and these were used to acquire the PP waveform of the aorta, and PWV was used as a marker of aortic stiffness^[29].

Biomarkers

Participants fasted overnight in preparation for blood sample analysis. Samples were analysed by an independent laboratory for high-sensitive C-reactive protein (CRP), insulin, glucose, and full blood count. The analysis was conducted offsite at Capital Pathology, Canberra, Australia.

Functional capacity

Lower body strength was measured using a repeated chair rise test (STS). The participants sat in a chair and were asked to stand and then sit as fast as possible five times, without the use of their arms^[30,31]. The six-minute walk test (6MWT) was used to delineate participants' cardiorespiratory fitness levels. Participants were asked

to walk as quickly as possible for six minutes and the distance traveled was recorded^[32]. The 6MWT is used extensively to assess cardiorespiratory fitness in cancer survivors^[33,34].

Intervention

An Accredited Exercise Physiologist (AEP) supervised all exercise sessions performed over the 12-wk intervention period (three sessions per week). Participants were asked to refrain from consuming food and caffeine and participating in any exercise for two hours before baseline and post-intervention assessments. Assessments were carried out within seven days before commencement and within seven days following completion of the program^[29]. The exercise sessions were carried out on a stationary bike. The LVHIIT group performed interval training ($\geq 85\%$ maximal heart rate), which consisted of a five-minute warm up, seven by 30 s intervals, with one-minute rest in between each interval, followed by a five-minute cool down (adapted from Gibala, 2012). A gradual increase in exercise was carried out by the LVHIIT group. Individuals started the first session with three intervals, with one interval added per week over the following four weeks and by the 5th week participants performed all seven intervals^[29]. The CLMIT group performed continuous aerobic training ($\leq 55\%$ predicted maximal heart rate) for 20 min also with a five-minute warm up and cool down^[29]. Age-predicted maximal heart rate was used to calculate relative intensity and the two exercise protocols were matched for appropriate energy expenditure using the calculation reported by Rognmo *et al.*^[36] (2004). For each participant, their heart rate (HR) and rate of perceived exertion (RPE) were logged every minute for the CLMIT sessions. The peak HR and RPE in each interval and the resting HR and RPE between each interval were recorded during the LVHIIT sessions. Blood pressure (BP) was monitored immediately before and after each exercise session.

Statistical analysis

Means and standard deviations were calculated for dependent variables. An ANOVA was performed to determine if pre-intervention differences existed between the three groups. A Bonferroni post-hoc multiple comparison test was conducted to determine where group differences existed. A 3 x 2 (group x time) repeated measures ANCOVA^[29] was used to evaluate main and intervention effects and was adjusted by baseline values. Effect sizes (ES) were calculated, and Cohen's *d* values were interpreted as follows: large ≥ 0.8 , medium ≥ 0.5 , small ≥ 0.2 and trivial < 0.2 ^[37]. The alpha level was set at $P < 0.05$, and SAS 9.3 (Cary, NC, United States) was used for all analyses.

RESULTS

Participant characteristics

Participant cancer diagnosis included 47 (82%) breast

Table 1 Baseline characteristics of participants

Characteristics	LVHIIT <i>n</i> = 24	CLMIT <i>n</i> = 21	Control <i>n</i> = 12
Sociodemographic			
Age, mean (SD), yr	48 (11.9)	52 (12.4)	57 (11.5)
Sex, <i>n</i> (%) male	F, 25 (0)	F, 21 (0)	F, 12 (0)
Comorbidity, <i>n</i> (%) yes	2 (0.8)	1 (0.4)	0 (0)
Diagnosis, <i>n</i> (%)			
Breast	21 (88)	16 (75)	10 (83)
Ovarian		1 (5)	1 (8.5)
Appendix		1 (5)	
Anal			1 (8.5)
Cervical	1 (4)		
Liver	1 (4)		
Oesophageal	1 (4)		
Melanoma		1 (5)	
Leiomyosarcoma		1 (5)	
Unknown primary		1 (5)	
Stage of disease, <i>n</i> (%)			
Stage I - II	19 (79)	16 (76)	10 (83)
Stage II -IV	5 (21)	5 (24)	2 (17)
Type of treatment, <i>n</i> (%)			
Surgery	21 (88)	20 (95)	12 (100)
Radiation therapy	18 (75)	13 (62)	10 (83)
Hormone therapy	19 (79)	15 (71)	9 (75)
Types of chemotherapy, <i>n</i> (%)			
TAC	7 (29)	4 (19)	1 (8)
FEC	5 (21)	3 (14)	3 (25)
TAC/FEC combinations	2 (8)	3 (14)	2 (17)
Capecitabine and oxaliplatin		1 (5)	
Carboplatin and paclitaxel	1 (4)		1 (8)
Cisplatin	1 (4)		
CHOP	1 (4)		
ABVD	1 (4)	1 (5)	1 (8)
Other	2 (8)	3 (14)	
No chemotherapy	4 (17)	6 (29)	4 (33)

LVHIIT: Low volume high-intensity training; CLMIT: Continuous low to moderate-intensity training; TAC: Taxotere, adriamycin, cyclophosphamide; FEC: Fluorouracil, epirubicin, cyclophosphamide; CHOP: Cyclophosphamide, doxorubicin, vincristine, prednisone; ABVD: Doxorubicin, bleomycin, vinblastine, dacarbazine.

cancer, two (3%) ovarian cancer and one diagnosis of appendix, anal, cervical, liver, oesophageal, melanoma, leiomyosarcoma and unknown primary (15%).

The age of the participants was 51.48 ± 12.45 years, with a BMI of 26.43 ± 4.08 kg/m² (Table 1). Baseline values for all variables were similar across the three groups except for white blood cell count, which was higher in the LVHIIT group compared with both the CLMIT group and control groups ($P < 0.02$).

For the LVHIIT group, the average HR during the 36 sessions was 147 ± 11 beats per minute (bpm), while RPE was 6 ± 3 using the Borg 1-10 scale^[38,39]. The average HR and RPE at the end of each 60s recovery was 117 ± 8 bpm and RPE of 3 ± 2 . The average HR for the CLMIT group was 98 ± 6 bpm and RPE was 3 ± 2 during the sessions. Overall mean session compliance was 92% (72%-100%). Ten participants attended all 36 sessions, and one participant missed ten sessions over the intervention period (data were included). There were no adverse events reported in the study.

Fitness, functional and body composition measures

There was a significant interaction effect ($P < 0.01$)

for 6MWT. Distance walked was significantly longer for the LVHIIT group ($d = 0.97$; 95%CI: 0.36, 1.56; large) when compared with the CLMIT ($d = 0.17$; CI: -0.23, 0.99; trivial) and control ($d = -0.13$; 95%CI: -0.93, 0.67; trivial) groups (Figure 2A). There was a significant interaction effect ($P < 0.01$) for the STS test with a faster performance in the LVHIIT group ($d = -0.83$; 95%CI: -1.40, -0.22; large) compared with the CLMIT ($d = -0.59$; 95%CI: -1.20, 0.42; unclear) and control ($d = 0.36$; CI: -0.44, 1.17; unclear) groups (Figure 2B). There was a significant interaction ($P = 0.01$) effect for waist circumference; post results were significantly lower for LVHIIT ($d = -0.48$; 95%CI: -1.10, 0.10; medium) compared with CLMIT ($d = -0.05$; 95%CI: -0.66, 0.55; trivial) and control group ($d = 0.11$; 95%CI: -0.69, 0.91; trivial).

Quality of life

Overall: There was an interaction effect for overall QoL ($P < 0.01$). The QoL score was significantly improved in the LVHIIT group ($d = 1.11$; 95%CI: 0.50, 1.72; large) compared with the CLMIT group ($d = 0.57$; 95%CI: -0.00, 1.20; moderate) and the control group ($d =$

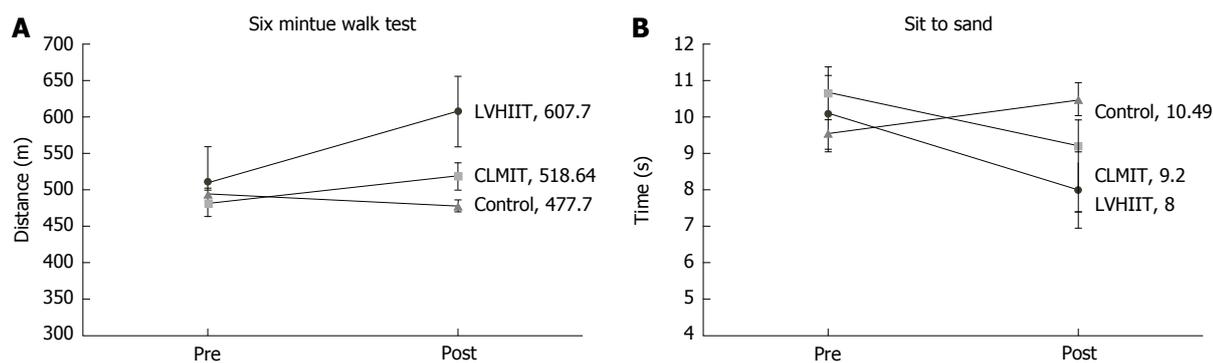


Figure 2 Changes in cardiorespiratory fitness and sit to stand for low volume high-intensity interval training, continuous low to moderate-intensity exercise training and control groups.

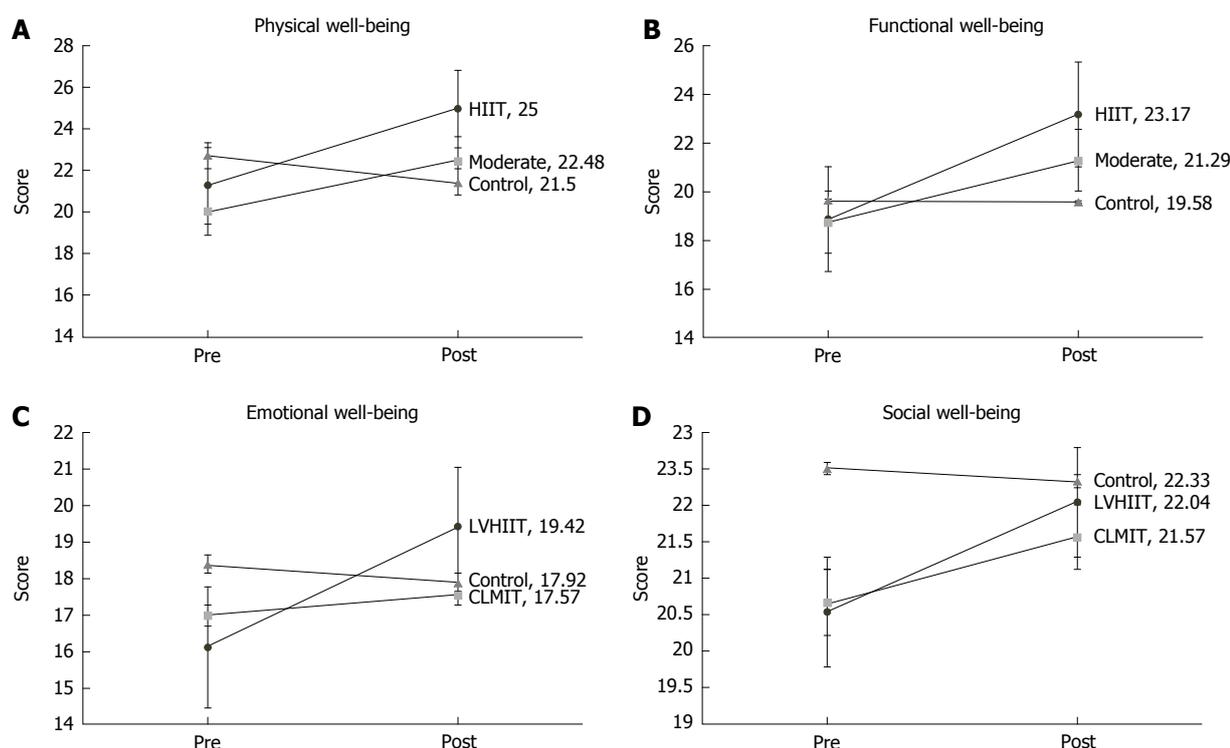


Figure 3 Changes in quality of life subscales for low volume high-intensity interval training, continuous low to moderate-intensity exercise training, and control groups.

-0.15; 95%CI: -0.95, 0.65; trivial) (Figure 3).

Well-being: An interaction effect was observed for physical well-being ($P = 0.02$). Improvements were seen in the LVHIIT ($d = 0.89$; 95%CI: 0.30, 1.48; large) and CLMIT ($d = 0.61$; 95%CI: -0.001, 1.23; medium) compared with the control group ($d = -0.30$; 95%CI: -1.09, 0.51; unclear) (Figure 3A). There was an interaction effect observed for functional well-being ($P = 0.02$). The LVHIIT group significantly improved ($d = 0.96$; 95%CI: 0.37, 1.56; large) compared to the CLMIT group ($d = 0.64$; 95%CI: 0.02, 1.26; medium) and the control group ($d = -0.02$; 95%CI: -0.82, 0.78; trivial) (Figure 3B). An interaction effect was also found for emotional well-being ($P < 0.01$). Improvements were observed for the LVHIIT group ($d = 1.04$, 95%CI:

0.43, 1.64; large) compared with the CLMIT group ($d = 0.15$; 95%CI: -0.45, 0.76; trivial) and the control group ($d = -0.11$; 95%CI: -0.92, 0.69; trivial) (Figure 3C). No interaction effect was observed for social well-being ($P = 0.057$) (Figure 3D). Changes were observed in the LVHIIT ($d = 0.35$; 95%CI: -0.22, 0.92; medium) compared to the CLMIT group ($d = 0.20$; 95%CI: -0.40, 0.80; unclear) and the control group ($d = -0.05$; 95%CI: -0.85, 0.75; trivial).

Cardiovascular function and biomarkers

There were no interaction effects for vessel stiffness parameters or biomarkers. However, time effects were found for markers of cardiovascular functioning. CSP ($P = 0.07$) in the LVHIIT group ($d = -0.51$; 95%CI: -1.07-0.10, moderate) which reduced by 4.94%. PP in

Table 2 Changes in risk factors from pre-to post intervention (Mean ± SD)

Variable	LVHIIT group n = 24			CLMIT group n = 21			Control group n = 12		
	Pre	Post	ES (95%CI)	Pre	Post	ES (95%CI)	Pre	Post	ES (95%CI)
Weight (kg)	72.9 ± 11.7	72.8 ± 11.4	-0.01 (-0.57, 0.56)	69.4 ± 14.3	70.4 ± 14.9	0.06 (-0.54, 0.67)	65.5 ± 13.1	65.9 ± 13.9	0.03 (-0.77, 0.83)
Body fat (%)	42.2 ± 7.9	41.4 ± 7.8	-0.1 (-0.67, 0.46)	43.0 ± 6.7	44.4 ± 9.5	0.17 (-0.44, 0.78)	37.7 ± 9.2	37.0 ± 10.5	-0.07 (-0.87, 0.73)
Fat mass (kg)	30.6 ± 9.1	29.2 ± 8.7	-0.16 (-0.72, 0.41)	30.5 ± 12.4	31.0 ± 12.1	0.05 (-0.56, 0.65)	24.3 ± 9.0	24.4 ± 9.5	0.01 (-0.79, 0.81)
Lean mass (kg)	40.7 ± 6.4	41.0 ± 7.2	0.05 (-0.52, 0.61)	38.8 ± 6.2	39.3 ± 6.8	0.07 (-0.53, 0.68)	38.8 ± 6.7	39.2 ± 6.9	0.06 (-0.74, 0.86)
Waist (cm) ^{1,2}	91.1 ± 11.7	85.7 ± 10.5 ¹	-0.48 (-1.10, 0.10)	93.1 ± 13.1	92.4 ± 13.3	-0.05 (-0.66, 0.55)	89.1 ± 9.5	90.3 ± 11.6	0.11 (-0.69, 0.91)
Hip (cm) ¹	108.3 ± 10.3	104.8 ± 10.5 ¹	-0.37 (-0.91, 0.23)	107.9 ± 11.3	107.0 ± 14.8	-0.07 (-0.67, 0.54)	104.1 ± 9.4	104.3 ± 8.9	-0.02 (-0.82, 0.78)
Resting HR (bpm)	76.3 ± 12.0	73.3 ± 12.4	-0.24 (-0.81, 0.32)	73.9 ± 11.9	72.3 ± 9.8	-0.14 (-0.75, 0.46)	74.5 ± 11.9	73.7 ± 12.6	-0.07 (-0.87, 0.74)
SBP (mmHg)	127.3 ± 18.3	121.8 ± 9.7	-0.39 (-0.95, 0.20)	130.9 ± 15.5	130.4 ± 14.7	-0.58 (-0.64, 0.57)	123.9 ± 15.4	128.1 ± 12.7	0.3 (-0.51, 1.10)
DBP (mmHg)	79.7 ± 8.3	77.8 ± 6.9	-0.25 (-0.82, 0.32)	81.5 ± 11.7	81.4 ± 6.5	-0.01 (-0.62, 0.59)	78.2 ± 5.3	79.9 ± 6.1	0.30 (-0.51, 1.10)
MAP	97.2 ± 10.8	93.9 ± 7.9	-0.36 (-0.92, 0.22)	100.7 ± 12.5	98.4 ± 8.9	-0.21 (-0.82, 0.39)	96.6 ± 6.2	95.9 ± 8.6	-0.09 (-0.89, 0.71)
CSP (mmHg) ¹	118.6 ± 17.7	111.3 ± 10.7 ¹	-0.51 (-1.07, 0.10)	121.8 ± 15.9	119.9 ± 8.9	-0.14 (-0.75, 0.46)	116.7 ± 12.1	115.3 ± 13.5	-0.11 (-0.91, 0.69)
PP (mmHg)	35.7 ± 12.8	30.8 ± 6.8	-0.5 (-1.05, 0.10)	35.7 ± 10.6	36.0 ± 7.5	0.04 (-0.57, 0.64)	35.0 ± 11.4	34.1 ± 11.4	-0.08 (-0.88, 0.72)
AP (mmHg) ¹	8.1 ± 8.1	5.9 ± 4.4 ¹	-0.35 (-0.91, 0.23)	9.3 ± 8.6	7.0 ± 4.8	-0.34 (-0.94, 0.28)	10.3 ± 6.6	8.0 ± 9.2	-0.29 (-1.09, 0.52)
Aix (%)	19.9 ± 14.7	18 ± 11.6	-0.14 (-0.71, 0.42)	22.5 ± 18.4	11.59 ± 18.8	-0.24 (-1.20, 0.03)	26.6 ± 12.5	10.0 ± 18.3	-1.06 (-1.91, -0.20)
CDP (mmHg)	83.25 ± 9.13	80.3 ± 7.9	-0.34 (-0.92, 0.22)	85.9 ± 10.6	82.8 ± 7.1	-0.34 (-0.95, 0.27)	82.7 ± 6.9	81.1 ± 7.1	-0.22 (-1.03, 0.57)
PWV (m/s)	6.6 ± 1.5	6.5 ± 1.2	-0.12 (-0.64, 0.49)	6.8 ± 1.5	6.9 ± 1.0	0.11 (-0.53, 0.68)	6.8 ± 1.5	6.2 ± 1.4	-0.41 (-1.22, 0.40)
STS (s) ^{1,2}	10.1 ± 2.8	8.1 ± 2.1 ¹	-0.83 (-1.40, -0.22)	10.6 ± 2.8	9.2 ± 2.0	-0.59 (-1.20, 0.42)	9.6 ± 2.3	10.49 ± 2.7	0.36 (-0.44, 1.17)
6MWT (m) ^{1,2}	510.7 ± 114.9	607.7 ± 85.5 ¹	0.97 (0.36, 1.56)	483.1 ± 72.3	518.6 ± 94.5	0.17 (-0.23, 0.99)	494.2 ± 128.7	477.7 ± 127.1	-0.13 (-0.93, 0.67)
Glucose (mmol/L)	4.9 ± 0.0	4.8 ± 0.5	-0.28 (-0.85, 0.29)	5.1 ± 0.6	4.9 ± 0.7	-0.31 (-0.92, 0.30)	5.1 ± 0.4	4.9 ± 0.4	-0.5 (-1.31, 0.31)
CRP (mg/L)	2.9 ± 3.5	2.7 ± 3.2	-0.07 (-0.63, 0.50)	4.5 ± 5.1	4.7 ± 4.9	0.04 (-0.56, -0.64)	2.0 ± 1.1	2.0 ± 1.6	0 (-0.80, 0.80)
Insulin (mU/L)	11.4 ± 6.8	9.0 ± 4.9	-0.41 (-1.36, -0.19)	13.1 ± 10.4	11.3 ± 9.3	-0.18 (-0.79, -0.42)	9.9 ± 5.6	10.7 ± 6.3	0.13 (-0.67, 0.94)
WBC (x 10 ⁹ /L) ¹	6.9 ± 2.5	5.7 ± 2.5 ¹	-0.46 (-1.05, 0.10)	5.6 ± 2.0	5.2 ± 1.8	-0.21 (-0.82, -0.40)	5.4 ± 0.7	4.9 ± 0.9	-0.62 (-1.44, 0.20)

¹Time effect; ²Interaction effect. ES: Effect size; HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; CSP: Central systolic pressure; PP: Central pulse pressure; AP: Arterial pressure; Aix: Augmentation index (stiffness); CDP: Central diastolic pressure; PWV: Pulse wave velocity; STS: Sit-to-stand test; 6MWT: 6-min walk test; CRP: C-reactive protein; WBC: White blood cell.

the LVHIIT group decreased by 7.96% ($d = 0.50$; 95%CI: -1.05 – 0.10, moderate). AP ($P = 0.02$) in the LVHIIT group ($d = -0.35$; 95%CI: -0.91 – 0.23, small) reduced by 27%. A 22% decrease was observed in the CLMIT group ($d = -0.34$; 95%CI: -0.94 – 0.28, small) (Table 2).

DISCUSSION

The aim of this study was to determine the impact of LVHIIT and CLMIT on CVD risk and health outcomes in cancer survivors. There were significant improvements in functional capacity, specifically cardiorespiratory fitness, lower-limb strength, and waist circumference in participants who completed the LVHIIT compared with the CLMIT and control groups. QoL improved in both the LVHIIT group and the CLMIT group when compared with the control group, however a greater effect was observed in the LVHIIT group.

Maintaining or improving functional capacity and lower limb strength in cancer survivors is essential as it enhances survivors' ability to move and carry out physical activities during and after treatment^[40]. It also provides the functional strength to start and adhere to an exercise program which increases levels of activity^[41,42]. Building lean mass through exercise builds a healthy metabolic profile, which is imperative as it assists in improving risk factors in those who have spent an increased volume of

time sedentary during and following, intensive cancer treatment^[43]. Participants in the LVHIIT group gained a larger effect in the sit to stand test compared with the other groups indicating improvements in lower limb strength. Possible mechanisms involved in this change could have been: (1) The increased power-output and the energy system/muscle fibre types recruited during the LVHIIT, similar to those recruited in the STS test; (2) an increased activation of the type IIa and type IIx fibres; and (3) an enhanced level of activation of the ATP/PC and glycolysis systems. An increased level of neuromuscular coordination is required at a higher-intensity of exercise, which also could have contributed to the improved strength and performance in the STS test seen in the LVHIIT group. Improvements were observed in the STS test in the LVHIIT group (20%), and in the CLMIT group (9.5%), highlighting greater increases in lower leg strength and functional capacity for those who completed the LVHIIT program. This finding was identified in our pilot study, however, due to small numbers, it was non-significant^[29].

Significant improvements in cardiorespiratory fitness levels were identified through the increased distance covered in the 6MWT, with a larger effect observed in the LVHIIT group. These findings were also detected in the authors pilot study^[29] and reported in other randomised controlled trials in cancer survivors^[7,29,44]. The greater improvements seen in the LVHIIT group suggests that more comprehensive cardiovascular adaptations may occur with the use of high-intensity exercise. Potential mechanisms involved in increases in cardiorespiratory fitness could be due to the increased level of mitochondrial enzymes recruited in high-intensity exercise^[45], which contributes to enhanced aerobic capacity of the skeletal muscles commonly seen after participating in high-intensity training. The positive impacts can contribute to changes in VO₂ difference, thereby increasing maximal aerobic capacity. Improvements in cardiorespiratory fitness using high-intensity interval training has been extensively reported in healthy people, but less in the cancer survivor population^[46]. LVHIIT could decrease the risk of developing additional chronic diseases such as CVD and diabetes^[47] and increase cancer survival rates^[48,49] faster than the commonly prescribed moderate-intensity exercise. It has been shown that cancer survivors have decreased levels of cardiorespiratory fitness levels in comparison with healthy people^[50].

A cancer diagnosis has a significant impact on behaviours which in turn can negatively affect QoL^[51]. QoL reductions can have a profound effect on the recovery of cancer survivors, reducing the probability of being able to move freely and maintain physical activity levels^[52]. A novel and clinically relevant finding of the present study was that QoL improvements were seen in both the LVHIIT and the CLMIT group, with a greater increase observed in the LVHIIT group. To date, very few studies have investigated how different exercise protocols or intensities impact QoL^[44]. While

current exercise recommendations for cancer survivors prescribe low to moderate intensity exercise, evidence is accumulating that there may be greater improvements in QoL when participating in more vigorous exercise^[11]. In most cases QoL changes are monitored from cancer diagnosis, to inform clinical decisions to improve patient outcomes. Linking exercise in with this conversation may assist clinicians in improving healthy behaviours to improve QoL^[53].

White blood cell count was significantly reduced from baseline to post-exercise intervention in the exercise groups, with the most pronounced reduction seen in the LVHIIT group, with a small effect found. Lung cancer participants who participated in a program using resistance band exercise over 12 wk in conjunction with chemotherapy treatment showed similar results^[54]. Normal WBC levels in cancer survivors are important because high levels of WBC's are associated with chronic inflammation, autonomic nervous system imbalances and may contribute to reductions in insulin sensitivity^[55]. Similarly, low WBC counts compromises an already compromised patient. Potentially both these factors would contribute to fatigue, obesity and increased risk for CVD^[56,57]. To date, little work has been carried out to determine the mechanism involved in the changes in WBC's in cancer survivors after different exercise programs^[57]. Insulin levels decreased in the LVHIIT group with a small effect and increased in the CLMIT group by 13.74% with an unclear effect. These results were not significant, yet they are potentially clinically relevant findings^[58]. Even a small decrease in insulin is essential in this population because of its reported role in the growth of cells, including the potential growth of tumour cells^[58-60].

In the current study, a moderate effect was found in the LVHIIT group for CSP and PP with unclear effects in the CLMIT and control groups. The importance of these changes relates to the negative impact of chemotherapy drugs on the cardiovascular system. Chemotherapy drugs have been found to have a long-lasting anti-angiogenic effect on the cardiovascular system^[61]. Specifically, chemotherapy has been shown to negatively impact vessel stiffness and CDP during the treatment period, with increases in BP remaining long after the treatment period^[61]. Anthracyclines, cyclophosphamide and tyrosine kinase inhibitors have all been shown to increase oxidative stress^[62,63]. Increases in oxidative stress can cause an overproduction of cytokines which damage the vessel wall causing endothelial dysfunction^[64-66]. Endothelial dysfunction can also be caused by radiotherapy; with the adverse effects potentially having a lifelong impact on cancer survivors^[65,67]. Little is known about the impact of exercise on endothelial dysfunction in cancer survivors. The current study suggests that exercise-induced cardiovascular improvements may be one mechanism whereby exercise diminishes the adverse effects that chemotherapy has on the cardiovascular system.

Limitations of this investigation were that diet; and

daily physical activity levels were not controlled for in the time periods between study sessions. Although 6MWT has been shown to be a valid and reliable measure of fitness in cancer survivors, a more robust cardiorespiratory fitness test such as VO₂ max testing could be used. There were no male participants in this study, and as such the data should be interpreted accordingly. Participants were prescribed different ongoing medications and treatment protocols, all of which could have impacted the results; this does however represent a real world group of cancer survivors.

In conclusion, this study shows promise for the use of LVHIIT in the cancer population. The encouraging results opens up the possibility of introducing LVHIIT in therapy programs, as a shorter and more efficacious exercise to increase the fitness levels in cancer survivors. The LVHIIT protocol improved fitness and functional capacity and decreased waist circumference compared with CLMIT. Both LVHIIT and CLMIT improved QoL. LVHIIT may be an effective alternative to traditional exercise prescription within this population. The benefit of LVHIIT is that for selected variables it produces more pronounced results compared with CMIT and it is short in duration which could entice more cancer survivors to participate in exercise as time is a barrier^[68]. This study highlights that the most commonly prescribed CLMIT may not be enough to induce clinically relevant changes in cancer survivors. Additional research is required to fully understand the mechanisms involved in the changes identified in this study in relation to different doses of exercise. This research would be highly beneficial to assist clinicians in the optimisation of clinical exercise recommendations for cancer survivors.

ARTICLE HIGHLIGHTS

Research background

Research into the optimum exercise guidelines for cancer survivors are not conclusive. Little evidence exists for the use of low-volume high-intensity interval training (LVHIIT) within the cancer population, even though it shows promise in other chronic populations. LVHIIT has been used in populations such as stroke, diabetes, cardiovascular disease (CVD), cardiac rehabilitation showing more pronounced health benefits than the more commonly prescribed continuous low-moderate intensity training (CLMIT). Therefore, it should be further investigated for use with cancer survivors as it is a time efficient exercise modality, with greater health benefits.

Research motivation

Using LVHIIT in the cancer population shows promise as a more efficient exercise prescription. The encouraging results of this study has opens the possibility of introducing LVHIIT into rehabilitation programs. LVHIIT is a time efficient exercise modality, which could be used to increase the fitness levels in cancer survivors. The LVHIIT protocol in this study improved fitness and functional capacity and decreased waist circumference compared with CLMIT and the control group. Both LVHIIT and CLMIT improved QoL. LVHIIT may be an effective alternative to traditional exercise prescription within this population. The benefit of LVHIIT is that for selected variables it produces more pronounced results compared with CMIT and it is short, which could entice more cancer survivors to participate in exercise as time is a barrier.

Research objectives

To determine the effectiveness of LVHIIT compared to CLMIT and a control

group and to determine if LVHIIT and CLMIT improved CVD risk and health outcomes in cancer survivors. The significance of these objectives is that this form of exercise can be used to achieve more pronounced improvements in health outcomes than the commonly prescribed CLMIT.

Research methods

The experiments and data analysis used in this study were a mix of validated methods used before within this population (6MWT, STS, DXA, hip/waist circumference) and unique protocols which have been used with other populations, but not commonly with cancer survivors (Sphygmocor). The use of the ANCOVA analysis and effect size analysis was chosen due to the robustness that this analysis provides for the data collected.

Research results

There were significant improvements in functional capacity, specifically cardiorespiratory fitness, lower-limb strength, and waist circumference in participants who completed the LVHIIT compared with the CLMIT and control groups. QoL improved in both the LVHIIT group and the CLMIT group when compared with the control group, however a greater effect was observed in the LVHIIT group. Additional research is required to fully understand the mechanisms involved in the changes identified in this study in relation to different doses of exercise. This research would be highly beneficial to assist clinicians in the optimisation of clinical exercise recommendations for cancer survivors.

Research conclusions

Present exercise guidelines for cancer survivors lack detail on the type, mode, duration and intensity of exercise necessary to achieve best outcomes. This current research was required to fill the gaps in current knowledge to further improve exercise recommendations. LVHIIT is the use of small doses of high-intensity exercise to elicit physiological responses such as improved VO₂ max and positive metabolic changes in skeletal muscle which seem greater than the commonly prescribed CLMIT. The LVHIIT physiological changes show potential for use in clinical practice in the rehabilitation of cancer survivors. At present there is limited research examining the effects of LVHIIT in improving health outcomes for cancer survivors. This study shows promise for the use of LVHIIT in the cancer population. The encouraging results opens up the possibility of introducing LVHIIT in therapy programs, as a shorter and more efficacious exercise to increase the fitness levels in cancer survivors. The benefit of LVHIIT is that for selected variables it produces more pronounced results compared with CMIT and it is short in duration which could entice more cancer survivors to participate in exercise. This study highlights that the most commonly prescribed CLMIT may not be enough to induce clinically relevant changes in cancer survivors.

Research perspectives

The use of VO₂ max testing would be beneficial if it can be tolerated well by cancer survivors post treatment. Future research should analyse ways to measure the mechanisms involved in the changes seen in the study results and clarify how and why these changes occur.

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