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Effects of Resistance vs High Intensity Interval Training on Myokines and Cancer Cell Suppression in Breast Cancer Survivors: A Randomized Trial

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ABSTRACT

Purpose: Reducing recurrence and mortality is crucial for breast cancer survivors. We investigated the effects of a 12-week resistance training (RT) vs high-intensity interval training (HIIT) program on myokines, cytokines secreted by skeletal muscle cells at rest in response to muscle contraction, and cancer cell inhibition. **Methods:** Twenty-eight survivors of breast cancer (age 55.5 ± 8.8 yr, body mass index 27.9 ± 5.1 kg/m², time since diagnosis 31 ± 12.3 months) were randomly allocated to a 12-week supervised moderate to high intensity RT (n = 14) or HIIT (n = 14) program 3 days per week. Resting blood was collected before and post exercise program (at least 48 hours before the first and after the last exercise session) to measure serum levels of myokines (decorin, interleukin 6 [IL-6], secreted protein acidic and rich in cysteine [SPARC], and oncostatin M [OSM]) and triple negative MDA-MB-231 cell growth *in vitro,* using real time cellular analysis to determine growth rate. **Results:** Exercise attendance was 85% for RT and 81% for HIIT. Serum levels of SPARC for RT and OSM for HIIT significantly ($p < 0.05$) increased (11 to 15%) after 12 weeks, with no significant differences between groups. MDA-MB-231 cell growth was significantly ($p < 0.05$) reduced for both RT and HIIT by 22% and 25%, respectively, with no significant difference between groups. Reductions in MDA-MB-231 cell growth in HIIT were associated with improvements in lean and fat mass. **Conclusions:** A program of RT or HIIT can increase levels of myokines (an effect considered beneficial given their potential cancer-suppressive effects) and inhibit growth of MDA-MB-231 cells in survivors of breast cancer. In addition, development of the anti-tumor environment may be mediated by exercise-related changes in muscle strength and body composition.

Key Words: BREAST CANCER, RESISTANCE TRAINING, HIGH INTENSITY INTERVAL TRAINING, MYOKINE, CANCER CELL

INTRODUCTION

Breast cancer is the most diagnosed and leading cause of cancer-related death in women worldwide (1). In addition, owing to the rising incidence, strategies to lower recurrence and mortality in survivors of breast cancer are necessary (2, 3). In this regard, exercise is widely recognized as a key therapeutic strategy in breast cancer management (4, 5). Existent evidence is that exercise is safe and effective during and after treatment, improving physical fitness, body weight and composition, fatigue, anxiety, and depression, while also enhancing immune function, lowering chronic inflammation, and reducing recurrence and mortality risk by ≈ 40% (6-12). Interestingly, we recently observed that elevated physical fitness (i.e., muscle strength and cardiorespiratory fitness [CRF]) are associated with a 31 to 46% reduction in the risk of all-cause mortality in this population (13), supporting the prescription of exercise medicine to be a promising anti-cancer treatment.

Preclinical and clinical studies have investigated the effects of exercise-conditioned serum (i.e., serum obtained from human participants before and after exercise) on different cancer cell lines *in vitro* (e.g., breast, prostate, and colon), revealing potential cancer-suppressive effects (14, 15). Notably, it has been observed that myokines, which are cytokines secreted by skeletal muscle cells at rest (e.g. irisin) and in response to muscular contractions (e.g., interleukin 6 [IL-6], secreted protein acidic and rich in cysteine [SPARC], oncostatin M [OSM]) (16, 17), can inhibit cancer cell growth (i.e., proliferation and metastatic capacity), survival (i.e., viability), and drive cell death (i.e., apoptosis and necrosis), even though the underlying mechanisms are yet to be fully understood (14, 15, 18). To further support this, from studies investigating the effects of a single bout of exercise (i.e., acute effects), with blood taken immediately after exercise, there were observed elevations in myokine levels as well as

reductions in the growth of different cancer cells *in vitro*, including those for breast cancer (14, 19-24). Despite the promising findings of the acute effects of exercise, it remains to be elucidated the effects of regular exercise programs on resting myokine expression (i.e., blood taken at rest to avoid arousal effects of exercise) and cancer cell suppression (15).

To date, only two clinical trials have examined the effects of regular exercise programs (defined as structured exercise program lasting at least 12 weeks, which is a duration generally required to induce physical and physiological adaptations (25)) on breast cancer cells in patients with breast cancer, with one study reporting inhibitory effects (26) and the other showing no significant impact (20). Interestingly, although resting myokines (with anti-cancer properties) were found to potentially inhibit cancer cell growth in another clinical population (i.e., prostate cancer) (27, 28), no studies have investigated the effects of regular exercise programs on resting myokine levels and cancer cell suppression in survivors of breast cancer. In addition, given that myokines are released by skeletal muscle, it needs to be determined whether exercise-induced increases in muscle mass could potentially enhance the volume of anti-cancer myokines and enhance cancer cell suppression. Moreover, owing to the strong associations between increased physical fitness and reduced cancer mortality (13), it is worthwhile to investigate if modifications in fitness components could affect the outcomes aforementioned (i.e., myokine responses and cancer cell suppression).

Regarding regular exercise exposure, it is yet to be investigated whether two distinct and independent exercise modes, that is resistance training (RT) and high intensity interval training (HIIT), drive differential adaptations in resting myokine levels and cancer suppressive effects. Indeed, RT can substantially improve muscle strength and mass, while HIIT can stimulate CRF and reduce fat mass (FM) (29, 30). Thus, it is of utmost relevance to determine whether the

effects driven by such exercise modes exert different responses on myokines and potential cancer cell suppression. Further to this, the precise exercise prescription, in terms of volume, intensity, duration, and frequency, to induce changes in resting myokine levels and cancer suppressive effects needs to be elucidated (14, 15). Although the independent effects of regular RT and HIIT are well known in terms of physical fitness (i.e., muscle strength and CRF) and body composition (e.g., lean mass [LM] and FM) in survivors of breast cancer (8), discoveries in this field related to myokine levels may lead to more optimal prescription of targeted and tailored exercise training programs to reduce risk of cancer progression, contributing to a lower recurrence rate (14, 15). Therefore, it is relevant to examine the effects of regular exercise programs, employing different exercise modes, on resting anti-cancer myokines (i.e., decorin, IL-6, OSM, and SPARC (14, 15, 17)), and their effects on breast cancer cell growth (i.e., MDA-MB-231) (14). Thus, the aims of the current study were to: 1) examine the effects of a 12-week RT vs HIIT on resting myokine expression and cancer cell suppression in survivors of breast cancer *in vitro*; and 2) determine whether changes in body composition and physical fitness are associated with alterations in resting myokine levels and cancer cell suppression.

METHODS

This was a two-arm randomized trial comparing 12-weeks of RT vs HIIT on resting myokine expression and cancer cell suppression in breast cancer survivors. We previously described the effects of this trial on body composition, muscle strength, CRF, and quality of life (8). Ethical approval was obtained from the Edith Cowan University Human Research Ethics Committee (ID: 2023-04617-BETTARIGA) and the trial was registered on ANZCTR (ID: ACTRN12624000820505).

Participants, recruitment, and allocation

Eligible participants consisted of women who had been diagnosed with stage I–III breast cancer, with or without endocrine therapy. In addition, participants were required to have completed their primary treatments (e.g., chemotherapy, radiation therapy, or surgery) at least 4 months prior, having a body mass index (BMI) between 18.5 and 35 kg/m², and medically cleared for exercise. Participants were excluded if they had any known absolute contraindication to exercise, had engaged in vigorous exercise in the past 3 months (i.e., aerobic training (AT) ≥ 150 or 75 minutes at moderate or high intensity, respectively, or RT ≥ 2 sessions per week), had a life expectancy of less than 12 months, or were pregnant or lactating. Additionally, all participants were required to maintain their habitual diet throughout the exercise training intervention. Recruitment was conducted at the Exercise Medicine Research Institute at Edith Cowan University in Perth, Western Australia, from 1 October 2023 to 1 July 2024. All participants signed written informed consent and were randomly allocated, using computer software, to RT or HIIT group in a 1:1 ratio.

Outcome measures

Body composition and physical fitness assessment. Assessment of body composition and physical fitness have been previously described (8). Briefly, whole body mass, LM and FM in kilograms, along with their respective percentages (LM% and FM%), were assessed using dual-energy x-ray absorptiometry (DXA; Horizon A, Hologic, Washington, USA) (31). Participants were required to be fasted, and the equipment was calibrated according to the manufacturer's specifications. Similarly, muscle strength testing for the chest press and leg press were examined using 1-repetition maximum (1RM) (32), while the sub-maximal Ekblom-Bak test on a cycle

ergometer pedalling at 60 RPM was employed to determine estimated maximal oxygen uptake (VO2max) (33, 34). All participants were familiarized with the testing procedures on two separate occasions before completing the actual tests, with a minimum of 48 hours of rest.

Blood assessment and analysis. A blood sample (16 ml) was drawn before (baseline) and after 12 weeks (post) of RT or HIIT. Blood was collected after 8 hours overnight fasting and at least 48 hours after the last exercise session. Serum levels of decorin, IL-6, OSM, and SPARC were analysed using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Human ELISA Kit, Abcam, Cambridge, UK). The assay sensitivities were 1.5 pg/mL for decorin, 0.97 pg/mL for IL-6, 1.2 pg/mL for OSM, and 125 pg/mL for SPARC. The intra- and inter-assay coefficients of variation for all assays were below 15%, indicating acceptable reliability.

Real time cellular analysis. The human triple negative breast cancer cell line MDA-MB-231 was cultured in DMEM supplemented with 10% fetal bovine serum and routinely passaged at ≈ 80% confluence. A Real-Time Cellular Analysis (RTCA) system using the xCELLigence DP unit and E-plate (ACEA Bioscience, CA, USA) was used to assess the growth of MDA-MB-231 cells in presence of serum collected from each participant at baseline and post exercise program. Each well was seeded with 10,000 cells in 100 µL of DMEM for 16 hours, then 100 µL of DMEM containing 40% human serum from each participant (i.e., final serum concentration of 20%) was added to each well. The proliferation of MDA-MB-231 cells in response to the serum was measured in duplicate over a 72-hour period, with cell growth monitored every 15 minutes using the Cell Index (i.e., Cell Index × Time) to calculate the area under the curve (AUC).

Exercise program

After randomization to RT or HIIT, participants exercised 3 days per week for 12 weeks under supervision. The exercise programs have been previously described in detail (8). Briefly, each session lasted approximately 60 min, including warm-up and cool-down. Participants allocated to RT performed 8 to 12 repetitions for 3 to 5 sets of 8 major muscle group exercises, alternating between the upper and lower body, with an intensity set according to participants' tolerance to achieve a rating of perceived exertion (RPE) of 5 to 9 (using the 1 to 10 RPE scale (35)) or 60 to 80% 1RM, avoiding reaching neuromuscular failure, that is 1-2 repetitions in reserve (Supplemental Table 1, Supplemental Digital Content) (36, 37). Participants assigned to HIIT completed 4 to 6 sets, comprising 5 to 7 high-intensity bouts of 30 seconds interspersed with active recovery periods lasting 30 to 60 seconds. Sessions were performed on a stationary cycle, treadmill, rower, or cross-trainer. The intensity for the high-intensity bouts was individualized based on participants' tolerance, aiming for a RPE of 5 to 9 on the 1 to 10 scale (38) or 60 to 90% of their estimated maximum heart rate (HRmax), calculated as 220 minus age. During active recovery, the target RPE was maintained at 3 (Supplemental Table 2, Supplemental Digital Content). For both RT and HIIT, the programs were progressive in nature with the aim to increase the exercise load over the 12-week period (39).

Statistical analysis

Regarding statistical power, we considered a difference of 1 standard deviation (SD) between groups (an effect size of 1.0) as a large effect size, consistent with previous exercise–oncology research where similar magnitudes in myokine changes have been interpreted as physiologically and clinically relevant (27, 40). To achieve 80% power with a two-tailed alpha of

0.05, 16 participants per group (a total of 32 participants), considering a 20% drop out, were required. We assessed the normality of the data using the Shapiro-Wilk test. Based on the distribution of the data, within-group comparisons (baseline vs post) were performed using paired t-tests for normally distributed and Wilcoxon signed-rank tests for non-normally distributed variables. Between-group differences were evaluated using ANCOVA adjusted for baseline values or a rank-based ANCOVA with estimated marginal means (EMM) and pairwise contrasts conducted when significant interactions were observed. Furthermore, Spearman's rank correlation analysis was used to assess associations between changes in myokine levels and AUC (i.e., delta) with changes in body composition (e.g., LM and FM) and physical fitness (i.e., muscle strength and VO2max). Statistical significance was set at $p < 0.05$, with adjustments for multiple comparisons using the Bonferroni correction applied as appropriate. R software (v4.4.2, The R Foundation, Vienna, Austria) was used for all statistical analyses.

RESULTS

Sixty survivors of breast cancer were screened for eligibility with 32 enrolled and randomized to either the RT or HIIT group (i.e., 16 participants in each group) (Figure 1) (8). Four participants (two from each group) dropped out due to family and health issues unrelated to the intervention, leading to 14 participants analysed at the end of intervention. Baseline characteristics were comparable between groups: mean age was 60 years, BMI was 28 kg/m², time since diagnosis was 31 months, and hormone therapy was undertaken by 70% of the RT group and 78% of the HIIT group (Table 1). The exercise attendance rates were 85% for RT and 81% for HIIT, with no adverse events reported.

Results of changes in body composition and physical fitness are presented in Table 2 and

have been reported elsewhere (8). Briefly, after 12 weeks, significant improvements ($p < 0.05$) in LM, LM%, and FM% were observed in the RT group, and in LM% and FM% in the HIIT group, with no significant differences between groups. Muscle strength and CRF also improved in both groups: chest press strength, leg press strength, and VO2max increased significantly ($p < 0.001$) in both RT and HIIT. Between-group comparisons showed greater gains in chest press strength in favour of RT ($p = 0.001$), and greater improvements in VO2max in favour of HIIT ($p < 0.001$).

Myokine expression

Within and between group changes of resting serum myokine levels at baseline and post exercise intervention are reported in Table 3 and Figure 2. When examining the between group changes, there were no significant changes between groups for decorin, IL-6, OSM and SPARC. Within groups, for RT, there was a significant change only in SPARC which increased by 15% from baseline to post exercise ($p = 0.048$). In addition, there were no significant correlations between change in myokine levels and change in body composition or physical fitness from baseline to post exercise. For HIIT, there was a significant change only in OSM which increased by 11% from baseline to post exercise ($p = 0.024$). In addition, there was a trend toward a significant correlation only between change in OSM and change in %FM ($r_s = -0.466$, $p = 0.092$), while a significant strong correlation was observed for change in OSM and change in chest press strength ($r_s = 0.660$, $p = 0.010$).

Real-time cellular analysis

Within and between group changes of AUC for MDA-MB-231 cells at baseline and post exercise intervention are reported in Table 3 and Figure 3. When examining the between group changes, there were no significant changes between groups. Within groups, for RT, there was a significant change for AUC which decreased cell growth of MDA-MB-231 by 22% from baseline to post exercise ($p < 0.001$). In addition, there were no significant correlations between change in AUC and change in body composition or change in physical fitness from baseline to post exercise. For HIIT, there was a significant change for AUC which decreased cell growth of MDA-MB-231 by 25% from baseline to post exercise ($p < 0.001$). In addition, a significant strong correlation was observed between change in AUC and change in %LM ($r = -0.578$, $p = 0.033$) and %FM ($r = 0.598$, $p = 0.023$), while no correlation with physical fitness was observed.

DISCUSSION

The aims of this trial were to investigate the effects of two different exercise interventions on resting myokines with anti-cancer properties and MDA-MB-231 cell suppression in survivors of breast cancer, and to determine whether such responses may be associated with changes in body composition and physical fitness. There were two important findings. First, SPARC for RT and OSM for HIIT significantly increased (11 to 15%) over 12 weeks of exercise intervention, with no significant differences between groups. In addition, increases in OSM in the HIIT group were associated with reductions in %FM, which approached significance, and with improvements in chest press strength. Second, MDA-MB-231 cell growth was significantly reduced for both RT and HIIT following the 12-week exercise programs by 22 and 25%, respectively, with no significant difference between groups. Interestingly, in the HIIT

group, reductions in MDA-MB-231 cell growth were associated with improvements in %LM and %FM. From this finding we suggest that regular exercise employing either exercise mode (i.e., RT or HIIT) have potential anti-cancer effects. It should also be noted that our two exercise programs had the desired mode specific effects regarding changes in muscle strength and VO2max, as we outlined previously (8). Thus, improvements in body composition and physical fitness may contribute to creating a less favourable environment for tumorigenesis (14, 15), potentially reducing the risk of recurrence in survivors of breast cancer.

Several researchers have examined the effects of a single bout of exercise (i.e., acute) on anti-cancer myokines and their inhibitory effects on cancer cells, including those for breast cancer (14, 19-24). However, no studies have explored the effects on resting myokine levels (i.e., blood taken at rest) with anti-cancer properties and the effects on breast cancer cell growth. Our group has previously examined the effects of regular exercise programs, employing combined RT and moderate intensity continuous training (MICT) or HIIT, on anti-cancer myokines in patients with prostate cancer and observed significant elevations in resting SPARC and OSM (27, 28). In addition, the exercise-conditioned serum at rest also inhibited the growth and proliferation of prostate cancer cells (i.e., DU145) *in vitro* by ≈ 20%. Here we demonstrated that resting myokines are increased after 12 weeks of exercise in survivors of breast cancer, which is considered beneficial given their potential cancer-suppressive effects. These findings are noteworthy as myokines are released by skeletal muscle; however, breast cancer and related treatment (e.g., hormone therapy) may impact various physical (e.g., muscle strength, CRF, LM and FM) as well as physiological functions (e.g., immune and metabolic function), hindering the benefits induced by exercise.

In addition, our study expands knowledge on the effects of regular exercise interventions

on resting myokine levels by investigating two distinct and independent exercise modes (i.e., RT and HIIT), and noting that resting SPARC was elevated in RT group by 15% and resting OSM in HIIT group by 11%. Although the underlying mechanisms remain to be determined, it could be speculated that resting myokine responses are exercise mode dependent as proposed by recent studies (14, 15, 17, 41). In addition, we noted that changes in resting OSM levels in the HIIT group were associated with changes in %FM and even more strongly in chest press strength change. Although speculative, it may be assumed that physical modifications (e.g., muscle strength) induced by our 12-week exercise program may have contributed to the elevated levels of resting OSM. This infers that changes in physical status (i.e., from untrained to trained) may alter the release of myokines, even though more research is needed to substantiate this. However, it is worth noting that regular exercise did not alter decorin and IL-6 levels. Although the reasons need to be more fully investigated, lack of changes may be attributed to the half-life of these myokines (17). Of note, variations in sample characteristics, such as chemotherapy exposure between groups, may have also influenced the observed outcomes. Indeed, chemotherapy is known to affect multiple physiological systems, including impairments in muscle function, modulation of immune responses, and alterations in circulating biomarker profiles (42). However, the extent to which these factors contributed to our findings remains unclear, and further research is warranted.

Regarding the effects of regular exercise programs on cancer cell suppression, Dethlefsen et al. (20) examined the effects of a 6-month combined RT and HIIT program in survivors of breast cancer. Findings were that resting exercise-conditioned serum did not alter MCF-7 and MDA-MB-231 cell viability *in vitro* compared to the control group. However, it should be acknowledged that frequency of the exercise program was only one session per week, which may

have limited exercise-related changes occurring (14, 15). Baldelli et al. (26) observed that a 12-week, 3 days per week, home-based MICT coupled with dietary advice resulted in a reduction of *in vitro* MDA-MB-231 spheroid formation by ≈ 13%. However, owing to the inclusion of dietary advice, no direct comparison with our findings can be made (15).

Our study is novel as it explores the distinct and independent effects of RT vs HIIT on MDA-MB-231 cell growth *in vitro* in survivors of breast cancer. Our results hold significant clinical implications as we found that resting exercise-conditioned serum inhibited the growth of MDA-MB-231 cancer cells *in vitro*, by 22 and 25%, resulting from RT and HIIT respectively. Furthermore, we noted that there were no differences between groups, meaning that RT and HIIT had similar potential cancer suppressive effects. Interestingly, we found that for HIIT, reductions in MDA-MB-231 cell growth were associated with increases in %LM and decreases in %FM after 12 weeks of exercise. In practical terms, changes in body composition in survivors of breast cancer induced by 12 weeks of exercise may have contributed to stimulate the inhibitory effects on cancer cell growth (8, 15). Indeed, in line with that, we recently proposed that exercise-related adaptations in body composition might modulate systemic levels of myokines with anti-cancer properties (15) as well as biomarkers of chronic inflammation (11, 12). Taken together, these alterations could create a less favourable environment for tumorigenesis, with an acute bout of exercise providing an additional "dose" of anti-cancer medicine (15), particularly through transient changes in myokines and immune function during the post-exercise window (15, 43).

From a clinical standpoint, our findings are that both regular RT and HIIT potentially alter the resting systemic environment to suppress the growth of MDA-MB-231 cells *in vitro* in survivors of breast cancer, reducing the risk of recurrence. In addition, by demonstrating that both exercise modes may exert similar inhibitory effects on breast cancer, the adoption of RT or

HIIT for survivors of breast cancer can be dictated by the distinct and independent physical and physiological changes (e.g., muscle strength, CRF, LM and FM) induced by each exercise mode (8). Taken together, such discoveries may lead to more precise exercise prescriptions for survivors of breast cancer.

Strengths and limitations

This study explored the distinct and independent effects of 12-weeks of RT or HIIT on resting anti-cancer myokine levels (i.e., decorin, IL-6, OSM, and SPARC), and the resulting cancer suppressive effects on MDA-MB-231 cell growth *in vitro* in survivors of breast cancer. In addition, our study not only employed a randomized trial design compared to previous studies employing a single-arm approach (28), but also explored potential associated factors (i.e., body composition and physical fitness) that may influence myokine response and cancer cell suppression. However, there are some limitations worth mentioning. The substantial variability in baseline myokine levels, even after statistical adjustment, indicates that modest absolute changes, particularly those smaller than the SD, should be interpreted cautiously and considered alongside the consistency of responses. Our study relied on a single breast cancer cell line (i.e., MDA-MB-231), which may limit its applicability to other breast cancer cell types. In addition, although *in vitro* studies have deepened our understanding of how exercise relates to cancer growth, culturing cancer cells with exercise-conditioned serum in a 2D format cannot replicate the complex 3D structure of tumors *in vivo* (26). Lastly, our analysis was limited to only several markers *in vitro*, and as such, the associations observed between exercise-conditioned serum and cancer cell suppression as well as the interactions with the immune system (e.g., myokines stimulating anti-tumor immunity) remain at this stage speculative and inconclusive (44). In this

regard, a major limitation of our study is that we did not directly assess anti-cancer immune function, which represents the primary natural mechanism of immune surveillance against tumors (43). Exercise has been shown to influence several immune pathways, including enhanced NK cell cytotoxicity, T cell proliferation, and the mobilization of immune cells into circulation, all of which may contribute to tumor control (43). Future studies should therefore incorporate key myokines, such as IL-6, IL-7, and IL-15, given their recognized roles in modulating NK cell activity and anti-tumor immunity (43). Indeed, the fact that considerable cancer cell suppression was observed with less convincing alteration of myokine levels suggests that other soluble factors may be at play.

CONCLUSIONS

This study examined the effects of regular RT and HIIT on resting myokines with anti-cancer properties and MDA-MB-231 cancer cell suppression in survivors of breast cancer. We observed that the myokines SPARC and OSM significantly increased after 12 weeks (an effect considered beneficial given their potential cancer-suppressive effects), and similar cancer inhibitory effects were found in both exercise groups. In addition, changes in %LM, %FM, and chest press strength from HIIT were associated with increases in myokine response and reductions in breast cancer cell growth, leading to the suggestion that improvements in such components may contribute to creating a less favourable environment for tumor development. Clinically, RT or HIIT interventions can inhibit the growth of MDA-MB-231 cells *in vitro* in survivors of breast cancer, making exercise a potential treatment to reduce risk of cancer recurrence.

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FIGURE LEGENDS

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram.

Figure 2. Myokine levels in resistance training and high intensity interval training groups.

Legend. RT = resistance training; HIIT = high intensity interval training; * = $p < 0.05$. Boxes indicate the interquartile range (IQR), from the 25th percentile (Q1) to the 75th percentile (Q3). The horizontal line inside the box represents the median (Q2). The black squares denote the mean, and error bars represent the standard error.

Figure 3. Area under the curve in resistance training and high intensity interval training groups.

Legend. RT = resistance training; HIIT = high intensity interval training; * = $p < 0.05$. Boxes indicate the interquartile range (IQR), from the 25th percentile (Q1) to the 75th percentile (Q3). The horizontal line inside the box represents the median (Q2). The black squares denote the mean, and error bars represent the standard error.

SUPPLEMENTAL DIGITAL CONTENT

SDC 1: Supplemental Digital Content.docx

Figure 1

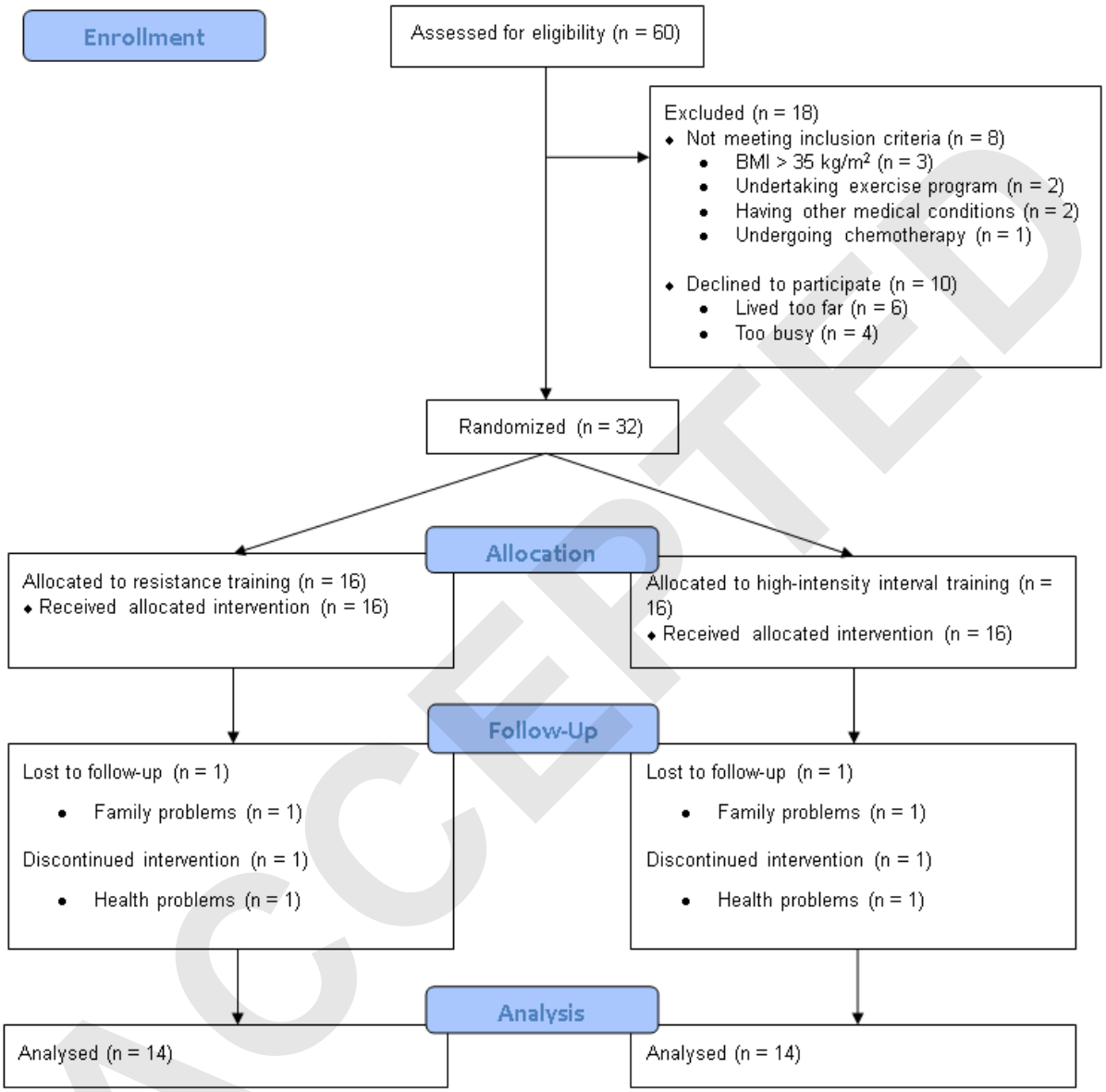

Figure 2

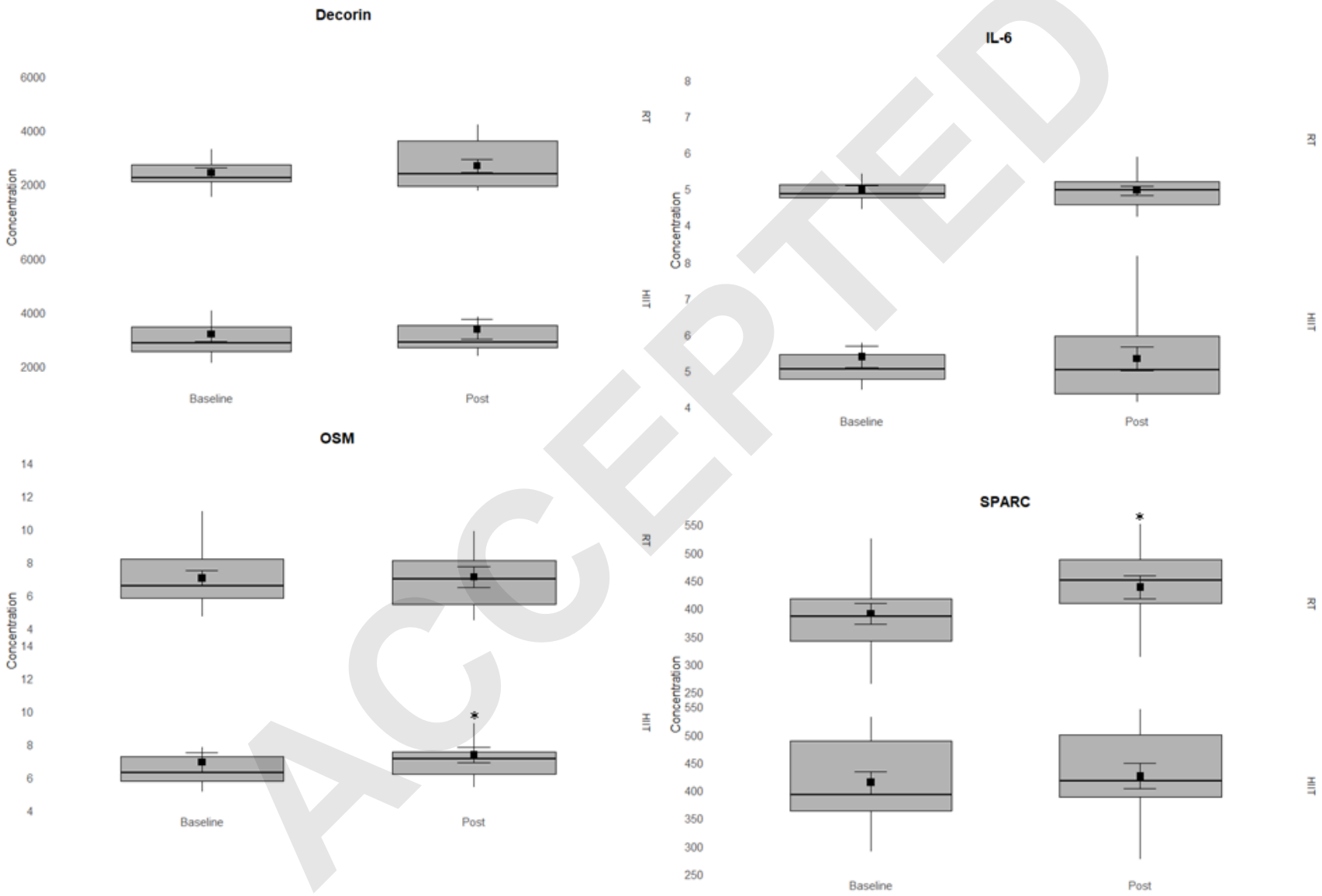

Figure 3

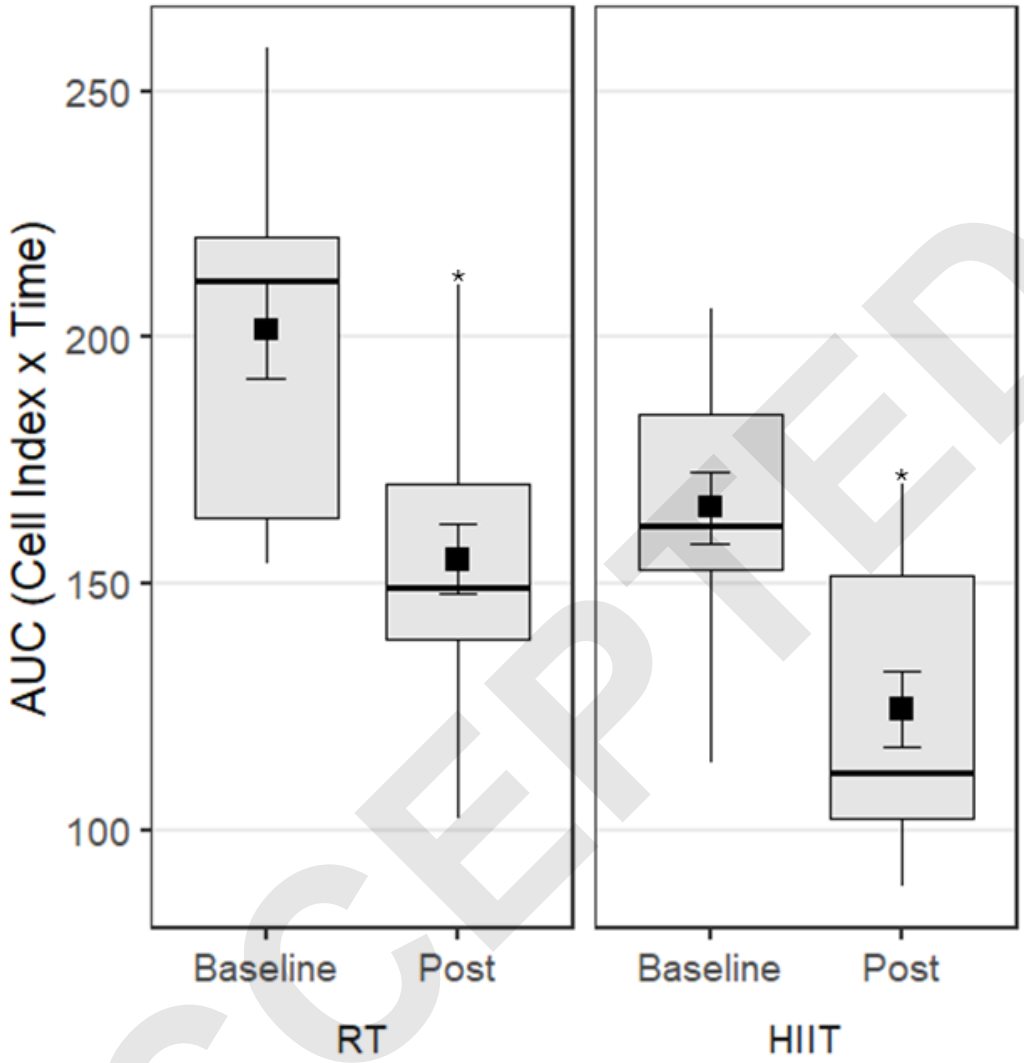

Table 1. Participant characteristics.

		RT (n = 14)	HIIT (n = 14)
Age (years)		61.8 ± 8.9	56.9 ± 8.9
Body weight (kg)		77.7 ± 11.8	78.1 ± 21.1
Height (cm)		165.7 ± 6.9	168.3 ± 7.1
BMI (kg/m2)		28.4 ± 4.2	27.5 ± 5.7
Time since diagnosis (months)		28.6 ± 8.5	34.7 ± 20.3
Cancer stage (%)	**1**	50	29
	2	35	42
	3	15	29
Undertaking hormone therapy (%)		70	78
Previous treatments (%)	**Chemotherapy**	50	93
	Radiation therapy	57	64
	Surgery	100	100
Postmenopausal status (%)		70	64
Hypertension (%)		28	21
Ethnicity (%)	**Non-Hispanic white**	70	70
	African-America	14	14
	Asian/Pacific islander	14	14
Married (%)		70	78
Completed university (%)		57	28
Full-time employed (%)		50	35
Current smoker (%)		0	0
Current drinker (%)		21	14
Undertaking other medications (e.g., metformin, vitamin D etc) (%)		43	43

Legend: RT = resistance training; HIIT = high intensity interval training; cm = centimetres; kg = kilograms; g = grams; % = percentage; VAT = visceral adipose tissue; VO2max = maximal oxygen uptake.

Table 2. Within and between-group changes in body composition and physical fitness for resistance training and high intensity interval training groups.

	RT (n = 14)					HIIT (n = 14)							
	Pre	Post	Within-group changes			Pre	Post	Within-group changes			Between-group changes		
	mean ± SD	mean ± SD	MD	95%CI	p-value	mean ± SD	mean ± SD	MD	95%CI	p-value	MD	95%CI	p-value *
Lean mass (kg)	42.2 ± 4.9	42.7 ± 4.7	0.56	0.12 to 1.13	0.049	42.1 ± 8.9	42.4 ± 8.7	0.36	-0.46 to 1.11	0.362	0.20	-0.75 to 1.16	0.662
% Lean mass	54.7 ± 3.9	55.3 ± 4.1	0.63	0.10 to 1.11	0.022	54.9 ± 5.8	55.5 ± 5.4	0.59	0.01 to 1.14	0.037	0.01	-0.01 to 0.01	0.897
Fat mass (kg)	33.3 ± 7.6	32.9 ± 7.7	-0.40	-1.10 to 0.30	0.239	33.9 ± 12.5	33.3 ± 11.9	-0.68	-1.50 to 0.15	0.100	0.28	-1.31 to 0.76	0.588
% Fat mass	42.5 ± 4.2	41.9 ± 4.4	-0.61	-1.16 to -0.06	0.031	42.3 ± 6.1	41.8 ± 5.7	-0.58	-1.13 to -0.03	0.039	0.02	-0.77 to 0.71	0.937
STR - Chest press (kg)	19.9 ± 6.2	27.8 ± 6.7	7.87	5.48 to 10.26	< 0.001	22.7 ± 6.6	25.9 ± 7.2	3.16	1.61 to 4.72	0.001	4.70	1.99 to 7.41	0.001
STR - Leg press (kg)	66.1 ± 28.7	90.2 ± 28.3	24.09	14.91 to 33.27	< 0.001	82.2 ± 18.8	98.3 ± 18.7	16.09	13.37 to 18.81	< 0.001	8.00	-1.11 to 17.11	0.083
CRF (ml/min/kg)	24.4 ± 3.9	25.3 ± 4.1	0.89	0.46 to 1.32	0.001	25.9 ± 3.8	28.7 ± 4.7	2.78	1.97 to 3.56	< 0.001	1.89	1.02 to 2.76	< 0.001

Legend: RT = resistance training; HIIT = high intensity interval training; STR = strength; CRF = cardiorespiratory function; kg = kilograms; SD = standard deviation; MD = mean difference; CI = confidence interval; * = group x time interaction p-values. Data have been already reported elsewhere (8).

Table 3. Myokine levels and cell index in resistance training and high intensity interval training groups.

	Within-group changes				Between group p-value
	RT		HIIT		
	Baseline	Post	Baseline	Post	
Decorin (pg/ml)	2403.2 ± 679.4	2663.4 ± 911.4	3174.3 ± 996.3	3364.3 ± 1379.9	0.278
IL-6 (pg/ml)	4.9 ± 0.4	4.9 ± 0.5	5.4 ± 1.1	5.3 ± 1.2	0.278
OSM (pg/ml)	7.1 ± 1.7	7.1 ± 2.3	6.9 ± 2.2	7.3 ± 1.7 *	0.689
SPARC (ng/ml)	389.9 ± 70.8	437.4 ± 78.1 *	413.7 ± 74.9	425.4 ± 84.5	0.278
AUC (Cell Index*Time)	201.5 ± 9.7	154.9 ± 7.1 *	165.5 ± 7.2	124.4 ± 7.7 *	0.268

Legend. pg = picogram; ng = nanogram; AUC = area under the curve; RT = resistance training; HIIT = high intensity interval training; * = $p < 0.05$. Data are reported as mean ± SD for myokines and mean ± SE for AUC.

Table 1. Resistance training program for survivors of breast cancer.

Periodization	Intra-week periodization	Reps	Sets	Inter-set rest	Load / Intensity	RPE	Total work
Week 1 to 4	Day 1	12	3	1 min	70% 1RM	6 to 8	45 min
	Day 2	10	3	2 min	80% 1RM	7 to 9	45 min
	Day 3	8	3	1 min	60% 1RM	5 to 7	45 min
Week 5 to 8	Day 1	8	4	2 min	80% 1RM	7 to 9	45 min
	Day 2	10	3	1 min	60% 1RM	5 to 7	45 min
	Day 3	8	4	2 min	80% 1RM	7 to 9	45 min
Week 9 to 12	Day 1	8	5	2 min	80% 1RM	7 to 9	45 min
	Day 2	10	3	1 min	60% 1RM	5 to 7	45 min
	Day 3	8	5	2 min	80% 1RM	7 to 9	45 min

Legend: RM = repetition maximum; RPE = rate of perceived exertion; min = minutes.

Note: Major muscle group exercises included chest press, seated row, shoulder press, lat pulldown, leg press, leg extension, leg curl, and lunges.

Table 2. High intensity interval training program for survivors of breast cancer.

Periodization	Intra-week periodization	Duration	Active recovery	Sets	Intensity	RPE	Work to rest ratio	Total work
Week 1 to 4	Day 1	5 x 30s	60s	4	60 to 70% HRmax	5 to 7	1:2	30 min
	Day 2	5 x 30s	60s	5	80 to 90% HRmax	7 to 9	1:3	37.5 min
	Day 3	5 x 30s	60s	4	60 to 70% HRmax	5 to 7	1:2	30 min
Week 5 to 8	Day 1	6 x 30s	30s	6	80 to 90% HRmax	7 to 9	1:1	36 min
	Day 2	6 x 30s	60s	4	60 to 70% HRmax	5 to 7	1:2	36 min
	Day 3	6 x 30s	30s	6	80 to 90% HRmax	7 to 9	1:1	36 min
Week 9 to 12	Day 1	7 x 30s	30s	6	80 to 90% HRmax	7 to 9	1:1	42 min
	Day 2	7 x 30s	60s	4	60 to 70% HRmax	5 to 7	1:2	42 min
	Day 3	7 x 30s	30s	6	80 to 90% HRmax	7 to 9	1:1	42 min

Legend: HR = heart rate; RPE = rate of perceived exertion; s = seconds; min = minutes.

Note: A 180-second rest period was provided between sets.