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SHORT COMMUNICATION

CARDIAC REHABILITATION FOR WOMEN WITH BREAST CANCER AND TREATMENT-RELATED HEART FAILURE COMPARED WITH CORONARY ARTERY DISEASE: A RETROSPECTIVE STUDY

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Objective: **To examine clinical outcomes and completion rates of cardiac rehabilitation in women with breast cancer and treatment-related heart failure.**
Methods: **Data for women with breast cancer and treatment-related heart failure were compared with those for age-matched women with coronary artery disease. Retrospective data were obtained from the Toronto Rehabilitation Institute database for dates between 1998 and 2011, for cardiopulmonary exercise test results at baseline and 6 months, body composition measures, and cardiac rehabilitation completion rates.**
Results: **A total of 29 women with breast cancer and treatment-related heart failure (mean 57 years (standard deviation (SD) 9.4)) and 29 age-matched women with coronary artery disease were identified. There was no significant difference between the proportion of women with breast cancer and treatment-related heart failure and those with coronary artery disease who completed the programme. Peak aerobic power (VO_{2peak}) increased in the breast cancer and treatment-related heart failure group (mean 16.2 $ml^{-1} \cdot kg^{-1} \cdot min^{-1}$ (SD 3.4) to mean 18.5 $ml^{-1} \cdot kg^{-1} \cdot min^{-1}$ (SD 4.5) ; $p = 0.002$) and in the coronary artery disease group (mean 18.9 $ml^{-1} \cdot kg^{-1} \cdot min^{-1}$ (SD 4.5) to mean 20.8 $ml^{-1} \cdot kg^{-1} \cdot min^{-1}$ (SD 4.9); $p = 0.01$). Body fat percentage increased in the breast cancer and treatment-related heart failure group (mean 34.8% (SD 8.5) to mean 36.3% (SD 6.9); $p = 0.04$).**
Conclusion: **Women with breast cancer and treatment-related heart failure participating in cardiac rehabilitation demonstrate similar significant gains in VO_{2peak} and similar completion rates to those of age-matched women with coronary artery disease. Further research is needed to determine interventions that improve body composition in women with breast cancer and treatment-related heart failure.**

Key words: breast cancer; exercise; cardiac rehabilitation; heart failure; women; coronary artery disease.

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Heart failure is a well-established adverse event associated with breast cancer treatment, which may lead to reduced fitness and functioning (1). Peak aerobic power (VO_{2peak}) is the gold standard for assessing cardiopulmonary fitness and is inversely correlated with cardiac-related mortality in women with cardiovascular disease (2). Recent data has demonstrated that women with breast cancer present with VO_{2peak} values that are consistently 30% below those of age- and sex-matched sedentary individuals with no history of breast cancer (3). Given that the risk of cardiovascular-related death is known to be increased among breast cancer survivors (4), and that breast cancer patients have reduced cardiopulmonary fitness (3), the development of treatment-related heart failure may contribute to an increased risk of cardiac-related death in the breast cancer population. Despite the importance of cardiopulmonary fitness among the breast cancer population, data to support interventions to improve VO_{2peak} for women with breast cancer and treatment-related heart failure (BC-HF) are insufficient. Moreover, interventions to improve body composition might be equally important due to its potential role in reduced physical activity following a diagnosis of breast cancer (5).

Cardiac rehabilitation (CR) is an outpatient secondary prevention programme that is recognized as an integral part of patient care for those who have experienced a cardiac event (6). The benefits of CR are well documented; it has been demonstrated to reduce cardiovascular mortality and improve VO_{2peak} (7). CR historically includes patients who have recently had a myocardial infarction or have undergone coronary artery bypass graft surgery. However, the spectrum of patients who benefit from CR also includes those who have stable chronic heart failure (6). Similarly, supervised exercise training has been identified as a safe and feasible therapy for women with breast cancer that is associated with significant improvements in VO_{2peak} and patient-reported outcomes (8).Thus, patients with BC-HF might benefit from attending CR. However, it is unknown whether women with BC-HF benefit to the same extent as women with coronary artery disease (CAD) who typically present in a formal CR programme. The primary objective of this investigation was therefore to examine the change in VO_{2peak} associated with participation in a CR programme for women with BC-HF compared with age-matched women with

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CAD. Secondary objectives were to examine changes in body composition, haemodynamic profiles and completion rates of CR compared with age-matched patients with CAD.

METHODS

Setting and participants

This was a retrospective hospital chart review of patients who participated in the Toronto Rehabilitation Institute (TRI) CR programme or the HEALTH programme (a specific exercise programme for women with breast cancer since 2010) from 1998 to 2011. Each programme followed the same structure, with the only differences being in the patient population receiving the intervention. Inclusion criteria were: women diagnosed with breast cancer and heart failure directly related to treatment for breast cancer. A comparison group of women enrolled in the CR programme with a diagnosis of CAD, but no cancer or heart failure, were matched based on age and most recent referral date. Informed written consent was obtained from all participants. This study was approved by the TRI Humans Ethics Board REB #10-024.

Exercise training programme

Patients participated in a 90-min exercise class consisting of aerobic training (AT) and resistance training (RT) once per week for 26 weeks. The classes were supervised by case managers (nurses, physiotherapists and kinesiologists). Patients were instructed to complete 4 additional AT and 1–2 RT sessions on 2 non-consecutive days in the community each week. The goal was to progress patients to 60 min of aerobic exercise, 5 times per week, at an intensity equivalent to 60–80% of VO_{2peak} (9). Exercise intensity or duration was increased every 2 weeks, or as indicated, to a maximum of 6.4 km and 80% of VO_{2peak}. RT was introduced during the 8th week of the programme, and consisted of 10 exercises targeting all major muscle groups. Patients were required to keep a detailed record of each exercise session completed in the community each week.

Cardiopulmonary fitness

Cardiopulmonary fitness was assessed using cardiopulmonary exercise tests (CPET) on an upright cycle ergometer or a treadmill. The test staff chose the protocol based on the health history and preference of the patient. Each participant completed the baseline and follow-up CPET using the same protocol. The patient was instructed to maintain a rate of 60 revolutions per minute (rpm) on the cycle ergometer at a workload of 8–16 watts. The workload increased by either 8.3 or 16.7 watts every 2 min thereafter. Treadmill tests followed the Bruce or modified Bruce protocol (10). Breath-by-breath gas samples were collected and averaged over a 20-s period using a calibrated metabolic cart (Vmax Encore, SensorMedics, Yorba Linda, CA, USA). Heart rate and blood pressure assessments were obtained at rest and at the end of each workload during exercise.

Body composition measures

Body mass index (BMI) was calculated as weight in kg/height in m^2 and waist circumference at the end of expiration was measured mid-way between the bottom of the rib cage and the iliac crest. Body fat percentage was assessed by bioelectrical impedance (Tanita TBF-300A, Tokyo, Japan).

Completion rates of cardiac rehabilitation

Completion rates were recorded once the patient completed the final CPET. If a patient withdrew from the programme, the reasons for terminating the programme were recorded in the patient charts.

Sample size calculation

The main comparison was the difference in VO_{2peak} between baseline and final CPET in women with BC-HF. Based on the effect size observed in studies of exercise training in cardiac populations we estimate the magnitude of this difference to be 2.5 $ml^{-1} \cdot kg^{-1} \cdot min^{-1}$. For the typical cardiac patient at the TRI who has a compromised VO_{2peak} at baseline (i.e. 17.7 $ml^{-1} \cdot kg^{-1} \cdot min^{-1}$ $n = 600$ patients, years 1999–2003) this improvement of 2.5 $ml^{-1} \cdot kg^{-1} \cdot min^{-1}$ would be clinically important. Therefore, for 90% power, an estimated sample size of 14 subjects would be needed to demonstrate a significant difference in VO_{2peak} for this study (2-sided test, $p < 0.05$).

Data analysis

Data were analysed using SPSS Version 20.0 software (SPSS Inc, Chicago, IL, USA). Descriptive data including means and standard deviations (SD) were included for all variables. Comparisons between groups at baseline were examined using 1-way analysis of variance (ANOVA). Our primary analysis measured changes over time for each cohort using paired-samples t-tests for continuous variables. Between-groups comparisons were completed using 1-way ANOVA of the mean change between baseline and outcome values. For the assessment of between-group differences for change in VO_{2peak} from pre- to post-intervention, analysis of covariance (ANCOVA) was used to determine whether differences in the baseline VO_{2peak} between groups influenced changes in VO_{2peak} from pre- to post-intervention. The p-value was set *a priori* at < 0.5.

RESULTS

A total of 29 women, mean age 57.2 (SD 9.4) years with BC-HF were referred to the CR programme and identified for this study (Fig. 1). Participant characteristics at entry to the exercise programme are shown in Table I. The mean time from breast cancer diagnosis

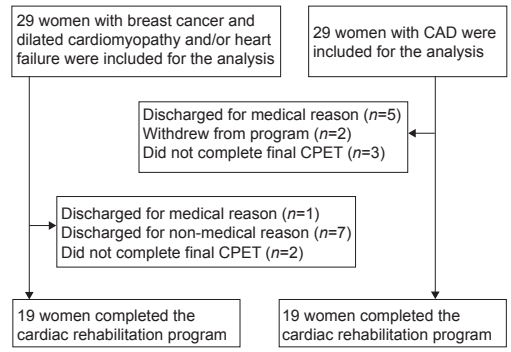

Fig. 1. Participant flow through the exercise rehabilitation programme. CAD: coronary artery disease; CPET: cardiopulmonary exercise test.

Table I. Participant characteristics at baseline

Variable	BC-HF ($n=29$)	CAD ($n=29$)	p-value
Age, years, mean (SD)	57.2 (9.4)	57.7 (9.5)	0.8
Body composition, mean (SD)			
Body mass index (kg/m^2)	26.6 (5.9)	29.9 (4.9)	0.03
Waist circumference (cm)	86.1 (12.1)	94.2 (12.8)	0.02
Body fat percentage (%)	34.6 (8.0)	39.2 (6.8)	0.02
Cardiopulmonary measures, mean (SD)			
VO_{2peak} (ml^{-1}·kg^{-1}·min^{-1})	15.5 (3.9)	17.7 (4.5)	0.06
Heart rate (bpm)	79.5 (13.0)	66.5 (19.2)	0.04
Systolic blood pressure (mmHg)	118.9 (19.7)	121.3 (19.8)	0.64
Diastolic blood pressure (mmHg)	74.9 (10.5)	73.4 (9.5)	0.54
Ejection fraction ($n=23$)	45.6 (11.9)	–	–
Cardiovascular medications, n (%)			
Beta-blockers	18 (62.1)	19 (65.5)	–
ACE inhibitors	14 (48.3)	16 (55.1)	–
Anticoagulants	10 (34.5)	22 (75.9)	–
Diuretics	9 (31.0)	1 (3.4)	–
Statins	5 (17.2)	20 (68.9)	–
Treatment for breast cancer, n (%)			
Trastuzumab (Herceptin™)	9 (31.0)	–	–
Tamoxifen	4 (13.8)	–	–
Doxorubicin	4 (13.8)	–	–
Epirubicin	6 (20.7)	–	–
Cyclophosphamide	5 (17.2)	–	–
5-Fluorouracil	2 (6.9)	–	–
Docetaxel	2 (6.9)	–	–
Unknown	12 (41.3)	–	–
Primary diagnosis (BC-HF), n (%)			
Breast cancer	29 (100)	–	–
Primary diagnosis and treatments (CAD), n (%)			
Myocardial infarction	0	19 (65.4)	–
Percutaneous transluminal coronary angioplasty	0	16 (55.1)	–
Coronary artery bypass	0	8 (27.5)	–
Secondary diagnoses (BC-HF and CAD), n (%)			
Heart failure/Cardiomyopathy	29 (100)	0	–
Atrial fibrillation	4 (13.6)	1 (3.4)	–
Congenital heart disease	1 (3.4)	0	–
Cardiac arrest	2 (6.9)	0	–
Hypertension	5 (17.2)	15 (52.7)	–
Pulmonary hypertension	1 (3.4)	0	–
Chronic obstructive pulmonary disease	1 (3.4)	0	–
Peripheral vascular disease	0	1 (3.4)	–

CAD: coronary artery disease; BC-HF: breast cancer and treatment-related heart failure.

to enrollment in the CR programme was 89.8 (SD 10.3) months. BMI, waist circumference, and body fat percentage were significantly lower in the BC-HF group than the CAD group (*all* $p<0.05$). In those who completed the CR programme, baseline VO_{2peak} was lower and, resting heart rate was higher for the BC-HF group compared with the CAD group ($p<0.05$).

Table II displays the change in outcome variables for the completers of the CR programme. VO_{2peak} increased significantly in both the BC-HF group ($p=0.002$) and the CAD group ($p=0.01$) (Fig. 2). There were no significant between-group differences in the mean change in any of the cardiopulmonary outcomes (all $p>0.05$).

There was a significant increase in body fat percentage compared with baseline in the BC-HF group ($p=0.04$), but not in the CAD group ($p=0.95$). There were no significant differences between groups in change in any of the body composition outcomes (all $p>0.05$).

There was no significant difference in the proportion of women with BC-HF and with CAD who completed the programme ($p=1.0$). Reasons for not completing the programme are outlined in Fig. 1 for each group.

DISCUSSION

The main findings of this retrospective study were that women with BC-HF had markedly lower VO_{2peak} values compared with age-matched women with CAD, and there were significant gains in VO_{2peak} following a CR programme in both groups. Secondary outcomes were that there were significant increases in body fat percentage in the BC-HF group following participation in CR. Moreover, completion rates for CR were the same for each group. This suggests that women with BC-HF are able to tolerate exercise training with similar dropout rates to those of women with CAD enrolled in CR. Similarly, women with BC-HF benefit to the same extent as women with CAD from a formal CR programme, as there were no significant differences between groups with the mean change in any of the outcomes.

Table II. Outcomes of the exercise rehabilitation programme

Variable	Baseline ($n = 19$) Mean (SD)	Inter-group comparison *p*-value	Follow-up ($n = 19$) Mean (SD)	Intra-group comparison Mean change	Intra-group comparison *p*-value	Inter-group comparison Mean change	Inter-group comparison **p*-value
Cardiopulmonary measures							
VO_{2peak} ($ml^{-1} \cdot kg^{-1} \cdot min^{-1}$)							
BC-HF	16.2 (3.4)		18.5 (4.5)	+2.3	0.002		
CAD	18.9 (4.5)	0.04	20.8 (4.9)	+1.9	0.01	+0.4	0.81
Heart rate (bpm)							
BC-HF	79.9 (12.4)		79.5 (13.0)	−0.4	0.83		
CAD	71.0 (13.1)	0.02	69.2 (13.8)	−1.8	0.34	−1.4	0.68
Systolic blood pressure (mmHg)							
BC-HF	120.4 (21.8)		118.7 (16.2)	−1.7	0.71		
CAD	117.4 (16.2)	0.76	121.6 (12.3)	+4.2	0.64	+5.9	0.56
Diastolic blood pressure (mmHg)							
BC-HF	74.6 (12.1)		74.6 (9.0)	0.00	1.00		
CAD	72.2 (9.5)	0.45	75.6 (7.3)	+3.4	0.41	+3.4	0.56
Body composition							
Body mass index (kg/m^2)							
BC-HF	26.7 (6.0)		27.1 (5.6)	+0.4	0.26		
CAD	28.5 (5.2)	0.15	28.6 (4.79)	+0.1	0.69	+0.3	0.71
Waist circumference (cm)							
BC-HF	85.2 (10.8)		85.5 (10.7)	+0.3	0.80		
CAD	90.9 (13.2)	0.11	89.8 (10.3)	−1.1	0.78	−1.4	0.72
Body fat percentage (%)							
BC-HF	34.8 (8.5)		36.3 (6.2)	+1.5	0.04		
CAD	37.8 (6.9)	0.18	37.3 (7.2)	−0.5	0.95	+2.0	0.18

p-value for inter-group comparisons at baseline including all participants who completed the programme. **p*-value for intra-group comparisons from pre- to post-intervention. ***p*-value for inter-group comparisons from pre- to post-intervention. Significance is set at 0.05.
BC-HF: breast cancer and treatment-related heart failure; CAD: coronary artery disease.

The magnitude of the treatment effect observed in this investigation of improvements in VO_{2peak} for women with BC-HF is lower than that observed in other investigations of exercise training for breast cancer survivors without heart failure (2.3 vs 3.5 $ml^{-1} \cdot kg^{-1} \cdot min^{-1}$, respectively) (11). However, the improvements in VO_{2peak} in women with BC-HF were slightly greater than those with CAD, although the difference between groups did not reach statistical significance. It would be expected that women with BC-HF might have greater gains in VO_{2peak} following CR owing to their lower baseline values, thus allowing for more room for improvement. This information demonstrates that women with BC-HF have similar functional gains following completion of a CR programme, and may benefit to the same extent as women with CAD.

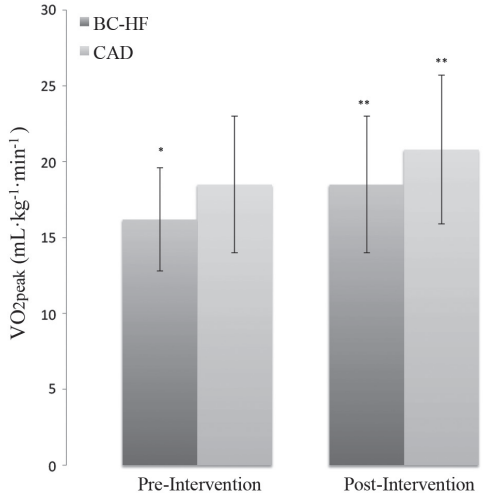

Fig. 2. Baseline and follow-up peak aerobic power (VO_{2peak}) ($ml^{-1} \cdot kg^{-1} \cdot min^{-1}$) measures following the 26-week exercise rehabilitation programme. Values are expressed as means and standard deviations. *Statistically significant differences between groups at baseline. **Statistically significant change following 26-week exercise programme. CAD: coronary artery disease; BC-HF: breast cancer and treatment-related heart failure.

Baseline VO_{2peak} values in the current study were also lower than reported in previous exercise trials for persons with breast cancer (11), due to the expected physiological limitations in those with BC-HF. In breast cancer, the systems governing VO_{2peak} (i.e. pulmonary, cardiac, vascular, oxygen-carrying capacity of the blood, and skeletal muscle function) may be impaired, mediated in part as a result of treatment (12). Moreover, patients with heart failure also experience reduced cardiopulmonary fitness due to reduced cardiovascular performance and skeletal muscle function (13). Thus, reduced muscle function and/or mass, lower haemoglobin values and reduced cardiovascular function due to breast cancer and co-morbid heart failure may explain the low baseline VO_{2peak} values on enrollment to the CR programme. Given that CR has been implemented as standard of care for women with CAD, such programmes should also be available to women with BC-HF in order to treat and/or mitigate the cardiovascular consequences associated with cancer treatments. Evidence concerning improvements in VO_{2peak} for non-cancer patients demonstrates that each 1.0 $ml^{-1} \cdot kg^{-1} \cdot min^{-1}$

improvement in VO_{2peak} is associated with a 10% increase in incidence of survival from a cardiac-related cause (2). As such, exercise training in a structured CR programme may reduce the risk of long-term cardiac-related mortality for women with BC-HF.

Secondary outcomes of this investigation revealed that women with BC-HF experience an increase in body fat percentage following CR. Conversely, outcomes of previous investigations demonstrate that exercise training is associated with a reduction in body fat percentage in breast cancer survivors (14). As such, it was expected that body fat percentage would be reduced in women with BC-HF following completion of CR. Further research is needed to determine optimal treatment strategies to improve body composition in women with BC-HF.

There are notable limitations to this study. First, the retrospective study design presented challenges in obtaining details regarding type of chemotherapy regimen, surgery type, and stage of disease, radiation therapy and hormone therapy. This limits the ability to draw conclusions based on type of treatment and/or disease stage, which may influence the outcomes of exercise. Furthermore, information regarding compliance with the prescribed exercise was not available. However, this study does provide pragmatic information regarding the efficacy of a structured CR programme to improve the clinical outcomes presented in this investigation. Moreover, the small sample size limits the power of the statistical analysis used in this investigation to detect differences in secondary outcomes in this investigation. However, the study was powered to detect differences between groups for our primary endpoint for changes in VO_{2peak}. Finally, due to the lack of a BC-HF study arm receiving usual care (i.e. no exercise rehabilitation) it was not possible to determine the magnitude of change in the outcome variables that is related to exercise or changes over time.

In conclusion, these data suggest that CR leads to gains in VO_{2peak} in women with BC-HF. It is also highlighted that, despite participation in CR, women with BC-HF experience unfavourable changes in body composition during survivorship. Moreover, for the first time it is demonstrated that CR may be a non-toxic adjunct therapy to ameliorate adverse cardiac effects related to breast cancer therapy for women with BC-HF. This research has the potential to lead to the development of informed treatment strategies to improve functional status for women with BC-HF.

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