Available online at www.sciencedirect.com
SCIENCE DIRECT®
Brain, Behavior, and Immunity 19 (2005) 381–388
BRAIN, BEHAVIOR, and IMMUNITY
www.elsevier.com/locate/ybrbi

Effect of exercise training on C-reactive protein in postmenopausal breast cancer survivors: A randomized controlled trial

Adrian S. Fairey [a,b], Kerry S. Courneya [a,b,*], Catherine J. Field [c], Gordon J. Bell [b], Lee W. Jones [b], Blair St. Martin [a], John R. Mackey [a]

[a] *Faculty of Medicine, University of Alberta, Edmonton, Canada*
[b] *Faculty of Physical Education, University of Alberta, E-424 Van Vliet Center, Edmonton, Canada T6G 2H9*
[c] *Faculty of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Canada*

Received 28 December 2004; received in revised form 22 March 2005; accepted 10 April 2005
Available online 26 May 2005

Abstract

The objective of this study was to determine the effects of exercise training on changes in C-reactive protein (CRP) and other cardiovascular risk factors in postmenopausal breast cancer survivors. Fifty-three postmenopausal breast cancer survivors were randomly assigned to an exercise ($n = 25$) or control group ($n = 28$). The exercise group trained on cycle ergometers 3 times per week for 15 weeks. The control group did not train. The primary end point was change in CRP between baseline and week 15. Secondary end points were changes in RHR, HRR, SBP, DBP, TC, LDL-C, HDL-C, TG, and TC:HDL-C ratio. Fifty-two participants completed the trial. Baseline values did not differ between groups except that TG ($p = .007$) and TC:HDL-C ratio ($p = .023$) were higher in the exercise group. Intention-to-treat analysis showed that CRP decreased by 1.39 mg/L in the exercise group whereas it increased by 0.10 mg/L in the control group (mean between group change, −1.49 mg/L; 95% CI, −3.09 to 0.10 mg/L; $p = .066$). Intention-to-treat analysis also showed a clinically and statistically significant difference between groups for change in HRR (mean change, +10.6 beats/min; 95% CI, +3.4 to +17.7 beats/min; $p = .004$) and clinically but not statistically significant differences between groups for change in RHR (mean change, −5.5 beats/min; 95% CI, −11.5 to +0.5 beats/min; $p = .073$), SBP (mean change, −5.5 mm Hg; 95% CI, −14.5 to +3.4 mm Hg; $p = .218$), DBP (mean change,−3.6 mm Hg; 95% CI, −9.3 to +2.1 mm Hg; $p = .214$), and HDL-C (mean change, +0.05 mmol/L; 95% CI, −0.03 to 0.14 mmol/L; $p = .214$). These data suggest that exercise training may have beneficial effects on CRP and other cardiovascular risk factors in postmenopausal breast cancer survivors. Larger randomized controlled trials are warranted.

Keywords: Exercise; C-reactive protein; Heart rate; Blood pressure; Lipids; Breast cancer; Randomized controlled trial

1. Introduction

Recent data from the National Cancer Institute Surveillance, Epidemiology, and End Results program suggest that approximately 20% of postmenopausal breast cancer survivors die from cardiovascular disease (Yancik et al., 2001). Independent cardiovascular risk factors include C-reactive protein (CRP)[1] (Ridker et al., 2002), resting heart rate (Benetos et al., 1999; Gillman et al., 1993; Greenland et al., 1999; Mensink and Hoffmeister, 1997), heart rate reserve (Cheng et al., 2002), blood pressure (Chobanian et al., 2003; Lewington et al., 2002; Vasan et al., 2002), and lipid profiles (Annon, 1993, 1996, 2002). Observational data suggest inverse

* Corresponding author. Fax: +1 780 492 8003.
E-mail address: kerry.courneya@ualberta.ca (K.S. Courneya).

[1] *Abbreviations used:* CRP, C-reactive protein; RHR, resting heart rate; HRR, heart rate reserve; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

0889-1591/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbi.2005.04.001

associations between physical activity and CRP (Abramson and Vaccarino, 2002; Church et al., 2002; Ford, 2002; Geffken et al., 2001; LaMonte et al., 2002; Manns et al., 2003; Pitsavos et al., 2003; Wannamethee et al., 2002) in adult men and women. Randomized controlled trials have shown that exercise can reduce resting heart rate (Hambrecht et al., 2000; Wood et al., 2001), reduce blood pressure (Whelton et al., 2002), and raise HDL-C and lower LDL-C (Leon and Sanchez, 2001) in adult men and women. To date, however, no study has examined the effects of exercise training on cardiovascular risk factors in postmenopausal breast cancer survivors.

Research examining the effects of exercise training on CRP and other cardiovascular risk factors in postmenopausal breast cancer survivors is novel for several reasons. First, it is unknown whether postmenopausal breast cancer survivors will be willing or able to tolerate an exercise regimen sufficient to change cardiovascular risk factors. Second, it is unknown whether exercise-induced changes in cardiovascular risk factors that are seen in healthy adult men and women are altered by the disease and/or its treatment. Third, most of the data on exercise and CRP in healthy populations comes from observational studies. Few studies have been randomized controlled trials (Hammett et al., 2004).

The rehabilitation exercise for health after breast cancer (REHAB) trial was a randomized controlled trial of exercise training in postmenopausal breast cancer survivors who had completed surgery, radiotherapy, and/or chemotherapy with or without current tamoxifen or anastrozole therapy use. We previously reported statistically and clinically significant changes in peak oxygen consumption and quality of life (Courneya et al., 2003) and insulin-like growth factors and insulin-like growth factor binding proteins (Fairey et al., 2003). We also previously reported statistically significant changes in natural killer cell cytotoxicity but no change in standard hematologic variables, whole blood neutrophil function, the phenotypes of isolated mononuclear cells, estimations of unstimulated and phytohemaglutinin-stimulated mononuclear cell function, and the production of pro-inflammatory and anti-inflammatory cytokines (Fairey et al., 2005). Here, we report the effects of exercise training on CRP and other traditional cardiovascular risk factors. We hypothesized that exercise training would have a beneficial effect on CRP.

2. Methods

The trial design and conduct have been previously described (Courneya et al., 2003). In brief, the study was conducted at the Cross Cancer Institute (CCI) and University of Alberta in Edmonton, Canada. The Alberta Cancer Board and the University of Alberta approved the study. Written informed consent was obtained for all procedures.

2.1. Participants

Eligibility criteria included: (1) histologically confirmed stage I to IIIB breast cancer, (2) diagnosed between January 1999 and June 2000, (3) completed surgery, radiotherapy, and/or chemotherapy with or without current tamoxifen or anastrozole therapy use, (4) postmenopausal, (5) non-smokers, and (6) between 50 and 69 years of age. Eligible participants were not admitted if they had: (1) known cardiac disease, (2) uncontrolled hypertension, (3) uncontrolled thyroid disease, (4) diabetes mellitus, (5) mental illness, (6) infection, (7) immune or endocrine abnormality, (8) body weight reduction $\geqslant 10\%$ in past 6 months, and (9) positive exercise stress test.

2.2. Design and randomization

The study was a randomized controlled trial. Participants were stratified by type of adjuvant therapy (previous chemotherapy versus no previous chemotherapy and current hormone therapy use versus no current hormone therapy use) and block randomized to an exercise or control group using a random-numbers table. A research assistant generated the allocation sequence and the project director assigned participants to groups.

2.3. Exercise training intervention

The exercise training intervention was designed to improve cardiopulmonary fitness and based on each participant's fitness level at baseline. The exercise group trained 3 times per week for 15 weeks on recumbent or upright cycle ergometers (Lifestyle Fitness 9500HR, Lifecycle Inc). Exercise intensity was set at the power output that elicited the ventilatory equivalent for carbon dioxide (approximately 70–75% of peak oxygen consumption). Exercise duration began at 15 min for weeks 1 through 3, and then systematically increased by 5 min every three weeks thereafter to 35 min for weeks 13 through 15. Warm-up and cool-down periods consisted of 5 min of cycling at the power output that elicited the ventilatory equivalent for oxygen (approximately 50% of peak oxygen consumption). Exercise physiologists supervised the exercise sessions, and monitored heart rate and blood pressure. The control group did not train and were asked not to begin a structured exercise program. To reduce attrition, the control group was offered the intervention after the trial.

2.4. End points and blinding

The primary end point was change in CRP between baseline and week 15. Secondary end points were changes in RHR, HRR, SBP, DBP, TC, HDL-C, LDL-C, TG, and TC:HDL-C ratio between baseline and week 15. Laboratory staff and those who assessed the trial end points were blinded to treatment assignment.

2.5. Blood collection

Participants were instructed not to exercise for at least 48 h prior to blood collection. Blood was collected between 07:00 and 10:00 after a 12-h water-only fast with participants in the seated position. Blood was drawn into tubes chilled on ice treated with sodium heparin (for plasma), EDTA, or no anticoagulant (for serum). Blood was centrifuged at 700*g* at 23 °C for 10 min. Plasma and serum were aliquoted and stored at −70 °C. Precautions were taken to prevent thawing or warming of specimens during storage. Blood samples were collected from 53 participants at baseline and 52 participants at week 15.

2.6. C-reactive protein

C-reactive protein was assessed in serum using an enzyme-linked immunosorbent assay kit (ELISA; DRG International, USA). Baseline and week 15 measurements of the analyte for both exercise and control group participants was performed in one batch. Duplicate measurements were made for each sample and the mean of the duplicate measurements was assigned as the sample value. Blind duplicates were used for determining coefficients of variation. The mean intra-assay coefficient of variation was 5.59%. The sensitivity of the assay was 5 μg/ml.

2.7. Heart rate variables

Resting heart rate was measured after the participant had rested for 5 min in the seated position. Heart rate reserve was calculated as the heart rate at peak exercise minus the heart rate at rest. All heart rate variables were measured using a Polar A1 Heart Rate Monitor (Woodbury, NY, USA).

2.8. Blood pressure

Blood pressure was assessed according to procedures recommended by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Chobanian et al., 2003). Blood pressure measurements were obtained by trained, certified individuals who used a random zero sphygmomanometer. After the participant sat quietly for 5 min, the observer measured blood pressure with an appropriately sized cuff. Two blood pressure measurements separated by at least 30 s were obtained. SBP was the appearance of the first Korotkoff sound and DBP was the disappearance of Korotkoff sounds.

2.9. Lipids

Total cholesterol, HDL-C, and TG were assayed in plasma using enzymatic methods according to procedures recommended by the Centers for Disease Control and Prevention and the National Heart, Lung, and Blood Institute (Allain et al., 1974). LDL-C was calculated using the Friedewald formula (Friedewald et al., 1972). The TC:HDL-C ratio was calculated as total cholesterol divided by HDL-C.

2.10. Statistical analysis

Sample size calculation was based on the primary cardiopulmonary and quality of life end points from the REHAB trial (Courneya et al., 2003). Data were analyzed using the intention-to-treat approach. The last-observation-carried-forward procedure was used for participants who did not complete the trial. All distributions were checked for skewness and outliers, and CRP levels $\geqslant 15$ mg/L were excluded from the analysis under the assumption that they represented acute illness or infection (Rifai and Ridker, 2001). This led to the deletion of data from one participant who had a CRP concentration of 89 mg/L at baseline. Baseline comparisons between the two groups were made using independent-samples *t* tests for continuous data and Pearson's chi-square tests for categorical data. The primary analysis used independent-samples *t* tests to compare changes between groups in end points from baseline to week 15. Change over the intervention period was calculated by subtracting the baseline value from the week 15 value. When significant differences between groups were observed at baseline, analyses of covariance procedures were performed in which the baseline value of the same variable was used as a covariate. Pearson's product moment correlations were used to evaluate associations between changes in CRP and changes in cardiopulmonary fitness and body composition. A two-sided *p* value less than .05 indicated statistical significance. No adjustments were made for multiple comparisons. Data are presented as the mean (± SD) with 95% confidence intervals (CI).

3. Results

3.1. Flow of participants through the trial

Flow of participants through the trial has been described (Courneya et al., 2003). In brief, 370 breast cancer survivors were assessed for eligibility and 323 were approved for contact by their physician (37 excluded because physician did not reply to request to contact survivor, 10 excluded because physician denied request to contact survivor). Ninety-one of 323 breast cancer survivors responded to a recruitment letter (225 excluded because they did not reply to recruitment letter, 7 excluded because recruitment letter was returned unopened) and 53 (14.3%) were randomly assigned to the exercise ($n = 25$) or

control group ($n=28$) (16 excluded because they did not meet inclusion criteria, 9 excluded because they were on holidays during the trial, 8 excluded because they were not interested, 4 excluded because of positive exercise stress test, and 1 excluded because they were unwilling to travel to the exercise facility). One participant (4.2%) dropped out in the exercise group compared to 0 participants in the control group ($p=.285$). The participant in the exercise group dropped out because of a gastrointestinal complication unrelated to exercise. Overall, 52 of 53 participants completed the trial (98.1%).

3.2. Baseline characteristics

Table 1 shows the baseline characteristics. No significant differences were observed between groups for demographic, medical, or past exercise variables.

3.3. Self-reported diet intake and medication use

Self-reported diet intake and medication use have been described (Fairey et al., 2003). No significant differences were observed between groups for any variable including total calories, total fat, total carbohydrate, total protein, or hormone replacement therapy use, to name only a few.

3.4. Adherence to the intervention

Adherence to the exercise intervention has been described (Courneya et al., 2003). The exercise group completed 44.3 of 45 (range 38/45 to 45/45) prescribed exercise sessions. Non-protocol-related exercise was not different between groups ($p=.890$). The exercise group reported 15 min of moderate/strenuous non-protocol-related exercise per week compared to 13 min in the control group.

3.5. Changes in cardiopulmonary fitness and body composition

Changes in cardiopulmonary fitness and body composition have been described (Courneya et al., 2003). In brief, baseline values for peak oxygen consumption ($p=0.254$), body weight ($p=0.983$), body mass index ($p=0.725$), and sum of skinfolds ($p=0.650$) did not differ between groups. A significant difference between groups was observed for change in peak oxygen consumption (mean difference, +0.29 L/min; 95% CI, 0.18–0.40 L/min; $p<0.001$). No significant differences between groups were observed for changes in body weight (mean difference, −0.6 kg; 95% CI, −1.6 to +0.6 kg; $p=0.339$) or body mass index (mean difference, −0.3 kg/m^2; 95% CI, −0.6 to +0.3 kg/m^2; $p=0.337$) but there was a trend toward a change in sum of skinfolds (mean difference, −10.2 mm; 95% CI, −21.6 to +1.8 mm; $p=0.095$).

3.6. Changes in CRP and other cardiovascular risk factors

Table 2 shows the changes in end points. Baseline values did not differ between groups except that TG ($p=.007$) and TC:HDL-C ratio ($p=.023$) were higher in the exercise group. CRP decreased by 1.39 mg/L in the exercise group whereas it increased by 0.10 mg/L in the control group (mean between group change, −1.49 mg/L; 95% CI, −3.09 to 0.10 mg/L; $p=.066$). RHR decreased by 4.4 beats/min in the exercise group whereas it increased by 1.1 beats/min in the control group (mean between group change, −5.5 beats/min; 95% CI, −11.5 to +0.5 beast/min; $p=.073$). HRR increased by 6.5 beats/

Table 1
Baseline characteristics

Variable	Overall ($n=52$)	Exercise group ($n=24$)	Control group ($n=28$)	p value*
Age (years)	59 (6)	59 (5)	58 (6)	.712
Weight (kg)	78.7 (18.1)	78.1 (20.4)	79.4 (16.4)	.801
Peak oxygen consumption (ml/kg/min)	18.7 (3.9)	18.6 (3.9)	18.8 (3.8)	.807
Body mass index (kg/m^2)	29.2 (6.6)	29.4 (7.4)	29.1 (6.1)	.880
Months after surgery, RT, CT	14 (6)	14 (6)	14 (7)	.856
Stage				
I (T1N0)	21 (40%)	10 (42%)	11 (39%)	.862
IIa (T1N1,T2N0)	17 (33%)	6 (25%)	11 (39%)	.274
IIb (T2N1,T3N0)	11 (21%)	6 (25%)	5 (18%)	.530
IIIa (T1N2,T2N2,T3N1-2)	3 (6%)	2 (8%)	1 (4%)	.463
Surgery				
Mastectomy	28 (54%)	15 (64%)	13 (46%)	.246
Lumpectomy	24 (46%)	9 (37%)	15 (54%)	.246
Radiation therapy	37 (71%)	16 (67%)	21 (75%)	.508
Chemotherapy	21 (40%)	10 (42%)	11 (39%)	.862
Current tamoxifen or arimidex use	24 (46%)	11 (46%)	13 (46%)	.966

Notes. Data are presented as the mean (standard deviation) for continuous variables and frequency (percentage) for categorical variables.
Abbreviations: RT, radiation therapy; CT, chemotherapy; HT, hormone therapy.
* p value for difference between groups.

Table 2
Changes in end points[a]

Risk factor	Baseline	*p* value*	Week 15	Mean change	Difference between groups in mean change [95%CI]	*p* value**
Inflammatory biomarker						
C-reactive protein (mg/L)						
Exercise group	5.19 (3.56)		3.79 (2.30)	−1.39 (3.60)		
Control group	4.28 (3.05)	.262	4.39 (3.87)	+0.10 (1.97)	−1.49 [−3.09 to 0.10]	.066
Heart rate variables						
Resting heart rate (beats/min)						
Exercise group	85.2 (12.0)		81.1 (8.2)	−4.4 (11.0)		
Control group	82.6 (15.4)	.481	83.3 (14.1)	+1.1 (10.4)	−5.5 [−11.5 to +0.5]	.073
Heart rate reserve (beats/min)						
Exercise group	69.8 (22.3)		76.2 (13.8)	+6.5 (16.2)		
Control group	78.4 (19.8)	.140	74.4 (17.4)	−4.1 (9.1)	+10.6 [+3.4 to +17.7]	.004
Blood pressure						
SBP (mm Hg)						
Exercise group	137.0 (13.1)		131.6 (13.1)	−5.4 (15.6)		
Control group	134.6 (20.2)	.615	134.7 (18.2)	+0.1 (16.6)	−5.5 [14.5 to +3.4]	.218
DBP (mm Hg)						
Exercise group	89.1 (12.1)		85.0 (8.9)	−4.1 (11)		
Control group	85.9 (12.3)	.348	85.4 (7.1)	−0.5 (10)	−3.6 [−9.3 to +2.1]	.214
Lipids						
Total cholesterol (mmol/L)						
Exercise group	5.64 (0.79)		5.53 (0.80)	−0.11 (0.59)		
Control group	5.62 (0.77)	.935	5.54 (0.71)	−0.09 (0.50)	−0.03 [−0.33 to 0.27]	.854
HDL-C (mmol/L)						
Exercise group	1.47 (0.26)		1.51 (0.27)	+0.04 (0.12)		
Control group	1.60 (0.30)	.116	1.58 (0.31)	−0.01 (0.19)	+0.05 [−0.03 to 0.14]	.214
LDL-C (mmol/L)						
Exercise group	3.45 (0.70)		3.37 (0.78)	−0.08 (0.55)		
Control group	3.45 (0.74)	.983	3.33 (0.63)	−0.12 (0.52)	+0.04 [0.25 to 0.34]	.784
Triglycerides (mmol/L)						
Exercise group	1.75 (0.74)		1.59 (0.57)	−0.16 (0.54)		
Control group	1.27 (0.48)	.007	1.39 (0.57)	+0.11 (0.37)	−0.28 [−0.53 to −0.02]	.033
Total cholesterol:HDL-C ratio						
Exercise group	4.20 (0.98)		3.99 (0.94)	−0.22 (0.41)		
Control group	3.64 (0.80)	.023	3.64 (0.86)	0.00 (0.55)	−0.22 [−0.49 to 0.05]	.109

Abbreviations used: SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein.

[a] Data are presented as the mean (standard deviation). Exercise group ($n = 25$). Control group ($n = 28$).

* *p* value for independent *t* tests comparing the exercise group and control group at baseline.

** *p* value for independent *t* tests comparing changes between the exercise group and control group from baseline to week 15.

min in the exercise group whereas it decreased by 4.1 beats/min in the control group (mean between group change, +10.6 beats/min; 95% CI, +3.4 beats/min to 17.7 beats/min; $p = .004$). SBP decreased by 5.4 mm Hg in the exercise group whereas it increased by 0.1 mm Hg in the control group (mean between group change, −5.5 mm Hg; 95% CI, −14.5 to +3.4 mm Hg; $p = .218$). DBP decreased by 4.1 mm Hg in the exercise group compared to 0.5 mm Hg in the control group (mean between group change, −3.6 mm Hg; 95% CI, −9.3 to +2.1 mm Hg; $p = .214$). TC decreased by 0.11 mmol/L in the exercise group compared to 0.09 mmol/L in the control group (mean between group change, −0.03 mmol/L; 95% CI, −0.33 to 0.27 mmol/L; $p = .854$). HDL-C increased by 0.04 mmol/L in the exercise group whereas it decreased by 0.01 mmol/L in the control group (mean between group change, +0.05 mmol/L; 95% CI, −0.03 to 0.14 mmol/L; $p = .214$). LDL-C decreased by 0.08 mmol/L in the exercise group compared to 0.12 mmol/L in the control group (mean between group change, +0.04 mmol/L; 95% CI, −0.25 to 0.34 mmol/L; $p = .784$). TG decreased by 0.16 mmol/L in the exercise group

whereas it increased by 0.11 mmol/L in the control group (mean between group change, −0.28 mmol/L; 95% CI, −0.53 to −0.02 mmol/L; $p = .033$). TC:HDL-C ratio decreased by 0.22 in the exercise group compared to no change in the control group (mean between group change, −0.22; 95% CI, −0.49 to 0.05; $p = .109$).

3.7. Analysis of covariance

Baseline values of TG and TC:HDL-C ratio differed between groups. Analyses of this data using univariate analysis of covariance procedures showed no significant difference between groups at week 15 (data not shown).

3.8. Association between change in CRP and change in cardiopulmonary fitness and body composition

Change in CRP did not correlate with change in cardiopulmonary fitness or change in body composition (body weight, BMI, sum of skinfolds) (data not shown).

3.9. Adverse events

Adverse events have been described (Courneya et al., 2003). In brief, five participants (20.8%) in the exercise group experienced an adverse event compared to two participants (7.1%) in the control group ($p = .168$). The adverse events in the exercise group were lymphedema ($n = 3$), gynecologic complication ($n = 1$), and influenza ($n = 1$) whereas the adverse events in the control group were metatarsal fracture ($n = 1$) and bronchitis ($n = 1$).

4. Discussion

The REHAB trial is the first randomized controlled trial to examine the effects of exercise training on cardiovascular risk factors in postmenopausal breast cancer survivors. We found that exercise training had a borderline statistically significant effect on CRP. In addition, we found that exercise training had a clinically and statistically significant effect on HRR and clinically but not statistically significant effects on RHR, SBP, DBP, HDL-C, and TG.

Our trial had strengths and limitations. Strengths include the randomized controlled trial design, standardized blood collection protocols, high exercise adherence rate, and minimal loss to follow-up. Limitations include the small sample size, 14% recruitment rate, short exercise intervention with no long-term follow-up, and use of a single blood measurement to classify participants.

The main finding from our trial was the effect of exercise on CRP. The mean between group change in C-reactive protein was −1.49 mg/L. This finding is in contrast with that seen in a recent randomized controlled trial. Hammett et al. (2004) showed that 6 months of exercise training had no effect on CRP in healthy elderly subjects. However, the effect we observed on CRP is consistent with previous observational and non-randomized intervention studies (Abramson and Vaccarino, 2002; Church et al., 2002; Ford, 2002; Geffken et al., 2001; LaMonte et al., 2002; Manns et al., 2003; Pitsavos et al., 2003; Smith et al., 1999; Wannamethee et al., 2002). For example, Smith et al. (1999) showed that 6 months of supervised exercise reduced CRP by 1.68 mg/dl in adult men and women at risk for developing ischemic heart disease. Reasons for these discrepant findings are unknown but may include the exercise intervention and/or trial participants. Our finding must be interpreted with caution because it only approached statistical significance ($p = .066$). Nonetheless, extrapolating from Women's Health Study data, the effect we observed on CRP would be predicted to reduce the risk factor adjusted relative risk of a first cardiovascular event from 2.3 to 2.0 (Ridker et al., 2002).

A second finding from our trial was the effects of exercise on heart rate variables. The mean between group changes in RHR and HRR were −5.5 and +10.6 beats/min, respectively. These findings are consistent with previous exercise trials (Hambrecht et al., 2000; Loimaala et al., 2000; Wood et al., 2001). For example, in a randomized controlled trial, Hambrecht et al. (2000) showed that 6 months of exercise training reduced RHR by 6 beats/min in chronic heart failure patients. Although our finding for RHR must be interpreted with caution because it only approached statistical significance ($p = 0.073$), the effects on heart rate variables observed in our trial are clinically important and may lower the risk of cardiovascular and all-cause mortality (Benetos et al., 1999; Greenland et al., 1999; Kristal-Boneh et al., 2000; Mensink and Hoffmeister, 1997).

A third finding from our trial was the effect of exercise on blood pressure. The mean between group changes in SBP and DBP were −5.5 and −3.6 mm Hg, respectively. The magnitude of these effects is larger than those observed in previous exercise trials. In a meta-analysis of randomized controlled trials, Whelton et al. (2002) showed that aerobic exercise reduced SBP and DBP by 3.8 and 2.6 mm Hg, respectively. These reductions were observed for all frequencies and intensities of aerobic exercise in both hypertensive and normotensive participants and overweight and normal-weight participants. The magnitude of the mean between group changes in blood pressure in our trial is also similar to that observed in the PREMIER Clinical Trial of comprehensive lifestyle modification (Appel et al., 2003). Our findings must be interpreted with caution, however, because the 95% confidence intervals included a zero mean between group change. Nonetheless, the effect on blood pressure observed in our trial is clinically important and may lower the risk of cardiovascular disease (Chobanian et al., 2003; Lewington et al., 2002; Whelton and He, 1999).

For example, in a meta-analysis of individual data in 61 prospective studies, Lewington et al. (2002) showed that a 2 mm Hg lower usual SBP lowered stroke and ischemic heart disease mortality by 10 and 7%, respectively.

A fourth finding from our trial was the effect of exercise on lipid levels. The mean between group changes in HDL-C, TG, and TC:HDL-C ratio were +0.05 mmol/L (+3.2%), −0.28 mmol/L (−18.5%), and −0.22 (−5.6%), respectively. The magnitude of these effects is consistent with those reported in previous exercise trials. In a comprehensive review of 51 studies (28 of which were randomized controlled trials), Leon and Sanchez showed that exercise increased HDL-C by 4.6% and reduced TC, LDL-C, and TG by 1.0, 5.0, and 3.7%, respectively, in adult men and women (Leon and Sanchez, 2001). Once again, however, our findings must be interpreted with caution because the 95% confidence intervals included a zero mean between group change. Nevertheless, the effects on lipids observed in our trial may lower the risk of cardiovascular disease. For example, the effect on HDL-C (+0.05 mmol/L) should reduce the risk for a coronary heart disease event by 6% (Pasternak et al., 1990).

There are several possible explanations for the lack of statistically significant effects on CRP, blood pressure, and lipid levels in our trial. First, the sample size of our trial may have been too small to detect a treatment effect. Support for this assertion comes from the fact that the direction and magnitude of the mean between group changes in our trial are similar to those reported in previous studies and that our intervention was consistent with current exercise training guidelines (Fletcher et al., 2001). Second, our exercise training intervention did not reduce body weight, which is known to improve cardiovascular risk factors in adult men and women (Gordon and Libby, 2003). However, exercise training does not necessarily need to reduce body weight to have beneficial effects on blood pressure (Whelton et al., 2002), lipids (Leon and Sanchez, 2001), or C-reactive protein (LaMonte et al., 2002).

Exercise-induced modulation of cardiovascular risk factors is biologically plausible. Mechanisms of change in CRP include alterations in pro- and anti-inflammatory cytokine production by blood mononuclear cells, natural killer cell cytotoxic activity, insulin resistance, intra-abdominal body fat, oxidized low-density lipoprotein cholesterol, antioxidants, nitric oxide, and leukocyte adhesion molecules (LaMonte et al., 2002; Petersen and Pedersen, 2005). The mechanism of change in heart rate variables is most likely parasympathetic activation (Arai et al., 1989; Imai et al., 1994). Mechanisms of change in blood pressure include reductions in insulin resistance and total cholesterol (Brett et al., 2000; Brown et al., 1997; He et al., 1999; Kokkinos et al., 1995; Reaven, 1988). Finally, mechanisms of changes in lipids include reductions in adiposity and/or insulin resistance and increases in lipoprotein lipase activity (Tall, 2002). Although our trial did not provide evidence of these mechanisms, these effects may represent clinically significant biologic mechanisms of action of exercise.

In summary, these data suggest that exercise training may have a beneficial effect on CRP and other traditional cardiovascular risk factors in postmenopausal breast cancer survivors. Larger randomized controlled trials are needed to confirm these findings. If our findings are confirmed in future trials, exercise training should be tested as an intervention to improve clinical outcome in this population.

Acknowledgments

A Research Team Grant from the National Cancer Institute of Canada (NCIC) funded this study with funds from the Canadian Cancer Society (CCS) and the CCS/NCIC Sociobehavioral Cancer Research Network. The Canada Research Chairs Program supports Kerry Courneya.

References

Abramson, J.L., Vaccarino, V., 2002. Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults. Arch. Intern. Med. 162 (11), 1286–1292.

Allain, C.C., Poon, L.S., et al., 1974. Enzymatic determination of total serum cholesterol. Clin. Chem. 20 (4), 470–475.

Annon. 1993. NIH Consensus conference. Triglyceride, high-density lipoprotein, and coronary heart disease. NIH Consensus Development Panel on Triglyceride, High-Density Lipoprotein, and Coronary Heart Disease. JAMA 269(4), 505–510.

Appel, L.J., Champagne, C.M., et al., 2003. Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. JAMA 289 (16), 2083–2093.

Arai, Y., Saul, J.P., et al., 1989. Modulation of cardiac autonomic activity during and immediately after exercise. Am. J. Physiol. 256 (1 Pt 2), H132–H141.

Benetos, A., Rudnichi, A., et al., 1999. Influence of heart rate on mortality in a French population: role of age, gender, and blood pressure. Hypertension 33 (1), 44–52.

Brett, S.E., Ritter, J.M., et al., 2000. Diastolic blood pressure changes during exercise positively correlate with serum cholesterol and insulin resistance. Circulation 101 (6), 611–615.

Brown, M.D., Moore, G.E., et al., 1997. Improvement of insulin sensitivity by short-term exercise training in hypertensive African American women. Hypertension 30 (6), 1549–1553.

Cheng, Y.J., Macera, C.A., et al., 2002. Heart rate reserve as a predictor of cardiovascular and all-cause mortality in men. Med. Sci. Sports Exerc. 34 (12), 1873–1878.

Chobanian, A.V., Bakris, G.L., et al., 2003. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA 289 (19), 2560–2572.

Church, T.S., Barlow, C.E., et al., 2002. Associations between cardiorespiratory fitness and C-reactive protein in men. Arterioscler. Thromb. Vasc. Biol. 22 (11), 1869–1876.

Courneya, K.S., Mackey, J.R., et al., 2003. Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: car-

diopulmonary and quality of life outcomes. J. Clin. Oncol. 21 (9), 1660–1668.
Fairey, A.S., Courneya, K.S., et al., 2003. Effects of exercise training on fasting insulin, insulin resistance, insulin-like growth factors, and IGF binding proteins in postmenopausal breast cancer survivors: a randomized controlled trial. Cancer Epidemiol. Biomarkers, Prevent. 12 (7), 721–727.
Fairey, A.S., Courneya, K.S., et al., 2005. Randomized controlled trial of exercise training and blood immune function in postmenopausal breast cancer survivors. J. Appl. Physiol. 98, 1534–1540.
Fletcher, G.F., Balady, G.J., et al., 2001. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. Circulation 104 (14), 1694–1740.
Ford, E.S., 2002. Does exercise reduce inflammation? Physical activity and C-reactive protein among US adults. Epidemiology 13 (5), 561–568.
Friedewald, W.T., Levy, R.I., et al., 1972. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin. Chem. 18 (6), 499–502.
Fuster, V., Gotto, A.M., et al., 1996. 27th Bethesda conference: matching the intensity of risk factor management with the hazard for coronary disease events. Task Force 1. Pathogenesis of coronary disease: the biologic role of risk factors. J. Am. Coll. Cardiol. 27 (5), 964–976.
Geffken, D.F., Cushman, M., et al., 2001. Association between physical activity and markers of inflammation in a healthy elderly population. Am. J. Epidemiol. 153 (3), 242–250.
Gillman, M.W., Kannel, W.B., et al., 1993. Influence of heart rate on mortality among persons with hypertension: the Framingham Study. Am. Heart J. 125 (4), 1148–1154.
Gordon, M.B., Libby, P., 2003. Atherosclerosis. Lippincott Williams and Wilkins, Baltimore, MD.
Greenland, P., Daviglus, M.L., et al., 1999. Resting heart rate is a risk factor for cardiovascular and noncardiovascular mortality: the Chicago heart association detection project in industry. Am. J. Epidemiol. 149 (9), 853–862.
Hambrecht, R., Gielen, S., et al., 2000. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: A randomized trial. JAMA 283 (23), 3095–3101.
Hammett, C.J., Oxenham, H.C., et al., 2004. Effect of six months' exercise training on C-reactive protein levels in healthy elderly subjects. J. Am. Coll. Cardiol. 44 (12), 2411–2413.
He, J., Klag, M.J., et al., 1999. Plasma insulin levels and incidence of hypertension in African Americans and whites. Arch. Intern. Med. 159 (5), 498–503.
Imai, K., Sato, H., et al., 1994. Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. J. Am. Coll. Cardiol. 24 (6), 1529–1535.
Kokkinos, P.F., Narayan, P., et al., 1995. Effects of regular exercise on blood pressure and left ventricular hypertrophy in African-American men with severe hypertension. N. Engl. J. Med. 333 (22), 1462–1467.
Kristal-Boneh, E., Silber, H., et al., 2000. The association of resting heart rate with cardiovascular, cancer and all-cause mortality. Eight year follow-up of 3527 male Israeli employees (the CORDIS Study). Eur. Heart J. 21 (2), 116–124.
LaMonte, M.J., Durstine, J.L., et al., 2002. Cardiorespiratory fitness and C-reactive protein among a tri-ethnic sample of women. Circulation 106 (4), 403–406.
Leon, A.S., Sanchez, O.A., 2001. Response of blood lipids to exercise training alone or combined with dietary intervention. Med. Sci. Sports Exerc. 33 (6 Suppl.), S502–S515 discussion S528–S5289.
Lewington, S., Clarke, R., et al., 2002. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 360 (9349), 1903–1913.
Loimaala, A., Huikuri, H., et al., 2000. Controlled 5-mo aerobic training improves heart rate but not heart rate variability or baroreflex sensitivity. J. Appl. Physiol. 89 (5), 1825–1829.
Manns, P.J., Williams, D.P., et al., 2003. Physical activity, body fat, and serum C-reactive protein in postmenopausal women with and without hormone replacement. Am. J. Human. Biol. 15 (1), 91–100.
Mensink, G.B., Hoffmeister, H., 1997. The relationship between resting heart rate and all-cause, cardiovascular and cancer mortality. Eur. Heart J. 18 (9), 1404–1410.
Pasternak, R.C., Grundy, S.M., Levy, D., Thompson, P.D., 1990. Spectrum of risk factors for CHD. J. Am. Coll. Cardiol. 27, 964–1047.
Petersen, A.M.W., Pedersen, B.K., 2005. The anti-inflammatory effect of exercise. J. Appl. Physiol. 98, 1154–1162.
Pitsavos, C., Chrysohoou, C., et al., 2003. Association of leisure-time physical activity on inflammation markers (C-reactive protein, white cell blood count, serum amyloid A, and fibrinogen) in healthy subjects (from the ATTICA study). Am. J. Cardiol. 91 (3), 368–370.
Reaven, G.M., 1988. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 37 (12), 1595–1607.
Ridker, P.M., Rifai, N., et al., 2002. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N. Engl. J. Med. 347 (20), 1557–1565.
Rifai, N., Ridker, P.M., 2001. High-sensitivity C-reactive protein: a novel and promising marker of coronary heart disease. Clin. Chem. 47 (3), 403–411.
Smith, J.K., Dykes, R., et al., 1999. Long-term exercise and atherogenic activity of blood mononuclear cells in persons at risk of developing ischemic heart disease. JAMA 281 (18), 1722–1727.
Tall, A.R., 2002. Exercise to reduce cardiovascular risk—How much is enough?. N. Engl. J. Med. 347 (19), 1522–1524.
Vasan, R.S., Beiser, A., et al., 2002. Residual lifetime risk for developing hypertension in middle-aged women and men: The Framingham Heart Study. JAMA 287 (8), 1003–1010.
Wannamethee, S.G., Lowe, G.D., et al., 2002. Physical activity and hemostatic and inflammatory variables in elderly men. Circulation 105 (15), 1785–1790.
Whelton, P.K., He, J., 1999. Blood Pressure Reduction. WB Saunders, Philadelphia.
Whelton, S.P., Chin, A., et al., 2002. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. Ann. Intern. Med. 136 (7), 493–503.
Wood, R.H., Reyes, R., et al., 2001. Concurrent cardiovascular and resistance training in healthy older adults. Med. Sci. Sports Exerc. 33 (10), 1751–1758.
Yancik, R., Wesley, M.N., et al., 2001. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA 285 (7), 885–892.