No Reduction in C-Reactive Protein following a 12-Month Randomized Controlled Trial of Exercise in Men and Women

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Abstract

Low-grade systemic inflammation is suggested to play a role in the development of several chronic diseases including cancer. Higher levels of physical activity and lower adiposity have been associated with reduced levels of markers of systemic inflammation, such as C-reactive protein (CRP); however, reductions in CRP have not been consistently observed in randomized controlled trials of exercise.

Purpose: **To examine the effect of a 12-month aerobic exercise intervention on CRP levels in men and women.**

Methods: **One hundred two men and 100 women, sedentary and of ages 40 to 75 years, with mean body mass index (BMI) of 29.9 and 28.7 kg/m^2, respectively, were randomly assigned to a 12-month moderate-to-vigorous aerobic exercise intervention (6 d/wk, 60 min/d, 60-85% maximum heart rate) or control group. Fasting blood samples were collected at baseline and at 12 months. CRP levels were measured by high-sensitivity latex-enhanced nephelometry.**

Results: **At baseline, CRP was 1.16 and 2.11 mg/L for men and women, respectively, and CRP was correlated with percent body fat ($r = 0.48$, $P \leq 0.001$), BMI ($r = 0.37$, $P \leq 0.001$), and aerobic fitness ($r = -0.49$, $P \leq 0.001$). No intervention effects were observed for CRP in men or women, or when stratified by baseline BMI (<30 versus ≥30 kg/m^2), baseline CRP (<3 versus ≥3 mg/L), or change in body weight, body composition, or aerobic fitness.**

Conclusion: **A 12-month moderate-to-vigorous aerobic exercise intervention did not affect CRP levels in previously sedentary men or women with average-risk CRP values at baseline.** (Cancer Epidemiol Biomarkers Prev 2008;17(7):1714–8)

Introduction

Systemic inflammation has been implicated in the pathogenesis of several chronic diseases, including cancer (1-3). In relation to cancer, systemic inflammation is suggested to play a role in both tumor development and promotion (4). C-reactive protein (CRP) is a nonspecific acute-phase protein secreted by the liver that is considered a surrogate marker of chronic low-grade systemic inflammation. Systemic inflammation has been suggested to be an important mechanistic link between physical activity and cancer risk (5).

CRP is positively associated with body fat (6, 7) and negatively associated with physical activity (8-11) and cardiorespiratory fitness (VO_{2max}; refs. 12-16) in observational studies. It is not clear whether improvements in cardiorespiratory fitness reduce CRP and whether such an effect is mediated entirely by a reduction in body fat. The results of previous randomized controlled trials of exercise effects on CRP levels have been mixed (17-25).

This study investigated the effects of a 12-month aerobic exercise intervention on CRP, a proposed biomarker of cancer risk, in 202 previously sedentary adults. We hypothesized that those in the exercise group would have a significant improvement in aerobic fitness (VO_{2max}) and a subsequent reduction in CRP at 12 months compared with controls.

Materials and Methods

Design Overview. This study was a 12-mo randomized controlled trial that compared the effect of a moderate-intensity exercise intervention to a usual lifestyle control program on biomarkers of colon cancer risk. Participants were men and women, 40 to 75 y old, who were sedentary (i.e., <90 min/wk of moderate-to-vigorous exercise in the past 3 mo), had a normal exercise tolerance test, and had no serious medical conditions. Participants were recruited to a trial examining biomarkers of colon cancer risk through

Received 1/28/08; revised 4/21/08; accepted 5/4/08.

Grant support: National Cancer Institute grants R01 CA77572-01 and U54 CA116847, Transdisciplinary Research on Energetics and Cancer Pilot Project. K.L. Campbell is supported by a Canadian Institutes of Health Research Fellowship. P.T. Campbell is supported by a Research Fellowship from the National Cancer Institute of Canada, with funds from the Canadian Cancer Society. R.E. Rudolph was supported in part by the Health Services Research and Development Program of Veterans Affairs Puget Sound Health Care System.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs.

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doi:10.1158/1055-9965.EPI-08-0088

media placements, flyers, a study web site, and referrals (2001-2004). One hundred two men and 100 women were enrolled. The study was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

Laboratory Analysis. Blood samples were obtained following a 12-h fast and stored at −70°C. Plasma CRP was measured by latex-enhanced nephelometry by high-sensitivity assays on the Behring Nephelometer II analyzer (Dade-Behring Diagnostics) at the University of Washington Clinical Immunology Laboratory, by staff blinded to group assignment. The lower detection limit for CRP was 0.2 mg/L. The interassay and intra-assay coefficients of variations were 0.3% and 0.3%, respectively.

Demographics, Anthropometrics, and Fitness. At baseline and 12 mo, participants were evaluated for demographics, medical history, weight, height, body composition as measured by DEXA whole-body scanner (GE Lunar), and cardiopulmonary fitness (VO_{2max}) as measured by oxygen update during a maximal graded treadmill test (Medgraphics).

Intervention. The intervention was an aerobic exercise program (12 mo, 6 d/wk, 60 min/d, at 60-85% of maximal heart rate, determined by the graded treadmill test) with both supervised facility (at least 3 d/wk) and home-based sessions. Exercisers and controls were asked during the trial not to change their dietary habits and controls were asked not to change their exercise habits.

Randomization and Statistical Analyses. Participants were randomly assigned to the exercise or control groups, blocked on sex and, among women, on menopausal status (premenopausal or perimenopausal versus postmenopausal) and current use of postmenopausal hormones (yes/no).

Intervention effects were determined by generalized estimating equations for linear regression. Baseline CRP data were available for 195 participants. Participants with missing end-of-study CRP data ($n = 7$) were not included in the analysis. Means and SDs are reported, except for the main outcome, CRP, where geometric means are reported to reduce the effect of outliers. Associations between CRP and baseline participant characteristics were examined using Spearman correlations. Secondary analyses examined intervention effects stratified by baseline body mass index (BMI; <30 and >30.0 kg/m^2), baseline CRP levels (<3 versus ≥3 mg/L), change in body weight (control, exercise: no change, ≤3 kg, or >3 kg), change in body fat (control, exercise: no change, ≤2%, >2%), or change in aerobic fitness (control, exercise: ≤5%, 5-15%, >15%). Statistical analyses were done using SAS software (version 9.1; SAS Institute, Inc.).

Results

No differences between groups were noted at baseline (Table 1). Male and female exercisers averaged 370 min (103% of goal) and 295 min (82% of goal) per week, respectively. Aerobic fitness (VO_{2max}) increased by 11% (3.3 mg/kg/min) and 10.5% (2.5 mL/kg/min) among male and female exercisers, respectively, and decreased in both female and male controls (−6.3% and −1.8%, respectively; $P < 0.001$, comparing exercise to control for both genders). The effect of the intervention on body composition has been reported in detail (26). In brief, exercisers lost weight and body fat compared with controls both among men [−1.8 versus −0.1 kg ($P = 0.03$) and −2.7% versus +0.2% ($P < 0.001$), respectively] and women [−1.4 versus +0.7 kg ($P = 0.008$) and −1.8% versus −0.1% ($P = 0.002$), respectively]. No differences were noted for dietary intake throughout the study.

At baseline, CRP was correlated with percent body fat ($r = 0.48$, $P \leq 0.001$), BMI ($r = 0.37$, $P \leq 0.001$), and aerobic fitness ($r = -0.49$, $P \leq 0.001$), with similar results for

Table 1. Participant characteristics at baseline

	Women		Men	
	Exercisers, $n = 49$	Controls, $n = 51$	Exercisers, $n = 51$	Controls, $n = 51$
	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)
Age (y)	54.4 (7.1)	53.7 (5.6)	56.2 (6.7)	56.6 (7.6)
Race				
White	42 (86)	47 (92)	48 (94)	48 (94)
Non-White	7 (14)	4 (8)	3 (6)	3 (6)
Menopausal status				
HRT user	23 (47)	22 (43)	NA	NA
No HRT	10 (20)	11 (22)		
Premenopausal	16 (33)	18 (35)		
Height (cm)	164.0 (6.9)	165.5 (6.4)	178.4 (6.3)	179.8 (8.0)
Weight (kg)	78.0 (17.8)	77.9 (12.8)	94.8 (14.9)	97.4 (18.2)
BMI (kg/m^2)	28.9 (5.5)	28.5 (4.8)	29.7 (3.7)	30.1 (4.8)
Body fat (%)*	43.3 (7.2)	43.0 (6.8)	31.5 (6.4)	29.7 (6.0)
Total fat mass (kg)*	34.4 (13.6)	33.9 (10.4)	30.3 (9.5)	29.0 (9.5)
V_{O_2}max (mL/kg/d)	23.8 (5.1)	24.8 (4.3)	30.1 (5.9)	30.3 (6.7)
Cigarette use				
Smoker	2 (4)	1 (2)	5 (10)	4 (8)
Nonsmoker	47 (96)	50 (98)	46 (90)	47 (92)

Abbreviation: HRT, hormone replacement therapy.
* One female control, 1 male control, and 2 male exercisers were missing baseline DEXA.

Table 2. Geometric means (95% confidence intervals) for the effect of exercise on CRP: differences at baseline and after 12 mo of exercise intervention

	Baseline				P*	Follow-up				P†
	Exercisers		Controls			Exercisers		Controls		
	n	Geometric mean (95% CI)	n	Geometric mean (95% CI)		n	Geometric mean (95% CI)	n	Geometric mean (95% CI)	
Men	49	1.16 (0.92-1.46)	49	1.16 (0.87-1.55)	0.99	46	1.23 (0.95-1.60)	49	1.01 (0.77-1.33)	0.29
Women	48	2.08 (1.48-2.91)	49	2.16 (1.57-2.97)	0.87	45	1.87 (1.35-2.59)	48	2.16 (1.57-2.98)	0.65

Abbreviation: 95% CI, 95% confidence interval.
* P value for exercisers vs controls at baseline.
† P value for changes from baseline to 12 mo, among exercisers vs controls, with adjustment for baseline values.

analysis limited to either men or women (data not shown). No intervention effects were observed for CRP in men or women overall (Table 2) or when stratified by baseline BMI (Table 3), baseline CRP (data not shown), change in aerobic fitness, or change in body composition (data not shown).

Conclusion

A 12-month randomized controlled aerobic exercise intervention resulted in improved cardiorespiratory fitness in both men and women. However, this improvement did not translate into a reduction in CRP. These findings are consistent with other randomized controlled trials of exercise alone (17-25) and a recent meta-analysis (27), which included five of these studies and reported that a 12% improvement in VO_{2max} resulted in a nonsignificant 3% decrease in CRP. However, previous trials have been hampered by small sample size, use of a clinical population, which may have altered CRP levels due to the underlying medical condition (23, 24), and type and duration of aerobic exercise intervention. The current study adds to the literature by examining this question in a large number (n = 202) of healthy, sedentary middle-aged adults, using a year-long exercise trial that achieved excellent adherence.

In our study, the exercisers lost weight and had a reduction in total body fat (26). A reduction in CRP has been reported with weight loss in randomized controlled trials of very low calorie diet interventions (28, 29), gastric bypass surgery (30), and lifestyle interventions (i.e., combined diet and exercise; refs. 31, 32). However, the change in CRP may be contingent on the associated change in body weight with the interventions. In our study, the exercise groups did not experience significant weight loss (<2.0 kg over 12 months).

Nevertheless, exercise is suggested to play an important role in reducing systemic inflammation beyond simply inducing weight loss. Lower cardiorespiratory fitness (VO_{2max}) is associated with higher CRP levels in cross-sectional studies (12-16). Therefore, examining the effect of a change in VO_{2max} on CRP would provide insight into the effect of aerobic exercise on CRP levels. You et al. (33) reported a 6% improvement in absolute VO_{2max} and a reduction in CRP in a 6-month randomized controlled trial of combined hypocaloric diet and exercise versus no change with hypocaloric diet alone in 34 obese, postmenopausal women with similar reductions in body weight and body fat in both groups. However, in our study, female and male exercisers had statistically significant improvements in VO_{2max}, 10.5% and 11%, respectively, but no intervention effect on CRP was noted.

The baseline characteristics of participants may impact the effect of lifestyle interventions on CRP. Our participants fell in the ''average' risk category (1-3 mg/L, based on criteria from the American Heart Association). Reductions in CRP level with lifestyle interventions have been successful in studies of individuals with much higher baseline CRP values (i.e., >5 mg/L; refs. 32-35)

Table 3. CRP levels at baseline and 12 mo in exercise intervention and control participants, stratified by baseline BMI

	Baseline				Follow-up			
	n	Exercisers geometric mean (95% CI)	n	Controls geometric mean (95% CI)	n	Exercisers geometric mean (95% CI)	n	Controls geometric mean (95% CI)
Men								
BMI <30 kg/m^2	26	0.85 (0.63-1.14)	26	0.89 (0.61-1.30)	22	0.82 (0.62-1.08)	26	0.74 (0.54-1.01) P = 0.61*
BMI ≥30 kg/m^2	23	1.67 (1.24-2.25)	23	1.57 (1.03-2.39)	24	1.80 (1.25-2.59)	25	1.40 (0.92-2.15) P = 0.38*
Women								
BMI <30 kg/m^2	29	1.32 (0.88-1.99)	30	1.60 (1.07-2.38)	28	1.27 (0.86-1.89)	29	1.59 (1.04-2.45) P = 0.82*
BMI ≥30 kg/m^2	19	4.14 (2.68-6.39)	19	3.47 (2.20-5.47)	17	3.54 (2.33-5.38)	19	3.44 (2.29-5.16) P = 0.73*

*P value for difference in CRP changes from baseline to 12 mo in exercise intervention vs control stratified by BMI group, controlling for baseline CRP values.

or in more obese participants (i.e., BMI >30-35 kg/m^2; refs. 31, 32, 34, 35). We found no change in CRP when stratified by baseline CRP level (i.e., <3 or ≥3 mg/L) and BMI (i.e., <30 or ≥30 kg/m^2). However, we have some unpublished data to support this, inasmuch as, in another study, women with a higher BMI (>30 kg/m^2) particularly showed a reduction in CRP over 12 months following a similar intervention regimen.[5]

A limitation of this study was that it was designed to look at a number of proposed biomarkers of colon cancer risk. Therefore, individuals were recruited based on a number of baseline characteristics that did not include CRP levels. As a result, participants had low CRP levels at baseline. From the literature, it would suggest that exercise and/or weight loss may be more effective in those with higher initial CRP values. In addition, oral hormone replacement therapy has also been shown to elevate CRP levels (36). Our sample included both premenopausal and postmenopausal women, as well as hormone replacement therapy users and nonusers, with approximately half of the women in the trial using hormone replacement therapy. The use of hormone replacement therapy may have counteracted reductions in CRP level due to a lifestyle intervention.

In conclusion, a 12-month randomized controlled trial of aerobic exercise in previously sedentary adults did not alter CRP, a marker of systemic inflammation, despite resulting in a significant improvement in aerobic fitness (VO_{2max}) and a decrease in body weight and body fat. This suggests that exercise may have a greater role to play in those with higher initial levels of systemic inflammation, such as obese individuals.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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We thank Clare Abbenhardt for her assistance with sample preparation, and the study participants for their time and dedication to the project.

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