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Research Article

Cancer Prevention Research

Inflammatory Marker Changes in Postmenopausal Women after a Year-long Exercise Intervention Comparing High Versus Moderate Volumes

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Abstract

This randomized dose comparison trial examined if higher exercise volume decreased inflammatory biomarkers, associated with postmenopausal breast cancer risk, more than moderate exercise volume. The Breast Cancer and Exercise Trial in Alberta was a two-center, two-armed randomized trial in 400 inactive, healthy, postmenopausal women, aged 50 to 74 years, with a body mass index of 22 to 40 kg/m^2. Participants were randomized to high (300 minutes/week) or moderate (150 minutes/week) volumes of aerobic exercise while maintaining usual diet. Fasting blood concentrations of C-reactive protein (CRP), IL6, and TNFα were measured at baseline, 6 and 12 months. Intention-to-treat (ITT) analysis was performed using linear mixed models adjusted for baseline biomarker concentrations. ITT analyses of 386 (97%) participants showed no statistically significant group differences for changes in biomarker levels at 6 and 12 months. In addition, we did not observe any modification of this effect by baseline characteristics of participants. In *post hoc* analyses based on self-selected exercise level (measured in minutes/week), CRP decreased by 22.45% for participants who exercised >246 minutes/week (highest quintile) and increased by 0.07% for those who exercised <110 minutes/week (lowest quintile, $P_{trend} = 0.04$), adjusted for baseline covariates. When this analysis was restricted to include exercise time in the target heart rate zone only, statistically significant trends were observed for both CRP ($P < 0.01$) and IL6 ($P = 0.04$). Prescribing 300 minutes/week of moderate-to-vigorous aerobic exercise did not improve inflammatory markers compared with 150 minutes/week in postmenopausal women. Decreases in CRP were observed with higher self-selected exercise volume. *Cancer Prev Res; 9(2); 196–203. ©2015 AACR.*

Introduction

Increased levels of proinflammatory biomarkers such as C-reactive protein (CRP), IL6, and TNFα are associated with chronic diseases, such as coronary heart disease, diabetes, and, more recently, cancer (1). Intra-abdominal adiposity generally increases in women post-menopause and can contribute to increased levels of adipocytokines, such as CRP, IL6, and TNFα (2, 3). Indeed, several recent case–control studies have demonstrated an association between breast cancer risk and increased levels of inflammatory cytokines (4, 5), predominantly in obese, postmenopausal women (6, 7), although these associations have not been consistently observed (8, 9). Of these three proinflammatory cytokines, CRP is the most studied as a risk factor for breast cancer in prospective studies. A newly published meta-analysis showed a modest significant increase in risk between the highest and lowest categories of circulating CRP (10), confirming the results of a previous meta-analysis of breast cancer risk with increased levels of both CRP and IL6 (11).

CRP, IL6, and TNFα are characteristic of a low-grade chronic inflammatory state that is increased with physical inactivity or sedentary behavior (12, 13). Increased physical activity has been shown to reduce chronic, low-grade inflammation and is therefore a promising lifestyle intervention for cancer prevention (14, 15). To date, there have been four randomized controlled trials in postmenopausal women that have examined the effect of physical activity on biomarkers for cancer prevention (16–19). Of these, three have examined the impact on inflammatory biomarkers and all found significant decreases in CRP levels with an exercise intervention (20–22). In addition, several recent RCTs and non-RCTs have demonstrated a decrease in inflammatory biomarkers following an exercise intervention (23–27); however, not all of these results were independent of dietary interventions, and some studies have shown no effect (28, 29). Although there is substantial evidence supporting the role of physical activity in decreasing circulating levels of inflammatory biomarkers, the optimal dose of exercise has yet to be determined.

In our previous RCT, the Alberta Physical Activity and Breast Cancer Prevention (ALPHA) Trial, we demonstrated that a one-year aerobic exercise intervention (prescribed 225 minutes/week)

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decreased circulating CRP, IL6, and TNFα levels compared with a usual inactive lifestyles defined as less than 90 minutes per week of physical activity (22). In an exploratory analysis, we also found that increasing exercise volume was associated with statistically significant linear trends of decreasing levels of these inflammatory markers. The Breast Cancer and Exercise Trial in Alberta (BETA) was designed to investigate the exploratory dose–response findings from the ALPHA Trial further to determine the effect of different volumes (150 versus 300 minutes per week) of aerobic exercise on circulating inflammatory biomarkers. The primary outcome of this trial was changes in adiposity (30), where we observed that higher volumes of exercise were more effective in reducing total fat and other adiposity measures compared with lower volumes. The objective of this study was to determine the effect of high compared with the moderate volume exercise intervention on circulating levels of CRP, IL6, and TNFα, which were secondary outcomes in BETA.

Materials and Methods

Study population

Detailed methods of BETA have been previously described elsewhere (31). Briefly, the trial was a two-centre, two-armed, year-long randomized controlled exercise intervention trial in 400 healthy, postmenopausal women conducted from 2010 to 2013. The study protocol was approved by the Alberta Cancer Research Ethics Committee, the Conjoint Health Research Ethics Board of the University of Calgary, and the Health Research Ethics Board of the University of Alberta. Eligibility criteria included (i) a resident of Calgary or Edmonton, (ii) 50 to 74 years of age, (iii) postmenopausal, (iv) no hormone replacement therapy within the 12 months prior to enrollment, (v) body mass index (BMI) from 22 to 40 kg/m^2, (vi) drinkers of $\leq$14 alcoholic drinks per week, (vii) nonsmoker, (viii) inactive, (ix) able to do unrestricted or progressive physical activity as assessed by physician screening, (x) levels in the normal ranges of cholesterol, fasting blood glucose (<7 mmol/L), thyroid stimulating hormone, and alanine aminotransferase, (xi) cancer-free, and (xii) not on a weight loss program or planning to commence one. Inactivity was defined as <90 minutes per week of exercise or if between 90 and 120 minutes per week, having a VO_{2max} <34.5 mL/kg/minute as assessed by a submaximal fitness test.

Exercise intervention

Women were randomized within each centre to either a moderate or high volume aerobic exercise intervention of 150 minutes per week ($n = 200$) or 300 minutes per week ($n = 200$), respectively, based on the physical activity guidelines from Health Canada (32, 33) and the American Cancer Society (34, 35). Exercise sessions took place five times per week at 65% to 75% heart rate reserve, with three days weekly supervised by certified exercise trainers and two days of home-based unsupervised sessions. Exercise adherence was monitored using weekly exercise logs, and usual diet was maintained. Heart rate monitors were worn to ensure that at least 50% of exercise sessions were completed within the target heart rate zone. Methods to ensure adherence to exercise interventions have been previously described (17, 31).

Biomarker assays

Blood samples were collected from each participant at baseline (60 mL), 6 and 12 months (40 mL) postrandomization. Blood draws were performed after a minimum 10-hour fast and complete abstinence from exercise and alcohol for 24 hours. High-sensitivity CRP assays were conducted at the Reproductive Endocrine Research Laboratory (University of Southern California, Los Angeles, CA). Hs-CRP (henceforth referred to as CRP) was quantified using solid-phase chemiluminescent immunometric assay on an Immulite 2000 analyzer (Siemens Healthcare Diagnostics Inc.), which had a sensitivity of less than 0.01 mg/dL and an intrabatch coefficient of variation (CV) of 8% and an interbatch CV of 9%. The remaining inflammatory biomarkers of interest were assayed at Eve Technologies using the Bio-Plex 200 system (Bio-Rad Laboratories, Inc.). The cytokine assay consisted of IL6 and TNFα, with sensitivities ranging from 0.05 to 0.48 pg/mL. The intrabatch CV was 9% for both IL6 and TNFα, and the interbatch CV was 14% for IL6 and 11% for TNFα. Individual analyte values and other assay details are available through Eve Technologies.

Statistical analysis

For all analyses, the natural logarithm transformation was applied to inflammatory biomarker levels because of the skewed distributions of these measurements, and results are presented after back-transformation. To account for possible acute inflammation at the time of blood sampling, participants with extremely high inflammatory biomarker concentrations were excluded from the analyses: the threshold concentration for exclusion was 30 mg/L for CRP, thereby excluding four participants, and 20 pg/mL for IL6, excluding two participants. There were no excluded participants for the TNFα analysis as no extreme outliers were identified. In addition, participants with missing blood samples at any time point were removed from the analysis ($n = 2$).

An intention-to-treat (ITT) analysis using linear mixed models was conducted to determine the intervention effect on inflammatory biomarker levels measured at 6 and 12 months between moderate and high volume exercise groups. Models for each biomarker were adjusted for baseline values of the biomarker and included the main effects of intervention and time, their interaction term, and a random intercept of subjects accounting for within-subject correlation of each biomarker. The models were used to determine the treatment effect ratio (TER) for the intervention effect, which is the ratio of adjusted geometric means of the biomarker level for the high volume over the moderate volume exercise group. Note that a TER that is greater than 1.0 indicates that the high volume exercise group has a higher adjusted geometric mean of the biomarker level (i.e., stronger inflammatory state) than the moderate volume exercise group. Potential confounding was assessed by examining the change in the β-coefficient with and without the potential confounder in the model. We confirmed that baseline differences between the two randomization groups in dietary intake, cholesterol levels, arthritis, and use of nonsteroidal anti-inflammatory drugs did not confound our inference on intervention effects.

Potential moderation (effect modification) of the intervention main effect was hypothesized *a priori*, as previously done in other analyses from the ALPHA Trial (22, 36). To assess moderation, the statistical significance of the interaction term ($P_{heterogeneity}$) between intervention group assignment and each proposed moderator at baseline was evaluated. Moderation was determined using the same models as in the ITT analysis with the addition of the hypothesized moderator. Potential moderators were assessed as continuous variables, and the models included baseline levels

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Table 1. Baseline characteristics of study participants, BETA, Canada, 2010–2013, $n = 400$

Baseline characteristic	Moderate volume exercisers ($n = 200$) Mean ± SD	High volume exercisers ($n = 200$) Mean ± SD
Age (y)	59.5 ± 5.1	59.4 ± 4.8
Body composition measurements		
BMI (kg/m^2)	29.4 ± 4.4	29.1 ± 4.4
Percent body fat	40.7 ± 5.9	40.5 ± 5.8
	n (%)	*n* (%)
Regular NSAID user	18 (9.0)	14 (7.0)
Regular statin user	25 (12.5)	21 (10.5)
Biomarkers	**Median (IQR)**	**Median (IQR)**
CRP (mg/L)	1.90 (0.95–4.27)	1.56 (0.86–3.47)
IL6 (pg/mL)	0.40 (0.25–0.71)	0.41 (0.28–0.69)
TNFα (pg/mL)	3.02 (2.15–3.78)	3.16 (2.12–3.96)

Abbreviations: IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug.

of fitness, age, past-year recreational physical activity, BMI, body fat percentage, CRP, IL6, and TNFα. In interpreting the relevance of the findings of the moderation analyses, intervention effects were further estimated between subgroups of each baseline characteristic that was deemed to be of interest *a priori*. Subgroups were divided at the median for each variable, with the exception of two variables. BMI was divided into clinically meaningful categories of normal weight (<25 kg/m^2), overweight (≥25 to <30 kg/m^2), and obese (≥30 kg/m^2). Baseline CRP was dichotomized using criteria from Pearson and colleagues (37), with which risk of cardiovascular disease and potentially cancer can be predicted.

In addition to the ITT analysis, an analysis by self-selected exercise volume was also evaluated. Participants were divided on the basis of quintiles of mean minutes of exercise completed per week, as well as by the mean minutes per week spent in their target heart rate zone. TERs were calculated within each exercise volume quintile. A linear trend test was used to test for a linear association between exercise volume quintile and change in inflammatory biomarker from baseline to 12 months, based on a linear model predicting change at 12 months from baseline, where volume quintiles were treated as a continuous variable. All analyses were conducted using SAS software (version 9.2; SAS Institute).

Results

Flow of participants through BETA has been reported elsewhere (30). In brief, there were 863 women who met the inclusion criteria. Of these, 400 women participated in the study and were randomized to either high or moderate volume exercise groups (Supplementary Fig. S1). Overall, 14 women did not complete the study, leaving a study population of 195 women in the high volume exercise group and 191 women in the moderate group (97% retention rate). Blood samples at 12 months postrandomization were obtained for each of these women and were included in the statistical analyses. Baseline characteristics were very similar between randomization groups (Table 1). There were no statistically significant differences between groups, with the exception of baseline CRP values, which were slightly higher in the moderate volume exercise group ($P = 0.04$).

In the ITT analysis, there were no significant differences between exercise intervention groups for all three biomarkers (Table 2). In terms of the intervention effect, the TERs for all three biomarkers were all greater than or equal to the null value of 1.0, although not statistically significantly so, indicating that changes favored the moderate volume exercise intervention compared with the high volume exercise intervention. No confounders were identified in our assessment for potential confounding based on the *a priori* criteria described in the Materials and Methods section.

When assessing moderation, we did not identify any significant moderators, although we did observe trends with CRP and TNFα when stratifying by physical fitness, age, BMI, and body fat percentage (Table 3). In general, we observed that TERs were higher and at times approaching statistical significance in participants with higher BMI (>30 kg/m^2), body fat percentage (>40.3%), and age at baseline (>60 years), as well as lower physical fitness (VO_{2max} < 27.2 mL/kg/minute) at baseline.

Finally, we performed an analysis stratified by self-selected exercise volume of all study participants who completed the trial, based on quintiles of mean minutes per week of exercise (Table 4), as well as mean minutes per week of exercise in their target heart rate zones (Table 5). In the analysis of mean minutes per week, we observed the highest percent changes for CRP and IL6 in the third and fifth quintiles of exercise volume; where CRP differences were statistically significantly different than the lowest adherence quintile. The highest percent changes for TNFα occurred in the first and

Table 2. ITT analysis of inflammatory biomarker concentrations for high volume and moderate volume exercisers in the BETA at 6 and 12 months from baseline

	Baseline Geometric mean (95% CI)[a]	6 months Geometric mean (95% CI)[a]	12 months Geometric mean (95% CI)[a]	*n*	Percent change from baseline to 12 months	TER of high/moderate (95% CI)[b]	Between-group *P*
CRP (mg/L)							
High	1.63 (1.41–1.88)	1.69 (1.46–1.95)	1.46 (1.26–1.68)	192	−10.56	1.07 (0.97–1.19)	0.15
Moderate	2.00 (1.73–2.31)	1.76 (1.54–2.02)	1.66 (1.45–1.89)	188	−17.16		
IL6 (pg/mL)							
High	0.43 (0.38–0.47)	0.43 (0.39–0.48)	0.40 (0.36–0.45)	191	−6.19	1.04 (0.96–1.13)	0.36
Moderate	0.43 (0.39–0.48)	0.41 (0.37–0.45)	0.41 (0.37–0.45)	190	−6.35		
TNFα (pg/mL)							
High	2.84 (2.65–3.04)	2.80 (2.62–3.00)	2.78 (2.60–2.98)	193	−1.91	1.00 (0.95–1.05)	0.96
Moderate	2.70 (2.51–2.90)	2.69 (2.50–2.90)	2.66 (2.47–2.87)	191	−1.46		

[a]Blood samples from $n = 386$ participants were obtained. Participants with extremely high inflammatory biomarker values were excluded from the analysis. The threshold for removal and number of participants removed for each biomarker were CRP: 30 mg/L, 4 participants; IL6: 20 pg/mL, 2 participants; TNFα: no extreme values, 0 participants. Participants missing a blood sample at any time point were also removed.

[b]The TER was calculated on the basis of a linear mixed model for each biomarker and adjusted for time and baseline value of the biomarker. The TER represents the adjusted ratio of geometric means for the high exercise group over the moderate exercise group. A TER of less than 1.0 indicates lower inflammatory marker levels in the high exercise group relative to the moderate exercise group at 6 and 12 months; a TER greater than 1.0 indicates higher inflammatory marker levels in the high exercise group; and a ratio of 1.0 indicates no difference between exercise groups.

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Table 3. Exercise intervention effects on inflammatory biomarkers, stratified by potential moderators in the BETA, 2010–2013

Potential moderator[a]	CRP[b]		IL6[b]		TNFα[b]	
Baseline level	***n*[c]**	**TER[d]**	***n*[c]**	**TER[d]**	***n*[c]**	**TER[d]**
Physical fitness (VO_{2max})						
<27.2 mL/kg/min	92/96	1.13 (1.00, 1.28)	92/96	1.11 (0.99, 1.24)	93/97	1.01 (0.94, 1.09)
≥27.2	96/96	1.03 (0.88, 1.19)	98/95	0.98 (0.86, 1.11)	98/96	0.99 (0.93, 1.05)
		$P^e = 0.41$		$P^e = 0.11$		$P^e = 0.99$
Age, y						
≤60	108/120	1.04 (0.92, 1.18)	108/119	1.01 (0.91, 1.12)	108/120	0.96 (0.91, 1.01)
>60	80/72	1.11 (0.94, 1.31)	82/72	1.10 (0.96, 1.27)	83/73	1.05 (0.97, 1.15)
		$P^e = 0.23$		$P^e = 0.22$		$P^e = 0.16$
Past-year recreational activity						
<5.7 MET-h/wk	97/93	1.03 (0.90, 1.18)	99/92	0.98 (0.88, 1.11)	99/93	0.98 (0.91, 1.06)
≥5.7	91/99	1.12 (0.97, 1.29)	91/99	1.11 (0.98, 1.25)	92/100	1.02 (0.96, 1.08)
		$P^e = 0.40$		$P^e = 0.84$		$P^e = 0.77$
BMI						
≤25 kg/m^2	38/41	1.00 (0.81, 1.23)	38/40	0.97 (0.78, 1.21)	38/41	0.98 (0.89, 1.08)
>25–≤30	76/77	1.00 (0.85, 1.18)	77/78	1.03 (0.90, 1.18)	78/78	0.98 (0.92, 1.05)
>30	102/94	1.17 (1.00, 1.36)	92/93	1.09 (0.97, 1.22)	89/102	1.03 (0.94, 1.13)
		$P^e = 0.19$		$P^e = 0.43$		$P^e = 0.28$
Body fat percentage						
<40.3%	93/96	1.01 (0.88, 1.17)	94/95	1.01 (0.88, 1.16)	95/96	0.99 (0.94, 1.05)
≥40.3	95/96	1.13 (1.00, 1.29)	96/96	1.07 (0.96, 1.19)	96/97	1.01 (0.94, 1.09)
		$P^e = 0.60$		$P^e = 0.97$		$P^e = 0.38$
CRP						
<3.0 mg/L	86/98	1.03 (0.90, 1.18)				
≥3.0	102/94	1.11 (0.96, 1.29)				
		$P^e = 0.36$				
IL6						
<0.4 pg/mL			98/98	1.03 (0.93, 1.14)		
≥0.4			92/93	1.06 (0.93, 1.21)		
				$P^e = 0.34$		
TNFα						
<1.4 pg/mL					102/91	1.01 (0.93, 1.10)
≥1.4					89/102	0.99 (0.94, 1.04)
						$P^e = 0.08$

Abbreviation: MET, metabolic equivalent of task.

[a]Level of potential moderator at baseline.

[b]Blood samples from $n = 386$ participants were obtained. Participants with extremely high inflammatory biomarker values were excluded from the analysis. The threshold for removal and number of participants removed for each biomarker were CRP: 30 mg/L, 4 participants, IL6: 20 pg/mL, 2 participants, TNFα: no extreme values, 0 participants. Participants missing a blood sample at any time point were also removed.

[c]Number of high volume exercisers/number of moderate volume exercisers.

[d]The TER represents the adjusted ratio of geometric means for the high exercise group over the moderate exercise group. A TER of less than 1.0 indicates lower inflammatory marker levels in the high exercise group relative to the moderate exercise group at 6 and 12 months; a TER greater than 1.0 indicates higher inflammatory marker levels in the high exercise group; and a ratio of 1.0 indicates no difference between exercise groups.

[e]*P* refers to the statistical significance of the interaction term between the high volume exercise group and the potential moderator. All moderators were treated as continuous variables for this calculation.

third quintiles. Overall, there is a linear trend in mean minutes per week and the reduction in CRP levels ($P = 0.04$), indicating a stronger association with increased exercise time. This trend was not found for IL6 or TNFα.

When considering the amount of time spent in the target heart rate zone, an even stronger trend was found across all quintiles of exercise time and reduction of CRP levels ($P_{trend} < 0.01$). A linear trend was also observed for the reduction in IL6 levels with increased exercise time spent in the target heart rate zone ($P_{trend} = 0.04$), despite non-statistically significant differences between the change in the four higher quintiles compared with the lowest, referent quintile. No trends or differences between exercise volume quintiles were observed for TNFα.

Discussion

In this year-long randomized dose comparison trial of 300 versus 150 minutes per week of aerobic exercise in postmenopausal women, we found no evidence of differential effects on inflammatory biomarkers related to breast cancer risk. Effect modification was not found by physical fitness (measured by VO_{2max}), age, past year recreational activity, BMI, body fat percentage, or baseline levels of CRP, IL6, and TNFα. In secondary analyses based on self-selected exercise volume levels, we found that there was a linear trend associated with increased reductions in CRP levels with increased exercise time in the target heart rate zone.

While baseline characteristics between randomization groups were similar, we observed a significant difference in baseline CRP values. Specifically, baseline CRP levels in both groups were low, overall, with median values of 1.90 mg/L in the moderate exercise group and 1.56 mg/L in the high group. These levels are expected for a healthy population. CRP values between 3 and 10 mg/L are considered as low-grade inflammation and levels above 10 mg/L are considered clinically inflammatory states (38, 39).

Interestingly, although we did not observe significant differences between groups in our ITT analysis, the point estimates of

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Table 4. Inflammatory biomarker concentrations at baseline and 12 months in controls and exercisers, stratified by adherence level in the BETA[a]

	Baseline Geometric mean (95% CI)[b]	12 months Geometric mean (95% CI)[b]	*n*	Ratio 12 months/ baseline (95% CI)[c]	Percent change[d]	*P*[e]	P_{trend}[f]
CRP (mg/L)							
<110 min/wk	2.14 (1.68–2.73)	2.06 (1.63–2.61)	76	1.00 (0.87–1.15)	0.07	Ref	0.04
110–135 min/wk	1.71 (1.38–2.13)	1.55 (1.26–1.92)	76	0.90 (0.78–1.03)	−10.37	0.26	
135–152 min/wk	2.12 (1.70–2.65)	1.53 (1.25–1.89)	77	0.76 (0.66–0.87)	−24.29	<0.01	
152–246 min/wk	1.60 (1.27–2.02)	1.55 (1.23–1.95)	77	0.93 (0.81–1.06)	−7.19	0.44	
>246 min/wk	1.50 (1.19–1.89)	1.22 (0.99–1.49)	77	0.79 (0.69–0.90)	−21.45	0.01	
IL6 (pg/mL)							
<110 min/wk	0.46 (0.39–0.54)	0.44 (0.38–0.51)	77	0.98 (0.87–1.10)	−2.42	Ref	0.24
110–135 min/wk	0.40 (0.34–0.48)	0.39 (0.32–0.48)	76	0.96 (0.86–1.08)	−3.71	0.87	
135–152 min/wk	0.45 (0.38–0.52)	0.41 (0.35–0.48)	77	0.91 (0.81–1.03)	−8.71	0.43	
152–246 min/wk	0.41 (0.35–0.48)	0.39 (0.33–0.47)	76	0.94 (0.84–1.06)	−5.52	0.70	
>246 min/wk	0.44 (0.37–0.53)	0.39 (0.32–0.47)	77	0.88 (0.78–0.99)	−11.80	0.23	
TNFα (pg/mL)							
<110 min/wk	2.68 (2.36–3.06)	2.58 (2.26–2.95)	77	0.96 (0.89–1.02)	−4.40	Ref	0.44
110–135 min/wk	2.94 (2.66–3.25)	2.89 (2.60–3.21)	77	0.99 (0.93–1.06)	−0.75	0.43	
135–152 min/wk	2.75 (2.47–3.07)	2.68 (2.40–2.98)	77	0.97 (0.91–1.04)	−2.90	0.74	
152–246 min/wk	2.67 (2.37–3.02)	2.70 (2.43–3.00)	77	1.01 (0.94–1.07)	0.54	0.29	
>246 min/wk	2.82 (2.54–3.13)	2.78 (2.48–3.12)	78	0.99 (0.93–1.06)	−1.06	0.47	

[a]Adherence was calculated as the mean minutes of exercise per week over 52 weeks of the study.
[b]Blood samples from $n = 386$ participants were obtained. Participants with extremely high inflammatory biomarker values were excluded from the analysis. The threshold for removal and number of participants removed for each biomarker were: CRP: 30 mg/L, 4 participants, IL6: 20 pg/mL, 2 participants, TNFα: no extreme values, 0 participants. Participants missing a blood sample at any time point were also removed.
[c]Ratio of geometric means at 12 months to geometric means at baseline, adjusted for the baseline inflammatory marker level, age, VO_{2max}, and BMI.
[d]Percentage change in adherence group mean of each inflammatory biomarker at 12 months from baseline, adjusted for the baseline inflammatory marker level, age, VO_{2max}, and BMI.
[e]*P* tests difference in changes in inflammatory biomarker levels between the lowest quintile adherence group and the specified adherence group, adjusted for the baseline value of the inflammatory biomarker, age, VO_{2max}, and BMI. A unified model, where the adherence group was treated as a categorical variable, was used to calculate the *P* values, which correspond to β-coefficients for the other quintile groups, using the lowest quintile group as the referent group.
[f]*P* for trend represents a test of linear association between adherence quintile and change in inflammatory marker from baseline to 12 months. This test is based on a linear model predicting change at 12 months from baseline, with predictors: baseline inflammatory marker, age, VO_{2max}, BMI, and adherence quintile, where quintiles are numbered 1–5, and these values are treated as a continuous variable.

the TERs suggested that the moderate volume exercise program may be more effective in reducing levels of CRP, IL6 and, TNFα. However, there were some differences in baseline levels of inflammatory biomarkers between randomization groups, and, in particular the high volume group had significantly lower CRP values at baseline. Although it is possible that a lower volume of exercise could be more effective in reducing inflammatory biomarkers, it is also possible a minimum threshold of CRP levels may exist in postmenopausal women, thereby making it more difficult for participants in the high volume group with lower CRP levels at baseline to reduce CRP levels further.

There has been one previous study, known as the Dose-Response to Exercise in postmenopausal Women (DREW) that examined the effect of physical activity dose response on inflammatory biomarkers in postmenopausal women for cardiopulmonary health. The DREW trial found no direct effect of any amount of exercise on levels of CRP, IL6, of TNFα (40–42). However, three previous RCTs of exercise interventions in postmenopausal women found that an exercise or exercise and diet intervention significantly reduced levels of CRP compared with nonexercise controls: this effect was predominantly mediated by changes in adiposity (20–22). Baseline BMI was a moderator in one study as the effectiveness of the exercise intervention was only evident in obese women (BMI > 30 kg/m^2) at baseline (21). Adipose tissue has been well-studied as a source of proinflammatory cytokines, thus larger decreases in adiposity can lead to decreased levels of circulating cytokines (43, 44).

In our analysis of potential moderation in this study, we did not find any statistically significant interactions between the intervention effects and the potential moderators examined. There were, however, trends in the data, as we found that the moderate volume exercise group had greater decreases in CRP and IL6 when the analysis was restricted to those participants who were, at baseline, below the median physical fitness ($VO_{2max} < 27.2$ mL/kg/minute), above the median body fat percentage (≥40.3%), older than 60 years of age, or obese (BMI > 30 kg/m^2). It is also noteworthy that these subgroups of women started with higher baseline values of CRP and IL6, regardless of randomization group (Supplementary Figs. S2 and S3), indicating that women who are older, less fit, or more obese have higher levels of chronic inflammation and may benefit more from a moderate volume exercise intervention compared with a high volume. In terms of treatment effects, we speculate that the high volume exercise prescription in older, less physically fit, or more obese women could potentially be causing more inflammation, thus making the moderate volume exercise prescription more effective in reducing levels of CRP and IL6. Analyses by subgroups of potential moderators were not performed for inflammatory markers in the DREW study (40–42), and thus there are no similar studies with which to compare our results.

In considering the overall effect of exercise time, there was indeed a significant trend of decreasing CRP levels with increasing exercise time. In these analyses stratified by self-selected exercise volume level, we observed a mild bimodal effect, with the strongest percent decreases in CRP values in the third and fifth quintiles of exercise time. The reason for this bimodal pattern is unclear. Our secondary analyses also revealed that the amount of time spent in the target heart rate zone is potentially more

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Table 5. Inflammatory biomarker concentrations at baseline and 12 months in controls and exercisers, stratified by adherence level based on time in heart rate zone in the BETA[a]

	Baseline Geometric mean (95% CI)[b]	12 months Geometric mean (95% CI)[b]	*n*	Ratio 12 months/ baseline (95% CI)[c]	Percent change[d]	*P*[e]	P_{trend}[f]
CRP (mg/L)							
<57 min/wk	2.29 (1.79–2.92)	2.30 (1.83–2.89)	76	1.07 (0.93–1.22)	6.60	Ref	0.01
57–86 min/wk	1.78 (1.46–2.18)	1.42 (1.15–1.75)	77	0.79 (0.69–0.90)	−21.03	<0.01	
86–111 min/wk	1.75 (1.41–2.17)	1.61 (1.33–1.96)	76	0.92 (0.80–1.05)	−8.46	0.12	
111–143 min/wk	1.78 (1.40–2.27)	1.51 (1.20–1.88)	76	0.84 (0.73–0.96)	−16.09	0.01	
>143 min/wk	1.48 (1.16–1.88)	1.18 (0.95–1.46)	78	0.77 (0.67–0.88)	−23.27	<0.01	
IL6 (pg/mL)							
<57 min/wk	0.47 (0.39–0.56)	0.46 (0.40–0.53)	77	1.00 (0.89–1.12)	−0.17	Ref	0.04
57–86 min/wk	0.42 (0.36–0.49)	0.40 (0.33–0.49)	78	0.96 (0.85–1.07)	−4.17	0.62	
86–111 min/wk	0.41 (0.34–0.49)	0.42 (0.35–0.51)	75	1.00 (0.89–1.13)	0.46	0.94	
111–143 min/wk	0.46 (0.40–0.54)	0.39 (0.33–0.45)	76	0.85 (0.76–0.96)	−14.76	0.06	
>143 min/wk	0.40 (0.34–0.48)	0.36 (0.29–0.43)	77	0.87 (0.78–0.98)	−12.77	0.11	
TNFα (pg/mL)							
<57 min/wk	2.81 (2.46–3.21)	2.76 (2.43–3.14)	77	0.98 (0.92–1.05)	−1.60	Ref	0.93
57–86 min/wk	2.66 (2.39–2.96)	2.60 (2.32–2.91)	78	0.97 (0.91–1.04)	−2.85	0.79	
86–111 min/wk	2.62 (2.34–2.95)	2.63 (2.36–2.93)	76	0.99 (0.93–1.06)	−0.85	0.88	
111–143 min/wk	3.00 (2.71–3.33)	2.92 (2.61–3.26)	77	0.99 (0.92–1.05)	−1.41	0.97	
>143 min/wk	2.78 (2.50–3.08)	2.73 (2.45–3.04)	78	0.98 (0.92–1.05)	−1.88	0.95	

[a]Mean time in zone was calculated as the mean minutes of exercise time in the target heart rate zone over weeks 1–52 of the study.
[b]Blood samples from $n = 386$ participants were obtained. Participants with extremely high inflammatory biomarker values were excluded from the analysis. The threshold for removal and number of participants removed for each biomarker were CRP: 30 mg/L, 4 participants, IL6: 20 pg/mL, 2 participants, TNFα: no extreme values, 0 participants. Participants missing a blood sample at any time point were also removed.
[c]Ratio of geometric means at 12 months to geometric means at baseline, adjusted for the baseline inflammatory marker level, age, VO_{2max}, and BMI.
[d]Percentage change in adherence group mean of each inflammatory biomarker at 12 months from baseline, adjusted for the baseline inflammatory marker level, age, VO_{2max}, and BMI.
[e]*P* tests difference in changes in inflammatory biomarker levels between the lowest quintile adherence group and the specified adherence group, adjusted for the baseline value of the inflammatory biomarker, age, VO_{2max}, and BMI. A unified model, where the adherence group was treated as a categorical variable, was used to calculate the *P* values, which correspond to β-coefficients for the other quintile groups, using the lowest quintile group as the referent group.
[f]*P* for trend represents a test of linear association between adherence quintile and change in inflammatory marker from baseline to 12 months. This test is based on a linear model predicting change at 12 months from baseline, with predictors: baseline inflammatory marker, age, VO_{2max}, BMI, and adherence quintile, where quintiles are numbered 1–5, and these values are treated as a continuous variable.

important than the total exercise time in inducing changes in inflammatory biomarkers, as we observed an even stronger association between exercise time and CRP levels and also observed a significant trend effect with IL6 in these analyses than in the analyses of total exercise time. Hence, exercise intensity, in addition to dose, is relevant when determining the impact of physical activity on inflammatory biomarkers in relation to breast cancer prevention. Limited research has examined the role of exercise intensity on changes in inflammatory biomarkers, although some observational studies have found that higher exercise intensity is associated with reduced levels of CRP (45–48), IL6 (45), and TNFα (45). One RCT in young adults found that higher intensity exercise reduced circulating TNFα levels more effectively than lower doses (49); however, this finding has not been consistently demonstrated in RCTs for TNFα or other inflammatory biomarkers (50, 51). Results from our study suggest that longer periods of vigorous exercise could be more beneficial in reducing chronic inflammation, although more research in this area is necessary to corroborate this finding.

In this study of inflammatory biomarkers, the strongest associations of exercise were with CRP which is known to be a very sensitive and objective systemic marker for inflammation and the acute phase response to tissue damage, infection, and malignant neoplasia, where concentrations of circulating CRP can increase up to 10,000 fold in response to stimulus (52). It is also one of the most studied biomarkers, particularly with respect to cardiovascular disease (53–55). Recent studies have shown the potential of IL6 as a myokine (a cytokine secreted from skeletal muscle that can have anti-inflammatory effects), despite IL6 being known as a proinflammatory cytokine when secreted from other tissues or in the blood. As a myokine, an increase in circulating IL6 can trigger an increase in other anti-inflammatory cytokines such as IL10 and IL1 receptor antagonist, leading to an overall anti-inflammatory effect (56). Although this increase in IL6 has been observed predominantly after an acute bout of higher intensity exercise, the anti-inflammatory effect of IL6 could be a possible mechanism by which physical activity reduces chronic inflammation. This situation could possibly explain why anti-inflammatory effects were strongest in those with the highest levels of high intensity exercise in our analysis of time in target heart rate zone.

To our knowledge, BETA is the first randomized controlled trial to examine the impact of aerobic exercise volume on biomarkers for breast cancer prevention. Overall, we did not observe significant differences between the high and moderate volume exercise groups. In secondary analyses based on self-selected exercise volume, we found that there was a stronger reduction of CRP and IL6 with increased exercise time. Further research based on exercise intensity and exercise volume is necessary to support our conclusions.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.M. Friedenreich, F.Z. Stanczyk, K.S. Courneya
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.M. Friedenreich, R. O'Reilly, E. Shaw, F.Z. Stanczyk, Y. Yasui, D.R. Brenner, K.S. Courneya
Writing, review, and/or revision of the manuscript: C.M. Friedenreich, R. O'Reilly, E. Shaw, F.Z. Stanczyk, Y. Yasui, D.R. Brenner, K.S. Courneya
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Inflammatory Marker Changes in Postmenopausal Women after a Year-long Exercise Intervention Comparing High Versus Moderate Volumes

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