No Effect of Exercise on Colon Mucosal Prostaglandin Concentrations: A 12-Month Randomized Controlled Trial

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Abstract

Background: **Epidemiologic studies provide evidence that exercise is associated with reduced risk of colon cancer. Exercise may exert protective effects on the colon by influencing prostaglandin production. We hypothesized that an exercise intervention would decrease prostaglandin E_2 concentrations and increase prostaglandin $F_{2\alpha}$ in colon biopsies compared with controls.**

Methods: **A 12-month randomized controlled trial testing the effects of exercise on colon mucosal prostaglandin concentrations was conducted in men (n = 95) and women (n = 89). The exercise intervention included moderate-to-vigorous aerobic activity, 60 min/d, 6 days/wk versus controls. Prostaglandin E_2 and $F_{2\alpha}$ concentrations were measured in colon biopsies using an enzyme-linked immunoassay at baseline and at 12 months to assess changes in mean concentration for each group.**

Results: **Baseline colon prostaglandin E_2 and $F_{2\alpha}$ concentrations were not correlated with age, race, education, family history of colon cancer, previous polyps, body size, diet, smoking, nonsteroidal anti-inflammatory drug use, metabolic factors, or sex hormone levels. For both men and women, the exercise and control groups showed no change in mean prostaglandin E_2 or $F_{2\alpha}$ between the baseline and 12-month biopsies. There was no difference in mean prostaglandin concentrations between exercisers and controls when exercisers were grouped by level of intervention adherence. Results were not modified by baseline age, body mass index, percentage of body fat, nonsteroidal antiinflammatory drug use, history of adenomatous polyps, or family history of colon cancer.**

Conclusion: **A 12-month moderate-to-vigorous intensity aerobic exercise intervention did not result in significant changes in colon mucosal prostaglandin concentrations.** (Cancer Epidemiol Biomarkers Prev 2007;16(11):2351–6)

Introduction

Exercise has been associated with a reduced risk of colon cancer in many epidemiologic studies (1, 2), but the biological basis for this association is not well understood (3). One possibility is that exercise reduces risk by modifying prostaglandin production in the colonic mucosa (4).

Prostaglandins play a role in inflammation, blood clotting, immune responses, and other important physiologic processes (5). In laboratory studies, prostaglandin E_2 promotes the development of colon cancer by increasing the proliferation of human colonic cells, decreasing colonic motility, and decreasing the rate of apoptosis; prostaglandin $F_{2\alpha}$ has opposite effects (6). Studies examining normal human colon tissue have shown increased prostaglandin E_2 concentrations in patients with adenomatous polyps or colon cancer compared with controls (7). The relationship between prostaglandins and colon cancer is also supported by studies that show reduced risk of colon neoplasia with aspirin and other nonsteroidal antiinflammatory drugs (NSAID) which inhibit cyclooxygenase (COX-1 and COX-2), thereby inhibiting prostaglandin production (5, 8).

Exercise has been hypothesized to inhibit prostaglandin E_2 synthesis and stimulate prostaglandin $F_{2\alpha}$ production (3), but few studies have investigated the effect of physical activity on colon (9) or serum (10, 11) prostaglandin concentrations. The objective of this study was to evaluate the effects of a 1-year moderate intensity aerobic exercise intervention versus control program in

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men and women on colon (sigmoid) mucosal prostaglandin concentrations.

Materials and Methods

Participants. The methods for this exercise intervention study have been described previously (12, 13). Briefly, participants were men and women, ages 40 to 75 years, who had a colonoscopy within the previous 3 years so that their recent history of polyps was known. Eligibility criteria included being sedentary; no uncontrolled hypertension, cardiac, or pulmonary disease; consuming less than two alcoholic drinks per day; no history of inflammatory bowel disease or any familial colorectal cancer syndrome; and normal blood count and blood chemistry. Furthermore, persons were excluded if currently using enemas, anticoagulants, corticosteroids, or excessive amounts of laxatives (>3/wk). Use of NSAIDs was allowed up to twice per week if the person was able to safely discontinue use for 2 weeks before and after each sigmoidoscopy. Informed consent was obtained following the requirements of the Fred Hutchinson Cancer Research Center Institutional Review Board.

Randomization and Blinding. Participants were randomized with equal probabilities to the exercise or control group (referred to respectively in this article as ''exercisers'' and ''controls''). Randomization was blocked on sex, use of NSAIDs (regular use of more than twice/wk versus less than twice/wk), current smoking status (yes versus no), and among women, on menopausal status (premenopausal or perimenopausal versus postmenopausal) and current use of hormone therapy (yes versus no). Staff and scientists involved in end point determinations were blinded to participant randomization status, and to prerandomization versus postrandomization status of samples. Randomization was done by the study coordinator via a computerized program, developed by the study biostatistician, that incorporated the blocking factors.

Baseline and Follow-up Measures in All Participants

Prostaglandin Assessment. Colonic epithelial cell biopsies were collected during a prerandomization visit and at 12 months post-study using flexible sigmoidoscopy. Prior to flexible sigmoidoscopy, participants self-administered up to five saline enemas, starting 1.5 h prior to the procedure. If the preparation was insufficient, an additional saline enema was administered at the time of sigmoidoscopy. During each sigmoidoscopy, 1-mm-thick biopsies were collected in a standard manner by experienced physicians using jumbo biopsy forceps (Olympus FB-50U1-1; Olympus America, Inc.). Fourteen biopsies were collected from each participant, of which one biopsy collected from the sigmoid colon (30-35 cm from the level of the external anal aperture), was processed for the prostaglandin analysis.

Upon procurement, biopsies were immediately placed in a solution of 5 μg of indomethacin to 1 mL of the sterile double-distilled water and then were snap-frozen in liquid nitrogen for transfer to a −80°C freezer. All analyses were done in batches of 10 study samples and 2 quality control samples. Within each batch, study participant samples from baseline and follow-up were included. Also, control and treatment groups were distributed within each batch, and the laboratory personnel and investigators were blind to participant identification and treatment using a code number maintained by a statistician.

After brief thawing, each biopsy was quickly weighed and placed into a siliconized tissue grinder containing ice-cold 0.5 mL (50 mmol/L) acetate buffer (pH 3.0) and 2.5 μg/mL of indomethacin. Tissue was homogenized by hand for ~2 min until there were no solid pieces of tissue visible. The homogenate was transferred into a 15 mL polypropylene tube and the tissue grinder was rinsed with another 0.5 mL of cold acetate buffer for a total homogenate of 1 mL. A 50-μL aliquot was taken for the protein assay. Next, 600 μL of 100% ethanol was added to the remaining homogenate and mixed well by vortexing. After 5 min on ice, [^{3}H]prostaglandin $F_{2\alpha}$ master mix was added to each sample to test for the recovery of both prostaglandins from the solid phase extraction as described by Finley et al. (14).

Next, samples were centrifuged at 4°C, clear supernatant was transferred to a clean 15 mL polypropylene tube and volume was adjusted to 4 mL with ice-cold 0.5 mmol/L acetate buffer (pH 3.0) for an ethanol concentration of 15%. Solid phase extraction C18 columns (100 mg; Alltech) were activated with 6 mL of 100% ethanol followed by 6 mL of ultrapure water (dripped under gravity). Samples were loaded and eluted under gravity. The columns were then rinsed with 5 mL of 15% ethanol followed by 5 mL of ultrapure water and finally with 2 × 2.5 mL of hexane. A hexane wash was done under 8 to 10 psi pressure. Prostaglandins were gravity-eluted at ~0.5 mL/min with 3 mL of methyl formate and collected into 15 mL polypropylene tubes. The methyl formate was evaporated to dryness under nitrogen at room temperature for the first 30 min and at 40°C in a water bath for another 10 to 20 min. Methyl formate was also added to the tubes containing [^{3}H]prostaglandin $F_{2\alpha}$ for the determination of total counts and evaporated similar to the study samples. The recoveries from the solid phase extraction averaged 78% with a 10% coefficient of variation (CV) between all samples. At this point, the samples were stored dry at −80°C until ready to quantify prostaglandins by the enzyme-linked immunoassay at which time samples were reconstituted in 500 μL of enzyme-linked immunoassay buffer.

Prostaglandin E_2 and prostaglandin $F_{2\alpha}$ were quantified using enzyme-linked immunoassay kits from Cayman Chemical according to the directions in the manufacturer's inserts. The prostaglandin E_2 and prostaglandin $F_{2\alpha}$ concentrations were determined spectrophotometrically using a SpectraMAX 250 microplate reader (Molecular Devices) equipped with four-parameter analysis software (SOFTmax Pro; Molecular Devices). The detection limits for prostaglandin E_2 and prostaglandin $F_{2\alpha}$ were 15 and 10 pg/mL, respectively. High out-of-range values were diluted and reanalyzed. The CV of quality control samples and the bias based on the known spiked samples that were prepared from vials of neat standards (Cayman) were as follows: for prostaglandin E_2 at 61 pg/mL, 13% CV, 18% bias; prostaglandin E_2 at 163 pg/mL, 13% CV, 8% bias; prostaglandin $F_{2\alpha}$ at 71 pg/mL, 25% CV, 8% bias; and

prostaglandin $F_{2\alpha}$ at 145 pg/mL, 18% CV, 3% bias. The intraclass correlation between baseline and 12-month measures of prostaglandin E_2 and $F_{2\alpha}$ among controls were 0.49 and 0.36, respectively.

Protein assays were done with the microplate procedure of the bicinchoninic acid kit method (Pierce) according to the manufacturer's instructions, except only 10 μL of sample was used for the assay. Each sample was stabilized with a protease inhibitor purchased from the same manufacturer. Protein quality control samples were prepared from a large colon biopsy (70 mg), processed in the same manner as the study samples. All samples were run in duplicate on each plate. The CV at the mean concentration of 314 μg/mL was 5%. The total amount of protein in each study sample was used to normalize the prostaglandin concentrations.

Exercise Data. We assessed the type, frequency, and duration of physical activity at baseline and at 3, 6, 9, and 12 months with an interview adapted from the Minnesota Physical Activity Questionnaire (15). We included 38 activities with a metabolic equivalent test level of >4.0 (16). Participants wore pedometers (Accusplit Inc.) during waking hours for 1 week at baseline and at 3, 6, 9, and 12 months; total daily steps were recorded in an exercise log. To measure cardiopulmonary fitness, we assessed maximal oxygen consumption (VO_2 max, mL/kg/min) at baseline and at 12 months (17).

At baseline and 12 months, demographic and medical history information was collected by questionnaire; dietary intake was estimated from a 120-item self-administered food frequency questionnaire (18), weight and height were measured by study personnel, and percentage of total body fat was measured by dual energy X-ray absorptiometry (12).

Exercise Intervention Group. The intervention was a 12-month moderate-to-vigorous intensity aerobic exercise program (12). The goal was 60 min per day, 6 days per week, to be gradually achieved over 12 weeks and continued for the duration of the 12-month intervention. Three days per week, participants exercised at a facility with an exercise physiologist overseeing their workout; participants also exercised at home 3 days per week. They were given heart rate monitors (Polar Electro Inc.) to wear during their facility and home exercise sessions. Exercisers were asked not to change their dietary habits during the trial. Mean caloric intake for women exercisers at baseline and 12 months was 1,543 and 1,508, respectively; for men, mean total calories were 1,693 at baseline and 1,644 at follow-up.

Adherence was calculated weekly as the number of facility sessions attended, minutes of exercise per week, metabolic equivalent minutes per week, and percentage of goal 360 min/wk, with metabolic equivalents determined by the Compendium of Physical Activities (16). Overall adherence to the program was excellent with 80% of exercisers meeting >80% of their 360 min/wk goal (12). From the exercise logs over the 12-month intervention, male exercisers completed a mean 370 min/wk (103% of goal), and female exercisers did a mean 295 min/wk (82% of goal). Over the course of the intervention, exercisers increased their mean minutes per day of moderate or vigorous activity, mean number of steps per day, and VO_2 max, whereas controls remained constant or decreased with regard to these variables. Exercisers significantly increased their mean amount of moderate-to-vigorous recreational physical activity at each time period (baseline, 3-, 6-, 9-, and 12-month means of 24, 309, 364, 306, and 298 min/wk, respectively). Only two males and five females in the exercise group dropped the intervention and all drops were after 3 months.

Control Group. Controls were asked not to change their exercise or diet habits during the 12-month trial. Mean caloric intake for women exercisers at baseline and at 12 months was 1,583 and 1,612, respectively; for men, mean total calories were 1,668 at baseline and 1,520 at follow-up. They were given the opportunity to participate in exercise classes for 2 months at the end of the trial, following completion of all study measures. They completed some of the same exercise variable data collection as exercisers, specifically, the quarterly pedometer use with daily logging of steps for 1 week, and quarterly physical activity interviews. Based on the exercise logs, controls increased moderate or vigorous exercise to a lesser degree compared with the exercise group (baseline, 3-, 6-, 9-, and 12-month means of 25, 90, 95, 81, and 61 min/wk, respectively). One male control exercised at moderate-to-vigorous levels at more than a mean of 360 min/wk (i.e., he was a ''drop in'' to the intervention; ref. 13).

Statistical Analyses. Sufficient biopsy samples were available to perform baseline and 12-month prostaglandin assays for 95 of 102 randomized men, and 89 of 100 randomized women. Participants with missing prostaglandin data were not included in the analyses. All analyses were conducted separately for men and women, according to study design.

Primary analyses were based on assigned treatment at the time of randomization, regardless of adherence status (i.e., intent-to-treat). We computed the geometric mean prostaglandin E_2 and prostaglandin $F_{2\alpha}$ concentrations (adjusted for the total amount of protein in the sample) at baseline and 12 months for the exercise and control groups. The intervention effects were evaluated by assessing the differences in change in geometric mean from baseline to 12 months between exercisers and controls using the generalized estimating equations modification to linear regression models in order to account for the longitudinal nature of the data. Primary analyses were unadjusted, on the basis of the randomized design of the study. Prostaglandin concentrations were log-transformed. We conducted stratified analyses to explore differential intervention effects by baseline age (<55, >55 years old), body mass index (<30, >30), percentage of body fat (median, by gender), history of adenomatous polyps (yes/no), first-degree family history of colon cancer (yes/no), current use of NSAIDs (two ways: none versus any or less than twice a week versus two or more times a week), and menopausal status (women only).

As a preplanned secondary analysis, we categorized exercisers into tertiles of several adherence measures over the course of the intervention (change in VO_2 max from baseline to 12 months, average number of minutes exercised per week, and change in pedometer steps per day) for comparison with the controls. We then assessed the change in geometric mean prostaglandin concentrations over 12 months within the control group and each adherence stratum. Tests for trend across the control

and the three strata of an adherence measure were done by placing the four-category adherence variable into the model as a continuous variable. All statistical tests were two-sided.

Results

Table 1 presents the baseline characteristics of study participants. For both women and men, there were no differences between exercisers and controls ($P > 0.10$ for all characteristics). Compared with women, men were somewhat older, less educated, and consumed more alcohol. Women were more likely to have a family history of colorectal cancer ($P < 0.0001$); more men had a previous adenomatous polyp ($P < 0.0001$). Both men and women, on average, were overweight with a mean body mass index of 28.7 and 29.8, respectively. Men had higher levels of cardiopulmonary fitness (VO_2 max) than women as expected from population norms, but both were low, indicating a sedentary population (17). Among women, there was no difference between exercisers and controls with respect to menopausal status or postmenopausal hormone use (data not shown).

Prior to analyzing the main intervention effects, we evaluated the correlations between the baseline colon prostaglandin concentrations and other factors available in the study (Table 2). Prostaglandins E_2 and $F_{2\alpha}$ were strongly correlated for both men ($P < 0.0001$) and women ($P < 0.0001$). Prostaglandin E_2 was slightly inversely correlated with serum glucose concentration in all study participants ($r = -0.15$, $P = 0.04$). Prostaglandin concentrations were not correlated with age, body size, dietary factors, or the remaining biomarkers presented in Table 2. Additional serum biomarkers were collected for men (estrogens, bioavailable testosterone, dihydrotestosterone, and 3α-androstanediol glucuronide) and women (dehydroepiandrostene sulfate, androstenedione, and prolactin); prostaglandin E_2 and prostaglandin $F_{2\alpha}$ were not associated with any of these factors (data not shown). There was no association between either of the prostaglandins and categorical variables available in this study (menopausal status, race, education, use of NSAIDs, family history of colorectal cancer, previous colon polyps, or cigarette use). We also investigated the correlations between change in prostaglandin concentrations from baseline to 12 months and change in the other characteristics listed in Table 2; no significant associations were observed with all study participants combined or after stratification by gender and intervention group (data not shown).

For both men and women, the exercise and control groups experienced no change in mean prostaglandin E_2 or prostaglandin $F_{2\alpha}$ between the baseline and 12-month colon biopsies (Table 3). There was no statistically significant intervention effect when evaluating the ratio of prostaglandin E_2 to prostaglandin $F_{2\alpha}$ (data not shown). We did not observe any intervention effects when categorizing exercisers by the measures of adherence described above (data not shown). Results for the main intervention effects and adherence factors did not change with adjustment for age or when stratifying by age, body mass index, percentage of body fat, NSAID use, history of adenomatous polyps, or family history of colorectal cancer.

Discussion

This randomized controlled clinical trial of a 12-month moderate-to-vigorous intensity exercise intervention did not result in changes in the average colon prostaglandin concentrations for men or women. No difference was found when evaluating the exercisers by the degree to which they adhered to the intervention (steps/d or min/wk of exercise) or by improvements in cardiopulmonary fitness (VO_2 max).

Table 1. Baseline characteristics of study participants by gender and intervention group

	Women		Men		*P**
	Exercisers (*N* = 42), mean (range %)	Controls (*N* = 47), mean (range %)	Exercisers (*N* = 47), mean (range %)	Controls (*N* = 48), mean (range %)	
Age (y)	54.4 (43-68)	53.8 (42-65)	56.3 (40-70)	56.7 (40-74)	0.02
Race					
White	36 (86)	43 (91)	44 (94)	45 (94)	
Non-White	6 (14)	4 (8)	3 (6)	3 (6)	0.24
Education: college degree or more	22 (52)	30 (64)	30 (63)	26 (55)	<0.0001
Any NSAID use	14 (33)	18 (38)	22 (47)	16 (33)	0.57
Family history of colorectal cancer	17 (40)	17 (36)	14 (30)	18 (38)	<0.0001
Previous polyps (adenomatous)	18 (43)	19 (40)	34 (72)	35 (73)	<0.0001
BMI (kg/m^2)	28.5 (21.4-42.9)	28.9 (21.1-39.9)	29.7 (23.3-41.7)	29.8 (21.3-44.9)	0.12
Body fat (%)	42.8 (27.4-61.7)	43.5 (28.7-57.4)	31.2 (12.4-43.7)	29.4 (14.5-38.4)	0.29
Steps/d	6,147 (1,573-12,644)	6,541 (1,717-14,652)	6,092 (2,192-12,955)	6,286 (1,610-15,737)	0.65
VO_2 max (mL/kg/min)	24.0 (14.9-37.1)	24.9 (17.5-36.9)	30.3 (21.6-44.8)	30.7 (15.0-49.3)	<0.0001
Alcohol (g/d)	6.0 (0-24.7)	6.3 (0-45.5)	11.7 (0-60.1)	14.0 (0-68.7)	0.001
Current smoker	2 (5)	1 (2)	4 (8.5)	5 (10.4)	0.09
PGE_2 (pg/mg protein)	1,020 (94-4,987)	1,295 (115-7,044)	699 (36.3-4,330)	1,143 (61-7,803)	0.21
$PGF_{2\alpha}$ (pg/mg protein)	849 (173-2,580)	960 (199-5,514)	706 (93.5-2,719)	876 (172-5,134)	0.30

Abbreviations: BMI, body mass index; PGE_2, prostaglandin E_2; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; VO_2 max, maximal oxygen consumption.
*P value comparing males and females at baseline.

Table 2. Pearson correlation coefficients for associations between baseline prostaglandin concentrations in sigmoid colon mucosal biopsies and participant characteristics at baseline

	Total population (N = 184)		Women (N = 89)		Men (N = 95)	
	PGE_2	$PGF_{2\alpha}$	PGE_2	$PGF_{2\alpha}$	PGE_2	$PGF_{2\alpha}$
Age (y)	−0.09	0.04	0.02	0.13	−0.14	−0.03
BMI (kg/m^2)	0.08	0.11	0.10	0.14	0.08	0.08
Body fat (%; DEXA)	0.09	0.14*	0.13	0.17	−0.07	0.03
Steps/d (pedometer)	−0.05	−0.08	−0.16	−0.19	0.03	0.02
VO_2 max (mL/kg/min)	−0.04	−0.08	−0.005	−0.04	0.02	−0.04
Energy intake in prior month (kcal/d)	0.02	0.03	−0.06	0.01	0.11	0.07
Fiber intake in prior month (g/d)	0.04	0.06	0.11	0.28	0.06	−0.03
Alcohol (g)	−0.10	−0.08	−0.09	−0.09	−0.09	−0.05
Colon tissue measures						
PGE_2 (pg/mg protein)	n/a	0.73*	n/a	0.73*	n/a	0.74*
$PGF_{2\alpha}$ (pg/mg protein)	0.73*	n/a	0.73*	n/a	0.74*	n/a
Serum measures						
Insulin (units/mL)	0.02	0.007	−0.09	−0.04	0.13	0.07
Glucose (mg/dL)	−0.15*	−0.13	−0.17	−0.09	−0.10	−0.14
IGF-I (ng/mL)	−0.07	−0.03	−0.07	−0.01	−0.02	0.01
IGFBP-3 (ng/mL)	0.05	0.04	−0.07	−0.09	0.15	0.19
SHBG (ng/mL)	0.07	0.01	0.08	−0.04	−0.18	−0.09
Testosterone (ng/dL)	−0.09	−0.06	0.06	0.03	−0.02	0.05
Free testosterone (pg/mL)	−0.07	−0.04	0.002	0.06	0.07	0.12

Abbreviations: BMI, body mass index; DEXA, dual energy X-ray absorptiometry; IGF-I, insulin-like growth factor I; IGFBP-3, insulin-like growth factor binding protein-3; PGE_2, prostaglandin E_2; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; SHBG, sex hormone binding globulin; VO_2 max, maximal oxygen consumption; n/a, not applicable.
*$P < 0.05$.

Our findings are inconsistent with the results reported by Martinez et al. (9) who observed reduced prostaglandin E_2 levels among individuals with higher levels of self-reported exercise. However, the Martinez study used a cross-sectional observational design and measured prostaglandins in rectal, not colon, tissue. It is possible that the relationship between exercise and prostaglandin concentrations is different in colon versus rectal tissue. However, exercise has been much more consistently associated with reduced risk of colon cancer than rectal cancer (2). Thus, exercise would be predicted to exert a stronger effect on prostaglandin concentrations in colon tissue. The discrepant results may be due to differences in the design of the two studies (randomized controlled trial versus cross-sectional observational) or characteristics of the study populations. The subjects in our study were, on average, younger, less physically active, of larger body size, and did not all have a history of colon adenomas as did the Martinez et al. study population. Furthermore, our prostaglandin analysis differed somewhat from the Martinez study, which used one or two biopsy samples per participant; in the present study, only one biopsy was done for each participant.

Another consideration is that either the length or intensity of the 12-month exercise intervention was insufficient to result in meaningful changes in prostaglandin concentrations in colon tissue. However, our exercise prescription of 360 min/wk of moderate-to-vigorous exercise is consistent with the minimum national recommendations of 30 to 60 min/d of moderate-to-vigorous physical activity (19, 20); thus, it is a likely level of fitness achievable by motivated adults. Furthermore, the prescribed intervention produced meaningful changes in other biomarkers (12). Contrary to the Martinez et al. (9) study, we did not find a correlation (using Pearson correlation coefficients) between prostaglandins and NSAID use, BMI or age in addition to several other factors studied here. The absence of an association between NSAIDs and prostaglandin concentrations could be explained by the low frequency (38%) of any NSAID use among our participants.

Table 3. Change in prostaglandin (geometric mean, pg/mg protein) concentrations in colon mucosa biopsies from baseline to 12 months

	Exercisers			Controls			β_{int}	P*
	Baseline geometric mean (95% CI)	12-Month geometric mean (95% CI)	$\%\Delta_E$	Baseline geometric mean (95% CI)	12-Month geometric mean (95% CI)	$\%\Delta_C$		
Women		N = 42			N = 47			
Prostaglandin E_2	6.49 (5.84-7.14)	6.40 (5.04-7.77)	−1.4	6.67 (6.40-6.94)	6.58 (6.03-7.14)	−1.3	−0.001	0.99
Prostaglandin $F_{2\alpha}$	6.53 (6.05-7.01)	6.51 (5.60-7.42)	−0.3	6.54 (6.34-6.74)	6.57 (6.18-6.96)	+0.5	−0.05	0.69
Men		N = 47			N = 48			
Prostaglandin E_2	6.14 (5.44-6.85)	6.18 (4.81-7.58)	+0.7	6.31 (6.01-6.62)	6.42 (5.83-7.02)	+1.7	−0.07	0.74
Prostaglandin $F_{2\alpha}$	6.36 (5.87-6.85)	6.47 (5.54-7.39)	+1.7	6.43 (6.22-6.64)	6.59 (6.19-6.98)	+2.5	−0.05	0.67

NOTE: 95% CI, 95% confidence interval; $\%\Delta_E$, percentage change of geometric mean in exercisers; $\%\Delta_C$, percentage change of geometric mean in controls; β_{int}, regression coefficient for intervention effect.
*Intervention effect comparing exercisers to controls.

An important strength of this study is its randomized trial design, which has the benefits of minimizing confounding and allowing prospective documentation of physical activity. To our knowledge, no other intervention trial has been conducted to test effects of exercise on tissue prostaglandin concentrations. Other strengths include the relatively large size, year-long duration of the trial, excellent adherence of the exercisers, and the low drop-out and drop-in rates (12). It is likely that diet did not influence the results in this study given that neither exercisers nor controls significantly changed their intake of any major dietary factor, including total daily calories, fat, fiber, or alcohol.

One limitation of this study is that home exercise sessions were self-reported and not validated by an exercise physiologist as were done at the facility-based sessions. However, the increases in cardiopulmonary fitness observed among only the exercisers supports high adherence to the entire exercise intervention. Because our study evaluated only precancer participants, we cannot rule out the protective effect of exercise on prostaglandin levels once the adenoma-carcinoma has been initiated.

Another consideration is the relatively high variability for the prostaglandin assays and wide range of prostaglandin concentrations among the participants. Prostaglandin concentrations may vary substantially at different sections of the colon and rectum both within and between individuals over time (21), which may explain, in part, the lack of observed effect of exercise in this study because using only one biopsy does not account for this variation. Furthermore, the low intraclass correlations found for the prostaglandin measures at baseline and at 12 months of follow-up among the control group highlights the likely variation in prostaglandin production from day to day within an individual. These sources of variability could have obscured meaningful differences between exercisers and controls.

In conclusion, our 12-month moderate-to-vigorous intensity aerobic exercise intervention did not result in significant changes in colon mucosal prostaglandin concentrations.

References

1. Samad AKA, Taylor RS, Marshall T, et al. A meta-analysis of the association of physical activity with reduced risk of colorectal cancer. Colorectal Dis 2005;7:204–13.
2. Slattery ML. Physical activity and colorectal cancer. Sports Med 2004; 34:239–52.
3. Slattery ML. Physical activity and colorectal cancer. In: McTiernan A, editor. Cancer prevention and management through exercise and weight control. Boca Raton (FL): CRC Press, Taylor & Francis Group; 2006. pp. 75–90.
4. Backlund MG, Mann JR, DuBois RN. Mechanisms for the prevention of gastrointestinal cancer: the role of prostaglandin E2. Oncology 2005;69:28–32.
5. Ulrich CM, Bigler J, Potter JD. Non-steroidal anti-inflammatory drugs for cancer prevention: promise, perils and pharmacogenetics. Nat Rev Cancer 2006;6:130–40.
6. Quadrilatero J, Hoffman-Goetz L. Physical activity and colon cancer. A systematic review of potential mechanisms. J Sports Med Phys Fitness 2003;43:121–38.
7. Pugh S, Gao T. Patients with adenomatous polyps and carcinomas have increased colonic mucosal prostaglandin E(2). Gut 1994;35: 675–78.
8. Baron JA, Cole BF, Sandler RS, et al. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med 2003;348:891–99.
9. Martinez ME, Heddens D, Earnest DL, et al. Physical activity, body mass index, and prostaglandin E2 levels in rectal mucosa. J Natl Cancer Inst 1999;91:950–3.
10. Demers LM, Harrison TS, Halbert DR, et al. Effect of prolonged exercise on plasma prostaglandin levels. Prostaglandins Med 1981;6: 413–8.
11. Vapaatalo H, Laustiola K, Seppala E, et al. Exercise, ethanol and arachidonic acid metabolism in healthy men. Biomed Biochim Acta 1984;43:S413–20.
12. McTiernan A, Sorensen BE, Irwin ML, et al. Effects of a 12-month exercise intervention on patterns of cellular proliferation in colonic crypts: a randomized controlled trial. Cancer Epidemiol Biomarkers Prev 2006;15:1588–97.
13. McTiernan A, Sorensen BE, Irwin ML, et al. Exercise effect on weight and body fat in men and women. Obesity 2007;15:1496–512.
14. Finley PR, Bogert CL, Alberts DS, et al. Measurement of prostaglandin E2 in rectal mucosa in human subjects: a method study. Cancer Epidemiol Biomarkers Prev 1995;4:239–44.
15. Taylor HL, Jacobs DR, Schucker B, et al. A questionnaire for the assessment of leisure time physical activities. J Chronic Dis 1978;31: 741–55.
16. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of Physical Activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32:S498–516.
17. Pate R, Blair S, Durstine J, et al. Guidelines for exercise testing and prescription. Philadelphia: Lea & Febiger, 1991.
18. Patterson RE, Kristal AR, Tinker LF, et al. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. Ann Epidemiol 1999;9:178–87.
19. Pate RR, Pratt M, Blair SN, et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. JAMA 1995;273:402–7.
20. U.S. Department of Health and Human Services and U.S. Department of Agriculture. Dietary guidelines for Americans. 6th ed. Washington (DC): Government Printing Office; 2005.
21. Wiese FW, Thompson PA, Warneke J, et al. Variation in cyclooxygenase expression levels within the colorectum. Mol Carcinog 2003;37:25–31.

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