Physical Activity and Colon Cancer Risk among Women in the California Teachers Study

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Abstract

Background: **Existing data suggest that physical activity reduces colon cancer risk, but the association is not consistently observed in women. One potential explanation for this inconsistency is that hormone therapy, which is associated with lower colon cancer risk, acts as a modifier of the physical activity/colon cancer relationship.**

Methods: **Participants in the California Teachers Study (N = 120,147), a prospective cohort of female teachers and administrators residing in California, ages 22 to 84 years at baseline and with no prior history of colon cancer were eligible for study. Between 1996 and 2002, 395 patients were diagnosed with invasive colon cancer. The relative risks (RR) associated with lifetime (high school through age 54 years or current age) and recent (past 3 years) strenuous and moderate recreational physical activity were estimated using Cox proportional hazards regression models.**

Results: **Combined lifetime moderate and strenuous recreational physical activity was only modestly associated with colon cancer risk in the cohort [≥4 versus ≤0.5 h/wk/y: RR, 0.75; 95% confidence interval, 0.57-1.00; P_{trend} = 0.23]. Lifetime physical activity reduced colon cancer risk among postmenopausal women who had never taken hormone therapy (≥4 versus ≤0.5 h/wk/y: RR, 0.51; 95% confidence interval, 0.31-0.85; P_{trend} = 0.02). Postmenopausal women with histories of hormone therapy use had lower colon cancer risk, but their risk was not associated with physical activity. The likelihood ratio test for interaction between hormone use and lifetime moderate plus strenuous physical activity was of borderline statistical significance (P = 0.05). We observed no effect modification by age, body mass index, smoking status, menopausal status, or folate intake.**

Conclusions: **Lifetime recreational physical activity may protect against colon cancer among postmenopausal women who have never used hormone therapy. Among hormone therapy users, who have lower risk of colon cancer, recreational physical activity does not seem to provide any additional benefit. With declining rates of hormone therapy use, physical activity offers one possible means for reducing women's colon cancer risk.** (Cancer Epidemiol Biomarkers Prev 2007;16(3):517–25)

Introduction

Colorectal carcinogenesis is a multistep process that can be influenced by behavioral factors such as physical activity and diet (1, 2). Garabrant et al. first reported an association between physical activity and colon cancer risk after observing that men with sedentary jobs had higher colon cancer risk than men with jobs requiring strenuous activity (3). Since then, several cohort and case-control studies have confirmed that both occupational and recreational physical activities are inversely associated with colon cancer, particularly among men (4-10). The risk reduction associated with physical activity has not been observed consistently for women, with some studies showing no statistically significant relationship (11-15). Yet, physical activity was associated with a lower colon cancer risk among women ages 30 to 55 years in the Nurses' Health Study II (16). The exact mechanisms by which physical activity reduces colon cancer risk remain unclear but could involve decreased bowel transit time, decreased serum cholesterol levels, increased bile acid metabolism, increased immune function, altered circulating levels of insulin and insulin-like growth factor-I (IGF-I), and changes in prostaglandin levels (4, 17-20). Moreover, the effect of intensity, duration, and timing of physical activity on women's colon cancer risk has not been clearly defined.

The reason why the findings are less consistent for women is unclear. Because hormone therapy is associated with reduced risk of colon cancer among postmenopausal women (10, 21-27), it may mask any beneficial effects of physical activity on colon cancer risk among women with a history of hormone use. To understand better the interplay between physical activity, hormone therapy use, and colon cancer risk, we examined in detail the relationship between recreational physical activity measures and invasive colon cancer among women in the California Teachers Study, a population in which hormone therapy use was exceedingly common.

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Materials and Methods

Study Population. A detailed description of the California Teachers Study has been reported previously (28). In brief, the California Teachers Study is a prospective cohort of current, recent, and retired female public school teachers and administrators who were members of the California State Teachers Retirement System at the time of study inception in 1995. Cohort members completed a detailed questionnaire, mailed in 1995, providing information on personal medical history, family history of colon and rectal cancer, reproductive factors, hormone therapy use, other medication use, and lifestyle factors (recreational physical activity, diet, alcohol consumption, and smoking). Use of human subject data in this study was approved by the University of Southern California Institutional Review Board in accord with an assurance filed with and approved by the U.S. Department of Health and Human Services.

A total of 133,479 women comprise the California Teachers Study cohort. For this analysis, we excluded in sequence women who had a prior history of colon or rectal cancer (n = 896) or whose history of cancer was unknown (n = 662), who were living outside California at the time they completed the baseline questionnaire (n = 8,867), who limited their participation in the cohort to breast cancer research (n = 18), who were 85 years or older at baseline (n = 2,115), or who had incomplete information on physical activity (n = 774). The resulting analytic cohort for this report consisted of 120,147 women. Analyses of physical activity by menopausal status excluded women with unknown menopausal status (n = 10,331), and analyses of the interaction between physical activity and hormone therapy use excluded postmenopausal women with missing hormone therapy information (n = 573).

Case Ascertainment and Follow-up. Incident diagnoses of invasive adenocarcinoma of the colon (International Classification of Diseases for Oncology topography codes C18.0-18.9) were identified through annual linkages with the California Cancer Registry. The California Cancer Registry receives reports of over 99% of all cancer diagnoses occurring in California from its regional registries as part of a state mandate (29). Overall, 395 California Teachers Study participants considered eligible for analysis were diagnosed with invasive adenocarcinoma of the colon during follow-up.

Follow-up began on the date the baseline questionnaire was completed and continued until the first diagnosis of colon cancer or the first occurrence of a censoring event: a move outside of California (defined as having left California for >4 months; n = 5,834), a diagnosis of rectal cancer (International Classification of Diseases for Oncology topography codes C19.9 and C20.9; n = 140) or *in situ* colon cancer (n = 38), death (n = 4,512), or the end of the follow-up period on December 31, 2002. The restriction requiring that women not leave California for >4 months was imposed to insure that cohort participants would be identified by the California Cancer Registry regional registries at diagnosis or during the first course of treatment. Residence in California was determined by close monitoring of the cohort using annual mailings of newsletters or questionnaires, annual linkage with the U.S. Postal Service National Change of Address database, and change-of-address postcards submitted by participants. Data on date and cause of death were obtained from the California state mortality files and the Social Security Administration death master file.

Measures of Recreational Physical Activity. Participants provided detailed information on the baseline questionnaire regarding their recreational physical activities during a series of time periods in their lives (while in high school; between the ages of 18 and 24, 25 and 34, 35 and 44, and 45 and 54 years; as well as during the 3 years before completing the questionnaire). For each time period, they were asked to indicate the average amount of time spent participating in all moderate activities (examples given for this question include brisk walking, recreational tennis, volleyball, golf, softball, and cycling on level street) and in all strenuous activities (examples given include swimming laps, aerobics, calisthenics, running, jogging, cycling on hills, and racquetball). Participants reported the average number of hours per week (categories: none, 0.5, 1, 1.5, 2, 3, 4-6, 7-10, and ≥11 h) and average number of months per year (categories: 1-3, 4-6, 7-9, and 10-12 months) they engaged in strenuous physical activities and in moderate physical activities. For each time period, we created separate ''hours per week'' variables for strenuous and moderate physical activity by multiplying the hours spent per week by the portion of the year in which the woman engaged in the activity. We assigned the midpoint value of the categories in making these calculations and assigned a value of 12 for the category ≥11 h/wk. We also summed the strenuous and moderate activity variables for each physical activity time/age period to create a third measure, ''strenuous plus moderate activity.'' Lifetime physical activity was calculated for each participant by multiplying the average hours per week per year of activity done during a time period (high school and between the ages of 18-24, 25-34, 35-44, and 45-54 years) by the number of years the woman spent in the relevant time period and then summing across all time periods. We then divided this cumulative measure by the total number of years spent in all of the time periods. This provides an average annual lifetime (beginning with high school through current age if <55 years at baseline) or quasi-average annual lifetime (if 55 years or older at baseline) measure of physical activity for each woman. All physical activity variables were created for strenuous activities, moderate activities, and a combined strenuous plus moderate activity variable. We categorized lifetime strenuous activity and lifetime moderate activity measures into three groups (≤0.50, 0.51-1.99, and ≥2.00 h/wk/y). The summed measure, average annual hours of strenuous plus moderate activity, was also classified into three groups (≤0.50, 0.51-3.99, and ≥4.00 h/wk/y).

Assessment of Colon Cancer Risk Factors. We collected information on other potential colon cancer risk factors in the baseline questionnaire, including race/ethnicity, family history of colon or rectal cancer, history of colon or rectal polyps, hormone therapy use, oral contraceptive use, nonsteroidal anti-inflammatory drug use, height, weight, diet, smoking history, and alcohol consumption (30). Hormone therapy use was asked separately for estrogen and progesterone. For estrogen, questions were asked about Premarin as well as other estrogens used. Dose of Premarin, ages of first and last use, and duration of use were collected separately from that of other estrogen formulations where information was collected on mode of administration (pill, patch, injection, and vaginal cream), ages at first and last use, and duration of use. For progesterone, participants were asked to report the type of progesterone used (medroxyprogesterone or Provera versus other types of progesterone), ages at first and last use, years of use, days per month of use, and dose.

Dietary intake was assessed using the validated 1995 version of the Block food–frequency questionnaire focusing on the year before baseline (30). Dietary assessment included questions on the frequency of consumption and portion size of 103 food and beverage items or groups, vitamin supplement use, alcohol consumption, and cooking practices. Daily intake of calories, total calcium and folate intake, dietary fiber, and alcohol consumption were calculated based on the questionnaire for each woman as previously described (30).

Body mass index was categorized into five groups: <20, 20-24.99, 25-29.99, and ≥30 kg/m^2 and unknown. Menopausal

Table 1. Selected baseline characteristics of women under age 85 years with no prior history of colorectal cancer in the California Teachers Study in relation to moderate lifetime physical activity

Characteristics	*N* (total)	Moderate lifetime activity (h/wk/y), *n* (% in each category)		
		≤0.50	0.51-1.99	≥2.00
No. participants (%)	120,147	25,620 (21.3)	41,756 (34.8)	52,771 (43.9)
No. invasive colon cancer cases (%)	395	131 (33.2)	114 (28.9)	150 (38.0)
Age at baseline (mean ± SD)		56.3 ± 14.2	52.0 ± 13.4	51.4 ± 13.7
Race (%)				
White	103,896	20,826 (20.0)	36,347 (35.0)	46,723 (45.0)
Black	3,223	1,087 (33.7)	1,025 (31.8)	1,111 (34.5)
Other	13,028	3,707 (28.4)	4,384 (33.6)	4,937 (37.9)
Family history of colon or rectal cancer				
No	106,138	22,528 (21.0)	36,992 (34.8)	46,888 (44.2)
Yes	10,200	2,282 (22.4)	3,563 (34.9)	4,355 (42.7)
Adopted	1,817	370 (20.4)	615 (33.8)	832 (45.8)
Unknown	1,992			
Menopausal status and hormone therapy				
Premenopausal	49,739	8,253 (16.6)	18,009 (36.2)	23,477 (47.2)
Postmenopausal				
Never used hormone	15,373	4,386 (28.5)	4,666 (30.4)	6,321 (41.2)
E only	19,172	5,080 (26.5)	6,275 (32.7)	7,817 (40.1)
E and P only	16,331	3,681 (22.5)	5,812 (35.6)	6,838 (41.9)
E/E and P mixed use	8,628	2,060 (23.9)	2,952 (34.2)	3,616 (41.9)
Unknown hormone use	573			
Unknown menopausal status	10,331			
Smoking				
Nonsmokers	22,440	4,663 (20.8)	7,885 (35.1)	9,892 (44.1)
Smokers, lifetime exposure in pack-years				
First quartile (0.05-5.73)	24,147	4,766 (19.7)	8,515 (35.3)	10,866 (45.0)
Second quartile (5.74-11.99)	24,101	4,547 (18.9)	8,554 (35.5)	11,000 (45.6)
Third quartile (12.00-23.05)	23,143	5,116 (22.1)	7,937 (34.3)	10,090 (43.6)
Fourth quartile (≥23.06)	22,275	5,429 (24.4)	7,552 (33.9)	9,294 (41.7)
Missing	4,041			
BMI, kg/m^2 (mean ± SD)	115,621	25.2 ± 5.4	25.0 ± 5.3	24.6 ± 4.9
Total caloric intake kcal/d (mean ± SD)	109,524	1,490.4 ± 547.7	1,556.6 ± 539.8	1,622.3 ± 567.9
Calcium intake, mg/d (mean ± SD)	109,524	767.2 ± 426.7	814.4 ± 434.1	863.7 ± 460.4
Folate intake, μg/d (mean ± SD)	109,524	481.9 ± 229.6	507.2 ± 229.2	534.8 ± 237.2
Dietary fiber, g/d (mean ± SD)	109,524	13.2 ± 6.0	14.0 ± 5.9	15.2 ± 6.5

Abbreviations: E, estrogen; P, progesterone.

status and hormone therapy use were combined into six categories: premenopausal, postmenopausal/never used any hormone therapy, postmenopausal/used only unopposed estrogen, postmenopausal/used only an estrogen plus progesterone regimen, postmenopausal/used both unopposed estrogen and estrogen plus progesterone regimen, and unknown as to menopausal status or hormone use status. Menopausal status was based on age at baseline, age at last menstrual period, reason for cessation of menstrual periods, and oophorectomy and hysterectomy status. Women whose menstrual periods stopped within 6 months of the baseline questionnaire were classified as perimenopausal and combined with premenopausal women for the analyses presented here. Postmenopausal women were those with a last menstrual period more than 6 months before the baseline questionnaire, including women with bilateral oophorectomy. Women older than 55 years of age who were not classified as premenopausal or perimenopausal were also considered postmenopausal. Menopausal status was considered unknown for women ages 55 years or younger whose menstrual periods were terminated by a hysterectomy but who did not have bilateral oophorectomy or who were taking hormone therapy at baseline but had not experienced a last menstrual period before starting hormone therapy use.

Statistical Analyses. We used multivariable Cox proportional hazards regression methods (31) to estimate the association between physical activity and colon cancer risk. Hazard rate ratios, presented as relative risks (RR), with 95% confidence intervals (95% CI) were estimated using ages in days at the start and the end of follow-up as the time metric. Models used to evaluate the relationship between the individual physical activity measures and colon cancer risk were stratified by age at baseline in years and adjusted for race (White versus Black and other). We assessed the effect of our combined menopausal status hormone therapy use variable, nonsteroidal anti-inflammatory drug use (no regular use, <5 years, and ≥5 years), body mass index, smoking (nonsmokers versus lifetime pack-years of exposure in quartiles: 0.05-5.73, 5.74-11.99, 12.00-23.05, and ≥23.06), total caloric intake (600-1,200, 1,201-1,500, 1,501-1,900, and ≥1,901 kcal/d), total folate intake (<250, 251-500, 501-750, and ≥751 μg/d), total calcium intake (<500, 501-750, 751-1,000, and ≥1,001 mg/d), and total dietary fiber intake (<10, 10-13.9, 14-17.9, and ≥18 g/d) on risk estimates. None of these factors altered risk estimates by at least 10%; thus, none were included in the final models. Tests for trend in the RR were done for each physical activity variable by fitting the median value for each activity level as a continuous variable in the age-stratified, race-adjusted models.

We examined the effect of physical activity on colon cancer risk according to the anatomic subsite of the tumor and the extent of disease. We grouped colon subsites into proximal colon (International Classification of Diseases for Oncology topography codes C18.0 and C18.2-C18.5) and distal colon (C18.6 and C18.7). Cases with nonspecific subsite (C18.8), overlapping subsite (C18.9), or subsite in the appendix (C18.1; total $n = 16$) were not included as cases in the subsite analyses and were censored at the time of diagnosis. Localized and nonlocalized colon cancer cases were categorized according to the Surveillance, Epidemiology and End Results summary stage indicator (32). Cases with unspecified extent of disease ($n = 12$) were not included as cases in the extent of disease

Table 2. RR and 95% CI for the association between physical activity and invasive colon cancer overall, by anatomic subsite, and by extent of disease among women under age 85 y in the California Teachers Study (RR stratified on age in years and adjusted for race)

Physical Activity (h/wk/y)	All cases			Anatomic subsites				Extent of disease			
				Proximal colon cancer		Distal colon cancer		Localized disease		Nonlocalized disease	
	Person-years	Cases (*n*)	RR (95% CI)	Cases (*n*)	RR (95% CI)	Cases (*n*)	RR (95% CI)	Cases (*n*)	RR (95% CI)	Cases (*n*)	RR (95% CI)
Lifetime											
Strenuous											
0-0.50	238,788	169	1	121	1	43	1	57	1	105	1
0.51-1.99	255,385	116	0.98 (0.77-1.24)	81	1.00 (0.75-1.32)	31	0.91 (0.57-1.45)	38	0.96 (0.63-1.45)	77	1.02 (0.76-1.37)
≥2.00	304,588	110	0.99 (0.78-1.27)	70	0.95 (0.71-1.28)	33	0.98 (0.62-1.57)	45	1.25 (0.84-1.86)	61	0.85 (0.62-1.18)
P_{trend}*			0.98		0.74		0.96		0.20		0.28
Moderate											
0-0.50	168,908	131	1	94	1	33	1	47	1	80	1
0.51-1.99	278,727	114	0.74 (0.57-0.95)	74	0.69 (0.51-0.94)	34	0.78 (0.48-1.27)	38	0.70 (0.46-1.08)	73	0.75 (0.54-1.03)
≥2.00	351,125	150	0.79 (0.62-1.00)	104	0.79 (0.60-1.05)	40	0.74 (0.46-1.19)	55	0.84 (0.57-1.25)	90	0.74 (0.55-1.00)
P_{trend}*			0.28		0.50		0.35		0.85		0.18
Strenuous + moderate											
0-0.50	77,849	79	1	55	1	22	1	26	1	49	1
0.51-3.99	381,405	188	0.79 (0.60-1.03)	133	0.84 (0.61-1.16)	48	0.62 (0.37-1.04)	63	0.83 (0.52-1.33)	122	0.79 (0.56-1.11)
≥4.00	339,506	128	0.75 (0.57-1.00)	84	0.77 (0.54-1.08)	37	0.63 (0.37-1.09)	51	0.97 (0.60-1.57)	72	0.64 (0.44-0.93)
P_{trend}*			0.23		0.24		0.49		0.62		0.04
Past 3 y											
Strenuous											
0-0.50	536,740	262	1	181	1	72	1	101	1	151	1
0.51-1.99	92,069	58	1.32 (0.99-1.75)	44	1.46 (1.00-2.03)	11	0.88 (0.47-1.67)	14	0.82 (0.47-1.44)	42	1.64 (1.16-2.31)
≥2.00	169,951	75	0.89 (0.69-1.15)	47	0.82 (0.59-1.24)	24	1.01 (0.64-1.60)	25	0.78 (0.50-1.20)	50	1.01 (0.74-1.40)
P_{trend}*			0.30		0.16		0.94		0.27		0.88
Moderate											
0-0.50	375,428	166	1	109	1	51	1	64	1	96	1
0.51-1.99	139,665	78	0.95 (0.72-1.24)	57	1.04 (0.75-1.43)	17	0.69 (0.40-1.20)	26	0.82 (0.52-1.29)	51	1.06 (0.76-1.50)
≥2.00	283,666	151	0.78 (0.62-0.97)	106	0.81 (0.61-1.06)	39	0.69 (0.45-1.06)	50	0.68 (0.47-0.99)	96	0.84 (0.63-1.12)
P_{trend}*			0.02		0.08		0.16		0.07		0.15
Strenuous + moderate											
0-0.50	303,720	125	1	81	1	39	1	52	1	68	1
0.51-3.99	267,478	154	0.97 (0.76-1.23)	114	1.08 (0.81-1.44)	35	0.74 (0.46-1.17)	48	0.73 (0.49-1.08)	101	1.16 (0.85-1.59)
≥4.00	227,562	116	0.81 (0.63-1.05)	77	0.81 (0.59-1.11)	33	0.78 (0.48-1.25)	40	0.68 (0.45-1.04)	74	0.93 (0.66-1.30)
P_{trend}*			0.08		0.07		0.54		0.19		0.31

*P_{trend} in the log-relative risk across categories of physical activity represented by the median activity level for each category.

analyses and censored at the time of diagnosis. Information on anatomic subsite and stage of colon cancer at diagnosis was obtained from the California Cancer Registry files. Differences in stage distribution across physical activity levels were examined using χ^2 test. We evaluated the possibility of heterogeneity of risk estimates by subsite and extent of disease using a χ^2 test (with 1 degree of freedom) based on the squared difference in the log RR estimates for two subgroups divided by the sum of the variances of the RR.

We examined effect modification for the entire cohort by age at baseline (<55 versus ≥55 years), menopausal status (premenopausal versus postmenopausal), body mass index (<25 versus ≥25 kg/m^2), smoking (never versus ever), and folate intake (<250 versus ≥250 μg/d). Women with unknown values for any of these variables were excluded from the corresponding analyses. A likelihood ratio test was used to examine homogeneity of trends comparing the model fitting trends in two groups to the model fitting only one trend for physical activity.

Several approaches were used to check the proportional hazards assumption for each physical activity variable. We visually examined Kaplan-Meier survivor curves and plotted scaled Schoenfeld residuals, for which parallel lines indicated proportionality of hazards (33). We also assessed the correlation of the scaled Schoenfeld residuals with age, and we examined the interaction of our activity variables with age (the time metric used). We did not observe any violations of the proportionality assumption.

Two-sided *P*s are reported for tests for trend and tests for interaction. We did not adjust *P*s for multiple comparisons. All statistical analyses were done using SAS version 9.1.

Results

By design, all participants in the eligible cohort were younger than 85 years of age. The overall mean length of follow-up of the cohort was 6.6 years. The average age for women diagnosed with invasive colon cancer was 70 ± 11 years (range, 38-91).

Approximately 21% of the women in the analytic cohort reported participating in no more than 0.5 h/wk of moderate recreational physical activity annually between high school and age 54 years (or current age, if younger than 54 years), whereas ~44% reported at least 2 h/wk of activity annually (Table 1). Women who reported higher levels of recreational physical activity were more likely to be White, younger in age and therefore premenopausal, and less likely to smoke. Caloric intake and consumption of folate, calcium, and fiber increased with increasing levels of activity.

For all women in the cohort, colon cancer risk was modestly associated with moderate and moderate plus strenuous physical activity (Table 2). Moderate plus strenuous activity was associated with a 25% risk reduction among women who exercised at least 4 h/wk/y over their lifetimes compared with women with little (≤0.5 h/wk/y) activity (RR, 0.75; 95% CI,

0.57-1.00; P_{trend} = 0.23). Measurement of strenuous lifetime activity alone had no effect on risk. We examined the effect of physical activity in different age and time periods (high school through ages 45-54 years) and observed no significant association between physical activity and colon cancer risk (data not shown). Recent moderate activity (within the past 3 years) was associated with a reduction in colon cancer risk (for ≥2 versus ≤0.5 h/wk: RR, 0.78; 95% CI, 0.62-0.97; P_{trend} = 0.02); however, similar to lifetime activity, recent strenuous activity was unrelated to risk.

Of the 379 cases occurring at a nonoverlapping site, 272 (72%) were proximal cancers, and of the 383 cases with a documented stage, 243 (63%) were nonlocalized disease at diagnosis. We evaluated the association between physical activity and colon cancer risk by anatomic sites (proximal versus distal) and by extent of disease at diagnosis (localized versus nonlocalized) but did not observe any meaningful differences in the risk estimates (Table 2). In addition, the distribution of localized and nonlocalized disease did not differ across the three physical activity levels (e.g., P = 0.74 for lifetime strenuous plus moderate physical activity).

We had few premenopausal colon cancer cases in the lowest lifetime physical activity category (≤0.5 h/wk/y) and few premenopausal cases with substantial amounts of recent activity (Table 3). Although we found no strong evidence that lifetime recreational physical activity was associated with lower risk of colon cancer among premenopausal women, the results for at least 2 h/wk of recent strenuous activity and recent moderate activity are consistent with a reduced risk. Results for postmenopausal women are similar to those observed for the entire cohort. We found no statistical evidence of effect modification by menopausal status (P > 0.19 for all physical activity measures).

Seventy-four percent of the postmenopausal women in this analytic cohort had used hormone therapy (Table 1). Among postmenopausal women who had never used hormone therapy, lifetime moderate plus strenuous physical activity was associated with a reduction in colon cancer risk (Table 4). Compared with women whose lifetime activity averaged ≤0.5 h/wk/y, those who averaged at least 4 h/wk/y had a 49% reduction in risk of colon cancer (RR, 0.51; 95% CI, 0.31-0.85; P_{trend} = 0.02). Moderate activities seem to account for most of this reduction in risk (for ≥2 versus ≤0.5 h/wk/y: RR, 0.67; 95% CI, 0.43-1.03; P_{trend} = 0.07 for moderate activity and RR, 0.80; 95% CI, 0.51-1.26; P_{trend} = 0.42 for strenuous activity). Among hormone nonusers, RR estimates for physical activity in the past 3 years were similar to those for lifetime activity. Hormone therapy use reduced colon cancer risk in postmenopausal women; however, we found no evidence of further risk reduction due to physical activity among hormone therapy users. The likelihood ratio test was of borderline statistical significance for interaction between hormone therapy use and lifetime strenuous plus moderate physical activity (P = 0.05). We display the joint effects of physical activity and hormone therapy use in Table 5. As is apparent, there is no joint protective effect of both hormone therapy use and physical activity. To the contrary, our previous table suggests that physical activity only had a protective effect among hormone therapy nonusers. Table 5 shows that the protective effect of physical activity overall seems to be rather similar to that afforded by hormone therapy use (regardless of physical activity level).

The results for hormone therapy users did not vary by type of hormone therapy used (estrogen use only versus estrogen use with a progestin; data not shown).

Table 3. RR and 95% CI for the association between physical activity and invasive colon cancer by menopausal status among women under age 85 y in the California Teachers Study

Physical activity (h/wk/y)	Premenopausal women			Postmenopausal women		
	Person-years	Cases (n)	RR (95% CI)	Person-years	Cases (n)	RR (95% CI)
Lifetime						
Strenuous						
0-0.50	61,308	7	1	158,782	158	1
0.51-1.99	108,720	20	1.97 (0.83-4.69)	122,279	91	0.90 (0.69-1.16)
≥2.00	164,510	18	1.45 (0.60-3.52)	113,398	87	0.98 (0.75-1.27)
P_{trend}*			0.92			0.99
Moderate						
0-0.50	55,664	9	1	100,023	116	1
0.51-1.99	121,470	15	0.85 (0.37-1.95)	131,028	95	0.74 (0.57-0.98)
≥2.00	157,406	21	0.99 (0.45-2.29)	163,407	125	0.79 (0.61-1.02)
P_{trend}*			0.77			0.28
Strenuous + moderate						
0-0.50	16,248	4	1	56,354	73	1
0.51-3.99	149,321	22	0.72 (0.24-2.09)	196,650	157	0.78 (0.59-1.03)
≥4.00	168,970	19	0.68 (0.23-2.02)	141,455	106	0.77 (0.57-1.04)
P_{trend}*			0.72			0.36
Past 3 y						
Strenuous						
0-0.50	234,161	32	1	257,914	222	1
0.51-1.99	35,588	8	1.34 (0.62-2.92)	47,044	49	1.36 (0.99-1.85)
≥2.00	64,790	5	0.47 (0.18-1.20)	89,501	65	0.92 (0.70-1.22)
P_{trend}*			0.10			0.47
Moderate						
0-0.50	206,905	26	1	138,037	132	1
0.51-1.99	48,909	9	0.95 (0.44-2.06)	76,433	67	0.98 (0.73-1.32)
≥2.00	78,724	10	0.64 (0.30-1.36)	179,989	137	0.80 (0.63-1.02)
P_{trend}*			0.23			0.06
Strenuous + moderate						
0-0.50	174,496	18	1	105,746	103	1
0.51-3.99	89,679	20	1.36 (0.70-2.63)	151,179	128	0.92 (0.71-1.19)
≥4.00	70,363	7	0.63 (0.26-1.53)	137,534	105	0.81 (0.62-1.07)
P_{trend}*			0.17			0.15

*P_{trend} in the log-relative risk across categories of physical activity represented by the median activity level for each category.

Table 4. RR and 95% CI for the association between physical activity and invasive colon cancer by hormone therapy use among postmenopausal women under age 85 y in the California Teachers Study

Physical activity (h/wk/y)	Postmenopausal women						$P_{interaction}$*
	Hormone nonusers			Hormone users			
	Person-years	Cases (*n*)	RR (95% CI)	Person-years	Cases (*n*)	RR (95% CI)	
Lifetime							
Strenuous							
0-0.50	41,920	62	1	115,167	94	1	0.29
0.51-1.99	29,252	30	0.81 (0.52-1.25)	92,120	60	0.97 (0.70-1.34)	
≥2.00	28,673	28	0.80 (0.51-1.26)	83,739	59	1.10 (0.79-1.53)	
P_{trend}†			0.42			0.49	
Moderate							
0-0.50	28,054	45	1	70,715	69	1	0.40
0.51-1.99	30,498	37	0.88 (0.56-1.36)	99,461	57	0.69 (0.49-0.99)	
≥2.00	41,294	38	0.67 (0.43-1.03)	120,850	78	0.87 (0.63-1.20)	
P_{trend}†			0.07			0.94	
Strenuous + moderate							
0-0.50	16,598	33	1	38,943	39	1	0.05
0.51-3.99	47,099	58	0.74 (0.48-1.14)	147,880	97	0.83 (0.57-1.21)	
≥4.00	36,149	29	0.51 (0.31-0.85)	104,203	77	0.98 (0.66-1.44)	
P_{trend}†			0.02			0.49	
Past 3 y							
Strenuous							
0-0.50	66,139	80	1	189,339	139	1	0.81
0.51-1.99	11,449	19	1.52 (0.92-2.51)	35,210	30	1.31 (0.88-1.94)	
≥2.00	22,258	21	0.85 (0.52-1.38)	66,477	44	0.98 (0.70-1.38)	
P_{trend}†			0.45			0.82	
Moderate							
0-0.50	37,994	56	1	98,545	73	1	0.24
0.51-1.99	17,834	22	0.87 (0.53-1.43)	57,962	45	1.11 (0.76-1.61)	
≥2.00	44,017	42	0.66 (0.44-0.99)	134,518	95	0.94 (0.69-1.28)	
P_{trend}†			0.05			0.52	
Strenuous + moderate							
0-0.50	29,362	39	1	75,228	61	1	0.30
0.51-3.99	36,269	53	1.14 (0.76-1.74)	113,551	75	0.84 (0.60-1.19)	
≥4.00	34,215	28	0.65 (0.40-1.06)	102,247	77	0.94 (0.67-1.32)	
P_{trend}†			0.02			0.92	

*$P_{interaction}$ between physical activity and hormone use.
†P_{trend} in the log-relative risk across categories of physical activity represented by the median activity level for each category.

We observed no statistical evidence for effect modification by age, smoking status, level of folate intake, or body mass index (data not shown).

Discussion

We observed modest inverse associations between recreational activity and colon cancer risk for both lifetime and recent moderate recreational activity as well as for our combined measure (strenuous plus moderate physical activity). Measurement of strenuous physical activity alone was not associated with colon cancer risk. Thus, moderate activity seems to have had a stronger influence on colon cancer risk in our cohort than strenuous activity, a finding that might seem to be at odds with our expectation. Similar results were observed in a Norwegian cohort study that found, among women, a greater reduction in the relative risk of colon cancer associated with moderately active recreational physical activity (RR, 0.62; 95% CI, 0.40-0.97) than for regular training (strenuous) recreational activity (RR, 0.84; 95% CI, 0.43-1.65;

Table 5. RR and 95% CI for the joint effect of physical activity and hormone therapy use on invasive colon cancer risk among postmenopausal women under age 85 y in the California Teachers Study

Physical activity (h/wk/y)	Postmenopausal women			
	Lifetime		Past 3 y	
	Hormone nonusers	Hormone users	Hormone nonusers	Hormone users
Strenuous				
0-0.50	1	0.65 (0.47-0.90)	1	0.73 (0.55-0.96)
0.51-1.99	0.81 (0.52-1.25)	0.62 (0.43-0.89)	1.52 (0.92-2.52)	0.94 (0.62-1.44)
≥2.00	0.82 (0.52-1.28)	0.71 (0.49-1.02)	0.86 (0.53-1.39)	0.71 (0.49-1.03)
Moderate				
0-0.50	1	0.73 (0.50-1.06)	1	0.62 (0.44-0.88)
0.51-1.99	0.89 (0.58-1.37)	0.50 (0.34-0.75)	0.89 (0.54-1.47)	0.68 (0.46-1.02)
≥2.00	0.69 (0.45-1.07)	0.63 (0.44-0.91)	0.68 (0.45-1.02)	0.58 (0.41-0.81)
Strenuous + moderate				
0-0.50	1	0.59 (0.37-0.95)	1	0.76 (0.51-1.13)
0.51-3.99	0.76 (0.50-1.17)	0.49 (0.33-0.73)	1.17 (0.77-1.77)	0.63 (0.43-0.94)
≥4.00	0.54 (0.32-0.88)	0.57 (0.38-0.86)	0.66 (0.41-1.08)	0.70 (0.47-1.03)

ref. 34). During follow-up of the Norwegian cohort (from the mid-1970s through 1991), hormone therapy use was less prevalent in Norway (35) than it was in population-based studies from the United States (36, 37).

Results from previous cohort studies on the association between physical activity and colon cancer risk in women have been inconsistent (6). The results from several studies have been null (11, 12, 14), whereas others have shown an inverse relationship of decreasing colon cancer risk with increasing amounts of activity (9, 16). Physical activity was not associated with decreased large bowel cancer risk among women in the Framingham Study (12) or among women in a cohort of residents in a retirement community (11). Similarly, Calton et al., with ~9 years of follow-up, did not observe any association between moderate, vigorous, or overall physical activity in the year before data collection and colon cancer risk in the Breast Cancer Detection Demonstration Project Follow-up Study (15). On the other hand, results from the Nurses' Health Study, with ~6 years of follow-up, showed that leisure time activity during the year before data collection was inversely associated with colon and, particularly, distal colon cancer risk (16). Compared with women with an energy expenditure level of <2 MET-hours per week, women with the highest level of metabolic energy expenditure (>21 MET-hours per week) had a 46% reduction in risk for colon cancer overall and 71% reduction in risk for distal colon cancer (16). We found no differences in the associations between physical activity and colon cancer risk by anatomic subsite (proximal versus distal).

Most previously published cohort studies focused on physical activities close in time to the baseline assessment (usually within 1-3 years of data collection). In this study, we did not observe any significant differences in the effects of the lifetime (or quasi-lifetime) measure of physical activity and the measure of physical activity in the 3 years before baseline questionnaire submission on colon cancer risk. Nor were we able to identify any period of time (between high school and age 54 years) where physical activity provided a greater degree of protection from colon cancer.

Several mechanisms have been proposed to explain the possible relationship between physical activity and colon cancer risk. Physical activity may decrease bowel transit time and thus reduce exposure of colonic mucosa to mutagens and carcinogens in feces (18, 38). A second potential mechanism involves insulin metabolism. High insulin and IGF-I levels have been implicated in the regulation of cell proliferation, differentiation, and apoptosis and have been associated with increased colon cancer risk in several studies (19, 39). Physical activity improves insulin sensitivity by reducing circulating insulin levels and may influence IGF-I and IGF-binding protein levels (4, 5, 19). Physical activity also may alter the metabolism of fecal bile acids whose high concentrations may be associated with increased colon cancer risk (17, 38, 40). Modification of prostaglandin levels is another potential means by which physical activity lowers colon cancer risk. Prostaglandin E_2 was found to induce colonic cell proliferation and decrease intestinal motility, whereas prostaglandin F_2 was found to reduce cell proliferation and increase intestinal motility (4, 17). Physical activity has been shown to result in elevated prostaglandin F_2 levels and reduced prostaglandin E_2 levels (4, 17).

We assessed whether the effect of physical activity on colon cancer risk was influenced by hormone therapy use to see if this explained the inconsistent results reported for prior studies. Two other studies have examined this potential effect modification (10, 15). Postmenopausal hormone use did not modify the association between physical activity and colon cancer risk among women participating in the Breast Cancer Detection Demonstration Project Follow-up Study (15). The interaction between body mass index and physical activity was examined in a large case-control study for women who were either premenopausal or postmenopausal and using hormone therapy (estrogen positive women) as well as for women who were postmenopausal and not using hormone therapy (estrogen-negative women; ref. 10). Results for both groups of women were similar. In our study, among postmenopausal women who reported no hormone therapy use, lifetime physical activity was associated with decreased colon cancer risk. However, we did not observe any risk reduction associated with physical activity in postmenopausal women who had used hormone therapy. It is not clear why our findings differ from those of the two earlier studies.

The Women's Health Initiative clinical trial results as well as those of cohort and case-control studies show that hormone therapy users have lower colon cancer risk than nonusers (21-27). Our findings showed evidence of ''single and joint'' protective effects (41) of physical activity and hormone therapy use on colon cancer, with physical activity having a stronger protective effect among hormone therapy nonusers.

How hormone therapy exerts its protective effect on colon cancer is not well understood. Among the mechanisms proposed are altered bile acid metabolism, direct effects on intestinal mucosa, and changes in insulin and IGF-I levels (23, 27, 42). In a study of anovulatory women, bile acid production was lower while they were taking Premarin than when they were not taking Premarin (43). Another speculation is that estrogen is involved in colonic mucosa differentiation and proliferation via the estrogen receptor in the epithelial cells (42, 44). Estrogen replacement therapy reduces circulating IGF-I levels by ~20% to 40%, with higher and more persistent effects seen with oral administration compared with other routes of administration. Progestins, on the other hand, reverse the effects of estrogen on IGF-I levels according to their androgenicity (45, 46). If changing IGF-I levels is the main mechanism of action through which hormone therapy reduces colon cancer risk, a stronger protective effect would be expected for estrogen alone compared with combined estrogen and progesterone. In the Women's Health Initiative study, however, a reduction in colorectal cancer risk was observed among postmenopausal women taking combined estrogen and progesterone but not among those who took estrogen alone (27, 47). We did not observe different physical activity/hormone therapy interaction effects among women who had only use estrogen therapy compared with women whose hormone therapy included a progestin.

Based on our findings, it is possible that physical activity and hormone therapy exert their protective effect on colon cancer risk through common pathways. However, it is also possible that the two risk factors operate independently on risk, but that the effect of hormone therapy overwhelms any potential effect of physical activity.

With the recent decline in postmenopausal hormone therapy use (48-50) resulting from the findings of the Women's Health Initiative Trial, our result suggests that physical activity may offer one approach to colon cancer risk reduction.

Potential limitations of our study must be considered. These include the short duration of follow-up (6.6 years) resulting in only a modest number of cases available for analyses (n = 395). Consequently, we were able to perform only limited analyses of interactions. Furthermore, we did not collect information on colon cancer screening practices in the cohort at enrollment or during follow-up. Colorectal cancer screening can be effective in reducing cancer incidence and mortality through polypectomy and early detection (51-55). It is possible that screening practices vary among women with different physical activity profiles, and that this may have influenced our results. To determine if there is evidence of an association between engaging in nonoccupational physical activity and colorectal cancer screening practices among residents in California, we examined the 2004 data collected by the Center for Disease

Control and Prevention's Behavioral and Risk Factor Surveillance System in California, where concurrent reports on colorectal cancer screening and physical activity were available (56). In this data set, individuals over age 50 years who reported ever having had colorectal cancer screening with either fecal occult blood test or endoscopy (sigmoidoscopy or colonoscopy) were no more likely to report engaging in nonoccupational physical activity in the previous month than unscreened individuals. However, these data do not have information pertaining to levels of physical activities in the past. In addition, because a number of studies have shown that colorectal cancers diagnosed, either at the time of initial screening or during follow-up, were more likely to be of earlier stages (57), we might expect that a higher proportion of early-stage disease among groups with higher prevalence of screening. In this cohort, the proportion of localized disease is similar to the stage distribution observed in the 1998 to 2001 cancer incidence data from 41 U.S. population-based registries (58). We also did not find any significant differences in the stage distribution across physical activity levels.

Our study has also several advantages. It is a prospective cohort study with a large sample size. Furthermore, colon cancer case ascertainment was virtually complete based on linkage with the high-quality, statewide California Cancer Registry. At baseline, all women were currently or recently employed teachers or school administrators or were receiving retirement benefits from the State Teachers Retirement System. Within any age cohort, these women would therefore be more likely to have similar levels of occupational physical activity. Because we used age as the time metric in our analyses, this ensured that women of the same age (and likely same occupational status) were compared with each other. In addition, we collected detailed information on physical activity over several time periods from high school to age 54 years. Thus, we were able to examine the effect of not only the intensity but also the timing and duration of physical activity on colon cancer risk.

In summary, our study showed a modest protective effect of recreational physical activity on colon cancer risk overall in a large group of women. Physical activity was strongly associated with colon cancer risk in postmenopausal women who had not previously used hormone therapy. However, no association was observed for postmenopausal women with a history of hormone therapy use. The explanation for this finding may involve the underlying mechanisms through which physical activity and hormone therapy influence colon carcinogenesis. Longer follow-up with repeated assessment of physical activity in our cohort as well as additional studies are needed to confirm our observation. Studies are also needed to understand better the biological mechanisms by which physical activity and hormone therapy influence colon cancer risk in women.

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