1993 as a subset of the 1,184,657 participants of the CPS II Mortality Cohort assembled in 1982 (41). Mortality Cohort participants in 1982 completed a self-administered questionnaire with information on exercise at work or play, diet, medical history, and other lifestyle habits. The 1992 Nutrition Cohort includes men and women ages 50 to 74 years residing in 1 of 21 states with population-based cancer registries that ascertained at least 90% of incident cancers by 1990. Median age at Nutrition Cohort entry in 1992 to 1993 was 63 years.

The Nutrition Cohort 1992 to 1993 questionnaire obtained information on physical activity, diet, medical history, and other lifestyle habits. Dietary assessment was based on a modified 68-item Block food frequency questionnaire (42); nutrient intakes were estimated using the Dietary Analysis System version 3.8a (43). This cohort was recontacted in 1997 and 1999 with self-administered questionnaires to update information on newly diagnosed cancers, medical history, and lifestyle factors. A pilot study linking Nutrition Cohort participants to state cancer registries found that cohort members were highly capable (sensitivity of 0.93) of self-reporting a previous cancer diagnosis (44). Mortality follow-up of the entire Nutrition Cohort is ongoing through automated linkage with the National Death Index for date and cause of death (41). CPS II Nutrition Cohort participants on the average reported higher educational attainment and more health conscious behaviors than the general U.S. population (41). All aspects of the CPS II Nutrition Cohort study protocol have been approved by the Emory University Institutional Review Board.

This study includes Nutrition Cohort members enrolled in 1992 to 1993; study observation period for each participant ended with the occurrence of one of the following: diagnosis of colon or rectal cancer, death, or August 31, 1999. Excluded from the study were persons who (1) were not known to be deceased but failed to respond to both 1997 and 1999 questionnaires (4.5%), (2) reported a colon or rectal cancer not subsequently verified by pathology report (0.2%), (3) reported a personal history of colon or rectal cancer at baseline (1.5%), or (4) reported missing or uninterpretable data for exercise level in 1982 (0.9%), recreational activities in 1992 (1.5%), body mass index (BMI; 1.3%), or dietary intake (8.1%). After exclusions, this study population consists of 70,403 men and 80,771 women, representing 82% of the CPS II Nutrition Cohort.

Incident Colon and Rectal Cancer. This study included 940 colon cancers (C18.0, C18.2-C18.9) and 390 cancers of the rectosigmoid junction or rectum (C19.0-C20.9) diagnosed between enrollment and August 31, 1999. Of these, 1,033 cases were self-reported colon or rectal cancers on the 1997 or 1999 questionnaires and verified by medical record abstraction (76%) or linkage with state cancer registries when medical records were unavailable (24%). Two hundred ninety-five cases were identified from the National Death Index linkage as interval cancer cases, defined as deaths with colon or rectal cancer recorded on death certificate among study participants who died after completing a questionnaire and did not report colon or rectal cancer on that questionnaire. We were able to verify 241 (82%) of the 295 interval cancer cases through cancer registry linkage. Subsite-specific analyses were conducted on 505 proximal (cecum to splenic flexure) and 339 distal (descending to sigmoid colon) colon cancers, excluding colon cancers with overlapping or not otherwise specified site codes.

Recreational Physical Activity. CPS II Nutrition Cohort participants reported in 1992 to 1993 the average number of hours per week (0, 1-3, 4-6, or ≥7) spent at seven recreational activities (walking, jogging/running, lap swimming, tennis or racquetball, bicycling/stationary bike, aerobics/calisthenics, and dancing) in the year before study enrollment (1991-1992). Activities other than walking were grouped together as "other activity." We categorized participants by report of any recreational activity; persons who reported no recreational activity served as the reference group for all analyses.

We computed total hours per week spent at recreational activities by summing the reported time spent at each activity (assigning the value of 0 for "none," 1.25 for "1-3," 5 for "4-6," and 7 for "≥7" hours per week) and then grouping participants into six exposure levels (no activity, <2, 2-3, 4-6, 7, or ≥8 hours per week). The 7 and ≥8 hours per week categories were combined for some analyses. Metabolic equivalent (MET) hours per week were estimated by multiplying the number of hours per week spent at each activity by its assigned MET intensity (45): walking (3.5), jogging/running (7.0), lap swimming (7.0), tennis or racquetball (6.0), bicycling/stationary bike (4.0), aerobics/calisthenics (5.0), and dancing (4.5). After summing across all activities, participants were grouped into six exposure levels (no activity, <7, 7-13, 14-23, 24-29, or ≥30 MET hours per week). We further examined gradients in hours per week (<4, 4-6, ≥7) spent at walking only and at a combination of walking plus other activities.

Past activity (none, slight, moderate, or heavy) was reported by participants in 1982 (10 years prior to Nutrition Cohort enrollment in 1992) in response to the question "How much exercise do you get (work or play)?" The "slight" category was used as the reference group due to the small number of persons who reported "none" to past activity; these two groups were combined for analyses of recent activity stratified by past activity.

Covariate Information. Potential confounders were chosen based on their observed association with colon and rectal cancer and with recreational physical activity (Table 1). Covariates included in final models for colon and rectal cancer were age (single years), education (some high school, high school graduate, some college or trade school, college graduate or postgraduate work, or unknown), cigarette smoking (never, former, current, ever smoker not specified, or status unknown), alcohol (nondrinker, <1 daily drink, 1 daily drink, ≥2 daily drinks, or unknown), red (including processed) meat intake (in quintiles), energy-adjusted total folate (in quintiles), energy-adjusted total dietary fiber (in quintiles), multivitamin use in 1982 (nonuser, occasional user, regular user, or status unknown), and hormone replacement therapy use in women (nonuser, former user, current user, ever user not specified, or status unknown). Multivariate-adjusted models of recent recreational activity and exercise level in 1982 were adjusted for one another, except in models stratified by past exercise. Other variables evaluated for potential confounding were race, family history of colorectal cancer, use of

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Table 1. Selected characteristics of study participants by total hours per week of recreational physical activity in the year before study enrollment, CPS II Nutrition Cohort men and women, 1992-1993

Recreational physical activity in the year before study enrollment (total h/wk)	Men (n = 70,403)					Women (n = 80,771)				
	0	<2	2-3	4-6	≥7	0	<2	2-3	4-6	≥7
No. participants	8,545	20,022	11,535	15,368	14,933	7,471	25,959	16,139	17,873	13,329
Median h/wk	0	1.3	2.5	5.0	7.5	0	1.3	2.5	5.0	8.3
Median MET h/wk	0	4.4	10.6	17.5	30.1	0	4.4	10.6	17.5	31.9
Low or no exercise reported in 1982 (%)	32	34	27	23	16	43	34	27	22	15
Median age at cohort enrollment	63	64	63	65	65	62	62	62	62	62
Race, non-White (%)	2	2	2	2	2	3	2	3	2	3
Education, none beyond high school (%)	41	27	19	23	25	45	37	31	34	33
Gained >4.545 kg between 1982 and 1992 (%)	26	23	19	19	16	40	35	34	30	27
BMI (median, kg/m^2)	26.5	26.3	25.8	25.8	25.5	25.9	25.1	24.7	24.2	23.9
Tendency to gain weight at the waist (%)	70	75	75	73	70	52	53	53	51	49
Current cigarette smoking (%)	17	9	5	7	8	13	8	7	7	8
Alcohol, ≥2 daily drinks (%)	15	12	11	12	13	6	5	5	5	6
Aspirin, current use (%)	46	51	54	54	53	38	40	42	40	40
Multivitamin use in 1982, ≥15 d/mo (%)	15	20	23	21	22	22	25	29	27	29
Current hormone replacement therapy use (%)						28	32	35	33	33
Total energy intake (median, cal)	1,818	1,698	1,672	1,681	1,763	1,303	1,297	1,296	1,282	1,320
Energy-adjusted total fiber (median, g)	11	12	13	13	13	9	10	11	11	12
Energy-adjusted total folate (median, μg)	273	307	339	331	347	256	297	351	339	365
>7 servings of red meat/wk (%)	43	32	25	27	29	17	13	11	10	10

NOTE: Proportions standardized to the age distribution of the CPS II Nutrition Cohort.

aspirin or other analgesics, vegetable and fruit intake, and total calcium intake. These factors had negligible effect on the relationship between recreational activity and colon or rectal cancer and were not included in final models. We examined BMI (<18.5, 18.5-24, 25-29, 30-39, ≥40 kg/m^2) and total daily energy intake (in quintiles) but did not include these in final models due to their potential to be intermediate in the relationship between physical activity and lower risk of colon or rectal cancer, although their inclusion made little difference in risk estimates.

Statistical Methods. We estimated age- and multivariate-adjusted colon and rectal cancer incidence rate ratio (RR) and 95% confidence interval (95% CI) using Cox proportional hazards modeling. *P*s for linear trend were estimated by modeling the number of hours or MET hours per week of total or specific types of activities as continuous variables, with and without the reference group. We examined effect measure modification by exercise level reported in 1982 (none or slight, moderate or heavy), change in body weight as reported in 1982 and 1992 (lost weight to having gained up to 4.545 kg, gained >4.545 kg, or 10 lb), BMI in 1992 (<25, 25-29, ≥30 kg/m^2), cigarette smoking (never, former, and current), aspirin use (nonuser and current user), and total daily energy intake (median intake or below, above median intake). Statistical interaction between covariates and any activity was evaluated using the likelihood ratio test. The Wald statistic was used to test for homogeneity of stratum-specific RRs associated with proximal and distal colon cancers and with hours of activity by type of activity. Analyses were done using SAS; all *P*s were two sided and considered significant at 0.05.

Results

Participant Characteristics by Recreational Physical Activity. During the study period, 536 colon and 247 rectal cancers were identified among men and 404 colon and 143 rectal cancers among women. Forty-eight percent of colon cancers among men originated proximal to the splenic flexure compared with 60% among women.

Twelve percent of men and 9% of women reported no recreational physical activity in the year before study enrollment, 46% of men and 47% of women reported walking as the only recreational activity, 6% of men and 5% of women reported engaging only in activities other than walking, and 36% of men and 39% of women reported walking plus at least one other activity including (in order of decreasing frequency) bicycling/stationary biking, aerobics/calisthenics, dancing, lap swimming, tennis or racquetball, or jogging/running.

Compared with men and women reporting any recreational activity in the past year, persons who reported none were more likely to report lower educational attainment, current cigarette smoking, greater consumption of red meat, and lower consumption of total folate and fiber (Table 1); they were also less likely to report long-term multivitamin use on a regular basis (≥15 days per month). Men who reported no activity were also more likely to report two or more daily alcoholic drinks and higher median daily energy intake compared with men reporting any activity; women who reported no activity were the least likely to report hormone replacement therapy use. In both men and women, increasing amount of physical activity reported in 1992 to 1993 was inversely associated with median BMI, with the proportion of persons reporting little or no exercise in 1982 and with weight gain of >4.545 kg between 1982 and 1992.

Amount of Recreational Physical Activity and Colon Cancer Incidence. Men who reported any recreational physical activity in 1992 to 1993 had an 18% lower risk of colon cancer (multivariate-adjusted RR, 0.82; 95% CI, 0.64-1.04); women who reported any activity were not at lower risk compared with those reporting none (Table 2).

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Table 2. Any activity, total hours, and MET h/wk of recreational physical activity and colon cancer incidence, number of cases, age- and multivariate-adjusted RR and 95% CI, CPS II Nutrition Cohort men and women, 1992-1993 to 1999

Recreational physical activity in year before study enrollment	Men			Women			Men and women
	No. cases	Age-adjusted RR (95% CI)	Multivariate-adjusted RR (95% CI)[*]	No. cases	Age-adjusted RR (95% CI)	Multivariate-adjusted[*] RR (95% CI)	Multivariate-adjusted[*] RR (95% CI)
Total	536			404			
No activity	79	1.00 (reference)	1.00 (reference)	39	1.00 (reference)	1.00 (reference)	1.00 (reference)
Any reported activity[†]	457	0.72 (0.57-0.91)	0.82 (0.64-1.04)	365	0.92 (0.66-1.28)	0.98 (0.70-1.37)	0.87 (0.71-1.06)
Recreational physical activity[†] (h/wk)							
No activity	79	1.00 (reference)	1.00 (reference)	39	1.00 (reference)	1.00 (reference)	1.00 (reference)
<2	164	0.83 (0.63-1.08)	0.91 (0.69-1.19)	136	0.97 (0.68-1.39)	1.01 (0.70-1.44)	0.94 (0.75-1.16)
2-3	72	0.62 (0.45-0.86)	0.72 (0.52-1.01)	80	0.94 (0.64-1.37)	1.01 (0.68-1.49)	0.83 (0.65-1.07)
4-6	124	0.76 (0.58-1.01)	0.86 (0.64-1.15)	92	0.92 (0.63-1.34)	0.97 (0.66-1.43)	0.89 (0.71-1.12)
7	59	0.71 (0.50-0.99)	0.77 (0.54-1.08)	34	0.99 (0.62-1.56)	1.03 (0.65-1.65)	0.85 (0.64-1.12)
≥8	38	0.51 (0.35-0.75)	0.58 (0.39-0.87)	23	0.60 (0.36-1.01)	0.65 (0.39-1.11)	0.60 (0.44-0.83)
P for trend, with and without reference group		0.001, 0.02	0.007, 0.03		0.07, 0.07	0.14, 0.11	0.002, 0.007
Recreational physical activity[†] (MET h/wk)							
No activity	79	1.00 (reference)	1.00 (reference)	39	1.00 (reference)	1.00 (reference)	1.00 (reference)
<7	158	0.82 (0.63-1.07)	0.90 (0.68-1.18)	135	0.98 (0.69-1.40)	1.02 (0.71-1.46)	0.93 (0.75-1.16)
7-13	68	0.72 (0.52-1.00)	0.83 (0.59-1.16)	63	0.91 (0.61-1.36)	0.98 (0.65-1.47)	0.88 (0.68-1.13)
14-23	106	0.67 (0.50-0.90)	0.75 (0.55-1.01)	96	0.94 (0.65-1.37)	1.00 (0.68-1.47)	0.84 (0.66-1.06)
24-29	77	0.79 (0.58-1.09)	0.86 (0.63-1.19)	38	0.89 (0.57-1.40)	0.94 (0.60-1.48)	0.89 (0.68-1.15)
≥30	48	0.52 (0.36-0.74)	0.60 (0.41-0.87)	33	0.70 (0.44-1.12)	0.77 (0.48-1.24)	0.65 (0.49-0.87)
P for trend, with and without reference group		0.0006, 0.008	0.005, 0.02		0.07, 0.08	0.15, 0.12	0.002, 0.006

[*] Models included age, education, exercise level in 1982, cigarette smoking, alcohol, red meat, folate, fiber, multivitamin use in 1982, and hormone replacement therapy (women). Models of men and women combined also included sex.

[†] Included walking, jogging/running, lap swimming, tennis or racquetball, bicycling/stationary bike, aerobics/calisthenics, and dancing.

Statistically significant decreasing risk of colon cancer was associated with increasing hours (*P* for trend without reference group = 0.007) or MET hours (*P* for trend = 0.006) per week of total activities in men and women combined (Table 2). The decrease in risk with greater amount of activity was observed predominantly among men; no dose-response was observed among women. Significantly lower risk of colon cancer was observed at >7 hours or ≥30 MET hours per week of activity; the RR (95% CI) among men were 0.58 (0.39-0.87) for those reporting >7 hours and 0.60 (0.41-0.87) for ≥30 MET hours per week of activities. Although the RR estimates were lower among men than women within each exposure level, there were no statistically significant differences by sex.

Adjusting for BMI in addition to other covariates made little difference in the RR estimates associated with hours or MET hours per week of activity in men or women. The multivariate-adjusted RRs (95% CIs) for colon cancer in models that included BMI were 0.95 (0.76-1.18) for men and women reporting <2 hours, 0.85 (0.66-1.08) for 2 to 3 hours, 0.91 (0.72-1.15) for 4 to 6 hours, 0.87 (0.66-1.14) for 7 hours, and 0.62 (0.45-0.85) for ≥8 hours per week.

Amount by Type of Recreational Physical Activity and Colon Cancer Incidence. People who reported increasing hours of walking without other activities were not at lower risk of colon cancer compared with those who reported no recreational physical activity (Table 3). The strongest inverse association between colon cancer risk and physical activity was observed among men and women who reported walking plus other activities (*P* for trend without reference group = 0.03). Among men, the RRs (95% CIs) were 0.74 (0.53-1.03) for those reporting <4 hours, 0.86 (0.59-1.26) for 4 to 6 hours, and 0.53 (0.36-0.79) for ≥7 hours per week of walking plus other activities. The corresponding RRs (95% CIs) estimates among women were 0.99 (0.66-1.46) for those reporting <4 hours, 0.72 (0.43-1.19) for 4 to 6 hours, and 0.59 (0.36-0.97) for ≥7 hours per week. For men and women combined, the RR estimate associated with reporting ≥7 hours of walking plus other activities was significantly lower than that associated with reporting ≥7 hours of walking only (*P* for homogeneity = 0.009). Persons who reported engaging in other activities without walking were not at reduced risk of colon cancer; the number of people in this category was too small for stable estimates or further analyses.

Past and Recent Physical Activity and Colon Cancer Incidence. Less than 30% of men and women reported none or slight physical activity at work or play in 1982 (10 years before Nutrition Cohort enrollment). We found little evidence that past activity was associated with lower risk of colon cancer. Compared with those who in 1982 reported slight exercise, the RRs (95% CIs) for colon cancer were 1.12 (0.66-1.90) for reporting none, 1.01 (0.87-1.18) for moderate, and 1.12 (0.87-1.44) for heavy level of exercise.

Among men and women who reported being inactive (none or slight exercise) in 1982 (Table 4), report of any recreational physical activity in the year before study enrollment in 1992 to 1993 (considered recently active) was associated with 16% lower risk of colon cancer

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Table 3. Hours of recreational physical activity and colon cancer incidence by type of activity, number of cases, age- and multivariate-adjusted RR and 95% CI, CPS II Nutrition Cohort men and women, 1992-1993 to 1999

Recreational physical activity in year before study enrollment	Men			Women			Men and women
	No. cases	Age-adjusted RR (95% CI)	Multivariate-adjusted* RR (95% CI)	No. Cases	Age-adjusted RR (95% CI)	Multivariate-adjusted* RR (95% CI)	Multivariate-adjusted* RR (95% CI)
Type of recreational physical activity (h/wk)							
No activity	79	1.00 (reference)	1.00 (reference)	39	1.00 (reference)	1.00 (reference)	1.00 (reference)
Walking only							
<4	143	0.80 (0.61-1.05)	0.87 (0.66-1.15)	125	0.98 (0.68-1.40)	1.00 (0.70-1.44)	0.91 (0.73-1.14)
4-6	72	0.77 (0.56-1.06)	0.83 (0.60-1.16)	60	1.04 (0.69-1.56)	1.08 (0.71-1.63)	0.92 (0.71-1.18)
≥7	51	0.84 (0.59-1.19)	0.88 (0.61-1.25)	25	1.15 (0.70-1.91)	1.18 (0.71-1.95)	0.96 (0.72-1.29)
P for trend, with and without reference group		0.39, 0.91	0.34, 0.84		0.47, 0.46	0.41, 0.46	0.76, 0.79
Walking plus other activities†							
<4	70	0.64 (0.46-0.88)	0.73 (0.53-1.02)	76	0.92 (0.63-1.36)	0.99 (0.67-1.47)	0.83 (0.64-1.06)
4-6	45	0.75 (0.52-1.08)	0.85 (0.58-1.24)	26	0.67 (0.41-1.11)	0.72 (0.43-1.19)	0.79 (0.58-1.06)
≥7	43	0.46 (0.32-0.67)	0.53 (0.36-0.78)	27	0.55 (0.33-0.89)	0.59 (0.36-0.98)	0.55 (0.40-0.74)
P for trend, with and without reference group		0.0004, 0.11	0.02, 0.16		0.01, 0.05	0.07, 0.07	0.003, 0.03

*Models included age, education, exercise level in 1982, cigarette smoking, alcohol, red meat, folate, fiber, multivitamin use in 1982, and hormone replacement therapy (women). Models of men and women combined also included sex.

† Included walking, jogging/running, lap swimming, tennis or racquetball, bicycling/stationary bike, aerobics/calisthenics, and dancing.

(RR, 0.84; 95% CI, 0.59-1.20) compared with report of no activity. Among men and women who reported being active (moderate or heavy exercise) in 1982, report of any recreational physical activity in the year before study enrollment (considered the continuously active) was associated with 13% lower risk of colon cancer (RR, 0.87; 95% CI, 0.68-1.10) compared with those reporting no activity. The RR associated with reporting ≥7 hours per week of physical activity in the year before study enrollment was identical in people who reported being inactive in 1982 (RR, 0.74; 95% CI, 0.44-1.25) and those who reported being active in 1982 (RR, 0.74; 95% CI, 0.56-0.99), but a significant dose-response was seen only among the continuously active (*P* for trend = 0.01).

Proximal and Distal Colon Cancer and Rectal Cancer. Although the inverse association between physical activity and colon cancer risk was somewhat stronger for proximal than distal colon cancer, the differences by subsite were not statistically significant (Table 5). We observed a 30% lower risk of rectal cancer among men and women who reported any recreational activity in the year before study enrollment than in those who reported none (Table 5). Rectal cancer risk decreased among those reporting modest amounts of total activity but not among people who reported the highest amounts of activity. The lower risk of rectal cancer associated with modest amounts of activity was similar for walking only or walking plus other activities (Table 5).

Table 4. Any and hours per week of recreational physical activity and colon cancer incidence, by exercise level reported in 1982, number of cases and multivariate-adjusted RR and 95% CI, CPS II Nutrition Cohort men and women, 1992-1993 to 1999

Recreational physical activity in the year before study enrollment (1991-1992)	Exercise level reported in 1982			
	None or slight		Moderate or heavy	
	No. cases	Multivariate-adjusted* RR (95% CI)	No. cases	Multivariate-adjusted* RR (95% CI)
Total	233		707	
Recreational physical activity				
No activity	38	1.00 (reference)	80	1.00 (reference)
Any activity†	195	0.84 (0.59-1.20)	627	0.87 (0.68-1.10)
Recreational physical activity† (h/wk)				
No activity	38	1.00 (reference)	80	1.00 (reference)
<2	92	0.90 (0.61-1.32)	208	0.93 (0.72-1.21)
2-3	37	0.78 (0.49-1.23)	115	0.85 (0.64-1.14)
4-6	43	0.83 (0.53-1.29)	173	0.91 (0.69-1.19)
≥7	23	0.74 (0.44-1.25)	131	0.74 (0.56-0.99)
P for trend, with and without reference group		0.28, 0.43		0.007, 0.01

*Models included age, sex, education, exercise level in 1982, cigarette smoking, alcohol, red meat, folate, fiber, multivitamin use in 1982, and hormone replacement therapy (women).

† Included walking, jogging/running, lap swimming, tennis or racquetball, bicycling/stationary bike, aerobics/calisthenics, and dancing.

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Table 5. Any and hours per week of recreational physical activity and incident cancer of the proximal colon, distal colon, and rectum, number of cases and multivariate-adjusted RR and 95% CI, CPS II Nutrition Cohort men and women, 1992-1993 to 1999

Recreational physical activity in the year before study enrollment	Men and women					
	Proximal colon		Distal colon		Rectosigmoid and rectum	
	No. cases	Multivariate-adjusted* RR (95% CI)	No. cases	Multivariate-adjusted* RR (95% CI)	No. cases	Multivariate-adjusted* RR (95% CI)
Total	505		339		390	
Recreational physical activity						
No activity	67	1.00 (reference)	41	1.00 (reference)	63	1.00 (reference)
Any activity†	438	0.77 (0.59-1.01)	298	0.91 (0.65-1.28)	327	0.70 (0.53-0.93)
Recreational physical activity† (h/wk)						
No activity	67	1.00 (reference)	41	1.00 (reference)	63	1.00 (reference)
<2	156	0.83 (0.62-1.10)	110	1.00 (0.69-1.43)	112	0.72 (0.52-0.98)
2-3	80	0.73 (0.52-1.01)	54	0.87 (0.57-1.32)	60	0.68 (0.47-0.97)
4-6	123	0.85 (0.62-1.15)	74	0.89 (0.60-1.32)	68	0.59 (0.41-0.83)
≥7	79	0.63 (0.45-0.88)	60	0.82 (0.55-1.24)	87	0.83 (0.59-1.16)
P for trend, with and without reference group		0.008, 0.03		0.15, 0.20		0.73, 0.45
Type of recreational activities (h/wk)						
No activity	67	1.00 (reference)	41	1.00 (reference)	63	1.00 (reference)
Walking only						
<4	145	0.84 (0.62-1.12)	95	0.93 (0.64-1.35)	100	0.71 (0.51-0.97)
4-6	70	0.82 (0.58-1.15)	48	0.97 (0.63-1.48)	41	0.60 (0.40-0.90)
≥7	38	0.83 (0.56-1.25)	30	1.08 (0.67-1.73)	36	0.89 (0.59-1.34)
P for trend, with and without reference group		0.44, 0.90		0.84, 0.56		0.44, 0.70
Walking plus other activities						
<4	74	0.69 (0.49-0.97)	54	0.89 (0.59-1.35)	57	0.67 (0.46-0.97)
4-6	44	0.80 (0.54-1.18)	22	0.71 (0.42-1.21)	23	0.53 (0.33-0.87)
≥7	39	0.50 (0.33-0.75)	24	0.55 (0.33-0.92)	46	0.72 (0.49-1.08)
P for trend, with and without reference group		0.008, 0.12		0.15, 0.27		0.30, 0.32

*Models included age, sex, education, exercise level in 1982, cigarette smoking, alcohol, red meat, folate, fiber, multivitamin use in 1982, and hormone replacement therapy (women).

†Included walking, jogging/running, lap swimming, tennis or racquetball, bicycling/stationary bike, aerobics/calisthenics, and dancing.

Recreational Physical Activity and Colon Cancer Incidence Stratified by Covariates. We observed significant modification of the RR for colon cancer associated with any activity by aspirin use in men and women (*P* for interaction = 0.02). Compared with those reporting none, the RRs (95% CIs) associated with reporting any recreational activity were 0.65 (0.48-0.86) among current users of aspirin and 1.04 (0.78-1.38) among nonusers. Although not statistically different, the inverse association between colon cancer and any activity was stronger among persons who reported having gained ≤4.545 kg weight between 1982 and 1992 (compared with having gained >4.545 kg) and who reported below median total daily energy intake (compared with median intake or above). We observed no statistically significant effect modification by BMI, history of chronic diseases (diabetes, cardiovascular, or pulmonary diseases), or current use of hormone replacement therapy (women).

Discussion

In this cohort of older adults in the United States, increasing amounts of recent recreational physical activity were associated with lower risk of colon cancer, even when the activity began later in life. Our results also showed that recreational physical activity was associated with significantly lower risk of rectal cancer in older men and women.

The significant dose-response relationship of decreasing colon cancer risk with increasing hours and MET hours per week of physical activity among men in this study has been reported by some but not all prospective studies (11-26). Ten (11, 12, 14, 15-17, 19, 23-25) of 14 studies of men reported significantly reduced risk of colon cancer with physical activity; seven of these studies (11, 15-17, 19, 23, 24) presented data beyond dichotomized activity levels. Whereas these seven studies generally showed lower risk with increasing activity, only three studies of men (15, 19, 24) reported a significant dose-response relationship; all three studies included the inactive (reference) group in trend analyses. Three (12, 20, 21) of the 10 prospective studies of women reported lower colon cancer risk with increasing physical activity; only one study of women (21) reported a statistically significant dose-response relationship. Case-control studies have generally reported significant test for trend in men but not in women (34-37). One study (39) reported a statistically significant dose-response relationship between colon cancer risk and long-term vigorous physical activity in men and women.

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Physical activity has been variably defined in published studies by amount (11, 31, 32, 35, 36, 38), frequency (22, 24, 32, 40), intensity (25-27, 33), or amount weighed by intensity (14-16, 19, 21, 24, 26, 34, 39). Most prospective studies, however, have not quantified the amount of specific types of activities associated with lower colon cancer risk. A British study (26), one of the few that reported risk estimates associated with walking only, reported a statistically nonsignificant 25% lower risk of colorectal cancer associated with walking for ≥40 minutes per day. Previous studies that reported only MET hours, or a similarly weighed index, are difficult to interpret for public health recommendations due to the inability to separate amount from intensity of activities. For example, 30 MET hours per week of activities may correspond to 8.6 hours of walking (assuming 3.5 METs) or 4.3 hours of swimming (assuming 7 METs).

In the CPS II Nutrition Cohort, reporting increasing amounts of walking plus other activities was associated with significantly lower risk of colon cancer in both men and women, with a clear gradient in lower risk seen even among women. The lack of a clear reduction in risk among persons who reported any or increasing amounts of walking only was unexpected and may be partly explained by our inability to assess the pace of walking, physical fitness, or disability in this elderly cohort. It is possible that participants in this study who reported walking as the only recreational physical activity were physically unable to engage in other activities or walked at a slower pace than persons who reported engaging in walking and other activities. We had limited statistical power to examine colon or rectal cancer risk in relation to increasing amounts of other activities, because <6% of participants reported engaging in these activities without walking. Whereas our results suggest that engaging in walking and activities more intense than walking may be necessary to substantially lower colon cancer risk in older men and women, we recognize the need for more refined assessment of the intensity of walking and other activities in elderly populations.

An important question concerns whether recreational physical activity begun later in life is associated with lower risk of colon cancer. In our study, recent activity is more strongly associated with reduced risk of colon cancer than past activity. Furthermore, increasing amounts of recent activity are associated with lower risk of colon cancer regardless of past activity level. Although these data suggest that physical activity begun later in life may be beneficial with respect to colon cancer, we had limited statistical power to examine these relations because <30% of participants reported little or no activity in the past. The lack of an association with past activity is consistent with some (16, 22, 40) but not all published studies (33). One case-control study (40) found no association between early adulthood activity and colon cancer; another study reported lower risk of colon cancer associated with long-term vigorous but not moderate activity (33). Two prospective studies (16, 22) have reported on physical activity information collected at different time points. Neither the Physicians' Health Study (22) nor the Harvard College Alumni study (16) found an inverse association with past physical activity. Whereas these findings support the hypothesis that physical activity may play a more important role later in the continuum of colon carcinogenesis (2), they should be interpreted cautiously because the lack of an inverse association with past activity may also be related to the generally crude measurement of past physical activity in this and other studies. Better measurements of physical activity, collected prospectively, are needed to evaluate the timing of physical activity in relation to colon and rectal cancer risk.

Few prospective studies have reported on physical activity and colon cancer by subsite (11, 20, 21); two studies have shown a stronger inverse association between physical activity and distal colon cancers (11, 21), whereas a third reported no difference by subsite in men and a stronger inverse association with proximal colon cancer in women (20). Case-control studies have not reported differences in the inverse association by colon subsite (32-36, 39). No statistically significant difference was observed between proximal and distal colon cancer risk in this study, but we had limited statistical power to examine subsite differences by sex.

The significantly lower risk of rectal cancer associated with recreational physical activity in this study is consistent with the results of a recent large case-control study (39) but is inconsistent with previous prospective studies (14, 16, 20, 25) that have generally reported null results. We observed no linear decrease in rectal cancer risk with increasing recreational physical activity; risk decreased with increasing amounts of activity but not at the highest level of activity, consistent with previous case-control studies (31, 34, 46). Only one large case-control study (39) has reported a significant dose-response relationship between increasing vigorous activity and decreasing risk of rectal cancer in men and women.

Several biological mechanisms have been proposed for the role of physical activity in colorectal carcinogenesis. Physical activity may reduce stool transit time, causing decreased exposure of the intestinal epithelium to carcinogens or mutagens. However, stool transit time has not been convincingly shown to be associated with colorectal cancer risk (47, 48). A related hypothesis is that exercise increases water intake, which has been associated with reduced risk of colorectal adenoma and cancer (49, 50). Physical activity also has been proposed to reduce colon cancer risk by reducing body weight or through mechanisms independent of body composition (1, 51). Physical inactivity and central adiposity are both associated with insulin resistance and the hyperinsulinemic state and may affect colon cancer risk through growth factors (52-54). Our results are consistent with physical activity being independently associated with colon cancer and not acting primarily through BMI. However, we did not have a measure of central adiposity. Nevertheless, our results support the importance of energy balance through physical activity and caloric intake (55) as suggested by the somewhat stronger inverse association with colon cancer seen among persons who reported modest daily energy intake and body weight maintenance. It is also possible that physical activity may play an anti-inflammatory role by acting directly on the immune system or through its effect on obesity (56), which is considered by some to cause low-grade systemic inflammation (57) and is associated with elevated serum levels of several inflammatory markers (57-59). Increased physical activity is associated with lower concentrations of C-reactive protein and fibrinogen

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(60, 61) and can induce several cytokine inhibitors and anti-inflammatory cytokines (59). Human and experimental studies show that cytokine expression and function are critical in regulating colonic epithelial cell growth, differentiation, and migration and in maintaining overall mucosal integrity (62-66). The significant interaction between physical activity and aspirin use in lowering colon cancer risk in this study lends support to an anti-inflammatory role of physical activity.

Limitations of these data include our inability to assess the frequency (times per week) separately from the duration (hours each time) of physical activity, participants' physical fitness or disability, and our limited statistical power to examine colon cancers by subsite of origin or rectal cancers by sex. Our measures of physical activity were self-reported and not validated, and we had limited numbers of people who reported higher amounts of other activities. We had no information on the intensity at which participants did each of the recreational physical activities and may have misclassified participants who engaged in activities not listed among the seven activities on our questionnaire. Strengths of this study include the ability to evaluate multiple potential confounders and effect modifiers. The prospective design of this study also enabled us to assess the importance of past and recent physical activity, change in body weight, and other covariates using data collected 10 years apart.

Our results show that increasing amounts of recreational physical activity are associated with substantially lower risk of colon cancer and that recreational physical activity is associated with significantly lower risk of rectal cancer in older men and women. We conclude that recreational physical activity should be an integral part of any colorectal cancer prevention program in older adults.

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論文名	Amount, type, and timing of recreational physical activity in relation to colon and rectal cancer in older adults: the Cancer Prevention Study II Nutrition Cohort.
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対象の内訳		**ヒト**	**動物**		**欧米**		**縦断研究**
	対象	一般健常者	空白	**地 域**	(　　)	**研究の種類**	コホート研究
	性別	男女混合	(　　)		(　　)		(　　)
	年齢	50-74			(　　)		前向き研究
	対象数	10000以上	空白		(　　)		(　　)
調査の方法	質問紙	(　　)					
アウトカム	**予 防**	な し	な し	ガン予防	な し	(　　)	(　　)
	維持・改善	な し	な し	な し	な し	(　　)	(　　)

図 表

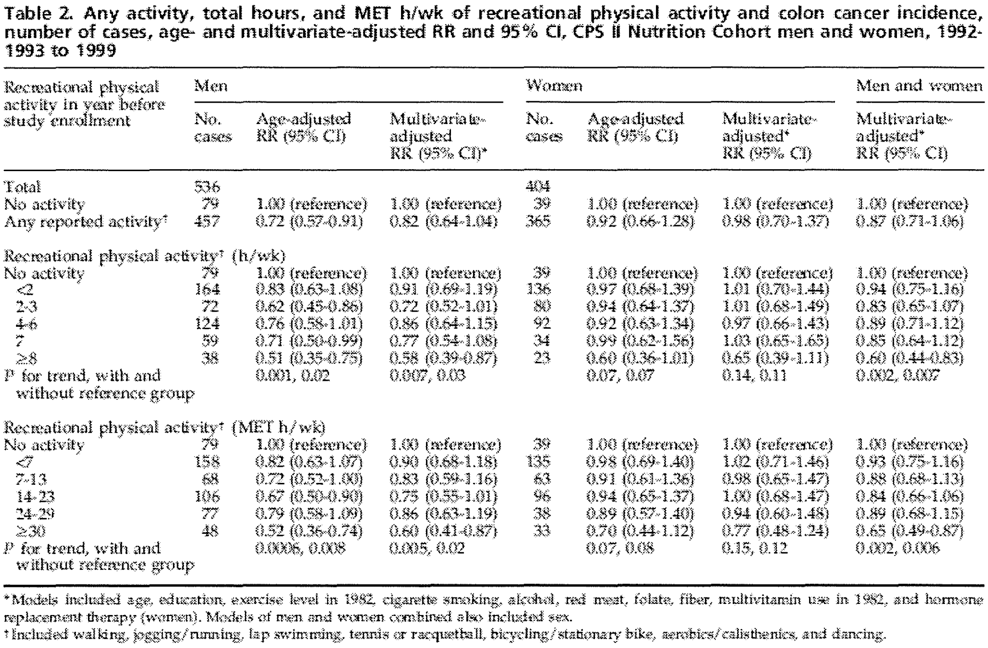

Table 2. Any activity, total hours, and MET h/wk of recreational physical activity and colon cancer incidence, number of cases, age- and multivariate-adjusted RR and 95% CI, CPS II Nutrition Cohort men and women, 1992-1993 to 1999

Recreational physical activity in year before study enrollment	Men			Women			Men and women
	No. cases	Age-adjusted RR (95% CI)	Multivariate-adjusted RR (95% CI)*	No. cases	Age-adjusted RR (95% CI)	Multivariate-adjusted* RR (95% CI)	Multivariate-adjusted* RR (95% CI)
Total	536			404			
No activity	79	1.00 (reference)	1.00 (reference)	39	1.00 (reference)	1.00 (reference)	1.00 (reference)
Any reported activity†	457	0.72 (0.57-0.91)	0.82 (0.64-1.04)	365	0.92 (0.66-1.28)	0.98 (0.70-1.37)	0.87 (0.71-1.06)
Recreational physical activity† (h/wk)							
No activity	79	1.00 (reference)	1.00 (reference)	39	1.00 (reference)	1.00 (reference)	1.00 (reference)
<2	164	0.83 (0.63-1.08)	0.91 (0.69-1.19)	136	0.97 (0.68-1.39)	1.01 (0.70-1.44)	0.94 (0.75-1.16)
2-3	72	0.62 (0.45-0.86)	0.72 (0.52-1.01)	80	0.94 (0.64-1.37)	1.01 (0.68-1.49)	0.83 (0.65-1.07)
4-6	124	0.76 (0.58-1.01)	0.86 (0.64-1.15)	92	0.92 (0.63-1.34)	0.97 (0.66-1.43)	0.89 (0.71-1.12)
7	59	0.71 (0.50-0.99)	0.77 (0.54-1.08)	34	0.99 (0.62-1.56)	1.03 (0.65-1.65)	0.85 (0.64-1.12)
≥8	38	0.51 (0.35-0.75)	0.58 (0.39-0.87)	23	0.60 (0.36-1.01)	0.65 (0.39-1.11)	0.60 (0.44-0.83)
P for trend, with and without reference group		0.001, 0.02	0.007, 0.03		0.07, 0.07	0.14, 0.11	0.002, 0.007
Recreational physical activity† (MET h/wk)							
No activity	79	1.00 (reference)	1.00 (reference)	39	1.00 (reference)	1.00 (reference)	1.00 (reference)
<7	158	0.82 (0.63-1.07)	0.90 (0.68-1.18)	135	0.98 (0.69-1.40)	1.02 (0.71-1.46)	0.93 (0.75-1.16)
7-13	68	0.72 (0.52-1.00)	0.83 (0.59-1.16)	63	0.91 (0.61-1.36)	0.98 (0.65-1.47)	0.88 (0.68-1.13)
14-23	106	0.67 (0.50-0.90)	0.75 (0.55-1.01)	96	0.94 (0.65-1.37)	1.00 (0.68-1.47)	0.84 (0.66-1.06)
24-29	77	0.79 (0.58-1.09)	0.86 (0.63-1.19)	38	0.89 (0.57-1.40)	0.94 (0.60-1.48)	0.89 (0.68-1.15)
≥30	48	0.52 (0.36-0.74)	0.60 (0.41-0.87)	33	0.70 (0.44-1.12)	0.77 (0.48-1.24)	0.65 (0.49-0.87)
P for trend, with and without reference group		0.0006, 0.008	0.005, 0.02		0.07, 0.08	0.15, 0.12	0.002, 0.006

*Models included age, education, exercise level in 1982, cigarette smoking, alcohol, red meat, folate, fiber, multivitamin use in 1982, and hormone replacement therapy (women). Models of men and women combined also included sex.

†Included walking, jogging/running, lap swimming, tennis or racquetball, bicycling/stationary bike, aerobics/calisthenics, and dancing.

図表掲載箇所	P2190, Table2
概 要 **(800字まで)**	the Cancer Prevention Study II Nutrition Cohortに参加している男性70403名、女性80771名を対象(50-74歳)に、約8年かの追跡調査を行い、身体活動と大腸がん(結腸、直腸)発症との関連を検討した研究である。身体活動に関しては、「平均で週何時間、次のようなレクレーション活動をしますか？という質問により調査した。レクレーション活動(括弧内はメッツを示す)として、ウォーキング(3.5)、自転車やエアロバイク(4)、エアロビクス(5)、ダンス(4.5)を聞き取り、週あたりの時間やメッツ・時で評価した。結腸の大腸がんに関しては、余暇身体活動を持たない群と比較して、7未満, 7-13, 14-23, 24-29, 30メッツ・時/週以上行っているグループでは、男性において、0.9(0.68-1.18), 0.83(0.59-1.16), 0.75(0.55-1.01), 0.86(0.63-1.19), 0.60(0.41-0.87)と30メッツ・時/週以上行っているグループで有意にリスク低下が認められ、身体活動量増加に伴い、リスク低下が認められた(P for trend: 0.02)。一方、女性では有意なリスク低下は認められなかった。直腸がんに関しては、男女を一緒にして分析した場合、身体活動を行っていない群に対して、2時間未満でも行っているグループで
結 論 **(200字まで)**	高齢の男女において、余暇時間に運動を行っているものは、大腸がん(結腸や直腸)のリスクを低下させることが示された。
エキスパートによるコメント **(200字まで)**	大腸がんの発症に対する身体活動・運動の予防的効果は、概ね一致した結論が導きだされていると思われる。今後、日本においても、大腸がんの発症予防に対する身体活動・運動の種類や強度、時間のより詳細の検討が行われることが期待される。

担当者　村上晴香

ORIGINAL INVESTIGATION

Long-term Recreational Physical Activity and Risk of Invasive and In Situ Breast Cancer

The California Teachers Study

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Background: Long-term physical activity may affect breast cancer risk. Few prospective studies have evaluated in situ or invasive breast cancer risk, or breast cancer receptor subtypes, in relation to long-term activity.

Methods: We examined the association between recreational physical activity and risk of invasive and in situ breast cancer in the California Teachers Study, a cohort of women established in 1995-1996. Of 110 599 women aged 20 to 79 years with no history of breast cancer followed up through December 31, 2002, 2649 were diagnosed as having incident invasive breast cancer and 593 were diagnosed as having in situ breast cancer. Information was collected at cohort entry on participation in strenuous and moderate recreational activities during successive periods from high school through the current age or age 54 years (if older at enrollment) and in the past 3 years. A summary measure of long-term activity up to the current age, or age 54 years if older, was constructed for each woman.

Results: Invasive breast cancer risk was inversely associated with long-term strenuous activity (>5 vs ≤0.5 h/wk per year: relative risk, 0.80; 95% confidence interval, 0.69-0.94; *P* trend=.02), as was in situ breast cancer risk (>5 vs ≤0.5 h/wk per year: relative risk, 0.69; 95% confidence interval, 0.48-0.98; *P* trend=.04). Strenuous and moderate long-term activities were associated with reduced risk of ER-negative (strenuous: *P* trend=.003; moderate: *P* trend=.003) but not ER-positive (strenuous: *P* trend=.23; moderate: *P* trend=.53) invasive breast cancer.

Conclusion: These results support a protective role of strenuous long-term exercise activity against invasive and in situ breast cancer and suggest differing effects by hormone receptor status.

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FEW ESTABLISHED RISK FACTORS for breast cancer are easily modifiable. Current evidence supports a reduction in breast cancer risk with regular physical activity, although data are based largely on case-control studies.[1] Biological mechanisms proposed to explain the protective relationship include pathways related to endogenous hormones, metabolism, and immune function.[2-4] Physical activity can modify menstrual characteristics, delaying age at menarche[5] and reducing the number of ovulatory cycles,[6] thus contributing to a potential decrease in lifetime exposure to ovarian hormones etiologically related to breast cancer.[7,8] Physical activity may also decrease bioavailable ovarian steroid hormone levels by increasing circulating levels of sex hormone binding globulin, a protein that binds and presumably inactivates estradiol.[2,3] Results of studies[3] regarding the immunomodulatory effects of physical activity are inconsistent but may involve effects on the number of natural killer cells and other immune factors, with effects varying with the intensity of activity.[3] In addition, physical activity may regulate energy balance, thereby reducing overall weight gain and abdominal adiposity and improving insulin sensitivity,[2-4] all of which have been linked to breast cancer risk.

Questions remain regarding the amount and intensity of physical activity and the periods when activity provides the greatest breast cancer risk reduction. Little information exists on whether impact varies by tumor receptor status.[9-12] Furthermore, the relationship between physical activity and in situ breast cancer is not well understood, as few studies have evaluated in situ separately from invasive breast cancer.[13,14] To address these issues, we examined the relationship between recreational physical activity measures and invasive and in situ breast cancer among women in the large California Teachers Study cohort.

METHODS

STUDY POPULATION

Details of the California Teachers Study have been described previously.[15] Briefly, the California Teachers Study is a prospective study of 133 479 current and retired female California public school teachers and administrators who were active members of the California State Teachers Retirement System when the cohort was established in 1995.

Participants with newly diagnosed first primary invasive or in situ breast cancer were identified through annual linkages with the California Cancer Registry, which has 99% complete reporting for breast cancer.[16] Person-time of follow-up began with the date the baseline questionnaire was completed in 1995-1996 and ended with the first of the following: a breast cancer diagnosis (invasive or in situ), a permanent move outside of California (n=5329), death (n=2898), or December 31, 2002.

We excluded women from the analytic cohort, sequentially, if they had a previous or unknown history of breast cancer (n=6274), were not California residents at baseline (n=8867), were 80 years or older at baseline (n=5133), or had incomplete data on physical activity (n=738) or menarche or reproductive history (n=1868). Of the 110 599 women remaining, 2649 were diagnosed as having invasive breast cancer during follow-up. For analyses of in situ breast cancer, we excluded the 2649 women diagnosed as having invasive breast cancer because the diagnosis of invasive disease presumes that the patients have passed through the in situ disease stage undetected. We also excluded 916 women with unknown smoking status (n=543) or unknown history of breast biopsy (n=373). In the cohort of 107 034 women eligible for in situ breast cancer analyses, 593 were diagnosed as having in situ breast cancer during follow-up, including 55 with lobular carcinoma in situ. For analyses of invasive breast cancer, we censored women who developed in situ breast cancer on the dates of their diagnoses.

The University of Southern California institutional review board approved the use of human subject data in these analyses in accord with an assurance filed with and approved by the US Department of Health and Human Services.

RECREATIONAL PHYSICAL ACTIVITY MEASURES

Participants provided information at baseline regarding their participation in moderate and strenuous recreational physical activities between high school and their current age or age 54 years if 55 years or older as well as recent activity. Participants were provided examples of moderate activities (eg, brisk walking, golf, and volleyball) and strenuous activities (eg, swimming laps, aerobics/calisthenics, running, and jogging) and reported their mean hours per week (none, 0.5, 1, 1.5, 2, 3, 4-6, 7-10, and ≥11 hours) and months per year (1-3, 4-6, 7-9, and 10-12 months) of participation at each level of activity during high school; from ages 18 to 24 years, 25 to 34 years, 35 to 44 years, and 45 to 54 years; and in the past 3 years. We created separate strenuous and moderate mean annual hours per week activity variables for each period by multiplying the hours 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, assigning a value of 12 for the category 11 h/wk or more.

Measures of long-term strenuous and long-term moderate physical activity were calculated for each participant by multiplying the average annual hours per week of activity during a period by the number of years the woman spent in that period, summing across all relevant periods, and dividing this cumulative measure by the total number of years spent across all periods. The categories established for strenuous and moderate long-term activity measures were 0.50 or less, 0.51-2.00, 2.01-3.50, 3.51-5.00, and more than 5.00 annual hours per week.

ASSESSMENT OF BREAST CANCER RISK FACTORS

We collected information on relevant breast cancer risk factors at baseline, including race/ethnicity, family history of breast cancer, age at menarche, reproductive history, menopausal status, use of hormone therapy (HT) and oral contraceptives, height, weight, diet, smoking history, alcohol consumption, mammography screening history, and breast biopsy history.[15] Quartiles of body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) were based on the distribution in the cohort. Women were considered premenopausal if they were having menstrual periods at baseline. Women whose menstrual periods stopped within 6 months of the baseline questionnaire were classified as perimenopausal. Women were postmenopausal if they reported that their periods had stopped more than 6 months earlier (natural menopause or both ovaries removed) or they were 56 years or older (whether or not they were currently taking HT) and were not considered premenopausal or perimenopausal. Younger women currently taking some form of HT for more than 1 year whose periods had not stopped and those who had a hysterectomy without bilateral oophorectomy were assigned unknown menopausal status.

STATISTICAL ANALYSES

We used multivariable Cox proportional hazards regression[17] to estimate the association (relative risk [RR] and 95% confidence interval [CI]) between physical activity and breast cancer risk, conducting analyses separately for invasive and in situ breast cancer. In the Cox regression models, the time scale was defined by age at baseline (entry) and age at event or censoring (exit). We evaluated the relationship between the individual physical activity measures and invasive and in situ breast cancer risk using 2 models: an age-adjusted model and a multivariable model with adjustments for race (white, black, Asian, Hispanic, or other/unspecified), family history of breast cancer in a first-degree relative (yes, no, or unknown/adopted), HT/menopausal status (premenopausal, perimenopausal, postmenopausal/never used HT, postmenopausal/estrogen only therapy, postmenopausal/estrogen plus progesterone combined therapy, postmenopausal/estrogen alone and estrogen plus progesterone therapy, or unknown menopausal status/unknown HT use), BMI (<21.4, 21.4-23.6, 23.7-27.2, ≥27.3, or unknown), history of smoking at least 100 cigarettes (never, current, past, or unknown), alcohol intake during the past year (≤15 g/d, >15 g/d, or unknown), screening mammogram in the past 2 years (yes, no, or unknown), and history of a breast biopsy (yes, no, or unknown). Invasive breast cancer models also included a combined age at first full-term pregnancy and parity variable (age 15-24 years/1-3 term pregnancies, age 15-24 years/≥4 term pregnancies, age 25-29 years/1-3 term pregnancies, age 25-29 years/≥4 term pregnancies, age ≥30 years/1-3 term pregnancies, age ≥30 years/≥4 term pregnancies, nulliparous, or unknown if had term pregnancies). The multivariable in situ breast cancer models included a less detailed pregnancy history variable (<25, 25-29, 30-34, ≥35 years at first term pregnancy, nulliparous, or unknown) due to the smaller number of in situ breast cancer cases in the expanded pregnancy categories. We did not include total caloric intake in the multivariable models because this was unrelated to either invasive or in situ breast cancer risk.[18]

Table 1. Baseline Characteristics in Relation to Long-term Strenuous Physical Activity in 110 599 Women Eligible for the Analysis of Invasive Breast Cancer*

Characteristic	Annual Strenuous Long-term Activity, h/wk					Women With Characteristic
	≤0.50	0.51-2.00	2.01-3.50	3.51-5.00	>5.00	
Participants, No. (%)	31 919 (28.9)	35 906 (32.5)	19 923 (18.0)	10 879 (9.8)	11 972 (10.8)	
Age at baseline, mean ± SD, y						
All women <80 y	56.7 ± 12.1	56.2 ± 12.4	48.4 ± 12.4	47.1 ± 12.9	46.5 ± 13.5	51.4 ± 13.1
Women 50-79 y	62.6 ± 8.4	60.6 ± 8.1	60.1 ± 8.0	60.3 ± 8.1	61.1 ± 8.1	61.3 ± 8.3
Women <50 y	42.2 ± 6.4	40.8 ± 6.8	39.9 ± 6.9	38.8 ± 7.1	37.9 ± 7.1	40.2 ± 7.0
Race, %						
White	86.1	86.7	86.3	85.6	85.5	95 330 (86.2)
Black	3.0	2.8	2.5	2.4	2.5	3008 (2.7)
Hispanic	3.8	4.4	5.1	5.5	5.0	5000 (4.5)
Asian	4.6	3.7	3.3	3.1	2.9	4126 (3.7)
American Indian, other, or unspecified	2.6	2.5	2.9	3.4	4.1	3135 (2.8)
First-degree family history of breast cancer, %†	13.3	12.3	11.4	11.2	10.6	12 920 (12.1)
History of breast biopsy, %	18.1	15.5	14.3	13.5	12.5	17 092 (15.5)
Had mammogram within 2 y of joining cohort, %	83.1	75.9	69.9	65.1	60.3	81 982 (74.1)
Age at menarche >13 y, %	19.5	19.1	20.4	21.6	24.3	22 438 (20.3)
Nulliparous, %	22.3	24.4	28.1	32.9	37.8	29 380 (26.7)
Menopausal status, %						
Premenopausal	27.9	47.0	57.0	60.4	61.7	46 642 (46.2)
Perimenopausal	2.4	2.6	2.2	2.2	1.9	2364 (2.3)
Postmenopausal, no hormone use	16.9	10.9	8.8	8.7	9.7	12 031 (11.9)
Postmenopausal, only estrogen alone use	22.4	15.5	12.6	11.4	11.1	16 258 (16.1)
Postmenopausal, only estrogen plus progestin use	19.3	15.9	12.7	11.2	10.4	15 384 (15.2)
Postmenopausal, estrogen alone and estrogen plus progestin use	11.1	8.2	6.7	6.1	5.2	8314 (8.2)
BMI, mean ± SD‡	25.4 ± 5.5	25.1 ± 5.3	24.7 ± 5.0	24.3 ± 4.9	23.9 ± 4.6	24.9 ± 5.2
Caloric intake, mean ± SD, kcal/d‡	1513 ± 534	1580 ± 552	1605 ± 559	1628 ± 579	1676 ± 605	1580 ± 559
Smoking status, %‡						
Never	65.3	65.9	67.3	67.7	69.1	73 163 (66.5)
Current	5.3	5.2	5.0	4.9	5.5	5696 (5.2)
Past	29.4	29.0	27.7	27.4	25.4	31 176 (28.3)
Alcohol use, %‡						
Nondrinker	38.1	32.0	31.0	30.6	30.2	34 953 (33.2)
<15 g/d	45.8	51.5	52.5	52.4	51.7	52 744 (50.2)
≥15 g/d	16.1	16.5	16.6	17.0	18.0	17 462 (16.6)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
*Covers the period from high school to entry into the cohort or to age 54 years if 55 years or older at cohort entry.
†Family history in at least 1 first-degree relative.
‡Patients with unknown values were excluded from the appropriate calculations.

Trend tests for each physical activity variable were performed by fitting the median value of exposure categories in the statistical models and determining whether the slope variable differed from zero (Wald test). We evaluated effect modification by age at baseline, HT use among postmenopausal women, first-degree family history of breast cancer, parity, and BMI using a 1-*df* likelihood ratio test for heterogeneity of 2 trends.[19]

We examined the association between physical activity and invasive breast cancer by estrogen receptor (ER) and progesterone receptor (PR) status of the tumors using information recorded by the California Cancer Registry. We had 1452 ER-positive/PR-positive (ER+/PR+), 305 ER+/PR-negative (PR–), and 309 ER-negative (ER–)/PR– tumors and 1879 ER+ and 345 ER– tumors. Too few breast cancers were ER–/PR+ for meaningful analysis (n=30). We tested for heterogeneity of trends in risk using a 1-*df* χ^2 test.

To determine the appropriateness of the proportional hazards assumption inherent in the Cox model, we visually examined Kaplan-Meier survival curves, plotted scaled Schoenfeld residuals,[20] and assessed the correlation of the residuals with time in the study. We observed no violations of the proportionality assumption. Two-sided *P* values are reported for tests for trend and for heterogeneity of trends. We did not adjust CIs or *P* values for multiple comparisons. All statistical analyses were performed using the SAS software program (SAS version 9.1; SAS Institute Inc, Cary, NC).

RESULTS

The mean±SD age of women diagnosed as having invasive breast cancer was 61.7±10.6 years (range, 27-86 years) and of women diagnosed as having in situ breast cancer was 60.9±10.4 years (range, 37-86 years). The mean length of follow-up was 6.6 years. The distribution of participant characteristics for several breast cancer risk factors is given in **Table 1** across categories of long-term strenuous physical activity. Women reporting higher levels of strenuous activity were more likely to be younger (as reflected by age, menopausal status, and rates of mammography), to have later menarche, to be nulliparous, and to have a lower BMI, but only mod-

Table 2. Relative Risk Estimates for the Association Between Physical Activity and Invasive Breast Cancer Risk in 110 599 Eligible Women

Annual Physical Activity, h/wk	Observed Person-years	Breast Cancer Cases, No.	RR (95% CI)	
			Age Adjusted*	Multivariable Adjusted†
Lifetime				
Strenuous				
0-0.50	209 529	980	1 [Reference]	1 [Reference]
0.51-2.00	237 143	855	0.95 (0.86-1.04)	0.93 (0.85-1.02)
2.01-3.50	131 905	392	0.89 (0.79-1.00)	0.88 (0.78-0.99)
3.51-5.00	72 038	231	1.03 (0.89-1.19)	1.02 (0.88-1.18)
>5.00	78 888	191	0.81 (0.69-0.95)	0.80 (0.69-0.94)
P trend			.03	.02
Moderate				
0-0.50	150 052	594	1 [Reference]	1 [Reference]
0.51-2.00	263 588	961	1.06 (0.95-1.17)	1.02 (0.92-1.13)
2.01-3.50	150 037	537	1.05 (0.93-1.18)	1.02 (0.91-1.15)
3.51-5.00	83 936	287	1.02 (0.88-1.17)	0.99 (0.86-1.14)
>5.00	81 890	270	0.95 (0.82-1.10)	0.94 (0.81-1.08)
P trend			.37	.29
Past 3 y				
Strenuous				
0-0.50	489 278	1733	1 [Reference]	1 [Reference]
0.51-2.00	110 302	431	1.01 (0.91-1.12)	1.00 (0.90-1.11)
2.01-3.50	53 303	188	0.88 (0.76-1.03)	0.87 (0.75-1.01)
3.51-5.00	51 269	198	1.00 (0.86-1.16)	0.99 (0.86-1.15)
>5.00	25 350	99	0.98 (0.80-1.20)	0.99 (0.81-1.21)
P trend			.57	.56
Moderate				
0-0.50	346 838	990	1 [Reference]	1 [Reference]
0.51-2.00	172 436	727	1.06 (0.96-1.16)	1.03 (0.94-1.14)
2.01-3.50	82 319	360	1.04 (0.92-1.17)	1.02 (0.90-1.15)
3.51-5.00	82 732	352	0.96 (0.85-1.09)	0.94 (0.83-1.07)
>5.00	45 177	220	1.04 (0.90-1.21)	1.03 (0.88-1.19)
P trend			.97	.80

Abbreviations: CI, confidence interval; RR, relative risk.

*Age (in months) is used as the time metric for the Cox proportional hazards models; models are stratified by age (in years).

†Adjusted for categories of race, family history of breast cancer, age at first full-term pregnancy and number of full-term pregnancies combined variable, hormone therapy and menopausal status combined variable, body mass index, smoking history, alcohol consumption, history of breast biopsy, and mammography screening.

Table 3. Relative Risk Estimates for the Association Between Physical Activity and In Situ Breast Cancer Risk in 107 034 Eligible Women

Annual Physical Activity, h/wk	Observed Person-years	Breast Cancer Cases, No.	RR (95% CI)	
			Age Adjusted*	Multivariable Adjusted†
Lifetime				
Strenuous				
0-0.50	204 179	215	1 [Reference]	1 [Reference]
0.51-2.00	232 279	202	0.98 (0.81-1.19)	0.96 (0.79-1.17)
2.01-3.50	129 378	89	0.88 (0.68-1.13)	0.86 (0.67-1.11)
3.51-5.00	70 652	50	0.97 (0.71-1.33)	0.95 (0.70-1.30)
>5.00	77 515	37	0.70 (0.49-0.99)	0.69 (0.48-0.98)
P trend			.052	.04
Moderate				
0-0.50	146 036	144	1 [Reference]	1 [Reference]
0.51-2.00	258 244	218	0.96 (0.78-1.19)	0.93 (0.75-1.15)
2.01-3.50	146 827	113	0.89 (0.69-1.14)	0.87 (0.68-1.12)
3.51-5.00	82 408	64	0.91 (0.68-1.22)	0.89 (0.66-1.20)
>5.00	80 487	54	0.78 (0.57-1.07)	0.78 (0.57-1.06)
P trend			.10	.11
Past 3 y				
Strenuous				
0-0.50	479 086	392	1 [Reference]	1 [Reference]
0.51-2.00	107 927	90	0.92 (0.73-1.16)	0.91 (0.72-1.14)
2.01-3.50	52 195	50	1.04 (0.77-1.39)	0.99 (0.74-1.33)
3.51-5.00	50 079	48	1.07 (0.80-1.45)	1.03 (0.76-1.40)
>5.00	24 717	13	0.58 (0.34-1.01)	0.57 (0.33-0.99)
P trend			.27	.17
Moderate				
0-0.50	339 880	235	1 [Reference]	1 [Reference]
0.51-2.00	168 618	145	0.89 (0.72-1.10)	0.86 (0.70-1.07)
2.01-3.50	80 536	82	1.02 (0.79-1.31)	0.99 (0.76-1.28)
3.51-5.00	80 861	92	1.10 (0.86-1.41)	1.05 (0.82-1.35)
>5.00	44 109	39	0.83 (0.59-1.17)	0.80 (0.57-1.14)
P trend			.81	.60

Abbreviations: CI, confidence interval; RR, relative risk.

*Age (in months) is used as the time metric for the Cox proportional hazards models; models are stratified by age (in years).

†Adjusted for categories of race, family history of breast cancer, age at first full-term pregnancy hormone therapy and menopausal status combined variable, body mass index, smoking history, alcohol consumption, history of breast biopsy, and mammography screening.

est differences were observed across activity categories for other variables.

Age- and multivariable-adjusted risk estimates for the association of invasive breast cancer (**Table 2**) and in situ breast cancer (**Table 3**) with recreational physical activity did not differ substantially. Invasive breast cancer risk was reduced among women annually participating in more than 5 h/wk of strenuous activity relative to the least active women (RR, 0.80; 95% CI, 0.69-0.94; *P* trend = .02). Long-term moderate physical activity and strenuous and moderate activity in the past 3 years were not associated with invasive breast cancer. In situ breast cancer risk was also reduced among women in the highest vs lowest long-term strenuous physical activity category (RR, 0.69; 95% CI, 0.48-0.98; *P* trend = .04). We observed no statistically significant inverse trends in risk of in situ breast cancer with increasing levels of moderate or recent activity. Exclusion of the 55 patients with lobular carcinoma in situ did not alter these results (data not shown).

The RR estimates did not change for invasive or in situ breast cancer when we fit strenuous and moderate long-term activity simultaneously in the same model (data not shown). We also observed no interaction between moderate and strenuous activity and no impact of moderate activity in the absence of strenuous activity (data not shown).

We evaluated the effects of strenuous and moderate recreational physical activity during different periods (data not shown). Risk patterns and risk estimates for the association between invasive and in situ breast cancer and strenuous physical activity performed at ages 25 to 34 years and 35 to 44 years were similar in magnitude to the estimates given in Tables 2 and 3; physical activity at ages 45 to 54 years was not associated with either invasive or in situ breast cancer. In situ but not invasive breast cancer was associated with strenuous activity during high school and at ages 18 to 24 years.

We observed significant decreases in invasive breast cancer risk with increasing levels of long-term strenuous recreational physical activity among younger women (*P* trend = .02), women with no first-degree family history of breast cancer (*P* trend = .01), women with a BMI less than 25 (*P* trend = .03), and parous women (*P* trend = .002), yet

Table 4. Strenuous Long-term Physical Activity and Multivariable-Adjusted Relative Risk of Invasive Breast Cancer by First-Degree Family History of Breast Cancer, BMI, Parity, and Age*

Variable	Breast Cancer Cases, No.	Annual Strenuous Long-term Physical Activity, h/wk†					*P* Trend	*P* Value for Homogeneity of Trends
		≤0.50	0.51-2.00	2.01-3.50	3.51-5.00	>5.00		
Family history								
No	2067	1 [Reference]	0.92 (0.83-1.02)	0.89 (0.78-1.02)	1.03 (0.88-1.22)	0.74 (0.62-0.89)	.01	.41
Yes	491	1 [Reference]	0.96 (0.78-1.19)	0.85 (0.64-1.13)	0.89 (0.62-1.28)	1.02 (0.73-1.43)	.72	
BMI								
<25.0	1455	1 [Reference]	0.97 (0.86-1.09)	0.95 (0.81-1.10)	1.02 (0.84-1.23)	0.74 (0.60-0.91)	.03	.81
≥25.0	1094	1 [Reference]	0.91 (0.80-1.04)	0.78 (0.65-0.94)	1.05 (0.84-1.31)	0.85 (0.67-1.09)	.12	
Parity								
Nulliparous	618	1 [Reference]	0.94 (0.77-1.15)	0.95 (0.74-1.21)	1.26 (0.96-1.65)	1.01 (0.77-1.33)	.43	.02
Parous	2016	1 [Reference]	0.93 (0.84-1.04)	0.86 (0.75-0.99)	0.94 (0.79-1.11)	0.73 (0.60-0.89)	.002	
Age, y								
<55	1062	1 [Reference]	0.87 (0.75-1.02)	0.83 (0.69-0.99)	1.00 (0.81-1.24)	0.68 (0.53-0.87)	.02	.25
≥55	1587	1 [Reference]	0.97 (0.86-1.09)	0.91 (0.77-1.06)	1.00 (0.82-1.22)	0.90 (0.74-1.10)	.27	

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

*Adjusted for categories of race, family history of breast cancer, age at first full-term pregnancy and number of full-term pregnancies combined variable, hormone therapy and menopausal status combined variable, BMI, smoking history, alcohol consumption, history of breast biopsy, and mammography screening.

†Data are given as relative risk (95% confidence interval).

Table 5. Long-term Physical Activity and Multivariable-Adjusted Relative Risk of Invasive Breast Cancer by Estrogen Receptor and Progesterone Receptor Status*

Annual Long-term Physical Activity, h/wk	ER Positive (n = 1879)		ER Negative (n = 345)		RR (95% CI)		
	Breast Cancer Cases, No.	RR (95% CI)	Breast Cancer Cases, No.	RR (95% CI)	ER Positive/ PR Positive (n = 1452)	ER Positive/ PR Negative (n = 305)	ER Negative/ PR Negative (n = 309)
Strenuous							
0-0.50	699	1 [Reference]	134	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
0.51-2.00	602	0.93 (0.83-1.04)	112	0.84 (0.65-1.09)	0.98 (0.86-1.11)	0.82 (0.62-1.07)	0.86 (0.66-1.12)
2.01-3.50	267	0.85 (0.74-0.99)	56	0.84 (0.61-1.15)	0.91 (0.77-1.07)	0.82 (0.57-1.16)	0.88 (0.63-1.22)
3.51-5.00	163	1.02 (0.86-1.21)	27	0.79 (0.52-1.20)	1.05 (0.86-1.28)	0.98 (0.64-1.50)	0.76 (0.48-1.19)
>5.00	148	0.89 (0.74-1.06)	16	0.45 (0.27-0.76)	0.94 (0.77-1.16)	0.75 (0.47-1.18)	0.35 (0.19-0.65)
P trend		.23		.003	.67	.31	.001
Moderate							
0-0.50	416	1 [Reference]	84	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
0.51-2.00	691	1.05 (0.93-1.19)	136	0.99 (0.75-1.31)	1.06 (0.93-1.22)	1.03 (0.75-1.40)	0.97 (0.73-1.30)
2.01-3.50	372	1.01 (0.88-1.17)	72	0.94 (0.68-1.29)	1.02 (0.87-1.20)	1.13 (0.80-1.59)	0.90 (0.64-1.26)
3.51-5.00	203	1.00 (0.85-1.19)	31	0.73 (0.48-1.10)	0.96 (0.79-1.17)	1.22 (0.82-1.81)	0.75 (0.49-1.15)
>5.00	197	0.98 (0.82-1.16)	22	0.53 (0.33-0.85)	1.02 (0.84-1.24)	0.95 (0.62-1.47)	0.50 (0.30-0.83)
P trend		.53		.003	.73	.86	.003

Abbreviations: CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; RR, relative risk.

*Adjusted for categories of race, family history of breast cancer, age at first full-term pregnancy and number of full-term pregnancies combined variable, hormone therapy and menopausal status combined variable, body mass index, smoking history, alcohol consumption, history of breast biopsy, and mammography screening.

only the trends in risk for parous vs nulliparous women differed statistically (*P*=.02) (**Table 4**). Reclassification of BMI to obese (>30) vs nonobese women provided results similar to those given in Table 4 (data not shown). Among postmenopausal women, results for users of HT did not differ from those of nonusers (data not shown). Risk patterns were similar for in situ breast cancer, although for parity the test for homogeneity of trends was not statistically significant (data not shown).

Neither strenuous nor moderate long-term physical activity was associated with risk of ER+ invasive breast cancer (**Table 5**). Similar results were observed for ER+/PR+ and ER+/PR− cancers. Participation in the highest categories of long-term physical activity was associated with a decreased risk of ER− invasive breast cancer, with risk reductions of 55% and 47% for strenuous and moderate long-term physical activity, respectively, relative to women who averaged 0.5 h/wk or less per year. The ER−/PR− cancer showed a similar risk pattern. All trends in risk for ER− breast cancer were statistically significant. These trends in risk for ER− breast cancer differed significantly from those for ER+ cancer (all *P*<.01). We also assessed the association with ER status in premenopausal and postmenopausal women separately. Results for postmenopausal women were similar to those given in Table 5. With the limited number of breast cancers in premenopausal women (79 ER− and 366 ER+), we did not detect differences in the trends in risk by ER status (data not shown). Analyses restricted to the 77% of women with a recent screening mammogram (within 2 years of baseline) differed minimally from those for the entire cohort in Tables 2, 3, 4, and 5 (data not shown).

COMMENT

Results of case-control studies evaluating lifetime physical activity suggest an inverse association between physical activity and invasive breast cancer.[1] However, to our knowledge, this is the first prospective cohort study to assess the impact of accumulated long-term physical activity on breast cancer risk. Previous cohort studies[1,14,21] have included measures of current or recent recreational activity or activity at specific ages or time points and show reductions in risk ranging from 15% to 40%. Some studies,[1,14,21,22] but not all,[1,11,23-25] support a reduction in breast cancer risk. The varying results may be due to age differences in the study populations, differences in physical activity measures used, or duration of follow-up after recording recent or current activity.

Of interest in this study is the inverse association between long-term physical activity and ER− breast cancer, as tamoxifen and raloxifene have not affected ER− breast cancer incidence in chemoprevention trials.[26,27] The few previous studies[9-12] evaluating the effect of physical activity on invasive breast cancer risk by hormone receptor status suggest little or no difference in risk. Although we previously reported no difference in the impact of lifetime physical activity on joint ER and PR status for premenopausal and postmenopausal women,[12] close inspection of the results suggests a stronger protective association for ER−/PR− than for ER+/PR+ breast cancer. Exercise during adolescence and in the past 10 years was associated with a reduced risk of ER+/PR+ and ER−/PR− breast cancer in a Shanghai-based case-control study.[9] Similarly, we reported that the beneficial impact of exercise activity did not vary by ER status in a population-based case-control study[10] of white and black women in the United States. Thus, the present finding that physical activity reduces the risk of ER− tumors is consistent with the limited case-control study results, but the finding of no association for ER+ is not. The Women's Health Study[11] evaluated the effect of physical activity on hormone receptor–positive tumors and observed no significant associations, consistent with the results presented herein.

An association between long-term physical activity and breast cancer that is restricted to ER− tumors seems inconsistent with the hypothesis that physical activity acts through estrogen mediated by its receptor[28-30] and suggests that physical activity does not exert its biological effects wholly through hormonal mechanisms. However, these findings do not preclude a hormonal mechanism, as some evidence exists that when ER+ progenitor cells are exposed to estrogen, they produce paracrine signals, which cause the proliferation of nearby ER− cells.[31] Furthermore, the Breast and Prostate Cancer Cohort Consortium showed that 2 common haplotypes of the 17β-hydroxysteroid dehydrogenase 1 gene (*HSD17B1*) are associated with risk of ER− but not ER+ breast cancer.[32] This gene encodes 17HSD1, which affects the conversion of estrone to estradiol, providing another potential link between estrogen and ER− tumors. The reduction in risk for ER− invasive breast cancer suggests that physical exercise may reduce tumor aggressiveness. Although this finding has enormous public health and therapeutic implications, it needs to be replicated in other studies, particularly in studies in which receptor status results collected through cancer registries can be verified in a single laboratory.

Few studies[13,14,21] have investigated the relationship between physical activity and in situ breast cancer. We previously reported a significant protective effect of lifetime physical activity on in situ breast cancer risk in a case-control study.[13] Physical activity at study entry was not associated with in situ breast cancer among 205 cases diagnosed in a cohort study of postmenopausal women.[21] The Women's Health Initiative Cohort Study[14] reported that women who engaged in strenuous physical activity at least 3 times per week at age 35 years had a modest, but not statistically significant, reduction in risk of in situ breast cancer; however, no specific data were provided in the publication. The present results support a protective effect of lifetime physical activity on the risk of in situ breast cancer. Most of these cancers are ductal carcinomas in situ, which are most often identified by mammography. The results for women with a screening mammogram within 2 years of baseline were consistent with those of the entire cohort. Thus, greater health consciousness of women is not a likely explanation for these findings. The risk reduction for in situ breast cancer suggests that physical activity acts at early stages in the development of breast cancer.

We did not identify ages when physical activity might have its greatest impact on breast cancer. We observed reductions in invasive and in situ breast cancer for activity at ages 25 to 34 years and 35 to 44 years that were similar to the long-term activity results. The modest, but not statistically significant, impact of activity during high school and at ages 18 to 24 years, coupled with the apparent greater impact of physical activity on invasive breast cancer among women younger than 55 years, may reflect greater misclassification of physical activity at younger ages, particularly among older women. In a recent case-control study,[10] which collected detailed age-specific data on physical activity using a calendar of life events, we also did not identify any particular ages when activity was most protective against breast cancer risk.

Several previous studies have looked at the effects of physical activity on breast cancer risk by subgroups of BMI[14,21,23,24,33-35] and family history,[14,33,35-41] but the results are inconsistent. Although we observed statistically significant results for younger women, women without a first-degree family history of breast cancer, leaner (BMI <25 or <30) women, and parous women, trends across the levels of these subgroups differed statistically significantly only for parity and invasive breast cancer.

The present results suggest that high levels of sustained strenuous but not moderate physical activity reduce breast cancer risk. Although this may be simply a dose threshold effect, an alternative explanation is that women can recall their participation in intense activities more accurately.[1,42] Previous cohort studies[1,14,35] supporting an inverse association with recreational physical activity have varied in terms of intensity levels measured and levels that confer a reduction in risk.

Strengths of this study include its prospective design, cohort size, large number of incident invasive and in situ breast cancer cases, and ability to identify and confirm cancer diagnoses through California's high-quality statewide cancer registry. We collected detailed measures of physical activity in multiple age periods, allowing for the assessment of cumulative long-term physical activity and recent activity.

A potential limitation of this study is that we did not collect information on occupational or household physical activity. These additional sources of physical activity may be important contributors to total energy expenditure[1,41] and may affect the association between physical activity and breast cancer risk.[1,37,41] A Canadian case-control study[37] examined all 3 sources of physical activity and reported an inverse association with occupational and household activity but not with recreational activity. The California Teachers Study cohort consists of active and retired teachers and administrators, and although we did not measure occupational activity, it is likely that most women who are active in the California public school system would have similar occupational activity levels, with the possible exception of physical education teachers. However, the length of time that the active teachers had been employed in the school system varies substantially, and we do not have information on other occupations held. We collected information on strenuous and moderate levels of physical activity by self-report, providing examples of activities at each level. Although it is possible that the reported levels may overestimate or underestimate actual activity, information was collected before breast cancer diagnosis and should not differ by disease status overall or by receptor status of the tumor.

In summary, these results provide additional evidence supporting a protective role for long-term strenuous recreational physical activity on risk of invasive and in situ breast cancer, whereas the beneficial effects of moderate activity are less clear. For invasive breast cancer, strenuous and moderate activity affect risk of ER− tumors, but neither affect risk of ER+ tumors.

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Author Contributions: Mss Dallal and Sullivan-Halley and Dr Bernstein each had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Ross, Deapen, Horn-Ross, Reynolds, Anton-Culver, West, Wright, and Bernstein. *Acquisition of data:* Ross, Deapen, Horn-Ross, Reynolds, Anton-Culver, Ziogas, West, Wright, and Bernstein. *Analysis and interpretation of data:* Dallal, Sullivan-Halley, Wang, Stram, and Bernstein. *Drafting of the manuscript:* Dallal, Sullivan-Halley, and Bernstein. *Critical revision of the manuscript for important intellectual content:* Ross, Wang, Deapen, Horn-Ross, Reynolds, Stram, Clarke, Anton-Culver, Ziogas, Peel, West, and Wright. *Statistical analysis:* Dallal, Sullivan-Halley, Wang, Stram, and Bernstein. *Obtained funding:* Ross, Deapen, Horn-Ross, Reynolds, Anton-Culver, West, Wright, and Bernstein. *Administrative, technical, and material support:* Ross, Deapen, Horn-Ross, Clarke, Peel, West, and Bernstein. *Study supervision:* Ross, Deapen, and Bernstein.

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Disclaimer: The ideas and opinions expressed herein are those of the authors, and endorsement by the State of California, Department of Health Services, the National Cancer Institute, and the Centers for Disease Control and Prevention or their contractors and subcontractors is not intended nor should be inferred.

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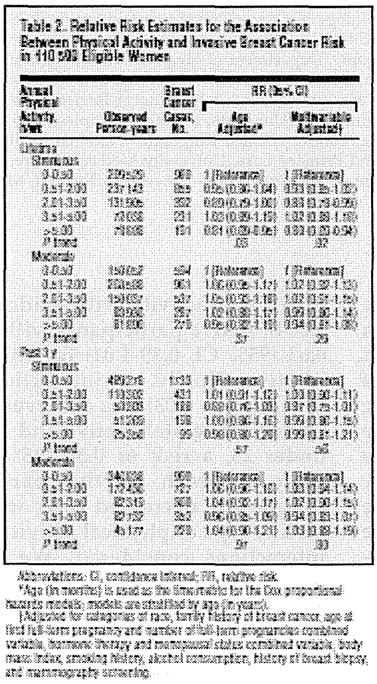
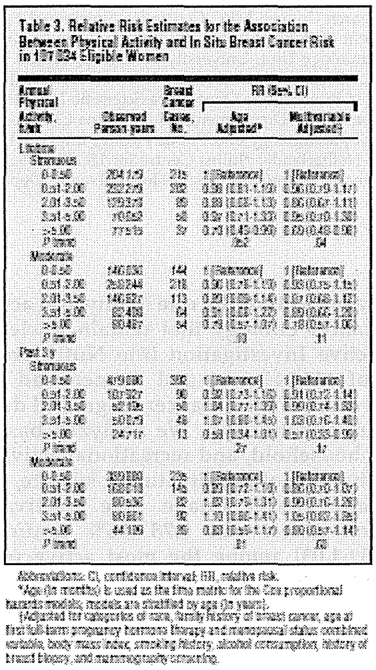
論文名	Long-term recreational physical activity and risk of invasive and in situ breast cancer: the California teachers study						
著 者	Dallal CM, Sullivan-Halley J, Ross RK, Wang Y, Deapen D, Horn-Ross PL, Reynolds P, Stram DO, Clarke CA, Anton-Culver H, Ziogas A, Peel D, West DW, Wright W, Bernstein L						
雑誌名	Arch Intern Med						
巻・号・頁	167　　408-415						
発行年	2007						
PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/17325304						
対象の内訳		**ヒト**	**動物**	**地 域**	欧米	**研究の種類**	縦断研究
	対象	一般健常者	空白		(　　)		コホート研究
	性別	女性	(　　)		(　　)		(　　)
	年齢	20-79歳			(　　)		前向き研究
	対象数	10000以上			(　　)		(　　)
調査の方法	質問紙	(　　)					
アウトカム	**予 防**	なし	なし	ガン予防	なし	(　　)	(　　)
	維持・改善	なし	なし	なし	なし	(　　)	(　　)
図 表	 Table 2. Relative Risk Estimates for the Association Between Physical Activity and Invasive Breast Cancer Risk in 110 [illegible] Eligible Women  Table 3. Relative Risk Estimates for the Association Between Physical Activity and In Situ Breast Cancer Risk in [illegible] Eligible Women						
図表掲載箇所	P411, Table2, Table3						
概 要 (800字まで)	本研究は、アメリカのThe California Teachers Studyに参加した女性110,599名を対象に平均6.6年間の追跡調査を行い、長期の余暇時間身体活動と浸潤性および上皮内乳がん発症リスクとの関連を検討したものである。中強度活動および高強度活動を行った週当たりの時間、年あたりの実施月数を各年齢別(高校生当時、18-24歳、25-34歳、35-44歳、45-54歳、過去3年間)に尋ね、それぞれの平均実施時間(時間/週/年)の合計を余暇時間総身体活動量とした。中強度活動、高強度活動をそれぞれ、0.50時間/週/年未満、0.51-2.00、2.01-3.50、3.51-5.00、5.00時間/週/年以上の5群に分類した。浸潤性乳がん関して、中強度活動では発症リスクに差はみられなかったが、高強度活動で、0.50時間/週/年未満の集団と比較すると、2.01-3.50時間/週/年、5.00時間/週/年以上で、発症リスクがそれぞれ0.88(95%信頼区間:0.78-0.99)、0.80(0.69-0.94)と量反応的なリスク減少がみられた(Ptrend=0.02)。上皮内乳がんに関しても、中強度活動では発症リスクに差はみられなかったが、高強度活動で、0.50時間/週/年未満の集団と比較すると、5.00時間/週/年以上で、発症リスクが						
結 論 (200字まで)	長期間の高強度身体活動の実施が、乳がん発症リスクに対する保護効果を発揮することが明らかとなったが、中強度活動に関しては明らかな関連はみられなかった。						
エキスパートによるコメント (200字まで)	身体活動基準の策定に使用された研究である。1時点での身体活動の評価だけでなく、複数時点での身体活動の多寡が乳がん発症に及ぼす影響を示した点に意義がある。一過性の身体活動だけでなく身体活動を継続する必要性を示唆した点にも注目したい。						

担当者　久保絵里子・村上晴香・宮地元彦

Physical Activity and Risk of Colon and Rectal Cancers: The European Prospective Investigation into Cancer and Nutrition

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Abstract

We investigated several aspects of the role of physical activity in colon and rectal cancer etiology that remain unclear in the European Prospective Investigation into Nutrition and Cancer. This cohort of 413,044 men and women had 1,094 cases of colon and 599 cases of rectal cancer diagnosed during an average of 6.4 years of follow-up. We analyzed baseline data on occupational, household, and recreational activity to examine associations by type of activity, tumor subsite, body mass index (BMI), and energy intake. The multivariate hazard ratio for colon cancer was 0.78 [95% confidence interval (95% CI), 0.59-1.03] among the most active participants when compared with the inactive, with evidence of a dose-response effect (P_{trend} = 0.04). For right-sided colon tumors, the risk was 0.65 (95% CI, 0.43-1.00) in the highest quartile of activity with evidence of a linear trend (P_{trend} = 0.004). Active participants with a BMI under 25 had a risk of 0.63 (95% CI, 0.39-1.01) for colon cancer compared with the inactive. Finally, an interaction between BMI and activity ($P_{\text{interaction}}$ = 0.03) was observed for right-sided colon cancers; among moderately active and active participants with a BMI under 25, a risk of 0.38 (95% CI, 0.21-0.68) was found as compared with inactive participants with BMI >30. No comparable decreased risks were observed for rectal cancer for any type of physical activity for any subgroup analyses or interactions considered. We found that physical activity reduced colon cancer risk, specifically for right-sided tumors and for lean participants, but not rectal cancer. (Cancer Epidemiol Biomarkers Prev 2006;15(12):2398–407)

Introduction

There is convincing evidence that physical activity reduces colon cancer risk; however, the evidence for rectal cancer is unclear (1). Of the 58 studies conducted to date on colon, rectal, or colorectal cancer and physical activity (2-59), 46 studies have found a risk reduction for colon cancer among the most physically active as compared with the least active study subjects despite many different physical activity assessment methods used in these studies (3, 4, 6, 9-24, 26, 27, 31-37, 40, 42-44, 47-52, 54-61). The risk reduction observed ranged from 10% to >50%, with 27 studies (3, 6, 9, 12, 17, 19-24, 27, 31, 32, 34, 35, 37, 44, 45, 47-50, 52, 56, 58, 59) finding an average risk reduction of at least 40% for colon cancer. Very few studies have had detailed measurements of physical activity and ~30 studies (2, 6, 8, 9, 12, 14-18, 20, 22, 24, 27, 31, 32, 34, 42, 44, 45, 51, 52, 55, 56, 58-60, 62-64) have been able to examine the risk by colon tumor subsite. Some evidence also suggests that the etiology of colon cancer may differ by subsite (65, 66);

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however, the evidence regarding the effect of physical activity on colon tumor subsite remains inconsistent. In addition, none of the large prospective cohort studies that examined these associations (10, 11, 18, 36, 57) has been conducted in a heterogeneous study population drawn from numerous different countries. We are conducting a large multinational cohort study in Europe in which data about physical activity were collected at baseline and with detailed data on confounders, effect modifiers, and tumor location. Given the important public health significance of physical activity for cancer risk reduction and the need for more definitive evidence on this topic, we examined these associations in the European Prospective Investigation into Cancer and Nutrition (EPIC).

Materials and Methods

Study Cohort. The EPIC study is a prospective cohort originally established to investigate the associations between dietary, lifestyle, genetic, and environmental factors and risk of specific cancers. The design and baseline data collection methods have previously been described (67). There were 366,521 women and 153,457 men enrolled between 1992 and 1998 in 23 regional or national centers in 10 European countries (Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, the Netherlands, and United Kingdom; ref. 67). These participants were recruited from the general population from defined areas in each country in most subcohorts with some exceptions: women who were members of a health insurance scheme for state school employees in France; women attending breast cancer screening in Utrecht, the Netherlands; blood donors in some components of the Italian and Spanish subcohorts; and a high number of vegans and vegetarians in the Oxford "Health conscious" cohort. Participants were mainly between 35 and 70 years of age at enrollment and provided written informed consent at the time they completed the baseline questionnaires on diet, lifestyle, and medical history. Approval for this study was obtained from the ethical review boards of the IARC and from all local institutions where subjects had been recruited for the EPIC study.

For this analysis, we excluded 26,040 cohort members with prevalent cancer at any site at enrollment based on the self-reported lifestyle questionnaire or based on information from the cancer registries; 65,648 members who had no physical activity questionnaire data including all study subjects from Norway and Umeå, Sweden, ~25% of the participants in Bilthoven, the Netherlands, and a few in the two UK centers; and 16,725 members with missing questionnaire data or missing dates of diagnosis or follow-up. We also excluded participants who were in the lowest and the highest 1% of the distribution of the ratio of reported total energy intake to energy requirement (68). The number of subjects included in this analysis was 413,044.

Identification of Colorectal Cancer Patients. Cases were identified through population-based cancer registries, except in France, Germany, and Greece, where a combination of methods, including health insurance records, cancer and pathology registries, and active follow-up through study subjects and their next-of-kin was used. Follow-up began at the date of enrollment and ended at either the date of diagnosis of colorectal cancer, death, or last complete follow-up. By April 2004, for the centers using record linkage with cancer registry data (Denmark, Italy, United Kingdom, the Netherlands, Spain, and Sweden), complete follow-up was available between December 31, 1999 and June 30, 2003, and for the centers using active follow-up (France, Germany, Greece), the last contact dates ranged between June 30, 2002 and March 11, 2004. The International Classification of Diseases for Oncology, 2nd version, was used to classify all incident cases of colon (C18) and rectal cancer (C19 and C20). Tumors of the anal canal were not included. For some analyses, colon cancers were subdivided into right colon tumors (codes C18.0-18.5 corresponding to tumors of the cecum, appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure) and left colon tumors (C18.6-18.7 including the descending and sigmoid colon).

Physical Activity Data. A description of the physical activity ascertainment used in the EPIC study has been described in detail elsewhere (69). The baseline questions on physical activity were derived from the more extensive modified Baecke questionnaire (70). An assessment of the relative validity and reproducibility of the nonoccupational physical activity questions was undertaken in a sample of men and women from the Netherlands and the short version of the questionnaire, similar to that used in EPIC, was found to be satisfactory for the ranking of subjects for their physical activity levels although less suitable for the estimation of energy expenditure (71). Physical activity data were obtained in either in-person interviews or self-administered using a standardized questionnaire in all centers included in this analysis.

Data on current occupational activity included employment status and the level of physical activity done at work (nonworker, sedentary, standing, manual, heavy manual. and unknown). In the Danish centers, the question focused on type of work activity done within the last year, and participants who did not answer this question were categorized as nonworking. Housewives were categorized as nonworkers except in the Spanish centers where housewives were categorized as "standing" most of the time. For comparability purposes, Spanish women who reported >35 h/wk of household activity were considered as housewives and their occupational physical activity data recoded to "nonworker."

The frequency and duration of nonoccupational physical activity data that were captured in all centers comprised household activities, including housework, home repair (do-it-yourself activities), gardening, and stair climbing, and recreational activities, including walking, cycling, and sports combined as done in winter and summer separately. Because the intensity of recreational and household activities was not directly recorded, a metabolic equivalent (MET) value was assigned to each reported activity according to the Compendium of Physical Activities (72). A MET is defined as the ratio of work metabolic rate to a standard metabolic rate of 1.0 (4.184 kJ) kg^{-1} h^{-1}; 1 MET is considered a resting metabolic rate obtained during quiet sitting. The MET values assigned to the nonoccupational data were 3.0 for walking, 6.0 for cycling, 4.0 for gardening, 6.0 for sports, 4.5 for home repair (do-it-yourself work), 3.0 for housework, and 8.0 for stair climbing. These mean MET values were obtained by estimating the average of all comparable activities in the Compendium. The mean numbers of hours per week of summer and winter household and recreational activities were estimated and then multiplied by the appropriate MET values to obtain MET-hours per week of activity.

Household and recreational activities in MET-hours per week were combined and cohort participants classified according to sex-specific EPIC-wide quartiles of total nonoccupational physical activity (low, medium, high, and very high). To derive an index of physical activity, quartiles of nonoccupational physical activity were cross-classified with the categories of occupational activity (Appendix Table 1). This index was developed based on a previous index constructed by Wareham and colleagues for the EPIC physical activity questionnaire data, which cross-classified occupational activity with hours spent doing cycling and sports. They validated the index against energy expenditure assessed by heart rate