monitoring in 173 men and women ages 40 to 65 years from Ely, Cambridgeshire (73). In this validation study, the index was found to be appropriate for ranking participants in large epidemiologic studies. To make the index more comprehensive, we cross-classified all household and recreational activity combined with occupational activity. In so doing, more information on each individual's actual activity done at baseline was included into the assessment of overall physical activity. We compared the results obtained using Wareham's index with those obtained with this new total physical activity index, and they were very similar.

As a way of indirectly assessing the validity of the total physical activity index derived by us, we also examined the means for each category of the index with the ratio of energy intake and basal metabolic rate adjusted for age, center, and BMI. The estimates of energy intake were taken from the dietary data collected in EPIC and the basal metabolic rate was estimated using prediction equations based on age, sex, height, and weight (74). We found that for men and women, there was a positive relationship between energy intake/basal metabolic rate and total activity, indicating that this index appropriately ranked the subjects according to their energy intake and requirements for their activity levels.

Statistical Methods. The analyses were conducted separately for colon and rectal cancers and tumor subsite within the colon because our a priori knowledge was that the association between physical activity and colon cancer differs according to site. Analyses were conducted using Cox proportional hazards regression. Attained age was used as the primary time variable. The analyses were stratified by center to control for differences in questionnaire design, follow-up procedures, and other center effects. Sex was included as a covariate when the analyses were conducted for the entire study population. In all models, age was used as the primary time variable, with time at entry and time when participants were diagnosed with cancer, died, lost to follow-up, or were censored at the end of the follow-up period, whichever came first, as the time at entry and exit, respectively. For descriptive purposes, mean values were computed after adjustment for age and center.

Physical activity was analyzed using categorical variables. For recreational and household activity, quartile cut points based on the cohort population distribution were used. Trend tests were estimated on scores (1-4) applied to the categories/quartiles of the physical activity variables and entered as a continuous term in the regression models. Relative risks were estimated from the hazard ratio within each category. Two sets of models are presented for each physical activity variable considered. The first are stratified for age and center and adjusted for the other types of physical activity (i.e., occupational, household, or recreational) and the second are adjusted for these factors and several other confounders.

A full examination of confounding was undertaken with the data on physical activity and cancer. Variables that were considered as potential confounders included the following dietary variables: total energy intake, intakes of red and processed meat, fish, fiber, fruits and vegetables, dairy products, current and lifelong alcohol, dietary calcium, folate, and the following lifestyle and demographic variables: education (none, primary school completed, technical/professional school, secondary school, university degree), marital status, smoking status (never, former, current, and unknown), ever use of hormone replacement therapy (for women only), height, weight, body mass index [BMI; weight (kg)/height $(cm)^2$], waist and hip circumference, and waist-hip ratio. The variables that were chosen as confounders either influenced the goodness-of-fit of the model (as assessed by examining the log likelihood) or were considered to be biologically relevant or important to control for in the final multivariate model. The final models for colon cancer were adjusted for education, smoking status, current alcohol intake (in grams per day, categorized into quartiles), height (in centimeters, categorized into sex- and center-specific tertiles), weight (in kilograms, categorized into sex- and center-specific tertiles), energy intake (in kilocalories, categorized into quartiles), and fiber intake (in grams per day, categorized into quartiles). The final models for rectal cancer were also adjusted for fish intake (in grams per day, categorized into quartiles). The confounders that were retained because they influenced the goodness-of-fit of the model were education, height, weight, alcohol intake, smoking, and fish intake (rectal cancer models only); energy and fiber intakes were retained because of their biological relevance in colorectal cancer etiology.

We also examined the possibility of effect modification by stratifying the population on BMI (<25, ≥25-<30, ≥30) and on energy intake (in tertiles) and by including an interaction term in our models. These factors were chosen as they are all considered independent risk factors for colon cancer and were considered a priori as effect modifiers of the relation between physical activity and colon cancer. Finally, we examined the heterogeneity of the results by country within the EPIC study by including country as a main effect and including interaction terms in the Cox models with dummy variables for each country. All analyses were done using SAS Statistical Software, version 8 (75); all statistical tests were two sided. To test hazard ratios for overall significance, P values for Wald χ^2 were computed with degrees of freedom equal to the number of categories minus one.

Results

We included 413,044 study participants who contributed 2,635,075 person-years for the mean follow-up of 6.38 years available for this analysis (Table 1). During the follow-up to 2003, there were 1,693 colorectal cancers, of which 1,094 were colon cancers and 599 rectal cancers. Histologic confirmation of these cancers was available for 1,376 of the tumors. The remaining tumors were confirmed with a variety of diagnostic methods and 22 (1.3%) were self-reported. The mean age at recruitment into this cohort was 51.9 years and 69.1% of the participants were female.

The demographic and lifestyle characteristics of the colon and rectal cancer cases and noncases were compared (Table 2). The case patients were older than the noncase participants, had slightly greater BMIs (weight/height^2), but had comparable mean total energy intake (kcal/d) and mean physical activity levels to the noncases. They also had similar smoking habits, education, and type of occupational activity. Differences were found between the cases and noncases in their dietary intakes, with cases having higher red meat and fish consumption, lower fruit and vegetable intakes, and higher alcohol intakes, particularly for the rectal cancer cases.

The first set of analyses examined the risk of colon cancer by type of physical activity. All analyses were initially conducted for men and women separately because our a priori hypothesis was that the associations differ by gender. No heterogeneity between sexes was observed and we present only the results for the total study population (for colon cancer, P values of the heterogeneity test for sex differences were 0.92, 0.83, 0.13, and 0.51 for total physical activity index, occupational, household, and recreational physical activities, respectively; for rectal cancer, the corresponding P values were 0.40, 0.48, 0.95, and 0.96, respectively).

For total physical activity, a statistically significant trend of decreasing relative risk estimates with increasing activity category was observed for colon cancer (P_{trend} = 0.04) in multivariate adjusted models (Table 3). Active study participants had a hazard ratio of 0.78 [95% confidence interval (95% CI), 0.59-1.03] as compared with the inactive participants.

Table 1. Size of the EPIC cohort for the analyses of physical activity and colon and rectal cancers, by country

Country	Cohort size	Age at recruitment (mean ± SD), y	Years of follow-up (mean ± SD)	Person-years	Female, %	No. colon cancer cases	No. rectal cancer cases	%Active*		%Inactive*	
								M	F	M	F
France	67,654	52.7 ± 6.6	8.41 ± 0.92	569,258	100	164	21	NA	2.0	NA	15.5
Italy	44,567	50.5 ± 7.9	5.91 ± 1.54	263,550	68.5	110	44	11.0	9.1	28.1	14.3
Spain	39,992	49.2 ± 8.0	6.68 ± 1.05	267,346	62.1	80	41	14.7	5.8	21.5	5.8
United Kingdom—general population	28,211	57.68 ± 9.3	5.47 ± 1.39	154,221	58.4	118	58	14.9	11.0	12.5	10.5
United Kingdom—health conscious	45,880	43.9 ± 14.4	5.38 ± 1.20	246,960	77.1	62	33	13.3	9.5	18.2	21.3
The Netherlands	32,394	49.8 ± 11.8	6.09 ± 2.03	197,235	76.3	107	52	26.0	19.0	12.5	8.5
Greece	25,574	53.1 ± 12.6	3.71 ± 0.76	94,809	58.6	13	12	9.8	12.7	18.1	5.5
Germany	49,498	50.6 ± 8.6	5.83 ± 1.43	288,761	56.4	103	69	12.4	7.9	20.6	20.6
Sweden	24,267	58.0 ± 7.6	7.61 ± 1.69	184,706	57.8	106	88	4.1	4.8	21.2	19.3
Denmark	55,007	56.7 ± 4.4	6.69 ± 1.07	368,229	52.2	231	181	18.3	8.5	22.7	26.5
Total	413,044	51.9 ± 10.0	6.38 ± 1.78	2,635,075	69.1	1,094	599	13.9	8.0	20.4	15.6

*Excluding all study subjects who had unknown or missing occupational physical activity data.

None of the different types of physical activity considered here, occupational, household, or recreational activity, independently accounted for the inverse association of total physical activity with colon cancer risk in multivariate models where each type of physical activity was mutually adjusted by the others. However, the inverse association seemed somewhat stronger with recreational activity than with occupational and household activity. The multivariate risk estimate for the highest quartile of recreational activity (≥42.8 MET-h/wk) was 0.88 (95% CI, 0.74-1.05) when compared with the lowest quartile (<12 MET-h/wk).

No association between rectal cancer and total physical activity or any specific type of activity was found (Table 3). Active compared with inactive study participants had a relative risk of 1.02 (95% CI, 0.73-1.44) for total physical activity and comparable null results were found for occupational, household, and recreational activity.

We next examined the association by tumor subsite within the colon (Table 4). The risk reductions seemed to be restricted to right-sided colon cancers. Participants who were in the moderately active or active category of physical activity had an up to 36% decreased relative risk of right-sided colon cancer compared with inactive subjects, with a statistically significant linear trend across categories (P_{trend} = 0.004). A 26% relative risk reduction was seen in the highest compared with lowest quartile of household activity with a marginal statistically significant trend (P_{trend} = 0.05) across quartiles. Occupational activity was also related to lower risk

Table 2. Demographic and lifestyle characteristics at time of enrollment among participants with incident colon and rectal cancer and individuals without cancer in EPIC

Characteristic*	Incident colon cancer cases (n = 1,094)		Incident rectal cancer cases (n = 599)		Individuals without incident colon or rectal cancer (n = 411,351)	
	Males (n = 417)	Females (n = 677)	Males (n = 293)	Females (n = 306)	Males (n = 127,050)	Females (n = 284,301)
Age (mean ± SD), y	57.8 ± 8.4	57.6 ± 8.8	57.4 ± 10.8	56.3 ± 10.0	52.6 ± 10.1	51.1 ± 10.2
BMI (mean ± SD), kg/m^2	27.5 ± 5.3	26.6 ± 5.5	26.7 ± 6.3	26.1 ± 6.4	26.4 ± 4.5	25.7 ± 4.5
Waist hip ratio (mean ± SD)	0.95 ± 0.08	0.82 ± 0.09	0.96 ± 0.12	0.82 ± 0.11	0.94 ± 0.07	0.80 ± 0.11
Dietary intake (mean ± SE)						
Energy intake, kcal	2,404.8 ± 31.5	2,018.8 ± 20.5	2,470.3 ± 37.6	1,985.5 ± 29.2	2,486.6 ± 1.9	2,005.6 ± 1.0
Total red meat, g	65.1 ± 2.4	46.8 ± 1.2	70.0 ± 2.6	49.1 ± 2.0	62.2 ± 0.1	42.1 ± 0.07
Total fish/shellfish, g	41.6 ± 1.8	33.2 ± 1.1	43.1 ± 2.0	31.3 ± 1.6	39.5 ± 0.1	32.8 ± 0.05
Fruits and vegetables, g	385.6 ± 12.8	478.1 ± 10.0	364.4 ± 13.4	439.6 ± 13.3	443.7 ± 0.9	505.8 ± 0.5
Fiber, g	21.6 ± 0.4	21.4 ± 0.3	21.2 ± 0.4	20.5 ± 0.4	23.6 ± 0.03	22.0 ± 0.01
Alcohol intake, g	24.0 ± 1.3	10.1 ± 0.6	29.3 ± 1.6	9.0 ± 0.7	22.4 ± 0.07	8.8 ± 0.02
Smoking status, %						
Never smoker	24.5	58.1	23.2	53.9	30.6	58.2
Ex-smoker	48.2	23.3	45.4	21.2	38.1	22.3
Current smoker	26.6	16.7	31.1	24.5	30.4	17.9
Education, %						
None	4.6	3.3	4.44	1.6	4.2	4.7
Primary school completed	34.8	26.7	32.4	32.7	27.0	21.5
Technical/professional school	22.8	19.5	23.2	27.8	24.3	19.9
Secondary school	13.0	26.0	10.6	17.3	14.7	25.4
University degree	21.6	19.1	26.3	14.1	27.1	23.8
Occupational activity, %						
Nonworker	38.1	52.4	36.9	51.3	23.0	39.1
Sedentary	29.7	18.5	30.7	17.0	36.5	24.8
Standing	15.6	20.2	17.8	18.6	20.2	26.4
Manual/heavy manual	15.1	6.9	13.7	10.1	19.1	7.1
Household activity (mean ± SD), MET-h/wk	34.4 ± 43.5	67.3 ± 46.0	36.4 ± 52.7	63.2 ± 49.1	30.0 ± 39.9	67.0 ± 40.6
Recreational activity (mean, SD), MET-h/wk	28.9 ± 29.5	26.1 ± 31.3	31.2 ± 39.5	32.0 ± 36.8	30.7 ± 27.3	28.8 ± 27.8

*All mean values were adjusted for age and center.

Table 3. Physical activity and risk of colon and rectal cancers, by type of activity for total study population

Type of activity	Colon cancer, total study population				Rectal cancer, total study population				
	No. cases	No. person-years	Age- and center-stratified hazard ratio (95% CI)*	Multivariate hazard ratio (95% CI)†	Quartile definitions/ cut points	No. cases	No. person-years	Age- and center-stratified hazard ratio (95% CI)*	Multivariate hazard ratio (95% CI)‡
Total physical activity									
Inactive	162	443,155	1.0	1.0	Inactive	91	442,864	1.0	1.0
Moderately inactive	397	942,463	0.91 (0.75-1.10)	0.92 (0.76-1.12)	Moderately inactive	192	941,684	1.01 (0.78-1.31)	1.02 (0.78-1.32)
Moderately active	436	943,626	0.84 (0.69-1.01)	0.86 (0.70-1.04)	Moderately active	246	944,956	1.00 (0.78-1.29)	1.02 (0.79-1.32)
Active	80	239,427	0.76 (0.58-1.00)	0.78 (0.59-1.03)	Active	58	239,318	1.01 (0.72-1.40)	1.02 (0.73-1.44)
P_{trend}			0.02	0.04	P_{trend}			0.98	0.91
Occupational activity									
Sedentary	249	727,785	1.0	1.0	Sedentary	142	727,363	1.0	1.0
Standing	202	689,087	0.96 (0.80-1.17)	0.98 (0.81-1.19)	Standing	109	688,712	1.11 (0.86-1.43)	1.11 (0.85-1.43)
Manual/heavy manual	110	274,166	0.89 (0.71-1.12)	0.91 (0.72-1.15)	Manual/heavy manual	71	274,015	0.97 (0.72-1.29)	0.96 (0.71-1.30)
Nonworker	514	879,634	0.90 (0.75-1.08)	0.91 (0.75-1.09)	Nonworker	265	878,734	1.15 (0.90-1.47)	1.16 (0.90-1.49)
P_{trend}§			0.29	0.38	P_{trend}§			0.97	0.82
Household activity (MET-h/wk)									
<19.5	289	673,316	1.0	1.0	<19.5	150	672,766	1.0	1.0
≥19.5-<39.6	281	682,023	0.94 (0.80-1.12)	0.95 (0.80-1.12)	≥19.5-<39.6	157	681,576	1.02 (0.81-1.28)	1.02 (0.81-1.28)
≥39.6-<73.9	272	659,317	0.90 (0.76-1.07)	0.90 (0.76-1.07)	≥39.6-<73.9	167	658,912	1.09 (0.87-1.38)	1.10 (0.87-1.39)
≥73.9	252	618,226	0.92 (0.76-1.13)	0.93 (0.76-1.13)	≥73.9	125	617,747	0.97 (0.74-1.26)	0.98 (0.75-1.29)
P_{trend}			0.34	0.35	P_{trend}			0.97	0.88
Recreational activity (MET-h/wk)									
<12.0	317	675,216	1.0	1.0	<12.8	139	488,157	1.0	1.0
≥12.0-<24.8	255	665,716	0.83 (0.70-0.98)	0.85 (0.71-1.00)	≥12.8-<24.0	144	490,903	1.14 (0.90-1.44)	1.15 (0.90-1.46)
≥24.8-<42.8	258	658,547	0.81 (0.68-0.96)	0.83 (0.70-0.98)	≥24.0-<42.0	158	477,489	1.20 (0.94-1.51)	1.22 (0.96-1.54)
≥42.8	264	633,403	0.85 (0.71-1.01)	0.88 (0.74-1.05)	≥45.8	158	426,419	1.18 (0.92-1.50)	1.21 (0.94-1.54)
P_{trend}			0.05	0.13	P_{trend}			0.18	0.12

*Base models are stratified by age and center and mutually adjusted for each type of physical activity (occupational, recreational, and household).
†Multivariate models are stratified by age and center and adjusted for energy (kilocalories per day in quartiles), education (none, primary school, technical/ professional school), smoking (never, former, current, unknown), height (centimeters in tertiles), weight (kilograms in tertiles), and fiber (grams per day in quartiles).
‡Multivariate models are stratified by age and center and adjusted for energy (kilocalories per day in quartiles), education (none, primary school, technical/ professional school), smoking (never, former, current, unknown), height (centimeters in tertiles), weight (kilograms in tertiles), fiber (grams per day in quartiles), and fish intake (grams per day in quartiles).
§Test for trend in occupational activity excluded all study participants categorized as nonworkers, missing, or unknown.

although no clear trends were observed by increasing intensity level in occupational activity. Recreational activity was not statistically significantly related to lower risk of right-sided colon cancer.

We examined the consistency of the results in the subcohorts participating in EPIC. There was no heterogeneity of the association of physical activity with colon cancer across the subcohorts participating in the EPIC study ($P_{heterogeneity}$ = 0.92).

When examining effect modifications by BMI, no statistically significant interaction was observed ($P_{interaction}$ = 0.67; Table 5). Some apparent heterogeneity in the association of physical activity with colon cancer across categories of BMI was observed in the participants in the "active" category of physical activity. This heterogeneity is probably explained by random variation due to low number of colon cancer patients with BMI >30 kg/m^2 in this category of physical activity.

Because the other major component of energy balance, besides physical activity, is energy intake, we also investigated effect modification of physical activity and colon cancer by energy intake. There was no statistically significant interaction ($P_{interaction}$ = 0.24; Table 5). In analyses stratified by tertiles of energy intake, the inverse association of physical activity with risk of colon cancer was statistically significant (P_{trend} = 0.003) across the categories of total activity for participants with energy intake in the middle tertile (≥1,827-<2,351 kcal/d) for whom a multivariate-adjusted relative risk of 0.59 (95% CI, 0.36-0.97) was found when comparing active with inactive subjects. A more moderate inverse association was observed for individuals in the lowest energy tertile. Among the highest energy intake tertile, there was no association of physical activity across any category of activity.

Finally, additional effect modification of BMI and energy intake by tumor subsite was investigated (Table 6). The interactions for both BMI and energy intake for right-sided colon cancers were statistically significant ($P_{interaction}$ = 0.03 and 0.003, respectively). We found a very strong risk reduction among moderately active and active normal weight participants (BMI <25) with a right-sided colon cancer (0.38; 95% CI, 0.21-0.68) as well as for overweight participants (BMI≥25-<30) for whom the risk was 0.43 (95% CI, 0.24-0.77) when compared with the inactive, obese study subjects. Participants with the lowest daily caloric intake (<1,827 kcal/d) who were most physically active had a 31% nonstatistically significant decreased risk as compared with the inactive, highest energy intake tertile of participants. There were no clear associations for any combination of BMI and energy intake and physical activity for left-sided colon cancers.

Discussion

In this large European prospective study of more than 400,000 participants, we found an inverse association between physical activity and risk of colon cancer, particularly for right-sided tumors. None of the different types of physical activity considered (occupational, household, and recreational) independently explained the inverse association, although the association was most apparent for recreational activity for all tumors whereas household activity showed the strongest inverse association for right-sided tumors. A particularly strong inverse association for physical activity was observed among lean and active participants and strong dose-response relations were found in those with lower energy intake. Physical activity was not related to rectal cancer in our study.

The strengths and limitations of this study need to be addressed before discussing the results. First, this large European prospective study of more than 400,000 participants provides a heterogeneity of exposures that is unparalleled in other prospective studies conducted to date. Furthermore, the availability of exposure data on a wide range of other risk factors for colon and rectal cancers, as well as of data on tumor location, has provided a detailed and comprehensive assessment of the role of physical activity in the etiology of colon and rectal cancers. Moreover, this is the only international cohort study with such a large number of cases for which the data could be stratified by BMI and energy intake separately for tumor subsites.

The main limitation of the study was in the physical activity assessment method. Although all types of activity were assessed in this study at the time of recruitment, there was no information on the duration and frequency of occupational activity that precluded estimating a sum of all types of activity in MET-hours per week. An assessment of the relative validity and reproducibility of the EPIC physical activity questions was also undertaken (71) and the short version of the questionnaire, used in EPIC and analyzed here, was found to be satisfactory for the ranking of subjects. Short-term reproducibility (i.e., 5 months) for the questionnaire was quite high, ranging from 0.58 to 0.89, whereas longer-term reproducibility (i.e., 11 months) was between 0.47 and 0.83 for the different measures of physical activity (71). Correlations for the relative validity ranged from 0.28 to 0.81 for comparisons between the questionnaire and activity diaries, which are not real gold standards of activity (71). Hence, the assessment of physical activity used in the EPIC study had some limitations but these were not sufficiently serious to preclude the analyses of physical activity and cancer outcomes.

At least 58 studies have been conducted on colon, rectal, or colorectal cancer and physical activity (2-59) including 22 prospective studies of incident cancer (3, 5, 8-12, 18, 19, 29, 30, 33, 37, 39, 41, 42, 46, 51, 53, 54, 57, 58) and three prospective mortality studies (23, 36, 38). A wide range of methods for defining physical activity has been used in these studies including the type, dose, and time period for assessment. When comparing these results with previous studies, the magnitude of the risk reduction found in the EPIC cohort is comparable to those found in most of these studies and, in some subgroups, equaling the largest risk reductions observed. Overall risk reductions of at least 40% in men, or men and women, have been found in nearly half of these studies (27 of 58 studies; refs. 3, 6, 9, 12, 17, 19-24, 27, 31, 32, 34, 35, 37, 44, 45, 47-50, 52, 56, 58, 59) and most associations do not seem to be confounded by other risk factors for colon cancer. Ten studies observed no effect of physical activity on colon or colorectal cancer (2, 5, 8, 25, 29, 39, 41, 46, 53) and no studies found an increased risk of colon cancer with increased activity levels. Evidence for a

Table 4. Physical activity and risk of right and left colon cancer, total study population

Type of activity	Right colon cancer				Left colon cancer				
	No. cases	No. person-years	Age- and center-stratified hazard ratio (95% CI)*	Multivariate† hazard ratio (95% CI)	Quartile definitions/ cut points	No. cases	No. person-years	Age- and center-stratified hazard ratio (95% CI)*	Multivariate† hazard ratio (95% CI)
Total activity									
Inactive	76	442,792	1.0	1.0	Inactive	60	442,726	1.0	1.0
Moderately inactive	157	941,581	0.77 (0.58-1.03)	0.79 (0.59-1.06)	Moderately inactive	161	941,593	1.11 (0.82-1.51)	1.10 (0.81-1.50)
Moderately active	161	944,680	0.61 (0.46-0.82)	0.64 (0.47-0.86)	Moderately active	220	955,076	1.17 (0.86-1.57)	1.15 (0.84-1.56)
Active	32	239,238	0.61 (0.40-0.94)	0.65 (0.43-1.00)	Active	40	239,255	0.98 (0.65-1.47)	0.96 (0.64-1.45)
P_{trend}			0.001	0.004	P_{trend}			0.74	0.83
Occupational activity									
Sedentary	111	727,225	1.0	1.0	Sedentary	102	727,203	1.0	1.0
Standing	67	688,569	0.77 (0.56-1.05)	0.79 (0.58-1.09)	Standing	95	688,670	1.24 (0.93-1.65)	1.22 (0.91-1.64)
Manual/heavy manual	47	273,925	0.85 (0.60-1.21)	0.90 (0.63-1.29)	Manual/heavy manual	54	273,938	0.99 (0.71-1.38)	0.95 (0.67-1.34)
Nonworker	201	878,573	0.77 (0.58-1.03)	0.81 (0.60-1.08)	Nonworker	230	878,612	1.06 (0.80-1.40)	1.01 (0.76-1.35)
P_{trend}			0.18	0.29	P_{trend}			0.89	0.91
Household activity (MET-h/wk)									
<19.5	112	672,660	1.0	1.0	<19.5	120	672,658	1.0	1.0
≥19.5-<39.6	117	681,388	0.97 (0.75-1.27)	0.97 (0.75-1.27)	≥19.5-<39.6	119	681,436	0.97 (0.75-1.26)	0.97 (0.75-1.26)
≥39.6-<73.9	110	658,749	0.85 (0.64-1.12)	0.84 (0.64-1.12)	≥39.6-<73.9	131	658,772	1.06 (0.82-1.38)	1.06 (0.82-1.38)
≥73.9	90	617,641	0.74 (0.54-1.01)	0.74 (0.54-1.02)	≥73.9	121	617,726	1.03 (0.77-1.37)	1.01 (0.75-1.36)
P_{trend}			0.04	0.05	P_{trend}			0.72	0.78
Recreational activity (MET-h/wk)									
<12.8	116	674,487	1.0	1.0	<12.8	144	674,544	1.0	1.0
≥12.8-<24.0	105	665,148	0.96 (0.73-1.26)	0.96 (0.74-1.26)	≥12.8-<24.0	109	665,176	0.79 (0.62-1.02)	0.80 (0.63-1.04)
≥24.0-<42.0	96	657,915	0.83 (0.62-1.09)	0.84 (0.63-1.11)	≥24.0-<42.0	117	657,989	0.82 (0.63-1.05)	0.84 (0.65-1.08)
≥45.8	112	632,888	0.98 (0.74-1.29)	1.01 (0.76-1.33)	≥45.8	121	632,883	0.83 (0.64-1.07)	0.86 (0.66-1.12)
P_{trend}			0.65	0.80	P_{trend}			0.19	0.31

*Base models are stratified by age and center and mutually adjusted for each type of physical activity (occupational, recreational, and household).

†Multivariate models are stratified by age and center and adjusted for energy (kilocalories per day in quartiles), education (none, primary school, technical/ professional school), smoking (never, former, current, unknown), height (centimeters in tertiles), weight (kilograms in tertiles), and fiber (grams per day in quartiles).

Table 5. Physical activity and risk of colon cancer by BMI and energy intake, total study population

Type of activity	BMI <25				BMI ≥25-<30				BMI ≥30			
	No. cases	No. person-years	Age- and center-stratified hazard ratios (95% CI)*	Multivariate† hazard ratios (95% CI)	No. cases	No. person-years	Age- and center-stratified hazard ratios (95% CI)*	Multivariate† hazard ratios (95% CI)	No. cases	No. person-years	Age- and center-stratified hazard ratios (95% CI)*	Multivariate† hazard ratios (95% CI)
Inactive	73	246,511	1.0	1.0	63	148,517	1.0	1.0	26	48,127	1.0	1.0
Moderately inactive	179	554,150	0.84 (0.63-1.11)	0.86 (0.64-1.15)	159	285,335	0.97 (0.71-1.31)	0.95 (0.69-1.29)	59	102,978	0.78 (0.51-1.33)	0.82 (0.50-1.33)
Moderately active	179	427,124	0.85 (0.63-1.13)	0.88 (0.66-1.19)	177	359,955	0.79 (0.58-1.07)	0.78 (0.57-1.07)	80	158,546	0.78 (0.51-1.29)	0.83 (0.51-1.34)
Active	24	111,597	0.60 (0.38-0.96)	0.63 (0.39-1.01)	37	93,589	0.81 (0.54-1.23)	0.81 (0.53-1.24)	19	34,241	1.01 (0.55-1.84)	1.03 (0.56-1.90)
P_{trend}			0.08	0.14			0.07	0.08			0.85	0.98
	<1,827 kcal/d				≥1,827-<2,351 kcal/d				>2,351 kcal/d			
Inactive	46	148,484	1.0	1.0	65	150,738	1.0	1.0	51	143,933	1.0	1.0
Moderately inactive	130	311,913	0.89 (0.63-1.27)	0.95 (0.66-1.36)	151	327,204	0.86 (0.63-1.17)	0.85 (0.62-1.16)	116	303,346	0.91 (0.65-1.27)	0.93 (0.66-1.31)
Moderately active	136	318,877	0.75 (0.52-1.07)	0.81 (0.56-1.18)	136	312,059	0.66 (0.48-0.91)	0.66 (0.48-0.92)	164	314,689	1.09 (0.79-1.51)	1.13 (0.81-1.57)
Active	19	61,979	0.74 (0.42-1.27)	0.81 (0.47-1.41)	22	72,610	0.58 (0.36-0.96)	0.59 (0.36-0.97)	39	104,837	0.96 (0.63-1.46)	1.01 (0.66-1.55)
P_{trend}			0.07	0.19			0.002	0.003			0.61	0.44

*Base models are stratified by age and center and mutually adjusted for each type of physical activity (occupational, recreational, and household).
†Multivariate models are stratified by age and center and adjusted for energy (kilocalories per day in quartiles), education (none, primary school, technical/professional school), smoking (never, former, current, unknown), and fiber (grams per day in quartiles).

"dose-response effect" (i.e., statistically significant linear trend with increasing levels of total activity and decreasing risks) was found for men, or men and women, in 20 of the 26 studies that examined the trend (3, 6, 7, 9, 12, 13, 17, 20, 22, 27, 31, 32, 35, 37, 42-45, 48-51, 54, 55, 58, 59). Our results for rectal cancer are in concordance with previous studies results because only 6 of 30 studies of rectal cancer (2, 7, 9, 12, 13, 15, 17, 18, 20, 24, 25, 27, 29, 31-33, 35-37, 39, 41, 42, 45, 48, 49, 51, 52, 54, 56, 64) in men, or men and women, have found a statistically significant risk reduction or inverse trend among the most physically active study participants. Indeed, there seems to be increasing convincing evidence for no association between rectal cancer and physical activity.

This study found no difference in colon cancer risk according to gender, which is consistent with the literature. In reviewing previously reported risk ratios and 95% CIs for colorectal and colon cancer incidence and mortality, 23 studies of occupational activity (2, 7, 13-19, 22-24, 31-33, 35, 38, 42, 51, 52, 55, 56, 59) and 23 studies of nonoccupational activity (5, 8, 9, 12, 19, 22, 26, 27, 29, 30, 32, 34, 37, 41, 42, 49, 51, 53-56, 58, 59) generally revealed no obvious differences between males and females.

Table 6. Interaction of BMI and energy intake with physical activity, by right and left colon cancers

Total activity	Right colon						Left colon					
	BMI <25		BMI ≥25-<30		BMI ≥30		BMI <25		BMI ≥25-<30		BMI≥30	
	No. cases	Multivariate* risk	No. cases	Multivariate* risk	No. cases	Multivariate* risk	No. cases	Multivariate* risk	No. cases	Multivariate* risk	No. cases	Multivariate* risk
Inactive	34	0.64 (0.34-1.20)	28	0.61 (0.32-1.16)	14	1.0	26	0.98 (0.42-2.30)	32	1.37 (0.60-3.13)	7	1.0
Moderately inactive	73	0.50 (0.28-0.90)	63	0.54 (0.30-0.98)	23	0.57 (0.29-1.12)	64	1.02 (0.46-2.25)	70	1.41 (0.64-3.07)	31	1.47 (0.64-3.39)
Moderately active and active	73	0.38 (0.21-0.68)	82	0.43 (0.24-0.77)	39	0.56 (0.30-1.05)	102	1.25 (0.58-2.70)	104	1.18 (0.56-2.54)	55	1.57 (0.70-3.45)
$P_{interaction}$				0.03						0.39		
	<1,827 kcal/d		≥1,827-<2,351 kcal/d		>2,351 kcal/d		<1,827 kcal/d		≥1,827-<2,351 kcal/d		>2,351 kcal/d	
Inactive	26	1.54 (0.83-2.90)	31	1.72 (0.96-3.08)	19	1.0	12	0.64 (0.30-1.33)	30	1.32 (0.74-2.35)	23	1.0
Moderately inactive	55	1.07 (0.61-1.91)	64	1.30 (0.76-2.23)	40	0.94 (0.54-1.63)	54	0.96 (0.55-1.68)	65	1.27 (0.76-2.13)	46	0.99 (0.59-1.67)
Moderately active and active	51	0.69 (0.39-1.24)	62	0.86 (0.50-1.48)	81	1.15 (0.69-1.92)	81	1.01 (0.59-1.72)	82	1.08 (0.65-1.78)	98	1.18 (0.73-1.92)
$P_{interaction}$				0.003						0.45		

*Multivariate risk models: BMI interaction adjusted for energy intake, fiber, alcohol, smoking, and education; energy interaction also adjusted for height, weight, alcohol, smoking, fiber, and education.

We also compared risks across three types of activity: occupational, household, and recreational. Neither occupational nor nonoccupational activity was clearly more effective in reducing risk. A review of risk estimates from incidence and mortality studies of colorectal and colon cancer [35 studies in men (2, 7, 9, 12-19, 22-24, 26, 27, 29-33, 35, 37, 38, 41, 42, 49, 51-56, 58, 59) and in 22 women (2, 5, 8, 9, 14, 16, 19, 22, 26, 27, 31, 33, 34, 37, 41, 49, 51, 54-56, 58, 59)] similarly suggested no sign of differential protective effects from occupational or nonoccupational activity.

No statistically significant interaction between BMI and physical activity was observed for right and left tumors combined. Of 58 colon and colorectal studies in the literature, only 11 (3, 20, 22, 27, 29, 31, 44, 48, 51, 59) stratified by BMI. These past studies collectively provide no convincing evidence of any statistically significant interaction between BMI, physical activity, and colon cancer in men or women. In contrast, the present study did find statistically significant effect modification by BMI for right-sided tumors. Slattery et al. (44) similarly examined this interaction according to multiple tumor subsites and reported the BMI interaction term as having statistically significantly improved model fit for right-sided (but not left-sided) tumors. Gerhardsson de Verdier et al. (20) also presented evidence of an interaction with BMI but only described left-sided tumors in this regard.

Like BMI, results stratified by energy intake showed no convincing evidence of effect modification for right- and left-sided tumors combined. Very few groups have previously reported on the same two-way stratification (20, 31, 44, 48) and the results have been inconsistent. After stratifying by tumor subsite, Slattery et al. (44) found that an interaction term improved model fit marginally for left-sided (but not right-sided) tumors in men and older individuals. Results of Gerhardsson de Verdier et al. (20) similarly implied effect modification for left-sided tumors. No other groups described interactions between physical activity, energy intake, and right-sided tumors, a statistically significant finding in the present study.

In the EPIC study, we were able to examine the risks by tumor subsite as has previously been done in 9 cohort studies (8, 9, 12, 18, 42, 51, 58, 62, 63) and 21 case-control studies (2, 6, 14-17, 20, 22, 24, 27, 31, 32, 34, 44, 45, 52, 55, 56, 59, 60, 64). Some of those that examined both subsites have found risk decreases that were stronger and often statistically significant for right-sided tumors (6, 9, 15, 18, 24, 31, 51, 52, 59, 60) or left-sided tumors (2, 12, 16, 17, 20, 58, 62-64). Others (8, 14, 22, 27, 34, 42, 44, 45, 55, 56) have found no clear difference between subsites. Although it seems that the associations are not consistently stronger for right- or left-sided tumors, differing methods could account for this. Of 29 studies that compared tumor subsites, only 15 compared two subsite categories (9, 12, 20, 22, 24, 27, 31, 44, 45, 51, 55, 56, 58, 62, 63) using six definitions for right- and left-sided tumors precluding any direct comparisons with our study results. Levi et al. (31) was the only group to dichotomize tumor subsites as in the EPIC study and similarly found a stronger association with right-sided tumors. Gerhardsson de Verdier et al. (18) also found stronger effects in right-sided tumors (cecum and ascending colon, and transverse colon and flexures) than in left (descending, sigmoid colon) and was, to our knowledge, the only other large prospective study to examine tumor subsites in the colon.

The exact biological mechanisms for the differential associations of physical activity with tumor subsites are not known. Previously hypothesized mechanisms for colon cancer include gastrointestinal transit time, immune function, prostaglandin levels, insulin-related pathways, gastrointestinal-pancreatic hormones, serum cholesterol, and bile acids (76, 77), only some of which may differ between the left or right colon. Physical activity, for example, accelerates movement of stool through the colon (78, 79), possibly providing less time for fecal carcinogens to contact colonic mucosa (80). Only the right colon is innervated by the vagus nerve, which induces peristalsis in response to physical activity. Hence, physical activity may affect motility more intensely in the right colon than in the left (81). The effect could be accentuated if foods that correlated with lower BMI (82, 83) and lower energy intake (84) are also those that traverse the colon more rapidly, such as fiber (80). Although plausible, the epidemiologic evidence for the association between gastrointestinal transit time and colon cancer risk has thus far been inconsistent (76).

In conclusion, this large prospective study conducted in a heterogeneous population of Europeans has found 20% to 25% risk reductions for colon cancer among the physically active population, which were particularly evident for right-sided colon tumors where reductions of 35% were observed. The inverse association of physical activity with right-sided colon cancer was very strong among the normal weight (BMI <25) population and among those with low energy intake (<2,351 kcal/d). Hence, there is a clear benefit of physical activity for right-sided colon cancer risk reduction, which is greatest when normal weight or low energy intake is also maintained. It is of public health importance to note that the benefits of physical activity for colon cancer risk were also observed among the overweight population (BMI >25-<30), suggesting that physical activity has a positive influence on colon cancer risk reduction for a large percentage of the at-risk population. The benefits are stronger among those who also maintain a lower BMI and a lower energy intake. The level of physical activity required for the risk reductions observed in this study translates into 1 hour per day of vigorous physical activity (MET = 6) or 2 h per day of moderate intensity physical activity (MET = 3). This activity could be in any combination of occupational, household, or recreational activity. Because these levels of activity are achievable by most of the at-risk population, the potential for colon cancer risk reduction with increased physical activity is worthy of consideration for cancer prevention programs.

Appendix Table 1. Creation of total physical activity index as the cross-classification of occupational and combined recreational and household activity

Occupational activity	Recreational and household activity (MET-h/wk in sex-specific quartiles)			
	Low	Medium	High	Very high
	Males, ≤34.00; females, ≤51.11	Males, >34.00-≤56.76; females, >51.11-≤82.43	Males, >56.76-≤87.06; females, >82.43-≤123.02	Males, >87.06; females, >123.02
Sedentary	Inactive	Inactive	Moderately inactive	Moderately active
Standing	Moderately inactive	Moderately inactive	Moderately active	Active
Manual	Moderately active	Moderately active	Active	Active
Heavy manual	Moderately active	Moderately active	Active	Active
Nonworker	Moderately inactive	Moderately inactive	Moderately active	Moderately active

References

1. Friedenreich CM, Orenstein MR. Physical activity and cancer prevention: etiologic evidence and biological mechanisms. J Nutr 2002;132:3456–64S.
2. Arbman G, Axelson O, Fredriksson M, et al. Do occupational factors influence the risk of colon and rectal cancer in different ways? Cancer 1993; 72:2543–9.
3. Ballard-Barbash R, Schatzkin A, Albanes D, et al. Physical activity and risk of large bowel cancer in the Framingham Study. Cancer Res 1990;50:3610–3.
4. Benito E, Obrador A, Stiggelbout A, et al. A population-based case-control study of colorectal cancer in Majorca. I. Dietary factors. Int J Cancer 1990;45: 69–76.
5. Bostick RM, Potter JD, Kushi LH, et al. Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). Cancer Causes Control 1994;5:38–52.
6. Boutron-Ruault MC, Senesse P, Meance S, et al. Energy intake, body mass index, physical activity, and the colorectal adenoma-carcinoma sequence. Nutr Cancer 2001;39:50–7.
7. Brownson RC, Chang JC, Davis JR, Smith CA. Physical activity on the job and cancer in Missouri. Am J Public Health 1991;81:639–42.
8. Calton BA, Lacey JV, Jr., Schatzkin A, et al. Physical activity and the risk of colon cancer among women: a prospective cohort study (United States). Int J Cancer 2006;119:385–91.
9. Chao A, Connell CJ, Jacobs EJ, et al. 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. Cancer Epidemiol Biomarkers Prev 2004;13:2187–95.
10. Chow WH, Dosemeci M, Zheng W, et al. Physical activity and occupational risk of colon cancer in Shanghai, China. Int J Epidemiol 1993;22:23–9.
11. Chow WH, Malker HS, Hsing AW, et al. Occupational risks for colon cancer in Sweden. J Occup Med 1994;36:647–51.
12. Colbert LH, Hartman TJ, Malila N, et al. Physical activity in relation to cancer of the colon and rectum in a cohort of male smokers. Cancer Epidemiol Biomarkers Prev 2001;10:265–8.
13. Dosemeci M, Hayes RB, Vetter R, et al. Occupational physical activity, socioeconomic status, and risks of 15 cancer sites in Turkey. Cancer Causes Control 1993;4:313–21.
14. Fernandez E, Gallus S, La Vecchia C, et al. Family history and environmental risk factors for colon cancer. Cancer Epidemiol Biomarkers Prev 2004;13: 658–61.
15. Fraser G, Pearce N. Occupational physical activity and risk of cancer of the colon and rectum in New Zealand males. Cancer Causes Control 1993;4: 45–50.
16. Fredriksson M, Bengtsson NO, Hardell L, Axelson O. Colon cancer, physical activity, and occupational exposures. A case-control study. Cancer 1989;63: 1838–42.
17. Garabrant DH, Peters JM, Mack TM, Bernstein L. Job activity and colon cancer risk. Am J Epidemiol 1984;119:1005–14.
18. Gerhardsson de Verdier M, Norell SE, Kiviranta H, et al. Sedentary jobs and colon cancer. Am J Epidemiol 1986;123:775–80.
19. Gerhardsson de Verdier M, Floderus B, Norell SE. Physical activity and colon cancer risk. Int J Epidemiol 1988;17:743–6.
20. Gerhardsson de Verdier M, Steineck G, Hagman U, et al. Physical activity and colon cancer: a case-referent study in Stockholm. Int J Cancer 1990;46: 985–9.
21. Hauret KG, Bostick RM, Matthews CE, et al. Physical activity and reduced risk of incident sporadic colorectal adenomas: observational support for mechanisms involving energy balance and inflammation modulation. Am J Epidemiol 2004;159:983–92.
22. Hou L, Ji BT, Blair A, et al. Commuting physical activity and risk of colon cancer in Shanghai, China. Am J Epidemiol 2004;160:860–7.
23. Hsing AW, McLaughlin JK, Chow WH, et al. Risk factors for colorectal cancer in a prospective study among U.S. white men. Int J Cancer 1998;77: 549–53.
24. Kato I, Tominaga S, Ikari A. A case-control study of male colorectal cancer in Aichi Prefecture, Japan: with special reference to occupational activity level, drinking habits and family history. Jpn J Cancer Res 1990;81:115–21.
25. Kune GA, Kune S, Watson LF. Body weight and physical activity as predictors of colorectal cancer risk. Nutr Cancer 1990;13:9–17.
26. Lam TH, Ho SY, Hedley AJ, et al. Leisure time physical activity and mortality in Hong Kong: case-control study of all adult deaths in 1998. Ann Epidemiol 2004;14:391–8.
27. Le Marchand L, Wilkens LR, Kolonel LN, et al. Associations of sedentary lifestyle, obesity, smoking, alcohol use, and diabetes with the risk of colorectal cancer. Cancer Res 1997;57:4787–94.
28. Larsen IK, Grotmol T, Almendingen K, Hoff G. Lifestyle as a predictor for colonic neoplasia in asymptomatic individuals. BMC Gastroenterol 2006;6:5.
29. Lee IM, Paffenbarger RS. Physical activity and its relation to cancer risk: a prospective study of college alumni. Med Sci Sports Exerc 1994;26:831–7.
30. Lee IM, Manson JE, Ajani U, et al. Physical activity and risk of colon cancer: the Physicians' Health Study (United States). Cancer Causes Control 1997;8: 568–74.
31. Levi F, Pasche C, Lucchini F, et al. Occupational and leisure-time physical activity and the risk of colorectal cancer. Eur J Cancer Prev 1999;8:487–93.
32. Longnecker MP, Gerhardsson de Verdier M, Frumkin H, Carpenter C. A case-control study of physical activity in relation to risk of cancer of the right colon and rectum in men. Int J Epidemiol 1995;24:42–50.
33. Lynge E, Thygesen L. Use of surveillance systems for occupational cancer: data from the Danish National system. Int J Epidemiol 1988;17:493–500.
34. Marcus PM, Newcomb PA, Storer BE. Early adulthood physical activity and colon cancer risk among Wisconsin women. Cancer Epidemiol Biomarkers Prev 1994;3:641–4.
35. Markowitz S, Morabia A, Garibaldi K, Wynder E. Effect of occupational and recreational activity on the risk of colorectal cancer among males: a case-control study. Int J Epidemiol 1992;21:1057–62.
36. Marti B, Minder CE. [Physical occupational activity and colonic carcinoma mortality in Swiss men 1979-1982]. Soz Praventivmed 1989;34:30–7.
37. Lund Nilsen TI, Vatten LJ. Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: exploring the hyper-insulinaemia hypothesis. Br J Cancer 2001;84:417–22.
38. Paffenbarger RS, Hyde RT, Wing AL. Physical activity and incidence of cancer in diverse populations: a preliminary report. Am J Clin Nutr 1987;45: 312–7.
39. Pukkala E, Kaprio J, Koskenvuo M, et al. Cancer incidence among Finnish world class male athletes. Int J Sports Med 2000;21:216–20.
40. Ravasco P, Monteiro-Grillo I, Marques VP, Camilo ME. Nutritional risks and colorectal cancer in a Portuguese population. Nutr Hosp 2005;20:165–72.
41. Schnohr P, Gronbaek M, Petersen L, et al. Physical activity in leisure-time and risk of cancer: 14-year follow-up of 28,000 Danish men and women. Scand J Public Health 2005;33:244–9.
42. Severson RK, Nomura AM, Grove JS, Stemmermann GN. A prospective analysis of physical activity and cancer. Am J Epidemiol 1989;130:522–9.
43. Slattery ML, Schumacher MC, Smith KR, et al. Physical activity, diet, and risk of colon cancer in Utah. Am J Epidemiol 1988;128:989–99.
44. Slattery ML, Potter J, Caan B, et al. Energy balance and colon cancer-beyond physical activity. Cancer Res 1997;57:75–80.
45. Slattery ML, Edwards S, Curtin K, et al. Physical activity and colorectal cancer. Am J Epidemiol 2003;158:214–24.
46. Steenland K, Nowlin S, Palu S. Cancer incidence in the National Health and Nutrition Survey I. Follow-up data: diabetes, cholesterol, pulse and physical activity. Cancer Epidemiol Biomarkers Prev 1995;4:807–11.
47. Steindorf K, Tobiasz-Adamczyk B, Popiela T, et al. Combined risk assessment of physical activity and dietary habits on the development of colorectal cancer. A hospital-based case-control study in Poland. Eur J Cancer Prev 2000;9:309–16.
48. Steindorf K, Jedrychowski W, Schmidt M, et al. Case-control study of lifetime occupational and recreational physical activity and risks of colon and rectal cancer. Eur J Cancer Prev 2005;14:363–71.
49. Tang R, Wang JY, Lo SK, Hsieh LL. Physical activity, water intake and risk of colorectal cancer in Taiwan: a hospital-based case-control study. Int J Cancer 1999;82:484–9.
50. Thun MJ, Calle EE, Namboodiri MM, et al. Risk factors for fatal colon cancer in a large prospective study. J Natl Cancer Inst 1992;84:1491–500.
51. Thune I, Lund E. Physical activity and risk of colorectal cancer in men and women. Br J Cancer 1996;73:1134–40.
52. Vena JE, Graham S, Zielezny M, et al. Lifetime occupational exercise and colon cancer. Am J Epidemiol 1985;122:357–65.
53. Wannamethee SG, Shaper AG, Walker M. Physical activity and risk of cancer in middle-aged men. Br J Cancer 2001;85:1311–6.
54. Wei EK, Giovannucci E, Wu K, et al. Comparison of risk factors for colon and rectal cancer. Int J Cancer 2004;108:433–42.
55. White E, Jacobs EJ, Daling JR. Physical activity in relation to colon cancer in middle-aged men and women. Am J Epidemiol 1996;144:42–50.
56. Whittemore AS, Wu-Williams AH, Lee M, et al. Diet, physical activity, and colorectal cancer among Chinese in North America and China. J Natl Cancer Inst 1990;82:915–26.
57. Will JC, Galuska DA, Vinicor F, Calle EE. Colorectal cancer: another complication of diabetes mellitus? Am J Epidemiol 1998;147:816–25.
58. Wu AH, Paganini-Hill A, Ross RK, Henderson BE. Alcohol, physical activity and other risk factors for colorectal cancer: a prospective study. Br J Cancer 1987;55:687–94.
59. Zhang Y, Cantor KP, Dosemeci M, et al. Occupational and leisure-time physical activity and risk of colon cancer by subsite. J Occup Environ Med 2006;48:236–43.
60. Brownson RC, Zahm SH, Chang JC, Blair A. Occupational risk of colon cancer. An analysis by anatomic subsite. Am J Epidemiol 1989;130:675–87.
61. Slattery ML, Caan BJ, Benson J, Murtaugh M. Energy balance and rectal cancer: an evaluation of energy intake, energy expenditure, and body mass index. Nutr Cancer 2003;46:166–71.
62. Giovannucci E, Ascherio A, Rimm EB, et al. Physical activity, obesity, and risk for colon cancer and adenoma in men. Ann Intern Med 1995;122:327–34.
63. Martinez ME, Giovannucci E, Spiegelman D, et al.; Nurses' Health Study Research Group. Leisure-time physical activity, body size, and colon cancer in women. J Natl Cancer Inst 1997;89:948–55.
64. Tavani A, Braga C, La Vecchia C, et al. Physical activity and risk of cancers of the colon and rectum: an Italian case-control study. Br J Cancer 1999;79: 1912–6.
65. Bufill JA. Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumor location. Ann Intern Med 1990;113:779–88.
66. Dubrow R, Bernstein J, Holford TR. Age-period-cohort modelling of large-bowel-cancer incidence by anatomic sub-site and sex in Connecticut. Int J Cancer 1993;53:907–13.
67. Riboli E, Hunt KJ, Slimani N, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr 2002;5:1113–24.

68. Ferrari P, Slimani N, Ciampi A, et al. Evaluation of under- and overreporting of energy intake in the 24-hour diet recalls in the European Prospective Investigation into Cancer and Nutrition (EPIC). Public Health Nutr 2002;5: 1329–45.
69. Haftenberger M, Schuit AJ, Tormo MJ, et al. Physical activity of subjects aged 50-64 years involved in the European Prospective Investigation into Cancer and Nutrition (EPIC). Public Health Nutr 2002;5:1163–76.
70. Pols MA, Peeters PH, Bueno-de-Mesquita HB, et al. Validity and repeatability of a modified Baecke questionnaire on physical activity. Int J Epidemiol 1995;24:381–8.
71. Pols MA, Peeters PH, Ocke MC, et al. Estimation of reproducibility and relative validity of the questions included in the EPIC Physical Activity Questionnaire. Int J Epidemiol 1997;26:S181–9.
72. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32:S498–504.
73. Wareham NJ, Jakes RW, Rennie KL, et al. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Public Health Nutr 2003;6:407–13.
74. James WP, Schofield EC. Human energy requirements: a manual for planners and nutritionists. Oxford: Oxford University Press; 1990.
75. SAS Institute. SAS statistical software [v8.2]. Cary (NC): SAS Institute; 2001.
76. Quadrilatero J, Hoffman-Goetz L. Physical activity and colon cancer. A systematic review of potential mechanisms. J Sports Med Phys Fitness 2003; 43:121–38.
77. McTiernan A, Ulrich C, Slate S, Potter J. Physical activity and cancer etiology: associations and mechanisms. Cancer Causes Control 1998;9:487–509.
78. Cordain L, Latin RW, Behnke JJ. The effects of an aerobic running program on bowel transit time. J Sports Med Phys Fitness 1986;26:101–4.
79. Koffler KH, Menkes A, Redmond RA, et al. Strength training accelerates gastrointestinal transit in middle-aged and older men. Med Sci Sports Exerc 1992;24:415–9.
80. Burkitt DP, Walker AR, Painter NS. Effect of dietary fibre on stools and the transit-times, and its role in the causation of disease. Lancet 1972;2:1408–12.
81. Bartram HP, Wynder EL. Physical activity and colon cancer risk? Physiological considerations. Am J Gastroenterol 1989;84:109–12.
82. Howarth NC, Huang TT, Roberts SB, McCrory MA. Dietary fiber and fat are associated with excess weight in young and middle-aged US adults. J Am Diet Assoc 2005;105:1365–72.
83. Lairon D, Arnault N, Bertrais S, et al. Dietary fiber intake and risk factors for cardiovascular disease in French adults. Am J Clin Nutr 2005;82:1185–94.
84. Howarth NC, Saltzman E, Roberts SB. Dietary fiber and weight regulation. Nutr Rev 2001;59:129–39.

論文名	Physical activity and risk of colon and rectal cancers: the European prospective investigation into cancer and nutrition
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雑誌名	Cancer Epidemiol Biomarkers prev
巻・号・頁	15(12)　　2398-2407
発行年	2006
PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/17164362

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	男女混合	( )		( )		( )
	年齢	35-70歳	[redacted]		( )		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 3. Physical activity and risk of colon and rectal cancers, by type of activity for total study population

Type of activity	Colon cancer, total study population: No. cases	No. person-years	Age- and center-stratified hazard ratio (95% CI)*	Multivariate hazard ratio (95% CI)†	Rectal cancer, total study population: Quartile definitions/cut points	No. cases	No. person-years	Age- and center-stratified hazard ratio (95% CI)*	Multivariate hazard ratio (95% CI)‡
Total physical activity									
Inactive	162	443,155	1.0	1.0	Inactive	91	442,864	1.0	1.0
Moderately inactive	397	942,463	0.91 (0.75-1.10)	0.92 (0.76-1.12)	Moderately inactive	192	941,684	1.01 (0.78-1.31)	1.02 (0.78-1.32)
Moderately active	436	943,626	0.84 (0.69-1.01)	0.86 (0.70-1.04)	Moderately active	246	944,956	1.00 (0.78-1.29)	1.02 (0.79-1.32)
Active	80	239,427	0.76 (0.58-1.00)	0.78 (0.59-1.03)	Active	58	239,318	1.01 (0.72-1.40)	1.02 (0.73-1.44)
P_{trend}			0.02	0.04	P_{trend}			0.98	0.91
Occupational activity									
Sedentary	249	727,785	1.0	1.0	Sedentary	142	727,363	1.0	1.0
Standing	202	689,087	0.96 (0.80-1.17)	0.98 (0.81-1.19)	Standing	109	688,712	1.11 (0.86-1.43)	1.11 (0.85-1.43)
Manual/heavy manual	110	274,166	0.89 (0.71-1.12)	0.91 (0.72-1.15)	Manual/heavy manual	71	274,015	0.97 (0.72-1.29)	0.96 (0.71-1.30)
Nonworker	514	879,634	0.90 (0.75-1.08)	0.91 (0.75-1.09)	Nonworker	265	878,734	1.15 (0.90-1.47)	1.16 (0.90-1.49)
P_{trend}§			0.29	0.38	P_{trend}§			0.97	0.82
Household activity (MET-h/wk)									
<19.5	289	673,316	1.0	1.0	<19.5	150	672,766	1.0	1.0
≥19.5-<39.6	281	682,023	0.94 (0.80-1.12)	0.95 (0.80-1.12)	≥19.5-<39.6	157	681,576	1.02 (0.81-1.28)	1.02 (0.81-1.28)
≥39.6-<73.9	272	659,317	0.90 (0.76-1.07)	0.90 (0.76-1.07)	≥39.6-<73.9	167	658,912	1.09 (0.87-1.38)	1.10 (0.87-1.39)
≥73.9	252	618,226	0.92 (0.76-1.13)	0.93 (0.76-1.13)	≥73.9	125	617,747	0.97 (0.74-1.26)	0.98 (0.75-1.29)
P_{trend}			0.34	0.35	P_{trend}			0.97	0.88
Recreational activity (MET-h/wk)									
<12.0	317	675,216	1.0	1.0	<12.8	139	488,157	1.0	1.0
≥12.0-<24.8	255	665,716	0.83 (0.70-0.98)	0.85 (0.71-1.00)	≥12.8-<24.0	144	490,903	1.14 (0.90-1.44)	1.15 (0.90-1.46)
≥24.8-<42.8	258	658,547	0.81 (0.68-0.96)	0.83 (0.70-0.98)	≥24.0-<42.0	158	477,489	1.20 (0.94-1.51)	1.22 (0.96-1.54)
≥42.8	264	633,403	0.85 (0.71-1.01)	0.88 (0.74-1.05)	≥45.8	158	426,419	1.18 (0.92-1.50)	1.21 (0.94-1.54)
P_{trend}			0.05	0.13	P_{trend}			0.18	0.12

*Base models are stratified by age and center and mutually adjusted for each type of physical activity (occupational, recreational, and household).
†Multivariate models are stratified by age and center and adjusted for energy (kilocalories per day in quartiles), education (none, primary school, technical/professional school), smoking (never, former, current, unknown), height (centimeters in tertiles), weight (kilograms in tertiles), and fiber (grams per day in quartiles).
‡Multivariate models are stratified by age and center and adjusted for energy (kilocalories per day in quartiles), education (none, primary school, technical/professional school), smoking (never, former, current, unknown), height (centimeters in tertiles), weight (kilograms in tertiles), fiber (grams per day in quartiles), and fish intake (grams per day in quartiles).
§Test for trend in occupational activity excluded all study participants categorized as nonworkers, missing, or unknown.

図表掲載箇所	P2402, Table3
概 要 (800字まで)	本研究は、The European Prospective Investigation into Cancer and Nutritionに参加した男女413,44名を対象に平均6.4年間の追跡調査を行い、身体活動と結腸直腸がん発症リスクとの関連を検討したものである。質問紙により、職業活動レベルと職業時以外で実施した身体活動の期間と頻度を尋ねた。それぞれの身体活動に相当するメッツ値と実施期間を乗じ、合計を総身体活動量とし、職業活動レベルとの組合せにより、不活動、やや不活動、やや活動的、活動的の4群に分類した。また、余暇時間活動と家事活動もそれぞれのメッツ値を合計し、身体活動量をメッツ時/週に換算し、4群に分類した。総身体活動量と家事活動量は結腸直腸がん発症リスクとの関連はなかった。結腸がん発症リスクに関して、余暇時間活動が12.0メッツ時/週未満の集団と比較すると、24.8-42.8メッツ時/週の集団で有意なリスク低下がみられた(0.83(95%信頼区間:0.70-0.98))。余暇時間活動と直腸がん発症リスクとの関連はなかった。部位別にみると、右結腸がん発症リスクと総身体活動量に有意な関連がみら
結 論 (200字まで)	本研究の大規模コホートにおいて、身体活動は直腸がん(特に右直腸がん)発症リスクに対して保護効果があることが明らかとなった。
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用いられた研究の1つである。週24メッツ時／週以上の身体活動が低い結腸がん発症と関係することを示した。身体活動のドメインと強度を詳細に検討し、実証した点に意義がある。

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A Prospective Study of Physical Activity and Incident and Fatal Prostate Cancer

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Background: Whether physical activity has benefits against prostate cancer incidence or progression is unclear. Therefore, we assessed physical activity in relation to prostate cancer incidence, mortality, and Gleason histologic grade.

Methods: We used data from the Health Professionals Follow-up Study, a prospective cohort study, to determine the number of cases of incident, advanced (seminal vesicle invasion, metastasis, or fatal), fatal, and high-grade prostate cancer in a cohort of 47 620 US male health professionals, followed up from February 1, 1986, to January 31, 2000.

Results: During 14 years of follow-up, we documented 2892 new cases of prostate cancer, including 482 advanced cases (280 of which were fatal). For total prostate cancer, no association was observed for total, vigorous, and nonvigorous physical activity. In men 65 years or older, we observed a lower risk in the highest category of vigorous activity for advanced (multivariable relative risk, 0.33; 95% confidence interval, 0.17-0.62, for more than 29 vs 0 metabolic equivalent hours) and for fatal (relative risk, 0.26; 95% confidence interval, 0.11-0.66) prostate cancer. No associations were observed in younger men. Differential screening by prostate-specific antigen or a reduction in physical activity due to undiagnosed prostate cancer did not appear to account for the results. Among cases, men with high levels of physical activity were less likely to be diagnosed with poorly differentiated cancers (Gleason grade ≥7).

Conclusion: Although the mechanisms are not yet understood, these findings suggest that regular vigorous activity could slow the progression of prostate cancer and might be recommended to reduce mortality from prostate cancer, particularly given the many other documented benefits of exercise.

Arch Intern Med. 2005;165:1005-1010

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Financial Disclosure: None.

SOME STUDIES[1-19] HAVE SUGgested that more physically active men may have a lower risk of prostate cancer, but the associations have tended to be moderate, not always statistically significant, and sometimes only evident among older subgroups[6,9,11,16] or for substantially high, but not moderate, levels of activity.[9,16,18] However, many of the studies were not designed to examine physical activity in detail and could not adequately consider the amount, timing, and intensity of each type of activity.[20] In addition, prostate cancers are heterogeneous, and evidence suggests differences in etiology by different groups of men (eg, younger or older subgroups) or by type of end point (eg, high vs low grade, incident vs fatal). Moreover, the diagnosis of prostate cancer is currently largely influenced by the use of prostate-specific antigen (PSA) for screening, which could bias results.

Our group previously examined physical activity relative to risk of prostate cancer in the Health Professionals Follow-up Study, a prospective cohort study of US male health professionals who were followed up from February 1, 1986, to January 31, 1994.[16] In that analysis, which was based on 1362 total incident cases of prostate cancer, we found no relationship for total, vigorous, and nonvigorous physical activity. However, for metastatic prostate cancer we observed a statistically significant 54% lower risk in the highest category of vigorous activity only, which was due to a 69% risk reduction in older men (those ≥67.5 years of age) but not younger men. Now, with follow-up to 2000 and with 2982 incident cases in this cohort, we assessed the specific relationship between vigorous activity and risk of advanced prostate cancer in older men. In addition, we examined whether any benefit of physical activity occurs relatively soon or requires a long time lag, assessed fatal prostate cancer and histologic tumor grade as additional end points, and accounted for PSA screening frequency.

METHODS

STUDY POPULATION

In 1986, 51 529 US male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians, aged 40 to 75 years, completed and returned a mailed questionnaire to initiate the Health Professionals Follow-up Study cohort. Through this 1986 baseline questionnaire, we elicited information on age, marital status, height and weight, ancestry, medications, smoking history, disease history, physical activity, and diet. Every 2 years, we mailed follow-up questionnaires to collect information on new medical diagnoses and lifestyle factors and to update data on physical activities. We updated dietary information through food frequency questionnaires that were administered every 4 years. Using reports from family members, the US Postal Service, and the National Death Index, we ascertained more than 98% of deaths.[21] Our follow-up response rate was 96%. This study was approved by the Human Subjects Committee of the Harvard School of Public Health, Boston, Mass.

IDENTIFICATION OF CASES OF PROSTATE CANCER

When participants reported new diagnoses in response to our questionnaires, we asked them for permission to obtain hospital records and pathology reports. Study investigators used the staging information received from any procedures or tests conducted during the initial diagnosis and treatment, including prostatectomies and bone scans. From 1986 to the end of this study period, we documented 3006 newly diagnosed cases of prostate adenocarcinoma in 596 756 person-years, after excluding 68 cases of stage T1a cancer (incidental histologic cancer found in ≤5% of tissue resected) because T1a cancers are relatively innocuous and especially prone to detection bias. Of the 3006 cases, we were able to document approximately 90% with the use of medical records and pathology reports; for most of the remaining 10%, participants provided information regarding the diagnosis and subsequent treatment. Based on the pathology report, we also recorded Gleason histologic grade, which was available for 2159 cases. Fatal prostate cancer was determined by study physicians after a review of the medical records.

ASSESSMENT OF PHYSICAL ACTIVITY

On the 1986 questionnaire, we asked men to report the average time per week that they engaged in the following activities during the past year: walking or hiking outdoors (including walking at golf), jogging (slower than 10 min/mile), running (10 min/mile or faster), bicycling (including stationary machine), lap swimming, tennis, squash or racquetball, and calisthenics or rowing. In addition, we asked about the number of flights of stairs climbed daily and the usual walking pace. We updated our physical activity assessment every 2 years. Heavy outdoor work was added in 1988 and weight training in 1990. To generate the total physical activity score, we summed activity-specific metabolic equivalent (MET)–hours per week. A MET-hour is the metabolic equivalent of sitting at rest for 1 hour. MET-hour values were obtained from a compendium of physical activities.[22] We also generated quintiles of total MET-hours per week for vigorous or high-intensity activities (running, jogging, biking, swimming, tennis, racquetball/squash, rowing/calisthenics, heavy outdoor work, and weight training) and nonvigorous activities (flights of stairs climbed and walking). The activity assessment has been previously validated.[23] Because the men are health professionals, occupational activity is low for most of them.

STATISTICAL ANALYSIS

After excluding men with diagnosed cancer (except for nonmelanoma skin cancer) at baseline and those who did not adequately complete a dietary or physical activity questionnaire, 47 620 men formed the analytic cohort. Each man accrued follow-up time beginning on the month of return of the baseline questionnaire and ending on the month of diagnosis for prostate cancer cases, or the month of death from other causes, or January 31, 2000, for noncases. We calculated incidence rates of prostate cancer for men in a specific category of physical activity level by dividing the number of incident total, advanced, nonadvanced, or fatal prostate cancer cases by the number of person-years in that category. Advanced cases were considered those with extension to the seminal vesicle or with evidence of metastasis to the lymph nodes or distant organs at the time of diagnosis, or those whose cases were fatal by January 31, 2000. The remaining cases, including those with minimal extension into the prostatic capsule, were considered nonadvanced.

Physical activity in MET-hours per week was categorized into quintiles. We considered separately total, vigorous, and nonvigorous physical activity. Because approximately half the cohort members reported no vigorous activity, those reporting no vigorous activity were considered in 1 category, and we then formed quartiles for those with any level of vigorous activity to form 5 total categories. To better assess timing of exposure to risk of prostate cancer, we examined baseline data (1986) without updating, with simple updating using the most recent assessment, and with cumulative updating, which uses the 1986 activity assessment to assess risk prospectively from 1986 to 1988, the average of the 1986 and 1988 assessments to assess risk prospectively from 1988 to 1990, and so forth. In addition, we considered 2-year and 4-year time lags (ie, updating information only up to 2 or 4 years, respectively), to the period of risk. For fatal prostate cancer, we updated data only until the time of the diagnosis.

We computed relative risks (RRs), which we defined as the incidence rate of disease in 1 category (eg, high level of vigorous activity) divided by the incidence rate in a specified reference category (eg, low activity level). We used the Mantel-Haenszel summary estimator to adjust for age (across 5-year categories). We used Cox proportional hazards modeling to control for multiple variables simultaneously and to compute 95% confidence intervals (CIs). Age (in 1-year intervals) and study period (in 2-year intervals) were controlled for as stratification variables in the Cox model. We tested for departures from the proportional hazards assumption by using likelihood tests. The following covariates were included in the models: body mass index at age 21 years, height, cigarette pack-years in the previous 10 years, family history of prostate cancer, history of diabetes mellitus, race, and intakes of total calories, red meat, fish, α-linolenic acid, calcium, zinc supplements, and tomato sauce.[24-29] When vigorous and nonvigorous activities were analyzed, they were mutually adjusted. We updated modifiable variables. We tested for trend across categories, controlling for multiple covariables by modeling the median values of categories of physical activity as a continuous variable in the multivariable model. We conducted tests for multiplicative interaction (Wald test) between age and physical activity by modeling si-

Table 1. Age-Standardized Characteristics of HPFS Men at 1986 Baseline

Characteristic	Total Activity Q1	Total Activity Q3	Total Activity Q5	Vigorous Activity* G1	Vigorous Activity* G2	Vigorous Activity* G3
Age, mean, y†	54.3	54.3	52.8	56.2	53.7	50.4
Total activity, mean, MET-h/wk	1.1	11.9	61.4	8.4	16.1	64.6
Vigorous activity, mean, MET-h/wk	0.1	5.3	41.3	0	8.0	56.0
BMI, mean	25.4	25.0	24.4	25.4	24.9	24.1
BMI at age 21 y, mean	22.9	22.9	23.2	23.0	23.0	23.1
Height, mean, cm	177.8	178.1	178.3	178.1	178.1	178.3
White, %	90.9	90.5	90.3	91.2	90.6	89.7
African American, %	1.4	0.95	0.8	1.0	1.0	0.96
Diabetes, %	4.3	3.1	2.2	3.7	2.7	2.1
Current smoker, %	14.6	9.5	6.4	13.8	8.1	4.7
Multivitamin use, %	37.1	42.2	44.5	36.3	44.8	46.7
Intake, mean‡						
Calories per day	1933	1978	2051	1980	1971	2014
Calcium, mg/d	862	893	923	866	904	942
α-Linolenic acid, g/d	1.09	1.08	1.05	1.08	1.08	1.05
Red meat, servings/d	0.68	0.61	0.54	0.69	0.58	0.48
Tomato sauce, servings/wk	0.90	0.95	1.04	0.93	0.95	1.04
Fish, servings/d	0.33	0.39	0.45	0.34	0.41	0.46

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent; Q, quintile.

*For vigorous activity, G1 indicates 0 MET-h/wk of vigorous activity; G2, second quartile of subjects with positive vigorous activity MET-hours; and G3, fourth quartile of subjects with positive vigorous activity MET-hours.

†Age is not age-standardized.

‡Red meat indicates beef, pork, or lamb as a main dish, and 1 serving equals 140 g; for tomato sauce, 1 serving equals 125 g; and for fish, 1 serving equals 112 g.

multaneously physical activity as a continuous variable, an indicator for age group (0 if <65 years; 1 if ≥65 years), and the product of age and vigorous activity (the interaction term). Using a case-case approach, we also assessed the odds ratio (OR) of being diagnosed as having a high-grade (Gleason grade ≥7) vs a low-grade (Gleason grade <7) cancer by using multivariable logistic regression. All reported *P* values are 2 sided.

RESULTS

AGE-STANDARDIZED CHARACTERISTICS ACCORDING TO PHYSICAL ACTIVITY LEVEL

Table 1 shows selected age-standardized characteristics in relation to total and vigorous physical activity. As expected, younger men tended to have more vigorous activity. In general, more physically active men had a more healthful lifestyle and diet.

TOTAL AND NONVIGOROUS PHYSICAL ACTIVITY

We examined total prostate cancer in relation to total physical activity by using the simple updated assessment (the most recent physical activity assessment) and found no association (multivariable-adjusted RR, 1.02 for the top vs bottom quintiles; 95%CI, 0.91-1.15; *P* for trend=.47), despite substantial power (approximately 600 cases per quintile). Moreover, no significant associations were observed for nonadvanced, advanced, or fatal prostate cancer. We found no evidence of a lower risk of total prostate cancer, or any subgroups of prostate cancer, associated with nonvigorous activities (data not shown). Use of baseline data (1986) without updating or cumulatively updated physical activity similarly yielded null results for total and nonvigorous activities.

VIGOROUS PHYSICAL ACTIVITY AND AGE STRATIFICATION

For vigorous physical activity in age-adjusted analyses, no appreciable association was observed with total prostate cancer (age-adjusted RR, 1.09; 95% CI, 0.97-1.23; *P* for trend=.05), and a modest positive association was noted for nonadvanced prostate cancer (age-adjusted RR, 1.21; 95% CI, 1.07-1.37; *P* for trend=.002). For advanced prostate cancer, in the Cox proportional regression analysis, there was strong evidence against the proportional hazards assumption (*P*<.001) because of strong heterogeneity by age, as was observed in a previous analysis by our group.[16] Thus, for the remaining analyses, we stratified the population into men younger than 65 years and those 65 years or older (**Table 2**). We found a decreased risk only in the older subgroup of men for advanced prostate cancer (*P*=.009, for interaction by age). The age-adjusted results (RRs across categories 1 through 5 for older men: 1.00, 0.88, 1.13, 1.03, and 0.31, respectively; *P* for trend=.001) were almost identical to the multivariable results (Table 2). For fatal prostate cancer, results were similar to those for advanced prostate cancer (*P*=.02, for interaction by age; multivariable RR for top vs bottom category, 0.26; 95% CI, 0.11-0.66). When we stratified advanced prostate cancer by study period and

Table 2. Relation Between Prostate Cancer and Vigorous Physical Activity in HPFS (1986-2000) by Age Group

Variable	MET-h/wk* 0	1-4	5-11	12-29	>29	*P* for Trend
Total prostate cancer						
Age <65 y, n	473	106	139	130	120	
RR (95% CI)†	1.00	0.95 (0.76-1.17)	1.15 (0.95-1.40)	1.03 (0.84-1.25)	1.08 (0.88-1.33)	.44
Age ≥65 y, n	1084	257	243	227	203	
RR (95% CI)†	1.00	1.06 (0.92-1.22)	0.99 (0.86-1.14)	1.08 (0.93-1.25)	1.09 (0.94-1.28)	.22
Nonadvanced prostate cancer						
Age <65 y, n	408	90	121	113	103	
RR (95% CI)†	1.00	0.94 (0.75-1.19)	1.17 (0.95-1.44)	1.02 (0.83-1.27)	1.06 (0.85-1.33)	.58
Age ≥65 y, n	874	217	192	189	193	
RR (95% CI)†	1.00	1.10 (0.95-1.28)	0.95 (0.81-1.12)	1.08 (0.92-1.27)	1.25 (1.06-1.46)	.009
Advanced prostate cancer‡						
Age <65 y, n	65	16	18	17	17	
RR (95% CI)†	1.00	0.98 (0.56-1.70)	1.06 (0.62-1.81)	1.02 (0.59-1.77)	1.23 (0.71-2.14)	.47
Age ≥65 y, n	210	40	51	38	10	
RR (95% CI)†	1.00	0.88 (0.63-1.25)	1.14 (0.83-1.56)	1.07 (0.75-1.52)	0.33 (0.17-0.62)	.003

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent; n, number of cases of prostate cancer; RR, relative risk.

*MET-hours of physical activity per week, updated every 2 years.

†Multivariable RR controlled for age, study period, body mass index at age 21 years, height, cigarette pack-years in the previous 10 years, family history of prostate cancer, history of diabetes mellitus, race, nonvigorous activity, and intake of total calories, red meat, fish, α-linolenic acid, calcium, zinc supplements, and tomato sauce.

‡A total of 280 of these cases were fatal.

Table 3. Relation Between Vigorous Physical Activity and Advanced Prostate Cancer in the HPFS (1986-2000)*

Study Period	MET-h/wk† 0	1-4	5-11	12-29	>29	*P* for Trend
1986 to January 1994 follow-up						
Age <65 y	1.00	1.22 (0.65-2.30)	1.16 (0.61-2.19)	1.28 (0.67-2.43)	1.19 (0.58-2.42)	.61
Age ≥65 y	1.00	0.83 (0.54-1.25)	1.00 (0.68-1.47)	1.05 (0.68-1.61)	0.35 (0.16-0.74)	.02
February 1994 to 2000 follow-up						
Age <65 y	1.00	0.53 (0.16-1.79)	0.85 (0.32-2.30)	0.62 (0.21-1.83)	1.32 (0.54-3.21)	.52
Age ≥65 y	1.00	1.00 (0.54-1.83)	1.46 (0.85-2.51)	1.07 (0.58-1.98)	0.27 (0.08-0.87)	.04

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent; RR, relative risk

*Analyses are stratified by study period and age group. Data are given as multivariable RR (95% CI), unless otherwise indicated. Multivariable RRs are controlled for age, study period, body mass index at age 21 years, height, cigarette pack-years in the previous 10 years, family history of prostate cancer, history of diabetes mellitus, race, nonvigorous activity, and intake of total calories, red meat, fish, α-linolenic acid, calcium, zinc supplements, and tomato sauce.

†MET-hours of physical activity per week, updated every 2 years.

Table 4. Relation Between Vigorous Physical Activity and Advanced Prostate Cancer for Men 65 Years or Older in the HPFS Accounting for Various Time Lags

Assessment	Q5 vs Q1, RR (95% CI)*	*P* for Trend
Simple updating	0.32 (0.17-0.61)	.002
Cumulative updating	0.62 (0.38-1.00)	.02
Cumulative updating, 2-y lag	0.65 (0.42-1.02)	.05
Cumulative updating, 4-y lag	0.47 (0.27-0.80)	.007

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; Q, quintile; RR, relative risk.

*Multivariable RR (see first footnote to Table 3) and 95% CI for high vs low category of vigorous physical activity.

age, a marked reduced risk in older men only was observed in both periods (**Table 3**).

TIME-LAGGED ANALYSES

Decreased risks of advanced prostate cancer for the high vs low category of physical activity for men 65 years or older were observed for simple updating, for cumulative updating (activity averaged for all questionnaires up to the period of risk), and for cumulative updating but considering 2-year or 4-year time lags (**Table 4**). Similar patterns were observed for fatal prostate cancer (data not shown). Furthermore, to determine whether morbidity from undiagnosed prostate cancer may have caused men to reduce their activity level, we examined the influence of recent changes in physical activity reported on the 2 questionnaires preceding the period of risk. Among men 65 years or older, relative to those who were consistently low in vigorous physical activity (ie, not in the top category), the multivariable RRs for advanced prostate cancer were as follows: for men who had reduced their physical activity from a high to a low category, 1.53 (95% CI, 0.95-2.44); for men who had increased their physical activity from a low to a high category, 0.37 (95% CI, 0.15-0.90); and for men consistently in a high category, 0.32 (95% CI, 0.13-0.78). Thus, although a modest, nonsignificant increased risk of advanced prostate cancer was observed for men who reduced their activity level from the top category, the overall reduced risk was not caused solely by a reduction in vigorous activity level shortly before the diagnosis.

VIGOROUS PHYSICAL ACTIVITY AND GLEASON GRADE

For 2159 cases with data on the Gleason grade, 849 (39%) were Gleason grade 7 or higher (high-grade). In a case-only analysis, the multivariable OR of high-grade vs low-grade prostate cancer was significantly reduced for men in the top quintile of vigorous physical activity (OR, 0.64; 95% CI, 0.47-0.87; $P=.004$) relative to the lowest category, especially in men 65 years or older (OR, 0.53; 95% CI, 0.36-0.79; $P=.002$). To better distinguish high-grade from advanced-stage prostate cancer, we further limited the analysis to the 1871 nonadvanced cancers at diagnosis only (634 of these were high-grade cases). In this group, we also found that the multivariable OR was significantly reduced in men in the top quintile of vigorous physical activity (OR, 0.70; 95% CI, 0.51-0.97; $P=.03$) relative to the lowest category, particularly in men 65 years or older (OR, 0.64; 95% CI, 0.43-0.97; $P=.04$).

VIGOROUS ACTIVITY AND FREQUENCY OF PSA EXAMINATION

The respective percentages of men 65 years or older who reported at least 1 PSA examination by 2000 according to level of vigorous physical activity in 1992, from lowest to highest category, were 86%, 89%, 91%, 92%, and 92%. The respective percentages of men who reported having had a PSA test on at least 3 of the 4 biennial questionnaires from 1994 to 2000, across levels of vigorous activity (lowest to highest), were 73%, 71%, 75%, 76%, and 74%. Thus, the frequency of PSA tests did not differ appreciably across levels of vigorous activity.

COMMENT

In this cohort of male health professionals, we did not observe a monotonic association between total or nonvigorous nonoccupational physical activity and risk of total or advanced prostate cancer. However, as observed in an analysis based on less follow-up,[16] men who were 65 years or older had an approximately 70% reduction in advanced prostate cancer if they achieved 30 MET-h/wk, which is roughly equivalent to at least 3 hours of vigorous activity weekly. In addition, we now observe a similar reduction for fatal prostate cancer.

Several analyses indicate that our results were highly unlikely to have resulted from chance. First, statistically significant findings were observed initially in follow-up to 1994, and results were replicated with independent follow-up to 2000. Second, the inverse association was apparent for advanced prostate cancer at diagnosis, for fatal prostate cancer, and for high-grade prostate cancer, even among men with nonadvanced prostate cancer. Third, findings were observed when using the baseline questionnaire data, cumulative updated assessments, or simple updated assessments, and with various time lags between exposure and time of diagnosis.

Although the possibility of confounding cannot be entirely ruled out in an observational study, several facts argue against it. We controlled for numerous factors, and the age-adjusted and fully multivariable analyses provided similar results. The risk reduction was 3- to 4-fold, and a putative uncontrolled confounding factor would have to be strongly related to both high levels of physical activity and a substantially reduced risk of advanced prostate cancer.

Because the inverse association was observed for advanced prostate cancer and prostate cancer mortality but not nonadvanced prostate cancer, early diagnosis by PSA screening and treatment could possibly have reduced mortality among physically active men. However, PSA screening was common throughout the cohort and did not vary appreciably by level of vigorous physical activity. Furthermore, we observed a 3- to 4-fold reduction in risk in older men from 1986 to 1994,[16] before any effects of widespread PSA screening on metastasis and mortality could have taken effect.

Another consideration is that the lower mortality was caused by a reduction in physical activity among men who were ill with undiagnosed metastatic prostate cancer. However, we found that most of the reduction in risk was due to men who were consistently high in activity or who had moved from a lower to the highest category rather than due to an excess risk from men who had recently reduced their activity level. Moreover, this potential bias could not explain the higher likelihood of high-grade vs low-grade prostate cancer in those diagnosed as having organ-confined cancers.

The consistent finding that high levels of physical activity reduce risk in men 65 years or older may suggest variant etiologies for early-onset and later-onset cancers. Our group has previously found in this cohort that higher body mass index and waist circumference[25] are associated with a lower risk of prostate cancer in younger men but not older men. These findings led us to hypothesize that in younger men, androgen stimulation may be a more important factor because obesity is associated with lower circulating testosterone and with higher estrogen concentrations.[30-32] This apparent paradoxical "benefit" of obesity in younger men may explain the lack of an association with physical activity in that age group. Prostate cancers that are fatal by age 65 years tend to have a strong genetic component and may have a different etiology than those that occur in older men.

The mechanism whereby physical activity may be protective is unknown, but physical activity may influence a number of hormones hypothesized to enhance prostate cancer carcinogenesis, including insulinlike growth factor 1,[33] insulin,[34,35] leptin[36,37] and testosterone.[38,39] In one study,[40,41] an exercise and low-fat diet intervention lowered circulating levels of insulinlike growth factor 1 and insulin in men, and increased levels of sex hormone–binding globulin and insulinlike growth factor binding protein 1. When used as a medium for cell culture to grow LNCaP cells, serum from the exercising men decreased proliferation by a third and increased apoptosis 4-fold.[42]

In conclusion, men 65 years or older engaging at least 3 hours of vigorous physical activity weekly had a markedly lower risk (almost 70%) of being diagnosed as having high-grade, advanced, or fatal prostate cancer. The findings were consistent over time, did not appear to be caused by bias or confounding, and are compatible with hormonal hypotheses regarding prostate cancer progression. Although the mechanisms still need to be understood, these findings suggest that vigorous activity could slow the progression of prostate cancer and might be recommended to reduce mortality from prostate cancer, particularly given the many other documented benefits of exercise.

Accepted for Publication: October 11, 2004.
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Funding/Support: This study was supported by research grant CA 55075 from the National Institutes of Health, Bethesda, Md.
Acknowledgment: We are indebted to Elizabeth Frost-Hawes, Barbara Vericker, Stacy DeCaro, Mira Kaufman, and Al Wing for expert help.

REFERENCES

1. Friedenreich CM, McGregor SE, Courneya KS, Angyalfi SJ, Elliott FG. Case-control study of lifetime total physical activity and prostate cancer risk. *Am J Epidemiol.* 2004;159:740-749.
2. Paffenbarger RS Jr, Hyde RT, Wing AL. Physical activity and incidence of cancer in diverse populations: a preliminary report. *Am J Clin Nutr.* 1987;45(suppl):312-317.
3. Vena JE, Graham S, Zielezny M, Brasure J, Swanson MK. Occupational exercise and risk of cancer. *Am J Clin Nutr.* 1987;45(suppl)1:318-327.
4. Brownson RC, Chang JC, Davis JR, Smith CA. Physical activity on the job and cancer in Missouri. *Am J Public Health.* 1991;81:639-642.
5. Hsing AW, McLaughlin JK, Zheng W, Gao Y-T, Blot WJ. Occupation, physical activity, and risk of prostate cancer in Shanghai, People's Republic of China. *Cancer Causes Control.* 1994;5:136-140.
6. Le Marchand L, Kolonel LN, Yoshizawa CN. Lifetime occupational physical activity and prostate cancer risk. *Am J Epidemiol.* 1991;133:103-111.
7. Yu H, Harris RE, Wynder EL. Case-control study of prostate cancer and socioeconomic factors. *Prostate.* 1988;13:317-325.
8. Albanes D, Blair A, Taylor PR. Physical activity and risk of cancer in the NHANES I population. *Am J Public Health.* 1989;79:744-750.
9. Lee IM, Paffenbarger RS Jr, Hsieh CC. Physical activity and risk of prostatic cancer among college alumni. *Am J Epidemiol.* 1992;135:169-179.
10. Paffenbarger RS Jr, Lee I-M, Wing AL. The influence of physical activity on the incidence of site-specific cancers in college alumni. In: Jacobs MM, ed. *Exercise, Calories, Fat and Cancer.* New York, NY: Plenum Press; 1992:7-15.
11. Thune I, Lund E. Physical activity and the risk of prostate and testicular cancer: a cohort study of 53,000 Norwegian men. *Cancer Causes Control.* 1994;5:549-556.
12. Steenland K, Nowlin S, Palu S. Cancer incidence in the National Health and Nutrition Survey I: follow-up data: diabetes, cholesterol, pulse, and physical activity. *Cancer Epidemiol Biomarkers Prev.* 1995;4:807-811.
13. Oliveria SA, Kohl HW III, Trichopoulos D, Blair SN. The association between cardiorespiratory fitness and prostate cancer. *Med Sci Sports Exerc.* 1996;28:97-104.
14. Severson RK, Nomura AMY, Grove JS, Stemmermann GN. A prospective analysis of physical activity and cancer. *Am J Epidemiol.* 1989;130:522-529.
15. Hartman TJ, Albanes D, Rautalahti M, et al. Physical activity and prostate cancer in the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study (Finland). *Cancer Causes Control.* 1998;9:11-18.
16. Giovannucci E, Leitzmann M, Spiegelman D, et al. A prospective study of physical activity and prostate cancer in male health professionals. *Cancer Res.* 1998;58:5117-5122.
17. Clarke G, Whittemore AS. Prostate cancer risk in relation to anthropometry and physical activity: the National Health and Nutrition Examination Survey I Epidemiological Follow-up Study. *Cancer Epidemiol Biomarkers Prev.* 2000;9:875-881.
18. Wannamethee SG, Shaper AG, Walker M. Physical activity and risk of cancer in middle-aged men. *Br J Cancer.* 2001;85:1311-1316.
19. Norman A, Moradi T, Gridley G, et al. Occupational physical activity and risk for prostate cancer in a nationwide cohort study in Sweden. *Br J Cancer.* 2002;86:70-75.
20. Lee IM, Sesso HD, Chen JJ, Paffenbarger RS Jr. Does physical activity play a role in the prevention of prostate cancer? *Epidemiol Rev.* 2001;23:132-137.
21. Stampfer MJ, Willett WC, Speizer FE, et al. Test of the National Death Index. *Am J Epidemiol.* 1984;119:837-839.
22. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc.* 1993;25:71-80.
23. Chasan-Taber S, Rimm EB, Stampfer MJ, et al. Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. *Epidemiology.* 1996;7:81-86.
24. Leitzmann MF, Stampfer MJ, Wu K, Colditz GA, Willett WC, Giovannucci EL. Zinc supplement use and risk of prostate cancer. *J Natl Cancer Inst.* 2003;95:1004-1007.
25. Giovannucci E, Rimm EB, Liu Y, et al. Body mass index and risk of prostate cancer in US health professionals. *J Natl Cancer Inst.* 2003;95:1240-1244.
26. Giovannucci E, Rimm EB, Colditz GA, et al. A prospective study of dietary fat and risk of prostate cancer. *J Natl Cancer Inst.* 1993;85:1571-1579.
27. Giovannucci E, Ascherio A, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Intake of carotenoids and retinol in relation to risk of prostate cancer. *J Natl Cancer Inst.* 1995;87:1767-1776.
28. Giovannucci E, Rimm EB, Wolk A, et al. Calcium and fructose intake in relation to risk of prostate cancer. *Cancer Res.* 1998;58:442-447.
29. Augustsson K, Michaud DS, Rimm EB, et al. A prospective study of intake of fish and marine fatty acids and prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2003;12:64-67.
30. Pasquali R, Casimirri F, Cantobelli S, et al. Effect of obesity and body fat distribution on sex hormones and insulin in men. *Metabolism.* 1991;40:101-104.
31. Amatruda JM, Harman SM, Pourmotabbed G, Lockwood DH. Decreased plasma testosterone and fractional binding of testosterone in obese males. *J Clin Endocrinol Metab.* 1978;47:268-271.
32. Zumoff B. Hormonal abnormalities in obesity. *Acta Med Scand Suppl.* 1988;723:153-160.
33. Chan JM, Stampfer MJ, Giovannucci E, et al. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. *Science.* 1998;279:563-566.
34. Hsing AW, Chua S Jr, Gao YT, et al. Prostate cancer risk and serum levels of insulin and leptin: a population-based study. *J Natl Cancer Inst.* 2001;93:783-789.
35. Lehrer S, Diamond EJ, Stagger S, Stone NN, Stock RG. Increased serum insulin associated with increased risk of prostate cancer recurrence. *Prostate.* 2002;50:1-3.
36. Chang S, Hursting SD, Contois JH, et al. Leptin and prostate cancer. *Prostate.* 2001;46:62-67.
37. Stattin P, Soderberg S, Hallmans G, et al. Leptin is associated with increased prostate cancer risk: a nested case-referent study. *J Clin Endocrinol Metab.* 2001;86:1341-1345.
38. Eaton NE, Reeves GK, Appleby PN, Key TJ. Endogenous sex hormones and prostate cancer: a quantitative review of prospective studies. *Br J Cancer.* 1999;80:930-934.
39. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. A prospective study of sex hormone levels and risk of prostate cancer. *J Natl Cancer Inst.* 1996;88:1118-1126.
40. Barnard RJ, Aronson WJ, Tymchuk CN, Ngo TH. Prostate cancer: another aspect of the insulin-resistance syndrome? *Obes Rev.* 2002;3:303-308.
41. Tymchuk CN, Barnard RJ, Ngo TH, Aronson WJ. Role of testosterone, estradiol, and insulin in diet- and exercise-induced reductions in serum-stimulated prostate cancer cell growth in vitro. *Nutr Cancer.* 2002;42:112-116.
42. Leung PS, Aronson WJ, Ngo TH, Golding LA, Barnard RJ. Exercise alters the IGF axis in vivo and increases p53 protein in prostate tumor cells in vitro. *J Appl Physiol.* 2004;96:450-454.

論文名	A prospective study of physical activity and incident and fatal prostate cancer
著 者	Giovannucci EL, Liu Y, Leitzmann MF, Stampfer MJ, Willett WC
雑誌名	Arch Intern Med
巻・号・頁	165　　　　1005-1010
発行年	2005
PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/15883238

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	男性	(　　)		(　　)		(　　)
年齢	40-75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	死亡	(　　)
維持・改善	な し	な し	な し	な し	(　　)	(　　)

図 表

Table 2. Relation Between Prostate Cancer and Vigorous Physical Activity in HPFS (1986-2000) by Age Group

Variable	MET-h/wk* 0	1-4	5-11	12-29	>29	P for Trend
Total prostate cancer						
Age <65 y, n	473	106	139	130	120	
RR (95% CI)†	1.00	0.95 (0.76-1.17)	1.15 (0.95-1.40)	1.03 (0.84-1.25)	1.08 (0.88-1.33)	.44
Age ≥65 y, n	1084	257	243	227	203	
RR (95% CI)†	1.00	1.06 (0.92-1.22)	0.99 (0.86-1.14)	1.08 (0.93-1.25)	1.09 (0.94-1.28)	.22
Nonadvanced prostate cancer						
Age <65 y, n	408	90	121	113	103	
RR (95% CI)†	1.00	0.94 (0.75-1.19)	1.17 (0.95-1.44)	1.02 (0.83-1.27)	1.06 (0.85-1.33)	.58
Age ≥65 y, n	874	217	192	189	193	
RR (95% CI)†	1.00	1.10 (0.95-1.28)	0.95 (0.81-1.12)	1.08 (0.92-1.27)	1.25 (1.06-1.46)	.009
Advanced prostate cancer‡						
Age <65 y, n	65	16	18	17	17	
RR (95% CI)†	1.00	0.98 (0.56-1.70)	1.06 (0.62-1.81)	1.02 (0.59-1.77)	1.23 (0.71-2.14)	.47
Age ≥65 y, n	210	40	51	38	10	
RR (95% CI)†	1.00	0.88 (0.63-1.25)	1.14 (0.83-1.56)	1.07 (0.75-1.52)	0.33 (0.17-0.62)	.003

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent; n, number of cases of prostate cancer; RR, relative risk.

*MET-hours of physical activity per week, updated every 2 years.

†Multivariable RR controlled for age, study period, body mass index at age 21 years, height, cigarette pack-years in the previous 10 years, family history of prostate cancer, history of diabetes mellitus, race, nonvigorous activity, and intake of total calories, red meat, fish, α-linolenic acid, calcium, zinc supplements, and tomato sauce.

‡A total of 280 of these cases were fatal.

図表掲載箇所	P1008, Table2
概 要 (800字まで)	本研究は、アメリカのThe Health Professionals Follow-up Studyに参加した男性47,620名を対象に14年間の追跡調査を行い、身体活動量と前立腺がん発症/死亡リスクとの関連を検討したものである。質問紙により、過去1年間の余暇時間における週当たりの運動スポーツの実施時間と頻度からメッツ時/週を算出した。種目はランニング、ジョギング、自転車、水泳、テニス、ラケットボール、健康体操、筋力トレーニングなどの高強度身体活動であった。週当たりの高強度身体活動量が0メッツ時/週、1-4メッツ時/週、5-11メッツ時/週、12-29メッツ時/週、29メッツ時/週以上の5群に分類した。65歳未満の集団では、高強度身体活動量と進行性前立腺がんとの間に有意な関連はみられなかったが、65歳以上の集団では、高強度身体活動量が0メッツ時/週の集団と比較すると、29メッツ時/週以上の集団で進行性前立腺がん発症リスクが0.33(95%信頼区間:0.17-0.62)と有意に減少し、高強度身体活動量との間に量反応的な関連がみられた(Ptrend=0.003)。
結 論 (200字まで)	65歳以上の高齢集団において、週当たり29メッツ時以上の高強度身体活動を実施することに進行性前立腺がん発症リスクに対する強力な保護効果があることが明らかとなった。
エキスパートによるコメント (200字まで)	本研究では、身体活動と前立腺がん発症との関連は、65歳以上の群で、かつ、高強度身体活動でのみ関連が認められている。高齢者において高強度身体活動を29メッツ・時/週行うことは非常に厳しい目標である。この数値の解釈には、質問紙の妥当性を含め、十分注意が必要であろう。

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Walking to Work and the Risk for Hypertension in Men: The Osaka Health Survey

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Background: It is not known whether physical activity is effective in reducing the risk for hypertension.

Objective: To investigate the association of the duration of the walk to work and leisure-time physical activity with the risk for hypertension.

Design: Prospective cohort study.

Setting: Work site in Osaka, Japan.

Participants: 6017 Japanese men 35 to 60 years of age with systolic blood pressure less than 140 mm Hg, diastolic blood pressure less than 90 mm Hg, normal glucose intolerance, and no history of hypertension or diabetes at baseline.

Measurements: Data on physical activity were obtained by using questionnaires. Blood pressure was measured by using a standard technique; a value of at least 160/95 mm Hg was used to diagnose hypertension.

Results: During 59 784 person-years of follow-up, 626 cases of hypertension were confirmed. The duration of the walk to work was associated with a reduction in the risk for incident hypertension; multivariate-adjusted relative risks were 1.00 for a walk of 10 minutes or less (reference category), 0.88 (95% CI, 0.75 to 1.04) for an 11- to 20-minute walk, and 0.71 (CI, 0.52 to 0.97) for a walk of 21 minutes or more (*P* for trend = 0.02). For every 26.3 men who walk more than 20 minutes to work, one case of hypertension will be prevented.

Conclusions: Walking to work and other types of physical activity decreased the risk for hypertension in Japanese men. Regular exercise can prevent hypertension.

Ann Intern Med. 1999;130:21-26.

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There is good evidence that physical activity reduces the risk for cardiovascular disease (1–6), possibly in part by lowering blood pressure (7). Although mild or moderate physical activity, such as brisk walking, is a recommended part of the treatment protocol for persons with hypertension (8, 9), it is not known whether mild physical activity, especially walking, reduces the risk for hypertension.

With few exceptions, epidemiologic studies of physical activity and hypertension have been cross-sectional rather than prospective. Physical activity was inversely related to blood pressure in cross-sectional and controlled studies (7), and in two prospective studies (10, 11), vigorous exercise was inversely related to the subsequent risk for hypertension. Physicians in Japan usually advise their patients to walk to work as often as they can, and indeed, for middle-aged working Japanese men, the journey to and from work seems to be the main source of exercise.

We prospectively examined the relation of mild physical activity, especially walking to work, and leisure-time physical activity to the risk for hypertension during 6 to 16 years of observation.

Methods

The Osaka Health Survey

The Osaka Health Survey is an ongoing cohort study of risk factors for chronic diseases, including hypertension and diabetes. Study participants are male employees of a gas company in Osaka, Japan. Japanese law requires all employers to conduct annual health screenings for all employees. For the purposes of the Osaka Health Survey, in addition to these annual screenings, all employees 35 years of age or older undergo more detailed biennial clinical examinations and complete questionnaires on health-related behaviors, including exercise.

Study Sample

Between 1981 and 1990, 7979 Japanese men 35 to 63 years of age at entry who had sedentary occupations were enrolled in the study. We excluded 1875 men because they had physician-diagnosed hypertension, borderline hypertension (systolic blood pressure ≥ 140 and < 160 mm Hg,

Table 1. Baseline Characteristics According to Duration of the Walk to Work*

Characteristics	All Participants (*n* = 6017)	Duration of the Walk to Work†		
		0–10 Minutes (*n* = 3066)	11–20 Minutes (*n* = 2373)	≥21 Minutes (*n* = 578)
Age, *y*	41.7 ± 6.5	41.3 ± 6.3	42.1 ± 6.6	42.3 ± 6.7
Body weight, *kg*	62.9 ± 8.3	63.1	62.7	62.3
Body mass index, *kg/m²*	22.6 ± 2.6	22.7	22.5	22.4
Regular physical exercise at least once weekly, %	31.5	30.3	32.6	33.3
Alcohol drinkers, %	82.0	81.7	82.4	81.2
Alcohol intake, *mL/d*	36.9 ± 25.8	37.4	36.1	37.3
Smokers, %	61.8	63.4	60.3	56.9
Cigarettes smoked per day, *n*	24.4 ± 9.9	24.6	24.1	23.6
Systolic blood pressure, *mm Hg*	121.6 ± 10.6	121.6	121.4	121.6
Diastolic blood pressure, *mm Hg*	67.4 ± 10.1	67.3	67.4	67.4
Heart rate, *beats/min*	71.7 ± 10.9	71.7	71.7	71.2
Fasting plasma glucose level, *mg/dL*‡	90.2 ± 8.5	90.0	90.3	90.9

* Values are the mean or the mean ± SD, except for regular physical exercise at least once weekly, alcohol drinkers, and smokers.
† All variables (except for age) across the duration of the walk to work were adjusted for age.
‡ To convert to mmol/L, multiply by 0.05551.

diastolic blood pressure ≥ 90 and < 95 mm Hg, or both in men without a history of hypertension), diabetes, or impaired glucose tolerance (fasting plasma glucose level ≥ 6.1 mmol/L [≥110 mg/dL] and < 7.8 mmol/L [<140 mg/dL] in men with no history of diabetes) at entry. The study sample ultimately consisted of 6104 men.

Data Collection and Measurements

The biennial clinical examination consisted of a medical history; a physical examination; blood pressure measurement; anthropometric measurements; measurement of the fasting plasma glucose level; and surveys of health-related behaviors, such as physical activity, smoking, and daily alcohol consumption. Trained nurses took all measurements. Participants were asked to fast for 12 hours and to avoid smoking and heavy physical activity for more than 2 hours before the examination. After a 5-minute rest in a quiet room, a standard mercury sphygmomanometer was used to measure systolic and diastolic blood pressures in the right arm while the participant was seated. Pressure was measured twice, at an interval of a few minutes. Anthropometric measurements included height and body weight, which were measured while the participant was wearing light clothing without shoes. Body mass index was calculated as the weight in kilograms divided by the height in meters squared.

The questionnaire completed by each participant elicited information on leisure-time physical activity, the duration of the walk to work, the nature of the participant's occupation, and the level of activity involved. Leisure-time physical activity was defined as physical activity unrelated to the participant's work. Questions about leisure-time physical activity were as follows: "Do you engage in any regular physical exercise, such as jogging, bicycling, swimming, and tennis, long enough to 'work up a sweat' (lasting 30 minutes or more)? If yes, how many times per week? What exercise is this?" The questions about regular physical exercise have been validated as a measure of physical exercise (12–15). In the analysis, participants were classified as engaging in regular physical exercise at least once per week or less than once per week. They were also classified into one of three categories of exercise frequency: 0 (less than once per week), once per week, or two or more times per week. The question about the duration of the walk to work was "How long does it take you to walk to this office?" Occupational activity was scored as 1 if the participant's work was mostly sedentary and 2 if he worked outside or if the job required a lot of lifting and walking. In the present study, we excluded all participants who reported a score of 2 for their occupational activities.

Questions about alcohol intake included items about the type of alcoholic beverage, the weekly frequency of alcohol consumption, and the usual amount consumed daily. Alcohol intake was converted to total alcohol consumption (in milliliters of ethanol per day) by using standard Japanese tables. Current and past smoking habits were classified according to the type and quantity of cigarettes smoked daily. Participants were classified as current smokers, past smokers, or nonsmokers.

Hypertension was also diagnosed during the biennial study clinical examinations. All participants underwent medical screening by a physician at least once annually, and hypertension was also diagnosed by the physicians. Hypertension was defined by using World Health Organization criteria as physician-diagnosed hypertension (systolic blood pressure ≥ 160 mm Hg, diastolic blood pressure ≥ 95 mm Hg, or both) or use of antihypertensive medication (16).

Statistical Analysis

Age-adjusted mean values and relevant population characteristics were computed for the duration of the walk to work by using analysis of covariance for continuous variables and the direct method for categorical variables.

For each participant, person-years of follow-up were counted from the date at study entry to the date of diagnosis of hypertension or 1 April 1997, whichever came first. The rate of follow-up was 94% of the total potential person-years of follow-up. Multivariate Cox proportional hazards regression models were used to evaluate the simultaneous effects of the duration of the walk to work, the frequency of leisure-time physical activity, age, body mass index, daily alcohol consumption, smoking status, and fasting plasma glucose level. Baseline systolic and diastolic blood pressure were not included in our primary analyses because they could presumably be in the causal pathway between the exposures (such as physical activity, age, body mass index, and alcohol consumption) and risk for hypertension. However, we included systolic and diastolic blood pressure in further models to assess the effect of physical activity on the risk for hypertension independent of their effects on systolic and diastolic blood pressure. The linear trends in risks were evaluated by entering indicators for each categorical level of exposure or by using the median value for each category. As a reference category, we used men with the lowest level of physical activity.

To address the potential misclassification of leisure-time physical activity over time, additional analyses were performed on the basis of the data at both study entry (1981 to 1990) and the examination done 4 years after (1985 to 1994) each participant was enrolled. We also performed analyses that excluded participants who developed hypertension between study entry (1981 to 1990) and the third examination done 4 years later (1985 to 1994).

We calculated the 95% CI for each relative risk (17), and all *P* values are two-tailed. Statistical analyses were performed by using the SPSS 7.5J software package (SPSS, Inc., Chicago, Illinois).

We estimated the "number needed to walk," a value analogous to the "number needed to treat." The number needed to treat for a given therapy is the reciprocal of the absolute risk reduction for that treatment (18). A 95% CI for the number needed to treat is obtained simply by taking reciprocals of the values defining the 95% CI of the absolute risk reduction (19). In our study, the number needed to walk was defined as the number of men who would have to adopt walking to avoid a single case of hypertension. The number needed to treat must always be based on an outcome for a specific period of time (20); thus, in estimating the number needed to walk, we chose an observation period of 10 years between study entry (1981 to 1986) and the examination done 10 years after (1991 to 1996) each participant was enrolled.

Role of the Funding Source

The funding agencies did not participate in the collection, analysis, or interpretation of data presented in this report or in the decision to submit the manuscript for publication.

Results

Of the 6104 men eligible for this study between 1981 and 1990, we excluded 87 men who did not undergo medical check-ups during the follow-up period. The study sample for analysis consisted of 6017 men. During the 59 784 person-years of follow-up between 1981 and 1997, 626 men developed hypertension. As the duration of the walk to work increased, body weight and the body mass index decreased (*P* for trend = 0.037 and 0.035, respectively) (**Table 1**). We identified no significant relation between the duration of the walk to work and the levels of leisure-time physical activity (*P* for trend = 0.062).

Table 2. Relative Risk for Hypertension According to Duration of the Walk to Work

Variable	Person-Years of Follow-up	Cases of Hypertension, *n*	Multivariate Relative Risk (95% CI)*	Further Multivariate Relative Risk (95% CI)†
Walk to work‡				
0–10 minutes	30 796	337	1.00 (reference)	1.00 (reference)
11–20 minutes	23 266	242	0.91 (0.77–1.08)	0.88 (0.75–1.04)
≥21 minutes	5722	47	0.70 (0.59–0.95)	0.71 (0.52–0.97)
Walk to work as a continuous variable (per 10 minutes)			0.88 (0.78–0.98)	0.88 (0.79–0.98)

* Adjusted for age, body mass index, alcohol consumption, leisure-time physical activity (regular physical exercise at least once weekly or less than once weekly), smoking status (current smoker, past smoker, or nonsmoker), and fasting plasma glucose level.
† Adjusted for age, body mass index, alcohol consumption, leisure-time physical activity (regular physical exercise at least once weekly or less than once weekly), smoking status (current smoker, past smoker, or nonsmoker), fasting plasma glucose level, systolic blood pressure, and diastolic blood pressure.
‡ *P* for trend = 0.02 for multivariate relative risk and further multivariate relative risk.

Table 3. Relative Risk for Hypertension According to Leisure-Time Physical Activity

Regular Physical Exercise	Person-Years of Follow-up	Cases of Hypertension, *n*	Multivariate Relative Risk (95% CI)*	Further Multivariate Relative Risk (95% CI)†
At least once weekly				
At study entry (1981–1990)‡				
No	40 644	461	1.00 (reference)	1.00 (reference)
Yes	19 140	165	0.70 (0.59–0.84)	0.70 (0.59–0.84)
From study entry (1981–1990) to the third examination (1985–1994)§				
No at both time points	29 934	262	1.00 (reference)	1.00 (reference)
Yes at both time points	10 734	68	0.64 (0.49–0.84)	0.61 (0.47–0.80)
Frequency (times per week)‡‖				
0	40 644	461	1.00 (reference)	1.00 (reference)
1	6058	42	0.62 (0.45–0.85)	0.65 (0.47–0.90)
≥2	13 082	123	0.74 (0.60–0.90)	0.72 (0.59–0.88)

* Adjusted for age, body mass index, alcohol consumption, duration of walk to work (as a continuous variable), smoking status (current smoker, past smoker, or nonsmoker), and fasting plasma glucose level.
† Adjusted for age, body mass index, alcohol consumption, duration of walk to work (as a continuous variable), smoking status (current smoker, past smoker or nonsmoker), fasting plasma glucose level, systolic blood pressure, and diastolic blood pressure.
‡ Based on data of leisure-time physical activity from the study entry and including cases of hypertension from 1981 through 1997.
§ Based on data of leisure-time physical activity from the study entry (1981 to 1990) and the third examination four years later (1985 to 1994) since each participant was enrolled and excluding cases of hypertension during the first 4-year follow-up period since each participant was enrolled.
‖ P for trend < 0.001 for multivariate relative risk and for further multivariate relative risk.

Duration of the Walk to Work

The duration of the walk to work was associated with a decreased risk for incident hypertension (**Table 2**). After adjustment for age, body mass index, daily alcohol consumption, smoking status, frequency of leisure-time physical activity, systolic blood pressure, diastolic blood pressure, and fasting plasma glucose level, the relative risk for hypertension was 0.71 (95% CI, 0.52 to 0.97) in men whose walk to work lasted 21 minutes or more compared with those whose walk to work lasted 10 minutes or less.

To further quantify the effect of the duration of the walk to work on hypertension, we modeled this duration as a continuous variable. The results suggested that the multivariate-adjusted risk for hypertension was reduced by 12% when the duration of the walk to work was increased by 10 minutes (relative risk, 0.88 [CI, 0.79 to 0.98]). Adjustments for other factors, including systolic blood pressure and diastolic blood pressure, did not influence our estimates of the relative risk.

Leisure-Time Physical Activity

Compared with men who engage in regular physical exercise less than once weekly, the multivariate-adjusted relative risk for hypertension in men who engaged in regular physical activity at least once weekly was 0.70 (CI, 0.59 to 0.84) (**Table 3**). Further adjustments for other factors changed the risk estimate only slightly. When we examined the data obtained at study entry (1981 to 1990) and at the third examination 4 years after each participant was enrolled (1985 to 1994), excluding cases of hypertension identified during the first 4-year follow-up period, we found that the multivariate-adjusted relative risk for hypertension was 0.64 (CI, 0.49 to 0.84) among men who engaged in regular physical exercise at least once weekly at both time points compared with those who reported regular physical exercise less than once weekly at both time points. Adjustments for other factors did not influence our estimates of the relative risk.

We also analyzed the association between the frequency of regular physical exercise and the risk for hypertension. The risk for hypertension was decreased even in men who engaged in regular physical exercise only once weekly. The multivariate-adjusted relative risk for hypertension decreased from 1.00 for exercise less than once weekly (reference category) to 0.62 for once-weekly exercise (CI, 0.45 to 0.85) and to 0.74 for exercise two or more times weekly (CI, 0.60 to 0.90). Adjustments for other factors did not influence our estimates of the relative risk.

Number Needed To Walk

Between 1981 and 1986, we enrolled 4410 normotensive men 35 to 60 years of age with normal glucose intolerance and no history of hypertension or diabetes at baseline. During 10 years of follow-up, 375 men developed hypertension. For men whose walk to work lasted 21 minutes or more compared with men whose walk to work lasted 10 minutes or less, the absolute risk reduction was 0.038 (CI, 0.0377 to 0.0383) and the number needed to walk was 26.3 (CI, 26.1 to 26.5). For men who reported an 11- to 20-minute walk to work, the absolute risk reduction was 0.009 (CI, 0.0088 to 0.0092) and the number needed to walk was 111.1 (CI, 108.7 to 113.6) compared with men whose walk to work was 10 minutes or less (**Table 4**).