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

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Abstract

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

Introduction

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

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

Materials and Methods

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

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

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

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

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

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

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

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