Physical Activity and Male Colorectal Cancer Survival

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Background: Although physically active individuals have a lower risk of developing colorectal cancer, few studies have examined whether exercise benefits colorectal cancer survivors.

Methods: Derived from the Health Professionals Follow-up Study, we studied colorectal cancer–specific and overall mortality in a cohort of 668 men with a history of stage I to stage III colorectal cancer according to predefined physical activity categories after diagnosis. To minimize bias by occult recurrences, we excluded men who died within 6 months of their postdiagnosis physical activity assessment.

Results: In a cohort of men with colorectal cancer and no apparent metastases at diagnosis, 50.4% exercised at least 18 metabolic equivalent task (MET) hours per week. Increased physical activity was significantly associated with improved colorectal cancer–specific mortality ($P = .002$ for trend) and overall mortality ($P < .001$ for trend). Men who engaged in more than 27 MET hours per week of physical activity had an adjusted hazard ratio for colorectal cancer–specific mortality of 0.47 (95% confidence interval, 0.24-0.92) compared with men who engaged in 3 or less MET hours per week of physical activity. The apparent benefit of physical activity was seen regardless of age, disease stage, body mass index, diagnosis year, tumor location, and prediagnosis physical activity.

Conclusion: In a large cohort of men with a history of nonmetastatic colorectal cancer, more physical activity was associated with a lower risk of colorectal cancer–specific and overall mortality.

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DESPITE APPRECIABLE ADvances in screening and treatment of colorectal cancer, more than 148 000 individuals in the United States will be newly diagnosed as having colorectal cancer each year, and almost 50 000 annually will die of the disease.[1] A host of modifiable factors have been associated with influencing the likelihood of developing the disease.[2] A recent meta-analysis[3] of 52 observational studies found an inverse relationship between physical activity and colon cancer development, with an overall relative risk of 0.76 (95% confidence interval [CI], 0.72-0.81).

See also pages 2096, 2109, and 2116

Although there is little debate about the benefit of physical activity in preventing the development of colorectal cancer, the role of physical activity in colorectal cancer survivors is less certain. Recently, findings from several studies suggest that prediagnosis physical activity[4] or postdiagnosis physical activity[5,6] reduces the risk of cancer recurrence and improves mortality in colorectal cancer survivors. However, because randomized data are unavailable, further studies with prospectively collected data, comprehensive follow-up, and postdiagnosis physical activity levels are needed.

See Invited Commentary on page 2124

We used the Health Professionals Follow-up Study (HPFS) to test the association between physical activity and colorectal cancer mortality. This study comprised a large prospective cohort of more than 50 000 men who have been diagnosed as having colorectal cancer.

METHODS

STUDY POPULATION

In 1986, the HPFS cohort was established when 51 500 male health professionals answered a mailed questionnaire on risk factors for cancer and cardiovascular disease (details were previously reported[7]). Every 2 years, participants receive follow-up questionnaires to update information on potential risk factors and to report new cancer and disease diagnoses. This study was approved by the human subjects committee at Harvard School of Public Health, Boston, Massachusetts.

ASCERTAINMENT OF COLORECTAL CANCER DIAGNOSIS

On each biennial follow-up questionnaire, participants were asked whether they had had a diagnosis of colorectal cancer during the prior 2 years. When a participant (or the next of kin for decedents) reported colorectal cancer, we sought permission to obtain medical records and pathology reports. Study physicians, blinded to exposure data, reviewed all medical records related to colorectal cancer and recorded the disease stage, histologic findings, and tumor location. For nonresponders, we searched the National Death Index to discover deaths and to ascertain any diagnosis of colorectal cancer that contributed to death or was a secondary diagnosis. It is estimated that 96% of the cases of colorectal cancer were identified through these various methods.[8] The subjects in this analysis were HPFS participants with nonmetastatic colorectal cancer diagnosed between January 1986 and January 2004.

Men were excluded if they had metastatic colorectal cancer at the time of the initial diagnosis. In total, 1041 men were diagnosed as having colorectal cancer in the HPFS between January 1986 and January 2004; however, 182 had metastatic disease and were excluded from our study. Of 859 remaining men, 680 reported physical activity levels between 6 months and 4 years after diagnosis (discussed in the "Exposure Assessment" subsection). To minimize bias by occult recurrences or other undiagnosed major illnesses, we excluded 12 men who died within 6 months of their postdiagnosis physical activity assessment. Using these variables, a total of 668 men were eligible for analysis.

MEASUREMENT OF MORTALITY

Men were followed up until death or January 31, 2006, whichever came first. Ascertainment of deaths included reporting by the family or by postal authorities. In addition, the names of persistent nonresponders were searched in the National Death Index.[9] The cause of death was assigned by study physicians blinded to exposure data. In the case of a man who died of colorectal cancer not previously reported, we obtained medical records of the colorectal cancer diagnosis after receiving permission from the next of kin. More than 98% of deaths in the HPFS have been identified using these methods.[9]

EXPOSURE ASSESSMENT

Leisure-time physical activity was assessed on each biennial questionnaire as previously described.[10] Briefly, men reported the duration of participation (range, 0 to ≥11 hours per week) in walking (along with their usual pace), jogging, running, bicycling, lap swimming, racket sports, other aerobic exercises, lower-intensity exercise (yoga, toning, and stretching), or other vigorous activities. The first physical activity assessment collected at least 6 months but no more than 4 years after diagnosis (median, 15 months) was used to avoid assessment during the period of active treatment. To avoid bias because of declining physical activity in a period around recurrence or death, physical activity was not updated (therefore, a single postdiagnosis measurement was determined).

Each physical activity on the questionnaire was assigned a metabolic equivalent task (MET) score.[11] One MET is the energy expenditure for sitting quietly. MET scores are defined as the ratio of the metabolic rate associated with specific activities divided by the resting metabolic rate. The values from the individual activities were summed for a total score of MET hours per week. Categories of MET hours per week were predefined as 3 or less, 3.1 to 9, 9.1 to 18, 18.1 to 27, or more than 27 to correspond to the equivalents of less than 1, 1 to less than 3, 3 to less than 6, 6 to less than 9, and 6 or more hours per week of walking at an average pace, consistent with prior analyses.[5,6] Our physical activity questions have been previously validated against physical activity diaries.[12,13]

COVARIATES

Disease stage, grade of tumor differentiation, diagnosis year, and tumor location were extracted from the medical record. The interval between cancer diagnosis and physical activity assessment was adjusted for in these analyses. Body mass index and smoking status (current, past, or never) were also obtained from the biennial questionnaire at the time of physical activity assessment.

STATISTICAL ANALYSIS

Cox proportional hazards models were used to calculate hazard ratios (HRs) of death or death from colorectal cancer, adjusted for other risk factors for cancer survival. In the main analysis, death from colorectal cancer was the primary end point, and deaths from other causes were censored. In secondary analyses, death from any cause was the end point. Participants were followed up from the date of return of postdiagnosis physical activity assessment to death or January 31, 2006, whichever came first. The 2-tailed *P* value for the linear trend test across physical activity categories was calculated using the median value of each category as a continuous variable. Tests of interactions between physical activity categories and potential effect modifiers were assessed by entering in the model the cross product of the dichotomized division of physical activity (≤27 or >27 MET hours per week) with the dichotomized covariate. All analyses were performed using commercially available statistical software (SAS version 9.1; SAS Institute Inc, Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS BY PHYSICAL ACTIVITY CATEGORIES

Among 661 eligible participants with stage I, II, or III colorectal cancer, there were 258 deaths, of which 88 were classified as colorectal cancer–specific deaths. The median follow-up period from the date of diagnosis among men who are alive was 8.6 years (with 75.2% followed up for ≥5 years). Baseline characteristics of the participants are given according to physical activity categories after diagnosis (**Table 1**). Men who were more active were less likely to have ever smoked cigarettes. There were no appreciable differences in body mass index, change in body mass index before and after diagnosis, primary

Table 1. Baseline Characteristics by Postdiagnosis Physical Activity

Characteristic	Postdiagnosis Physical Activity, MET h/wk, %				
	≤3 (n = 102)	3.1-9 (n = 125)	9.1-18 (n = 101)	18.1-27 (n = 81)	>27 (n = 252)
MET h/wk, mean	**0.4**	**6.3**	**13.5**	**23.3**	**49.1**
Age, median, y	72	69	69	68	69
Body mass index[a]					
Mean	25.9	26.2	25.6	24.7	25.6
Change	–0.3	–0.1	–0.2	0	0
Disease stage at diagnosis					
I or II	58	54	62	57	62
III	21	26	24	23	16
Missing, not metastatic	21	20	14	20	22
Tumor location					
Colon	77	79	77	81	76
Rectum	23	21	23	19	24
Grade of tumor differentiation					
Well or moderate	61	52	69	64	60
Poorly or undifferentiated	7	12	10	9	8
Missing	32	36	21	27	32
Smoking status					
Never	37	34	33	43	33
Past	49	48	58	44	56
Current	4	7	6	3	3
Missing	10	11	3	10	8
Diagnosis year					
Before 1990	15	18	20	15	14
1990 to 2000	64	58	64	64	57
After 2000	21	24	16	21	29
Time to physical activity measurement, median, mo	15	15	17	17	17

Abbreviation: MET, metabolic equivalent task. (See "Exposure Assessment" subsection of the "Methods" section for a definition.)
[a] Calculated as weight in kilograms divided by height in meters squared.

Table 2. Colorectal Cancer–Specific Mortality and Overall Mortality by Postdiagnosis Physical Activity[a]

Postdiagnosis Physical Activity, MET h/wk	Events/No. of Risk	HR for Colorectal Cancer–Specific Mortality		Events/No. of Risk	HR for Overall Mortality	
		Unadjusted[b]	Adjusted[c]		Unadjusted[d]	Adjusted[d]
≤3	17/102	1 [Reference]	1 [Reference]	52/102	1 [Reference]	1 [Reference]
3.1-9	21/125	0.95 (0.50-1.80)	1.06 (0.55-2.08)	57/125	0.79 (0.54-1.15)	1.00 (0.68-1.48)
9.1-18	18/101	0.98 (0.51-1.91)	1.30 (0.65-2.59)	48/101	0.79 (0.53-1.17)	1.12 (0.74-1.70)
18.1-27	9/81	0.60 (0.27-1.34)	0.76 (0.33-1.77)	27/81	0.50 (0.31-0.80)	0.74 (0.46-1.20)
>27	23/252	0.51 (0.27-0.96)	0.47 (0.24-0.92)	74/252	0.51 (0.36-0.73)	0.59 (0.41-0.86)

Abbreviations: HR, hazard ratio; MET, metabolic equivalent task. (See "Exposure Assessment" subsection of the "Methods" section for a definition.)
[a] Hazard ratio adjustments include age at diagnosis (<50, 50-59, 60-69, ≥70 years), disease stage, grade of tumor differentiation, colon or rectal primary tumor location, diagnosis year, body mass index at diagnosis, time from diagnosis to physical activity measurement, change in body mass index before and after diagnosis, and smoking status (current, past, or never).
[b] $P = .01$ for trend.
[c] $P = .002$ for trend.
[d] $P < .001$ for trend.

tumor location, or grade of tumor differentiation across physical activity categories.

PHYSICAL ACTIVITY AFTER DIAGNOSIS AND MORTALITY

We assessed the association between physical activity after diagnosis of nonmetastatic colorectal cancer on patient survival (**Table 2**). Compared with men who reported 3 or less MET hours per week of physical activity (15.4% of the cohort), men reporting more than 27 MET hours per week of physical activity (38.1% of the cohort) had an adjusted HR for colorectal cancer–specific mortality of 0.47 (95% CI, 0.24-0.92; $P = .002$ for trend). Similarly, the adjusted HR for overall mortality was 0.59 (95% CI, 0.41-0.86; $P < .001$ for trend).

Because lower levels of physical activity among men at risk for cancer recurrence could reflect occult cancer recurrence or impending death, we excluded 12 men who developed cancer recurrence or died within 6 months of

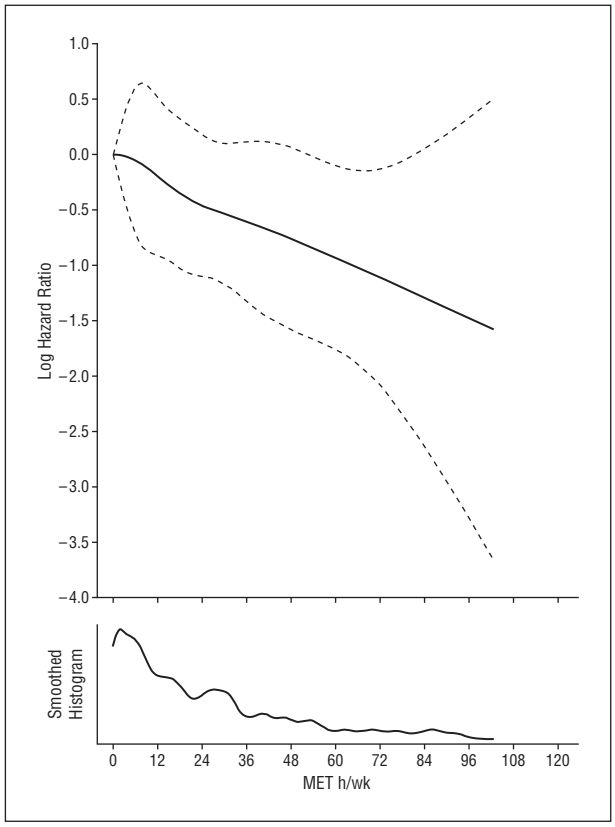

Figure 1. Log hazard smoothing spline plot. Solid line represents the log hazard ratio, and dashed lines represent 95% confidence intervals. MET indicates metabolic equivalent task. (See "Exposure Assessment" subsection of the "Methods" section for a definition.)

completing the physical activity assessment in our primary analyses. When we extended this restriction to 12 months (reducing the sample size to 646), men in the highest physical activity category had an HR of 0.46 (95% CI, 0.23-0.95) for colorectal cancer–specific mortality ($P=.003$ for trend) and an HR of 0.59 (95% CI, 0.40-0.87) for overall mortality ($P<.001$ for trend) compared with men in the lowest physical activity category. Further extension of this restriction to 2 years (n=553) continued to demonstrate similar point estimates for colorectal cancer–specific mortality (HR, 0.64; 95% CI, 0.28-1.45; $P=.08$ for trend) and for overall mortality (HR, 0.65; 95% CI, 0.43-0.99; $P=.005$ for trend).

To better characterize the amount of physical activity necessary to have a benefit, we generated a smoothing spline of log hazard vs the total MET score (**Figure 1**), a method independent of predetermined MET-hour categorizations. A log hazard less than 0 represents a favorable HR (<1). The initial inflection of the slope of the spline suggests initial protection between 6 and 12 MET hours per week. Furthermore, the leveling of the slope of the curve beyond 35 MET hours per week suggests that exercise beyond certain levels does not lead to further substantial improvements in disease-free survival.

To estimate 5-year survival, activity levels were collapsed into 3 physical activity categories (<3, 3-27, and >27 MET hours per week). To reduce bias, the follow-up period in this analysis begins at the time of completion of the questionnaire that assessed physical activity rather than at the date of diagnosis of colorectal cancer, as is typically reported in studies of adjuvant chemotherapy. Nevertheless, the proportions of men free of colorectal cancer–specific death at 5 years (**Figure 2**) were 85.2% for men who engaged in less than 3 MET hours per week, 87.4% for men engaging in 3 to 27 MET hours per week, and 92.1% for men engaging in more than 27 MET hours per week ($P=.05$, log-rank test); at 10 years, the proportions of men free of colorectal cancer–specific deaths were 79.4%, 81.2%, and 88.3%, respectively. There was also a statistically significant difference in overall survival across physical activity tertiles ($P<.001$) (**Figure 3**).

We examined the association between postdiagnosis physical activity across strata of other predictors of cancer recurrence and mortality (**Figure 4**). The inverse relationship between postdiagnosis physical activity and colorectal cancer–specific mortality remained largely unchanged across strata of age, disease stage, body mass index, tumor location, and diagnosis year.

PHYSICAL ACTIVITY BEFORE DIAGNOSIS AND MORTALITY

Prior analyses demonstrated that the level of physical activity before diagnosis (most immediate prior questionnaire completed ≥6 months before diagnosis) was not significantly associated with mortality in colorectal cancer survivors.[5] In the present analysis, we similarly did not detect a statistically significant trend in colorectal cancer–specific mortality ($P=.65$) or overall mortality ($P=.26$) with increasing exercise. The correlation between prediagnosis physical activity and postdiagnosis physical activity was modest (correlation coefficient, 0.40; $P<.001$). Prediagnosis physical activity did not confound the association between postdiagnosis physical activity and colorectal cancer–specific mortality. When prediagnosis physical activity was entered in the multivariate model, men who exercised more than 27 MET hours per week had an adjusted HR for colorectal cancer–specific mortality of 0.43 (95% CI, 0.20-0.98) compared with men who exercised less than 3 MET hours per week. Similarly, prediagnosis physical activity did not modify the effect of postdiagnosis physical activity on colorectal cancer–specific mortality ($P=.92$ for interaction) (Figure 4).

COMMENT

Men who were physically active after diagnosis of nonmetastatic colorectal cancer experienced a significantly decreased risk of colorectal cancer–specific death, as well as death from any cause. Men who engaged in more than 27 MET hours per week had more than 50% lower risk of colorectal cancer–specific mortality compared with inactive men. This association was consistently detected regardless of age, disease stage, body mass index, diagnosis year, tumor location, and prediagnosis physical activity.

These findings are consistent with 2 prior studies[5,6] of physical activity after diagnosis among prospectively

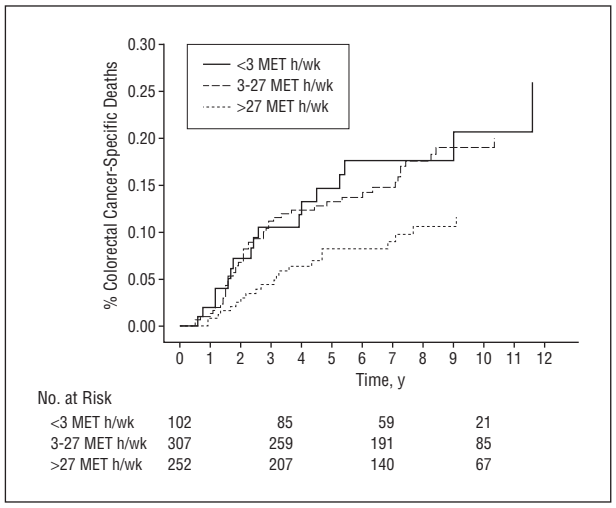

Figure 2. Cumulative incidence of colorectal cancer–specific deaths (P=.01, log-rank test). MET indicates metabolic equivalent task. (See "Exposure Assessment" subsection of the "Methods" section for a definition.)

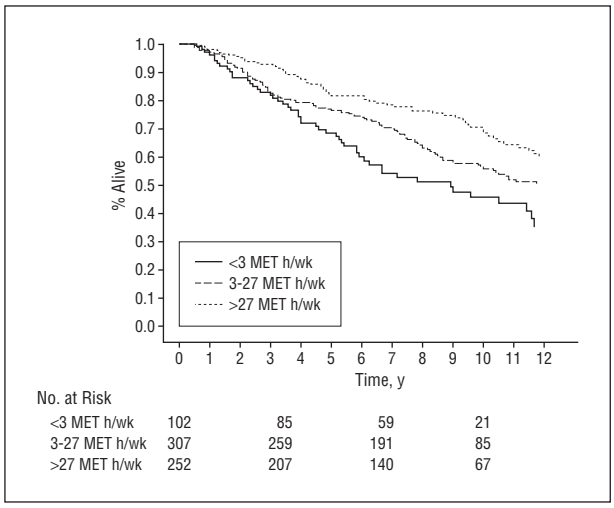

Figure 3. Kaplan-Meier curves for overall mortality (P< .001, log-rank test). MET indicates metabolic equivalent task. (See "Exposure Assessment" subsection of the "Methods" section for a definition.)

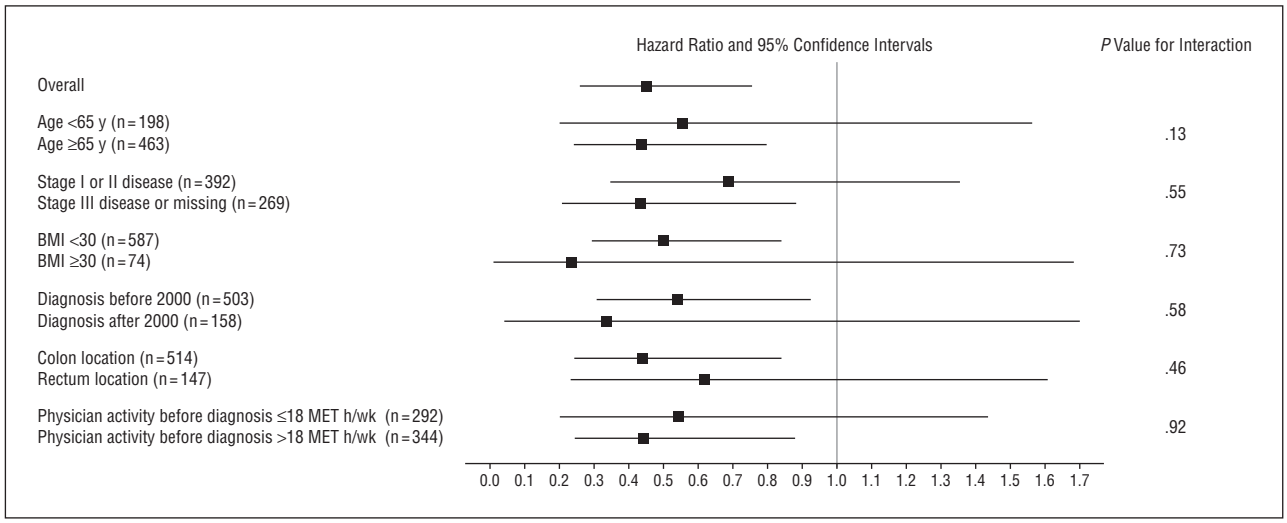

Figure 4. Stratified analysis of disease-free survival (≤27 vs >27 metabolic equivalent task [MET] hours per week [See "Exposure Assessment" subsection of the "Methods" section for a definition.]). BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared). At the bottom of the figure the number of patients do not sum to 661 because not all patients had prediagnosis physical activity measured.

observed colorectal cancer survivors. In a cohort of 573 women with colorectal cancer, the most active women had an adjusted HR for colorectal cancer–specific mortality of 0.39 (95% CI, 0.18-0.82) compared with inactive women.[5] Similarly, in a cohort of 832 men and women with stage III colon cancer who received adjuvant therapy in a clinical trial sponsored by the National Cancer Institute (Bethesda, Maryland), the adjusted HR for disease-free survival was 0.55 (95% CI, 0.33-0.91).[5] Therefore, the adjusted HR of 0.47 detected in the present cohort of men is consistent with those studies. Furthermore, the spline curves in this study and in the study using the clinical trial cohort[5] suggest a measurable risk reduction between 6 and 12 MET hours per week, with a potential threshold between 30 and 35 MET hours per week. A notable difference in the present cohort is that 50.4% of colorectal cancer survivors engaged in at least 18 MET hours per week compared with 25.9% of survivors in the Nurse's Health Study and 28.2% of survivors in the National Cancer Institute–sponsored trial.[5,6]

The mechanism for this consistent association between physical activity and colorectal cancer–specific survival is unknown; however, hyperinsulinemia is a potential cause.[14-16] Insulin and the insulinlike growth factor (IGF) family have been associated with enhanced tumor growth and antiapoptosis,[16] and colorectal cancer risk is elevated in individuals with higher circulating levels of insulin or C-peptide (a marker of insulin secretion) and IGF-1.[17-22] Patients who develop recurrence of colorectal cancer have micrometastases at diagnosis. An environment that allows such microscopic tumors to proliferate could be detrimental. Physical activity may lower tissue insulin and IGF levels and raise beneficial IGF-binding protein levels to influence exposure of these growth factors on micrometastases. Other mechanisms proposed in the association between exercise and colon

cancer development may be relevant to the progression of established cancer, including immune modulation and anti-inflammatory actions.[23-25]

Advantages of this cohort derived from the HPFS are the prospective collection of exposure data, the diligent medical record review of self-reported colorectal cancer and of deaths, and the sample size. There are limitations that are worth noting. Beyond cause of mortality, data on cancer recurrences were unavailable in this cohort. Nevertheless, because the median survival for metastatic colorectal cancer was approximately 10 to 12 months during much of the period of this study,[26] colorectal cancer–specific mortality should be a reasonable surrogate for cancer-specific outcomes. Treatment data are not collected in this cohort. However, almost 60% of men had stage I or stage II disease, in which surgery alone would generally be the standard of care, and no interaction by disease stage was observed. Furthermore, although there are differences in the likelihood of use of adjuvant chemotherapy based on factors such as socioeconomic class, the fairly homogenous nature of this cohort (professional male health care workers) would likely increase the probability of at least standard therapy.[27,28] Comorbidities and access to health care may also confound these findings. Given the population studied, we would expect the latter to be diminished. Although comorbidities have been shown to affect mortality in colorectal cancer survivors,[29-31] such diseases are less likely to affect disease recurrence and colorectal cancer–specific mortality. Finally, our data are limited to leisure-time exercise; occupational physical activity is not surveyed in the questionnaires.

As in prior studies,[5,6] we considered the possibility that sick patients (with cancer recurrence and limited survival) will exercise less. To minimize the bias by occult cancer recurrence, we excluded recurrences or deaths within 6 months of physical activity assessment in the primary analysis and continued to observe a positive effect of exercise when extending this restriction to 12 months. Finally, we would expect few patients to have undetected recurrences over extended periods given the brief natural history of recurrent colon cancer.

Patients who underwent treatment for colorectal cancer may be considered limited in their ability to exercise. However, Arndt et al[32] reported that 1 year after surgery of the primary tumors for colorectal cancer, patients reported their physical functioning and global quality of life almost identical to those of a population without cancer.

These results provide further support that physical activity after colorectal cancer diagnosis may lower the risk of death from that disease. A randomized study among high-risk stage II and stage III colon cancer survivors that will compare the use of general education materials with a program that includes supervised physical activity sessions and behavioral support delivered over 3 years will soon open; the primary end point is disease-free survival.[33] The findings from the present study further support that effort.

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Correction

Errors in Text. In the Original Investigation titled "*APOE* Genotype, Lipids, and Coronary Heart Disease Risk: A Prospective Population Study" by Ward et al, published in the August 10/24 issue of the *Archives* (2009;169[15]:1424-1429), errors occurred in the last paragraph of the "Introduction" on page 1425. The third sentence should have read, "Within this cohort, it was previously observed that the LDL-C level was relatively lower among **E2* carriers and higher among **E4* carriers[8]; however, the association between *APOE* and CHD risk within the EPIC-Norfolk cohort was not characterized in previous analyses." An error also occurred in the first paragraph of the "Comment" section on pages 1426 and 1427. The first sentence should have read, "The respective lower and marginally higher CHD risk observed among the **E2*+ and **E4*+ groups in the age- and sex-adjusted analyses of the EPIC-Norfolk cohort is similar to the results obtained in the recent meta-analysis of 17 studies, in which the odds ratios were 0.80 (95% CI, 0.70-0.90) for **E2* carriers and 1.06 (0.99-1.13) for **E4* carriers relative to the **E3* homozygous group.[7]"