Physical activity and survival in male colorectal cancer survivors

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Abstract

Background—While physically active people have a lower risk of developing colorectal cancer, few studies have examined whether exercise benefits colorectal cancer survivors.

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

Results—In a cohort of men with colorectal cancer and no apparent metastases at diagnosis, 50% exercised at least 18 metabolic equivalent tasks (MET)-hours per week. Increasing amount of physical activity was significantly associated with improved colorectal-cancer specific mortality (p = 0.002) and overall mortality (p = 0.0003). Men who engaged in 27 MET-hours/week of physical activity had an adjusted hazard ratio for colorectal-cancer specific mortality of 0.47 (95% CI, 0.24–0.92), compared to those who did less than 3 MET-hours/week. The apparent benefit of physical activity was seen regardless of age, stage, body mass index, year of diagnosis, location of tumor and pre-diagnosis physical activity (p interaction all non-significant).

Conclusion—In a large cohort of men with history of non-metastatic colorectal cancer, greater physical activity was associated with lower risk of colorectal cancer-specific and overall mortality.

Introduction

Despite appreciable advances in screening and treatment of colorectal cancer, over 148,000 individuals in the United States will be newly diagnosed with colorectal cancer and nearly 50,000 will die of the disease each year.[1] A host of modifiable factors have been associated with influencing the likelihood of developing the disease.[2] A recent meta-analysis of 52 observational studies found an inverse association between physical activity and colon

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cancer development, with an overall relative risk of 0.76 (95% confidence interval, 0.72–0.81).[3]

While there is little debate on 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, several studies suggest that pre-diagnosis physical activity[4] or post-diagnosis activity [5, 6] reduces the risk of cancer recurrence and improves mortality in colorectal cancer survivors. However, since randomized data are not available, further studies with prospectively collected data, comprehensive follow-up and post-diagnosis physical activity levels are needed.

We utilized the Health Professional Follow-Up Study, a large prospective cohort of over 50,000 men to test the association between physical activity and colorectal cancer mortality in patients who have been diagnosed with the disease.

Methods

Study population

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

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 two years. When a subject (or next of kin for decedents) reported colorectal cancer, we sought permission to obtain records and pathology reports. Study physicians, blinded to exposure data, reviewed all records related to colorectal cancer and recorded stage, histology, and tumor location. For non-responders, we searched the National Death Index to discover deaths and ascertain any diagnosis of colorectal cancer that contributed to death or was a secondary diagnosis. We estimate that we identified 96% of the cases of colorectal cancer through these various methods.[8] The subjects in this analysis were HPFS participants with nonmetastatic colorectal cancer diagnosed between 1986 and 2004.

Men were excluded if they presented with metastatic colorectal cancer at time of initial diagnosis. In total, 1,041 men were diagnosed with colorectal cancer in HPFS between 1986 and 2004; however, 182 had metastatic disease and were excluded. Of the 859 remaining men, 680 reported physical activity levels between 6 months and 4 years after diagnosis (see "Exposure assessment" below). To minimize bias by occult recurrence or other undiagnosed major illnesses, we excluded 12 men who died within 6 months of their post-diagnosis physical activity assessment. With these parameters, 668 men were eligible for analysis.

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

Exposure assessment—Leisure-time physical activity was assessed on each biennial questionnaire as previously described.[10] Briefly, subjects reported duration of participation (ranging from 0 to 11 or more hours per week) in walking (along with usual pace); jogging; running; bicycling; swimming laps; racket sports; other aerobic exercises; lower intensity exercise (yoga, toning, 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 due to declining activity in a period around recurrence or death, physical activity was not updated (thereby a single post-diagnosis measurement was determined).

Each 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 MET-hours per week score. 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 greater than 27, to correspond to the equivalent of less than 1, 1 to less than 3, 3 to less than 6, 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 activity diaries.[12, 13]

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

Statistical analyses—Cox proportional hazards models were used to calculate hazard ratios 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 endpoint and deaths from other causes were censored. In secondary analyses, death from any cause was the endpoint. Participants were followed from the date of return of post-diagnosis physical activity assessment to either death or January 2006, whichever came first. The 2-tailed *P* value for the linear trend test across categories was calculated by 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 ($\leq$ or > 27 MET-hours/week) with the dichotomized covariate. All analyses utilized SAS version 9.1 (SAS Institute Inc, Cary, NC).

Results

Baseline characteristics by physical activity category

Among the 661 eligible participants with stages I, II or III colorectal cancer, there were 258 deaths, of which 88 were classified as colorectal cancer-specific deaths. The median time of follow-up from date of diagnosis of men who are alive was 8.6 years (with 75% followed for 5 or more years). Baseline characteristics of the participants are shown according to categories of physical activity 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, site of primary tumor and grade of differentiation across physical activities categories.

Physical activity after diagnosis

We assessed the influence of physical activity after the diagnosis of non-metastatic colorectal cancer on patient survival (Table 2). Compared to patients who reported less than 3 total MET-hours per week of recreational exercise (15% of the cohort), those reporting greater than 27 MET-hours per week (38% of the cohort) had an adjusted hazard ratio for colorectal cancer-specific mortality of 0.47 (95% confidence interval [CI] 0.24–0.92, p trend = 0.002). Similarly, the adjusted hazard ratio for overall mortality was 0.59 (95% CI, 0.41–0.86; p for trend = 0.0003).

Since lower levels of physical activity among patients at risk for cancer recurrence could reflect occult cancer recurrence or impending death, we excluded patients who developed cancer recurrence or died within six months of completing the physical activity assessment in our primary analyses (n = 12). When we extended this restriction to 12 months (reducing the sample size to 646), men in the highest category had a hazard ratio of 0.46 (95% CI, 0.23–0.95) for colorectal cancer-specific mortality (p for trend = 0.003) and a hazard ratio of 0.59 (95% CI, 0.40–0.87) for overall mortality (p for trend = 0.0004), compared to the least active men. 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 trend = 0.08) and overall mortality (HR 0.65 [95% CI, 0.43–0.99], p trend = 0.005).

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

To estimate 5-year survival, activity levels were collapsed into three categories (≤ 3, 3–27, and >27 MET-hours per week). Of note, follow-up in this analysis begins at the time of completion of the questionnaire that assessed physical activity to reduce bias rather than the date of diagnosis of colorectal cancer, as is typically reported in studies of adjuvant chemotherapy. Nonetheless, the proportion of patients free of colorectal cancer-specific deaths at 5-years (Figure 2) was 85% for patients who engaged in no more than 3 MET-hours per week, 87% for 3–27 MET-hours per week, and 92% for more than 27 MET-hours per week (p log rank = 0.05). At 10 years, the proportions of patients free of colorectal cancer-specific deaths were 79%, 81% and 88%, respectively. There was also a statistically significant difference in overall survival across physical activity tertile (p < 0.0007, Figure 3).

We examined the influence of post-diagnosis physical activity across strata of other predictors of cancer recurrence and mortality (Figure 4). The inverse relation between post-diagnosis physical activity and cancer-specific mortality remained largely unchanged across strata of age, pathological stage, body mass index, site of disease, or year of diagnosis.

Physical activity prior to diagnosis and mortality

In prior analyses, we demonstrated that level of physical activity prior to diagnosis (most immediate prior questionnaire completed at least 6 months prior to diagnosis) was not significantly associated with mortality in colorectal cancer survivors.[5] In this current analysis, we similarly did not detect a statistically significant trend in colorectal cancer-specific mortality (p = 0.65) nor overall mortality (p = 0.26) with increasing exercise. The correlation between pre-diagnosis and post-diagnosis physical activity was relatively modest

(correlation coefficient = 0.40, p < 0.001). Pre-diagnosis physical activity did not confound the association between post-diagnosis activity and colorectal cancer-specific mortality. When pre-diagnosis activity was entered in the multivariate model, men who exercised greater than 27 MET-hours/week had an adjusted hazard ratio for colorectal cancer-specific mortality of 0.43 (95% CI, 0.20–0.98), compared to those engaging in no more than 3 MET-hours/week. Similarly, pre-diagnosis activity did not modify the effect of post-activity on colorectal cancer-specific mortality (Figure 4, p for interaction = 0.92)

Comment

Men who were physically active after the diagnosis of non-metastatic colorectal cancer experienced a significantly decreased risk of colorectal cancer-specific death as well as death from any cause. Men who engaged in at least 27 MET-hours per week had > 50% lower risk of colorectal cancer-specific mortality compared to relatively inactive men. This association was consistently detected, regardless of age, stage, body mass index, year of diagnosis, location of tumor and pre-diagnosis physical activity.

These findings are consistent with 2 prior reports of physical activity after diagnosis in prospectively observed colorectal cancer survivors.[5, 6] In a cohort of 573 women with colorectal cancer, the most active women had an adjusted hazard ratio for colorectal cancer-specific mortality of 0.39 (95% CI, 0.18 to 0.82), compared to inactive women.[5] Similarly, in a cohort of 832 men and women with stage III colon cancer who received adjuvant therapy on a National Cancer Institute-sponsored clinical trial, the adjusted hazard ratio for disease-free survival amongst those was 0.55 (95% CI, 0.33 to 0.91).[5] Thus, the adjusted hazard of 0.47 detected in this cohort of men is consistent with those studies. Further, the spline curves in this study and from the study utilizing the clinical trial cohort[5] both suggest a measurable risk reduction between 6–12 MET-hours per week, with a potential threshold between 30–35 MET-hours per week. A notable difference in this cohort is that 51% of colorectal cancer survivors in this current cohort engaged in at least 18 MET-hours/week, compared to 26% of survivors in the Nurse's Health Study and 28% of survivors in the NCI-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 etiology.[14–16] Insulin and the insulin-like growth factor (IGF) family have been associated with enhanced tumor growth and anti-apoptosis [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 proteins to influence exposure of these growth factors on micrometastases. Other mechanisms proposed in the association between exercise and colon cancer development may also be relevant towards the progression of established cancer, including immune modulation and anti-inflammatory actions.[23–25]

Advantages of this cohort derived from the Health Professionals Follow-up Study are the prospective collection of exposures, the diligent medical record review of self-reported colorectal cancer and deaths and the sample size. Nonetheless, there are limitations that are worth noting. Beyond cause of mortality, data on cancer recurrences were not available in this cohort. Nonetheless, as median survival for metastatic colorectal cancer was approximately 10 to 12 months during much of the time 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, nearly 60% of patients had stage I

or II disease, in which surgery alone would generally be standard of care and no interaction by stage was observed. Further, 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 providers) would likely increase the probability of at least standard therapy.[27, 28] Co-morbidities and access to healthcare may also confound these findings. Given the population studied, we would expect the latter to be relatively diminished. Though co-morbidities have been shown to affect mortality in colorectal cancer survivors,[29–31] such diseases are less likely to affect disease recurrence and thereby colorectal-cancer specific mortality. Finally, our data are limited to leisure-time exercise; occupational physical activity is not surveyed in our questionnaires.

As in prior analyses[5, 6], we considered the possibility that sick patients (with cancer recurrences and limited survival) will exercise less. To minimize the bias by occult cancer recurrence, we excluded recurrences or deaths within six months of the activity assessment in the primary analysis and continued to observe a positive impact of exercise when extending this restriction to 12 months. Finally, we would expect few patients to have undetected recurrences over extended periods of time, given the relatively 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 and colleagues reported that one year after surgery of the primary tumor, patients with colorectal cancer reported their physical functioning and global quality of life nearly identical to those of a non-cancer population.[32]

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

Acknowledgments

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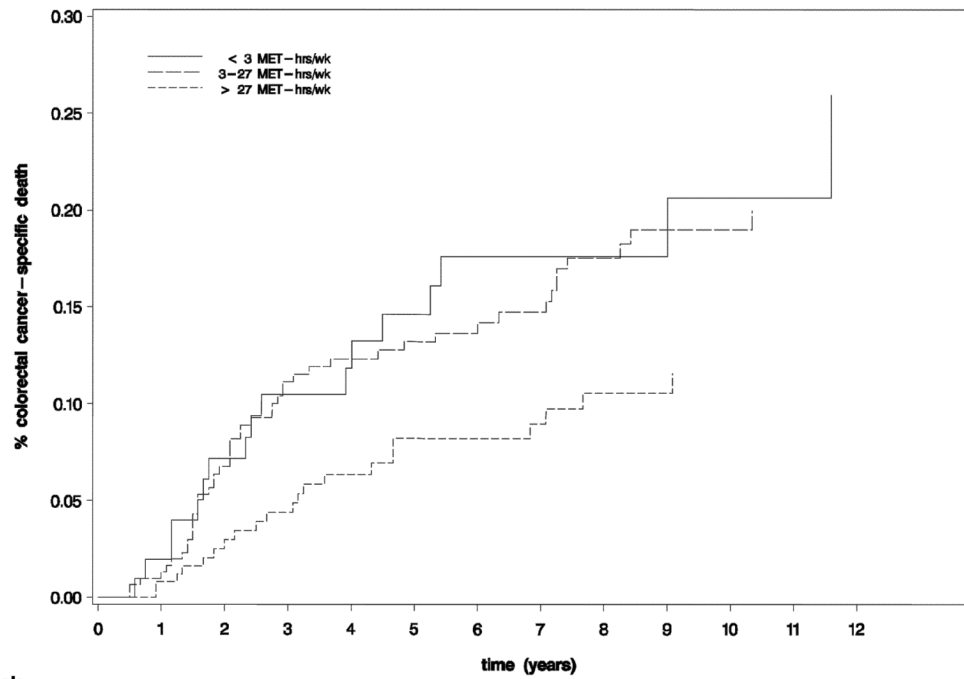
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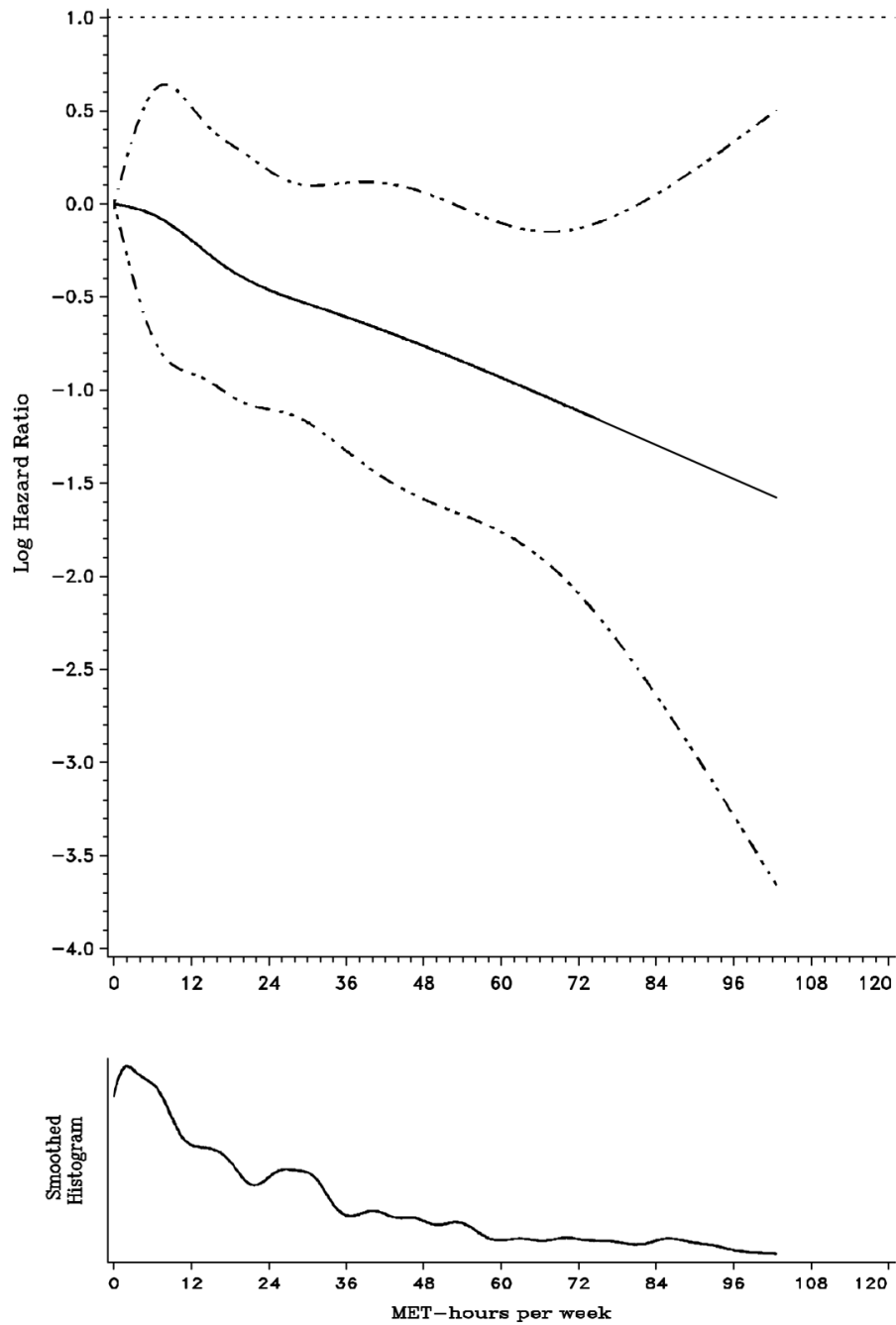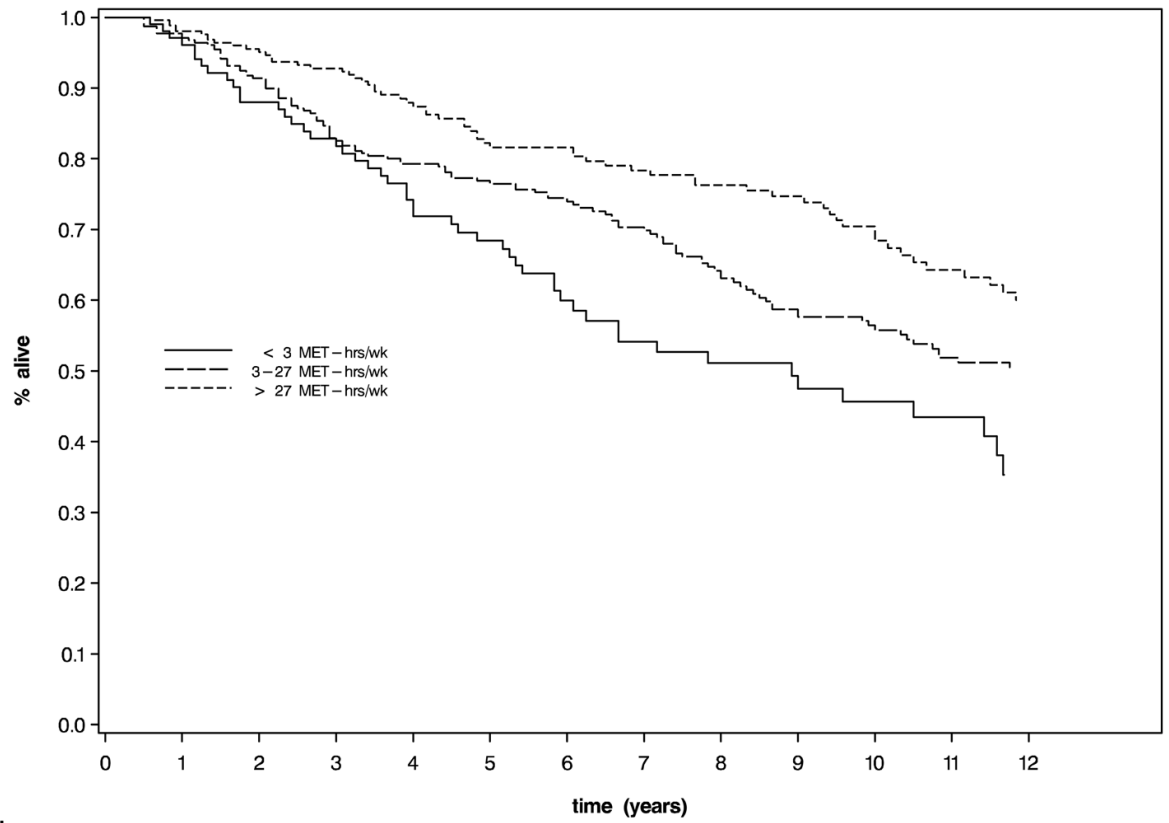
Figure 1. Log hazard smoothing spline plot
Note: MET = metabolic equivalent task. Solid line is the log hazard ratio and dashed lines represent 95% confidence interval

Figure 2.
Cumulative incidence of colorectal cancer-specific deaths (log rank p = 0.01)

The graph shows % alive on the y-axis (0.0 to 1.0) versus time (years) on the x-axis (0 to 12), with three curves:

- < 3 MET − hrs/wk
- 3 − 27 MET − hrs/wk
- > 27 MET − hrs/wk

Number at Risk

< 3 MET − hrs/wk	102	85	59	21
3 − 27 MET − hrs/wk	307	259	191	85
> 27 MET − hrs/wk	252	207	140	67

Figure 3.
Kaplan Meier
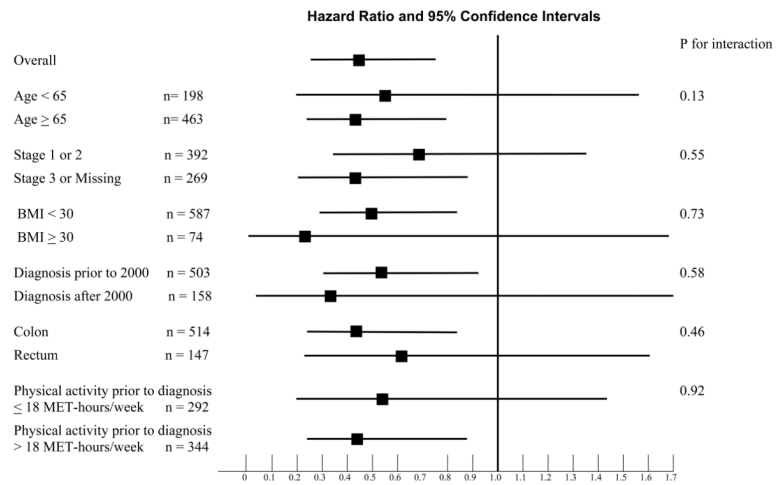
Figure 4.
Stratified Analysis of Disease-Free Survival (Comparison of < 27 MET-hours/week to > 27 MET-hours/week of Exercise)

Table 1

Baseline Characteristics by Level of Exercise after Diagnosis

| | Post-Diagnosis Activity* | | | | | |
	≤ 3	3.1 – 9	9.1 – 18	18.1 – 27	> 27	
N	102	125	101	81	252	
Median MET-hours/week	0.4	6.3	13.5	23.3	49.1	
Median age (years)	72	69	69	68	69	
Mean body mass index (kg/m²)	25.9	26.2	25.6	24.7	25.6	
Change in body mass index	−0.3	−0.1	−0.2	0	0	
Stage of disease at diagnosis (%)						
I/II	58	54	62	57	62	
III	21	26	24	23	16	
Missing (not metastatic)	21	20	14	20	22	
Site of disease (%)						
Colon	77	79	77	81	76	
Rectal	23	21	23	19	24	
Grade of differentiation (%)						
Well/moderate	61	52	69	64	60	
Poorly/undifferentiated	7	12	10	9	8	
Missing	32	36	21	27	32	
Smoking status (%)						
Never smoker	37	34	33	43	33	
Past smoker	49	48	58	44	56	
Current smoker	4	7	6	3	3	
Missing	10	11	3	10	8	
Year of diagnosis (%)						
Prior to 1990	15	18	20	15	14	
1990–2000	64	58	64	64	57	
After 2000	21	24	16	21	29	
Median time to physical activity measurement (months)	15	15	17	17	17	

*
by total metabolic equivalent tasks (METS) – hours per week

Table 2

Colorectal Cancer-Specific and Overall Mortality by Level of Post-Diagnosis Physical Activity

	Colorectal Cancer Specific Mortality			Overall Mortality		
	Events/# of risk	Unadjusted	Adjusted*	Events/# of risk	Unadjusted	Adjusted*
Post-diagnosis Activity (n=661)						
≤ 3 MET-hours/week	17/102	Referent	Referent	52/102	Referent	Referent
3.1 – 9 MET-hours/week	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 MET-hours/week	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 MET-hours/week	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 MET-hours/week	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)
p for trend		0.01	0.002		0.0001	0.0003

MET = metabolic equivalent tasks

*
adjusted for age at diagnosis (<50, 50–59, 60–69, ≥ 70), stage of disease, grade of tumor differentiation, colon or rectal primary, year of diagnosis, body mass index at diagnosis, time from diagnosis to physical activity measurement, change in body mass index prior and after diagnosis, smoking status (current, past, never)