

Impact of Physical Activity on Cancer Recurrence and Survival in Patients With Stage III Colon Cancer: Findings From CALGB 89803

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A B S T R A C T

Purpose

Regular physical activity reduces the risk of developing colon cancer, however, its influence on patients with established disease is unknown.

Patients and Methods

We conducted a prospective observational study of 832 patients with stage III colon cancer enrolled in a randomized adjuvant chemotherapy trial. Patients reported on various recreational physical activities approximately 6 months after completion of therapy and were observed for recurrence or death. To minimize bias by occult recurrence, we excluded patients who experienced recurrence or died within 90 days of their physical activity assessment.

Results

Compared with patients engaged in less than three metabolic equivalent task (MET)-hours per week of physical activity, the adjusted hazard ratio for disease-free survival was 0.51 (95% CI, 0.26 to 0.97) for 18 to 26.9 MET-hours per week and 0.55 (95% CI, 0.33 to 0.91) for 27 or more MET-hours per week. The adjusted *P* for trend was .01. Postdiagnosis activity was associated with similar improvements in recurrence-free survival (*P* for trend = .03) and overall survival (*P* for trend = .01). The benefit associated with physical activity was not significantly modified by sex, body mass index, number of positive lymph nodes, age, baseline performance status, or chemotherapy received. Moreover, the benefit remained unchanged even after excluding participants who developed cancer recurrence or died within 6 months of activity assessment.

Conclusion

Beyond surgical resection and postoperative adjuvant chemotherapy for stage III colon cancer, for patients who survive and are recurrence free approximately 6 months after adjuvant chemotherapy, physical activity appears to reduce the risk of cancer recurrence and mortality.

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INTRODUCTION

Physically active people have a reduced risk of developing colon cancer.¹⁻¹¹ A meta-analysis of 19 cohort studies showed a statistically significant 22% reduction in the risk of colon cancer in active males and 29% reduction in active females.¹² Several biologic mechanisms have been proposed for this association, including decreasing circulating levels of insulin and free insulinlike growth factor-1 (IGF-1); decreasing central deposition of adipose tissue; and altering prostaglandin synthesis, bile acid secretion, and gut flora.¹³ The insulin-colon cancer hypothesis has generated the most attention.¹³⁻¹⁵ Both insulin and IGF-1 promote cell proliferation and inhibit apoptosis in colon cancer cells.¹⁶⁻¹⁹ Colon cancer risk is elevated in individuals with higher circulating

levels of insulin or C-peptide²⁰⁻²² and IGF-1.²³⁻²⁷ Recent reports suggest that patients with colorectal cancer and lower IGF-binding protein-3 (which decreases circulating IGF-1) may have inferior survival.^{28,29}

Beyond cancer incidence, few studies have assessed the impact of physical activity on the survival of patients after diagnosis.³⁰ Recent data suggest that physical activity may reduce cancer recurrences and mortality among patients treated for early breast cancer³¹ and prostate cancer.³² Whether physical activity influences recurrence or survival rates among patients with colon cancer remains uncertain.

We examined the association of exercise on cancer recurrences and survival after surgery and chemotherapy for stage III colon cancer. Within a large clinical trial of adjuvant chemotherapy

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sponsored by the National Cancer Institute (NCI), we prospectively assessed physical activity approximately 6 months after completion of postoperative chemotherapy and monitored patients thereafter for cancer recurrence.³³

PATIENTS AND METHODS

Study Population

Patients in this prospective cohort study were participants in the NCI-sponsored Cancer and Leukemia Group B (CALGB) adjuvant therapy trial for stage III colon cancer comparing therapy with weekly fluorouracil and leucovorin to weekly irinotecan, fluorouracil, and leucovorin (CALGB 89803).³³ Between April 1999 and May 2001, 1,264 patients were enrolled onto the treatment trial. A self-administered questionnaire capturing diet and lifestyle habits was given to patients midway through their adjuvant therapy (4 months after surgical resection) and again 6 months after completion of adjuvant therapy (14 months after surgical resection). Given that an amendment to the protocol to survey diet/lifestyle was activated after the first 87 patients were enrolled, only the subsequent 1,177 patients were eligible for the diet and lifestyle study. Figure 1 illustrates the compliance with completion of questionnaires 1 (midway through adjuvant therapy) and 2 (approximately 6 months after completion of adjuvant therapy) and reasons for ineligibility at various time points. The final sample size for this study was 832.

Patients in the treatment trial were eligible if they underwent a complete surgical resection of the primary tumor within 56 days of study entry and had regional lymph node metastases (stage III colon cancer) but no evidence of distant metastases. Moreover, patients were required to have a baseline Eastern Cooperative Oncology Group performance status of 0 to 2 (ambulatory)^{34,35} and have adequate bone marrow, renal, and hepatic func-

tion. All patients signed informed consent, approved by the internal review board of the local institution.

Physical Activity Assessment

The physical activity questions used have been validated extensively and described previously.^{31,36,37} Briefly, participants were asked, "During the past 2 months, what was your average time per week spent at each of the following recreational activities?" Patients reported duration of participation (ranging from 0 to 11 or more hours per week) in walking, jogging, running, bicycling, swimming laps, racket sports, other aerobic exercises, lower intensity exercise (yoga, toning, stretching), or other vigorous activities. In addition, participants were asked the number of flights of stairs climbed daily and their usual walking pace (slow, < 2 miles per hour [mph]; normal or average, 2 to 2.9 mph; brisk, 3 to 3.9 mph; very brisk, \geq 4 mph; or unable to walk).

Each activity on the questionnaire was assigned a metabolic equivalent task (MET) score (Table 1)³⁸ One MET is the energy expenditure for sitting quietly for 1 hour. MET scores for walking were assigned based on the pace reported; for other activities, a leisurely to moderate intensity score was selected. The scores for MET-hours per week for each activity were calculated from the reported hours per week engaged in that activity multiplied by the assigned MET score, and individual activities were summed to derive a total MET-hours per week. Categories of MET-hours per week were defined as less than 3, 3 to 8.9, 9 to 17.9, 18 to 26.9, and 27 or more, chosen to correspond to the equivalent of less than 1, 1 to less than 3, 3 to less than 6, 6 to less than 9, and 9 or more hours per week of walking at an average pace, consistent with prior analyses.³⁹

For these analyses, we used the physical activity assessment collected on the second questionnaire (approximately 6 months after completion of adjuvant therapy) to avoid measurements during the period of active treatment. The median time from completion of chemotherapy to assessment was 7.1 months. The median time from study entry (which had to be within 8 weeks of surgery) was 13.4 months. Only patients who did not experience recurrence or die before the second questionnaire were included in these analyses. To avoid biases due to declining physical activity immediately before recurrence or death, we also excluded patients who experienced either event within 90 days of the physical activity assessment (46 patients).

Study End Points

In this ancillary study, the primary end point was disease-free survival (DFS), defined as time from the completion of the second questionnaire to tumor recurrence, occurrence of a new primary colon tumor, or death as a result of any cause. In addition, we defined recurrence-free survival (RFS) as the time from the completion of the second questionnaire to tumor recurrence or occurrence of a new primary colon tumor. For RFS, patients who died without known tumor recurrence were censored at the last documented evaluation by the treating provider. Finally, overall survival (OS) was defined as the time from the completion of the second questionnaire to death as a result of any cause.

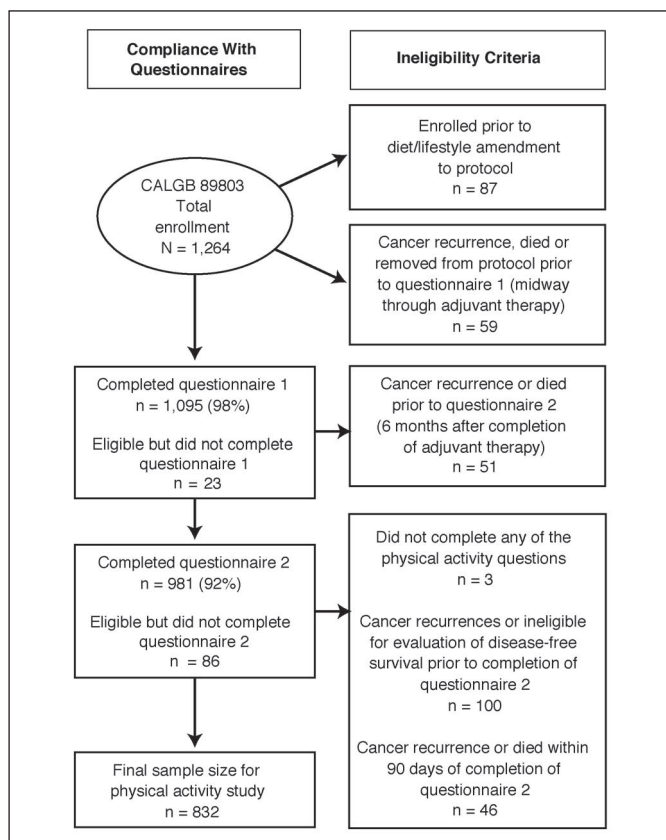


Fig 1. Derivation of cohort size. CALGB, Cancer and Leukemia Group B.

| Leisure-Time Activity | MET-Hours |
|--|-----------|
| Normal pace walking (2 to 2.9 mph) | 3 |
| Brisk pace walking (3 to 3.9 mph) | 4 |
| Very brisk pace walking (4+ mph) | 4.5 |
| Jogging (slower than 10 min/mile) | 7 |
| Running (faster than 10 min/mile) | 12 |
| Bicycling | 7 |
| Tennis, squash, racquetball | 7 |
| Lap swimming | 7 |
| Calisthenics, ski or stair machine, other aerobic exercise | 6 |
| Yoga, stretching, toning, lower intensity exercise | 4 |
| Other vigorous activities (lawn mowing) | 6 |

Abbreviations: MET, metabolic equivalent task; mph, miles per hour.

Statistical Analyses

During interim analysis of the treatment trial (comparing two chemotherapy regimens), it was determined that no difference in either DFS or OS would be observed between the treatment arms.³³ Thus, data for patients in both treatment arms were combined and analyzed according to categories of physical activity. DFS, RFS, and OS were examined using Kaplan and Meier curves and the log-rank test.⁴⁰ Cox proportional hazards regression⁴¹ was used to determine the simultaneous impact of potential confounders. Covariates with missing variables were coded with indicator variables in adjusted models. The less than 3 MET-hours per week category was the reference group. Tests for linear trend across categories were calculated by using the median value of each category of physical activity (total MET-hours per week) as a continuous variable in a proportional hazards model, consistent with prior studies.^{3,31} The degree of nonlinearity was evaluated using a penalized Cox model and smoothing splines.⁴⁰ A level of significance less than .05 was considered statistically significant. Tests of interactions between physical activity categories and potentially modifying covariates were assessed by entering the cross product of the physical activity (dichotomized at 18 total MET-hours per week) and the dichotomized covariate. We used SAS version 9.1 (SAS Institute, Cary, NC) and S-Plus version 7.0 (Insightful Corp, Seattle, WA) for all statistical analyses. All *P* values are two sided and were not adjusted for multiple comparisons.

Patient registration and clinical data collection were managed by the CALGB Statistical Center and all analyses were based on the study database frozen on March 18, 2005.

RESULTS

Baseline Characteristics by Physical Activity Category

Study participants were drawn from a multicenter study of post-operative adjuvant chemotherapy in patients with stage III colon cancer who underwent a curative-intent surgical resection. Baseline characteristics of the 832 patients in this analysis are shown in Table 2. Patients with higher activity tended to be male, leaner, and younger, although the median body mass index for each activity category was still in the overweight range (body mass index, 25 to 30 kg/m²). Similarly, although physically active patients experienced less weight gain after diagnosis, patients in each activity category gained a median of at least 2 kg, and at least 75% of patients in each category experienced weight gain. There was a trend toward an increased level of

Table 2. Baseline Characteristics of 832 Patients

| Characteristic | Total MET-Hours per Week | | | | | <i>P</i> * | No. With Missing Variable |
|---|--------------------------|-------|--------|---------|------|------------|---------------------------|
| | < 3 | 3-8.9 | 9-17.9 | 18-26.9 | ≥ 27 | | |
| No. of patients | 273 | 187 | 137 | 84 | 151 | | |
| Median MET-hours per week | 0.6 | 5.9 | 13.3 | 21.5 | 42.6 | | 0 |
| Male, % | 44 | 57 | 64 | 67 | 66 | < .0001 | 0 |
| Median age, years | 61 | 61 | 59 | 59 | 59 | .05† | 0 |
| Race or ethnicity | | | | | | .055 | 3 |
| White | 83 | 92 | 94 | 93 | 92 | | |
| African American | 11 | 5 | 3 | 5 | 4 | | |
| Other | 6 | 3 | 3 | 2 | 4 | | |
| Median body mass index, kg/m ² (at time of second questionnaire) | 29.8 | 28.6 | 27.9 | 28.5 | 27.3 | .0002† | 5 |
| Median weight change, ‡ kg | +3.6 | +3.6 | +3.6 | +3.2 | +2.0 | .006† | 5 |
| Baseline PS, § % | | | | | | .06 | 24 |
| 0 | 71 | 76 | 83 | 77 | 81 | | |
| 1-2 | 29 | 24 | 17 | 23 | 19 | | |
| Invasion through bowel wall (T stage) | | | | | | .92 | 24 |
| T1-2 | 15 | 15 | 14 | 18 | 17 | | |
| T3-4 | 85 | 85 | 86 | 82 | 83 | | |
| No. of positive lymph nodes, % | | | | | | .14 | 22 |
| 1-3 (N1) | 74 | 63 | 69 | 64 | 66 | | |
| 4+ (N2) | 26 | 37 | 31 | 36 | 34 | | |
| Clinical bowel perforation, % | 5 | 3 | 1 | 6 | 3 | .33 | 32 |
| Clinical bowel obstruction, % | 24 | 24 | 19 | 15 | 25 | .38 | 24 |
| Postoperative CEA > 5 ng/dL, % | 5 | 4 | 4 | 4 | 5 | .95 | 63 |
| Grade of differentiation, % | | | | | | .11 | 23 |
| Well | 9 | 3 | 4 | 5 | 5 | | |
| Moderate | 69 | 78 | 76 | 72 | 68 | | |
| Poor | 22 | 19 | 20 | 23 | 27 | | |
| Treatment arm, % | | | | | | .99 | 0 |
| FU/LV | 50 | 49 | 52 | 50 | 50 | | |
| IFL | 50 | 51 | 48 | 50 | 50 | | |

NOTE. Age, performance status, and postoperative CEA based on patient's status at initiation of chemotherapy (entry into the treatment trial).

Abbreviations: MET, metabolic equivalent task; CEA, carcinoembryonic antigen; PS, performance status; FU, fluorouracil; LV, leucovorin; IFL, irinotecan, FU, and leucovorin.

*By χ^2 test unless otherwise noted.

†By Wilcoxon rank sum.

‡Change of weight between questionnaire 1 (within 4 months of surgery) and questionnaire 2 (around 6 months after completion of chemotherapy).

§PS 0, fully active; PS 1, restricted in physically strenuous activity but ambulatory and able to carry out light work; PS 2, ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours.

||T1-2, level of invasion through the bowel wall not beyond the muscle layer; T3-4, level of invasion through the bowel wall beyond the muscle layer.

physical activity with a higher baseline performance status (measured at the time of initiation of adjuvant therapy). Although this difference did not reach statistical significance ($P = .06$), we did adjust for this factor in multivariate analyses as well as stratify for performance status. In contrast, other characteristics, particularly tumor characteristics known to predict prognosis, did not differ significantly across physical activity categories.

Cancer Recurrences and Survival by Level of Physical Activity

The median follow-up from the time of completion of the second questionnaire was 2.7 years (10th and 90th percentiles were 1.7 and 3.6 years, respectively). However, given that the median follow-up from study entry for these patients was 3.8 years, most colon cancer recurrences would be anticipated by this time. In total, 159 of the 832 patients included in this analysis had cancer recurrence and 84 patients died (either with or without recurrent disease).

The predefined, primary study end point of this analysis was DFS (time to cancer recurrence or death as a result of any cause). Higher postdiagnosis physical activity among patients who survived without disease progression 3 months after completion of the questionnaire was associated with a significant reduction in the risk of cancer recurrence or mortality (Fig 2), and this relation remained largely unchanged after adjusting for other predictors of cancer recurrence (Table 3). Compared with patients who reported less than 3 total MET-hours per week of activity, those reporting 18 to 26.9 total MET-hours per week had a multivariate hazard ratio of 0.51 (95% CI, 0.26 to 0.97) and those with greater than 27 total MET-hours per week had a hazard ratio of 0.55 (95% CI, 0.33 to 0.91; P for trend = .01).

To isolate the influence of physical activity on cancer recurrences, we used the end point RFS and confirmed that physical activity conferred a significant reduction in cancer recurrence (P for trend = .03; Table 3). Finally, although OS follow-up for this study remains active, we observed a significant inverse relation between physical activity and all-cause mortality, after adjusting for other predictors of survival (P for trend = .01; Table 3).

Given that lower levels of physical activity could reflect occult cancer or impending death, we excluded patients who developed cancer recurrence or died within 90 days of completing the physical activity assessment in our primary analyses. To address this issue further, we repeated the Cox proportional hazards models after excluding patients who developed cancer recurrence or died within 180 days of completing the physical activity assessment. Although statisti-

cal power was somewhat diminished by this more stringent exclusion, our results remained largely unchanged. Increasing physical activity was still associated with a decreased risk of cancer recurrence or death (adjusted DFS; P for trend = .02). Moreover, the adjusted linear tests for trend for cancer recurrence (RFS) and overall mortality (OS) were .05 and .06, respectively.

The Kaplan-Meier curves (Fig 2) suggest a difference in DFS among patients reporting MET-hours above and below 18 total MET-hours per week. Collapsing activity levels into two categories (< 18 and ≥ 18 total MET-hours per week), as suggested by Figure 2, those with at least 18 total MET-hours per week had a hazard ratio of 0.57 (95% CI, 0.39 to 0.85), compared with those engaging in less than 18 MET-hours per week. The 3-year DFS (from the time of questionnaire completion) was 75.1% for patients who engage in less than 18 MET-hours per week and 84.5% for patients who engage in 18 or more MET-hours per week. To better characterize the amount of activity necessary to have a benefit, we generated a smoothing spline of log hazard versus the log of the total MET score (Fig 3), a method independent of predetermined MET-hour categorizations. A log hazard less than zero represents a favorable hazard ratio (< 1). The spline suggests the protective hazard ratio may occur at approximately 9 total MET-hours per week or sooner. Furthermore, the slope of the curve beyond 27 total MET-hours per week suggests that there is a threshold beyond which additional exercise does not lead to further improvements in DFS.

Stratified Analyses by Potential Effect Modifiers

We examined the influence of physical activity across strata of other predictors of cancer recurrence and mortality (Fig 4). Calculation of adjusted hazard ratios and 95% CIs comparing 18 or more to less than 18 MET-hours per week showed that the reduced risk of cancer recurrence or death was apparent in all subgroups defined on the basis of prognostic factors at entry into the treatment trial. The effect of physical activity was not significantly modified by sex, body mass index, number of positive lymph nodes, age, baseline performance status, or treatment arm.

DISCUSSION

In a cohort of patients with stage III colon cancer treated with surgery and adjuvant chemotherapy surviving without recurrence 6 months after chemotherapy, physical activity after diagnosis was associated with a significant reduction in cancer recurrence and overall mortality. Patients who engaged in at least 18 MET-hours per week of activity (the equivalent of walking 6 or more hours per week at an average pace) had a statistically significant 47% improvement in DFS, compared with inactive patients.

Physical activity has been shown consistently to affect colon cancer incidence,¹⁻¹¹ though no studies have been reported on physical activity after the diagnosis of colon cancer. Haydon et al⁴² reported that prediagnosis physical activity was not associated with colorectal cancer-specific survival.

There are several advantages of using a cohort within a NCI-sponsored clinical trial. First, all patients had lymph node-positive cancer, reducing the impact of heterogeneity by disease stage. Second, treatment and follow-up care are standardized, and the date and nature of recurrence are recorded prospectively. Finally, detailed information on other prognostic variables is collected routinely.

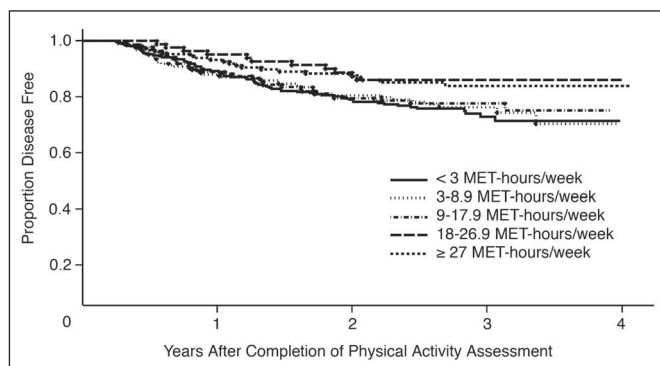


Fig 2. Disease-free survival based on second questionnaire. MET, metabolic equivalent task.

Table 3. Impact of Physical Activity on Colon Cancer Recurrence and Mortality (median follow-up of alive patients 2.7 years from completion of questionnaire 2; 3.8 years from trial entry)

| Outcome | Total MET-Hours per Week | | | | | | | | | | P for Trend |
|--|--------------------------|--------|-------|--------------|--------|--------------|---------|--------------|------|--------------|-------------|
| | < 3 | | 3-8.9 | | 9-17.9 | | 18-26.9 | | ≥ 27 | | |
| | HR | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI | |
| Cancer recurrence or death from any cause (disease-free survival) | | | | | | | | | | | |
| No. of events | 67 | | 42 | | 30 | | 11 | | 22 | | |
| No. at risk | 273 | | 187 | | 137 | | 84 | | 151 | | |
| Unadjusted | Referent | | 0.94 | 0.64 to 1.38 | 0.89 | 0.58 to 1.37 | 0.51 | 0.27 to 0.97 | 0.58 | 0.36 to 0.94 | .01 |
| Adjusted* | Referent | | 0.87 | 0.58 to 1.29 | 0.90 | 0.57 to 1.40 | 0.51 | 0.26 to 0.97 | 0.55 | 0.33 to 0.91 | .01 |
| Cancer recurrence (recurrence-free survival) | | | | | | | | | | | |
| No. of events | 62 | | 38 | | 27 | | 10 | | 22 | | |
| No. at risk | 273 | | 187 | | 137 | | 84 | | 151 | | |
| Unadjusted | Referent | | 0.92 | 0.61 to 1.37 | 0.87 | 0.55 to 1.37 | 0.50 | 0.26 to 0.98 | 0.63 | 0.39 to 1.02 | .03 |
| Adjusted* | Referent | | 0.86 | 0.57 to 1.30 | 0.89 | 0.55 to 1.42 | 0.51 | 0.26 to 1.01 | 0.60 | 0.36 to 1.01 | .03 |
| Overall mortality | | | | | | | | | | | |
| No. of events | 33 | | 21 | | 13 | | 8 | | 9 | | |
| No. at risk | 273 | | 187 | | 137 | | 84 | | 151 | | |
| Unadjusted | Referent | | 0.93 | 0.53 to 1.60 | 0.75 | 0.39 to 1.43 | 0.79 | 0.37 to 1.72 | 0.50 | 0.24 to 1.04 | .05 |
| Adjusted* | Referent | | 0.85 | 0.49 to 1.49 | 0.71 | 0.36 to 1.41 | 0.71 | 0.32 to 1.59 | 0.37 | 0.16 to 0.82 | .01 |

Abbreviations: MET, metabolic equivalent task; HR, hazard ratio; CEA, carcinoembryonic antigen.

*Adjusted for sex, age, depth of invasion through bowel wall (T1-2 v T3-4), number of positive lymph nodes (one to three v four or more), presence of clinical perforation at time of surgery, presence of bowel obstruction at time of surgery, baseline CEA (≤ 5 v > 5 ng/dL), grade of tumor differentiation (poorly or undifferentiated v well or moderately), baseline performance status (0 v 1-2), treatment arm, weight change between first and second questionnaire, body mass index at time of second questionnaire, and time between study entry and completion of second questionnaire.

Patients who enroll in randomized trials may differ from the population at large. To participate, a patient must meet eligibility criteria, be selected as an appropriate candidate, and be motivated to participate. However, we did observe reasonable variability in exercise levels among participants. Moreover, because the study included patients throughout North America, as well as both community and academic centers, our findings should reflect the general population of stage III patients.

We cannot exclude completely the possibility that lower levels of physical activity may be reflective of other occult predictors for poor prognosis. However, we did not observe any significant asso-

ciation between physical activity and other predictors associated with cancer recurrence or survival. Given that patients were enrolled onto a clinical trial, they all initiated fluorouracil-based adjuvant chemotherapy after surgery. Moreover, the benefit associated with exercise remained largely unchanged across the number of positive lymph nodes as well as baseline performance status. Furthermore, we considered the possibility that sick patients (with cancer recurrences and limited survival) will exercise less. To minimize this bias, we excluded recurrences or deaths within 90 days of the physical activity assessment in the primary analysis. Furthermore, we continue to see a positive impact of exercise even when we extended this restriction to exclude events 6 months after physical activity assessment. Finally, because all patients were observed on a clinical trial with prescribed follow-up visits and testing, 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 colon cancer may be considered limited in their ability to exercise. However, Arndt et al⁴³ reported that 1 year after surgery of the primary tumor, patients with colorectal cancer reported that their physical functioning and global quality of life was nearly identical to those of a noncancer population. Furthermore, the distribution of levels of recreational activity are consistent with those seen in noncancer populations.^{3,11}

Given that patients who are more physically active after cancer diagnosis may have been similarly active before diagnosis, we cannot exclude the possibility that active individuals who develop colon cancer acquire tumors that are biologically less aggressive. Nonetheless, as stated above, we did not observe any significant

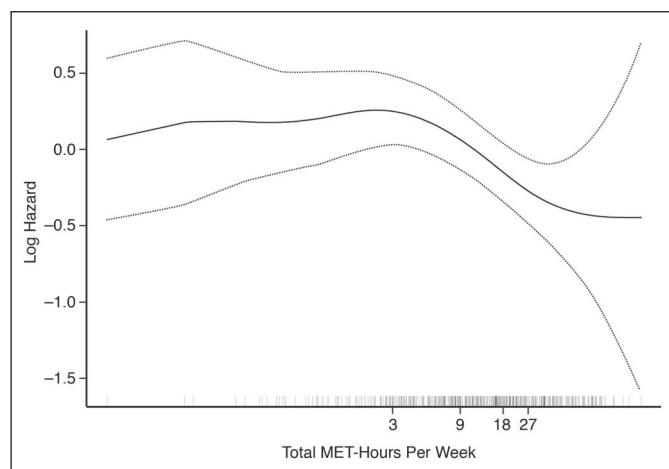


Fig 3. Log hazard smoothing spline plot. MET, metabolic equivalent task.

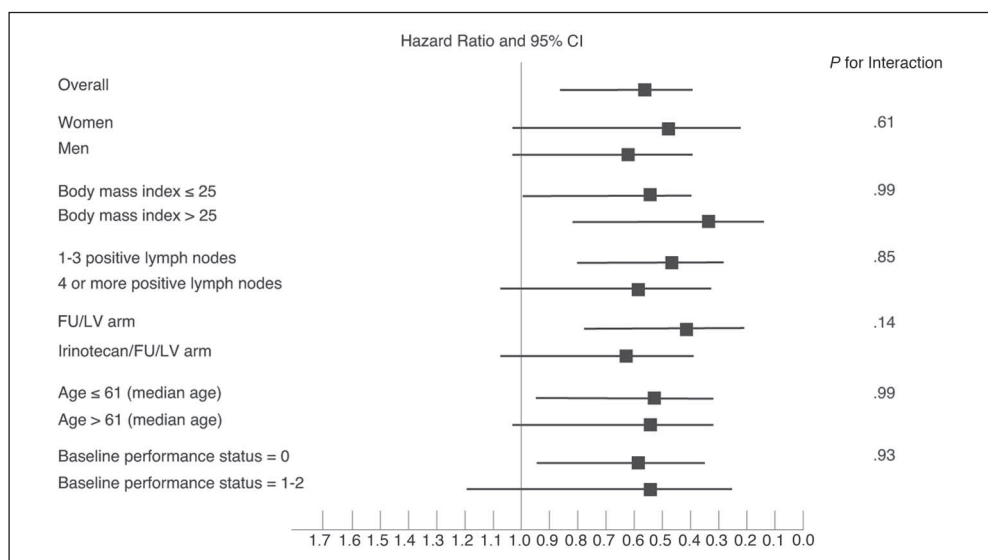


Fig 4. Stratified analysis of disease-free survival (comparison of < 18 v ≥ 18 metabolic equivalent task (MET)-hours per week of physical activity). FU, fluorouracil; LV, leucovorin.

association between physical activity and tumor-related characteristics associated with cancer recurrences. Moreover, in a recent study of colorectal cancer survival nested within the Nurses' Health Study, prediagnosis physical activity among those women diagnosed with colorectal cancer did not influence colorectal cancer-specific or overall mortality, whereas physical activity after diagnosis also conferred a significant reduction in cancer mortality.⁴⁴

An important caveat to these results is that patients included in the analysis remained disease free and alive 14 months after surgery (6 months after completion of adjuvant chemotherapy). Although we believe that this approach is the most appropriate to measure an ongoing lifestyle habit after the effects of cancer treatment resolve, a limitation is that the data do not address the role of exercise before that time period (ie, immediately after treatment).

Physical activity was self-reported in this study. However, the questions have been validated previously^{36,37} and shown to be predictive of other health outcomes, including cardiovascular,^{45,46} cancer,^{3,32,47,48} and total mortality.^{49,50} Furthermore, exercise levels were recorded before any knowledge of colon cancer-related outcomes, thus reducing the likelihood of reporting biases.

Studies have shown an improved DFS among patients who receive adjuvant chemotherapy after the surgical resection of stage III colon cancer. These findings along with data from the Nurses' Health Study cohort suggest that exercise may confer additional improvements in cancer survival beyond surgery and chemotherapy. Efforts are underway to determine the optimal way to promote exercise in cancer survivors⁵¹; once such interventions are established, our data support the need for a randomized trial in colon cancer survivors.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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