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Impact of physical activity after cancer diagnosis on survival in patients with recurrent colon cancer: Findings from CALGB 89803 / ALLIANCE

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Abstract

Background—The impact of physical activity on survival outcomes of recurrent colon cancer has not been studied. We tested the association between the level of post-diagnosis physical activity and survival outcome of patients with recurrent colon cancer.

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All authors have no conflicts of interest.

Materials and Methods—We conducted a prospective observational study of 237 stage III colon cancer patients who had a recurrence. Physical activity was measured approximately six months after the completion of therapy (14 months after the surgical resection) but before detection of recurrent disease. The primary endpoint of the study was survival time after recurrence.

Results—The hazard ratio comparing patients who reported at least 18 metabolic equivalent task (MET)-hours per week of physical activity to those engaging in less than 3 MET-hours / week was 0.71(95% confidence interval 0.46–1.11). Increasing total MET-hours per week of physical activity was associated with a borderline statistical significance trend for improved survival after recurrence (P=0.052). The benefit of physical activity on survival was not significantly modified by sex, body mass index, number of positive lymph nodes, age, baseline performance status, adjuvant chemotherapy regimen or recurrence-free survival period.

Conclusion—To our knowledge, this is the first study that studied the association of physical activity with survival outcome of recurrent colon cancer patients. While the association exceeded our pre-defined P trend <0.05 for statistical significance, these findings warrant further studies of physical activity in patients with recurrent colorectal cancer.

Keywords

Physical activity; Exercise; Recurrent colon cancer; Cancer recurrence; Survival

Introduction

Physically active individuals have a reduced risk of colorectal cancer development(1). Physical activity further reduces the risk of recurrence and mortality in colon cancer patients (2–6). We have previously reported the influence of exercise on recurrence and survival in patients with stage III colon cancer (4). Individuals engaging in more than 18 total metabolic equivalent task (MET) hour per week experienced approximately 50% reduction in recurrence or death compared to those who were inactive. Similarly, among 573 stage I–III colorectal cancer patients in the Nurses' Health Study, post-diagnosis physical activity was inversely associated with colorectal cancer-specific mortality and overall mortality (3).

Advancements in surgery and perioperative therapies have significantly improved survival of colon cancer patients without metastases at the time of diagnosis (7); however, 5-year recurrence rates for patients with stage I, II and III colon cancer are still 10%, 20% and 30–50%, respectively.(8) Many colon cancer patients still develop tumor recurrence and the median survival following recurrence is less than 2 year (9, 10). Factors such as initial tumor stage, tumor grade, performance status, weight loss, and anatomic sites of metastatic disease have been known to contribute to survival after recurrence. A few studies have investigated the effects of physical activity on palliative care and quality of life in metastatic cancer patients (11–13). However, the impact of physical activity on survival time once colon cancer recurs has not been studied. Therefore, it is important to identify whether physical activity would have positive impact on the outcome of recurrent colon cancer. The current study aims to identify the association between post-diagnosis physical activity and overall survival after the recurrence of colon cancer.

Materials 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) (14). Between April 1999 and May 2001, a total of 1,264 patients were recruited for the trial. The detailed study methods have been described previously (4). In brief, a self-administered questionnaire including diet and lifestyle habits was obtained from patients midway through their adjuvant therapy (Questionnaire 1: 4 months after surgical resection) and again 6 months after completion of adjuvant therapy (Questionnaire 2: 14 months after surgical resection). As the purpose of this current study is to examine the effects of post-diagnosis physical activity on outcome of recurrent colon cancer, patients whose colon cancer recurred after the completion of questionnaire 2 were included in the analysis. Among 1,264 patients, 981 patients completed questionnaire 2 (Figure 1A). Of these 981 patients, we excluded from these analyses the 653 patients who did not recur and 91 patients who recurred before the completion of the second questionnaire (Figure 1B). The final sample size for this study was 237. All patients signed informed consent, approved by the internal review boards of the local institution.

Physical Activity Assessment

The physical activity questions used in this study have been described and validated previously (3, 4, 15). The method for calculation of scores for MET hour per week based on the physical activity questionnaire was explained in detail in a previous publication (4). Categories of MET-hours per week were defined as less than 3, 3 to 17.9, and 18 or more, consistent with prior analyses (3, 4).

Study End Points and Covariates

In this ancillary study, the primary end point was survival after recurrence, defined as the time from the recurrence to death as a result of any cause. Covariates included gender, age, body mass index (BMI), depth of invasion through bowel wall (T stage), the number of positive lymph nodes, and baseline performance status (at time of adjuvant therapy).

Statistical Analyses

Cox proportional hazards regression was used to determine association between physical activity and survival outcome, controlling potential confounders which may influence the outcome. Total MET-hours was considered as a continuous variable in tests of trend and interaction. A categorical variable based on total MET-hours was defined as <3, 3–17.9, and ≥ 18 MET-hours per week. In survival comparisons, the physical activity less than 3 MET-hours per week category was the reference group. P values less than or equal to 0.05 were considered statistically significant. Tests of interaction between physical activity categories and potential confounders were assessed by entering the cross product of the physical activity and the dichotomized covariate. Patient registration and clinical data collection were managed by the CALGB (Alliance) Statistics and Data Center, and all analyses were performed by CALGB (Alliance) statisticians based on the study database, frozen on November 9th, 2009.

Results

Baseline Characteristics by Physical Activity Category

Baseline characteristics by activity levels for the 237 participants with colon cancer recurrence included in this analysis are shown in Table 1. Patients with higher physical activity tended to be male and have a higher performance status (measured at the time of initiation of adjuvant therapy). Other characteristics did not differ significantly across physical activity levels.

Survival after recurrence by level of physical activity

Of the 237 participants, 169 had confirmed deaths as of November 9th 2009, the date the CALGB 89803 database was frozen. The overall median follow-up time for the entire CALGB 89803 cohort was 7.3 years. The primary endpoint of this study was survival time after recurrence. Post-diagnosis physical activity was inversely associated with the risk of death after recurrence, though the P trend = 0.052 exceeded our pre-specified level of statistical significance (Table 2). Compared with patients who reported less than 3 total MET-hours per week of physical activity, those reporting 18 or more MET-hours per week had a multivariate hazard ratio of 0.71 (95% CI, 0.46–1.11).

We examined the influence of physical activity across strata of other predictors of cancer recurrence and mortality. No significant interactions were detected on the association between physical activity and survival after recurrence by gender (P interaction =.97), baseline performance status (0 vs. 1–2, P interaction =.51), extent of invasion through bowel wall (T 1–2 vs. 3–4, P interaction =.58), number of positive nodes (≤3 vs. ≥4, P interaction = 0.32), body mass index (≤25 vs. >25, P interaction =0.98) or adjuvant chemotherapy regimen (P interaction = 0.89). Further, there was no interaction between the level of physical activity and survival after recurrence when tested by time from diagnosis to recurrence (<2 years or ≥ 2 years; P interaction = 0.94).

Discussion

Despite improvements in the treatment of colorectal cancer, over 30% of patients with stage III colon cancer will recur identification of prognostic markers that influence survival rate in recurrent colon cancer patients is of a major importance. We previously demonstrated that physical activity significantly reduces the likelihood of recurrence in colorectal cancer survivors, and thus increases overall and colorectal cancer specific survival (3–5). No prior studies have reported the impact of physical activity after the diagnosis on the survival of patients who experience recurrence of colon cancer. In the current study, we observed that the level of physical activity after the diagnosis of cancer may be associated with survival of recurrent colon cancer patients, though the association just exceeded our pre-specified level of statistical significance. Recurrent colon cancer patients who engaged in at least 18 MET-hours per week of activity had a non-significant 29% improvement in mortality compared with inactive patients after controlling for potential factors which may influence survival.

O'Connell and colleagues reported that patients who recur later live longer than those who recur earlier (16). To control for this factor, we have stratified our participants into two groups: those who had recurrence-free survival less than two years and those who had a recurrence-free survival of two years or more. We did not observe a significant interaction in overall survival between the level of physical activity and earlier or later recurrence time from diagnosis (P=0.94).

There are only two studies that have investigated the association between either functional capacity or physical activity behavior and survival in recurrent cancer (13, 17). One study (13) found that functional capacity measured by a 6-minute walk test and the level of physical activity (more versus less than 9 MET hours per week) were predictors for survival in metastatic non-small cell lung cancer patients. In another study (17), the level of physical activity but not functional capacity was a significant predictor for patients with malignant recurrent glioma. The result from the current study is in agreement with previously reported studies in recurrent cancer patients; however, the current study was the first performed in colon cancer patients. Taken together with previously reported studies, we may be able to suggest that our patients with recurrent colon cancer should increase or at least maintain their level of physical activity if there is no contraindication to exercise.

There are limitations in this study that are important to consider. First, the sample size is limited both by the number of recurrences detected overall in this adjuvant therapy study and the requirement that patients did not recur prior to the second questionnaire (approximately 14 months after surgery). While the point estimated for overall survival for 18 or more MET-hours per week of physical activity suggests a benefit, the confidence interval crosses 1; this could be due to sample size or lack of a true benefit. In addition, the P value for the test for trend with increasing physical activity on survival time after recurrence was at the borderline significance at 0.052. Second, physical activity was measured before the recurrence and it is not known if that level of activity was maintained after recurrence and for how long. Further studies of the effects of physical activity on survival of recurrent colon cancer patients, as well as the associated biological mechanism, are needed.

In summary, physical activity after completion of therapy but prior to recurrence seems to be a factor that influences the prognosis of recurrent colon cancer patients.

Conclusion

The impact of physical activity after cancer recurrence on the risk of mortality in colon cancer patients was first investigated in the current study. In the current study, a trend toward statistical significance in association between the physical activity after completion of therapy but prior to recurrence and the risk of mortality was observed. In the future, we need a larger prospective cohort study as well as randomized controlled trial with physical activity intervention and control groups to confirm the findings of our study.

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Clinical Practice Points

- What is already known about this subject?

  The positive impact of physical activity participation on cancer prevention, prevention of recurrence and survival in colorectal cancer patients has been reported. In addition, the safety and efficacy of physical activity and exercise have been tested adequately and oncologists can recommend physical activity and exercise to their patients. However, the association between physical activity and mortality has not been tested in metastatic colorectal cancer patients and there is no evidence on whether physical activity and exercise would have a positive impact of survival of recurrent colorectal cancer.

- What are the new findings?

  The current study is the first study which investigated the association between physical activity levels and survival outcome in recurrent colon cancer patients. We have observed that increasing total MET-hours per week of physical activity was associated with a borderline statistical significance trend for improved survival after recurrence (P=0.052).

- How might it impact on clinical practice in the foreseeable future?

  Although it was not statistically significant, this study provides some evidence that physical activity may have positive impact on survival of recurrent colorectal cancer.

Figure-1 A

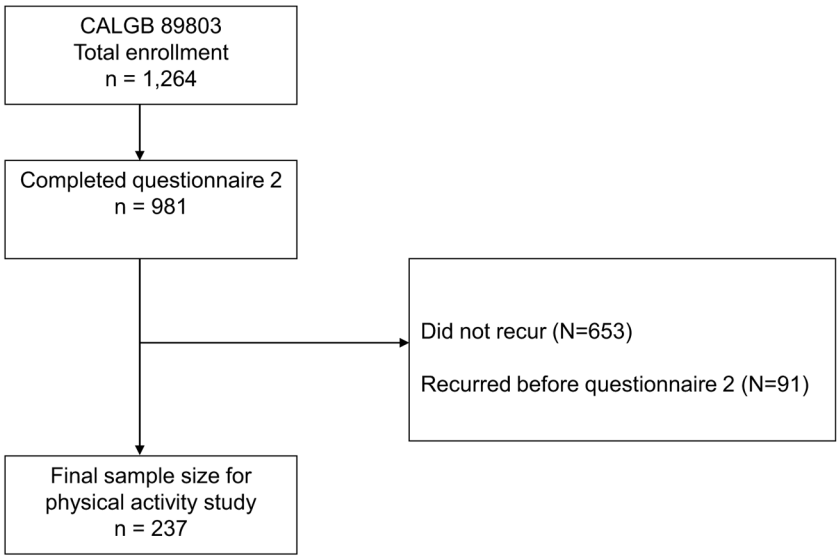

Figure 1-B

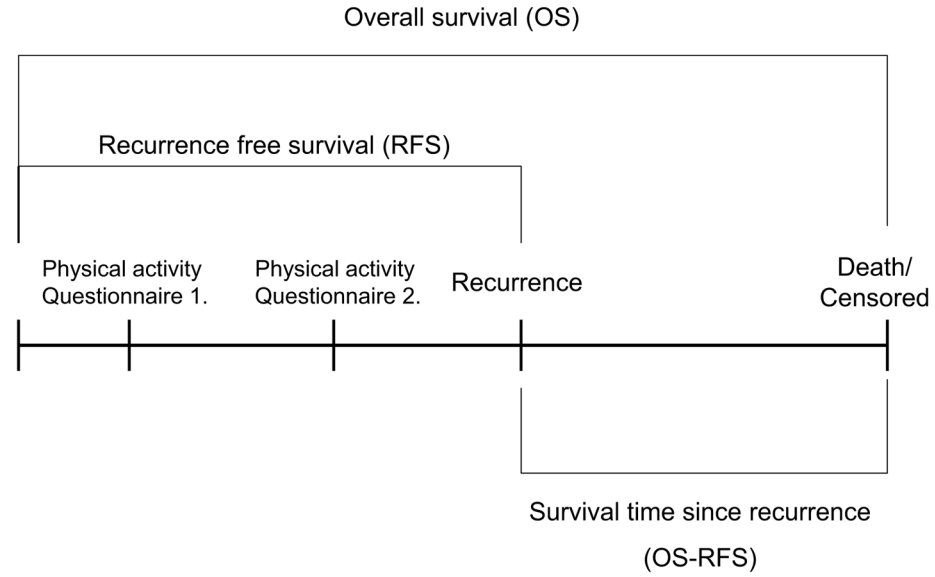

Figure 1.

Table 1

Baseline characteristics

	Total Met-Hours per Week			
Characteristic	**< 3**	**3 – 17.9**	**≥ 18**	**overall**
Number. of patients	81	96	60	237
Median total MET-hours per week	0.6	8.3	36	7.7
Median age (years)	63	60	59.5	61
Gender, n (%)				
Male	38 (46.9)	59 (61.5)	43 (71.7)	140 (59.1)
Female	43 (53.1)	37 (38.5)	17 (28.3)	97 (40.9)
Race, n (%)				
White	70 (86.4)	91 (94.8)	55 (91.7)	216 (91.1)
Black	8 (9.9)	3 (3.1)	3 (5)	14 (5.9)
Other	3 (3.7)	2 (2.1)	2 (3.3)	7 (3.0)
Time from diagnosis to recurrence, years, n (%)				
< 2 years	34 (42.0)	45 (46.9)	28 (46.7)	107 (45.1)
≥ 2 years	47 (58.0)	51 (53.1)	32 (53.3)	130 (54.9)
BMI, median	30.3	28	29.6	28.8
Depth of invasion through bowel wall, n (%)				
T1–2	6 (7.4)	7 (7.3)	5 (8.3)	18 (7.6)
T3–4	72 (88.9)	88 (91.7)	54 (90)	214 (90.3)
missing	3 (3.7)	1 (1)	1 (1.7)	5 (2.1)
Number of positive lymph nodes, n (%)				
1–3 (N1)	54 (66.7)	54 (56.3)	32 (53.3)	140 (59.1)
4+ (N2)	24 (29.6)	41 (42.7)	27 (45.0)	92 (38.8)
Missing	3 (3.7)	1 (1)	1 (1.7)	5 (2.1)
Baseline performance status, n (%)				
0	52 (64.2)	70 (72.9)	48 (80)	170 (71.7)
1,2	26 (32.1)	25 (26.0)	11 (18.3)	62 (26.2)
Missing	3 (3.7)	1 (1)	1 (1.7)	5 (2.1)
Treatment, n (%)				
5FU/LV	41 (50.6)	44 (45.8)	27 (45)	112 (47.3)
CPT-11/5FU/LV	40 (49.4)	52 (54.2)	33 (55.0)	125 (52.7)

5-FU = 5-fluorouracil; LV = leucovorin; IFL = irinotecan,; kg = kilograms; m^2 = meters squared; MET = metabolic equivalent tasks

† Baseline performance status: 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.

Table 2

Association between post-diagnosis physical activity and overall survival in patients with recurrent colon cancer

	Total Met-Hours per Week			P for Trend [b]
	<3	3 – 17.9	18 +	
No. of events / No. at risk	58/81	72/96	39/60	
Unadjusted	1.0 (Referent)	0.95 (0.67–1.35)	0.84 (0.56–1.26)	0.172
Adjusted [a]	1.0 (Referent)	0.85 (0.58–1.23)	0.71 (0.46–1.11)	0.052

MET = metabolic equivalent task

[a] Adjusted for sex, age, BMI, depth of invasion through bowel wall, number of positive lymph nodes, baseline performance status and treatment group

[b] Based on the Cox model with continuous total METs per week