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Association between physical activity and the time course of cancer recurrence in stage III colon cancer

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ABSTRACT

Objective We determined if postoperative physical activity prevents or delays cancer recurrence in patients with stage III colon cancer.

Methods This cohort study nested within a randomised trial enrolled 1696 patients with surgically resected stage III colon cancer. Physical activity was calculated based on self-reporting during and after chemotherapy. Patients were classified as physically active (≥9 MET-h/wk, comparable with the energy expenditure of 150 min/wk of brisk walking, consistent with the current physical activity guidelines for cancer survivors) or physically inactive (<9 MET-h/wk). The confounder-adjusted hazard rate (risk of recurrence or death) and HR by physical activity category were estimated with continuous time to allow non-proportionality of hazards.

Results During a median 5.9 years follow-up, 457 patients experienced disease recurrence or death. For physically active and physically inactive patients, the risk of disease recurrence peaked between 1 and 2 years postoperatively and declined gradually to year 5. The risk of recurrence in physically active patients never exceeded that of physically inactive patients during follow-up, suggesting that physical activity prevents—as opposed to delays—cancer recurrence in some patients. A statistically significant disease-free survival benefit associated with physical activity was observed during the first postoperative year (HR 0.68, 95% CI 0.51 to 0.92). A statistically significant overall survival benefit associated with physical activity was observed during the first three postoperative years (HR 0.32, 95% CI 0.19 to 0.51).

Conclusions In this observational study of patients with stage III colon cancer, postoperative physical activity is associated with improved disease-free survival by lowering the recurrence rate within the first year of treatment, which translates into an overall survival benefit.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

⇒ Physical activity after surgical resection for stage III colon cancer is associated with significantly longer disease-free survival.

⇒ Physical activity may confer a disease-free survival benefit by preventing or merely delaying the time of cancer recurrence.

WHAT ARE THE FINDINGS?

⇒ In this cohort study of 1696 patients with stage III colon cancer, the rate of cancer recurrence in physically active patients never exceeded that of physically inactive patients during follow-up.

⇒ The disease-free survival benefit of physical activity persisted for approximately 1 year after surgical resection, and the overall survival benefit of physical activity persisted for approximately 3 years after surgical resection.

⇒ Postoperative physical activity may prevent, as opposed to delay, cancer recurrence in some patients with stage III colon cancer.

HOW MIGHT IT IMPACT ON CLINICAL PRACTICE IN THE FUTURE?

⇒ These findings refine our understanding of how physical activity improves cancer survivorship in a manner relevant to tumour biology and cancer care delivery.

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INTRODUCTION

Physical activity after surgical resection for stage III colon cancer is associated with significantly longer disease-free survival.[1 2] However, the biological mechanisms by which physical activity improves disease-free survival remain incompletely understood.[3 4] Common hypotheses of biological mechanisms include eradicating circulating tumour cells and reducing stimuli within the host microenvironment that foster micro-metastatic growth, such as inflammation, hyperinsulinemia and immune suppression.[5] Physical activity affects all cells and tissues distinctly[6 7]; therefore, physical activity may confer a disease-free survival benefit by preventing or merely delaying the time of cancer recurrence.

Graphical depictions of disease-free survival from randomised studies are often presented with Kaplan-Meier plots.[8] Although these plots offer information about the absolute rate of disease recurrence and death, they do not directly depict the risk of an event at a specific time.[9] A separation in Kaplan-Meier curves does not explicitly communicate if an advantage is achieved early and maintained longitudinally or achieved incrementally over time.[9] In non-randomised studies, the unadjusted Kaplan-Meier plot may be misleading due to confounding.[10 11] Confounders in non-randomised studies are often adjusted using Cox regression, which assumes that the hazard rate between two groups is proportional over time, and the effect is estimated as a single HR.[12 13] Consequently, the

detailed time course of cancer recurrence by physical activity in colon cancer is unknown.

To determine if postoperative physical activity prevents or delays cancer recurrence, we estimated the confounder-adjusted hazard rates and HR by physical activity category with continuous time.[14 15] This method was previously applied to randomised trial data to describe the time course of benefit from fluoropyrimidine and oxaliplatin chemotherapy in stage II and III colon cancer.[16 17] We used data from a prospective cohort of patients with stage III colon cancer enrolled in a randomised multicentre trial of postoperative treatment that the National Cancer Institute sponsored.[18] We hypothesised that physical activity would prevent cancer recurrence (online supplemental figure 1), translating into an overall survival benefit.

METHOD

Study design

The Cancer and Leukemia Group B (now part of the Alliance for Clinical Trials in Oncology) and Southwest Oncology Group (SWOG) trial 80702 was a phase III double-blinded randomised study that used a 2×2 factorial design to test the primary hypothesis of the superiority of celecoxib compared with placebo and the secondary hypothesis of the non-inferiority of 3 months compared with 6 months of chemotherapy. The primary and secondary hypotheses have been published.[18–20] At the time of trial enrolment, patients were offered the option to participate in a nested cohort study of lifestyle factors, including completing standardised assessments at specified time intervals. The randomised trial and nested cohort study were designed in collaboration with the National Cancer Institute.

Study population

Patients were enrolled at community and academic centres across the National Cancer Trials Network in the USA and Canada. Eligible patients had surgically resected (margin negative) and histologically documented colonic adenocarcinoma. Patients were enrolled ≥21 days and ≤56 days after surgical resection. Tumours had at least one pathologically confirmed metastatic lymph node or N1c designation (tumour deposit(s) in the subserosa, mesentery, or non-peritonealised pericolic tissue without regional lymph node metastases). Patients were aged ≥18 years, with an Eastern Cooperative Oncology Group (ECOG) performance status ≤2.[18]

Physical activity assessment

Physical activity was assessed midway through postoperative chemotherapy (4 months following surgical resection) and 6 months after completing postoperative chemotherapy (14 months after surgical resection). Patients reported their average weekly time spent on a range of recreational physical activities during the preceding 2 months using a validated questionnaire.[21] Each physical activity was assigned a metabolic equivalent (MET) energy expenditure according to standardised criteria.[22] We calculated the MET-hours per week (MET-h/wk) for each activity by multiplying the MET value by the patient's reported number of hours of physical activity each week. We classified patients who reported ≥9 MET-h/wk as physically active (comparable with the energy expenditure of 150 min/wk of brisk walking, consistent with the current physical activity guidelines for cancer survivors[23]) and patients who reported <9 MET-h/wk as physically inactive. Considering the potential for declining health to bias the physical activity assessment, we pre-specified that the patients who experienced disease recurrence or death within 60 days after completing the first physical activity assessment would be excluded from the analysis.

Study endpoints

The endpoints included disease-free survival, time to cancer recurrence and overall survival. Disease-free survival was defined as the time from completing the first physical activity assessment to the date of documented disease recurrence or death from any cause. Time to cancer recurrence was defined as the time from completion of the first physical activity assessment to the date of documented disease recurrence. Overall survival was defined as the time from completing the first physical activity assessment to the date of death from any cause. Patients were assessed for cancer recurrence by history, physical examination and carcinoembryonic antigen measures every 3 months following randomisation and subsequently every 6 months for 6 years or until recurrence, whichever came first. All patients had surveillance imaging of the chest, abdomen and pelvis every 6 months for at least 3 years and then yearly for 3 years, or until recurrence.

Confounders

Confounders were selected using the modified disjunctive cause criterion.[24] Data for patient demographic factors, including age, sex, race and ethnicity, were self-reported. Clinical factors, including the extent of tumour invasion through the bowel wall (T-stage), the extent of lymph node metastases (N-stage), pathological risk group (low (T1, T2 or T3, N1) or high (T4, N2 or both)), tumour location, performance status and low-dose aspirin use, were obtained from a combination of physician assessment and the medical record. Smoking history was self-reported. Body mass index was abstracted from a combination of the electronic medical record and self-report. Diet was assessed using a 131-item food frequency questionnaire[25]; prudent and western dietary patterns were defined using previously validated factor loadings in this population.[26] Body mass index and diet were updated when physical activity was reassessed. All statistical models included the previously described confounders.

Statistical analysis

To test for differences in baseline patient characteristics by physical activity category, the χ^2 test was used for categorical variables, and the independent t-test was used for continuous variables. Physical activity was modelled using cumulative averaging, which quantifies the time-weighted average of all reported physical activity.[26 27] Follow-up started at the first physical activity assessment, and we updated physical activity based on the results of the second questionnaire that was weighted proportional to the linear function of time between the first and the second questionnaire and the time between the second questionnaire and the disease-free survival period. Repeatedly measured variables (eg, body mass index and dietary patterns) were included as time-varying confounders.

We used the method of Müller and Wang to plot the continuous-time and confounder-adjusted cause-specific hazard of recurrence from completion of the first physical activity assessment up to year 6 of follow-up, stratified by physical activity category (physically active vs physically inactive).[14] This method allows for the intuitive visualisation of the instantaneous risk of recurrence or death over time. Comparisons of physically active and physically inactive patients were calculated as continuous-time log-hazard ratios (with time starting at the first physical activity assessment) with 95% pointwise CIs estimated using the method of Zhang *et al* to allow for confounder adjustment, where a

Table 1 Baseline patient demographic, clinical, behavioural and randomisation characteristics, overall and stratified by physical activity category

Characteristic	Total cohort N=1696 (100.0%)	Physically active N=795 (46.9%)	Physically inactive N=901 (53.1%)	P Value
Demographic factors				
Age, years, mean (SD)	60.8 (10.6)	59.8 (10.4)	61.6 (10.7)	<0.001
Female, n (%)	755 (44.5)	297 (37.4)	458 (50.8)	<0.001
Race, n (%)				<0.001
White	1378 (81.3)	688 (86.5)	690 (76.6)	
Black or African American	195 (11.5)	56 (7.0)	139 (15.4)	
Asian	62 (3.7)	27 (3.4)	35 (3.9)	
All others or not reported	61 (3.6)	24 (3.0)	37 (4.1)	
Hispanic or Latino, n (%)	99 (5.8)	37 (4.7)	62 (6.9)	0.051
Clinical factors				
Extent of invasion through the bowel wall, n (%)*				0.088
T1 or T2	312 (18.6)	163 (20.5)	149 (16.5)	
T3	1123 (66.8)	518 (65.2)	605 (67.1)	
T4	245 (14.6)	107 (13.5)	138 (15.3)	
Missing	16	7 (0.9)	9 (1.0)	
Nodal stage, n (%)†				0.051
N1	1240 (73.1)	599 (75.3)	641 (71.1)	
N2	456 (26.9)	196 (24.7)	260 (28.9)	
Risk group, n (%)				0.053
Low (T1, T2 or T3, N1)	1068 (63.6)	520 (65.4)	548 (60.8)	
High (T4, N2 or both)	612 (36.4)	268 (33.7)	344 (38.2)	
Missing	16	7 (0.9)	9 (1.0)	
Tumour location, n (%)				0.07
Left	805 (47.9)	396 (49.8)	409 (45.4)	
Right/transverse/multiple	876 (52.1)	391 (50.2)	485 (55.6)	
Missing	15	8 (1.0)	7 (0.8)	
ECOG performance status, n (%)‡				<0.001
0	1220 (71.9)	638 (80.3)	582 (64.6)	
1–2	476 (28.1)	157 (19.7)	319 (35.4)	
Low-dose aspirin use, n (%)	386 (22.8)	180 (22.6)	206 (22.9)	0.91
Behavioural factors§				
Body mass index, kg/m^2, mean (SD)	28.3 (6.6)	27.5 (5.74)	29.1 (7.11)	<0.001
Smoking history, n (%)				0.029
Never	840 (49.5)	416 (52.3)	424 (47.1)	
Former	701 (41.3)	322 (40.5)	379 (42.1)	
Current	129 (7.6)	48 (6.0)	81 (9.0)	
Not reported	26 (1.5)	9 (1.1)	17 (1.9)	
Western dietary pattern, n (%)				0.63
< Median	851 (50.2)	394 (49.6)	457 (50.7)	
≥ Median	845 (49.8)	401 (50.4)	444 (49.3)	
Prudent dietary pattern, n (%)				<0.001
< Median	847 (49.9)	317 (39.9)	530 (58.8)	
≥ Median	849 (50.1)	478 (60.1)	371 (41.2)	
Physical activity, MET-h/wk				
Mean (SD)	16.1 (24.1)	31.1 (28.5)	2.82 (2.60)	<0.001
Median (IQR)	7.6 (2.0–20.0)	21.5 (13.9–38.8)	2.2 (0.4–4.8)	<0.001
Randomisation groups				
Chemotherapy, n (%)				0.44
3 Months	879 (51.8)	420 (52.8)	459 (50.9)	
6 Months	817 (48.2)	375 (47.2)	442 (49.1)	
Pharmacotherapy, n (%)				0.59
Celecoxib	861 (50.8)	398 (50.1)	463 (51.4)	
Placebo	835 (49.2)	397 (49.9)	438 (48.6)	

Continued

Table 1 Continued

Characteristic	Total cohort N=1696 (100.0%)	Physically active N=795 (46.9%)	Physically inactive N=901 (53.1%)	P Value

*T1 indicates that the tumour has grown into the submucosa; T2, growth into the muscularis propria; T3, growth through the muscularis propria and into the subserosa; T4, growth into the surface of the visceral peritoneum or into or has attached to other organs or structures.
†N1 indicates 1 to 3 lymph nodes tested positive for cancer (or for this table, N1c: tumour deposit(s) in the subserosa, mesentery or non-peritonealised pericolic or perirectal tissues without regional lymph node metastases); N2, four or more lymph nodes tested positive for cancer.
‡Performance status: 0 indicates fully active; 1, restricted in physically strenuous activity but ambulatory and able to carry out light work; and 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.
§Body mass index, western dietary pattern, prudent dietary pattern and physical activity were calculated using the cumulative average method.
ECOG, Eastern Cooperative Oncology Group.

pointwise interval that excludes zero represents a statistically significant effect at that time.[15] These methods permit different risk patterns to be examined without modelling assumptions.

In supplementary analyses, we used flexible parametric proportional hazards survival models to quantify the association between physical activity and cancer recurrence.[28] Parametric survival models estimate absolute and relative effects while permitting flexibility in the baseline hazard function shape (3 knots at default 25th, 50th and 75th centiles of log-time).[29 30] The absolute risk of cancer recurrence is presented as risk differences with bootstrapped 95% CIs, and the relative risk is presented as a HR using all observed data in a time-to-event framework.[31] The number needed to treat (eg, the number of patients who would need to increase their postdiagnosis physical activity to prevent one cancer recurrence) was quantified as the inverse of the absolute risk difference. In sensitivity analysis, we modelled the endpoints without excluding patients with cancer recurrence or death within 60 days after completing the first physical activity assessment.

Data were collected by the Alliance Statistics and Data Management Center. Data quality was ensured by review of data by the Alliance Statistics and Data Management Center and by the study chairperson following Alliance policies. Data analysis was conducted by the Alliance Statistics and Data Management Center using SAS (V.9.4) and R (V.4.1.0) on a data set locked on 10 August 2020.

Equity, diversity and inclusion

The author group is gender balanced and consists of investigators from different disciplines and two countries. Our study population included both male and female subjects.

RESULTS

Between June 2010 and November 2015, 1696 patients from 654 academic and community oncology centres in the USA and Canada were enrolled in the prospective nested cohort study. Among these patients, 795 (46.9%) were classified as physically active, and 901 (53.1%) were classified as physically inactive. Physically active patients were younger (59.8 vs 61.6 years; p<0.001), more likely to be male (62.6 vs 49.2%; p<0.001), more likely to be white (86.5 vs 76.6%; p<0.001), with better ECOG performance status (80.3 vs 64.6% with ECOG zero; p<0.001), a lower body mass index (27.5 vs 29.1 kg/m^2; p<0.001), more likely to be never smokers (52.3 vs 47.1%; p=0.029) and consume a prudent diet pattern (60.1 vs 41.2%; p<0.001) (table 1). During a median follow-up of 5.9 years (IQR 4.9, 6.0), 457 patients experienced disease recurrence or death; 397 patients experienced cancer recurrence, and 281 patients died from any cause. The censoring proportions for disease-free survival, time to cancer recurrence and overall survival were 0.73, 0.77 and 0.83, respectively; the primary reason for censoring was the last disease evaluation date, as reported previously.[18]

The confounder-adjusted hazard rates over time for the endpoints of disease-free survival, time to recurrence and overall survival by physical activity group are plotted (figure 1). For both physically active and physically inactive patients, the hazard of disease recurrence peaks between 1 and 2 years postoperatively and declines gradually to year 5. For the disease-free survival and time to recurrence endpoints, the hazard in physically active patients is consistently lower than in physically inactive patients. For the overall survival endpoint, the hazard in physically active patients is initially lower until approximately year 4, when the risks converge, then the hazard in physically active patients begins to separate again. For no endpoint does the hazard rate in physically active patients ever exceed that of the physically inactive patients during the follow-up period.

The confounder-adjusted HRs with 95% pointwise CIs comparing physically active to physically inactive patients, plotted on the logarithmic scale, for the endpoints of disease-free survival, time to cancer recurrence and overall survival are plotted (figure 2). Physical activity is associated with a statistically significant disease-free survival benefit for approximately the first postoperative year (estimated log-hazard ratio: −0.38; HR 0.68, 95% CI 0.51 to 0.92), then diminishes in magnitude during follow-up; this pattern is comparable for the endpoint of time to recurrence. Physical activity is associated with a statistically significant overall survival benefit for approximately the first three postoperative years, with the largest risk reduction occurring at postoperative year 2 (estimated log-hazard ratio: −1.16; HR 0.32, 95% CI 0.19 to 0.51).

Sensitivity analyses that did not exclude patients with cancer recurrence or death within 60 days after completing the first physical activity assessment did not substantively change the previously described patterns. In supplementary analyses, the confounder-adjusted 5-year cumulative cancer recurrence rate was 20.4% in physically active patients and 31.5% in physically inactive patients (absolute risk difference: 11.1 percentage points, 95% CI 7.0 to 15.2, p<0.001; HR 0.65, 95% CI 0.49 to 0.82, p<0.001 (online supplemental table 1)). Comparing the model fit between the parametric Weibull and Cox regression demonstrated an improved fit using the parametric model (online supplemental table 2).

DISCUSSION

In this nested cohort study of 1696 patients with stage III colon cancer enrolled in a randomised multicentre trial, the risk of cancer recurrence in physically active patients never exceeded that of physically inactive patients during follow-up. These results are consistent with the hypothesis that postoperative

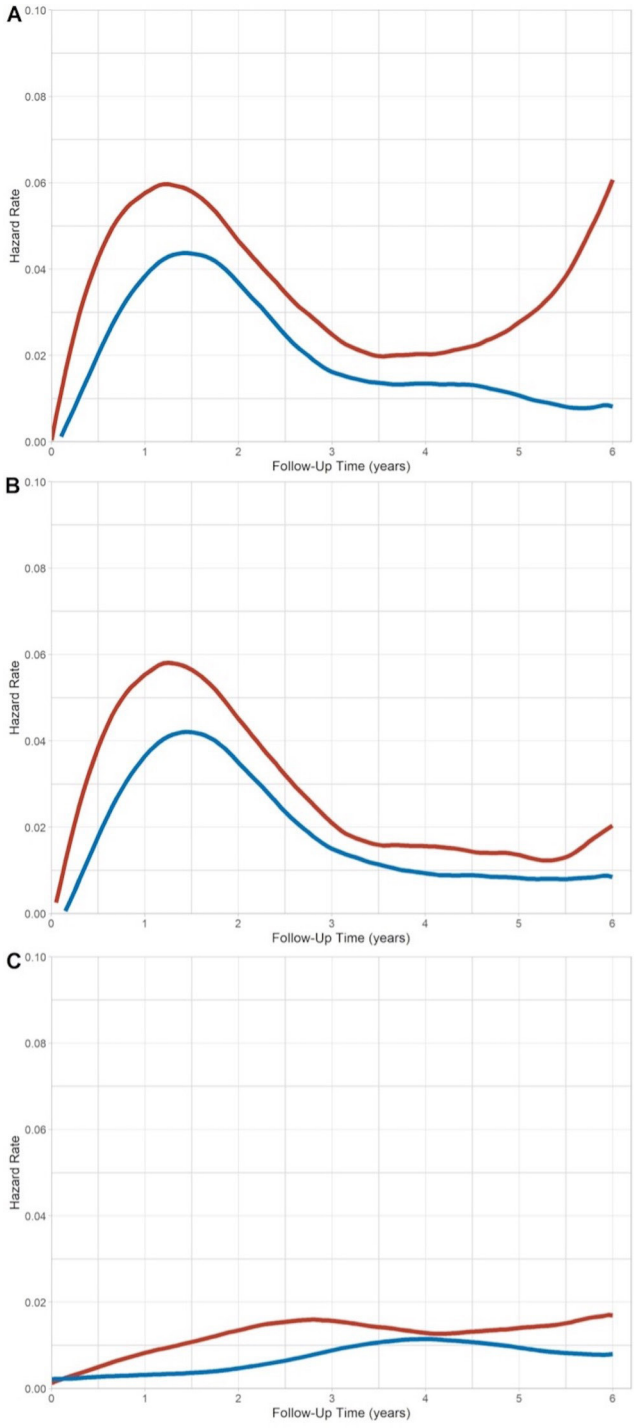

Figure 1 Plots of the confounder-adjusted hazard rates by time from the first assessment of physical activity for (A) disease-free survival, (B) time to recurrence and (C) overall survival by physical activity group over the follow-up period. The hazard rate of physically inactive patients is plotted in red, and physically active patients are plotted in blue.

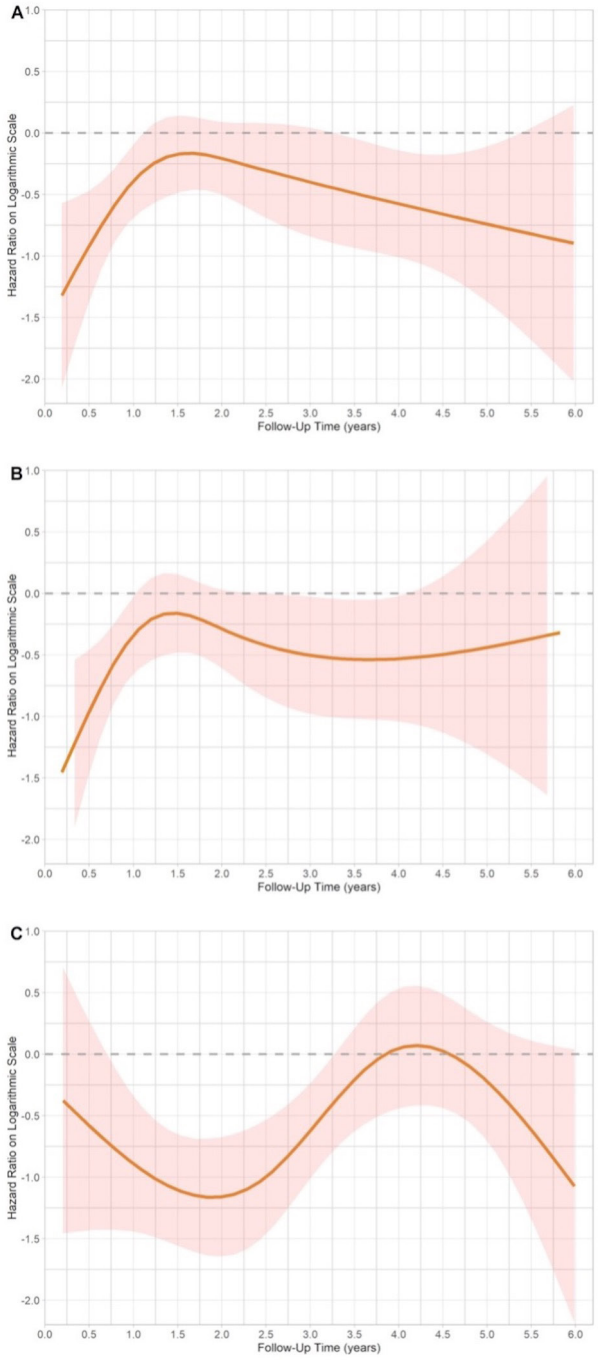

Figure 2 Plots of the confounder-adjusted continuous-time estimate of the log-hazard ratios for (A) disease-free survival, (B) time to recurrence and (C) overall survival by physical activity group over the follow-up period, with 95% pointwise CIs. Values less than 0 indicate a benefit associated with physical activity. For example, a value of −0.35 on the log-hazard scale is a HR of 0.70, comparing physically active to physically inactive groups ($e^{-0.35} = 0.70$), a 30% relative reduction in the risk of an event.

physical activity may prevent, as opposed to delay, cancer recurrence in some patients with stage III colon cancer. Based on these data, we speculate that postoperative physical activity improves disease-free survival by reducing the cancer recurrence rate within the first year of treatment, which translates into an overall survival benefit. These findings refine our understanding of how physical activity improves cancer survivorship in a manner that may be relevant to tumour biology and cancer care delivery.

The pleiotropic effects of physical activity may impede several mechanistic determinants of metastatic colonisation by circulating tumour cells.[5] The proportion of circulating tumour cells in the bloodstream that undergo cell fragmentation, cell cycle arrest and cell death is positively related to the magnitude and duration of shear stress exposure.[32] Physical activity causes significant increases in shear stress,[33] and aerobic activity

reduces circulating tumour cells in patients with stage I–III colon cancer.[34] Physical activity improves immune surveillance (eg, NK cell activity)[35] and may foster improved distant organ tissue defences against infiltrating tumour cells.[36] Physical activity reduces inflammation and hyperinsulinemia in patients with colon cancer,[37 38] and may limit the availability of niches that can support the metabolic demands for metastatic cell growth.[39]

We previously reported that physical activity was associated with improved chemotherapy relative dose intensity.[2] Postoperative fluoropyrimidine and oxaliplatin chemotherapy in colon cancer eradicate residual cancer cells and micro-metastases, thereby curing some patients.[16 17] In our prior study, randomised chemotherapy length (3 months vs 6 months) did not significantly modify the association between physical activity and disease-free survival.[2] However, we cannot rule out the possibility that physical activity reduces cancer recurrence by improving chemotherapy adherence. In 2022, the National Cancer Institute funded a Bayesian randomised trial (U01-CA271279) to test the primary hypothesis that aerobic exercise improves chemotherapy relative dose intensity in patients with colon cancer.

In patients with metastatic colorectal cancer, physical activity during chemotherapy is associated with a significantly longer progression-free survival but not overall survival.[40] Therefore, prior to this analysis, it was plausible that in stage III colon cancer, physical activity may simply delay cancer recurrence, for example, by inducing the cellular dormancy of disseminated tumour cells (single cancer cells that have survived infiltration into distant organs) or by inducing tumour mass dormancy.[41] However, during a median 5.9-year follow-up, we found no evidence to support this hypothesis. Standard-of-care follow-up and surveillance protocols for recurrent cancer remain appropriate for physically active patients.[42]

Clinical implications

Physical activity is safe for cancer survivors and recommended during chemotherapy.[43] Our analysis indicates that the magnitude of benefit from physical activity on cancer recurrence is larger in the early postoperative period and attenuates with time. This time course may be relevant to patients who seek to understand the optimal time to begin physical activity to reduce their cancer recurrence risk. In addition, randomised trials demonstrate that physical activity during chemotherapy reduces cancer-related fatigue and improves physical functioning and health-related quality of life.[44]

The association between physical activity and the overall survival endpoint did appear to be a combination of prevention and delay. In patients with resected colon cancer, approximately 80% of deaths that occur within the first three to five postoperative years are attributed colon cancer and preceeded by tumour recurrence.[45] However, beyond 5 years, cardiovascular events (eg, myocardial infarction, stroke) become the principal cause of death.[46] Physical activity is associated with a lower risk of cardiovascular disease.[47] We speculate that the hazard pattern between physical activity and the overall survival endpoint may illustrate the time when the principal causes of death transition from cancer related to cardiovascular related.

Limitations

There are several limitations of the current analysis. This cohort study was not randomised, although it was nested within a randomised clinical trial, and residual confounding cannot be ruled out because of the non-randomised design. Our analysis accounted for numerous factors that we judged as causally related to physical activity, cancer recurrence or both.[48] However, some of these factors may have measurement error (eg, smoking status) which may bias our effect estimates. Our time-varying HRs may be subject to selection bias due to differential selection of less susceptible subjects over time.[49]

It is known that patients who enrol in clinical trials differ from the underlying population, which may reduce the generalisability of our findings.[50] Physical activity was self-reported and was restricted to specific recreational physical activities. However, the physical activity questionnaire is validated[21] and was completed by patients before knowledge of any clinical events, such as cancer recurrence, which reduces the potential for reporting bias. We did not measure physical activity before cancer diagnosis; thus, we cannot exclude the possibility that patients with higher physical activity develop biologically less aggressive tumours. Patients in our analysis were all treated with 5-fluorouracil and oxaliplatin (FOLFOX) chemotherapy. It is unknown whether our findings apply to capecitabine and oxaliplatin (CAPEOX) or fluoropyrimidine monotherapy.

There are several strengths of the current analysis. Nesting an observational cohort within a randomised trial to examine the time course of cancer recurrence with physical activity offers several advantages over other data sources. Due to eligibility criteria, the disease status of study participants was extensively characterised to maximise patient homogeneity. Chemotherapy dosing, follow-up care and endpoint ascertainment were standardised within the trial. Prospectively collected detailed information on baseline and time-varying variables, such as smoking status, body mass index and diet, permitted comprehensive multivariable adjustment to minimise bias from confounding.

In this observational study of patients with stage III colon cancer, postoperative physical activity may be associated with improved disease-free survival by lowering the recurrence rate within the first year of treatment, which translates into an overall survival benefit. Postoperative physical activity may prevent, as opposed to delay, cancer recurrence in some patients with stage III colon cancer.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Obtained.

Ethics approval This study involves human participants and Institutional Review Board approval was obtained at all 654 participating centres. Participants gave informed consent to participate in the study before taking part.

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Supplementary Material

The Time-Course of Cancer Recurrence with Physical Activity in Stage III Colon Cancer

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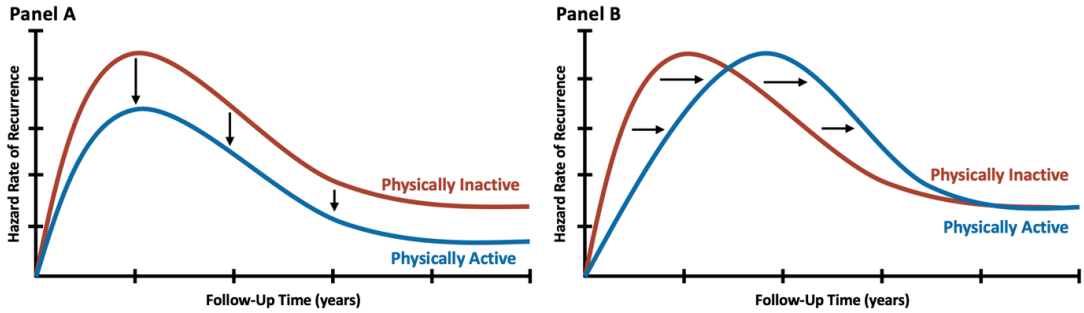
Supplementary Figure 1. Graphical sketch of confounder-adjusted hazard rates by physical activity category. In Panel A, the hazard rate of cancer recurrence in the physically active group (blue line) is never higher than in the physically inactive group (red line), and the lines remain separated during follow-up. Panel A is consistent with the hypothesis that physical activity prevents cancer recurrence. In Panel B, the hazard rate of recurrence is initially higher in the physically inactive group, but with advancing time, the hazard rate of the physically active group becomes higher, and the lines eventually converge during follow-up. Panel B is consistent with the hypothesis that physical activity delays cancer recurrence.



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Supplementary Table 1. Association of physical activity with time to cancer recurrence

Physical Activity Volume (MET-h/wk)	1-y Recurrence Rate (95% CI)[a,b]	2-y Recurrence Rate (95% CI)[a,b]	3-y Recurrence Rate (95% CI)[a,b]	5-y Recurrence Rate (95% CI)[a,b]	Hazard Ratio (95% CI)[a]
<9.0	6.7 (4.8, 9.5)	13.1 (9.5, 18.3)	19.3 (14.0, 26.8)	31.5 (22.8, 44.2)	1.00–Reference
≥9.0	4.4 (3.1, 6.0)	8.5 (6.1, 11.5)	12.5 (9.1, 16.9)	20.4 (14.8, 27.6)	0.65 (0.49, 0.82)
Absolute Risk Difference[c]	2.3 (0.1, 4.5)	4.6 (1.7, 7.5)	6.8 (3.3, 10.2)	11.1 (7.0, 15.2)	—
P[d]	0.040	0.002	<0.001	<0.001	<0.001
NNT[e]	44 (22, 1000)	22 (13, 59)	15 (10, 30)	9 (7, 14)	—

Abbreviations: MET-h/wk, metabolic equivalent total physical activity energy expenditure; y, year; NNT, number needed to treat

[a]Adjusted for age, sex, race, extent of invasion through the bowel wall, nodal stage, tumor location, ECOG performance status, low dose aspirin use, smoking history, body mass index (time-varying), western dietary pattern (time-varying), prudent dietary pattern (time-varying), chemotherapy randomization, and pharmacotherapy randomization. Continuous covariates were modeled linearly, and categorical covariates were modeled using the categories presented in Table 1.

[b]Covariates for predicting recurrence rates were set to the mean of the study population for continuous variables and most common categories for categorical variables.

[c]95% confidence intervals were calculated via the bootstrap method with 1,0000 replicates.

[d]P values are two-sided.

[e]The number needed to treat (NNT) was calculated as 1/Absolute Risk Difference. The NNT quantifies the number of patients who would need to be become physically active to prevent one cancer recurrence.

Supplementary Table 2. Model performance between the flexible parametric model with Weibull distribution and Cox proportional hazards model

	Akaike Information Criterion (AIC)		Bayesian Information Criterion (BIC)	
Endpoint	**Weibull**	**Cox**	**Weibull**	**Cox**
Disease-Free Survival	3177	6384	3303	6462
Time to Cancer Recurrence	2843	5551	2968	5626
Overall Survival	2308	3932	2434	4001

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