The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 3, 2025 VOL. 393 NO. 1

Structured Exercise after Adjuvant Chemotherapy for Colon Cancer

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ABSTRACT

BACKGROUND

Preclinical and observational studies suggest that exercise may improve cancer outcomes. However, definitive level 1 evidence is lacking.

METHODS

In this phase 3, randomized trial conducted at 55 centers, we assigned patients with resected colon cancer who had completed adjuvant chemotherapy to participate in a structured exercise program (exercise group) or to receive health-education materials alone (health-education group) over a 3-year period. The primary end point was disease-free survival.

RESULTS

From 2009 through 2024, a total of 889 patients underwent randomization to the exercise group (445 patients) or the health-education group (444 patients). At a median follow-up of 7.9 years, disease-free survival was significantly longer in the exercise group than in the health-education group (hazard ratio for disease recurrence, new primary cancer, or death, 0.72; 95% confidence interval [CI], 0.55 to 0.94; P=0.02). The 5-year disease-free survival was 80.3% in the exercise group and 73.9% in the health-education group (difference, 6.4 percentage points; 95% CI, 0.6 to 12.2). Results support longer overall survival in the exercise group than in the health-education group (hazard ratio for death, 0.63; 95% CI, 0.43 to 0.94). The 8-year overall survival was 90.3% in the exercise group and 83.2% in the health-education group (difference, 7.1 percentage points; 95% CI, 1.8 to 12.3). Musculoskeletal adverse events occurred more often in the exercise group than in the health-education group (in 18.5% vs. 11.5% of patients).

CONCLUSIONS

A 3-year structured exercise program initiated soon after adjuvant chemotherapy for colon cancer resulted in significantly longer disease-free survival and findings consistent with longer overall survival. (Funded by the Canadian Cancer Society and others; CHALLENGE ClinicalTrials.gov number, NCT00819208.)

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This article was published on June 1, 2025, at NEJM.org.

N Engl J Med 2025;393:13-25.
DOI: 10.1056/NEJMoa2502760

CME

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Colorectal cancer is the third most common cancer and second leading cause of cancer-related death worldwide.[1] Standard management of stage III or high-risk stage II colon cancer includes surgery followed by 3 to 6 months of FOLFOX (5-fluorouracil and oxaliplatin), CAPOX (capecitabine and oxaliplatin), or monotherapy fluoropyrimidine. Despite these treatments, recurrent disease develops in 20 to 40% of the patients.[2] Moreover, surgery and adjuvant chemotherapy for colon cancer cause side effects that undermine quality of life and reduce physical functioning.[3,4] Interventions that improve both survival and quality of life in this patient population are needed.

Preclinical studies have shown that exercise can reduce the growth of cancer,[5] including colon cancer.[6,7] In addition, observational studies have shown that patients with colorectal cancer who perform an increased amount of recreational physical activity after treatment have a lower risk of cancer recurrence and death,[8] including those with stage III colon cancer.[9,10] Possible mechanisms for these associations include the effects of exercise on metabolic growth factors, inflammation, and immune function.[11] Although these findings are suggestive of an exercise-related survival benefit, results are inconclusive, given the methodologic limitations of observational designs.[8]

To address this research gap, the Canadian Cancer Trials Group (CCTG) launched the CO.21 Colon Health and Lifelong Exercise Change (CHALLENGE) trial,[12,13] a phase 3 randomized trial comparing the effects of providing health-education materials alone or such materials plus a 3-year structured exercise program in patients with colon cancer who had completed adjuvant chemotherapy. We previously reported the feasibility of a change in exercise behavior in the trial.[14] Here, we report the final results regarding disease-free survival (the primary end point) and the key secondary end points of overall survival, patient-reported physical functioning, objective physical functioning and fitness, and recreational moderate-to-vigorous physical activity.

Methods

Patients

Patients were eligible for the trial if they had complete resection of stage III or high-risk stage II adenocarcinoma of the colon (with the latter defined as a T4 tumor with resection of fewer than 12 lymph nodes and poorly differentiated histologic findings). All the patients also had completed adjuvant chemotherapy within the past 2 to 6 months, had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a 5-point scale, with higher numbers reflecting greater disability), reported that they were currently exercising less than the equivalent of 150 minutes per week of moderate-to-vigorous intensity,[15] and were able to complete at least two stages of a submaximal treadmill test (walking at a casual pace for 6 minutes) or the 6-minute walk test. Full eligibility criteria are described in the trial protocol, available with the full text of this article at NEJM.org.

Trial Design and Treatments

Eligible patients were stratified according to trial center, disease stage, body-mass index (≤27.5 or >27.5, calculated as the weight in kilograms divided by the square of the height in meters), and ECOG performance-status score (0 or 1) before being randomly assigned in a 1:1 ratio to participate in a structured exercise program (exercise group) or to receive health-education materials only (health-education group) with the use of a dynamic minimization procedure.

Patients in the health-education group received general health-education materials promoting physical activity and healthy nutrition in addition to standard surveillance. Those in the exercise group received the same materials plus an exercise guidebook developed for colon cancer survivors[16] and support from a certified physical activity consultant for 3 years. This support program was guided by the Theory of Planned Behavior[17] and consisted of 17 evidence-based techniques for behavioral change[14] delivered over three phases. In the first 6 months of the program (phase 1), patients attended a total of 12 mandatory, in-person behavioral-support sessions scheduled every 2 weeks, combined with 12 mandatory supervised exercise sessions plus 12 recommended supervised exercise sessions during alternate weeks. During the second 6 months (phase 2), patients attended 12 mandatory behavioral-support sessions (either in person or remotely by telephone or video) every 2 weeks combined with a supervised exercise session if the patient attended in person. During the last 2 years (phase 3), pa-

tients attended 24 mandatory monthly in-person or remote behavioral-support sessions combined with a supervised exercise session if the patient attended in person.

The goal of the exercise program was to increase recreational aerobic exercise from baseline by at least 10 metabolic equivalent task (MET)–hours per week during the first 6 months and then to maintain or further increase the amount during the final 2.5 years. The focus was on promoting aerobic exercise of at least moderate intensity, such as brisk walking, which has an intensity of approximately 4 METs. (MET values indicate the intensity of the activity, not time. Brisk walking for an hour has a value of 4 MET-hours.) However, patients could choose the type, frequency, intensity, and duration of aerobic exercise. Additional details regarding the exercise program have been reported previously[14] and are provided in the Supplementary Appendix, available at NEJM.org.

EXERCISE ASSESSMENTS

We assessed recreational physical activity over the past month at baseline and every 6 months during the intervention using the Total Physical Activity Questionnaire.[18] We calculated moderate-to-vigorous physical activity on the basis of activities with MET values of 3 or more. Cardiorespiratory fitness, body weight and circumferences, and objective physical functioning were assessed at baseline, at 6 months, and at 1, 2, and 3 years. We assessed cardiorespiratory fitness using a submaximal, multistage, modified Balke treadmill protocol[19] with a validated formula to predict the maximum volume of oxygen consumption.[20] Waist and hip circumferences were determined with the use of an anthropometric measuring tape.[21] Objective physical functioning was assessed with the Seniors' Fitness Test, which includes a 6-minute walk test.[22] Physical activity and fitness assessments were discontinued in patients who had a disease event.

EFFICACY ASSESSMENTS

Disease-free survival (the primary end point) was assessed in the intention-to-treat population and was defined as the time from randomization to the first event that was either recurrent (local or distant) colon cancer, a new primary colorectal cancer, a second primary cancer, or death from any cause.[23] Overall survival was defined as the time from randomization to death from any cause. The prespecified quality-of-life outcome of interest — physical functioning, as reported by the patient — was assessed according to the physical-functioning subscale on the 36-Item Short Form (SF-36) survey[24] every 6 months during the intervention and at years 4 and 5. Patients who had a disease event were included in this assessment. Higher scores on the physical-functioning subscale indicate better functioning. Adverse events were monitored for 36 months after randomization with the use of the Common Terminology Criteria for Adverse Events, version 3.0, with data reported for the patients according to the intervention they actually received (as-treated population). Musculoskeletal adverse events were of special interest in this assessment.

OVERSIGHT

The trial was led by the CCTG and conducted in accordance with the provisions of the Declaration of Helsinki and the International Council for Harmonisation guidelines for Good Clinical Practice. The trial was funded by the Canadian Cancer Society, the Australian National Health and Medical Research Council, and Cancer Research UK. The protocol and subsequent amendments were developed by the CCTG and approved by the research ethics board at each participating institution. The CCTG was responsible for the collection, maintenance, and analysis of the data. International cooperative groups were responsible for regulatory submissions and for the conduct and monitoring of the trial within their own jurisdictions. An independent data and safety monitoring committee confidentially reviewed data biannually.

All the authors contributed to the writing of the manuscript and the decision to submit the manuscript for publication and vouch for the accuracy and completeness of the reported data and adherence to the protocol. There were no confidentiality agreements between the authors and their affiliated institutions or trial sponsors.

STATISTICAL ANALYSIS

The trial was designed to detect a hazard ratio of 0.75 for disease-free survival, corresponding to an increase in 3-year disease-free survival from an expected 75% in the health-education group to 80.6% in the exercise group. A total of 380 events of disease recurrence, new primary cancer, or

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Exercise Group (N = 445)	Health-Education Group (N = 444)	All Patients (N = 889)
Age			
Median (range) — yr	61 (26–84)	61 (19–83)	61 (19–84)
≥65 yr — no. (%)	150 (33.7)	155 (34.9)	305 (34.3)
Female sex — no. (%)	233 (52.4)	224 (50.5)	457 (51.4)
Geographic region — no. (%)			
Canada	270 (60.7)	273 (61.5)	543 (61.1)
Australia	146 (32.8)	146 (32.9)	292 (32.8)
Other†	29 (6.5)	25 (5.6)	54 (6.1)
Median weight (IQR) — kg	80.7 (69.1–95.6)	81.9 (70.0–96.7)	81.2 (69.5–96.2)
Median body-mass index (IQR)‡	28.5 (25.4–32.6)	28.6 (25.3–32.4)	28.5 (25.4–32.5)
Obesity — no. (%)	169 (38.0)	167 (37.6)	336 (37.8)
ECOG performance-status score — no. (%)§			
0	323 (72.6)	324 (73.0)	647 (72.8)
1	122 (27.4)	120 (27.0)	242 (27.2)
Smoking status — no. (%)			
Current	26 (5.8)	16 (3.6)	42 (4.7)
Ever smoked	206 (46.3)	211 (47.5)	417 (46.9)
Major medical problem — no. (%)	263 (59.1)	258 (58.1)	521 (58.6)
Hypertension	103 (23.1)	114 (25.7)	217 (24.4)
High cholesterol level¶	57 (12.8)	74 (16.7)	131 (14.7)
Diabetes or hyperglycemia	47 (10.6)	52 (11.7)	99 (11.1)
Cardiac history	36 (8.1)	42 (9.5)	78 (8.8)
Depression or anxiety	36 (8.1)	37 (8.3)	73 (8.2)
Disease stage — no. (%)			
High-risk stage II adenocarcinoma	43 (9.7)	44 (9.9)	87 (9.8)
Stage III adenocarcinoma	402 (90.3)	400 (90.1)	802 (90.2)
Clinical tumor stage — no. (%)			
T1	26 (5.8)	28 (6.3)	54 (6.1)
T2	42 (9.4)	54 (12.2)	96 (10.8)
T3	273 (61.3)	246 (55.4)	519 (58.4)
T4	104 (23.4)	116 (26.1)	220 (24.7)
Chemotherapy regimen — no. (%)			
FOLFOX	267 (60.0)	275 (61.9)	542 (61.0)
CAPOX	58 (13.0)	71 (16.0)	129 (14.5)
Capecitabine	76 (17.1)	74 (16.7)	150 (16.9)
Other	44 (9.9)	24 (5.4)	68 (7.6)
Treatment history			
Median interval from diagnosis to trial randomization (IQR) — yr	0.9 (0.8–1.1)	1.0 (0.9–1.1)	1.0 (0.8–1.1)
Median interval from chemotherapy to trial randomization (IQR) — mo	3.9 (3.1–5.3)	3.9 (3.1–5.2)	3.9 (3.1–5.3)

Table 1. (Continued.)

Characteristic	Exercise Group (N = 445)	Health-Education Group (N = 444)	All Patients (N = 889)
History of recreational physical activity			
Moderate-to-vigorous physical activity — MET-hr/wk‖	12.8±18.4	10.2±15.0	11.5±16.8
Median predicted maximum volume of oxygen consumption (IQR) — ml/kg/min	31.0 (24.7–36.7)	30.7 (24.3–37.1)	30.7 (24.3–37.1)
Median 6-minute walk distance (IQR) — m	530 (465–584)	530 (466–591)	530 (466–591)
Median physical-function score on SF-36 (IQR)**	80.0 (65.0–94.4)	85.0 (65.0–95.0)	85.0 (65.0–95.0)

* Plus–minus values are means ±SD. CAPOX denotes capecitabine and oxaliplatin, FOLFOX fluorouracil, leucovorin, and oxaliplatin, and IQR interquartile range.
† Other sites were located in the United Kingdom (5 sites with 30 patients), France (1 site with 10 patients), the United States (3 sites with 9 patients), and Israel (1 site with 5 patients).
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The Eastern Cooperative Oncology Group (ECOG) performance-status scale ranges from 0 (fully active) to 5 (death).
¶ The cholesterol level was considered to be high according to local institutional criteria.
‖ Moderate-to-vigorous physical activity was evaluated on the basis of activities with metabolic equivalent task (MET) values of 3 or more (e.g., brisk walking).
** Scores on the 36-Item Short Form Survey (SF-36) range from 0 to 100, with higher scores indicating better functioning.

death would provide a power of 80% to determine a two-sided alpha value of 0.05. It was anticipated that 962 patients would undergo randomization during a 3-year period and that the required number of events would be observed 4 to 5 years after the last patient had been randomly assigned. Four interim analyses were planned: one assessing the feasibility of recruitment of patients to the trial, one assessing the feasibility of a change in exercise behavior, and two assessing the efficacy of the intervention after the occurrence of approximately one third of the target number of events (in 125 patients) and the occurrence of approximately two thirds of the target number (in 250 patients).

The feasibility of change in exercise behavior was confirmed in May 2015, and these results were published with permission of the data and safety monitoring committee.[14] The first interim efficacy analysis was completed in November 2019, when the committee recommended that the trial continue. However, because of slow recruitment and a lower-than-expected pooled-event rate (which suggested that both the second interim and final efficacy analyses would be considerably delayed), the committee approved a request from the trial committee to set an accrual deadline of December 31, 2023, and a target for declaring a clinical data-cutoff date for the final statistical analysis by the end of 2024, conditional on the occurrence of at least 200 confirmed events. With at least 200 events in the final analysis, the trial would have a power of 80% to detect a hazard ratio of 0.67 (corresponding to an increase in 3-year disease-free survival from 75% in the health-education group to 82.5% in the exercise group) at a two-sided 0.05 level. Registration of patients stopped on December 21, 2023, and the final patient underwent randomization on January 24, 2024. A clinical data-cutoff date was declared on August 29, 2024, with 224 events confirmed, and a corresponding final analysis was performed on a locked database on January 24, 2025.

We summarized time-to-event variables using Kaplan–Meier plots and descriptive estimates at 5 and 8 years, respectively, for disease-free survival and overall survival. Survival was compared between intervention groups primarily by a two-sided log-rank test with adjustment for stratification factors assessed at the time of randomization except for the trial center. The annual incidence of events was calculated by dividing the observed number of events by person-years of follow-up. Methods for the analysis of the repeated measurements of moderate-to-vigorous physical activity, predicted maximum volume of oxygen

consumption, 6-minute walk distance, and the SF-36 physical-functioning subscale are detailed in the Supplementary Appendix. All reported 95% confidence intervals are two-sided. The widths of the confidence intervals for secondary end points have not been adjusted for multiplicity and thus may not be used in place of hypothesis testing.

RESULTS

PATIENTS

Between 2009 and 2024, a total of 889 patients at 55 sites (mostly in Canada and Australia) were randomly assigned to the exercise group (445 patients) or to the health-education group (444 patients) (Fig. S1 in the Supplementary Appendix). The median age of the patients was 61 years (range, 19 to 84), 51% were women, 90% had stage III disease, and 61% had received FOLFOX treatment (Table 1). At baseline, the patients reported participating in 11.5 MET-hours per week of moderate-to-vigorous physical activity, had a predicted maximum volume of oxygen consumption of 30.7 ml per kilogram of body weight per minute, and walked 530 m in 6 minutes. The trial groups were well balanced with respect to their characteristics at baseline.

INTERVENTION ADHERENCE AND CHANGES IN PHYSICAL ACTIVITY

Adherence to the exercise program during phase 1 was 83% for the 12 mandatory behavioral-support sessions, 79% for the 12 mandatory supervised exercise sessions, and 20% for the 12 recommended supervised exercise sessions (Table 2). During phase 2, adherence was 68% for the 12 mandatory behavioral-support sessions and 54% for the 12 recommended supervised exercise sessions. During phase 3, adherence was 63% for the 24 mandatory behavioral-support sessions and 44% for the 24 recommended supervised exercise sessions.

Completion rates for the measures of physical activity and fitness were similar in the exercise group and the health-education group: 94 to 99% at baseline and 54 to 63% at 36 months (Table S1). Least-square-mean estimates from a regression model for repeated measurements (including a term of interaction between time and intervention) indicated that the patients in the exercise group achieved and maintained larger improvements than those in the health-education group over the entire 3-year intervention with respect to moderate-to-vigorous physical activity (between-group differences ranging from 5.2 to 7.4 MET-

Table 2. Adherence to the Structured Exercise Program.*

Component of Exercise Program	Phase 1†	Phase 2‡	Phase 3§			
	1–6 Months	7–12 Months	13–18 Months	19–24 Months	25–30 Months	31–36 Months
Patient was eligible to receive intervention — no. (%)¶	445 (100)	414 (93)	388 (87)	373 (84)	354 (80)	343 (77)
Attendance at mandatory behavioral-support sessions — %	83±28	68±37	71±41	64±43	59±44	59±45
Attendance at mandatory supervised exercise sessions — %‖	79±32	NA	NA	NA	NA	NA
Attendance at recommended supervised exercise sessions — %	20±32	54±41	52±45	46±45	40±45	38±45

* Plus–minus values are means ±SD.
† Phase 1 consisted of a total of 12 mandatory in-person behavioral-support sessions schedule every 2 weeks combined with 12 mandatory supervised exercise sessions plus 12 recommended supervised exercise sessions during alternate weeks.
‡ Phase 2 consisted of a total of 12 mandatory in-person or remote behavioral-support sessions scheduled every 2 weeks. If the behavioral-support session was in person, a supervised exercise session was strongly recommended.
§ Phase 3 consisted of a total of 24 mandatory monthly in-person or remote behavioral-support sessions (reported every 6 months). If the behavioral-support session was in person, a supervised exercise session was strongly recommended. Additional behavioral-support or supervised exercise sessions could be added at the discretion of the physical activity consultant and patient.
¶ Patients were eligible to receive the intervention if they had not had a cancer recurrence or new primary cancer during that phase.
‖ Data for phase 2 and phase 3 were not applicable (NA) because supervised exercise sessions were not mandatory after the first 6 months.

hours per week), predicted maximum volume of oxygen consumption (between-group difference, 1.3 to 2.7 ml per kilogram per minute), and 6-minute walk distance (between-group difference, 13 to 30 m) (Fig. 1 and Table S3.1). Minimal between-group differences were observed for body weight and waist circumference (Fig. S2). The use of aspirin was similar in the exercise group and the health-education group (13.7% vs. 16.4%) during the intervention.

EFFICACY

At a median follow-up of 7.9 years, disease recurrence, new primary cancer, or death had occurred in 224 patients (93 in the exercise group and 131 in the health-education group), and 107 had died from any cause (41 in the exercise group and 66 in the health-education group) (Table 3). Disease-free survival was significantly longer in the exercise group than in the health-education group (hazard ratio for disease recurrence, new primary cancer, or death, 0.72; 95% confidence interval [CI], 0.55 to 0.94; P=0.02) (Fig. 2A), with an annual incidence of recurrence, new primary cancer, or death of 3.7% (95% CI, 3.0 to 4.5) in the exercise group and 5.4% (95% CI, 4.5 to 6.4) in the health-education group. The 5-year disease-free survival was 80.3% in the exercise group and 73.9% in the health-education group (difference, 6.4 percentage points; 95% CI, 0.6 to 12.2). In prespecified subgroup analyses, the hazard ratios for disease-free survival varied among the subgroups but were 0.87 or less in all subgroups and 0.76 or less in 20 of 22 subgroups (Fig. S3A).

Results support longer overall survival in the exercise group than in the health-education group (hazard ratio for death, 0.63; 95% CI, 0.43 to 0.94) (Fig. 2B), with an annual incidence of death of 1.4% (95% CI, 1.0 to 1.8) in the exercise group and 2.3% (95% CI, 1.7 to 2.8) in the health-education group. The 8-year overall survival was 90.3% in the exercise group and 83.2% in the health-education group (difference, 7.1 percentage points; 95% CI, 1.8 to 12.3). Prespecified subgroup analyses indicated that the hazard ratios for overall survival varied among the subgroups but were 0.84 or less in all subgroups and 0.76 or less in 21 of 22 subgroups (Fig. S3B).

PATIENT-REPORTED PHYSICAL FUNCTIONING

Completion rates for the SF-36 survey were similar in the two trial groups and exceeded 96% at baseline and 78% at 36 months (Table S2). Least-squares estimates that were calculated from a regression model for repeated measurements (including a term of interaction between time and intervention) indicated that patients in the exercise group reported having larger improvements from baseline on the physical-functioning subscale than did those in the health-education group at 6 months (7.1 vs. 1.3), 1 year (6.8 vs. 3.3), 18 months (7.2 vs. 2.4), 2 years (6.1 vs. 2.6), and 3 years (6.1 vs. 3.0) (Fig. 1D and Table S3.1). A reduced model without interaction showed an improvement associated with exercise over health education alone on the physical-functioning subscale over time, which was confirmed by a sensitivity analysis based on multiple imputation with the use of a pattern mixture model (Table S3.2).

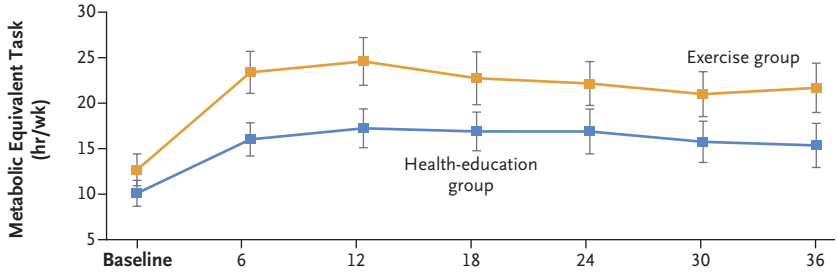
SAFETY

The as-treated safety analyses included 428 patients who had been randomly assigned to the exercise group and had participated in at least one exercise session and 461 patients who had been randomly assigned to the health-education group (444 patients) or to the exercise group but had not participated in any exercise sessions (17 patients) (Table S4). At least one adverse event of any grade occurred during the intervention in 351 patients (82.0%) in the exercise group and in 352 patients (76.4%) in the health-education group. Musculoskeletal adverse events occurred in 79 patients (18.5%) in the exercise group and in 53 (11.5%) in the health-education group. Of the 79 musculoskeletal adverse events in the exercise group, 8 (10%) were considered to be related to the exercise intervention. A grade 3 or higher adverse event was reported by 66 patients (15.4%) in the exercise group and by 42 patients (9.1%) in the health-education group.

DISCUSSION

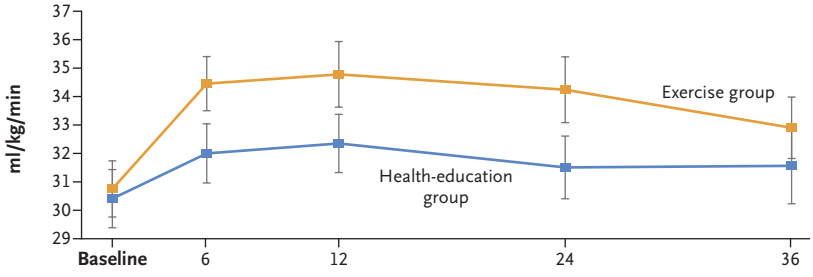
Observational studies report consistent associations between self-reported postdiagnosis physical activity and colorectal cancer outcomes. In a recent systematic review and meta-analysis,[8] the

A Recreational Moderate-to-Vigorous Physical Activity



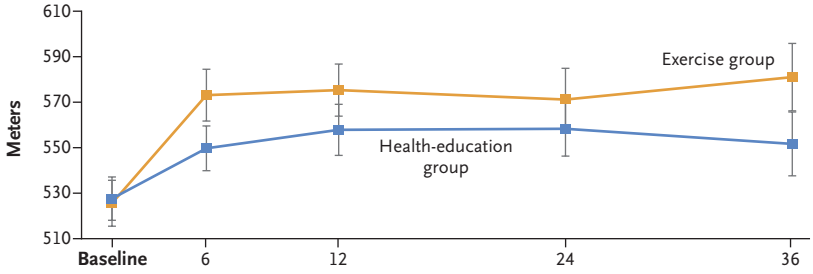
No. of Patients							
Exercise group	420	380	353	310	296	258	250
Health-education group	420	369	341	297	279	252	227

B Predicted Maximum Volume of Oxygen Consumption



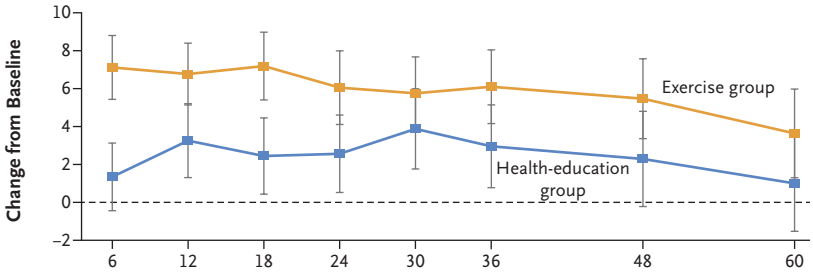
No. of Patients					
Exercise group	386	321	282	215	186
Health-education group	371	282	251	206	162

C 6-Minute Walk Distance



No. of Patients					
Exercise group	422	366	313	250	210
Health-education group	425	331	299	236	186

D SF-36 Physical-Functioning Subscale



No. of Patients								
Exercise group	383	366	333	317	286	278	250	224
Health-education group	370	344	312	304	278	265	237	195

Figure 1 (facing page). Measures of Physical Activity, Fitness, and Functioning.

Shown are results in the group assigned to participate in a structured exercise program (exercise group) and those assigned to receive health-education materials (health-education group) with respect to measures of recreational moderate-to-vigorous physical activity (Panel A), the predicted maximum volume of oxygen consumption (Panel B), the 6-minute walk distance (Panel C), and the physical-functioning subscale on the 36-Item Short Form Survey (SF-36) (Panel D).

highest levels of self-reported postdiagnosis recreational physical activity were associated with a lower risk of death from any cause than were the lowest activity levels in 12 studies (relative risk, 0.67; 95% CI, 0.60 to 0.75), death from colorectal cancer in 6 studies (relative risk, 0.63; 95% CI, 0.47 to 0.84), and cancer recurrence in 3 studies (relative risk, 0.80; 95% CI, 0.70 to 0.92). Despite these consistent associations, the evidence for a causal relationship between postdiagnosis recreational physical activity and recurrence of colorectal cancer or death was graded as "limited suggestive."

In this phase 3 randomized trial, we examined the effects of exercise on cancer-related survival in patients with colon cancer who had completed adjuvant chemotherapy. Exercise significantly reduced the relative risk of disease recurrence, new primary cancer, or death by 28%. The disease-free survival curves began to separate at about 1 year and continued to separate over the 10-year follow-up, with an absolute between-group difference of 6.4 percentage points at 5 years. Moreover, exercise reduced the relative risk of death by 37%. The overall survival curves began to separate at about 4 years and continued to separate over the 10-year follow-up, with an absolute between-group difference of 7.1 percentage points at 8 years. The magnitude of benefit from exercise delivered after surgery and adjuvant chemotherapy was similar to that of many currently approved standard drug treatments.

Improvement in disease-free survival from exercise was primarily driven by reductions in liver recurrence (3.6% vs. 6.5%) and new primary cancers (5.2% vs. 9.7%), particularly breast (0.4% vs. 2.7%), prostate (1.1% vs. 2.0%), and colorectal (0% vs. 1.1%) cancers. No significant differences in deaths without recurrence or without a second primary cancer (1.3% versus 1.8%) were noted, which suggests that the benefit of exercise came from improved cancer outcomes. Exercise may be an effective treatment for colon cancer micrometastases and prevention of second primary cancers through various mechanisms, including increased fluid shear stress, enhanced immune surveillance, reduced inflammation, improved insulin sensitivity, and altered microenvironment of major sites of metastases.[11,25,26] In particular, exercise may affect metabolic growth factors such as insulin and insulin-like growth factors that promote cancer-cell proliferation and progression.[27] Planned analyses of serial blood samples will address questions related to possible mechanisms.

The exercise intervention met its goal of increasing moderate-to-vigorous physical activity from baseline by about 10 MET-hours per week throughout the entire 3-year intervention. This increase is the equivalent of adding about 45 to 60 minutes of brisk walking 3 or 4 times per week or 25 to 30 minutes of jogging 3 or 4 times per week. The exercise intervention also resulted in meaningful improvements in cardiorespiratory fitness and physical functioning over the 3-year intervention, measures that are established predictors of an increased risk of death,[28-31] including in patients with cancer.[32,33] Structured exercise did not reduce body weight or waist circumference, which suggests that weight loss is an unlikely explanation for the observed effects of exercise on cancer outcomes.

Not unexpectedly, patients in the health-education group also increased their moderate-to-vigorous physical activity, cardiorespiratory fitness, and physical functioning over the 3-year intervention, albeit to a much lesser extent than those in the exercise group. The difference between the exercise group and the health-education group in recreational moderate-to-vigorous physical activity over the 3-year intervention ranged from 5.2 to 7.4 MET-hours per week, which is equivalent to about 1.5 to 2.25 hours per week more of walking at 3 mph (approximately 3.3 METs). The improvements among patients in the health-education group highlight the challenges faced in the evaluation of lifestyle interventions and raise the possibility of an even more powerful effect of exercise on cancer outcomes as compared with a completely sedentary control group.

No unexpected safety signals for the exercise intervention were observed. Musculoskeletal ad-

Table 3. Disease Recurrence, New Primary Cancer, or Death.

Event	Exercise Group (N=445)		Health-Education Group (N=444)	
	Patients with Event	Annual Event Rate	Patients with Event	Annual Event Rate
	number	*% (95% CI)*	*number*	*% (95% CI)*
Disease recurrence, new primary cancer, or death				
Any event	93	3.7 (3.0–4.5)	131	5.4 (4.5–6.4)
Recurrence*	65	2.5 (1.9–3.1)	81	3.1 (2.5–3.8)
Local colon	12		12	
Distant recurrence	58		75	
Liver	16		29	
Lung	20		19	
Peritoneum	8		9	
Lymph node	10		9	
Other	12		15	
New primary cancer*	23	0.8 (0.5–1.2)	43	1.6 (1.1–2.1)
Breast	2		12	
Prostate	5		9	
Colorectal	0		5	
Other	17		17	
Death without recurrence or new primary cancer	6	0.2 (0.0–0.4)	8	0.3 (0.1–0.5)
Patients with censored data regarding disease recurrence, new primary cancer, or death	352	13.7 (12.2–15.1)	313	12.8 (11.4–14.2)
Cancer at baseline	10		7	
Consent withdrawal	18		13	
Loss to follow-up	6		6	
Alive without recurrence or new primary cancer	318		287	
Death				
From any cause	41	1.4 (1.0–1.9)	66	2.3 (1.7–2.9)
Colon cancer	31		48	
Other primary cancer	2		8	
Other condition or circumstance	8		10	
Patients with censored data regarding death	404	13.9 (12.6–15.3)	378	13.1 (11.8–14.5)
Consent withdrawal	22		16	
Loss to follow-up	8		6	
Still alive	374		356	

* Patients may have had more than one site of recurrence or new primary cancer.

verse events occurred more often in the exercise group than in the health-education group (19% vs. 12%); however, such events are a well-documented risk of exercise[34] that can be managed by individualized exercise prescription. Moreover, patient-reported physical functioning improved in the exercise group as compared with the health-education group across most of the 3-year intervention. Numerous randomized trials have shown the benefits of exercise on outcomes reported by patients with cancer.[35] However, evidence in patients with colon cancer has come primarily from

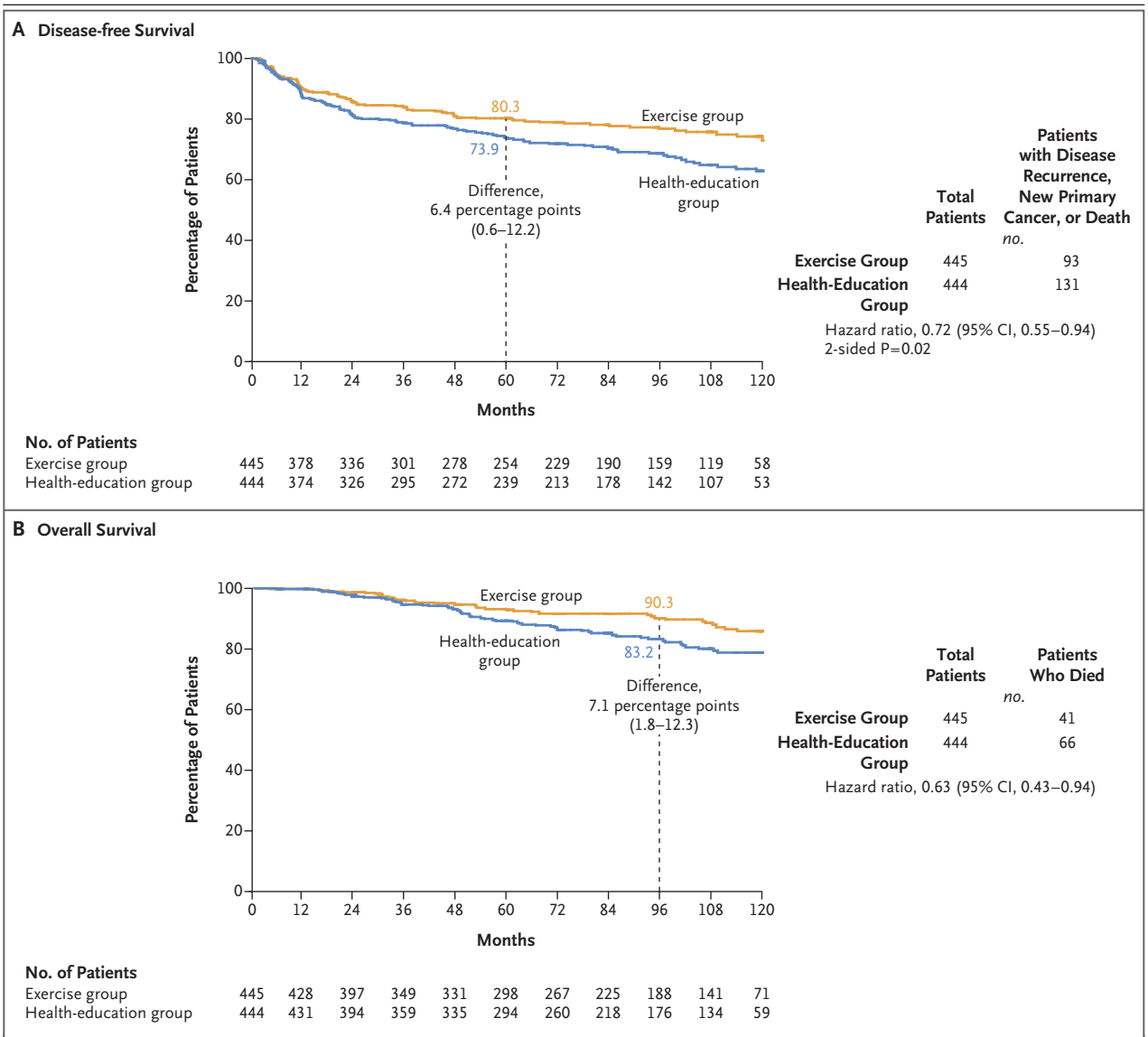


Figure 2. Disease-free and Overall Survival (Intention-to-Treat Population).

Shown is the probability of disease-free survival according to investigator assessment (Panel A) and overall survival (Panel B) in the exercise group and the health-education group.

small pilot studies with short follow-up.[36] Planned analyses of additional patient-reported outcomes will provide more detailed evidence regarding quality-of-life effects.

Our trial has some limitations. The recruitment of patients was slow and spanned a 15-year period. However, during that time, the only change in standard treatment was from 6 months to 3 months of FOLFOX or CAPOX therapy. A total of 92.4% of our planned sample (889 of 962 patients) underwent randomization, but we observed only 58.9% of our targeted number of events (224 of 380 events). The 3-year disease-free survival was higher than expected, probably because of a selection bias toward higher-functioning patients but also because of the timing of our intervention. We enrolled patients 2 to 6 months after they had undergone chemotherapy, so we excluded patients with recurrences during the first year after diagnosis who were likely to have had more biologically aggressive disease. Whether initiating an exercise intervention earlier in the treatment tra-

jectory (e.g., before surgery or during chemotherapy) would further improve cancer outcomes remains to be determined.

The patients in the exercise group also received more social contacts with physical activity consultants than those in the health-education group, so we cannot completely rule out benefits related to social interaction. Nevertheless, previous oncology trials involving group psychosocial support[37] and nutrition interventions[38-40] have also provided substantially more contacts to intervention patients but did not report a survival benefit. Moreover, we did not track the number of patients with Lynch syndrome who would have been at higher risk for second primary cancers; however, randomization would be expected to balance groups with respect to such deleterious genetic mutations. Finally, we relied on patients' retrospective recall of moderate-to-vigorous physical activity over the past month, a procedure that has known limitations. However, we confirmed the self-reported increases in physical activity with improvements in objective cardiorespiratory fitness and physical functioning.

In our trial, we found that a 3-year structured exercise program that was initiated within 6 months after the completion of adjuvant chemotherapy for colon cancer improved disease-free survival. The intervention also resulted in findings that were consistent with improved overall survival, patient-reported physical functioning, and objective physical functioning and fitness as compared with health education alone, with only a modest increase in musculoskeletal adverse events. Our trial provides robust evidence of a substantial benefit-to-harm ratio in favor of structured exercise over a sedentary lifestyle and supports its incorporation into standard care. Knowledge alone, however, is unlikely to change patient behavior and outcomes. To achieve meaningful increases in exercise will require that health systems invest in behavior-support programs.

Supported by the Canadian Cancer Society, the Australian National Health and Medical Research Council, and Cancer Research UK.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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