Original Study

# Dose-response Effects of Aerobic Exercise Among Colon Cancer Survivors: A Randomized Phase II Trial

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## Abstract

**Postdiagnosis physical activity is associated with a lower risk of disease recurrence among survivors of colon cancer. Thirty-nine stage I to III survivors of colon cancer were randomized to usual-care control, 150 minutes per week, or 300 minutes per week of aerobic exercise for 6 months. Exercise was feasible, well-tolerated, and elicited changes in physiologic markers associated with disease recurrence. This study informs future phase II/III trials.**

**Background:** Observational studies suggest that higher volumes of physical activity are associated with a lower risk of disease recurrence among survivors of colon cancer. However, the feasibility and safety of prescribing higher volumes of physical activity to survivors of colon cancer are unknown. Furthermore, the pathways through which exercise may reduce disease recurrence are unknown. **Patients and Methods:** Survivors of stage I to III colon cancer were randomized to usual-care control, 150 minutes per week of aerobic exercise (low-dose), or 300 minutes per week of aerobic exercise (high-dose). Changes in soluble intercellular adhesion molecule-1 and vascular adhesion molecule-1 prognostic biomarkers were examined. **Results:** From January 2015 to February 2016, 39 patients were enrolled (n = 13 usual-care control; n = 14 low-dose; n = 12 high-dose), and 38 participants completed the study (97% follow-up). Over 6 months, the low-dose group completed 142 minutes per week (92.8% adherence), and the high-dose group completed 247 minutes per week (89.0% adherence) of exercise. Compared with the control group, changes in soluble intercellular adhesion molecule-1 were −134.9 ng/mL (95% confidence interval, −238.1 to −31.6 ng/mL) in the low-dose group and −114.8 ng/mL (95% confidence interval, −222.5 to −7.1 ng/mL) in the high-dose group (linear $P_{trend}$ = .023; nonlinear $P_{trend}$ = .044). No changes were observed for soluable vascular adhesion molecule-1 (linear $P_{trend}$ = .791; nonlinear $P_{trend}$ = .604). Non-serious adverse events occurred at similar rates among randomized groups. No serious adverse events occurred. **Conclusion:** Higher volumes of moderate-intensity aerobic exercise, up to 300 minutes per week, are feasible, safe, and elicit favorable changes in prognostic biomarkers among patients recently treated for stage I to III colon cancer. These data can be used to guide clinical recommendations for patients, and inform future trials.

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## Introduction

Approximately 1 million people are diagnosed with colon cancer each year worldwide.[1] Three-quarters of patients are diagnosed with disease that is localized to the primary site (stage I-II) or spread to regional lymph nodes (stage III). Despite surgical resection, either alone or in combination with adjuvant chemotherapy, 5-year disease recurrence rates for stage I, II, and III colon cancer are 10%, 20%, and 30% to 50%, respectively.[2-4] Consequently, there exists a need to identify additional adjuvant therapies that reduce the risk of recurrent disease in this population.

The prescription of physical activity or exercise is a potential adjuvant therapy that has been reported by prospective cohort studies to be associated with a reduction in the risk of recurrence and death among colon cancer survivors.[5-7] The relationship between physical activity and disease outcomes is independent of known prognostic factors, and occurs in a dose-response fashion,[8] such that larger volumes of physical activity or exercise, up to 300 minutes per week, are associated with a lower risk of recurrence and premature mortality.[5-7]

However, it is unknown if doses of exercise as large as 300 minutes per week are behaviorally feasible and have tolerable safety profiles for survivors of colon cancer when compared with smaller doses of exercise, such as 150 minutes per week as is currently recommended by various professional organizations including the National Comprehensive Cancer Network.[9-11] The FITT-VP principle is the cornerstone of exercise prescription by specifying the frequency, intensity, time, type, volume, and progression of exercise that is appropriate to achieve a desired health outcome.[12] Prior trials of exercise among survivors of colon cancer have not fully described FITT-VP principles, which may limit the specificity of guidance that oncology providers can offer to patients.[13] In addition, the safety profile of exercise among survivors of colon cancer has not been characterized.[14] These limitations may hinder the prescription of exercise as an adjuvant therapy in clinical practice.[15] Furthermore, the biological pathways through which exercise may reduce the risk of disease recurrence and premature mortality among survivors of colon cancer are unknown. Soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular adhesion molecule-1 (sVCAM-1) are endothelial cell-adhesion molecules that promote the growth of existing micro-metastases and the formation of new micro-metastases.[16] Concentrations of sICAM-1 and sVCAM-1 increase with disease stage,[17,18] and elevated concentrations of sICAM-1 and sVCAM-1 are independently associated with disease recurrence and premature death among survivors of colon cancer.[17-21] sICAM-1 and sVCAM-1 have been recommended as therapeutic targets[22,23] and represent novel pathways through which exercise may reduce the risk of disease recurrence among survivors of colon cancer.

The COURAGE trial was a randomized controlled trial with the primary objectives to test the feasibility, safety, and biological efficacy of 2 distinct doses of aerobic exercise compared with a usual-care control group among patients with stage I to III colon cancer.[24] Our primary hypotheses were that both doses of exercise would be feasible and safe, and that exercise would induce dose-dependent improvements in sICAM-1 and sVCAM-1.

## Materials and Methods

### *Study Design and Patients*

The COURAGE trial was a single-center, phase II, randomized, 3-arm dose-response exercise trial. Detailed methods for the COURAGE trial have been published.[24] Patients were eligible if they were diagnosed with stage I to III colon cancer; completed surgical resection and adjuvant chemotherapy within 36 months of entering the study; self-reported $<$ 150 minutes per week of moderate or vigorous intensity physical activity using the Paffenbarger Physical Activity Questionnaire[25]; age $\geq$ 18 years; provided written physician approval; had no additional surgery planned within the 6-month intervention period; and had the ability to walk unaided for 6 minutes. Patients were ineligible if they had a history of another primary cancer (other than nonmelanoma skin cancer); had evidence of distant metastatic disease; were pregnant or breast feeding; were unable to provide a baseline blood sample; had a myocardial infarction or coronary revascularization procedure within the past 3 months; had uncontrolled hypertension; had high-risk or uncontrolled cardiac arrhythmias; had clinically significant heart valve disease; had decompensated heart failure; had a known aortic aneurysm; or had any other condition which, in the opinion of the investigator, may impede testing of study hypotheses or make it unsafe to engage in the exercise program. All participants provided written informed consent.

### *Randomization and Blinding*

Participants were randomly allocated to 1 of 3 groups: usual-care control, low-dose aerobic exercise (150 minutes per week), or high-dose aerobic exercise (300 minutes per week). Randomization was stratified by cancer stage. Participants were not blinded to treatment assignment. Outcome measures were obtained by assessors blinded to treatment assignment.

### *Exercise Treatment Plan*

Aerobic exercise was performed for 6 months using study-provided in-home treadmills (LifeSpan Fitness, TR1200i, Salt Lake City, UT). Participants were provided with a heart rate monitor to objectively record heart rate during each exercise session (Polar Electro Inc, RS400, Lake Success, NY). The heart rate monitors had sufficient memory to record 8 to 12 weeks of exercise using a 1-minute epoch. Participants also completed exercise logs to record the date, time, average heart rate, and exercise duration. Participants met with a clinical exercise physiologist to introduce the exercise prescription, and familiarize the participant with use of the treadmill, completion of exercise logs, use of the heart rate monitor, appropriate warm-up and cool-down, stretches, and proper footwear for aerobic exercise. Participants were encouraged to individualize their frequency (days per week), fractionation (sessions per day), and duration (minutes per session) of exercise according to a schedule that promoted a high level of adherence to the prescribed exercise volume. The exercise physiologist provided ongoing behavioral and clinical support and monitored exercise adherence throughout the duration of the study with the use of weekly telephone and email communications. Exercise intensity was prescribed at 50% to 70% of the age-predicted maximum heart rate. The low-dose and high-dose groups progressed towards of the goal of 150 or 300 minutes per week of exercise, respectively. Details of the exercise prescription have been published.[24] The study outcome of exercise feasibility was operationalized as the average weekly adherence to the prescribed exercise dose, defined using the completed number of minutes divided by the prescribed number of minutes.[24] The