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A randomized phase II dose–response exercise trial among colon cancer survivors: Purpose, study design, methods, and recruitment results

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ABSTRACT

Background: Observational studies indicate that higher volumes of physical activity are associated with improved disease outcomes among colon cancer survivors. The aim of this report is to describe the purpose, study design, methods, and recruitment results of the COURAGE trial, a National Cancer Institute (NCI) sponsored, phase II, randomized, dose–response exercise trial among colon cancer survivors.

Methods/results: The primary objective of the COURAGE trial is to quantify the feasibility, safety, and physiologic effects of low-dose (150 min·week^{-1}) and high-dose (300 min·week^{-1}) moderate-intensity aerobic exercise compared to usual-care control group over six months. The exercise groups are provided with in-home treadmills and heart rate monitors. Between January and July 2015, 1433 letters were mailed using a population-based state cancer registry; 126 colon cancer survivors inquired about participation, and 39 were randomized onto the study protocol. Age was associated with inquiry about study participation ($P < 0.001$) and randomization onto the study protocol ($P < 0.001$). No other demographic, clinical, or geographic characteristics were associated with study inquiry or randomization. The final trial participant was randomized in August 2015. Six month endpoint data collection was completed in February 2016.

Discussion: The recruitment of colon cancer survivors into an exercise trial is feasible. The findings from this trial will inform key design aspects for future phase 2 and phase 3 randomized controlled trials to examine the efficacy of exercise to improve clinical outcomes among colon cancer survivors.

1. Introduction

There are 103,000 people diagnosed annually with colon cancer in the United States [1]. Among those diagnosed, 39% will have localized colon cancer (confined to the primary site; stage I-II), 36% will have regional colon cancer (spread to regional lymph nodes; stage III), and 20% will have metastatic disease (spread to distant organs; stage IV) [1,2]. Among those without metastatic disease, five year survival rates for localized and regional colon cancer are 90% and 70%, respectively [1]. Surgery is the primary treatment modality for localized and regional colon cancer, with curative resection occurring in 80–85% of patients [3,4]. Those with regional disease may also receive adjuvant chemotherapy to reduce the risk of recurrent disease [5]. Despite the efficacy of surgical resection and adjuvant chemotherapy, 20–50% of patients with localized and regional colon cancer develop recurrent disease [6,7]. Eighty percent of recurrences occur within the first three years after treatment, and 91% of patients who develop a recurrence by three years, die before five years [8]. Consequently, there exists a need to identify additional adjuvant therapies that can be prescribed at the conclusion of standard colon cancer therapy (e.g., surgery and chemotherapy) to minimize the risk of recurrence. Such adjuvant therapies may include the modification of lifestyle behaviors.

Physical activity or exercise is a modifiable lifestyle behavior that is associated with disease outcomes among colon cancer survivors. Among 832 stage III colon cancer survivors, participation in approximately 300 min·week^{-1} (18 to 27 MET-hours) of physical activity after diagnosis was associated with a 45–49% improvement in disease-free survival (defined as cancer recurrence or death from any cause), and a 29–63% improvement in overall mortality [9]. This observation has been replicated in multiple cohorts of men [10,11] and women [11–13], and is independent of known demographic, clinico-pathologic, and treatment-related prognostic factors [9–13]. A consistent finding in all of these cohort studies is that post-diagnosis physical activity is associated with disease outcomes in a dose–response fashion, such that larger doses of physical activity or exercise, up to

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approximately 300 min per week (min·week^{-1}), is associated with more favorable disease outcomes [9–13]. This dose–response pattern has been confirmed in several meta-analyses [14–16]. However, it is unknown if doses of exercise as large as 300 min·week^{-1} are behaviorally feasible and have tolerable safety profiles for colon cancer survivors when compared to smaller doses of exercise, such as 150 min·week^{-1} as is currently recommended by the American Cancer Society [17], American College of Sports Medicine [18], and the National Comprehensive Cancer Network [19]. Furthermore, the biological or biobehavioral pathways through which exercise may impact disease outcomes among colon cancer survivors are unknown. Evaluating potential biomarkers and/or mediators involved in the anti-cancer effects of exercise and the sensitivity of such biomarkers and/or mediators to respond to different doses of exercise will help to identify the optimal dose of exercise to improve outcomes and guide clinical decisions and recommendations.

2. Aims of this report

The aims of this report are two-fold. First, we describe the purpose, study design, and methods of the COURAGE trial, a National Cancer Institute (NCI) sponsored, phase II, randomized, dose–response exercise trial of two distinct doses of moderate-intensity aerobic exercise compared to a usual-care control group among colon cancer survivors. Second, we present recruitment results to describe what demographic, clinical, or geographic characteristics are associated with inquiry about study participation and randomization onto the study protocol. Identifying the characteristics associated with inquiry about study participation and randomization onto the study protocol will provide empirical evidence to describe trial generalizability to the broader population of colon cancer survivors.

3. Study objectives & outcomes

The primary objective of the COURAGE trial is to quantify the feasibility, safety, and physiologic effects of low-dose (150 min·week^{-1}) aerobic exercise, high-dose (300 min·week^{-1}) aerobic exercise, or usual-care control, among non-metastatic colon cancer survivors over six months (Fig. 1). The primary outcomes include exercise adherence, adverse events, soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular adhesion molecule-1 (sVCAM-1) prognostic biomarkers. Key secondary outcomes include visceral adipose tissue (VAT), and fasting insulin. Exploratory outcomes include the enumeration of circulating tumor cells (CTCs), functional status, and patient-reported outcomes and quality of life measures.

4. Methods

All study activities as described below were reviewed and approved by the University of Pennsylvania Human Subjects Protection Programs. The trial was registered with ClinicalTrials.gov as NCT02250053.

4.1. Eligibility criteria

To balance the goals of recruiting a homogeneous study cohort with recruitment feasibility we a priori implemented a phased recruitment strategy which systematically broadened eligibility criteria in each successive phase of recruitment. In phase 1 (most strict) the inclusion criteria were as follows: histologically-confirmed stage II-III colon cancer; completed surgical resection and adjuvant chemotherapy ≤24 months before entering the study; ≤120 min·week^{-1} of self-reported moderate or vigorous intensity physical activity using the *Paffenbarger Physical Activity Questionnaire* [20]; age ≥ 18 years; written physician approval; no additional surgery planned within the six month intervention (including colostomy reversal); and the ability to walk unaided for six minutes. In phase 2 (less restrictive) the inclusion criteria were broadened to increase the baseline self-reported physical activity level from ≤120 min·week^{-1} to <150 min·week^{-1}, and expanded the time since completing surgical resection and adjuvant chemotherapy from ≤24 months to ≤36 months. In phase 3 (least restrictive) the inclusion criteria were broadened from histologically-confirmed stage II-III colon cancer to histologically-confirmed stage I-III colon cancer, and expanded the time since completing surgical resection and adjuvant chemotherapy to any period.

During all phases of recruitment, the exclusion criteria were as follows: history of another primary cancer (other than non-melanoma skin-cancer); evidence of metastatic colon cancer; planning to receive any additional adjuvant chemotherapy or surgery (i.e., ostomy reversal); pregnant or breast feeding; unable to provide baseline blood sample; cardiac conditions, including the following: myocardial infarction or coronary revascularization procedure within the past three months, uncontrolled hypertension, defined as a systolic blood pressure ≥ 180 mm Hg or diastolic blood pressure ≥ 100 mm Hg, high-risk or uncontrolled heart arrhythmias, clinically significant heart valve disease, decompensated heart failure, or known aortic aneurysm; and any other condition which, in the opinion of the investigator, may impede testing of the study hypothesis or make it unsafe to engage in the exercise program.

4.2. Participant recruitment

Potentially-eligible study participants were recruited through the Pennsylvania Cancer Registry (PCR) [21]. The PCR is a member of the North American Association of Central Cancer Registries (NAACCR)

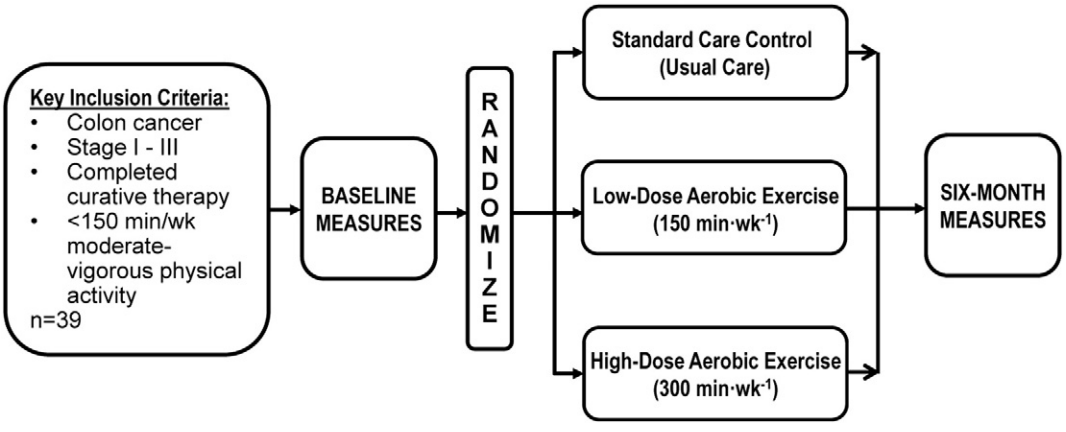

Fig. 1. Study schema.