THE COURAGE TRIAL: A PHASE II RANDOMIZED CLINICAL TRIAL TO EVALUATE THE DOSE-RESPONSE EFFECTS OF EXERCISE ON PROGNOSTIC BIOMARKERS AMONG COLON CANCER SURVIVORS

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DEDICATION

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ABSTRACT

THE COURAGE TRIAL: A PHASE II RANDOMIZED CLINICAL TRIAL TO EVALUATE THE DOSE-RESPONSE EFFECTS OF EXERCISE ON PROGNOSTIC BIOMARKERS AMONG COLON CANCER SURVIVORS

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Observational epidemiologic data suggest that participation in physical activity after a diagnosis of colon cancer reduces the risk of cancer recurrence, cancer-specific mortality, and all-cause mortality. However, the biologic mechanisms that mediate the relationship between physical activity and disease outcomes among colon cancer survivors have not been characterized. Excess visceral adipose tissue and hyperinsulinemia promote the growth and progression of existing micro-metastases and the development of new distant metastases. Exercise reduces visceral adipose tissue and hyperinsulinemia among non-diabetic persons with obesity. However, it is unknown if exercise alters visceral adipose tissue and hyperinsulinemia among colon cancer survivors. We conducted a phase II, randomized, six month, dose-response exercise trial that compared 150 min·wk^{-1} or 300 min·wk^{-1} of moderate-intensity aerobic exercise to a usual care control group among 39 colon cancer survivors. We examined the efficacy of exercise to reduce visceral adipose tissue and fasting insulin. To understand the generalizability of this trial we examined demographic, clinical, and geographic characteristics of trial participants as compared to the cancer registry population from which they were recruited. Mean age was 56.5±10.0 years, 51% had stage III disease, 72% were treated with chemotherapy, and the mean time since finishing treatment was 10.9±6.1 months. Over six months, the low-dose group completed 141.5±9.9 min·wk^{-1} of aerobic exercise, and the high-dose group completed 247.2±10.7 min·wk^{-1} of aerobic

exercise. VAT increased 5.31±4.80 cm^2 in the control group, and decreased 4.13±4.53 in the low-dose group, and 8.27±4.89 in the high-dose group (linear P_{trend}=0.008). Fasting insulin concentrations decreased 7.4±9.4 pmol/L in the control group, 28.0±8.3 pmol/L in the low-dose group, and 20.7±9.3 pmol/L in the high-dose group (nonlinear P_{trend}=0.042). Colon cancer survivors screened for eligibility and enrolled in the study were younger (screening P<0.001, enrollment P=0.007) and more likely to have been treated with chemotherapy (screening P<0.001, enrollment P=0.006) than the population from which they were recruited. The findings from this trial inform key design aspects for future phase II and phase III randomized controlled trials among colon cancer survivors.

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CHAPTER 1. INTRODUCTION

Prologue

Each year 83,000 people are diagnosed with stage I-III colon cancer in the United States [Siegel *et al*, 2015]. Despite being cured of their primary cancer, 25-50% will experience recurrent disease within three years of diagnosis, and 91% of those with recurrent disease die within five years after their initial diagnosis [Sargent *et al*, 2005]. Colon cancer survivors consistently cite fear of recurrent disease as their chief health concern [Baker *et al*, 2005]. Consequently, physicians often field questions such as "Should I exercise? Should I lose weight? What will improve my chances?" Unfortunately, colon cancer survivors soon learn there are few definitive answers to such basic inquiries. Understanding how modifiable lifestyle behaviors such as physical activity or exercise may affect disease outcomes will advance the management of colon cancer and empower patients with practical solutions to improve their outcomes.

Observational studies indicate that participation in physical activity or exercise after a diagnosis of colon cancer is associated with a 50% reduction in the risk of cancer recurrence and mortality [Meyerhardt *et al*, 2006, Meyerhardt *et al*, 2006]. Physical activity is associated with improved disease outcomes in a dose-response fashion, such that increasing volumes of physical activity are associated with more favorable outcomes [Schmid and Leitzmann, 2014]. However, the biologic or biobehavioral pathways through which physical activity or exercise may favorably alter disease outcomes among colon cancer survivors have not been elucidated. Two pathways hypothesized to mediate the relationship between exercise and disease outcomes among colon cancer survivors include alterations in body composition and alterations in insulin metabolism and glucose homeostasis. This study will help to clarify how exercise may alter

pathways hypothesized to influence disease outcomes and the sensitivity of such pathways to respond to different doses of exercise. We will also examine the generalizability of these findings to the broader population of colon cancer survivors. The data gathered from this study will improve the specificity of exercise prescriptions provided to colon cancer survivors, strengthen the rationale that a causal relationship exists between exercise and disease outcomes, and help to refine key design aspects for future randomized trials in this population.

Colon Cancer Treatment and Prognosis

Each year, 103,000 people are diagnosed with colon cancer in the United States [Siegel *et al*, 2015]. Among those diagnosed, 39% will have stage I-II colon cancer (localized to the primary site), 36% will have stage III colon cancer (spread to regional lymph nodes), and 20% will have stage IV colon cancer (distant metastatic disease) [DeSantis *et al*, 2014, Siegel *et al*, 2014]. For patients with metastatic colon cancer, the five-year survival rate is 10%. In contrast, five-year survival rates for stage I-II and stage III colon cancer are 90% and 70%, respectively [DeSantis *et al*, 2014]. Surgery is the primary treatment modality for stage I-III colon cancer, with a curative resection occurring in 80–85% of patients. Adjuvant chemotherapy is used to lower the risk of recurrence in patients with stage II disease who have high-risk features (such as T4 lesions, inadequate lymph node resection, poorly differentiated histology, presence of lymphovascular invasion, and bowel obstruction or perforation) and in patients with stage III disease [André *et al*, 2004, Quasar Collaborative Group, 2007]. Despite surgical resection, either alone or in combination with adjuvant chemotherapy, five-year recurrence rates for stage I, II, and III colon cancer are 10%, 20%, and 30-50%, respectively [André *et al*, 2004, Clinical Outcomes of Surgical Therapy Study Group,

2004, Quasar Collaborative Group, 2007]. Although many patients may be cured with standard therapy, there remains a critical need to identify additional adjuvant therapies to reduce recurrent disease in this population.

Colon Cancer Outcomes: Recurrence and Metastasis

The high rate of recurrent and metastatic disease is a critical barrier to the health and longevity of colon cancer survivorship. Cancer recurrence and metastasis are the leading causes of morbidity and mortality in colon cancer, marking the transition from localized, potentially curable to disseminated, usually incurable disease [Renfro *et al*, 2015]. Colon cancer recurrence is often characterized by loco-regional relapse and/or distant metastasis to the liver or lung [Tsikitis *et al*, 2009]. Eighty percent of recurrences occur in the first three years after treatment, and 91% of those with recurrent disease die within five years after their initial diagnosis [Sargent *et al*, 2005]. The timing and pattern of colon cancer recurrence is consistent with the hypothesis that colon cancer survivors have residual local and distant micro-metastases remaining at the completion of curative therapy [Chambers *et al*, 2002, Meyerhardt *et al*, 2010], which cannot be identified using contemporary surveillance methods such as computed tomography (CT) and serum levels of carcinoembryonic antigen (CEA) [Primrose *et al*, 2014].

Interventions that attenuate host factors that are hypothesized to promote the progression of these residual local and distant micro-metastases may improve long-term outcomes among colon cancer survivors. Two such host factors include body composition, specifically excess visceral adipose tissue (VAT), and metabolic factors, specifically insulin [Schwartz and Yehuda-Shnaidman, 2014, Vigneri *et al*, 2015]. The prevention of cancer recurrence and metastasis are key health priorities for colon cancer survivors [Baker *et al*, 2005]. Developing interventions that colon cancer survivors can

accomplish autonomously, such as modification of lifestyle with exercise, will equip colon cancer survivors with practical solutions to improve their outcomes.

Colon Cancer Outcomes and Visceral Adipose Tissue

The two main compartments in which adipose tissue are stored include: 1) subcutaneous adipose tissue (SAT) and 2) VAT [Ibrahim, 2010]. SAT represents a usual physiologic buffer to store excess energy. When the storage capacity of SAT is exceeded, VAT is accrued. Accordingly, 80–90% of all body fat is SAT, and the remaining 10–20% is VAT [Tchernof and Despres, 2013]. The adipocytes that constitute VAT are physiologically and pathologically distinct from SAT [Ibrahim, 2010, Tchernof and Despres, 2013]. The adipocytes of VAT are more deleterious to health than the adipocytes of SAT, due to their metabolic secretion of bioactive compounds such as adipokines, cytokines, hormone-like factors, and other metabolites [Ahima and Flier, 2000, Balistreri *et al*, 2010]. The deleterious metabolic activity of VAT, coupled with anatomic proximity to vital organs, and direct drainage into portal venous vasculature (a key route of many colon cancer metastases), manifests as a pro-tumorigenic milieu (**Figure 1.1**) [Doyle *et al*, 2012].

Excess VAT independently predicts poor colon cancer outcomes. Seven observational epidemiologic studies have examined the relationship between VAT and colon cancer outcomes. Five studies have quantified VAT using CT imaging [Ballian *et al*, 2012, Guiu *et al*, 2010, Lee *et al*, 2015, Moon *et al*, 2008, Rickles *et al*, 2013], and two studies have quantified VAT using waist circumference as an anthropometric proxy [Haydon *et al*, 2006a, Prizment *et al*, 2010]. All seven of these studies concluded that higher levels of VAT are associated with poorer colon cancer outcomes such as disease-free survival, cancer-specific mortality, and all-cause mortality. For example, among 62 colon cancer

survivors, above-median values of VAT were associated with four-fold increase in the risk of disease recurrence or mortality over five years [Lee *et al*, 2015]. Among 526 colon cancer survivors, each 10-centimeter increase in waist circumference is associated with a 20% increase in the risk of colon cancer-specific mortality [Haydon *et al*, 2006a]. In addition, excess VAT is a strong independent predictor of all-cause mortality among older adults without a history of cancer. Among 1,089 men and women aged 18–84, each 70.1 cm^2 (standard deviation) increase in VAT was associated with a 74% increase in the risk of all-cause mortality, independent of age, smoking status, and cardiovascular disease [Katzmarzyk *et al*, 2012]. The relationship between VAT and mortality is j-shaped, such that as VAT increases, the risk of mortality increases exponentially [Kuk *et al*, 2006].

Body mass index (BMI), defined as weight (in kilograms) divided by height (in meters) squared (kg/m^2), is a widely used metric to quantify body composition. Elevated BMI is associated with the development of incident colon cancer [Larsson and Wolk, 2007], however several studies have concluded that BMI does not consistently influence colon cancer outcomes after diagnosis [Vrieling and Kampman, 2010]. For example, among 1,053 stage III colon cancer survivors, greater BMI at diagnosis was not associated with recurrence (P_{trend}=0.86), disease-free survival (P_{trend}=0.65), or all-cause mortality (P_{trend}=0.63) [Meyerhardt *et al*, 2008]. These findings are in contrast to the consistent deleterious impact of VAT on colon cancer outcomes, as described above. BMI and VAT are poorly correlated [Ballian *et al*, 2012]; for example, a patient may have a normal weight BMI, but have pathogenic levels of VAT, or vice-versa (**Figure 1.2**). BMI as a measure of adiposity assumes that fat tissue is distributed uniformly across the body, ignoring the known heterogeneity of regional deposition of adiposity [Tchernof and

Despres, 2013]. There exists substantial inter-individual variation between BMI and VAT. For example at a given BMI (30.0 kg/m^2), VAT may vary by as much as 40% [Després, 2011]. Among colon cancer survivors, BMI accounts for only 30.4% of the variability in VAT [Rickles *et al*, 2013]. Thus, the location of adiposity may be more influential on colon cancer outcomes than the quantity of total-body adiposity (i.e, VAT may be a better marker of recurrence risk than BMI). Together, these observations support that hypothesis that VAT is a metabolically active tissue that lends rise to deleterious colon cancer outcomes [Doyle *et al*, 2012]. VAT is associated with insulin resistance and resultant hyperinsulinemia among colon cancer survivors (r=0.519; P<0.001) [Jiang *et al*, 2014], which is implicated in the progression of recurrent and metastatic colon cancer [Vigneri *et al*, 2015].

Colon Cancer Outcomes and Hyperinsulinemia

Hyperinsulinemia is characterized by an elevated concentration of insulin and exaggerated insulin response to increases in glucose concentration [Shanik *et al*, 2008]. The adipocytes of VAT are more insulin-resistant than the adipocytes of SAT [Ibrahim, 2010]. VAT is positively associated with fasting insulin [Seidell *et al*, 1990], and accounts for 18–40% of the variability in fasting insulin [Colman *et al*, 1995]. Each 10-cm^2 increase in VAT area is associated with a 0.46 μU/mL increase in fasting insulin [Goodpaster *et al*, 2003]. VAT is an independent predictor of insulin sensitivity, a measure of how efficiently insulin acts to lower blood glucose [Racette *et al*, 2006]. The relationship between VAT and insulin is important because colon cancer cells have insulin and insulin-like growth factor-I (IGF-I) receptors on their surface [Belfiore and Malaguarnera, 2011]. Insulin and IGF-I promote colon cancer cell proliferation and inhibit apoptosis [Koenuma *et al*, 1989], thereby increasing the aggressiveness of the

tumor phenotype [Vigneri *et al*, 2015]. *In vitro* studies demonstrate the state of hyperinsulinemia increases colon cancer cell resistance to 5-fluorouracil [Chen *et al*, 2011b] and oxaliplatin chemotherapy [Chen *et al*, 2011a, Volkova *et al*, 2014]. Preclinical models demonstrate that exposure to insulin promotes colonic tumor multiplicity [Tran *et al*, 1996].

Colon cancer survivors have fasting insulin levels that are 58% higher than age- and sex-matched controls without a history of colon cancer [Jiang *et al*, 2014]. Hyperinsulinemia is often observed among people diagnosed with early stage type 2 diabetes mellitus (T2DM). Colon cancer survivors with T2DM have significantly worse prognosis than those without T2DM [Dehal *et al*, 2012, Jeon *et al*, 2013, Luo *et al*, 2014, Meyerhardt *et al*, 2003]. For example, among 3,759 stage II/III colon cancer survivors, those with T2DM had shorter five-year disease-free survival (48% vs. 59%), and shorter five-year overall survival (57% vs 66%) [Meyerhardt *et al*, 2003]. Markers of insulin secretion, such as C-peptide, are associated with a two-fold increase in the risk of death among men and women diagnosed with colon cancer [Wolpin *et al*, 2009]. Hyperinsulinemia also promotes IGF-I biosynthesis, which inhibits production of insulin-like growth factor binding protein (IGFBP)-3 [Sandhu *et al*, 2002]. Low levels of IGFBP-3 are associated with a higher risk of death among non-metastatic colon cancer survivors [Haydon *et al*, 2006b, Wolpin *et al*, 2009]. Together, this evidence which spans from *in vivo* models to human observational studies, supports the hypothesis that hyperinsulinemia is associated with recurrence and metastasis among colon cancer survivors. The relationship between VAT and hyperinsulinemia yields a pro-tumorigenic environment which may facilitate the progression of recurrent and metastatic disease among colon cancer survivors [Doyle *et al*, 2012]. Interventions that reduce VAT and/or

reduce hyperinsulinemia/insulin resistance may therefore have considerable impact on understanding colon cancer biology and improving the longevity of colon cancer survivorship.

Mechanisms of VAT and Insulin Relevant to Colon Cancer Outcomes

Though not completely elucidated, the PI3K-Akt-mTOR signaling pathway is a point of convergence that links both excess VAT and hyperinsulinemia to poor colon cancer outcomes [Huang and Chen, 2009, Weijenberg *et al*, 2013]. The PI3K-Akt-mTOR pathway is often hyper-activated in colon cancer [Wang and Zhang, 2014], and inhibition of this pathway has been considered a therapeutic target [Huang and Chen, 2009]. mTOR is activated by Akt, inhibited by AMPK, and the activation of mTOR regulates cell survival, proliferation, and growth. mTOR expression in colonic tumor tissue increases with disease stage, lymph node metastasis, and lymphovascular invasion [AlQurashi *et al*, 2013]. Activation of the PI3K-Akt-mTOR pathway is associated with the growth and progression of colon cancer metastases [Gulhati *et al*, 2011]. Patients whose tumors express mTOR tend to have lower median survival rates than patients whose tumors do not express mTOR (43 *v* 60 months, respectively; P=0.06) [AlQurashi *et al*, 2013]. mTOR is sensitive to signals that reflect the nutritional and energetic states of the cellular environment. In cellular environments with energy surplus, such as that with excess VAT, hyperinsulinemia, and IGF-1, mTOR is activated via PI3K-Akt signaling [McCurdy and Klemm, 2013]. This activation creates a competitive growth advantage for cancer cells, and promotes metastatic potential and chemotherapy resistance [Porta *et al*, 2014]. Conversely, in states of energy depletion, such as that required for exercise, mTOR is inhibited via AMPK [Chen *et al*, 2003]. Favorably altering the energetic states of the cellular environment by reducing excess VAT, hyperinsulinemia,

and IGF-1 may down-regulate the PI3K-Akt-mTOR pathway. In a preclinical model, silencing of mTOR inhibited the growth of colon cancer metastases and induced cell-cycle arrest and apoptosis [Zhang *et al*, 2009]. Considerable evidence has accumulated that implicates the PI3K-Akt-mTOR pathway in mediating the effects of excess VAT and hyperinsulinemia on colon cancer outcomes [Huang and Chen, 2009, Weijenberg *et al*, 2013].

Colon Cancer Outcomes and Exercise or Physical Activity

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 physical activity after diagnosis was associated with a 45% improvement in disease-free survival (defined as cancer recurrence or death from any cause), and a 63% improvement in overall mortality [Meyerhardt *et al*, 2006]. This observation has been replicated in multiple cohorts of men [Campbell *et al*, 2013, Meyerhardt *et al*, 2009] and women [Campbell *et al*, 2013, Kuiper *et al*, 2012, Meyerhardt *et al*, 2006], and is independent of known demographic, clinico-pathologic, and treatment-related prognostic factors [Campbell *et al*, 2013, Kuiper *et al*, 2012, Meyerhardt *et al*, 2006, Meyerhardt *et al*, 2006, Meyerhardt *et al*, 2009].

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 approximately 300 minutes per week ($min \cdot wk^{-1}$), are associated with more favorable disease outcomes [Campbell *et al*, 2013, Kuiper *et al*, 2012, Meyerhardt *et al*, 2006, Meyerhardt *et al*, 2006, Meyerhardt *et al*, 2009]. The relationship between physical activity volume and colon cancer outcomes has been depicted as a linear or quadratic pattern using spline models (**Figure 1.3**) [Meyerhardt *et*

al, 2006, Meyerhardt *et al*, 2009]. The splines suggest 225 min·wk^{-1} may be the minimum threshold necessary to improve colon cancer outcomes, however, outcomes continue to improve beyond 225 min·wk^{-1}, suggesting that larger doses up to 300 min·wk^{-1} may provide favorable disease-specific health benefits to colon cancer survivors. This dose-response pattern has been confirmed in several meta-analyses [Des Guetz *et al*, 2013, Je *et al*, 2013, Schmid and Leitzmann, 2014]. However, the dose-response effects of exercise have not been studied among colon cancer survivors.

Interestingly, levels of physical activity before diagnosis of colon cancer are not associated with colon cancer-specific mortality [Haydon *et al*, 2006a, Kuiper *et al*, 2012, Meyerhardt *et al*, 2006, Pelser *et al*, 2014]. This suggests the biologic or biobehavioral pathways through which physical activity reduces the primary development of colon cancer may differ from that of the prevention of recurrence and metastases, yielding greater focus upon the pro-tumorigenic milieu created by excess VAT and hyperinsulinemia [Doyle *et al*, 2012, Quadrilatero and Hoffman-Goetz, 2003, Vigneri *et al*, 2015]. The importance of the PI3K-Akt-mTOR pathway (as described earlier) is supported by observations that examine the impact of molecular marker expression as modifiers of the relationship between physical activity and colon cancer-specific death. Among colon cancer survivors whose tumor is PI3KCA wild-type, participation in physical activity is associated with a lower risk of colon cancer-specific death, whereas colon cancer survivors whose tumor harbors a PI3KCA mutation do not reap any cancer specific-survival benefit from physical activity [Meyerhardt *et al*, 2009]. The PI3KCA mutation allows the PI3K-Akt-mTOR pathway to signal without regulation from the cellular environment. Consequently, altering states of energy balance (via exercise or other interventions) do not influence cell survival, proliferation, and growth. Furthermore,

the PI3K-Akt-mTOR pathway regulates p27 expression, a cyclin-dependent kinase inhibitor that controls cell cycle progression. Among colon cancer survivors whose tumors express p27, participation in physical activity is associated with a lower risk of colon cancer-specific death, whereas colon cancer survivors whose tumors do not express p27 do not reap benefit from physical activity [Meyerhardt *et al*, 2009]. Together, these data provide further evidence that suggest the PI3K-Akt-mTOR pathway may have an important intercellular role in mediating the impact of excess VAT and hyperinsulinemia on colon cancer outcomes.

The American College of Sports Medicine (ACSM), the American Cancer Society (ACS), and the National Comprehensive Cancer Network (NNCN) guidelines for cancer survivors recommend 150 $min \cdot wk^{-1}$ of moderate-intensity physical activity [National Comprehensive Cancer network, 2013, Rock *et al*, 2012, Schmitz *et al*, 2010]. This recommendation is inconsistent with the dose of physical activity necessary to improve disease outcomes in colon cancer survivors, as suggested by the epidemiologic literature. Several reviews, including the ACSM statement for exercise among cancer survivors, have called for more research to empirically investigate the dose-response effects of exercise among cancer survivors [Brown *et al*, 2012b, Schmitz *et al*, 2010].

Exercise and Visceral Adipose Tissue

Exercise is an efficacious modality to reduce excess VAT. The "Studies of a Targeted Risk Reduction Intervention through Defined Exercise" (STRRIDE) trial [Kraus *et al*, 2001], established the dose-response effects of exercise on VAT [Slentz *et al*, 2005, Slentz *et al*, 2004]. The STRRIDE study was a four-arm randomized controlled trial that compared three-doses of exercise to a control group for six months among 330 men and women who were overweight or obese with mild to moderate lipid abnormalities [Kraus

et al, 2001]. The STRRIDE study demonstrated a significant dose-response reduction in VAT, quantified using computed tomography (P_{trend}<0.001; **Figure 1.4**) and waist circumference (P_{trend}<0.001) [Slentz *et al*, 2005, Slentz *et al*, 2009, Slentz *et al*, 2004]. The dose-response effects of exercise on VAT have been replicated among adults with the metabolic syndrome [Dutheil *et al*, 2013], and in meta-analyses of randomized exercise trial using weighted regression models [Ohkawara *et al*, 2007, Vissers *et al*, 2013]. However, no study has examined the dose-response effects of exercise on VAT among colon cancer survivors.

Exercise and Hyperinsulinemia

Exercise significantly reduces fasting insulin levels in dose-response fashion [Friedenreich *et al*, 2011, Heydari *et al*, 2012, Houmard *et al*, 2004]. The STRRIDE study demonstrated a significant reduction in fasting insulin (*P*<0.001), and significant improvement in insulin sensitivity quantified using an intravenous glucose tolerance test (*P*<0.05) [Houmard *et al*, 2004]. These findings have been corroborated in a *post-hoc* analysis of a two-group randomized exercise study among overweight or obese post-menopausal women [Friedenreich *et al*, 2011]. Exercise-induced improvements in VAT are associated with reductions in insulin resistance [O'Leary *et al*, 2006, Slentz *et al*, 2005].

Characterizing Eligibility Screening and Enrollment of Clinical Trials

Randomized clinical trials (RCTs) are considered the gold-standard study design to quantify the efficacy of an intervention [Piantadosi, 2005]. Validity is commonly cited as the primary reason why RCTs are the gold standard study design. There are two forms of validity: internal validity and external validity. Internal validity relates to whether the comparison of treatments is likely to be unbiased and un-confounded by external factors.

External validity, also known as generalizability, relates to whether the study results can be extended to the majority of patients for whom the results of the study may apply. RCTs are frequently designed in such a way that maximizes internal validity, subsequently reducing external validity [Gross *et al*, 2002, Wright *et al*, 2006]. Lack of external validity is a frequent criticism of RCTs, because patients enrolled in RCTs may differ from the general patient population with respect to demographic, clinical, and geographical characteristics such as age, sex, race, disease stage, and place of residence [Rothwell, 2005, Unger *et al*, 2014]. The enrollment process of RCTs has been presented in a conceptual framework by Gross *et al*. in "who are these patients and how did they get here?" [Gross *et al*, 2002]. This conceptual framework depicts flow of potential study participants through three distinct stages of recruitment (**Figure 1.5**). In stage one, investigators approach persons who are thought to represent a random sample of the underlying target population. In stage two, persons who are approached and interested in participating in the RCT are screened to determine eligibility. In stage three, persons who are interested in participating and are determined to be eligible are offered an opportunity to enroll in the RCT. In each of these distinct stages of RCT enrollment, it is plausible that persons who proceed to the next stage represent a distinct subset of the population from which they were sampled (i.e., the target population). For example, persons screened in stage two may differ demographically, clinically, or geographically, relative to persons identified in stage one [Rothwell, 2005]. Furthermore, persons enrolled in stage three, may also differ demographically, clinically, or geographically, compared to persons identified in stage one [Rothwell, 2005]. Systematic differences in characteristics among persons in each of these stages may lead to selection bias that reduces the representativeness of RCT participants from the

underlying target population. This lack of representativeness consequently reduces the external validity of the RCT.

Lack of external validity in RCTs is hypothesized to partially explain the underuse of efficacious interventions in clinical practice despite recommendations for their use in clinical practice guidelines [Rothwell, 2005]. For example, the ACSM, ACS, and NCCN recommend that healthcare providers prescribe exercise to all colon cancer survivors [National Comprehensive Cancer network, 2013, Rock *et al*, 2012, Schmitz *et al*, 2010]. However only 16.3% of colon cancer survivors are prescribed exercise by their healthcare provider, compared to 26.9% of matched adults without a history of cancer (P=0.003) [Sabatino *et al*, 2007]. Survivors of breast, prostate, cervical, and uterine cancer are prescribed exercise by their healthcare provider at rates similar to matched adults without a history of cancer. These data indicate that healthcare providers may be particularly reluctant to prescribe exercise to colon cancer survivors [Brown and Schmitz, 2014a].

To promote the prescription of exercise to colon cancer survivors in clinical practice, RCTs of exercise need to systematically characterize how colon cancer survivors who participate in an exercise RCT differ from those who do not participate. To date, few exercise RCTs have characterized these differences. Characterizing these differences would fill an evidence gap that may begin to solve several problems for healthcare providers who are being asked to prescribe exercise and study investigators who are generating data to support the prescription of exercise. First, healthcare providers would have evidence to understand how colon cancer survivors who participate in an exercise RCT may differ from patients who receive care in their clinical practice. Second, study investigators would be able to identify colon cancer survivor subgroups that may be less

likely to participate in an exercise RCT. These subgroups can subsequently become the focus of targeted and tailored recruitment efforts to improve RCT participation and generalizability. Characterizing how RCT participants differ from the population will also provide investigators evidence to empirically describe the generalizability of their trial. Filling this evidence gap may help to promote exercise as a standard component of colon cancer care and improve clinical trial methodology among colon cancer survivors [Brown and Schmitz, 2014a].

Study Design

Together, this evidence formed the basis for the COURAGE trial. The COURAGE trial was 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 non-metastatic colon cancer survivors.

Primary Research Questions & Hypotheses

The primary research questions and hypotheses addressed by the COURAGE trial in this dissertation were as follows:

> **Specific Aim 1:** To quantity and describe the dose-response effects of moderate-intensity aerobic exercise on VAT, measured with a novel and validated method using dual energy x-ray absorptiometry.
>
> **Hypothesis:** We hypothesized that exercise will favorably reduce VAT in dose-response fashion.
>
> **Specific Aim 2**: To quantify and describe the dose-response effects of moderate-intensity aerobic exercise on levels of fasting insulin.

Hypothesis: We hypothesized that exercise will favorably reduce levels of fasting insulin in dose-response fashion.

Specific Aim 3: To quantify and describe demographic, clinical, and geographical characteristics that associate with eligibility screening and study enrollment in the COURAGE trial.

Hypothesis: We hypothesized that demographic, clinical, and geographical characteristics will be associated with eligibility screening and study enrollment.

Placing the Courage Trial into Larger and Longer-Term Context

Exercise has potential pharmacologic properties that are similar to many drugs [Vina *et al*, 2012]. Exercise and drug interventions are similar in terms of their mortality benefits in the secondary prevention of coronary heart disease, rehabilitation after stroke, treatment of heart failure, and the prevention of diabetes [Naci and Ioannidis, 2013]. The developmental pipeline for bringing exercise to the standard of clinical care for adjuvant colon cancer should progress through a similar pipeline to that of drug development. Because exercise is a complex and multifaceted behavior, the level of preliminary evidence required to undertake a definitive phase III randomized controlled trial should be abundant and consistently demonstrate the safety, feasibility, and physiologic alterations that support the hypothesis of a causal relationship. We have proposed a sequential phased process that systematically evaluates the critical questions that should be answered prior to undertaking a phase III trial in this area (**Figure 1.6**). At each sequential phase the physiologic specificity of the potential benefits of exercise on disease outcomes is deepened. First, as with a drug, the feasibility and safety of various exercise doses must be established. Second, we aim to

understand how biomarkers representing various physiologic pathways respond to an exercise stimulus. Such biomarkers may include VAT (adiposity), insulin (metabolic), C-reactive protein (inflammation), or soluble intercellular adhesion molecules (endothelial axis). The COURAGE trial will address these two phases. Subsequent to the COURAGE trial, it will be necessary to examine how specific pathways (i.e., PI3K-Akt-mTOR) change in response to exercise and how this may affect metastatic potential. Assuming these hypotheses are supported, smaller multisite trials can be undertaken to demonstrate the ability to coordinate and concentrate research efforts. After a successful multi-site feasibility study, a definitive phase III trial with a clinical endpoint can be initiated. This process is likely to be iterative as new questions and unanticipated logistical, methodological, and scientific barriers arise. This proposed human developmental pipeline should be supplemented with ongoing preclinical studies. This proposed human developmental pipeline will systematically generate high quality data that will help to inform the standard of clinical care for adjuvant colon cancer.

Summary

The propensity to recur is a formidable reality for colon cancer survivors and presents a critical barrier to promote long term survivorship. Excess VAT and hyperinsulinemia are hypothesized as important host factors that may promote colon cancer recurrence and metastasis. Exercise has emerged as an adjuvant intervention that may confer recurrence and survival benefits for people with colon cancer. However, the underlying biologic or biobehavioral pathways that mediate the relationship between exercise and colon cancer outcomes remain unidentified. It is plausible that exercise reduces VAT and/or insulin levels, thereby reducing the pro-tumorigenic milieu, and minimizing the growth and progression of residual local and distant micro-metastases. The preliminary

data supporting these associations are strong, consistent with biologic plausibility, occur in dose-response fashion, and have select aspects that are supported with randomized data. Interventions to decrease VAT and/or fasting insulin among colon cancer survivors will help to clarify how exercise may alter pathways that are hypothesized to influence disease outcomes and the sensitivity of such pathways to respond to different doses of exercise. Such data will improve the specificity of exercise prescriptions provided to colon cancer survivors and strengthen the hypothesis of a causal relationship between exercise and disease outcomes. In addition, the data from this dissertation will help to refine key trial design characteristics for future randomized controlled trials in this area.

The long-term goal of this line of research is to generate definitive answers to the questions “Should I exercise? Should I lose weight? What will improve my chances?” that are asked by the 83,000 men and women who will be told “you have colon cancer” each year. Seven in ten colon cancer survivors cite fear of disease recurrence as their principal health concern [Baker *et al*, 2005]. Thoughts about recurrence are intrusive, physically and psychologically debilitating, and alter long-term family and financial planning [Simard *et al*, 2013]. These patients deserve to know how the choices they make to purposefully alter lifestyle behaviors may influence their disease outcomes. This information will empower patients, families, and providers with practical solutions to improve outcomes.

Figure 1.1 Mechanistic pathway describing how visceral adipose tissue promotes a pro-tumorigenic environment. Adapted from [Doyle *et al*, 2012].

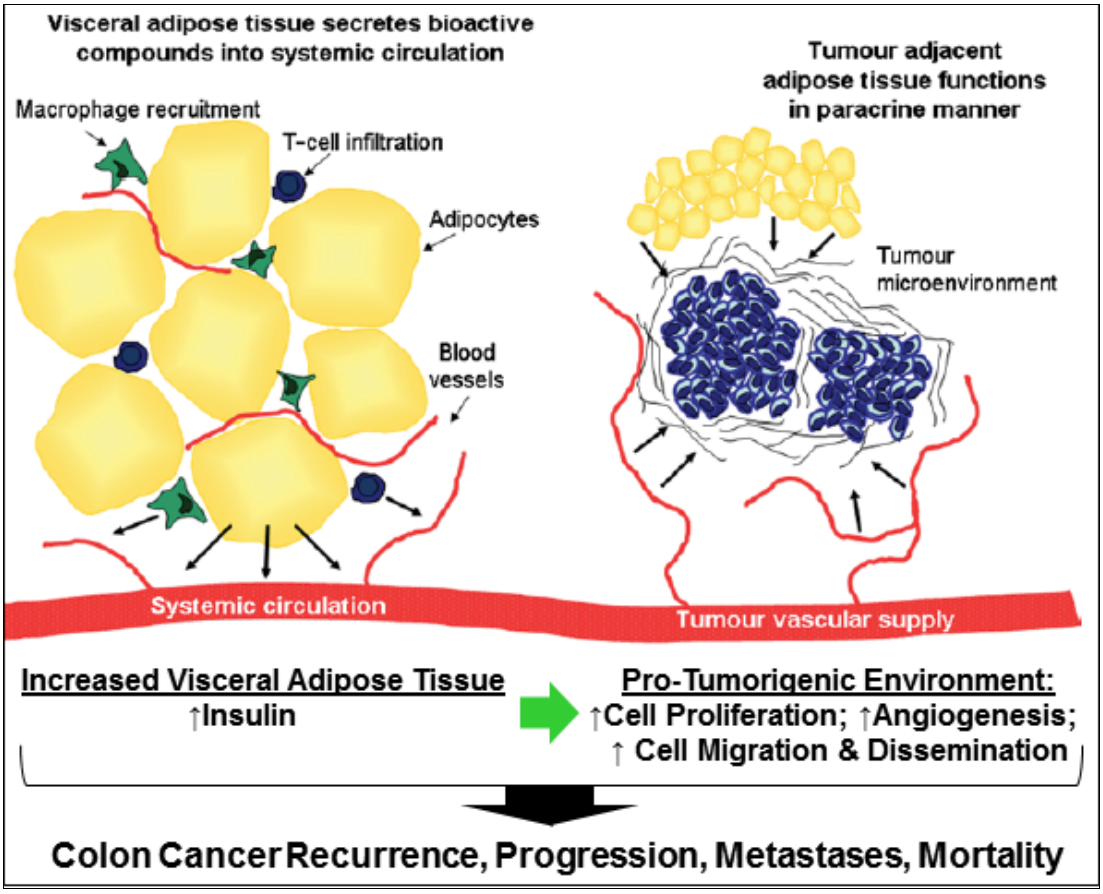


Figure 1.2 Illustration of differences in body mass index (BMI) and visceral adipose tissue among colorectal cancer patients using computed tomography at the level of the umbilicus.

Red shading indicates visceral adipose tissue area (VFA). Blue shading indicates subcutaneous tissue area (SFA). Patient 'a' has a BMI of 24.0 kg/m^2 with a VFA/SFA of 1.49. Patient 'b' has a BMI of 48.0 kg/m^2 and a VFA/SFA ratio of 0.35. Adapted from [Ballian *et al*, 2012].

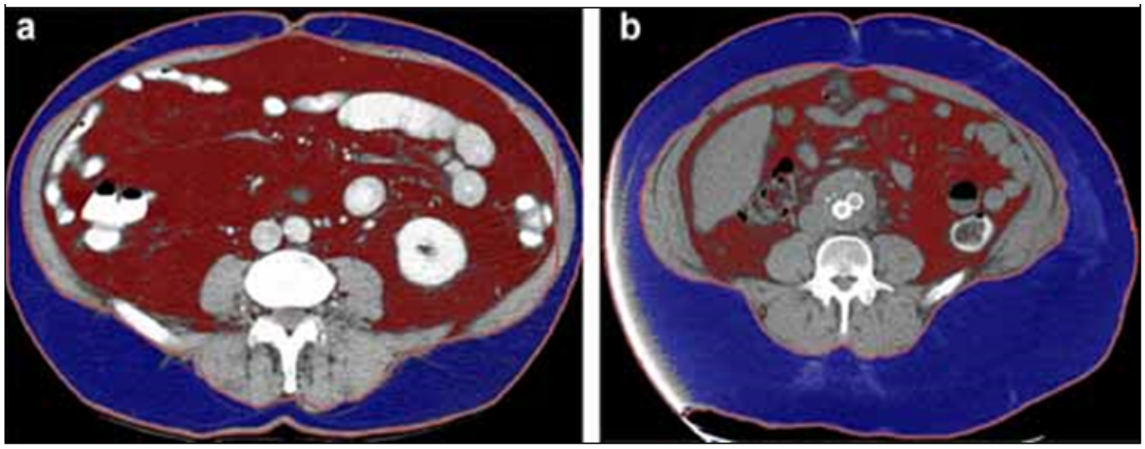


Figure 1.3 Smoothing spline plot of disease-free survival and hours per week of walking.

Thick solid line represents that hazard ratio and dashed lines represent the 95% confidence intervals. Adapted from [Meyerhardt *et al*, 2006].

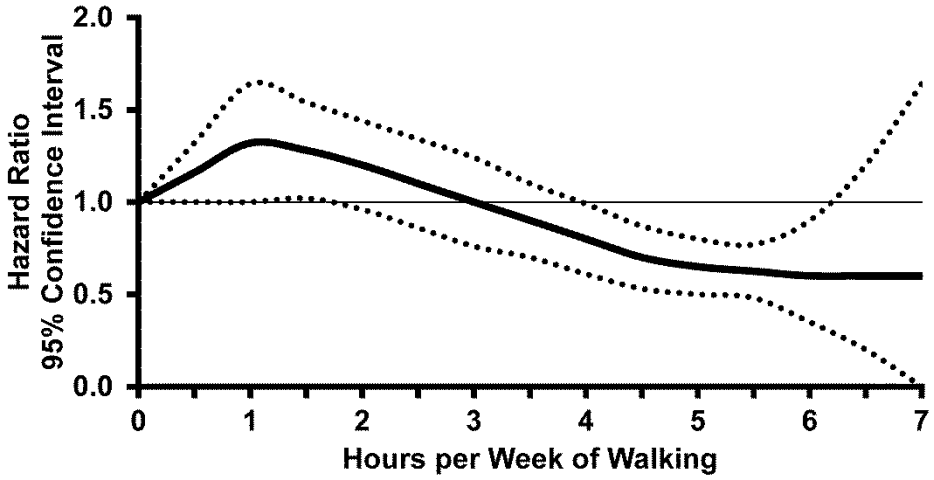


Figure 1.4 Relationship between amount of exercise per week and percent visceral fat change. Adapted from [Slentz *et al*, 2009].

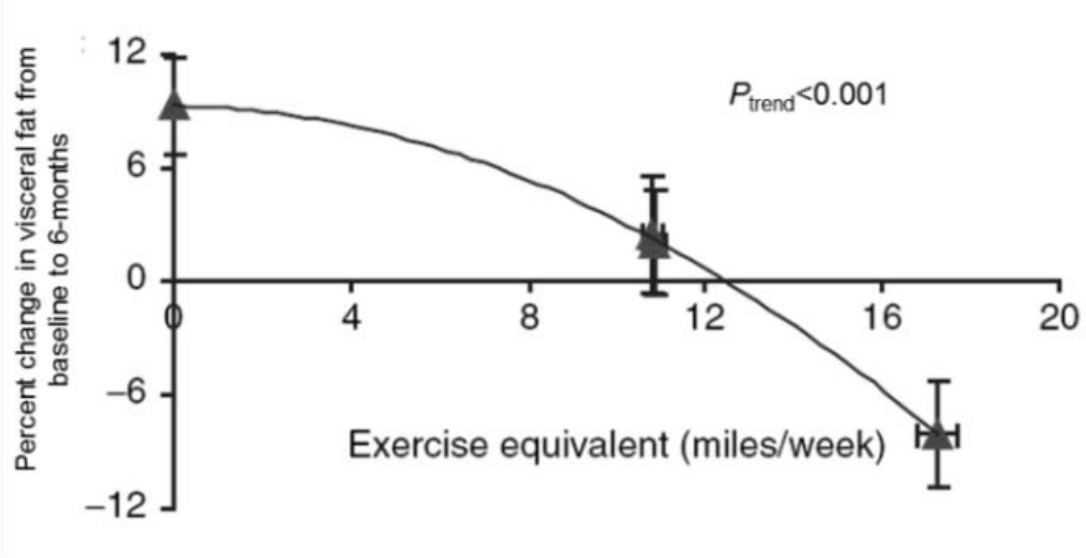


Figure 1.5 The trial enrollment process: "who are these patients and how did they get here?" Adapted from [Gross *et al*, 2002].

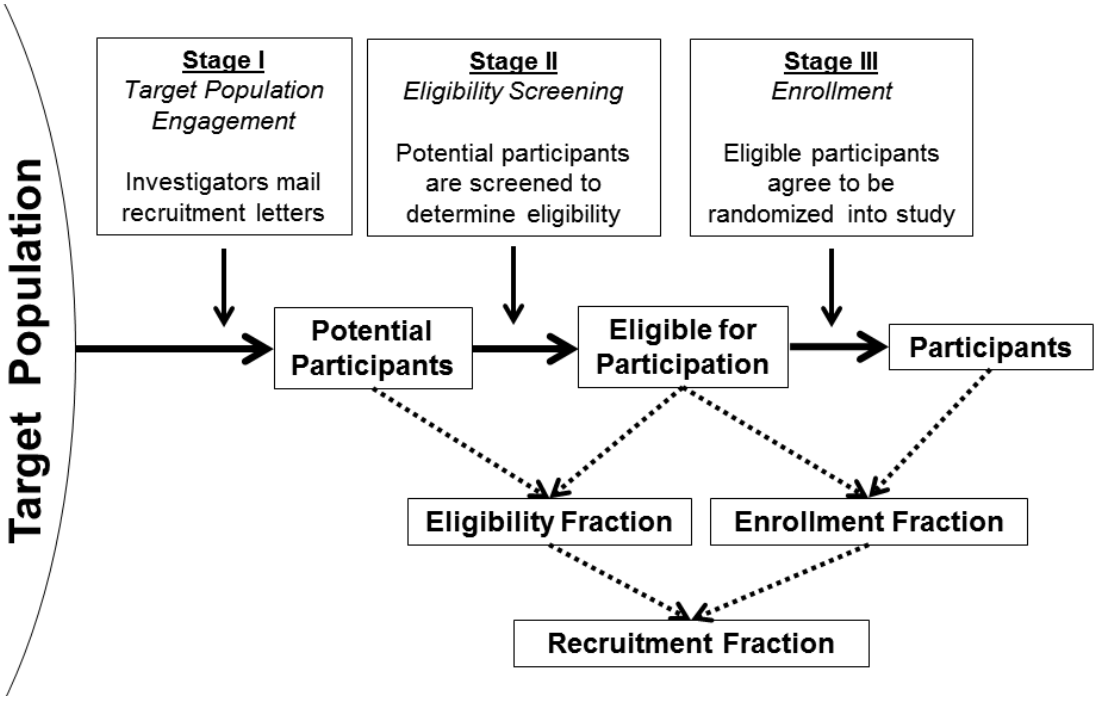
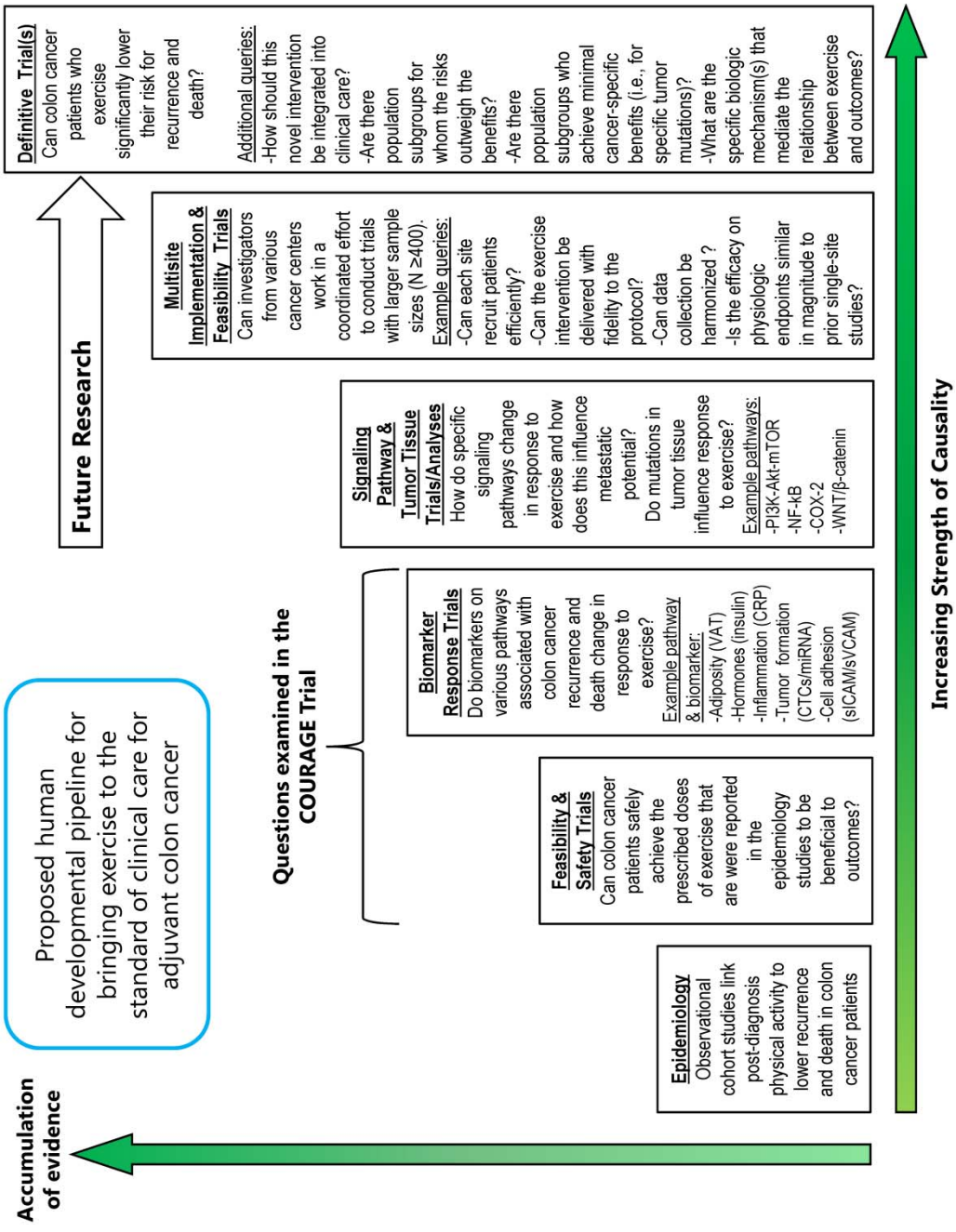


Figure 1.6 Sequential phases of developing randomized controlled trials to examine the relationship between exercise and disease outcomes in colon cancer. Adapted from [Campbell *et al*, 2000].



CHAPTER 2. 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·wk^{-1}) and high-dose (300 min·wk^{-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, 1,433 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.

Introduction

There are 103,000 people diagnosed annually with colon cancer in the United States [Siegel *et al*, 2014]. 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) [DeSantis *et al*, 2014, Siegel *et al*, 2014]. Among those without metastatic disease, five year survival rates for localized and regional colon cancer are 90% and 70%, respectively [Siegel *et al*, 2014]. Surgery is the primary treatment modality for localized and regional colon cancer, with curative resection occurring in 80-85% of patients [Clinical Outcomes of Surgical Therapy Study Group, 2004, Lacy *et al*, 2002]. Those with regional disease may also receive adjuvant chemotherapy to reduce the risk of recurrent disease [Meyerhardt and Mayer, 2005]. Despite the efficacy of surgical resection and adjuvant chemotherapy, 20-50% of patients with localized and regional colon cancer develop recurrent disease [André *et al*, 2004, Quasar Collaborative Group, 2007]. 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 [Sargent *et al*, 2005]. 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 $min \cdot wk^{-1}$ (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 [Meyerhardt *et al*, 2006]. This observation has been replicated in multiple cohorts of men [Campbell *et al*, 2013, Meyerhardt *et al*, 2009] and women [Campbell *et al*, 2013, Kuiper *et al*, 2012, Meyerhardt *et al*, 2006], and is independent of known demographic, clinico-pathologic, and treatment-related prognostic factors [Campbell *et al*, 2013, Kuiper *et al*, 2012, Meyerhardt *et al*, 2006, Meyerhardt *et al*, 2006, Meyerhardt *et al*, 2009]. 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 approximately 300 minutes per week ($min \cdot wk^{-1}$), is associated with more favorable disease outcomes [Campbell *et al*, 2013, Kuiper *et al*, 2012, Meyerhardt *et al*, 2006, Meyerhardt *et al*, 2006, Meyerhardt *et al*, 2009]. This dose-response pattern has been confirmed in several meta-analyses [Des Guetz *et al*, 2013, Je *et al*, 2013, Schmid and Leitzmann, 2014]. However, it is unknown if doses of exercise as large as 300 $min \cdot wk^{-1}$ are behaviorally feasible and have tolerable safety profiles for colon cancer survivors when compared to smaller doses of exercise, such as 150 $min \cdot wk^{-1}$ as is currently recommended by the American Cancer Society [Rock *et al*, 2012], American College of Sports Medicine [Schmitz *et al*, 2010], and the National Comprehensive Cancer Network [National Comprehensive Cancer network, 2013]. 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.

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.

Study Objectives & Outcomes

The primary objective of the COURAGE trial is to quantify the feasibility, safety, and physiologic effects of low-dose (150 min·wk^{-1}) aerobic exercise, high-dose (300 min·wk^{-1}) aerobic exercise, or usual-care control, among non-metastatic colon cancer survivors over six months (**Figure 2.1**). 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.

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.

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 $min \cdot wk^{-1}$ of self-reported moderate or vigorous intensity physical activity using the *Paffenbarger Physical Activity Questionnaire* [Paffenbarger *et al*, 1993]; 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 $min \cdot wk^{-1}$ to <150 $min \cdot wk^{-1}$, 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.

Participant Recruitment

Potentially-eligible study participants were recruited through the Pennsylvania Cancer Registry (PCR) [Pennsylvania Department of Health]. The PCR is a member of the North American Association of Central Cancer Registries (NAACCR) that is responsible for collecting information on all new cases of cancer diagnosed and/or treated in the state of Pennsylvania (i.e., the PCR is population-based). The PCR has received Gold Certification from the NAACCR for excellence in areas of completeness, quality, and timeliness of cancer incidence reporting. Potentially-eligible study participants were listed in the PCR with international classification of diseases for oncology third edition (ICD-O-3) codes for colon cancer (C18.0, C18.2-C18.9). Cancer of the rectum (C20.9) was not eligible for participation. To minimize anticipated concerns regarding travel burden into the city of Philadelphia from surrounding suburbs, potentially-eligible participants were recruited from Philadelphia County and four surrounding counties (Bucks, Montgomery, Chester, and Delaware). Using an envelope with the University of Pennsylvania School of Medicine logo, potentially-eligible participants were sent one letter via postal mail that included an invitation to participate signed by the principal

investigator, a one page flyer describing the study, the name and contact information (email, telephone) of the study coordinator, and a brochure describing the PCR. The one page flyer that described the study included statements that mentioned the provision of an in-home treadmill and an individualized exercise program. Mailings were completed in four successive waves as new incident data became available from the PCR (January, March, May, and July). This recruitment approach has been used by our research group in prior studies among breast cancer survivors [Rogerino *et al*, 2009].

Participant Screening

Screening was conducted via a telephone interview. The telephone interview included a brief description of the study, systematically queried callers about each of the above-described inclusion and exclusion criteria, and administered the physical activity readiness questionnaire (PAR-Q) [Shephard, 1994]. The PAR-Q is a seven item questionnaire that identifies signs of cardiovascular disease, orthopedic conditions, and medications that could affect physiologic responses to an increase in physical activity. The PAR-Q has excellent sensitivity (close to 100%) and specificity (80%) for detecting medical contraindications to exercise [Shephard, 1994]. After screening, eligible participants were invited to the University of Pennsylvania to meet with the study coordinator for 30-45 minutes to discuss the goals, objectives, risks, and benefits of the study in detail. At that time, written informed consent was obtained from eligible participants wishing to enroll in the study.

Study Measures

After obtaining written informed consent, the study coordinator sent a physician approval form to each of the participant's physicians, which often included the primary care physician, surgical and/or medical oncologist, and other appropriate internal medicine

specialists (e.g., cardiologist for participants with pre-existing cardiac conditions). The physician approval form included a brief description of the study, the results of the PAR-Q screening questionnaire, and a request that the physician review this information and provide approval that they believe their patient is medically fit to participate in a moderate-intensity aerobic exercise study. After obtaining written physician approval, the study participant completed a clinic visit at the University of Pennsylvania Center for Clinical and Translational Research Center. The specific measures of the clinic visit are described in detail below. All measures described below are completed at baseline and at six months (except clinical characteristics 4.4.1). All measures are conducted by staff blinded to study group.

Clinical Characteristics

Tumor-related characteristics including date of diagnosis and treatment completion, stage (American Joint Committee on Cancer, 7th edition [Edge *et al*, 2010]), primary tumor location within the colon, depth of tumor invasion (T-stage), number of positive resected lymph nodes (N-stage), grade of histologic differentiation, presence of lymphovascular invasion, and adjuvant chemotherapy are abstracted from the PCR database, medical record review, and from treatment summary reports obtained from the providing physician. Comorbidities and current medication and supplement use are obtained using the Chronic Disease Scale [Von Korff *et al*, 1992]. The above-described variables that were extracted from the PCR database were utilized to examine how demographic, clinical, or geographic characteristics were associated with inquiry about study participation and randomization onto the study protocol.

Blood Sample

A total of 50mL of blood is collected by a licensed phlebotomist. Blood is collected after a minimum of six hours of fasting, which is verified prior to venipuncture. Blood samples are processed using standardized laboratory procedures and aliquots of serum and EDTA-preserved plasma are stored in -80°C freezers. In addition to the biomarker assays described below, additional aliquot samples are stored for future exploratory analyses.

sICAM-1 is analyzed using an R&D systems enzyme linked immunoabsorbent assay [Adamopoulos *et al*, 2001, Craft *et al*, 2008]. The inter-assay coefficient of variation and sensitivity are 5.4%, and 0.049-0.254 ng/mL, respectively. sVCAM-1 is analyzed using an R&D systems enzyme linked immunoabsorbent assay [Adamopoulos *et al*, 2001, Craft *et al*, 2008]. The inter-assay coefficient of variation and sensitivity are 7.7%, and 0.17-1.26ng/mL, respectively. Fasting insulin is analyzed with a radioimmunoassay (Millipore). The inter-assay coefficient of variation is 6%, and sensitivity ranges from 2.0-200.0 µU/mL. Fasting glucose is analyzed with immuno-nephelometry assay. The inter-assay coefficient of variation is 2%, and sensitivity ranges from 0.6-45.0mmol/L. The measurement of glucose serves as a quality control to enable the attribution of elevated fasting levels to insulin resistance, rather than latent type 2 diabetes or blood samples that were collected in a non-fasting manner. The homeostatic model (HOMA) is calculated to quantify insulin resistance [Wallace *et al*, 2004]. Other associated metabolic biomarkers including glycated hemoglobin (HbA1c), insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein 3 (IGFBP3), and C-peptide are also analyzed.

CTCs from venous blood are isolated using geometrically enhanced differential immunocapture (GEDI) [Gleghorn *et al*, 2010]. GEDI is a microfluidic platform that

utilizes antibody coated obstacles to capture rare cells within anticoagulated whole blood. To capture CTCs, obstacles are coated with an antibody specific to epithelial cell-adhesion molecule (EpCAM), an epithelial cell-specific marker. After washes, captured cells are stained with the nuclear marker DAPI and fluorescently labeled antibodies to the leukocyte marker CD45 and the epithelial cell marker Pdx-1. Using fluorescence microscopy, Pdx1+/DAPI+/CD45- EpCAM captured cells with intact cellular morphology are counted as CTC's by a blinded technician.

Anthropometric Measures

For all anthropometric measures participants wear study-provided medical scrubs (top and trousers). Height is measured using a wall-mounted digital stadiometer without shoes to the nearest 0.1 centimeter. Weight is measured using a calibrated digital scale to the nearest 0.1 kilogram. Height and weight are used to calculate body mass index (kg/m^2). Waist and hip circumference are measured using a Gulick spring-loaded tape measure to the nearest 0.1 centimeter. Sagittal abdominal diameter is measured using an abdominal caliper (Holtain-Kahn) to the nearest 0.1 centimeter [Zamboni *et al*, 1998]. Body composition is measured using whole-body dual-energy x-ray absorptiometry (DXA; Hologic Discovery; APEX v 13.4 software). DEXA is used to quantify VAT (cm^2), subcutaneous adipose tissue (cm^2), total fat mass (kg), and lean mass (kg). DXA-derived VAT correlates with computed tomography derived VAT (r=0.93; P<0.001) [Micklesfield *et al*, 2012], and is reliable across a large weight spectrum [Bredella *et al*, 2013].

Cardiopulmonary & Functional Status

A resting electrocardiogram is completed to identify any clinically-significant cardiac conduction abnormalities [i.e., 3rd degree heart block, uncontrolled arrhythmia, or ST-

segment depressions (>3 mm)] that may preclude participation in exercise. Functional status is measured using the six minute walk test (6MWT), following the guidelines of American Thoracic Society [ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002]. The outcome of the 6MWT is the distance walked in six minutes, recorded to the nearest meter. The 6MWT is reliable, and correlated with physiologic impairments of strength and power of the lower extremities [Guyatt *et al*, 1985]. The 6MWT is also used to identify persons who may develop signs and symptoms of cardiac distress, such as chest pain or severe shortness of breath during exertion, which may preclude participation in exercise.

Physical Activity

Physical activity is measured using both self-reported and objective measures. The *Paffenbarger Physical Activity Questionnaire* queries activities including flights of stairs climbed, blocks walked, and other leisure-time physical activities performed on a typical day or week [Paffenbarger *et al*, 1993]. The outcome of the *Paffenbarger Physical Activity Questionnaire* is the total energy expenditure associated with leisure-time physical activity, quantified in multiples of resting energy expenditures (METs) using the compendium of physical activities [Ainsworth *et al*, 2000]. The ActiGraph model GT3X+ accelerometer is worn for seven consecutive days. Participants are provided with a diary to document accelerometer wear time. The ActiGraph is a valid and reliable objective measure of ambulatory activity [Bassett *et al*, 2000]. The main outcomes obtained from the ActiGraph accelerometer will be the number of minutes of moderate-to-vigorous physical activity (≥3 METs) and activity-related energy expenditure (kcals), calculated using validated cut-points appropriate for adults [Troiano *et al*, 2008].

Dietary Intake

Dietary intake is measured using three day dietary records collected during two weekdays and one weekend day [Luhrmann *et al*, 1999]. Food records are entered into the Nutrition Data System for Research software (2009 version) by registered dietitians. The resulting data includes 165 micro- and macronutrient variables. Daily caloric intake is the primary covariate of interest to determine if any observed physiologic changes are due to exercise or the result of concurrent dietary alterations.

Patient-Reported Outcomes & Quality of Life Measures

In addition to the above-described physiologic measures, participants complete questionnaires relating to demographics, alcohol and smoking habits, and various self-report questionnaires that are known to influence the quality of life of colon cancer survivors [Committee on Cancer Survivorship: Institute of Medicine and national Research Board, 2006, Harrington *et al*, 2010]. Overall quality of life is assessed using the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) [Ward *et al*, 1999], and the SF-36 [Ware and Sherbourne, 1992]. Pain is assessed using the Brief Pain Index [Cleeland and Ryan, 1994]. Sleep quality is assessed using the Pittsburgh Sleep Quality Index [Buysse *et al*, 1989]. Bowel function is assessed using the Assessment of Bowel Function Questionnaire [Haddock *et al*, 2007]. Cancer-related fatigue is assessed using the Brief Fatigue Inventory [Mendoza *et al*, 1999]. Concerns about cancer recurrence are measured with the Fear of Cancer Recurrence Inventory [Simard and Savard, 2009].

Safety & Adverse Events

Participants in all study groups are asked each week by the study coordinator to identify any incident health events. All reported health events are graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [US Department

of Health and Human Services, 2009]. At the end of the study, all participants complete a healthcare utilization and musculoskeletal injury questionnaire asking about any healthcare encounters and injuries experienced while in the study that may have not been previously reported [Brown *et al*, 2012a, Warren and Schmitz, 2009]. The data safety monitoring plan for this study focuses on monitoring by the principal investigator, along with prompt reporting of excessive adverse events and any serious adverse events to the National Institutes of Health and the Institutional Review Board at the University of Pennsylvania.

Randomization

After completion of baseline measurements, participants were stratified by stage of colon cancer (I vs. II vs. III) and randomized in a 1:1:1 ratio to either the low-dose (150 $min \cdot wk^{-1}$) aerobic exercise group, the high-dose (300 $min \cdot wk^{-1}$) aerobic exercise group, or the usual-care control group.

Treatment Plan

Participants randomized into the low-dose and high-dose exercise groups increase their exercise to 150 $min \cdot wk^{-1}$ and 300 $min \cdot wk^{-1}$, respectively. Participants randomized into the low-dose and high-dose exercise groups are provided with an in-home treadmill (LifeSpan Fitness, TR1200i, Salt Lake City, UT). Treadmills are ordered for participants on the day of randomization. Participants who were unable to accommodate a treadmill in their home were provided with a one-year health club membership (or other membership of similar monetary value) to a facility of the participants choosing. After treadmill delivery and setup, participants meet with a certified clinical exercise physiologist at the University of Pennsylvania to introduce the exercise prescription, and familiarize the participant to use of the treadmill, the completion of exercise logs, use of

a heart rate monitor (described below), appropriate warm-up and cool-down, stretches, and proper footwear for aerobic exercise. The exercise physiologist provides ongoing behavioral support and monitoring of exercise adherence to the study protocol throughout the duration of the study. Behavioral support is individualized to each participant to include the benefits of exercise for colon cancer survivors, strategies to integrate exercise into day-to-day activities, how to identify and overcome barriers to exercise, recruiting friends and family members to provide support in reaching their exercise goals, and how to set simple, measureable, attainable, realistic, and timely (SMART) goals [Weinberg, 1994] to promote exercise self-efficacy and compliance [Courneya *et al*, 2008]. The modes through which behavioral support is delivered are tailored to participant preference to maximize effectiveness of communication and include in-person sessions (as described below), complemented with weekly telephone/text, or email contact. If participants have upcoming scheduled medical procedures that may result in missed exercise (i.e., the day of a surveillance colonoscopy) the participant works with the exercise physiologist to develop a plan for maintaining optimal exercise adherence. If injury or illness prevents exercise for ≥1 week, minutes are allowed to be made-up upon return to exercise.

Exercise compliance is monitored through the use of self-reported and objective measures. All participants randomized to the low-dose and high-dose exercise groups are provided with an exercise log to record the date, modality of aerobic exercise used (any form of aerobic exercise will be acceptable, though most participants elect to use the study provided in-home treadmill), treadmill speed and incline, average heart rate obtained from a study-provided heart rate monitor, duration of exercise, completion of appropriate warm up and cool down, and any new or worsening musculoskeletal

symptoms. Participants are provided with a Polar Heart Rate Monitor (Polar Electro Inc., RS400, Lake Success, NY). The heart rate monitors record up to 99 sessions of exercise. Heart rate monitor data is downloaded to a computer to enable objective monitoring of exercise adherence. Participant exercise logs and objective heart rate data are discussed and reviewed by the exercise physiologist to provide feedback including encouragement, problem solving, and long-term planning to the study participant.

For both the low-dose and high-dose exercise groups, the initial exercise dose prescribed in week one of the study is 60 min. This relatively low volume of exercise allows participants to gain confidence in exercising, allows for time to determine how exercise will be integrated into their schedule, and allows the participant to work towards a practical initial exercise goal that is not overwhelming. Exercise is titrated by 30 $min \cdot wk^{-1}$ as the participant successfully responds to the exercise dose prescribed in the prior week. During the exercise titration phase, participants meet with the exercise physiologist at the university research center each week to review the exercise completed in the prior week, discuss any new musculoskeletal symptoms, side effects, or barriers to exercise. At that time exercise is then titrated for the following week. The planned exercise volume of the low-dose and high-dose exercise groups are 150 $min \cdot wk^{-1}$ and 300 $min \cdot wk^{-1}$, respectively. In the absence of dose-limiting toxicity, low-dose and high-dose study participants have their exercise volume fully titrated by week 4 and 9 of the study, respectively. Delivered over six months, the planned total dose of exercise delivered to the low-dose and high-dose exercise groups is 3,720 minutes and 6,740 minutes, respectively. The intensity of all exercise is prescribed between 50 and 70% of the age-predicted maximum heart rate, consistent with that of moderate-intensity

aerobic exercise (3-6 METs) [Ainsworth *et al*, 2000]. Participants are allowed to complete exercise sessions that are ≥10 minutes to ≤75 minutes in length toward the goal of increasing behavioral feasibility of completing the planned exercise dose.

Exercise adherence is quantified using objective heart rate monitoring. However, heart rate monitors may fail due to technical error or exceed the available memory capacity. In our prior dose-response exercise trial this situation occurred <5% for all exercise sessions [Schmitz *et al*, 2015a, Schmitz *et al*, 2015b]. In this scenario, objective monitoring is used to validate at least three weeks of self-report logs. Upon validation, self-report logs are accepted as a valid substitute for objective heart rate data until heart rate monitor function has been restored. Exercise adherence outcomes include the number of minutes of exercise completed within the target heart rate range for each week of the study and over six months, and the percent of prescribed minutes completed in each week of the study and over six months.

Participants randomized into the usual-care control group are asked to maintain their pre-study levels of physical activity and/or follow the recommendations provided by their physician. After completing six month measures, control group participants are provided with an in-home treadmill and individualized exercise program, similar to that prescribed to the two exercise groups. Upon study completion, all participants are allowed to keep their study-provided treadmills.

Statistical Considerations

Thirty nine participants were randomized to the three study arms (control, 150 $min \cdot wk^{-1}$, 300 $min \cdot wk^{-1}$), toward the goal of having 30 participants (10 per arm) with study endpoint data (76% completion rate). This sample size provides adequate statistical power for

the primary outcome biomarkers (sICAM-1 and sVICAM-1) with a hypothesis for a linear dose-response trend. Against the hypothesis of a dose-response relationship with decreases of 22 and 44 units for low-dose and high-dose respectively for sICAM-1 and 74 and 148 units for sVCAM-1, 30 participants provide 80% power for two tests (one for sICAM-1 and one for sVCAM-1), each tested with a type I error rate of 0.025, to maintain the experiment-wise overall error rate of 0.05. The estimated change in sICAM-1 and sVCAM-1 is clinically meaningful and consistent with prior exercise interventions in non-cancer populations [Adamopoulos *et al*, 2001, Hamdy *et al*, 2003, Leinonen *et al*, 2003, Saetre *et al*, 2011, Tonjes *et al*, 2007].

The target sample size provides sufficient statistical power to examine key secondary outcomes that include VAT and fasting insulin. Against the hypothesis of a dose-response relationship with an increase in VAT of +8.6% (+14 cm^2) in the control group, +1.7% (+2.9 cm^2) in the low-dose group, and -6.9% (-11.6 cm^2) in the high-dose group and a pooled standard deviation of ±17%, 30 participants provide 80% power tested with a type I error rate of 0.05. These changes are estimated from a prior dose-response exercise study [Slentz *et al*, 2005, Slentz *et al*, 2009, Slentz *et al*, 2004]. Against the hypothesis of a dose-response relationship with an increase in fasting insulin of +1.1 μU/mL in the control group, –0.5 μU/mL in the low-dose group, and –0.9 μU/mL in the high-dose group, and a pooled standard deviation of ±0.7 μU/mL, 30 participants provide 80% power tested with a type I error rate of 0.05. These changes are estimated from a prior dose-response exercise study [Houmard *et al*, 2004]. The exploratory outcomes for this trial include enumeration of CTCs, functional status, and patient-reported outcomes and quality of life measures. There are limited data to determine what proportion of colon cancer survivors who have completed adjuvant therapy for colon

cancer will have enumerable CTCs. Further, it is unknown how exercise may impact CTC volume. Consequently, this outcome is considered exploratory with no directional hypothesis. We hypothesize that functional status, and patient-reported outcomes and quality of life measures will improve in dose-response fashion.

To identify characteristics associated with inquiry about study participation and randomization onto the study protocol we had 80% power to detect an odds ratio as small as 1.3 and 1.7, respectively. Both sets of analyses were tested with the type I error rate of 0.05.

Statistical Analysis

The feasibility of exercise is quantified by comparing the proportion of participants in each group who achieve ≥80% of their prescribed exercise dose. The safety of exercise is quantified by comparing the proportion of participants who experience adverse events in each of the three study groups. For each of the primary and secondary physiologic outcomes, a linear mixed-effects regression model is used to compare the change in biomarker levels for each group while adjusting for the baseline value of the dependent variable. All analyses follow an intention-to-treat approach. Models are fit to include dose as a linear term, and model fit is examined using standard methods. Alternatives to a linear dose trend include transformations of dose, such as average actual dose, log-transformed dose per week, or second-order polynomial (i.e., dose and dose^2). In the absence of a dose-response relationship, each of the two intervention groups (low-dose and high-dose exercise) is compared to the control arm using a two-sided t-test. Characteristics associated with inquiry about study participation and randomization onto the study protocol are identified using two sets of logistic regression analyses: one set to compare characteristics between those who inquired about study participation versus

those who do not inquire about participation; and one set to compare characteristics between those who were randomized onto the study protocol versus those who were not randomized onto the study protocol. Characteristics with $P<0.20$ in univariable models are entered simultaneously in a multivariable model.

Results

Between January and July 2015, 1,435 letters were delivered to potentially-eligible persons with an ICD-O-3 code for colon cancer (**Table 2.1**). Two recipients of the study letter expressed concern about disclosure of private health information (0.001%). These two recipients clarified their concerns with the principal investigator and were provided with the appropriate contact at the PCR. These two participants were excluded from the analyses presented herein reducing the analytic sample to 1,433. Colon cancer survivors who were invited to participate in this trial were representative of colon cancer survivors in the United States with respect to age, sex, race, and disease stage [Siegel *et al*, 2014]. The median distance from the University of Pennsylvania to the zip-code centroid of survivors invited to participate was 20 kilometers [interquartile 25-75% range: 10-33] and ranged from 0.4 (~4 city blocks) to 71 kilometers.

Among the 1,433 colon cancer survivors invited to participate, 126 (8.8%) inquired about participation (**Figure 2.2**). Eleven letters were mailed to screen one potentially-eligible participant. In univariate analysis, colon cancer survivors who inquired about participation were younger [Odds Ratio: 0.82 per 5-year increment (95% CI: 0.76-0.88); $P<0.001$; **Table 2.1**], and were more likely to be treated with chemotherapy [Odds Ratio: 1.68 (95% CI: 1.15-2.44); $P=0.007$], compared to those who did not inquire about participation. In a multivariable model, age was associated with inquiring about study

participation [Odds Ratio: 0.83 per 5-year increment (95% CI: 0.77-0.89); *P*<0.001], but treatment with chemotherapy was no longer statistically significant [Odds Ratio: 1.43 (95% CI: 0.98-2.10); *P*=0.066].

Among the 126 colon cancer survivors who inquired about participation, 102 were screened (81%). The remaining 24 inquiries were not screened due to the study reaching its accrual goal. Among the 102 colon cancer survivors screened, 46 (45%) were not interested in participating after learning more about the study. The most commonly cited reasons for not being interested in the study were: being too busy (n=27; 59%); traveling into the city of Philadelphia would be too burdensome (n=13; 28%); having other health concerns (n=5; 11%); and not wanting to be randomized to a group that may not include exercise (n=1; 2%). Among the 102 colon cancer survivors screened, 17 (17%) were not eligible for participation after completing the telephone interview. The most common reasons for ineligibility included: having a history of another cancer (n=8; 47%); currently exercising ≥150 $min \cdot wk^{-1}$ (n=3; 18%); having a cardiac condition (n=3; 18%); having recurrent or metastatic colon cancer (n=2; 12%); and being ≥36 months post cancer therapy (n=1; 5%).

Among the 102 colon cancer survivors who were screened, 39 (38%) were randomized onto the study protocol. Thirty seven letters were mailed to randomize one participant onto the study protocol. Thirty-two participants were recruited during phase 1 eligibility (82%; most strict, January and March letter mailings), two participants in phase 2 (5%; less strict, May letter mailing), and five participants in phase 3 (13%; least strict, July letter mailing). It is not clear why recruitment was most successful during the more restrictive phases of recruitment. This may be due in part to the month in which participants were recruited which may have influenced their willingness to participate in a

trial of lifestyle modification. Compared with mailings in the month of January, mailings in the months of March, May, and July were associated with lower study inquiry and randomization rates, though these comparisons did not reach the threshold for statistical significance. No participants had their physician decline approval to participate in the study. In univariate analyses, colon cancer survivors who were randomized onto the study protocol were younger [Odds Ratio: 0.69 per 5-year increment (95% CI: 0.60-0.78); $P<0.001$], and were more likely to be treated with chemotherapy [Odds Ratio: 2.66 (95% CI: 1.32-5.39); $P=0.006$]. In a multivariable model, age was associated with randomization onto the study protocol [Odds Ratio: 0.70 per 5-year increment (95% CI: 0.61-0.79); $P<0.001$], and treatment with chemotherapy was attenuated to marginal statistical significance [Odds Ratio: 2.01 (95% CI: 0.98-4.13); $P=0.056$].

Among participants randomized to one of the two exercise groups, the median time from randomization to treadmill delivery and setup was 12 days [interquartile 25-75% range: 10-15]. The final trial participant was randomized in August 2015. Six month endpoint data collection was completed in February 2016.

Discussion

The COURAGE trial is an NCI sponsored, phase II, randomized, dose-response exercise trial that seeks to test the feasibility, safety, and physiologic effects of two distinct doses of moderate-intensity aerobic exercise compared to a usual-care control group among colon cancer survivors. The results of this trial will provide preliminary information regarding the appropriate dose of aerobic exercise to optimize biomarkers that may mediate the relationship between exercise and colon cancer recurrence and clarify important design aspects for future phase 2 and phase 3 randomized controlled trials.

The primary recruitment method for the COURAGE trial was postal mailings to potentially-eligible colon cancer survivors identified within the PCR. Historically the recruitment of survivors of colon cancer into lifestyle modification trials has been challenging [Courneya *et al*, 2014, Ligibel *et al*, 2012, Meyerhardt, 2013, Pinto *et al*, 2013, van Waart *et al*, 2015]. The reasons for this have not been fully explained, but may be due in part to the fact that colon cancer survivors are often older, have other comorbid health conditions, or residual toxicity from treatment (i.e., neuropathy), each of which may influence willingness to participate in a program of lifestyle modification [Brown and Schmitz, 2014b]. Several studies have described their experience in recruiting colon cancer survivors into trials of lifestyle modification. Pinto *et al*. recruited colon cancer survivors to a telephone-based physical activity intervention that aimed to increase participation in physical activity and improve self-reported quality-of-life outcomes [Pinto *et al*, 2013]. Despite implementing various recruitment strategies (informational mailings, in-clinic recruitment, and community presentations), they were unable to recruit the required sample size of 134 participants; only randomizing 46 colon cancer survivors over 39 months (~1.5 participants per month). The CHALLENGE trial is a randomized phase 3 trial that seeks to recruit high-risk stage II and stage III colon cancer survivors to a three year physical activity program that aims to improve disease-free survival [Courneya *et al*, 2008]. When the CHALLENGE trial was designed, recruitment of 962 colon cancer survivors was estimated to require 36 months (~27 participants per month). Despite being open at 20 centers in Canada and 22 centers in Australia, over 55-months, 250 colon cancer survivors have been randomized (~4.5 participants per month) [Courneya *et al*, 2014]. At a single institution over seven months, the COURAGE trial randomized 39 colon cancer survivors (~5.5 participants per month). At the time the trial met its planned accrual goal and closed to enrollment, an additional 24 potentially-eligible colon cancer

survivors expressed interest in participating and were waiting to be screened for trial enrollment.

Each of the above-described trials is unique in their eligibility criteria, intervention characteristics, and endpoints of interest; our recruitment experience indicates that utilizing population-based cancer registries to recruit colon cancer survivors into a lifestyle modification trial is feasible. The use of population-based cancer registries is disseminable to other cancer centers for accrual in multicenter trials, and may help to address an important barrier in the conduct of future lifestyle modification trials in this population. A potential limitation to the use of population-based cancer registries is the six to nine month delay that may occur from the time of diagnosis to entry into the registry. This limitation is of importance for trials that seek to modify behavior during or shortly after the completion of adjuvant therapy. To address this limitation, many cancer registries now offer rapid case ascertainment which accelerates the reporting process to within one month of diagnosis [Beskow *et al*, 2006]. Another explanation to the high inquiry and screening rates in this study was the provision of an in-home treadmill. The mailed flyer did describe this novel feature of the study. As intended, this may have provided additional incentive to inquire about participation. Given the potential benefit of exercise to improve disease outcomes, developing methods to recruit colon cancer survivors to participate in lifestyle modification trials is of critically high importance.

Colon cancer survivors who inquired about trial participation were younger than those who did not inquire about trial participation. Similarly, colon cancer survivors who were randomized onto the trial protocol were younger than those who were not randomized. This pattern is common to many trials, regardless of the intervention. In an analysis of 21 Southwest Oncology Group (SWOG) therapeutic trials that included 5,190 cancer

patients with 21 types of cancer, trial enrollees were significantly younger than non-enrollees (P<0.001) [Unger *et al*, 2014]. These findings underscore the need for continued research to identify methods to communicate opportunities about clinical trial participation to older adults in an efficient and scalable manner. In our multivariable model, treatment with chemotherapy was of marginal statistical significance for both inquiry about study participation (P=0.066) and randomization onto the study protocol (P=0.056). This finding indicates the interest of patients with a higher probability of recurrence (i.e., high-risk stage II and stage III) to inquire and participate in a clinical trial of lifestyle modification. Collectively, these data indicate that with exception of age, COURAGE trial participants are similar to the broader community of colon cancer survivors on measured characteristics, such as sex, race, time since diagnosis, clinico-pathologic tumor features, and geographic proximity to the University of Pennsylvania.

In addition to obtaining important information about the feasibility and safety of the dose-response effects of exercise among colon cancer survivors, this trial will gather preliminary data regarding physiologic changes in biomarkers that are hypothesized to mediate the relationship between exercise and disease outcomes. sICAM-1 and sVCAM-1 are cell-adhesion molecules that promote the growth of existing micro-metastases, and promote CTC differentiation, contact inhibition, and apoptosis [Paschos *et al*, 2009]. The down regulation of ICAM-1 attenuates the invasive potential of colon cancer cells and has been recommended as a therapeutic target [Howard *et al*, 2014]. VCAM-1 has also been recommended as a therapeutic target [Schlesinger and Bendas, 2015]. ICAM-1 and VCAM-1 have also been demonstrated to influence the metastatic potential of melanoma and gastric cancers [Giavazzi *et al*, 1992, Nakashio *et al*, 1997]. We hypothesize that exercise may inhibit both seeding of distant organs and the

cultivation of the angiogenic milieu that is thought to be required for the growth of micro-metastases. We speculate that exercise may have direct effects on anti-cancer myokines, such as secreted protein acidic and rich in cysteine (SPARC) [Aoi *et al*, 2013], and may also have indirect effects through pathways that include improved metabolic homeostasis (i.e., VAT and insulin). Several studies have demonstrated that abdominal adiposity, particularly VAT, is associated with poor colon cancer outcomes [Ballian *et al*, 2012, Guiu *et al*, 2010, Haydon *et al*, 2006a, Moon *et al*, 2008, Prizment *et al*, 2010, Rickles *et al*, 2013]. VAT associates with insulin among colon cancer survivors (r=0.519; P<0.001) [Jiang *et al*, 2014], and is implicated in the recurrence of colon cancer [Giovannucci, 2001, Sandhu *et al*, 2002]. We hypothesize that exercise may reduce VAT and fasting insulin and potentially inhibit the growth of existing micro-metastases. As an exploratory aim, we will examine CTCs using the innovative GEDI platform [Gleghorn *et al*, 2010]. We hypothesize that CTCs disseminate via the circulation during the earliest stages of recurrent metastatic growth, mirroring what occurs during the primary tumor setting. If this does indeed occur, we are uniquely situated to detect this phenomenon using GEDI. If exercise delays or inhibits metastases, this may be reflected in CTC concentration.

There are several strengths of this trial. The use of two intervention groups, each prescribed a distinct dose of exercise will allow us examine how feasibility, safety, and physiologic effects differ along the exercise dose curve. Given the eligibly criteria, these two different doses of exercise will require that some participants modestly increase their exercise and others to increase over 10-fold. The exercise intervention was designed to allow for scalability to larger phase 2 and ultimately a phase 3 clinical trial. The exercise program allows for flexibility, emphasizing a home-based program, blended with

supervised training and ongoing behavioral and clinical support from an exercise physiologist. The provision of home-based treadmills serves a dual purpose of providing a reasonable incentive for participation, and promoting feasibility and favorable adherence to the exercise prescription over six months.

There exist several limitations to this trial. The primary limitation to this study is the small sample size which may limit interpretation of the study findings. However, this study was designed to gather important feasibility, safety, and preliminary physiologic data to refine important design aspects for future phase 2 and phase 3 trials. We acknowledge 300 min·wk^{-1} is a large weekly dose of aerobic exercise. We elected to compare 150 and 300 min·wk^{-1} of aerobic exercise to complement ongoing work which prescribes 225 min·wk^{-1} [Courneya *et al*, 2008, Meyerhardt, 2013] and to parallel the epidemiologic data that suggest a dose-response relationship with disease outcomes [Campbell *et al*, 2013, Des Guetz *et al*, 2013, Je *et al*, 2013, Kuiper *et al*, 2012, Meyerhardt *et al*, 2006, Meyerhardt *et al*, 2006, Meyerhardt *et al*, 2009, Schmid and Leitzmann, 2014]. Our research team has been successful in promoting adherence to the prescription of 300 min·wk^{-1} of aerobic exercise in our prior studies [Schmitz *et al*, 2015a, Schmitz *et al*, 2015b]. The high-dose exercise group received five additional in-person sessions with the exercise physiologist which may differentially impact adherence rates between the low-dose and high-dose exercise groups. Although VAT and fasting insulin are secondary outcomes of this trial, participants were not recruited on the basis of being overweight or obese at baseline and/or having high levels of fasting insulin. Consequently this may limit our ability to detect significant exercise-induced improvements in these outcomes. We considered the inclusion of survivors of rectal cancer, but restricted inclusion to colon cancer survivors, as there is limited

evidence to support the benefit of exercise in improving rectal cancer outcomes [Meyerhardt *et al*, 2009].

Conclusion

In conclusion, the findings from this trial will be useful in understanding the feasibility, safety, and physiologic effects of two doses of aerobic exercise among colon cancer survivors. These findings contribute toward the goal of conducting a definitive trial to assess the effects of exercise on disease outcomes among colon cancer survivors.

Disclosure Statement

The authors declare no conflicts of interest. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Table 2.1 Demographic, clinical, and recruitment characteristics associated with study inquiry and randomization.

	Invited to Participate (n=1,433)	Inquired about Participation (n=126)			Randomized (n=39)		
Characteristic	n (%) or Median [IQR]	n (%) or Median [IQR]	OR (95% CI)[a]	*P*	n (%) or Median [IQR]	OR (95% CI)[b]	*P*
Age,[c] y	68 [58-77]	59 [53-59]	0.82 (0.76-0.88)	<0.001	55 [47-61]	0.69 (0.60-0.78)	<0.001
<70 y	769 (54%)	95 (75%)	1.00		36 (92%)	1.00	
≥70 y	664 (46%)	31 (25%)	0.35 (0.23-0.53)	<0.001	3 (8%)	0.09 (0.03-0.30)	<0.001
Sex, n (%)							
Male	710 (50%)	55 (44%)	1.00		15 (38%)	1.00	
Female	723 (50%)	71 (56%)	1.29 (0.90-1.87)	0.167	24 (62%)	1.59 (0.83-3.06)	0.164
Race, n (%)							
White	1,086 (76%)	97 (77%)	1.00		31 (79%)	1.00	
Nonwhite	320 (22%)	29 (23%)	1.02 (0.66-1.57)	0.943	8 (21%)	1.59 (0.83-3.06)	0.164
Missing or Unknown	27 (2%)	0 (0%)	—	—	0 (0%)	—	—
Time Since Diagnosis,[c] mo	16 [10-22]	16 [11-21]			15 [10-21]		
≤12 mo.	466 (32%)	37 (29%)	1.00		14 (36%)	1.00	
12-18 mo.	384 (27%)	36 (29%)	1.20 (0.74-1.94)	0.458	8 (20%)	0.69 (0.28-1.65)	0.403
≥18 mo.	583 (41%)	53 (42%)	1.16 (0.75-1.80)	0.509	17 (44%)	0.97 (0.47-1.99)	0.933
Anatomical Location, n (%)							
Left Colon	534 (38%)	57 (45%)	1.00		18 (46%)	1.00	
Right Colon	866 (60%)	67 (53%)	0.70 (0.48-1.02)	0.061	21 (54%)	0.71 (0.38-1.35)	0.298
Unknown or Multiple	33 (2%)	2 (2%)	0.54 (0.13-2.31)	0.407	0 (0%)	—	—
AJCC Stage,[d] n (%)							
I	349 (24%)	28 (22%)	1.00		5 (13%)	1.00	
II	523 (37%)	44 (35%)	1.05 (0.64-1.73)	0.838	14 (36%)	1.89 (0.67-5.30)	0.225
III	561 (39%)	54 (43%)	1.22 (0.76-1.97)	0.412	20 (51%)	2.54 (0.95-6.84)	0.064
Invasion Through Bowel Wall (T Stage), n (%)							
T1	247 (17%)	23 (18%)	1.00		4 (10%)	1.00	
T2	174 (12%)	10 (8%)	0.59 (0.27-1.28)	0.184	2 (5%)	0.71 (0.13-3.90)	0.690
T3	773 (54%)	74 (59%)	1.03 (0.63-1.68)	0.903	25 (64%)	2.03 (0.70-5.89)	0.193
T4	239 (17%)	19 (15%)	0.84 (0.44-1.59)	0.594	8 (21%)	2.10 (0.62-7.08)	0.230
Lymph Node Involvement (N Stage), n (%)							
N0 (0)	872 (61%)	72 (57%)	1.00		19 (49%)	1.00	
N1 (1-3)	381 (27%)	34 (27%)	1.09 (0.71-1.67)	0.696	15 (38%)	1.84 (0.92-3.66)	0.082
N2 (≥4)	180 (12%)	20 (16%)	1.39 (0.82-2.34)	0.219	5 (13%)	1.28 (0.47-3.48)	0.625
Grade of Differentiation, n (%)							
Well (low)	123 (9%)	6 (5%)	1.00		2 (5%)	1.00	
Moderate (intermediate)	940 (66%)	85 (67%)	1.94 (0.83-4.54)	0.127	29 (74%)	1.92 (0.45-8.17)	0.374
Poor or Undifferentiated (high)	275 (19%)	25 (20%)	1.94 (0.78-4.88)	0.154	5 (13%)	1.12 (0.21-5.85)	0.893
Unknown	95 (6%)	10 (8%)	2.29 (0.80-6.56)	0.121	3 (8%)	1.97 (0.32-12.05)	0.462
Lymphovascular Invasion, n (%)							
Absent	876 (61%)	73 (58%)	1.00		23 (59%)	1.00	
Present	391 (27%)	36 (29%)	1.11 (0.73-1.69)	0.609	12 (31%)	1.17 (0.58-2.38)	0.657
Unknown	166 (12%)	17 (13%)	1.25 (0.72-2.19)	0.423	4 (10%)	0.91 (0.31-2.68)	0.872
Chemotherapy, n (%)	709 (50%)	77 (61%)	1.68 (1.15-2.44)	0.007	28 (72%)	2.66 (1.32-5.39)	0.006
Month Study Letter Mailed, n (%)							
January	865 (60%)	85 (67%)	1.00		31 (79%)	1.00	
March	100 (7%)	7 (6%)	0.69 (0.31-1.54)	0.365	1 (3%)	0.27 (0.04-2.01)	0.202
May	119 (8%)	6 (5%)	0.49 (0.21-1.14)	0.098	2 (5%)	0.46 (0.11-1.94)	0.291
July	349 (24%)	28 (22%)	0.80 (0.51-1.25)	0.328	5 (13%)	0.39 (0.15-1.01)	0.053
Distance to Institution,[c] km	20 [10-34]	21 [9-26]	1.03 (0.97-1.09)	0.327	20 [9-40]	1.07 (0.97-1.17)	0.182

[a]Odds Ratio (OR) and 95% Confidence Interval (CI) comparing those who inquired about participation to those who were invited to participate.
[b]Odds Ratio (OR) and 95% Confidence Interval (CI) comparing those who were randomized to those who were invited to participate.
[c]Median and Interquartile [25-75%] range.
[d]AJCC: American Joint Committee on Cancer (7th edition).

Figure 2.1 Study Schema

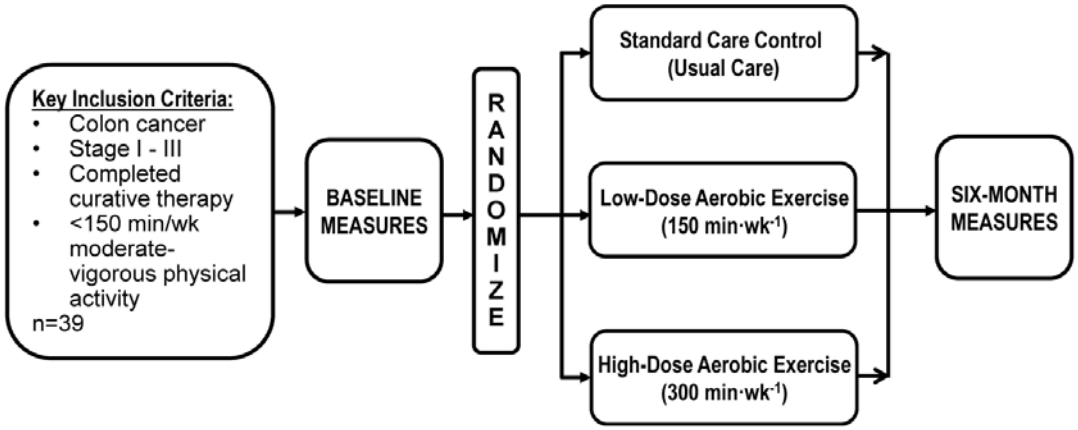
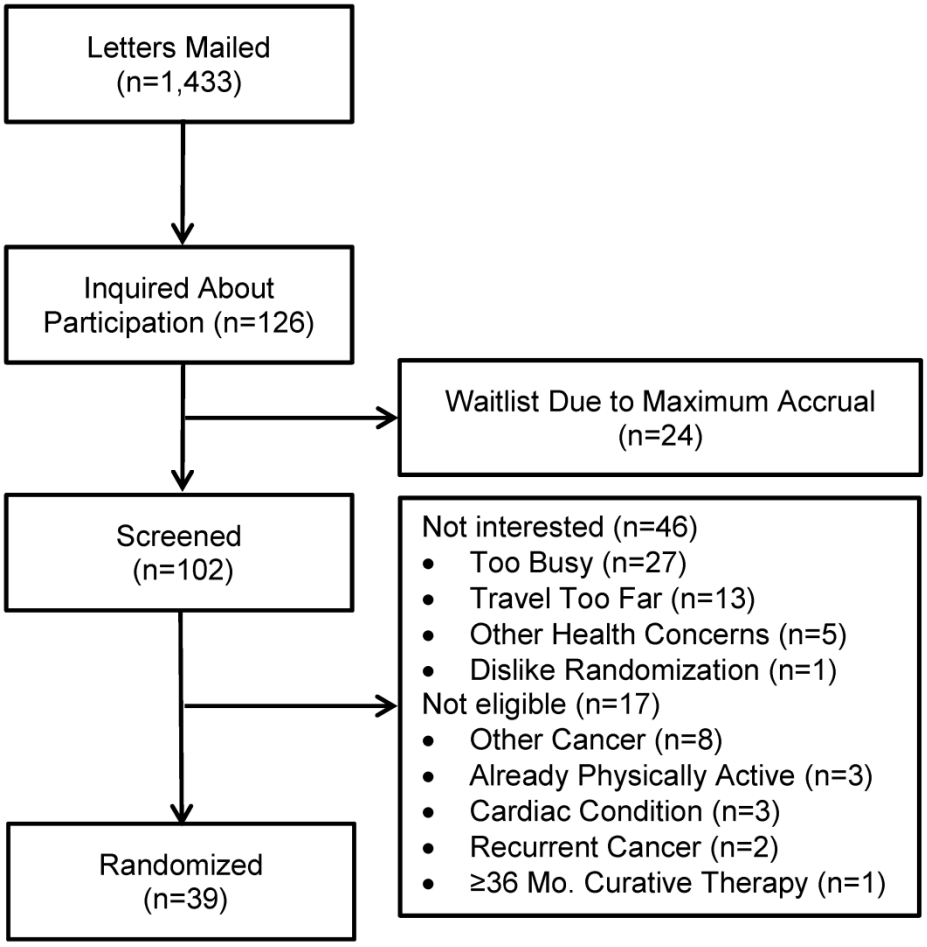


Figure 2.2 CONSORT Diagram



CHAPTER 3. The Dose-Response Effects of Exercise on Body Composition among Colon Cancer Survivors: A Randomized Controlled Trial

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Abstract

Background: Physical activity is associated with a lower risk of disease recurrence among colon cancer survivors. Excess visceral adipose tissue (VAT) is associated with a higher risk of disease recurrence among colon cancer survivors. The pathways through which physical activity alters disease outcomes are unknown, but may be mediated by changes in VAT.

Methods: Between January 2015 and August 2015, 39 stage I-III colon cancer survivors were randomized to one of three groups: usual-care control, 150 min·wk^{-1} of aerobic exercise (low-dose), and 300 min·wk^{-1} of aerobic exercise (high-dose) for six months. The pre-specified key body composition outcome was VAT quantified using dual energy x-ray absorptiometry. Other body composition outcomes were exploratory.

Results: Exercise reduced VAT in dose-response fashion (P_{trend}=0.008). Compared to the control group, the low-dose and high-dose exercise groups lost 9.5 cm^2 (95% CI: –22.4, 3.5) and 13.6 cm^2 (95% CI: –27.0, –0.1) in VAT, respectively. Each 60 min·wk^{-1} increase in exercise predicted a 2.7 cm^2 (95% CI: –5.4, –0.1) reduction in VAT. Exercise reduced waist circumference in dose-response fashion (P_{trend}<0.001). Compared to the control group, the low-dose and high-dose exercise groups lost 1.5 cm (95% CI: –4.0, 1.1) and 4.5 cm (95% CI: −7.1, –1.9) in waist circumference, respectively. Each 60 min·wk^{-1} increase in exercise predicted a 0.9 cm (95% CI: –1.4, –0.4) reduction in waist circumference.

Conclusion: Aerobic exercise reduces VAT in dose-response fashion among patients with stage I-III colon cancer. Continued research to elucidate the mechanistic pathways through which physical activity alters disease outcomes is warranted.

Introduction

Each year 83,000 people are diagnosed with non-metastatic colon cancer in the United States [Siegel *et al*, 2014]. Despite efficacious surgical and chemotherapeutic interventions, 25-40% will experience recurrent and metastatic disease within three-years of diagnosis [André *et al*, 2004, Clinical Outcomes of Surgical Therapy Study Group, 2004, Quasar Collaborative Group, 2007], and 91% of those who recur within three-years, die by five-years [Sargent *et al*, 2005]. Therefore it is critical to study additional therapies that reduce the risk of recurrent disease and promote long-term survival in this population.

Participation in physical activity after diagnosis of colon cancer is associated with a lower risk of recurrence and mortality [Meyerhardt *et al*, 2006]. This observation is independent of various demographic, clinico-pathologic, and treatment-related prognostic factors [Campbell *et al*, 2013, Kuiper *et al*, 2012, Meyerhardt *et al*, 2006, Meyerhardt *et al*, 2006, Meyerhardt *et al*, 2009]. A consistently reported observation 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 approximately 300 minutes per week ($min \cdot wk^{-1}$), are associated with more favorable disease outcomes [Campbell *et al*, 2013, Kuiper *et al*, 2012, Meyerhardt *et al*, 2006, Meyerhardt *et al*, 2006, Meyerhardt *et al*, 2009].

The biologic or biobehavioral pathways through which exercise may favorably alter disease outcomes among colon cancer survivors are unknown. One plausible pathway includes exercise-induced alterations in body composition [Parkin *et al*, 2014]. Excess visceral adipose tissue (VAT) is associated with an increased risk of disease recurrence and mortality among colon cancer survivors [Lee *et al*, 2015, Moon *et al*, 2008, Rickles

et al, 2013]. In addition, waist circumference (an anthropometric proxy for VAT) is associated with cancer-specific and all-cause mortality among colon cancer survivors [Haydon *et al*, 2006a]. These observations are further strengthened by evidence that the VAT of colon cancer survivors exhibits extensive metabolomic activity [Liesenfeld *et al*, 2015], and polymorphisms within adiposity-related genes predict disease recurrence among colon cancer survivors [Sebio *et al*, 2015].

Exercise reduces VAT among non-diabetic persons with obesity in a dose-response fashion [Slentz *et al*, 2005]; however the dose-response effects of exercise on VAT and other body composition measures, such as waist circumference, have not been examined among colon cancer survivors. Understanding how exercise may alter pathways that are hypothesized to influence disease outcomes and the sensitivity of such pathways to respond to different doses of exercise will help to improve the specificity of exercise prescriptions in this population, and provide experimental evidence to support the findings of observational studies that document the benefits effects of exercise among colon cancer survivors.

The COURAGE trial was a randomized controlled trial with the primary aim of examining the safety, feasibility, and biological efficacy of 150 and 300 $min \cdot wk^{-1}$ of aerobic exercise versus usual care control over six months among men and women with a history of non-metastatic colon cancer [Brown *et al*, 2016]. Here we report body composition outcomes. VAT quantified using dual-energy x-ray absorptiometry (DXA) was pre-specified as the key body composition outcome of this trial. Our hypothesis was that exercise would reduce VAT in a dose-response fashion.

Methods

Participants

Detailed study methods of the COURAGE trial were published previously [Brown *et al*, 2016]. Potentially-eligible participants were recruited throughout the metropolitan Philadelphia region. Participants were eligible if they: 1) were diagnosed with histologically-proven stage I-III colon cancer; 2) completed surgical resection and adjuvant chemotherapy within 36 months of entering the study; 3) self-reported participating in ≤150 min·wk^{-1} of moderate or vigorous intensity physical activity using the Paffenbarger Physical Activity Questionnaire [20]; 4) were of age ≥18 years; 5) provided written physician approval; 6) had no additional surgery planned within the six month intervention period (including colostomy reversal); 7) had the ability to walk unaided for six minutes. Participants were ineligible if they: 1) had a history of another primary cancer (other than non-melanoma skin-cancer); 2) had evidence of metastatic cancer; 3) were pregnant or breast feeding; 4) were unable to provide a baseline blood sample; 5) had a myocardial infarction or coronary revascularization procedure within the past three months; 6) had uncontrolled hypertension, defined as a systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥100 mm Hg; 7) had high-risk or uncontrolled heart arrhythmias (not including atrial fibrillation); 8) had clinically significant heart valve disease; 9) had decompensated heart failure; 10) had a known aortic aneurysm; or 11) 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.

Participants were stratified on cancer stage (AJCC 7th Edition: I vs II vs III) and randomized into one of three groups: low-dose aerobic exercise (150 min·wk^{-1}), high-dose aerobic exercise (300 min·wk^{-1}), or usual care control. This study was approved by

the University of Pennsylvania Institutional Review Board. Participants provided written informed consent and written approval from their physician prior to participation.

Intervention

Aerobic exercise was performed over six 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. Participants also used 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 a 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 day) 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 to the study protocol throughout the duration of the study through the use of weekly telephone and email communications. Exercise intensity was prescribed at 50-70% of the age-predicted maximum heart rate (3-6 METs [Ainsworth *et al*, 2000]). The low-dose and high-dose groups progressed towards of the goal of 150 or 300 $min \cdot wk^{-1}$ of exercise, respectively. Detailed methods of the exercise intervention were published previously [Brown *et al*, 2016].

Participants randomized into the usual-care control group were asked to maintain their pre-study levels of physical activity and/or follow the recommendations provided by their physician. After completing six month measures, control group participants were

provided with an in-home treadmill and individualized exercise program, similar to that prescribed to the two exercise groups. Upon study completion, all participants were allowed to keep their study-provided treadmills.

Measurements

Baseline and follow-up measurements were obtained by trained staff members who were blinded to treatment assignment. Demographic characteristics including age, sex, race, and education were self-reported. Smoking status was obtained from a standardized questionnaire [Pleis *et al*, 2009]. Daily caloric intake was quantified using three-day food records that were analyzed by a registered dietitian using the Nutrition Data System for Research software (v.2014). Moderate to vigorous intensity physical activity was quantified using an accelerometer (ActiGraph GT3X+) with validated cut-points [Troiano *et al*, 2008]. Clinical information including cancer stage, treatment with chemotherapy, and performance status were obtained from the Pennsylvania State Cancer Registry, pathology reports, or physician records. Five-year predicted overall survival was calculated using a validated prognostic model for colon cancer [Weiser *et al*, 2011].

Body Composition Outcomes

The pre-specified key body composition outcome was VAT quantified using DXA. All other body composition outcomes were considered exploratory. All participants underwent whole-body DXA (Hologic Horizon, Bedford MA). All DXA scans were reviewed for quality assurance by a certified DXA technician who was blinded to study group [Powers *et al*, 2014]. The DXA scanner was calibrated daily using an anthropomorphic spine phantom and thrice weekly using a whole body phantom. DXA was used to quantify VAT (cm^2), subcutaneous adipose tissue (cm^2), fat mass (kg), lean

mass (kg), and bone mineral density (g/m^2) using Hologic APEX v.13.5 software. DXA-derived VAT has been validated against computed tomography-derived VAT (r=0.93; P<0.001) [Micklesfield *et al*, 2012], and has been used across a large body mass spectrum [Bredella *et al*, 2013]. Other anthropometric outcomes that were measured in duplicate included height (m), body mass (kg), waist & hip circumferences (cm), and sagittal abdominal diameter (cm). Height and body mass were used to calculate body mass index (BMI; kg/m^2).

Statistical Analysis

Descriptive statistics presented for baseline variables include counts and proportions for categorical variables and means ± standard deviations for continuous variables. Categorical baseline characteristics were compared among the three groups using Fisher's exact test, and continuous baseline characteristics were compared among the three study groups using the Kruskal-Wallis test. Based on prior research [Slentz *et al*, 2005, Slentz *et al*, 2009, Slentz *et al*, 2004], we estimated a change in VAT of +14 cm^2 (+8.6%) in the control group, +2.9 cm^2 (+1.7%) in the low-dose group, and –11.6 cm^2 (−6.9%) in the high-dose group with a pooled standard deviation of ±11 cm^2 (±17%) over six months. Against the hypothesis of a dose-response relationship, 39 participants provided ≥80% power with a type I error rate of 5% (α=0.05). All inferential analyses were conducted on an intention-to-treat basis. Change in VAT (and other outcomes) was evaluated from baseline to six months in the three groups using repeated-measures mixed-effects regression models. This statistical approach includes all available data and accounts for the correlation between repeated measures. The baseline value of the dependent variable and cancer stage (randomization stratification factor) were included as covariates in the regression models [Fitzmaurice *et al*, 2004]. Group-by-time

interaction terms were estimated as fixed-effects in the regression model. Results from the repeated-measures mixed-effects regression models are presented as least-square means (LS Mean) ± standard error (SE). To evaluate the presence of a dose-response relationship across randomized groups, a test of trend was conducted by examining linear contrasts. All statistical analyses were completed using Stata/MP Version 14.1 (StataCorp, College Station, TX).

Results

Between January 2015 and August 2015, 39 colon cancer survivors were recruited and randomized with data collection ending in February 2016. Baseline characteristics of study participants are presented in **Table 3.1**. Age ranged from 35–81 years. BMI ranged from 20–43 kg/m^2; 51% of participants were obese (BMI ≥30 kg/m^2). Objectively-measured moderate to vigorous intensity physical activity ranged from 3–34 $min \cdot d^{-1}$; 61% of participants self-reported not participating in any physical activity since their colon cancer diagnosis. Time since finishing colon cancer treatment ranged from 1–21 months. Five-year predicted overall survival ranged from 35–92%. **Figure 3.1** shows the flow of the 39 randomized participants through the study. One participant was lost to follow-up (97% follow-up rate).

Exercise prescription program variables are presented in **Table 3.2**. Over six months, adherence to the prescribed volumes of exercise in the low-dose and high-dose groups were 92.8±2.44% and 89.0±2.64%, respectively (P=0.287). Average exercise volume in the low-dose and high-dose groups were 141.5±9.92 $min \cdot wk^{-1}$ and 247.2±10.71 $min \cdot wk^{-1}$, respectively (∆ between groups: 105.7±14.60; P<0.001). The high-dose group exercised on more days per week (P=0.001), more sessions per day (P=0.001), longer duration per session (P<0.001), and required more weeks to progress to the full dose of

prescribed exercise (P=0.007), as compared to the low-dose group. Exercise intensity was 70.7±0.85% of the age-predicted maximal heart rate, the proportion of exercise sessions using the study-provided treadmill was 76.5±9.4%, and the proportion of exercise sessions validated with objective heart rate data was 96.8±0.59%, all of which did not differ between the two exercise groups. Accelerometer-quantified moderate to vigorous intensity physical activity increased in dose-response fashion (P_{trend}<0.001); over six months the control group increased by 4.2±6.5 min·d^{-1}, whereas the low-dose and high-dose groups increased by 26.5±6.1 and 33.1±6.5 min·d^{-1}, respectively.

Body composition outcomes are presented in **Table 3.3**. At baseline, no differences in body composition were observed among the three groups. Exercise reduced VAT, the pre-specified key body composition outcome, in dose-response fashion (P_{trend}=0.008; **Figure 3.2A**). Compared to the control group, the low-dose and high-dose exercise groups lost 9.5 cm^2 (95% CI: –22.4, 3.5) and 13.6 cm^2 (95% CI: –27.0, –0.1) in VAT, respectively. Each 60 min·wk^{-1} increase in exercise predicted a 2.7 cm^2 (95% CI: –5.4, –0.1) reduction in VAT. This finding was reinforced by the observation that exercise reduced waist circumference (an anthropometric proxy for VAT) in dose-response fashion (P_{trend}<0.001; **Figure 3.2B**). Compared to the control group, the low-dose and high-dose exercise groups lost 1.5 cm (95% CI: –4.0, 1.1) and 4.5 cm (95% CI:–7.1, –1.9) in waist circumference, respectively. Each 60 min·wk^{-1} increase in exercise predicted a 0.9 cm (95% CI: –1.4, –0.4) reduction in waist circumference. Changes in VAT were correlated with changes in waist circumference (r=0.42; P=0.009). Improvements in waist-to-hip ratio were of marginal significance (P_{trend}=0.054). An unexpected finding was the observed improvement in bone mineral density (P_{trend}=0.015). Compared to the control group, the low-dose and high-dose exercise

groups gained 0.015 g/m^2 (95% CI: 0.001, 0.029) and 0.013 g/m^2 (95% CI: -0.001, 0.028) in bone mineral density, respectively. This improvement was not hypothesized to occur and bone mineral density was an exploratory outcome; therefore, this finding should be viewed as hypothesis generating and may be a type I error (false positive). No significant change in body mass was observed (P_{trend}=0.280), this was expected because self-reported caloric consumption did not change (P_{trend}=0.743). No serious (grade ≥3) adverse events occurred.

Discussion

A six month moderate-intensity aerobic exercise program among stage I-III colon cancer survivors resulted in significant linear dose-response reductions in VAT measured by DXA and waist circumference. The findings from this randomized trial provide mechanistic data to support observational evidence that suggests physical activity may lower the risk of recurrence and mortality among colon cancer survivors.

The linear reductions in VAT and waist circumference with increasing exercise volume are similar to prior dose-response exercise interventions in other populations (reviewed here [Kay and Singh, 2006]). For example, among overweight and obese men and women with dyslipidemia, increasing exercise volume was associated with larger reductions in VAT [Slentz *et al*, 2005], and waist circumference [Slentz *et al*, 2004]. In our study, the usual-care control group increased VAT and waist circumference over six months. This observation has been reported in the control groups of prior exercise trials [Slentz *et al*, 2005, Slentz *et al*, 2004], and underscores the deleterious effect of continued sedentary behavior. Excess energy is preferentially stored as VAT during extended periods of inactivity [Belavý *et al*, 2014]. It is also important to note that we did

not observe significant changes in body mass. Exercise preferentially utilizes VAT as an energetic substrate, often without altering total body mass [Johnson *et al*, 2009, Lee *et al*, 2005]. Healthcare providers who prescribe exercise to colon cancer survivors should inform patients that exercise may not significantly reduce body mass, and that body mass alone should not be used as an indicator of exercise success, as important physiologic changes are likely to occur in the absence of weight loss.

The biologic or biobehavioral pathways through which exercise may favorably alter disease outcomes among colon cancer survivors are unknown. Excess VAT and waist circumference are associated with an increased risk of disease recurrence and mortality among colon cancer survivors [Haydon *et al*, 2006a, Lee *et al*, 2015, Moon *et al*, 2008, Rickles *et al*, 2013]. VAT is an active endocrine organ that secretes various bioactive compounds such as adipokines, cytokines, hormone-like factors, and other metabolites [Ahima and Flier, 2000, Balistreri *et al*, 2010, Liesenfeld *et al*, 2015] that have been hypothesized to influence disease recurrence and progression [Park *et al*, 2014]. Excess VAT and other states associated with adiposity such as hyperinsulinemia activate the PI3K-Akt-mTOR pathway [McCurdy and Klemm, 2013]. Activation of the PI3K-Akt-mTOR pathway is associated with the growth and progression of colon cancer metastases [Gulhati *et al*, 2011], and silencing of this pathway inhibits the growth of metastases by inducing cell-cycle arrest and apoptosis [Zhang *et al*, 2009]. Several polymorphisms within adiposity-related genes predict disease recurrence among colon cancer survivors [Sebio *et al*, 2015]. For example, PPAR-γ rs1801282 regulates transcription factors for several genes that influence colon cancer growth [Sarraf *et al*, 1998]. Furthermore, PPAR-γ rs1801282 predicts the progression from impaired glucose tolerance to type 2 diabetes [Brito *et al*, 2009, Kilpelainen *et al*, 2008]. Participation in

physical activity significantly reduces the risk of progression from impaired glucose tolerance to type 2 diabetes that is associated with this polymorphism [Brito *et al*, 2009, Kilpelainen *et al*, 2008]. Type 2 diabetes is associated with a worsened prognosis in colon cancer [Jeon *et al*, 2013, Meyerhardt *et al*, 2003]. Future research will be needed to discern if the disease-specific benefits of physical activity for colon cancer survivors are achieved through similar pathways.

There are several limitations to this trial. The primary limitation to this trial is the small sample size, which limited our statistical power to examine other body composition outcomes. The small sample size also reduces the generalizability of our findings. As we have previously described [Brown *et al*, 2016], trial participants were younger than the population from which they were recruited. This has important implications for the generalizability of our findings to the broader population of colon cancer survivors. The duration of the exercise intervention was six months, which is modest relative to other trials of 12 to 36 months. It is unknown if the dose-response effects of exercise on VAT are maximized or sustained over longer periods of time. Trial participants were not recruited on the basis of having high levels of VAT. It is unknown if the exercise-induced reductions in VAT would be similar or larger in magnitude among a sample with high levels of VAT at baseline.

There are several strengths to this trial. The use of two intervention groups, each prescribed a distinct dose of exercise, allowed us examine how VAT responded along the exercise dose curve. The exercise program was flexible, emphasizing a home-based program, blended with ongoing behavioral and clinical support from an exercise physiologist. The provision of home-based treadmills succeeded in providing a reasonable incentive for participation as recruitment was completed ahead of schedule,

and succeeded in promoting favorable adherence to the exercise prescription over six months. Completion of the prescribed exercise dose was objectively quantified using heart-rate monitors with long-term (≥3 month) memory. Data collection was completed by staff blinded to study group who followed standardized protocols. Participants in this trial had later stage of disease than the population from which they were recruited [Brown *et al*, 2016], which represents colon cancer survivors at highest risk for disease recurrence. Participants had a variety of comorbid conditions that are common among colon cancer survivors including hypertension, hyperlipidemia, diabetes, and cardiovascular disease. Endpoint data collection was satisfactory (97% complete).

In conclusion, the findings from this randomized trial demonstrate the dose-response effects of moderate intensity aerobic exercise to favorably reduce VAT among selected patients recently treated for stage I-III colon cancer. The findings from this randomized trial may be useful to healthcare providers to improve the specificity of exercise prescriptions for colon cancer survivors. The findings from this randomized trial are also useful to investigators to begin to understand the mechanistic pathways that are hypothesized to mediate the relationship between exercise and disease outcomes in this population. Continued research to elucidate the mechanistic pathways through which physical activity alters disease outcomes is warranted.

Disclosure Statement

The authors declare no conflicts of interest. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Table 3.1 Baseline characteristics of the participants

Characteristic	Total (*n*=39)	Control (*n*=13)	Low-Dose (*n*=14)	High-Dose (*n*=12)	*P*
Age, years	56.5±10.0	57.9±9.7	58.2±9.8	53.1±10.5	0.493
Sex, %					
Male	15 (38%)	4 (31%)	7 (50%)	4 (33%)	0.601
Female	24 (62%)	9 (69%)	7 (50%)	8 (67%)	
Race, %					
White	31 (80%)	8 (62%)	12 (86%)	11 (92%)	0.332
Black	6 (15%)	3 (23%)	2 (14%)	1 (8%)	
Other	2 (5%)	2 (15%)	0 (0%)	0 (0%)	
Education, %					
High School or Less	7 (18%)	1 (8%)	4 (29%)	2 (17%)	0.765
Some College	8 (20%)	3 (23%)	2 (14%)	3 (25%)	
College Degree or More	24 (62%)	9 (69%)	8 (57%)	7 (58%)	
Smoking History, %					
Never	23 (59%)	10 (77%)	6 (43%)	7 (58%)	0.407
Former	14 (36%)	3 (23%)	7 (50%)	4 (33%)	
Current	2 (5%)	0 (0%)	1 (7%)	1 (8%)	
Caloric Consumption, $kcal \cdot d^{-1}$	1747±542	1749±545	1816±569	1665±543	0.725
Moderate or Vigorous Physical Activity, $min \cdot d^{-1}$	15.7±8.7	12.2±8.1	18.8±9.6	15.7±7.3	0.175
Body Mass Index, $kg \cdot m^{-2}$	30.3±5.8	29.2±6.0	29.5±4.3	32.4±6.9	0.408
Stage, %					
I	5 (13%)	1 (8%)	2 (14%)	2 (17%)	0.999
II	14 (36%)	5 (38%)	5 (36%)	4 (33%)	
III	20 (51%)	7 (54%)	7 (50%)	6 (50%)	
Chemotherapy, %	28 (72%)	10 (77%)	10 (71%)	8 (67%)	0.906
Time Since Treatment Completion, Months	10.9±6.1	11.3±6.7	8.8±5.8	11.3±5.7	0.417
ECOG Performance Status, %					
0, Fully active	29 (74%)	10 (77%)	9 (64%)	10 (83%)	0.595
1, Ambulatory, but restricted in strenuous activity	10 (26%)	3 (23%)	5 (36%)	2 (17%)	
Comorbid Conditions, %					
Hypertension	13 (33%)	4 (31%)	6 (43%)	3 (25%)	0.695
Hyperlipidemia	6 (15%)	1 (8%)	2 (14%)	3 (25%)	0.480
Type 2 Diabetes	5 (13%)	1 (8%)	1 (7%)	3 (25%)	0.409
Cardiovascular Disease	4 (10%)	2 (15%)	1 (7%)	1 (8%)	0.827
5-Year Predicted Survival, %	68 [60-87]	68 [61-85]	71 [60-88]	65 [60-83]	0.713

P values are from the overall test of group differences.

Table 3.2 Exercise prescription program variables[a]

Characteristic	Low-Dose (*n*=14)	High-Dose (*n*=12)	Δ Between Groups (LS Mean ± SE)	*P*
Frequency (days of exercise per week)	3.5±0.15	4.3±0.16	0.75±0.22	0.001
Fractionization (sessions of exercise per day)	1.1±0.07	1.4±0.07	0.31±0.10	0.001
Intensity (% of heart rate maximum)	71.6±1.16	69.6±1.27	-1.89±1.72	0.272
Time (minutes of exercise per day)	41.6±2.38	59.1±2.57	17.4±3.50	<0.001
Type (% of exercise sessions using treadmill)	72.3±12.9	81.3±15.5	8.0±18.71	0.669
Volume (minutes of exercise per week)	141.5±9.92	247.2±10.71	105.7±14.60	<0.001
Progression (weeks to full dose of exercise)[b]	4 [4-5]	8 [7-10]	4 [2-6]	0.007
% of exercise confirmed with HRM	97.3±0.81	96.2±0.87	-1.1±1.19	0.344
% adherence to prescribed exercise dose	92.8±2.44	89.0±2.64	-3.8±3.60	0.287
% with ≥80% adherence, *n* (%)	12 (86%)	9 (75%)	-10.6±15.2	0.488
MET hours per week[c]	13.7±0.96	23.9±1.03	10.2±1.41	<0.001

[a]Data are least squares mean (LS Mean) ± standard error (SE) unless otherwise noted. [b]Median [interquartile 25-75% range]. [c]Calculated using available treadmill speed and incline, and averaged across all exercise sessions.

Table 3.3 Body composition outcomes at baseline and change during six months

Outcome	Baseline (Mean ± SD)	Δ Baseline to Month 6 (LS Mean ± SE)	Δ from Control (LS Mean ± SE)
Body Mass, kg			
Control	83.7±22.1	0.43±0.61	—
Low-Dose	86.2±13.1	−0.51±0.57	−0.95±0.84
High-Dose	92.2±24.3	−0.32±0.62	−0.76±0.87
Test for trend		*P*=0.280	
BMI, kg/m^2			
Control	29.2±6.0	0.14±0.22	—
Low-Dose	29.5±4.3	−0.17±0.21	−0.31±0.30
High-Dose	32.5±6.9	−0.11±0.23	−0.25±0.32
Test for trend		*P*=0.354	
Waist Circumference, cm			
Control	98.0±17.1	1.62±0.94	—
Low-Dose	98.7±11.9	0.16±0.89	−1.46±1.29
High-Dose	106.9±14.6	−2.90±0.96[a]	−4.52±1.34[b]
Test for trend		*P*<0.001	
Hip Circumference, cm			
Control	103.4±13.5	1.85±1.42	—
Low-Dose	104.5±10.3	0.18±1.34	−1.67±1.95
High-Dose	110.6±15.0	0.02±1.45	−1.84±2.03
Test for trend		*P*=0.518	
Waist to Hip Ratio			
Control	0.94±0.09	−0.005±0.011	—
Low-Dose	0.94±0.07	0.001±0.011	0.005±0.016
High-Dose	0.97±0.09	−0.029±0.012[a]	−0.023±0.016
Test for trend		*P*=0.054	
Sagittal Abdominal Diameter, cm			
Control	22.6±4.0	0.45±0.32	—
Low-Dose	22.4±3.6	0.01±0.30	−0.43±0.44
High-Dose	23.9±4.0	0.01±0.32	−0.45±0.46
Test for trend		*P*=0.200	
Visceral Adipose Tissue, cm^2			
Control	112.6±55.2	5.31±4.80	—
Low-Dose	131.3±45.6	−4.13±4.53	−9.45±6.60
High-Dose	154.2±60.5	−8.27±4.89	−13.58±6.86[b]
Test for trend		*P*=0.008	
Subcutaneous Adipose Tissue, cm^2			
Control	388.4±142.6	−3.87±8.64	—
Low-Dose	381.1±138.6	1.70±8.15	5.57±11.88
High-Dose	461.9±110.9	−17.86±8.81[a]	−14.00±12.34
Test for trend		*P*=0.222	
Fat Mass, kg			
Control	32.8±10.0	−0.01±0.49	—
Low-Dose	32.6±7.6	−0.13±0.47	−0.12±0.68
High-Dose	38.1±11.9	−0.71±0.50	−0.70±0.71
Test for trend		*P*=0.238	
Lean Mass, kg			
Control	49.9±13.1	0.30±0.35	—
Low-Dose	52.6±11.1	−0.06±0.33	−0.36±0.48
High-Dose	53.4±13.8	0.01±0.36	−0.29±0.50
Test for trend		*P*=0.450	
Bone Mineral Density, g/cm^2			
Control	1.08±0.10	0.006±0.005	—
Low-Dose	1.03±0.12	0.021±0.005[a]	0.015±0.007[b]
High-Dose	1.02±0.09	0.020±0.005[a]	0.013±0.007
Test for trend		*P*=0.015	

SD, standard deviation; LS Mean, least squares mean; SE, standard error. [a]Signifcantly different from baseline (within-group), $P \leq 0.05$. [b]Significantly different from control, $P \leq 0.05$.

Figure 3.1 Flow of participants through the study

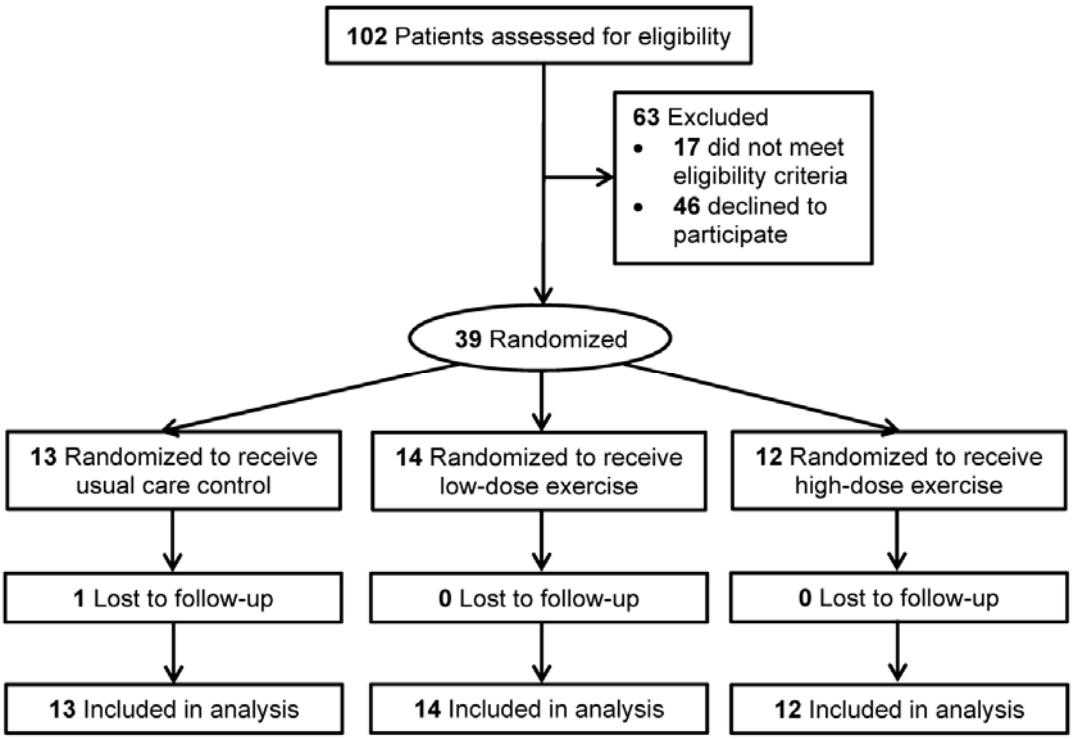
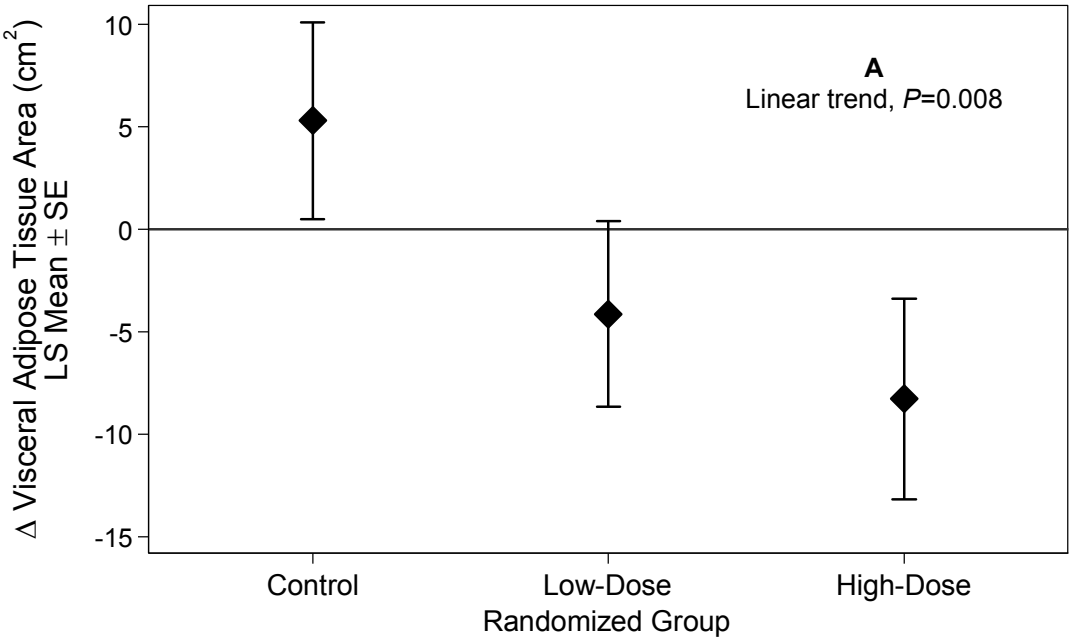
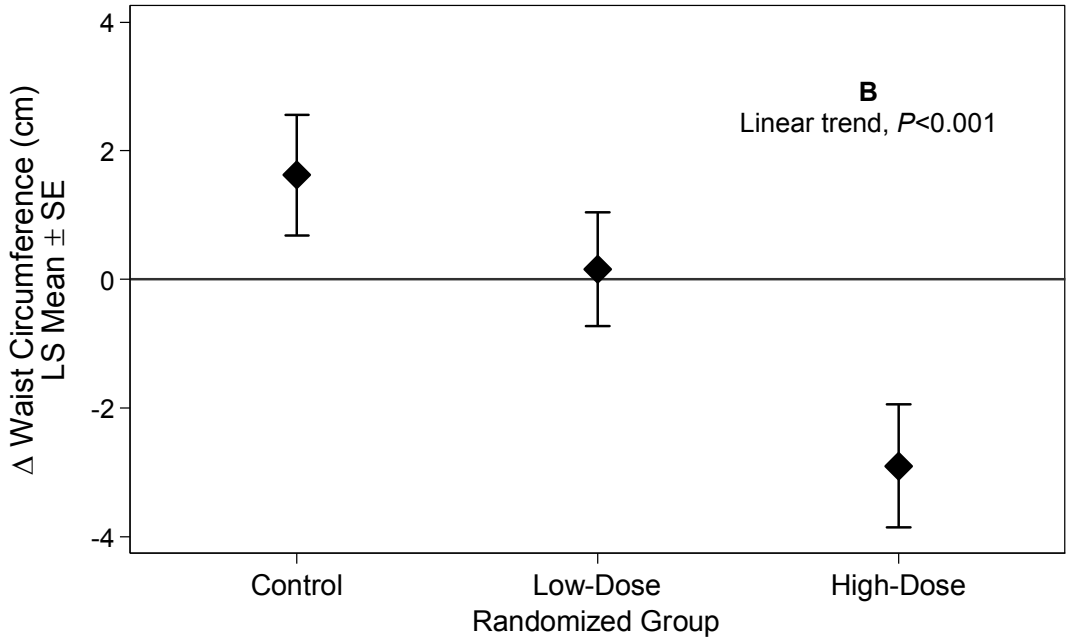


Figure 3.2 Between group changes in A) visceral adipose tissue and B) waist circumference from baseline to six months





CHAPTER 4. The Dose-Response Effects of Exercise on Fasting Insulin among Survivors of Colon Cancer: A Randomized Controlled Trial

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Abstract

Background: Physical activity is associated with a lower risk of disease recurrence among colon cancer survivors. The pathways through which physical activity alters disease outcomes are unknown, but may be mediated by changes in metabolic growth factors, such as insulin.

Methods: Between January 2015 and August 2015, 39 stage I-III colon cancer survivors were randomized to one of three groups: usual-care control, 150 min·wk^{-1} of aerobic exercise (low-dose), and 300 min·wk^{-1} of aerobic exercise (high-dose) for six months. The pre-specified key metabolic growth factor outcome was fasting insulin. Insulin resistance was quantified using the homeostatic model assessment.

Results: Mean age was 56.5±10.0 years, 51% had stage III disease, 72% were treated with chemotherapy, and the mean time since finishing treatment was 10.9±6.1 months. Over six months, the low-dose group completed a mean 141.5±9.9 min·wk^{-1} of aerobic exercise, and the high-dose group completed a mean 247.2±10.7 min·wk^{-1} of aerobic exercise. Fasting insulin concentrations decreased 7.4±9.4 pmol/L in the control group, 28.0±8.3 pmol/L in the low-dose group, and 20.7±9.3 pmol/L in the high-dose group (nonlinear P_{trend}=0.042). Insulin resistance decreased 0.11±0.20 in the control group, 0.63±0.17 in the low-dose group, and 0.43±0.19 in the high-dose group (nonlinear P_{trend}=0.012).

Discussion: Aerobic exercise reduces insulin concentrations and insulin resistance among patients with stage I-III colon cancer. Prescribing 150 min·wk^{-1} of aerobic exercise may be sufficient for reducing insulin concentrations and insulin resistance,

which may partially mediate the relationship between physical activity and colon cancer prognosis.

Introduction

Each year more than 103,000 people are diagnosed with colon cancer in the United States [Siegel *et al*, 2015]. Approximately three-quarters of patients will be 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, five-year recurrence rates for patients with stage I, II, and III colon cancer are 10%, 20%, and 30-50%, respectively [André *et al*, 2004, Clinical Outcomes of Surgical Therapy Study Group, 2004, Quasar Collaborative Group, 2007]. 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 in multiple observational studies to be associated with a reduction in the risk of recurrence and death among colon cancer survivors [Campbell *et al*, 2013, Kuiper *et al*, 2012, Meyerhardt *et al*, 2006, Meyerhardt *et al*, 2006, Meyerhardt *et al*, 2009]. The relationship between physical activity and disease outcomes is independent of known prognostic factors, and occurs in a dose-response fashion, such that higher volumes of physical activity or exercise, up to 300 minutes per week ($min \cdot wk^{-1}$), are associated with more favorable disease outcomes [Campbell *et al*, 2013, Kuiper *et al*, 2012, Meyerhardt *et al*, 2006, Meyerhardt *et al*, 2006, Meyerhardt *et al*, 2009].

The biologic or biobehavioral pathways through which exercise may favorably alter colon cancer outcomes have not been elucidated, but may include exercise-induced

alterations in metabolic growth factors, such as insulin, C-peptide, insulin-like growth factor-1 (IGF-1), and insulin-like growth factor-binding protein-3 (IGFBP-3). Colon cancer cells have insulin/IGF-1 receptors on their surface [Belfiore and Malaguarnera, 2011] and insulin/IGF-1 promote colon cancer cell proliferation and inhibit apoptosis [Koenuma *et al*, 1989]. *In vitro* studies demonstrate that states of hyperinsulinemia increase colon cancer cell resistance to 5-fluorouracil [Chen *et al*, 2011b] and oxaliplatin chemotherapy [Chen *et al*, 2011a, Volkova *et al*, 2014]. Preclinical models demonstrate that exposure to insulin promotes colonic tumor multiplicity [Tran *et al*, 1996]. Elevated levels of C-peptide and lower levels of IGFBP-3 are associated with a higher risk of death among men and women with colon cancer [Haydon *et al*, 2006b, Wolpin *et al*, 2009]. Together, this evidence supports the hypothesis that insulin and IGF-1 may be important mediators of the relationship between exercise and disease outcomes among colon cancer survivors.

Colon cancer survivors have fasting insulin concentrations that are 58% higher than healthy controls without a history of colon cancer [Jiang *et al*, 2014]. A pilot study of 17 colon cancer survivors demonstrated that a three-month prescription of exercise reduced insulin and increased IGF-1 and IGFBP-3 concentrations [Lee *et al*, 2013]. However, no randomized trials have examined the dose-response effects of exercise on metabolic growth factors among colon cancer survivors.

These observations provided the scientific rationale for the COURAGE trial, a randomized controlled trial investigating the safety, feasibility, and biological efficacy of 150 and 300 $min \cdot wk^{-1}$ of aerobic exercise versus usual care control over six months among men and women recently-treated for stage I-III colon cancer [Brown *et al*, 2016]. Here we report on fasting insulin as the pre-specified key metabolic growth factor of interest. We have

previously demonstrated that visceral adipose tissue is reduced with exercise [Brown *et al,* to be submitted]. As an exploratory aim of this report, we characterized the relationship between changes in visceral adipose tissue with changes in fasting insulin. Our hypotheses were that: 1) exercise would reduce fasting insulin concentrations in a dose-response fashion; and 2) reductions in visceral adipose tissue would correlate with reductions in fasting insulin.

Methods

Participants

Study methods of the COURAGE trial were published [Brown *et al*, 2016]. Participants were recruited from the metropolitan Philadelphia region and surrounding counties. Participants were eligible if they: 1) were diagnosed with histologically-proven stage I-III colon cancer; 2) completed surgical resection and adjuvant chemotherapy within 36 months of entering the study; 3) self-reported participating in ≤150 $min \cdot wk^{-1}$ of moderate or vigorous intensity physical activity using the Paffenbarger Physical Activity Questionnaire [20]; 4) were of age ≥18 years; 5) provided written physician approval; 6) had no additional surgery planned within the six month intervention period (including colostomy reversal); and 7) had the ability to walk unassisted for six-minutes. Participants were ineligible if they: 1) had a history of another primary cancer (other than non-melanoma skin-cancer); 2) had evidence of metastatic cancer; 3) were pregnant or breast feeding; 4) were unable to provide a baseline blood sample; 5) had a myocardial infarction or coronary revascularization procedure within the past three months; 6) had uncontrolled hypertension, defined as a systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥100 mm Hg; 7) had high-risk or uncontrolled heart arrhythmias (not including atrial fibrillation); 8) had clinically significant heart valve disease; 9) had

decompensated heart failure; 10) had a known aortic aneurysm; or 11) had 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.

Participants were stratified by cancer stage (AJCC 7th Edition: I vs II vs III) and randomized into one of three groups: low-dose aerobic exercise (150 min·wk^{-1}), high-dose aerobic exercise (300 min·wk^{-1}), or usual care control. This study was approved by the University of Pennsylvania Institutional Review Board. All participants provided written informed consent and written approval from their physician prior to participation in any study-related activities.

Intervention

Participants randomized to the low-dose or high-dose exercise groups were provided with an in-home treadmill (LifeSpan Fitness, TR1200i, Salt Lake City, UT) to promote exercise adherence, and a heart rate monitor (Polar Electro, RS400, Kempele Finland) to objectively record exercise intensity and duration. Participants also documented their exercise in a written log book. Exercise intensity was prescribed at 50-70% of the age-predicted maximum heart rate (3-6 METs [Ainsworth *et al*, 2000]). The low-dose and high-dose groups progressed towards of the goal of 150 or 300 min·wk^{-1} of exercise, respectively. Participants met with a certified clinical exercise physiologist to introduce the exercise prescription, and familiarize the participant with use of the treadmill, completion of exercise logs, use of a 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 day) 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 to the study protocol throughout the duration of the study. Detailed methods of the exercise intervention were published [Brown *et al*, 2016].

Participants randomized to the usual-care control group were asked to maintain their pre-study levels of physical activity or follow the recommendations provided by their physician. After completing six month measures, control group participants were provided with an in-home treadmill and individualized exercise program, similar to that prescribed to the two exercise groups. Upon completion of study-related activities, all participants were allowed to keep their study-provided treadmills.

Measurements

Baseline and follow-up measurements were obtained by trained staff members who were blinded to treatment assignment. Demographic characteristics including age, sex, race, and education were self-reported. Smoking status was obtained from a standardized questionnaire [Pleis *et al*, 2009]. Daily caloric intake and the proportion of calories from carbohydrate sources were quantified using three-day food records that were analyzed using the Nutrition Data System for Research software (v.2014) by a registered dietitian who was blinded to study group. Moderate to vigorous intensity physical activity was quantified using an accelerometer (ActiGraph GT3X+) with cut-points appropriate for adults [Troiano *et al*, 2008]. Clinical information including cancer stage, treatment with chemotherapy, and performance status were obtained from the Pennsylvania State Cancer Registry, pathology reports, and physician records. Five-year predicted overall survival was calculated using a validated prognostic model for colon cancer [Weiser *et al*, 2011]. Body mass index (BMI; kg/m^2) was calculated using standard anthropometric measures [weight (kg) and height (m)], and dual-energy x-ray

absorptiometry was used to quantify visceral adipose tissue, as previously described [Brown *et al*, 2016].

Metabolic Growth Factor Outcomes

All study participants underwent a fasting blood draw at baseline and follow-up. EDTA-preserved plasma was stored at −80°C. Insulin and C-peptide concentrations were quantified using a radioimmunoassay (EMD Millipore, Billerica, MA). IGF-1, IGFBP-3, and fructosamine concentrations were quantified using an enzyme-linked immunosorbent assay (DSL, Webster, TX). Glucose concentrations were quantified spectrophotometrically (Roche, Indianapolis, IN). Baseline and follow-up plasma samples were assayed simultaneously and in duplicate at the end of the study. Coefficients of variation for all samples were ≤10%. The homeostatic model assessment (HOMA) was used to quantify insulin resistance [Levy *et al*, 1998].

Statistical Analysis

Descriptive statistics presented for baseline variables include counts and proportions for categorical variables and means ± standard deviations for continuous variables. Categorical baseline characteristics were compared among the three groups using Fisher's exact test, and continuous baseline characteristics were compared among the three study groups using the Kruskal-Wallis test. Based on prior research [Houmard *et al*, 2004], we estimated a mean change in fasting insulin concentrations of +6.6 pmol/L in the control group, −3.3 pmol/L in the low-dose group, and −5.9 pmol/L in the high-dose group with a pooled standard deviation of ±4.6 pmol/L over six months. Against the hypothesis of a dose-response relationship, 39 participants provided 80% power with a type I error rate of 5% (α=0.05). All inferential analyses were conducted on an intention-to-treat basis. Dependent variables were log transformed in the inferential

analysis to improve normality and back transformed to facilitate interpretation. Changes were evaluated from baseline to follow-up in the three groups using repeated-measures mixed-effects regression models. This statistical approach includes all available data and accounts for the correlation between repeated measures. The baseline value of the dependent variable and cancer stage (randomization stratification factor) were included as covariates in the regression models [Fitzmaurice *et al*, 2004]. Group-by-time interaction terms were included as fixed-effects in the regression model. Results from the repeated-measures mixed-effects regression models are presented as least-square means ± standard error. To evaluate the presence of a dose-response relationship across randomized groups, a test of trend was conducted by examining linear and nonlinear (quadratic) contrasts. Linear regression models were used to characterize changes in visceral adipose tissue with changes in growth factor concentrations from baseline to six months. All statistical analyses were completed using Stata/MP Version 14.1 (StataCorp, College Station, TX).

Results

Between January 2015 and August 2015, 39 colon cancer survivors were recruited and randomized with data collection ending in February 2016. Baseline characteristics of study participants are presented in **Table 4.1**. Age ranged from 35–81 years. BMI ranged from 20–43 kg/m^2; 31% of participants were overweight (BMI 25.0–29.9 kg/m^2) and 51% were obese (BMI≥30 kg/m^2). Time since finishing colon cancer treatment ranged from 1–21 months. Five-year predicted overall survival ranged from 35–92%. Five participants had type 2 diabetes mellitus at baseline, all were diagnosed ≥3 years prior to study enrollment, and all were using metformin (one as monotherapy, four as combination therapy with a sulfonylurea or DPP-4 inhibitor). **Figure 4.1** shows the flow

of the 39 randomized participants through the study. One participant was lost to follow-up.

Exercise prescription program variables are presented in **Table 4.2**. Over six months, the average exercise volumes in the low-dose and high-dose groups were 141.5±9.92 $min \cdot wk^{-1}$ (92.8±2.44% of prescribed dose) and 247.2±10.71 $min \cdot wk^{-1}$ (89.0±2.64% of prescribed dose), respectively. The high-dose group completed on average an additional 105.7±14.60 $min \cdot wk^{-1}$ of exercise than the low-dose group (P<0.001). Exercise intensity was 70.7±0.85% of the age-predicted maximal heart rate and did not differ between groups (P=0.272). The proportion of exercise sessions validated with objective heart rate data was 96.8±0.59% and did not differ between groups (P=0.344). Accelerometer-quantified moderate to vigorous intensity physical activity increased in dose-response fashion (linear P_{trend}<0.001); over six months the control group increased by 4.2±6.5 $min \cdot d^{-1}$, whereas the low-dose and high-dose groups increased by 26.5±6.1 and 33.1±6.5 $min \cdot d^{-1}$, respectively. Daily caloric intake and the proportion of daily calories from carbohydrate sources were not significantly different from baseline in any of the groups (data not shown).

Metabolic growth factor concentrations are presented in **Table 4.3**. At baseline, no differences were observed among the three groups. Fasting insulin concentration, the key growth factor outcome, decreased 7.4±9.4 pmol/L in the control group, 28.0±8.3 pmol/L in the low-dose group, and 20.7±9.3 pmol/L in the high-dose group (nonlinear P_{trend}=0.042; **Figure 4.2**). Similarly, insulin resistance decreased 0.11±0.20 in the control group, 0.63±0.17 in the low-dose group, and 0.43±0.19 in the high-dose group (nonlinear P_{trend}=0.012). Fasting glucose concentration decreased in the low-dose group, whereas no difference was observed high-dose and control groups (nonlinear

P_{trend}=0.004). IGF-1, IGFBP-3, fructosamine, and C-peptide did not change in any of the study groups. Adjustment for type 2 diabetes mellitus as a covariate in the regression models did not substantively alter the above-described findings. No serious (grade ≥3) adverse events occurred.

As we have previously reported, exercise reduced visceral adipose tissue in a dose-response fashion (linear P_{trend}=0.008), such that each 60 min·wk^{-1} increase in exercise volume predicted a –2.7±1.4 cm^2 reduction in visceral adipose tissue [Brown *et al*]. For each 1 cm^2 reduction in visceral adipose tissue, fasting insulin concentration was lowered by 0.96±0.41 pmol/L (*P*=0.025; **Table 4.4, Figure 4.3**) and changes in visceral adipose tissue accounted for 13.5% of the shared variance in changes in fasting insulin concentrations. Changes in visceral adipose tissue also correlated with changes in fasting glucose and insulin resistance.

Discussion

A six month moderate-intensity aerobic exercise program among stage I-III colon cancer survivors reduced fasting insulin concentrations and insulin resistance in a predominately overweight and obese population. The findings from this randomized trial support the hypothesis that the relationship between physical activity and colon cancer prognosis may be mediated, in part, by changes in fasting insulin concentrations or insulin resistance.

The reductions in fasting insulin concentrations and insulin resistance with exercise are similar to those observed in a prior dose-response study in overweight and obese adults [Ross *et al*, 2015]. This study indicated that fasting insulin concentrations and insulin resistance may be lowered uniformly across distinct exercise doses in an L-shaped

pattern [Ross *et al*, 2015]. The absolute magnitude of reduction in fasting insulin concentrations in the current study was larger compared to other studies [Houmard *et al*, 2004, Ross *et al*, 2015]. This may be the result of our sample having higher baseline fasting insulin concentrations (111 pmol/L vs 49 pmol/L [Houmard *et al*, 2004] and 67.5 pmol/L [Ross *et al*, 2015]), which is consistent with a prior report that colon cancer survivors have significantly higher fasting insulin concentrations than matched healthy controls [Jiang *et al*, 2014]. Our findings are consistent with studies in breast cancer survivors that exercise reduces fasting insulin concentrations [Irwin *et al*, 2009, Ligibel *et al*, 2008].

In cross-sectional analyses, fasting insulin concentrations are higher with larger volumes of visceral adipose tissue, an effect that is attributable to increased insulin resistance [Goodpaster *et al*, 2003]. We demonstrated that changes in visceral adipose tissue account for only 13.5% of the shared variance in insulin concentration, consistent with a prior study in obese men that estimated the shared variance to be 22% [Rice *et al*, 1999]. These data suggest that the effects of exercise to lower fasting insulin may include mechanisms beyond that of changes in visceral adipose tissue. We hypothesize that alterations in skeletal muscle insulin resistance and free fatty acid (FFA) metabolism may help to further explain this effect [Abdul-Ghani and DeFronzo, 2010, DeFronzo and Tripathy, 2009]. Insulin resistance in skeletal muscle is associated with hyperinsulinemia [Abdul-Ghani and DeFronzo, 2010, DeFronzo and Tripathy, 2009], and the inability to lower FFA in the postprandial state [Jensen, 2008]. Skeletal muscle preferentially oxidizes FFA [Randle *et al*, 1963], suppressing insulin-stimulated glucose uptake into the muscle [Boden *et al*, 1994, Dresner *et al*, 1999]. Exercise improves the insulin suppression of FFA release [Shadid and Jensen, 2006], corrects the mismatch

between FFA uptake and FFA oxidation [Turcotte and Fisher, 2008], and promotes insulin-stimulated glucose uptake into skeletal muscle [Hayashi *et al*, 1997].

The biologic or biobehavioral pathways through which exercise may alter disease outcomes are unknown. States of hyperinsulinemia activate the PI3K-Akt-mTOR pathway [McCurdy and Klemm, 2013]. In preclinical experiments, activation of the PI3K-Akt-mTOR pathway promotes the growth of colon cancer metastases [Gulhati *et al*, 2011], and inhibition of this pathway induces cell-cycle arrest and apoptosis [Zhang *et al*, 2009]. Insulin receptor substrate 1 (IRS1) is a mediator of glucose homeostasis, and the down regulation of IRS1 is associated with insulin resistance [Karlsson and Zierath, 2007]. Tumor expression of IRS1 and physical activity interact to influence colon cancer outcomes [Hanyuda *et al*, 2015]. Among patients with decreased expression of IRS1, physical activity is associated with a significant reduction in the risk of colon cancer-specific mortality (P_{trend}=0.005) whereas no relationship was observed with IRS2. IRS1 is associated with insulin metabolism in skeletal muscle, whereas IRS2 is associated with insulin metabolism in the liver [Karlsson and Zierath, 2007]. These observational data provide additional data to support the hypothesis that exercise may have an insulin sensitizing effect that is produced through skeletal muscle contractions, and this insulin sensitization may influence disease outcomes.

There are several limitations to this trial. The main limitation is the small size of the study sample which limits the generalizability of our findings. We have previously demonstrated that participants in this trial were younger than the population from which they were recruited [Brown *et al*, 2016]. The small sample size precluded our ability to undertake formal mediation analysis to explore the relationships among exercise dose, insulin concentrations, and visceral adipose tissue [Friedenreich *et al*, 2011]. The small

sample size also limited our statistical power to examine other metabolic growth factors such as IGF-1. Our study was only six months in duration. It is unknown if the observed improvements in outcomes would be sustained or improved upon over a longer time horizon. Participants were not recruited on the basis of having hyperinsulinemia; however 82% of our study sample was overweight or obese, consequently hyperinsulinemia was common. We examined two distinct volumes of moderate-intensity aerobic exercise, but we did not examine the effects of low-intensity aerobic exercise.

There are several strengths to this trial. The use of two intervention groups, each prescribed a distinct dose of exercise allowed us to examine changes in fasting insulin along the exercise dose curve. The exercise program, which emphasized home-based treadmill walking, promoted good intervention adherence that was confirmed with objective heart rate monitor measures. The majority of participants (97%) completed the study.

In summary, the findings from this randomized dose-response trial demonstrate that moderate-intensity aerobic exercise reduces fasting insulin concentrations and insulin resistance among patients who have recently completed treatment for stage I-III colon cancer. The findings from this randomized trial may be useful to help guide exercise prescriptions in this population. The relationship between physical activity and colon cancer prognosis may be mediated, in part, by changes in insulin concentrations or insulin resistance. Continued research to examine this hypothesis is warranted.

Disclosure Statement

The authors declare no conflicts of interest. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Table 4.1 Baseline characteristics of the participants

Characteristic	Total (*n*=39)	Control (*n*=13)	Low-Dose (*n*=14)	High-Dose (*n*=12)	*P*
Age, years	56.5±10.0	57.9±9.7	58.2±9.8	53.1±10.5	0.493
Sex, %					
Male	15 (38%)	4 (31%)	7 (50%)	4 (33%)	0.601
Female	24 (62%)	9 (69%)	7 (50%)	8 (67%)	
Race, %					
White	31 (80%)	8 (62%)	12 (86%)	11 (92%)	0.332
Black	6 (15%)	3 (23%)	2 (14%)	1 (8%)	
Other	2 (5%)	2 (15%)	0 (0%)	0 (0%)	
Education, %					
High School or Less	7 (18%)	1 (8%)	4 (29%)	2 (17%)	0.765
Some College	8 (20%)	3 (23%)	2 (14%)	3 (25%)	
College Degree or More	24 (62%)	9 (69%)	8 (57%)	7 (58%)	
Smoking History, %					
Never	23 (59%)	10 (77%)	6 (43%)	7 (58%)	0.407
Former	14 (36%)	3 (23%)	7 (50%)	4 (33%)	
Current	2 (5%)	0 (0%)	1 (7%)	1 (8%)	
Caloric Consumption, $kcal \cdot d^{-1}$	1747±542	1749±545	1816±569	1665±543	0.725
Calories from Carbohydrate, %	45.6±8.8	45.0±10.6	46.6±7.3	45.2±9.2	0.701
Moderate or Vigorous Physical Activity, $min \cdot d^{-1}$	15.7±8.7	12.2±8.1	18.8±9.6	15.7±7.3	0.175
Body Mass Index, $kg \cdot m^{-2}$	30.3±5.8	29.2±6.0	29.5±4.3	32.4±6.9	0.408
Stage, %					
I	5 (13%)	1 (8%)	2 (14%)	2 (17%)	0.999
II	14 (36%)	5 (38%)	5 (36%)	4 (33%)	
III	20 (51%)	7 (54%)	7 (50%)	6 (50%)	
Chemotherapy, %	28 (72%)	10 (77%)	10 (71%)	8 (67%)	0.906
Time Since Treatment Completion, Months	10.9±6.1	11.3±6.7	8.8±5.8	11.3±5.7	0.417
ECOG Performance Status, %					
0, Fully active	29 (74%)	10 (77%)	9 (64%)	10 (83%)	0.595
1, Ambulatory, but restricted in strenuous activity	10 (26%)	3 (23%)	5 (36%)	2 (17%)	
Comorbid Conditions, %					
Hypertension	13 (33%)	4 (31%)	6 (43%)	3 (25%)	0.695
Hyperlipidemia	6 (15%)	1 (8%)	2 (14%)	3 (25%)	0.480
Type 2 Diabetes	5 (13%)	1 (8%)	1 (7%)	3 (25%)	0.409
Cardiovascular Disease	4 (10%)	2 (15%)	1 (7%)	1 (8%)	0.827
5-Year Predicted Survival, %	68 [60-87]	68 [61-85]	71 [60-88]	65 [60-83]	0.713

P values are from the overall test of group differences.

Table 4.2 Exercise prescription program variables[a]

Characteristic	Low-Dose (*n*=14)	High-Dose (*n*=12)	Δ Between Groups (LS Mean ± SE)	*P*
Frequency (days of exercise per week)	3.5±0.15	4.3±0.16	0.75±0.22	0.001
Fractionization (sessions of exercise per day)	1.1±0.07	1.4±0.07	0.31±0.10	0.001
Intensity (% of heart rate maximum)	71.6±1.16	69.6±1.27	-1.89±1.72	0.272
Time (minutes of exercise per day)	41.6±2.38	59.1±2.57	17.4±3.50	<0.001
Type (% of exercise sessions using treadmill)	72.3±12.9	81.3±15.5	8.0±18.71	0.669
Volume (minutes of exercise per week)	141.5±9.92	247.2±10.71	105.7±14.60	<0.001
Progression (weeks to full dose of exercise)[b]	4 [4-5]	8 [7-10]	4 [2-6]	0.007
% of exercise confirmed with HRM	97.3±0.81	96.2±0.87	-1.1±1.19	0.344
% adherence to prescribed exercise dose	92.8±2.44	89.0±2.64	-3.8±3.60	0.287
% with ≥80% adherence, *n* (%)	12 (86%)	9 (75%)	-10.6±15.2	0.488
MET hours per week[c]	13.7±0.96	23.9±1.03	10.2±1.41	<0.001

[a]Data are least squares mean (LS Mean) ± standard error (SE) unless otherwise noted. [b]Median [interquartile 25-75% range]. [c]Calculated using available treadmill speed and incline, and averaged across all exercise sessions.

Table 4.3 Metabolic growth factor outcomes at baseline and change during six months

Outcome	Baseline (Mean ± SD)	Δ Baseline to Month 6 (LS Mean ± SE)	Δ from Control (LS Mean ± SE)
Insulin, pmol/L			
Control	99.2±60.5	−7.36±9.41	—
Low-Dose	101.8±40.5	−28.02±8.35[a]	−20.66±12.58
High-Dose	135.1±87.1	−20.70±9.35[a]	−13.34±13.26
Test for trend		Linear, *P*=0.170	
		Nonlinear, *P*=0.042	
Glucose, mmol/L			
Control	5.3±1.0	0.01±0.16	—
Low-Dose	5.3±0.8	−0.39±0.15[a]	−0.39±0.22
High-Dose	6.1±2.3	−0.09±0.17	−0.09±0.24
Test for trend		Linear, *P*=0.931	
		Nonlinear, *P*=0.004	
Insulin Resistance (HOMA)			
Control	2.2±1.3	−0.11±0.20	—
Low-Dose	2.2±0.9	−0.63±0.17[a]	−0.52±0.26[b]
High-Dose	2.9±2.0	−0.43±0.19[a]	−0.32±0.27
Test for trend		Linear, *P*=0.125	
		Nonlinear, *P*=0.012	
IGF-1, nmol/L			
Control	58.0±15.9	−4.57±3.23	—
Low-Dose	59.8±13.2	−0.94±3.21	3.63±4.55
High-Dose	64.7±17.5	1.62±3.57	6.19±4.82
Test for trend		Linear, *P*=0.054	
		Nonlinear, *P*=0.850	
IGFBP-3, nmol/L			
Control	1765.1±446.8	−103.71±69.15	—
Low-Dose	1925.7±449.5	−30.01±68.04	73.69±97.27
High-Dose	2290.0±748.2	−154.28±71.97[a]	−50.58±100.13
Test for trend		Linear, *P*=0.685	
		Nonlinear, *P*=0.093	
C-Peptide, nmol/L			
Control	0.64±0.4	0.007±0.033	—
Low-Dose	0.58±0.3	−0.003±0.032	−0.010±0.046
High-Dose	0.75±0.3	−0.013±0.035	−0.020±0.048
Test for trend		Linear, *P*=0.701	
		Nonlinear, *P*=0.934	
Fructosamine, mmol/L			
Control	201.4±20.5	2.60±16.82	—
Low-Dose	183.0±51.2	22.91±15.84	20.31±23.11
High-Dose	204.1±28.6	−12.65±16.96	−15.26±23.89
Test for trend		Linear, *P*=0.380	
		Nonlinear, *P*=0.382	

SD, standard deviation; LS Mean, least squares mean; SE, standard error; HOMA, homeostatic model assessment. [a]Signifcantly different from baseline (within-group), $P \leq 0.05$. [b]Significantly different from control, $P \leq 0.05$.

Table 4.4 Relationship between change in visceral adipose tissue (per 1 cm^2 reduction) and change in metabolic growth factor concentration during six months

Outcome	∆ in Metabolic Growth Factor Concentration (LS Mean ± SE)	R^2	*P*
Insulin, pmol/L	−0.96±0.41	13.5%	0.025
Glucose, mmol/L	−0.03±0.01	21.9%	0.004
Insulin Resistance (HOMA)	−0.024±0.009	16.5%	0.013
IGF-1, nmol/L	−0.22±0.13	7.6%	0.098
IGFBP-3, nmol/L	−1.22±3.16	0.4%	0.701
C-Peptide, mmol/L	0.0007±0.001	0.6%	0.650
Fructosamine, mmol/L	−0.16±0.47	0.3%	0.736

LS Mean, least squares mean; SE, standard error; R^2, proportion of variability of change in metabolic growth factor concentration explained by change in visceral adipose tissue.

Figure 4.1 Flow of participants through the study

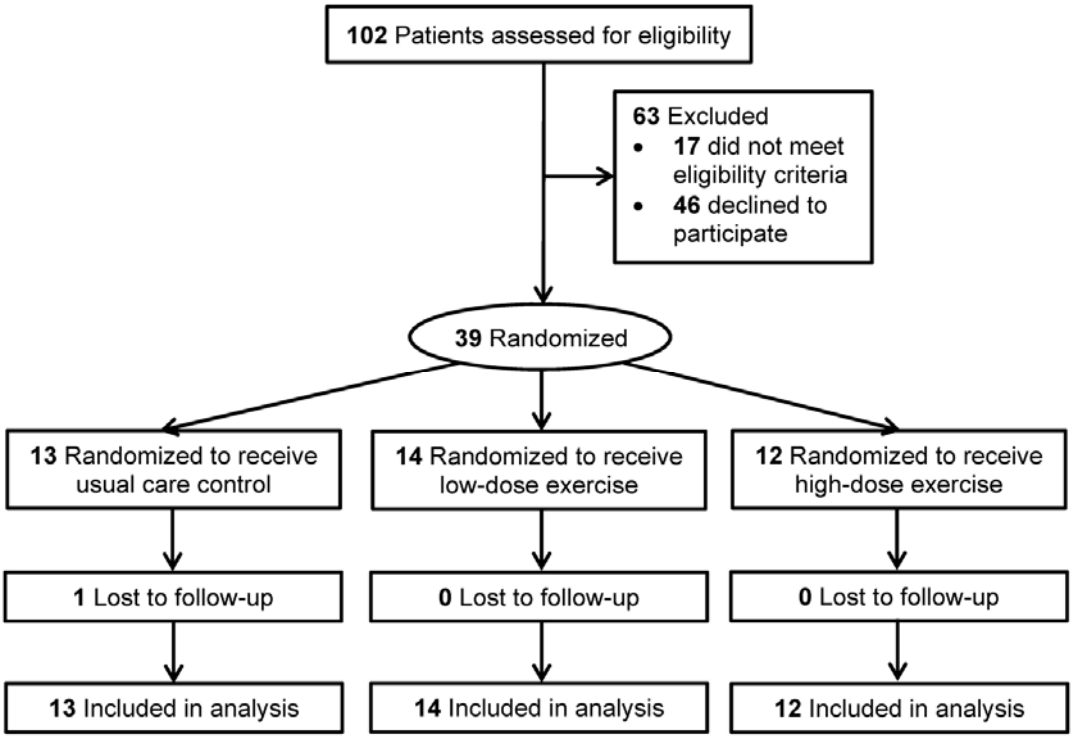


Figure 4.2 Between group changes in fasting insulin concentration from baseline to six months

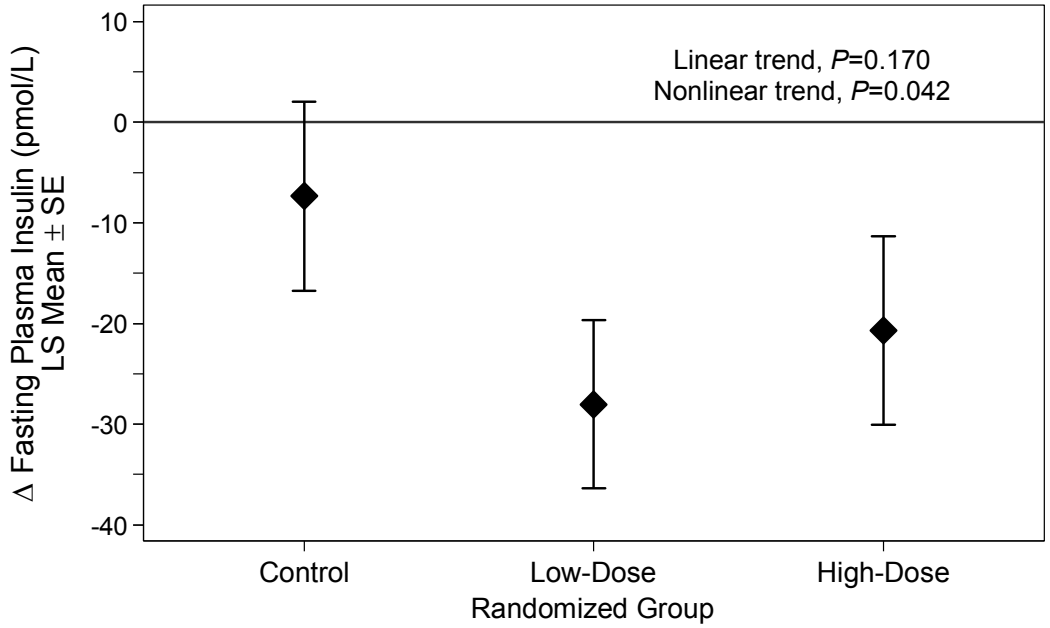
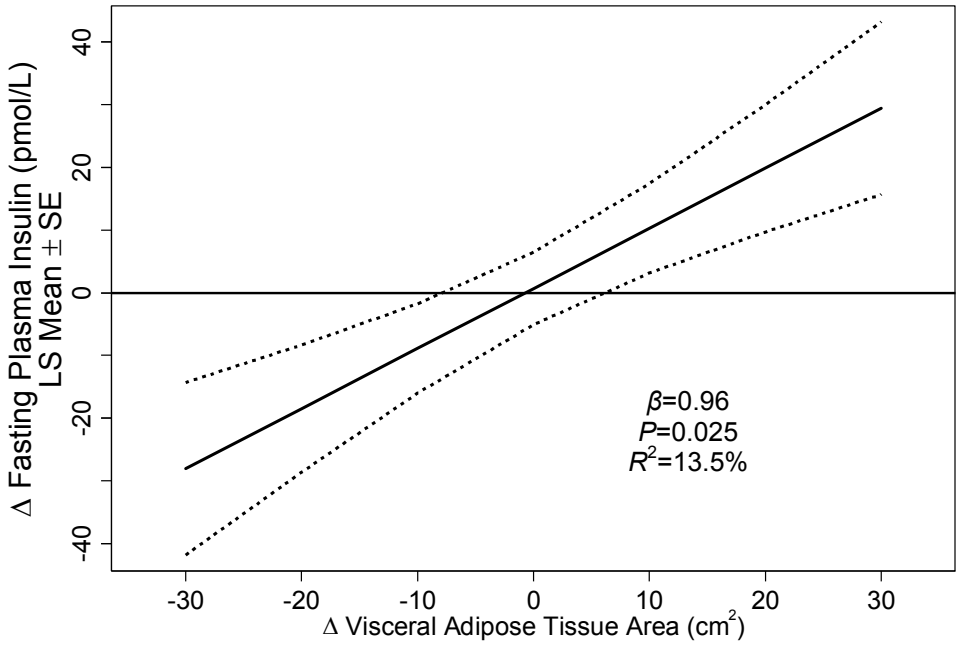


Figure 4.3 Relationship between changes in visceral adipose tissue area and changes in fasting insulin concentration from baseline to six months



CHAPTER 5. CONCLUSIONS & FUTURE DIRECTIONS

The purpose of this dissertation was to clarify how exercise may alter pathways that are hypothesized to influence disease outcomes among colon cancer survivors. We also examined the generalizability of our study population to the broader population of colon cancer survivors. The data gathered from this dissertation help to improve the specificity of exercise prescriptions provided to colon cancer survivors, strengthen the rationale that a causal relationship exists between exercise and disease outcomes, and refine key design aspects for future randomized trials in this population.

Specific aim one sought to quantify and describe the dose-response effects of moderate-intensity aerobic exercise on visceral adipose tissue (VAT). We hypothesized that exercise would favorably reduce VAT in dose-response fashion. Our hypothesis was supported as moderate-intensity aerobic exercise significantly reduced VAT in linear dose-response fashion (P_{trend}=0.008). Specific aim two sought to quantify and describe the dose-response effects of moderate-intensity aerobic exercise on levels of fasting insulin. We hypothesized that exercise would favorably reduce levels of fasting insulin in dose-response fashion. Our hypothesis was supported as moderate-intensity aerobic exercise significantly reduced levels of fasting insulin in nonlinear fashion (P_{trend}=0.042). Specific aim three sought to quantify and describe demographic, clinical, and geographical characteristics associated with eligibility screening and study enrollment. We hypothesized that demographic, clinical, and geographical characteristics would be associated with eligibility screening and study enrollment. Our hypothesis was supported as colon cancer survivors who were screened for eligibility and enrolled in the study were significantly younger (screening P<0.001, enrollment P=0.007) and more

likely to have been treated with chemotherapy (screening $P<0.001$, enrollment $P=0.006$) than the population from which they were recruited.

Since the initiation of the COURAGE trial, research has continued to accumulate that further strengthens the rationale and scientific basis for this line of inquiry. Epidemiologic data have provided additional evidence supporting the association between physical activity and disease outcomes among colon cancer survivors [Campbell *et al*, 2013] and these data have now been summarized in systematic reviews and meta-analyses that demonstrate a dose-response relationship between physical activity and outcomes [Je *et al*, 2013, Schmid and Leitzmann, 2014]. Molecular epidemiology studies have characterized tumor features that help to identify patients who may reap the largest cancer-specific benefits from exercise [Hanyuda *et al*, 2015, Yamauchi *et al*, 2013]. Preclinical models have provided important mechanistic data to guide clinical studies [Huffman *et al*, 2013]. Evidence continues to emerge that VAT and hyperinsulinemia are associated with disease recurrence and mortality among colon cancer survivors [Cakir *et al*, 2015, Devin *et al*, 2015].

Understanding how the dose of physical activity influences cancer prognosis is one of the most provocative unanswered questions in oncology [Lam *et al*, 2013]. The National Cancer Institute has expanded its funding portfolio to support research to answer this question [Alfano *et al*, 2016, Ballard-Barbash *et al*, 2013]. Elucidating if and how physical activity reduces the risk for cancer recurrence and/or improves survival is currently the #1 research question in the field of exercise-oncology [Courneya *et al*, 2015]. The importance of this line of research has been echoed by various national organizations including the Institute of Medicine (IOM), American Society of Clinical Oncology (ASCO), American Association of Cancer Research (AACR), American

Society of Preventive Oncology (ASPO), and the American Cancer Society (ACS), as all of these organizations have hosted meetings with themes focused on energy balance, exercise, obesity, and lifestyle practices to promote healthy cancer survivorship. Some organizations have published position papers from these meetings [Alfano *et al*, 2014, Demark-Wahnefried *et al*, 2012, Ligibel *et al*, 2014, Ligibel *et al*, 2015]. Given the recent surge of enthusiasm in this area, the findings from the COURAGE trial are timely, are of high interest to the clinical and research communities, and will provide important data to guide the field over the next decade.

As described in Chapter 1, oncologists will continue to field questions such as "Should I exercise? Should I lose weight? What will improve my chances?" from the 83,000 people who are diagnosed with non-metastatic colon cancer each year. Oncology providers are uniquely positioned to offer guidance about exercise to patients. Patients often view oncologists as decision-makers for their health, and the oncologist recommendation is possibly the biggest catalyst to initiate behavior change [Brown and Schmitz, 2014a]. Patients are likely to remember recommendations about physical activity from their oncologist if there is the perception that the provider values such behaviors. A diagnosis of cancer is often viewed as a teachable moment where patients may be amenable to adopting recommendations about physical activity and other lifestyle behaviors, such as quitting smoking, losing weight, and improving their diet [Brown and Schmitz, 2014a]. Clinical practice guidelines encourage oncology providers to recommend that patients engage in a physically active lifestyle [Meyerhardt *et al*, 2013]. After making this recommendation to patients, providers often field the follow-up question of "How much should I do?" or "How much is enough?" The data generated from this dissertation begins to answer these questions. The linear dose-response

reductions observed for VAT, and the nonlinear dose-response reductions observed for fasting insulin suggest that providers should encourage patients work towards the goal of 300 min·wk^{-1} as long as the provider believes it is safe to do so. This recommendation is also grounded in behavioral science practices, wherein higher exercise goals result in more exercise completed, even if the goals themselves are not achieved [Hultquist *et al*, 2005, Perri *et al*, 2002].

These data are useful to begin to fill the developmental pipeline for binging exercise to the standard of clinical care for adjuvant colon cancer (see **Figure 1.6** in Chapter 1). Recruitment, adherence, and follow-up are three critical aspects to success for any trial, particularly a behavioral trial such as COURAGE. Perhaps the most novel feature of this trial was the provision of permanent in-home treadmills. The purpose of providing in-home treadmills was three-fold. First, it served as a reasonable incentive for participation. This effort was successful as recruitment was completed ahead of schedule. Second, it was provided to promote high levels of exercise adherence. This effort was successful as exercise adherence in the low-dose and high-dose groups were 92% and 89%, respectfully. The provision of a treadmill was cited by nearly every participant as being central to their exercise success and motivation to meet the study goals. For example: “I feel blessed for that treadmill in my living room, I wouldn’t be this good with my exercise if I had to go outside all the time” [participant 025 in the low-dose group quoted at month 5 of the study. This participant finished with 100% adherence] and “I feel like you have positioned me for lifelong success with this treadmill, knowing that you invested this much in me provided the motivation to do my exercise on the days I was feeling sluggish” [participant 016 in the high-dose group quoted at the end of the study. This participant finished with 98% adherence]. Third, it provided an incentive for

control group participants to successfully complete the study. This effort was successful as 12 of 13 control group participants, and all 26 participants in the two exercise groups, completed the trial (97% completion rate). Although it is possible to conduct trials of exercise without providing in-home exercise equipment, the experience from this trial is consistent with the hypothesis that the provision in-home exercise equipment may improve recruitment, adherence, and follow-up. If the principal goal of prescribing exercise to colon cancer survivors is to prevent disease recurrence, then an in-home treadmill is similar to durable medical equipment. Future studies that provide in-home exercise equipment should aim to quantify the cost-effectiveness of such an approach. The treadmills provided in our study cost $1,000 per person. The cost of treating recurrent colon cancer with palliative chemotherapy often exceeds $100,000 per person per year [Wong *et al*, 2009]. Empirical data that integrate costs, patient satisfaction, and the magnitude of health benefit will help to guide the development of interventions that are designed to succeed from a patient, provider, and third-party payor perspective when adopted into the standard of care for colon cancer.

This area is rich with opportunities to understand how exercise can be used to promote healthy colon cancer survivorship. This dissertation contributes to advancing that mission. Additional data from future trials are urgently needed. These additional data will allow for more definitive guidance to colon cancer survivors. As described in Chapter 1, future studies should build upon this work by investigating the specific pathways through which exercise improves disease outcomes. The collaboration of clinical and basic scientists will accelerate progress in this area [Gehlert *et al*, 2014]. Future single-center studies should continue to monitor the safety and feasibility of exercise, while documenting the physiologic changes that are hypothesized to mediate

the relationship between exercise and disease outcomes. In the near future, multicenter feasibility trials will be necessary to increase sample sizes and commence a coordinated effort to improve efficiency and concentrate synergy. The planning and design of these multicenter feasibility trials are of critical importance given that their purpose will be to establish a robust foundation on which to build definitive phase III trials.

In conclusion, we have demonstrated that exercise induces several favorable physiologic changes among colon cancer survivors. Such changes include reductions in VAT and reductions in fasting insulin concentration. The participants in this trial were younger and more likely to have been treated with chemotherapy than the population from which they were recruited. Disease recurrence is a formidable reality for many colon cancer survivors and presents a critical barrier to long term survivorship. Continued efforts to elucidate the biologic or biobehavioral pathways through which exercise improves colon cancer outcomes are necessary. Generating the compendium of evidence that is sufficiently persuasive to shift clinical practice will be complex, time consuming, and undoubtedly encounter bumps in the process. However, the satisfaction of empowering patients, families, and providers with practical evidence-based solutions to reduce the risk of disease recurrence is well worth the necessary sacrifice.

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