5-7-2011

The Efficacy of Exercise Interventions on Cancer-Related Fatigue and Depression among Adult Cancer Survivors: A Meta-Analysis of Randomized Control Trials

Justin C. Brown
justin.brown@uconn.edu

The Efficacy of Exercise Interventions on Cancer-Related Fatigue and Depression among Adult Cancer Survivors: A Meta-Analysis of Randomized Control Trials

Justin C. Brown

B.S., Eastern Connecticut State University, 2009

A Thesis

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Master of Arts

At the

University of Connecticut

2011

APPROVAL PAGE

Master of Arts Thesis

The Efficacy of Exercise Interventions on

Cancer-Related Fatigue and Depression among Adult Cancer Survivors:

A Meta-Analysis of Randomized Control Trials

Presented by:

Justin C. Brown, B.S.

Major Advisor Linda S. Pescatello

Linda S. Pescatello, Ph.D.
University of Connecticut, Department of Kinesiology

Associate Advisor Blair T. Johnson

Blair T. Johnson, Ph.D.
University of Connecticut, Department of Psychology

Associate Advisor

Robert D. Siegel, M.D.
Hartford Hospital, Division of Medical Oncology

University of Connecticut

2011

Table of Contents

Chapter 1 — Introduction

Background and Significance

Cancer Survivorship

Cancer is a major public health problem. In 2009 there were an estimated 11 million cancer survivors in the United States. Cancer is the leading cause of death among women 40 to 79 yr and men 60 to 79 yr. The most common forms of cancer among men are prostate, lung, and colorectal cancer with rates of 158.2, 87.3, and 61.2 diagnoses per 100,000 persons, respectively. The cancer incidence rate among White non-Hispanic men is 551 diagnoses per 100,000 people compared to African American men with 652 diagnoses per 100,000 people. The most common forms of cancer among women are breast, lung, and colorectal with rates of 123.6, 55.4, and 44.8 diagnoses per 100,000 persons, respectively. White non-Hispanic women are at higher risk for developing cancer with 423 diagnoses per 100,000 people compared to African American women with 398 diagnoses per 100,000 people. Cancers of the breast, prostate, lung, and colon accounted for an estimated 751,061 new diagnoses (~50% of all cancer diagnoses) and 276,000 deaths (~49% of all cancer related deaths) in 2009 in the United States. The lifetime probability of developing cancer for men is 50% (1 in 2) and for women 38% (~1 in 3) (1).

Despite high incidence rates among the general population, advances in screening, surgical procedures, and pharmacological interventions have increased the 5 yr survival rate among all cancers survivors from 50% in 1974 to 66% in 2009 (1). This 16% increase equates to ~1.7 million people living with cancer for ≥5 yr after diagnosis in 2004 that if diagnosed in 1969 may have not been alive in 1974 (1).

While living longer after diagnosis, cancer survivors frequently report physical and psychological symptoms associated with cancer or cancer treatment(s) including loss of appetite, nausea, difficulty concentrating, fatigue, and depression (2). Nearly all cancer survivors report one or more symptoms affecting their sense of well-being that negatively affects physical and social quality of life (QOL) (3).

Management of symptoms associated with cancer or cancer treatment may have limited or no treatment so that clinicians are often left with the option of advising their patients that cancer related symptoms are something they have to learn to live with (3). However, there is a variety of established interventions to aid in modulating symptom severity. These interventions include individual and family counseling, coping skill development, and communication skill development. These above-mentioned interventions broadly focus on improving psychological components of cancer survivor well-being rather than physical well-being (4, 5). However, in the past two decades, literature has accumulated that indicates *exercise* after cancer diagnosis reduces the incidence and severity of a variety physiologic and psychosocial symptoms' frequently reported by cancer survivors. However, the magnitude of symptom improvement among exercise interventions in cancer survivors is highly variable among individual exercise interventions. These variations in symptom improvement may due to differences among exercise interventions including the type of cancer targeted, stage and type of treatment, type of exercise performed, and the primary health outcomes examined (2, 6).

Exercise Interventions

The accumulation of literature addressing the effect of exercise on symptom management among cancer survivors has spurred various professional organizations to develop exercise recommendations tailored for cancer survivors. These organizations

include the American Cancer Society (7), National Comprehensive Cancer Network (3), and American College of Sports Medicine (ACSM) (2, 8). The two sets of ACSM exercise guidelines were developed differently; one in the form of guidelines based on limited literature-based evidence (8), and the other, an expert panel consensus (2). A noteworthy comment, each exercise recommendation from the American Cancer Society, National Comprehensive Cancer Network and the ACSM suggest different "Exercise Prescription's (Ex R_x)" elicit favorable outcomes among cancer survivors. For example, the American Cancer Society and National Comprehensive Cancer Society make no recommendation of resistance training among cancer survivors, whereas the ACSM suggests resistance training performed two days per week to achieve the health-benefits associated with exercise.

The current professional exercise recommendations for cancer survivors (2, 3, 7, 8) are generic, in that one set of recommendations is used for all cancer survivors. However, due to the variety of cancers, their varying pathophysiology, and varying treatment regimes, Ex R_x's may need tailoring specific to the health outcome of interest (i.e., reducing depression) for the most efficacious benefits of exercise to be achieved (8). The components of any Ex R_x are *frequency* (F), *intensity* (I), *time* (T), and *type* (T) of exercise performed, labeled the *FITT* principle of Ex R_x (8). *Frequency* refers to *how often* the exercise sessions take place (i.e., 2 $d \cdot wk^{-1}$). *Intensity* refers to *how hard* or the level of physical exertion is (i.e., low, moderate, or vigorous). Intensity of exercise can be quantified using metabolic equivalent units (METs). One MET is equal to 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$, representing oxygen consumption (ml) per kg of body weight per minute while sitting quietly. METs are categorized into light intensity (<3 METs), moderate intensity (3 to 6 METs), or vigorous intensity (>6 METs). *Time* refers to *how long* each exercise session is (i.e., 30 $min \cdot d^{-1}$). *Type* refers to the *modality* or *kind* of activity completed (i.e.,

cycling, walking, weight training).

ACSM's Guidelines for Exercise Testing and Prescription, eighth edition (8) provide the most detailed FITT recommendations for cancer survivors. These recommendations focus on a balanced health-fitness program consisting of cardiovascular fitness, muscular strength, muscular endurance, and flexibility activities (8). These guidelines suggest moderate-intensity aerobic and resistance exercise, complimented with flexibility exercise (Table 1) are appropriate for the general physical and mental health of cancer survivors. However, this FITT Ex R_x is **not** symptom specific and thus, may not be the most effective FITT when attempting to maximize the modulation of specific symptoms and health outcomes of cancer survivors.

Table 1. American College of Sports Medicine Exercise Guidelines for Cancer Survivors (8)

Modality	Frequency	Intensity	Time	Type
Aerobic	3-5 $d \cdot wk^{-1}$	40–60% $V0_2R$ 3-6 MET	20-60 $min \cdot d^{-1}$	Walking Cycling Swimming
Resistance	2-3 $d \cdot wk^{-1}$	40-60% 1RM <3 MET	1-3 Sets 8-12 Repetitions	Weight Machines
Flexibility	2-7 $d \cdot wk^{-1}$	Tension	10-30 Seconds 4 Repetitions	Stretching

MET: Metabolic equivalent, 1 MET = 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$.
$V0_2R$: Maximal Oxygen Consumption Reserve.
1RM: 1 Repetition Maximum.

The panel of ACSM exercise experts among cancer survivors (2) advised cancer survivors to follow the recommendations set forth by the American Cancer Society (7). The American Cancer Society guidelines emphasize cancer survivors accumulate ≥150 $min \cdot wk^{-1}$ of aerobic exercise and make no mention of resistance training or flexibility exercise (7). The ACSM expert panel recommended in addition to the American Cancer Society Guidelines of 150 $min \cdot wk^{-1}$ of aerobic exercise (7), moderate intensity, resistance and flexibility exercise be performed to achieve the general health benefits

associated with exercise among cancer survivors. The expert panel concluded exercise is safe among cancer survivors during and after completion of primary pharmacological treatment (i.e., radiation, chemotherapy). However, the panel acknowledged there are considerable gaps in the dose of exercise most effective in reducing the incidence and severity of specific symptoms associated with cancer or cancer treatment. Similar to the ACSM expert consensus statement (2), the National Comprehensive Cancer Network and American Cancer Society suggest accumulating 150 $min \cdot wk^{-1}$ of aerobic exercise is efficacious to achieve the health related benefits of exercise specific to cancer survivors (3, 7). However, these guidelines set forth by the ACSM (2, 8) are a general framework that may require adaptation and tailoring as appropriate for the cancer survivor based on disease and functional status, and presence of other comorbidities (2).

Cancer-Related Symptoms and Side Effects

Cancer-Related Fatigue (CRF)

CRF is the most frequent symptom experienced by 70-100% of all cancer survivors (9). CRF is as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment (3). The magnitude of CRF is not proportional to recent activity and may interfere with usual functioning and QOL (3). CRF should not to be confused with general fatigue. General fatigue differs from CRF in general fatigue is proportional to recent activity and is usually relieved after rest periods of sleep. In contrast, the magnitude of CRF does not diminish after a rest period of sleep and may persist for weeks or even years (3).

van den Beuken-van Everdingen *et al.* (10) surveyed 1,429 cancer patients at 11 cancer treatment centers. The primary aims of this study were to: (i) measure the prevalence of symptoms related to all types of cancer; (ii) determine the impact

symptoms have on QOL; and (iii) inquire whether patients receive treatment for their complaints/symptoms. Patients were diagnosed with a variety of cancer types, most commonly breast (24%) followed by colorectal (14%), prostate (13%), and lung (5%) in all stages of treatment. The symptoms "need to rest" and "tiredness" were the most commonly reported symptoms when compared to all other symptoms associated with any type of cancer (Table 2). The symptoms "need to rest" and "tiredness" did not appear to diminish after completion of curative treatment and affected survivors regardless of treatment status. The symptoms "need to rest" and "tiredness" diminished QOL among this sample ($\beta = -0.261$, $p < .001$) (10).

Table 2. Most Commonly Reported Symptoms in Cancer Survivors (10)

Treatment Stage	Symptoms	
	"Need to rest"	*"Tiredness"*
≥ 6 months after curative treatment (n = 384)*	24% (n = 92)	28% (n = 107)
≤ 6 months after curative treatment (n = 384)*	36% (n = 138)	36% (n = 138)
Palliative Therapy (n = 571)**	43% (n = 245)	45% (n = 256)

*Includes treatments chemotherapy, radiation therapy, hormone therapy, and bone marrow transplant procedures.
**Includes treatments of physical or occupational therapy, psychosocial counseling, and hormone therapy.

Despite the growing literature examining CRF, outcomes have varied considerably, ranging from one-fold *increases* in CRF to two-fold reductions from baseline in response to exercise (11). In addition to the previously discussed literature, five meta-analyses examining the role of exercise in the modulation in CRF have quantified the high variability in randomized controlled exercise trials examining CRF (6, 11-14). Three of these meta-analyses (11, 13, 14) examined CRF moderators or variables that may influence the magnitude of CRF reduction in response to exercise. Moderators included type of cancer, a CRF driven hypothesis, methodological quality, and supervision of exercise sessions. Breast cancer survivors decreased CRF more than non-breast cancer survivors (11, 13, 14). Exercise interventions with an '*a priori'*

CRF related hypothesis achieved greater reductions in CRF than studies without an *a priori* CRF hypothesis, and studies of lower methodological quality reduced CRF more than exercise interventions of higher methodological quality (14). However, *no meta-analysis has examined the Ex Rx FITT components as they modulate CRF among adult cancer survivors.* Further, no meta-analysis has examined any potential interactions between the Ex Rx FITT components and clinical characteristics of cancer survivors (i.e., the interaction of stage of treatment with intensity of exercise and the subsequent modulation on CRF).

Depression

Sixteen to 60% of cancer survivors experience depression (15). Depression among cancer survivors may constitute any of the following symptoms: recurrent feeling or thought of death, changes in body image, negative self-esteem or societal role or lifestyle changes, or concern over money and legal matters (16). Prior to treatment, cancer survivors experiencing less depression had a lower incidence and severity of depression at 5 yr follow-up than cancer survivors reporting more depression prior to treatment (4).

The use of physical activity as a non-pharmacological modality to aid in the treatment of depression or depression-related symptoms among healthy populations has been investigated for more than a century (17). Meta-analyses of prospective intervention studies examining the effects of exercise and depression have supported the use of exercise as a non-pharmacological modality to reduce depression among apparently healthy populations, with small to moderate sized standardized mean reductions (18, 19). These meta-analyses (18, 19) have examined moderators of exercise related reductions in depression including age, length of the exercise

intervention, exercise modality, and type of depression questionnaire used. Lawlor *et al*. (18) meta-analyzed 14 exercise interventions among men and women aged 24 to 88, apparently healthy population only diagnosed with clinical depression. They found studies with a shorter exercise intervention length were more efficacious in reducing depression than standard care. Conn *et al.* (19) meta-analyzed 60 exercise interventions among non-cancer survivors, apparently healthy population only diagnosed depression, and concluded studies providing low intensity, aerobic exercise reduced depression to the greatest extent. Additional moderators identified by Conn *et al*. (19) included methodological considerations relating to random assignment and control group management, with studies of higher methodological rigor reducing depression to a lesser extent than studies of poor methodological quality. Additionally, studies providing a true control group reducing depression more than studies providing a placebo, attention control (19).

Despite a large majority of research examining the efficacy of exercise in apparently healthy populations, there is emerging observational and interventional researching examining exercise and depression among cancer survivors. Chen *et al.* (20) observed 1,399 women diagnosed with stage 0 to III breast cancer. Concluding women with higher exercise levels (≥8.3 MET $h \cdot wk^{-1}$) were less likely to have depression at 18 months post diagnosis; the multivariate adjusted odds ratio was 0.56 (95% CI 0.35 to 0.88). Yet, contrary to observational studies, prospective exercise intervention studies exhibit moderate to large amounts of heterogeneity among RCTs with improvements in depression ranging from negligible to three-fold improvements relative to baseline (6, 12).

Due to the high variability between individual prospective RCTs, two meta-analyses have examined the standardized mean exercise-related reduction of

depression among cancer survivors (6, 12). Schmitz *et al*. (6) and Speck *et al.* (12) concluded evidence is suggestive, but not statistically significant effects, of exercise providing a small reduction in depression among cancer survivors (standardized mean reductions of 0.20 and 0.30, respectively). Due to small sample sizes of six (6) and seven (12) studies, these meta-analyses may have lacked sufficient statistical power to detect a significant effect in the exercise-induced reduction of depression. In addition, Speck *et al.* (12) reported statistically significant heterogeneity of 85% among depression outcomes. Despite the heterogeneity between studies in this meta-analysis, neither (6, 12) examined moderators of the exercise related reduction of depression among cancer survivors. Lack of moderator analyses in these studies (6, 12) is a research gap in the literature. There is high variability between individual exercise trials with respect to varying Ex R_x characteristics, and clinical cancer survivor characteristics making moderator analysis appropriate to perform (6, 12).

In summary, cancer survivors are clinically heterogeneous with respect to demographic characteristics (i.e., gender, age at diagnosis), disease pathophysiology (i.e., type of cancer, tumor location, and staging), treatment protocols, and symptoms and side effects impairing activities of daily living (2). Clinical characteristics specific to each cancer survivor may influence the efficacy of an exercise intervention on CRF and depression outcomes (5, 13, 14). For example, type of cancer has been shown to be predictive of QOL levels, with gastrointestinal and gynecologic cancer survivors experiencing lower QOL relative to lung, breast and prostate cancer survivors among others ($\beta = -4.490$, $\beta=2.202$, $p<.001$, respectively) (10). Therefore, the purpose of this research is to *meta-analytically* investigate the influence of clinical (i.e., type of treatment, tumor location, and staging) and demographic characteristics (i.e., gender,

ethnicity, and age) individually, as well as their interactions with Ex R_x FITT characteristics on CRF and depression modulation among cancer survivors.

Meta-Analysis

Meta-analysis or quantitative reviewing of the literature is the combining of numerical results of individual studies to generate a "summary" result. In the context of this research the effect of the Ex R_x FITT characteristics effects on the modulation of CRF and depression among cancer survivors. Another purpose of the study is to examine the extent to which clinical characteristics moderate the exercise-induced reductions in depression. Further, we will examine interactions among the Ex R_x FITT characteristics and clinical characteristics influencing the efficacy of exercise to reduce CRF and depression among adult cancer survivors. Findings from this analysis may provide guidance as to what specific FITT Ex R_x may prove most efficacious for cancer survivors suffering from CRF and depression.

Specific Aims and Hypotheses

The primary aims of this study are:

Specific Aim 1. To meta-analyze the literature to determine the efficacy of exercise interventions on reductions in CRF and depression among cancer survivors.

Hypothesis 1. *Cancer survivors engaging in exercise will demonstrate a statistically significant reduction in CRF and depression when compared to non-exercising controls.*

Specific Aim 2. To meta-analyze the literature to examine the influence of the Ex Rx FITT components on reductions in CRF and depression among cancer survivors.

Hypothesis 2. *Ex Rx FITT components will modulate the magnitude of the reduction in CRF and depression.*

Specific Aim 3. To meta-analyze the literature to examine the influence of patient clinical characteristics (i.e., cancer type, treatment staging, and age) on reductions in CRF and depression among cancer survivors.

Hypothesis 3. Patient clinical characteristics of cancer survivors will modulate the magnitude of the reduction in CRF and depression that result from exercise.

Specific Aim 4. To meta-analyze the literature to examine the influence of the interactions among Ex Rx FITT components (specific aim 2 & hypothesis 2) and patient clinical characteristics (specific aim 3 & hypothesis 3) on reductions in CRF and depression among cancer survivors.

Hypothesis 4. The interactions among Ex Rx FITT components and patient clinical characteristics will modulate the magnitude of the reduction among cancer survivors.

B. Significance

Cancer is a disease of global impact with an estimated 25 million cancer survivors worldwide (21). Globally, the World Health Organization (WHO) has assembled a panel of cancer experts to develop long-term cancer goals and objectives (21). Specifically the WHO has established goals for cancer survivorship. The specific WHO goals are to increase the QOL among those living with cancer, and to provide relief from pain and other distressing symptoms among all survivors of cancer. The long-term goal of the WHO is to establish National Cancer Control Programs for holistic cancer guidance in all countries, worldwide (21).

Nationally, the US has developed 10 yr health and disease prevention goals and objectives (22). The two over-arching goals of Healthy People 2010 were to increase quality and years of health life, and to eliminate health disparities. Healthy People 2010 included a target area specific to cancer, addressing a variety of screening, treatment and long-term survivorship goals. Specific to this research project, goal three, objective

15, was to increase the proportion of cancer survivors who are living 5 yr or longer after diagnosis to 70%. Healthy People 2010 failed to reach the target set at 70%, but did increase 5 yr survivorship to 64%. Despite not reaching the objective of 70%, the percentage of cancer survivors living ≥5 yr after diagnosis did increase by 45% from year 2000. Increasing 5 yr survivorship among cancer survivors has been a renewed objective in Healthy People 2020 (22). The desired percentage of cancer survivors living ≥5 yr after diagnosis for Healthy People 2020 is 76%.

The clinical significance of this research is two-fold. No study to date has meta-analyzed exercise intervention FITT Ex R_x characteristics that influence CRF and depression among cancer survivors. This study may provide further support for the use of exercise as a non-pharmacological modality for clinicians to recommend to cancer survivors with CRF and depression. This study may also provide quantitative evidence for the use of *specific* Ex R_x FITT recommendations targeted to those patients suffering with CRF or depression based on desired health outcome and clinical characteristics.

In summary, the purpose of this research is to quantitatively summarize the effect of exercise on the modulation of CRF and depression among cancer survivors and generate hypotheses for future research. Quantitatively summarizing the literature on exercise and cancer survivorship will shape future exercise interventions, and more importantly, improve current palliative care practices for those cancer survivors currently living with CRF and depression.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009 Jul-Aug;59(4):225-49.

2. Schmitz KH, Courneya KS, Matthews C, et al. American college of sports medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010 Jul;42(7):1409-26.

3. NCCN Clinical practice Guidelines in Oncology. Cancer-related fatigue. J Natl Compr Cancer Netw. 2009;1.

4. Jacobsen PB, Jim HS. Psychosocial interventions for anxiety and depression in adult cancer patients: Achievements and challenges. CA Cancer J Clin. 2008 Jul-Aug;58(4):214-30.

5. Jacobsen PB, Donovan KA, Vadaparampil ST, Small BJ. Systematic review and meta-analysis of psychological and activity-based interventions for cancer-related fatigue. Health Psychol. 2007 Nov;26(6):660-7.

6. Schmitz KH, Holtzman J, Courneya KS, Masse LC, Duval S, Kane R. Controlled physical activity trials in cancer survivors: A systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2005 Jul;14(7):1588-95.

7. Doyle C, Kushi LH, Byers T, et al. Nutrition and physical activity during and after cancer treatment: An american cancer society guide for informed choices. CA Cancer J Clin. 2006 Nov-Dec;56(6):323-53.

8. Thompson, WR., Gordon, NF., Pescatello LS., editor. ACSM's guidelines for exercise testing and prescription. 8th ed. Lippincott, WIlliams & Wilkins; 2010.

9. Stone PC, Minton O. Cancer-related fatigue. Eur J Cancer. 2008 May;44(8):1097-104.

10. van den Beuken-van Everdingen MHJ, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Quality of life and non-pain symptoms in Patients with cancer. J Pain Symptom Manage. 2009 [cited 5 December 2009];38(2):216-33.

11. Cramp F, Daniel J. Exercise for the management of cancer-related fatigue in adults. Cochrane Database Syst Rev. 2008 Apr 16;(2)(2):CD006145.

12. Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: A systematic review and meta-analysis. J Cancer Surviv. 2010 Jan 6.

13. Velthuis MJ, Agasi-Idenburg SC, Aufdemkampe G, Wittink HM. The effect of physical exercise on cancer-related fatigue during cancer treatment: A meta-analysis of randomised controlled trials. Clin Oncol (R Coll Radiol). 2010 Jan 26.

14. Kangas M, Bovbjerg DH, Montgomery GH. Cancer-related fatigue: A systematic and meta-analytic review of non-pharmacological therapies for cancer patients. Psychol Bull. 2008 Sep;134(5):700-41.

15. Osborn RL, Demoncada AC, Feuerstein M. Psychosocial interventions for depression, anxiety, and quality of life in cancer survivors: Meta-analyses. Int J Psychiatry Med. 2006 [cited 6 October 2010];36(1):13-34.

16. Holland JC, Andersen B, Breitbart WS, et al. Distress management. J Natl Compr Canc Netw. 2010 Apr;8(4):448-85.

17. Franz SL, Hamilton GV. Effect of exercise upon the retardation in condition of depression. Am J Insanity. 1905;62:239-256.

18. Lawlor DA, Hopker SW. The effectiveness of exercise as an intervention in the management of depression: Systematic review and meta-regression analysis of randomised controlled trials. BMJ. 2001 Mar 31;322(7289):763-7.

19. Conn VS. Depressive symptom outcomes of physical activity interventions: Meta-analysis findings. Ann Behav Med. 2010 May;39(2):128-38.

20. Chen X, Lu W, Zheng Y, et al. Exercise, tea consumption, and depression among breast cancer survivors. J Clin Oncol. 2010 Feb 20;28(6):991-8.

21. World Health Organization Cabinet on Cancer Prevention. WHO's fight against cancer: Strategies that prevent, cure and care. . 2010.

22. Secretary's Advisory Committee on Health Promotion and Disease Prevention Objectives for 2020. Healthy people 2020.

Chapter 2 — Methods

We investigated the variability in FITT Ex R_x and the extent to which exercise modulated CRF and depression among cancer survivors using meta-analytic techniques. This chapter describes the procedures used for the meta-analysis including the literature search, initial screening of studies, full-text review, data extraction, calculation of study level effect size, calculation of the pooled effect, tests for heterogeneity, publication bias, and meta-regression techniques.

Literature Search

Types of participants: Studies considered for inclusion investigated the use of exercise in attempt to modulate CRF or depression levels in adults 18 yr or older. We included both, men and women, all cancer types, stages of cancer, and types of cancer treatment. Subjects were currently receiving treatment, in long-term follow-up, or receiving palliative care.

Types of interventions: Studies considered for inclusion evaluated and reported the effect of exercise on CRF or depression levels in cancer survivors. Studies compared an exercise intervention group to a non-exercise, usual care group, or compared an exercise group to an alternative non-physical intervention such as audio therapy or aroma therapy. The exercise intervention occurred in any setting; home, public location, or medical center. Exercise interventions may have been conducted in group-format (e.g., group exercise classes) or individually (i.e., personal training). All modalities of exercise were considered for inclusion (i.e., aerobic, strength, neuromotor, and flexibility exercises).

Types of outcome measures: The primary outcome measures were self-reported CRF or depression levels. To be included, assessment of CRF and depression levels occurred at the start of the exercise intervention and at completion, for each group, intervention and control, respectively.

Search methods for identifying relevant studies: The following databases were searched for relevant studies to be included in this meta-analysis; MEDLINE; The Cochrane Controlled Trials Register; PsycINFO, Dissertation Abstracts International, and OregonPDF in Health and Human Performance. The CRF systematic search ended February 2010, and the depression systematic search ended December 2010. Citation lists of all relevant literature were reviewed for additional studies and journals relating to cancer survivors were searched (i.e., *Journal of Cancer Survivorship*). There were no language restrictions when attempting to locate studies for inclusion. Searches included medical subject headings (MeSH) to conduct the systematic literature search (Figure 1).

Screening of all studies in the comprehensive literature search were completed by reviewing the title and abstract for inclusion criteria. Reviewers (i.e., JB and SP) were not blinded to journal title or author. The reviewers (JB, SP) screened both title and abstract for inclusion in this meta-analysis. To ensure proper screening, approximately 10% of all excluded studies were re-screened to validate inclusion/exclusion of appropriate literature.

The inclusion criteria included RCTs that use an exercise intervention compared to a usual care, or non-exercising control group with CRF or depression measured as an outcome variable. The intervention took place in adults of any age, caner type, treatment stage, or other demographic characteristics.

Data Extraction: After appropriate title and abstract screening, the literature was subject to a full-text review. Studies reviewed were issued a unique identification number to ensure organization and quality control. After full-text review, if studies continued to meet the inclusion/exclusion criteria, data were extracted via a comprehensive coding form (see Appendix). Data extracted included information on subject demographics (e.g., age, gender, socioeconomic status), study design characteristics (i.e., randomization and blinding procedures, length of exercise intervention, and location of exercise intervention), and subject cancer characteristics (e.g., cancer type, treatment type, and time length since diagnosis). Characteristics regarding the FITT Ex R_x employed were also extracted. Specifically, *how often* (frequency), *how hard* (intensity), *time* (duration) and *mode* (type) of exercise were extracted. Intensity of exercise was coded in metabolic equivalent units (METs) using the compendium of MET intensities (1). This compendium is valid and widely used in physical activity disciplines for coding absolute energy expenditures.

Data Extraction Agreement: Kappa statistic and Pearson's *r* assessed individual coder agreement for categorical variables and continuous variables, respectively. The Kappa statistic accounts for the degree of chance occurrence agreement between the two coders. This statistic provides information on the reliability and reproducibility of the coders, and accounts for the degree of chance occurrence between coders in addition to actual agreement (2). Superior to simply calculating percent agreement, the Kappa statistic ensures quality control in data extraction.

The guidelines for interpreting the Kappa statistic were <0 = poor, 0.00-0.20 = slight, 0.21-0.40 = fair, 0.41-0.60 = moderate, 0.61-0.80 = substantial, and 0.81-1.00 = almost perfect agreement (2, 3). Even in the presence of substantial or almost perfect agreement, the Kappa statistic may appear low, ranging from 0.61-1.00, respectively.

The guidelines for interpreting Pearson's *r* were 0.00-0.49 = low to no agreement, 0.50-0.79 = moderate or medium agreement, 0.80-1.00, strong, or perfect agreement (2). The Kappa statistic was applied to categorical study dimensions and Pearson's *r* was applied to continuous study dimensions.

Individual Effect Size Estimates: Because the majority of randomized controlled trials (RCTs) reported continuous measures of CRF and depression, standardized mean difference effect sizes were used. Effect sizes were used to estimate the efficacy of the FITT Ex R_x on the modulation of CRF and depression. The standardized mean difference effect size (*d*) was the mean difference between the treatment and control groups divided by the pooled standard deviation (4). The effect size *d* has a slight bias tending to overestimate the true population mean (δ) when studies have small sample sizes. We removed this bias by applying a correction factor that yields an unbiased estimate of (δ) (5). Applying this correction yielded an error <0.007 and less than 0.035% when $df \geq 10$ (6). This application was applied to all effect sizes prior to analysis. CRF effect sizes are positive when the treatment group reduced their fatigue more when compared to the usual care group. Depression effect sizes are negative when the treatment group reduced their depression more when compared to the usual care group. Some studies included more than one treatment group. In this situation, we compared each treatment group to the control group, producing two effect size estimates from one study (7).

Mean Effect Size Calculation (Fixed Effects vs. Random Effects)

Fixed Effects Modeling: The overall estimate of the effect was calculated using two models for each CRF and depression outcomes. The first, a fixed effect model assumed all studies in the meta-analysis were treated as sharing a common effect size. All

factors that could influence the effect size were the same in all studies. Each individual study was assigned a weight. This weight corresponded to the inverse within study variance.

Random Effects Modeling: In a random-effects model, as with a fixed effects model, each study was weighted by the inverse of its variance. The difference between fixed and random effects model was that the weighting not only included within study variance (as seen with fixed-effects assumptions) but the *between* study variance as well, denoted τ^2 (tau-squared). Random effects modeling provided wider confidence intervals around the mean effect size, due to added between study variance.

Fixed vs. Random Effects Modeling*:* The mean effect was the weighted average of the means of individual study effects. We implemented both the fixed and random effects models in our analysis to calculate the mean effect. These values provided an estimate on the efficacy of CRF and depression modulation in repose to an exercise intervention.

Publication Bias: We examined both forest and funnel plots for publication bias. These graphical techniques illustrated the variability among sampled studies (forest plot) and the expected effect size (funnel plot) by plotting calculated effect size against variance. We also assessed publication bias statistically via Begg and Egger publication bias methods (6) and the non-parametric "Trim and Fill" method, a non-parametric test for asymmetry in the distribution of effect sizes (8).

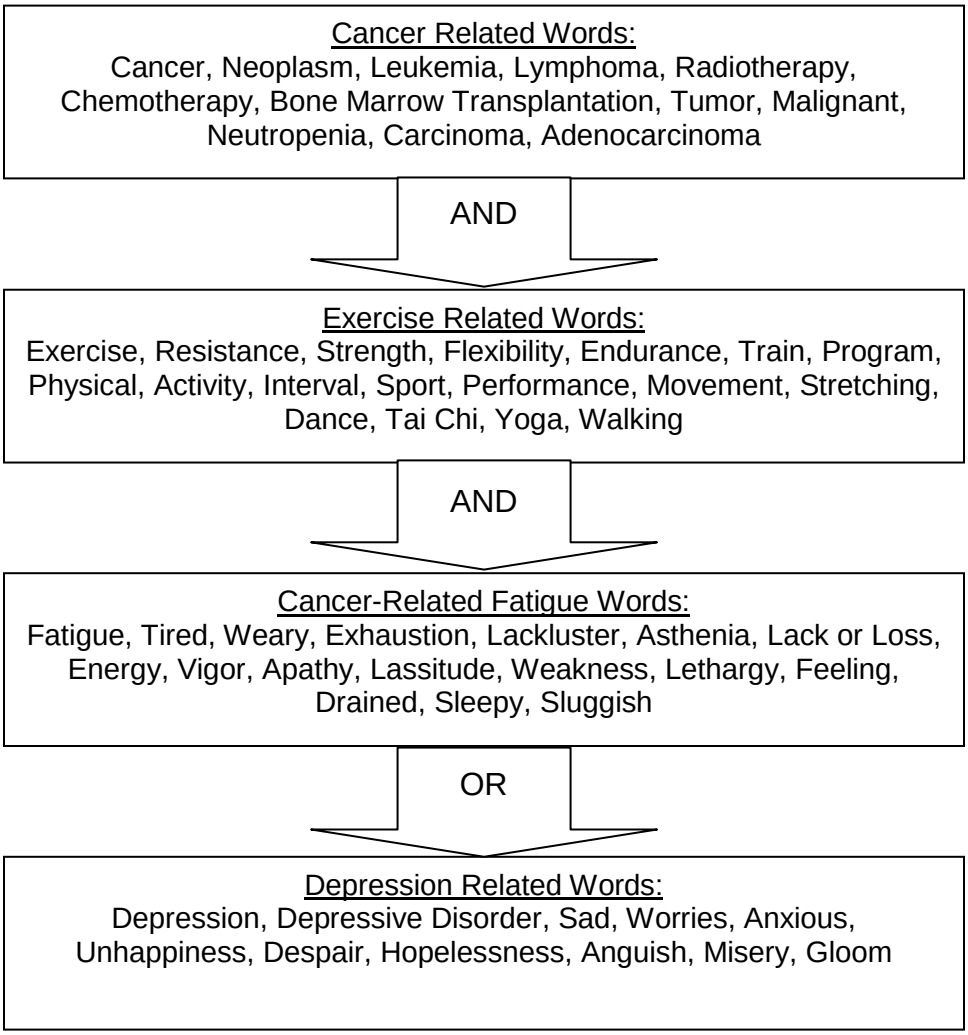
Heterogeneity: The *homogeneity* in effect sizes measured the differences of similarities between studies (9). Homogeneity (*Q*) was then calculated to determine if there was more variance between studies than would be produced by random sampling alone. *Q* is not a standardized statistic, making its interpretation difficult in a given context. *Q* was

then transformed to I^2, a standardized measure of homogeneity. I^2 values assumed a range of 0-100%, indicating homogeneity (0%) or heterogeneity (100%) between studies (9).

Meta-Regression: Moderators (i.e. covariates) were tested with the FITT Ex R_x and clinical characteristics with respect to CRF or depression outcomes, respectively. Specific subject demographic characteristics were also examined. Specific characteristics included age, gender, ethnicity, socioeconomic status, education, type of cancer, type of treatment, stage of treatment, and time since diagnosis. Moderators listed above were also included within the comprehensive coding form (Appendix A).

Statistical Computing: The statistical software package Intercooled Stata version 11.1 (College Station, Texas) performed all statistical analysis (10). Although Stata does not have built in meta-analytic tools, macros exist for meta-analysis. These macros were freely downloadable and included: meanes, metareg, metaf, metan, metabias, and confunnel. Two-sided statistical significance was set at $p < 0.05$.

Figure 1. Systematic search terms for CRF and Depression among Cancer Survivors.



References

1. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: An update of activity codes and MET intensities. Med Sci Sports Exerc. 2000 Sep;32(9 Suppl):S498-504.

2. Meyer GJ. Simple procedures to estimate chance agreement and kappa for the interrater reliability of response segments using the rorschach comprehensive system. J Pers Assess. 1999;72(2):230.

3. Cohen J. Weighted kappa: Nominal scale agreement provision for scaled disagreement or partial credit. Psychol Bull. 1968 [cited 31 January 2010];70(4):213-20.

4. Cohen J. Statistical power analysis for the behavioral sciences. New York, NY: Erlbaum; 1998.

5. Hedges LV, Olkin I. Statistical methods for meta-analysis. Orlando, FL: Academic Press Inc; 1985.

6. Borenstein M, Hedges L, Higgins J, Rothestein H. Introduction to meta-analysis. West Sussex, United Kingdom: Wiley; 2009.

7. B.J. Becker. Handbook of applied multivariate statistics and mathematical modeling. In: H. E. A. Tinsley and S. D. Brown, editor. San Diego, CA.: Academic Press; 2000. p. 499-525.

8. Duval S, Tweedie R. A nonparametric ``trim and fill'' method of accounting for publication bias in meta-analysis. Journal of the American Statistical Association. 2000;95(449):89-98.

9. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ: British Medical Journal. 2003;327(7414):557.

10. StataCorp. Stata statistical software [computer program]. 2005;Version 10.

Chapter 3 — Cancer-Related Fatigue

Efficacy of Exercise Interventions in Modulating Cancer-Related Fatigue among Adult Cancer Survivors: A Meta-Analysis

Justin C. Brown[1]*, Tania B. Huedo-Medina[1], Linda S. Pescatello[1], Shannon M. Pescatello[2], Rebecca A. Ferrer[3], Blair T. Johnson[1]

[1] University of Connecticut
[2] Western New England College
[3] National Cancer Institute

Financial Disclosure: This research was supported by University of Connecticut Research Advisory Council Foundation Grant # 433527 (PIs: Blair T. Johnson and Linda S. Pescatello)

*Corresponding Author:
Justin C. Brown
University of Connecticut
Department of Kinesiology
2095 N. Hillside Road, U-1110
Storrs, CT 06269-1110
Phone: (860)-486-2812
Fax: (860)-486-3149

Running Title: Exercise and cancer-related fatigue: a meta-analysis

Previous presentation of manuscript: American College of Sports Medicine, National Meeting, Baltimore, 2010.

Disclaimers: None

Abstract

Background: The purpose of this meta-analysis was to explore the efficacy of exercise as a non-pharmacological intervention to reduce cancer-related fatigue (CRF) among adult cancer survivors. We also investigated how different components of the exercise prescription (Ex R_x), methodological considerations, and subject characteristics modulate CRF. **Methods:** A systematic search for randomized controlled trials was conducted using words related to cancer, exercise, and fatigue. **Results:** In total 44 studies with 48 interventions qualified, including 3,254 participants of varying cancer types, stages of diagnosis, treatments, and exercise interventions. Cancer survivors in exercise interventions reduced their CRF levels to a greater extent than usual care controls, $d_+ = 0.31$ (95% confidence interval = 0.22 to 0.40), an effect that appeared to generalize across several types of cancer. CRF levels improved in direct proportion to the intensity of resistance exercise ($\beta = 0.60$, $p = .01$), a pattern that was stronger in higher quality studies ($\beta = 0.23$, $p < .05$). CRF levels also reduced to a greater extent when interventions were theoretically-driven ($\beta = 0.48$, $p < .001$) or cancer survivors were older ($\beta = 0.24$, $p = .04$). **Conclusions:** Exercise reduced CRF especially in programs that involved moderate intensity, resistance exercise among older cancer survivors and that were guided by theory. **Impact:** Our results indicate exercise interventions for adult cancer survivors should be multi-dimensional and individualized according to health outcome and cancer type.

Brown JC, et al. 2011. *Cancer Epidemiology, Biomarkers & Prevention* Jan 2011;20:123-133.

Introduction

Currently, there are over 11-million cancer survivors in the United States (1). The 5-yr survival rate for cancer survivors has steadily increased from 50% in 1974 to 66% in 2004 (1). Despite living longer after diagnosis, cancer survivors commonly report having one or more cancer-related symptoms that impact their quality of life and activities of daily living (2). One of the most commonly reported symptoms by cancer survivors is cancer-related fatigue (CRF) (3). CRF is a reported side-effect of all types of cancer treatment (4) affecting nearly 100% of cancer survivors, and persists for years after treatment cessation (5, 6). Cancer survivors often state CRF is the most distressing symptom related to cancer or cancer treatment, more so than pain, nausea, and vomiting (2, 7, 8).

Cancer survivors often are told by medical providers to learn to live with CRF by limiting activity, conserving energy expenditure, and relying on others to complete activities of daily living (3). Yet, new evidence is accumulating that indicates cancer survivors who engage in exercise experience numerous physical and mental health benefits including increased functional capacity (4), improved quality of life (9), and diminished depression (10) and anxiety (10). In addition, meta-analyses (11-14) and systematic reviews (15) suggest exercise interventions may be moderately efficacious in modulating CRF.

Despite the promise of exercise in the management of CRF, an exercise prescription (Ex R_x) tailored for adult cancer survivors experiencing CRF does not exist (3, 4, 16, 17). The available Ex R_x guidelines for cancer survivors (3, 4, 16, 17) broadly focus on the general well-being of cancer survivors, encouraging 150 min/wk of aerobic exercise, 2 d/wk of strength training, and flexibility exercise on days when aerobic or

resistance exercise is not performed. An American College of Sports Medicine (ACSM) panel of experts in Ex R_x for cancer survivors recently concluded exercise is safe for cancer survivors, all cancer survivors should avoid inactivity, and exercise programs should be adapted for the individual survivor on the basis of health status, cancer treatment type, targeted health outcomes, and disease trajectory (4). Yet, the panel acknowledged research in the area of Ex R_x for cancer survivors is in the developmental stage with significant research gaps in the dose of exercise required to ensure cancer survivors receive safe and effective Ex R_x for targeted disease end points such as CRF.

We conducted a quantitative review evaluating the efficacy of exercise as an intervention to reduce CRF among adult cancer survivors. The primary purpose was to investigate which Ex R_x characteristics were associated with the greatest reductions in CRF. We also examined whether study methodological considerations and subject characteristics combined or interacted with the dose of exercise prescribed to reduce CRF further.

Methods

Inclusion Criteria

Included were randomized controlled trials (RCTs) that examined the effects of exercise on CRF in adult patients (≥18 years) diagnosed with any type of cancer, stage of diagnosis, and type or stage of treatment including those who have completed treatment. Exercise interventions may have occurred in any setting with or without supervision. RCTs may have compared exercise with a usual care group receiving either (*a*) standard, usual care (e.g., no exercise program prescribed and to maintain

current activity levels), or (*b*) non-exercise related information during the intervention period.

[See online appendix I for detailed systematic search information]

CRF Outcome Measure

The outcome variable examined was patient-reported CRF (3), which studies assessed either separately or as a component of a comprehensive psychological questionnaire with a CRF subscale (see: bottom Table 1) (18-23).

Coding and Reliability

Two independent raters (JB, SP) coded information related to the study (see Table 1). Intensity of exercise was estimated using metabolic equivalent units (METs), where 1 MET = 3.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$. Corresponding MET values for a given exercise intervention were coded from the Compendium of Physical Activity; these include low (<3 METs), moderate (3-≥6 METs), and vigorous (>6 METs) intensity levels (24). *Methodological quality* was assessed via the Physiotherapy Evidence Database scale (PEDro). PEDro guidelines categorize high quality studies from 6-11, fair quality 4-5, and poor quality <4. Reliability of the raters was high across dimensions (*M* Cohen κ (25) = 0.78 for categorical variables, *M* Spearman-Brown reliability (26) = 0.90 for continuous variables). Disagreements between coders were resolved through discussion.

Study Outcomes and Calculation of Effect Sizes

Because a majority of RCTs reported continuous measures, effect sizes (*d*) were defined as the standardized mean difference between the exercise and control groups divided by the pooled standard deviation, correcting for sample size bias and baseline

differences (27). Multiple effect sizes were calculated from individual studies when they included more than one exercise intervention group (e.g., aerobic and resistance training groups compared to a control group). Subsequent sensitivity analyses were conducted to confirm the dependence did not influence the mean estimate of the 48 effect sizes (28). Consequently, the 44 included studies provided 48 exercise vs. control group comparisons.

[Insert Figure 1 here]

Prior to analysis, data were assessed for publication bias using Begg (29) ($z = 1.01$, $p = 0.31$) and Egger (30) ($t = 0.06$, $p = 0.95$) methods, and yielded no evidence of publication bias (Figure 3 funnel plot, online). The trim-and-fill technique (31) identified no added or omitted studies were necessary to normalize the effect size distribution. Analyses were conducted in Stata 10.1 with macros for meta-analysis (32). The homogeneity statistic, *Q*, was calculated to determine whether a weighted mean effect size (d_+) characterized a common effect size. A significant *Q* indicated the absence of homogeneity (i.e, more variation in effect sizes than sampling error alone would predict). To standardize *Q,* the I^2 statistic and its 95% *CI* were calculated (33, 34). I^2 ranges from 0% to 100% with low values suggesting homogeneity and large values suggesting heterogeneity. To explain variability in the effect size estimates, the relation between study-level characteristics and the magnitude of the effects, was examined in modified least squares regression analysis with the weights equivalent to the variance for each study effect size (viz., meta-regression). Bivariate analysis was conducted using fixed-effects assumptions, and the final, multi-moderator analysis was conducted using random-effects assumptions. To reduce multicollinearity in multiple moderator

models, all retained continuous moderators were zero-centered, and categorical variables were contrast coded.

[Insert Table 1 and Table 2 here]

Results

Potentially relevant reports included 7,245 articles of which 44 (*N*= 3,254*)* satisfied the selection criteria. Of the studies identified, 40 provided one CRF effect size estimate and four studies provided two estimates, yielding 48 effect sizes among 44 studies (See Table 1 for descriptive statistics). Studies providing two effect sizes included two independent exercise intervention groups that were compared to one standard-care group (46, 49, 55, 69). Three interventions with multiple intervention groups were randomized to aerobic exercise, resistance exercise, or control condition (49, 55, 69); whereas the fourth study randomized participants to either supervised exercise, unsupervised exercise, or a control condition (46). The mean methodological quality of the 44 included studies was 6.8±1.4 out of 11 (range: 3-10) (Table 2).The mean age of cancer survivors was 53.8±10.5 yr, and they averaged 6.7±13.8 months post diagnosis. The majority of cancer survivors were women (86%). Approximately half (46%) of cancer survivors were currently being treated with primary pharmacological therapy during the exercise intervention. For those undergoing therapy, a majority of cancer survivors in the sample (75%) were being treated with a combination of chemotherapy and radiotherapy, whereas 13% were treated with only chemotherapy, 6% were treated with only radiation, and 6% were treated with only hormone therapy.

Twenty-five studies examined exercise interventions exclusively in breast cancer survivors (44-55, 57-68), four in prostate cancer survivors (69-72), four in lymphoma (73-

76), one in leukemia (78), and one in colorectal cancer (77). The remaining nine studies examined exercise interventions in a mixed group of cancer survivors (35-43). Twenty-four studies included only aerobic exercise (35, 38, 39, 42-44, 46, 49, 50, 52-59, 61, 65, 69, 70, 74, 77, 78), six studies included only resistance exercise (49, 55, 63, 68, 69, 71), 11 studies included a combination of aerobic and resistance exercise (40, 41, 48, 51, 60, 62, 64, 67, 72, 75, 76), and another six included neuromuscular exercise such as tai-chi, or yoga (36, 37, 45, 47, 66, 73) (Table 5 characteristics of included studies, online).

The average length of the exercise intervention was 11.5±5.2 wk. Cancer survivors exercised 3.5±1.4 d/wk for 48.5±22.8 min/session. The level of physical exertion or average intensity of the aerobic exercise interventions was 5.6±3.0 METs, corresponding to moderate intensity exercise (40-60% $V0_{2max}$), and included walking (48%), stationary cycle ergometry (30%), a combination of walking and cycling (16%), or other modalities of aerobic exercise such as the elliptical trainer or self-selected (6%). The average intensity of resistance training was 4.5±2.0 METs, corresponding to moderate intensity exercise (60-80% one-repetition maximum, 1-RM), and included weight-machines, resistance bands, or free weights (75%). The remaining studies prescribed neuromuscular exercise which commonly included tai-chi or yoga (25%). Flexibility exercise was a component of the exercise in 52% of exercise interventions. Supervision of exercise sessions was provided in 60% of the exercise interventions.

Ten studies used a theoretical basis for the exercise intervention (44, 48, 50, 54, 57-59, 61, 62, 65). Three interventions (48, 58, 62) followed the Transtheoretical model of behavior change (79, 80), two studies (54, 57) followed the model of self-efficacy and stages of exercise change (81), three studies (50, 59, 61) followed the Roy adaptation

model (82), one study (44) followed the Payne adaptation model (83) and one study (65) followed the Levine conservation model (84).

Overall Efficacy of Exercise Interventions on Modulation of CRF

Table 3 summarizes weighted mean effect sizes, d_+, for all cancer types collectively, as well as cancer type individually. This analysis indicated exercise reduced CRF (Table 3 and Figure 2), yet its impact did not attain significance for survivors of lymphoma, colorectal, or leukemia cancer, which may have lacked sufficient statistical power to detect a difference. Pooled, the effect sizes for the 48 interventions lacked homogeneity, as did the collection of studies addressing breast cancer survivors.

[Insert Table 3 and Figure 2 here]

Factors Related to the Magnitude of CRF Modulation

Bivariate regression analyses examined potential sample, methodological, and exercise intervention characteristics. Significant bivariate models were then integrated into a combined moderator model to explain unique study variance (Table 4). When integrated the following moderators no longer remained significant: session length (min), number of exercise sessions, and treatment with radiation therapy. Four moderators impacting CRF modulation in adult cancer survivors remained significant. Reductions in CRF were greater to the extent interventions: (1) adhered to a theoretical model (compared to those that did not do so) ($\beta = 0.48$, $p = <.001$); and (2) sampled older cancer survivors ($\beta = 0.24$, $p = .04$). Also (3), the greatest reductions in CRF occurred with moderate intensity (3-6 METs, 60-80%, 1-RM) resistance exercise ($\beta = 0.60$, $p = .01$), particularly for higher quality interventions (interaction $\beta = 0.23$, $p < .05$). In contrast, lower quality interventions were efficacious in reducing CRF at low (<3 METs)

and moderate intensity (3-6 METs, 60-80% 1-RM) resistance exercise. Intensity of resistance exercise, use of theory, age, and methodological quality together explained 52% of the variance among exercise interventions for adult cancer survivors. The estimates in Table 4 reveal exercise interventions of moderate intensity (3-6 METs, 60-80% 1-RM) resistance exercise were successful in reducing CRF, regardless of the use of theory in the exercise intervention, age of the cancer survivor, and methodological intervention quality. In contrast, interventions of low intensity resistance (<3 METs, <60% 1-RM) exercise showed no significant reduction of CRF when theory was absent or in high methodological quality interventions. Time since diagnosis, aerobic exercise, flexibility exercise, or supervision of exercise sessions did not moderate CRF modulation.

[Insert Table 4 here]

Discussion

Overall, we found exercise moderately reduced CRF among cancer survivors with an effect size of 0.31 (95% CI: 0.22, 0.40), consistent with prior reviews (12, 15). Of note is our new finding that resistance exercise has a positive, quadratic, and exercise intensity dose response effect on CRF. For cancer survivors engaging in moderate intensity, resistance exercise (3-6 METs, 60-80% 1-RM) reduced CRF more so than those engaging in lower intensity resistance or aerobic exercise of any level of physical exertion. Another interesting finding was exercise interventions based upon a theoretical model of behavior change or adaptation were more successful in reducing CRF than those interventions not based upon such models. Age was also related to CRF reduction, with older cancer survivors reducing CRF to greater levels than younger cancer survivors. Lastly, RCTs of stronger methodological quality (i.e., higher PEDro

score) reduced CRF less than those of weaker methodological quality. Our findings about exercise interventions based upon theoretical models and of higher methodological quality support previous meta-analytic work examining the influence of exercise on CRF (11). They also update the literature with a larger, more diverse sample of cancer survivors and types of exercise interventions (11).

Sub-group analysis relating to cancer type revealed exercise moderately reduced CRF, 0.39 (95% CI: 0.27, 0.51) and 0.42 (95% CI: 0.27, 0.57), among breast and prostate cancer survivors, respectively. These findings update and support previous meta-analytic reviews advocating the use of exercise as a non-pharmacological intervention to reduce CRF among breast and prostate cancer survivors (11, 12). Sub-group analysis among leukemia, lymphoma, and colorectal cancer survivors yielded non-significant reductions in CRF.

Four meta-analyses have been conducted examining the effect of exercise on CRF (11-14). Two of these meta-analysis have examined the mean reduction of exercise on CRF (13, 14) without accounting for exercise characteristics that may moderate the efficacy of exercise on CRF. The remaining two meta-analyses (11, 12) have examined moderators relating to the efficacy of exercise in reducing CRF, however, these meta-analyses were comprised of a smaller number of studies (i.e., 17 (11) and 18 studies (12)), and did not examine specific Ex R_x characteristics included in our analysis that may impact CRF modulation. In our meta-analysis of 48 interventions, we found exercise intensity was a significant moderator of CRF among adult cancer survivors participating in resistance training programs. A positive, quadratic pattern emerged suggesting moderate intensity resistance exercise interventions were more efficacious in diminishing CRF than those of lower intensity or aerobic exercise of any

level of intensity. Our finding of the efficacy of resistance exercise reducing CRF was somewhat unexpected. Current exercise guidelines for cancer survivors emphasize the importance of participating in aerobic exercise, complimented with resistance and flexibility exercises (ACSM Roundtable) (4) and often make no (National Comprehensive Cancer Network) (3) or minimal mention (American Cancer Society) (17) of resistance exercise.

A possible mechanism for the effectiveness of resistance exercise in reducing CRF among breast and prostate cancer survivors is the attenuation of the progressive muscle wasting and disruptions in muscle metabolism that occur with cancer and associated treatments (85). Several hypotheses related to muscle protein synthesis, adenosine triphosphate dysregulation, cytokine dysregulation and progressive muscle wasting have all been postulated as mechanistic underpinnings of CRF (85, 86). Moderate intensity resistance training increases muscle protein synthesis (87), improves cytokine response (88), and diminishes the rate of sarcopenia (89) among healthy human populations as well as those with compromised muscle function such as those with cerebral palsy, and other musculoskeletal disorders (90). Further, recent evidence suggests resistance exercise may provide health benefits such as improved total body muscular strength, self-esteem, and vitality in breast and prostate cancer survivors (49, 72, 91).

Another interesting finding was older cancer survivors reduced CRF to greater levels than younger cancer survivors engaging in any form of exercise. This finding is of particular importance as most cancer survivors are older $\geq$65 yr (1), yet most exercise interventions have focused on younger cancer survivors (4). Older cancer survivors are frequently challenged with age-related declines in health (i.e., sarcopenia, decreased

functional capacity) as well as cancer-related declines in health (e.g., cachexia, body composition changes, decreased bone mineral density) (92). Exercise has been shown to elicit favorable health outcomes among older prostate cancer survivors including, increased lean body mass and muscle strength, and increase distance walked in 6 minutes (72). Improving the status of these health parameters (e.g., body-composition, muscular strength, and cardiorespiratory fitness) may influence the modulation of CRF among other populations of cancer survivors.

Exercise interventions that adhered to a theoretical model of behavior change(86, 88) or adaptation model (82) achieved larger reductions in CRF than those that did not adhere to such models. Theoretical models provide empirically supported frameworks that inform behavior change, and may offer useful information about determinants of exercise behavior (93, 94). An understanding of exercise behavior and behavioral determinants among cancer survivors may help clinicians identify specific intervention strategies to facilitation adoption and maintenance of an existing exercise program in this population. Theoretical models of adaptation for cancer survivors may be efficacious in improving psychological components of mental health (e.g., distress of cancer diagnosis) potentially influencing CRF modulation. Despite the promise of such interventions, relatively few of the studies implementing a theoretical framework elaborated on the specific role of theory in the exercise intervention. Therefore, the current meta-analysis is limited in its ability to determine the specific underpinnings of theory mediating the reduction in CRF.

This study is subject to several limitations. Despite our comprehensive review of the literature examining CRF in all types of cancer, our search yielded 28 of the 48 exercise interventions that targeted breast (58%) and prostate cancer (10%) survivors

exclusively. The large number of interventions examining the impact of exercise on CRF modulation among breast cancer survivors limits the generalizibility of our findings to other types of cancer survivors. Moreover, we acknowledge that theories of behavior change and adaptation models are hypothesized to influence fatigue through different mechanisms. As noted, we combined them into a single category because there were relatively few instantiations of theory-led interventions. Despite this limitation, the efficacy of the application of either behavior change or adaptation models is promising when compared to those not adhering to a pre-specified theory or model.

Another limitation relates to the major finding of this meta-analysis, that moderate intensity resistance exercise may be beneficial in reducing CRF. In particular, no study examined resistance exercise interventions >6 METs (>80% 1-RM). It remains unknown if more vigorous intensity resistance training would provide greater or lesser reductions in CRF. We did not evaluate adherence to the exercise interventions in this meta-analysis because most studies did not report this information. This variable should have important moderating effects on CRF modulation.

In summary, we confirm with the largest meta-analysis of RCTs conducted to date that moderate resistance exercise reduces CRF among adult cancer survivors, particularly breast and prostate cancer survivors and those of older age. Cancer survivors engaging in moderate-intensity resistance exercise modulated CRF levels more than those engaging in low-intensity resistance exercise or low to moderate intensity, aerobic exercise. Further, the most efficacious exercise interventions were based upon behavior change and adaptation theory. Our findings reinforce the notion that exercise interventions for adult cancer survivors should be individualized based upon the targeted health outcome and possibly cancer type. In addition, exercise

interventions should be multi-dimensional, combining sound exercise as well as behavioral science.

Supporting Information (Included in article)

Table 1. Descriptive characteristics of included studies (Means ± SD)

Table 2. Methodological quality of included studies by cancer type modulation by cancer type

Table 3. Weighted mean effect of exercise modulating CRF by type of cancer

Table 4. Intervention characteristics related to CRF reduction for all cancer survivors

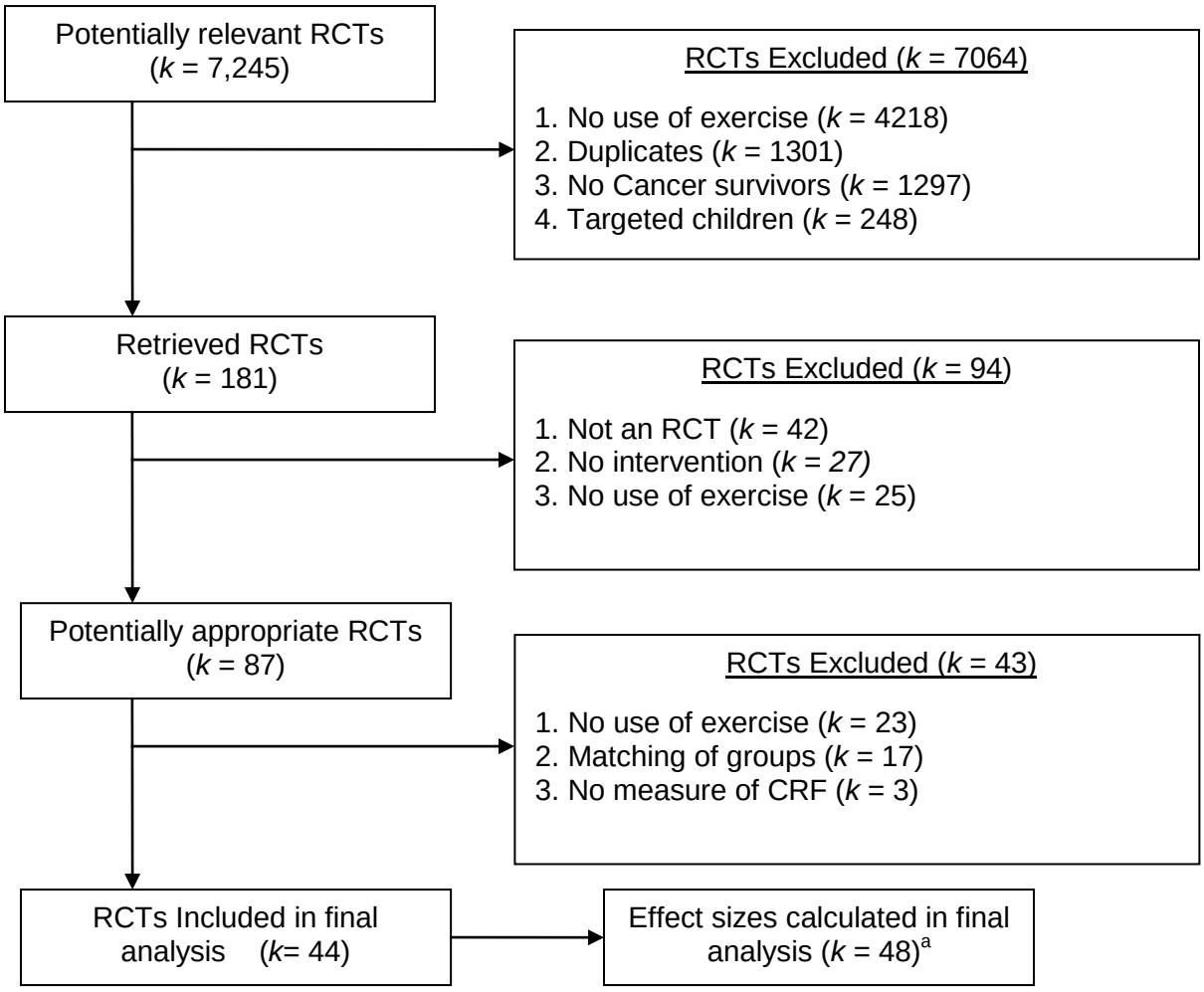
Figure 1. Flow diagram of trial identification and selection

Figure 2. Forest plot of effect sizes gauging impact of exercise on CRF

Acknowledgements

We kindly thank Robert D. Siegel, M.D., Gray Cancer Center, Hartford Hospital, Hartford, CT. for reviewing this manuscript and providing valuable feedback.

Figure 1. Flow diagram of trial identification and selection.



[a]Four studies provided two interventions, yielding two effect size calculations

Table 1. Descriptive characteristics of included studies. Means (±SD), except where noted

Descriptive Characteristic	All Cancer	Breast	Prostate	Lymphoma
Study Characteristics				
Number of studies, *k*	44	25	4	4
Year of study	2005±3.5	2004±3.4	2006±2.7	2006±3.4
Use of theory	27%	22%	0%	0%
Published in journal	88%	84%	100%	100%
Subject Characteristics				
Age	53.8±10.5	52.6±4.4	67.9±1.6	49.8±7.4
Type of treatment				
Chemotherapy	13%	12%	0%	25%
Radiation	6%	8%	0%	0%
Hormones	6%	4%	80%	0%
Combination	75%	76%	20%	75%
Stage of treatment				
Currently treated	46%	33%	80%	100%
Previously treated	54%	66%	20%	0%
Time since diagnosis, mo.	6.7±13.8	6.9±13.1	6.4±14.3	7.3±14.6
Intervention Characteristics				
Intervention length, wk	11.5±5.2	11.8±4.4	16.0±7.5	12.3±8.3
Frequency, d/wk	3.5±1.4	3.4±1.1	2.6±0.4	3.3±1.7
Length, min/session	48.5±22.8	46.6±21.9	60.0±18.4	60.0±21.2
Aerobic Intensity, METs	5.6±3.0	4.9±2.1	4.9±5.2	5.6±3.5
Strength Intensity, METs	4.5±2.0	4.5±1.7	2.4±3.2	2.0±1.2
Flexibility				
Included	52%	60%	40%	50%
Excluded	48%	40%	60%	50%
CRF scale used				
FACT	30%	36%	60%	25%
Piper fatigue	20%	32%	0%	0%
POMS	13%	8%	0%	25%
Brief fatigue index	11%	4%	0%	0%
Linear analog scale	4%	4%	0%	0%
EORTC QOL-C30	11%	0%	20%	25%
Other	11%	16%	20%	25%

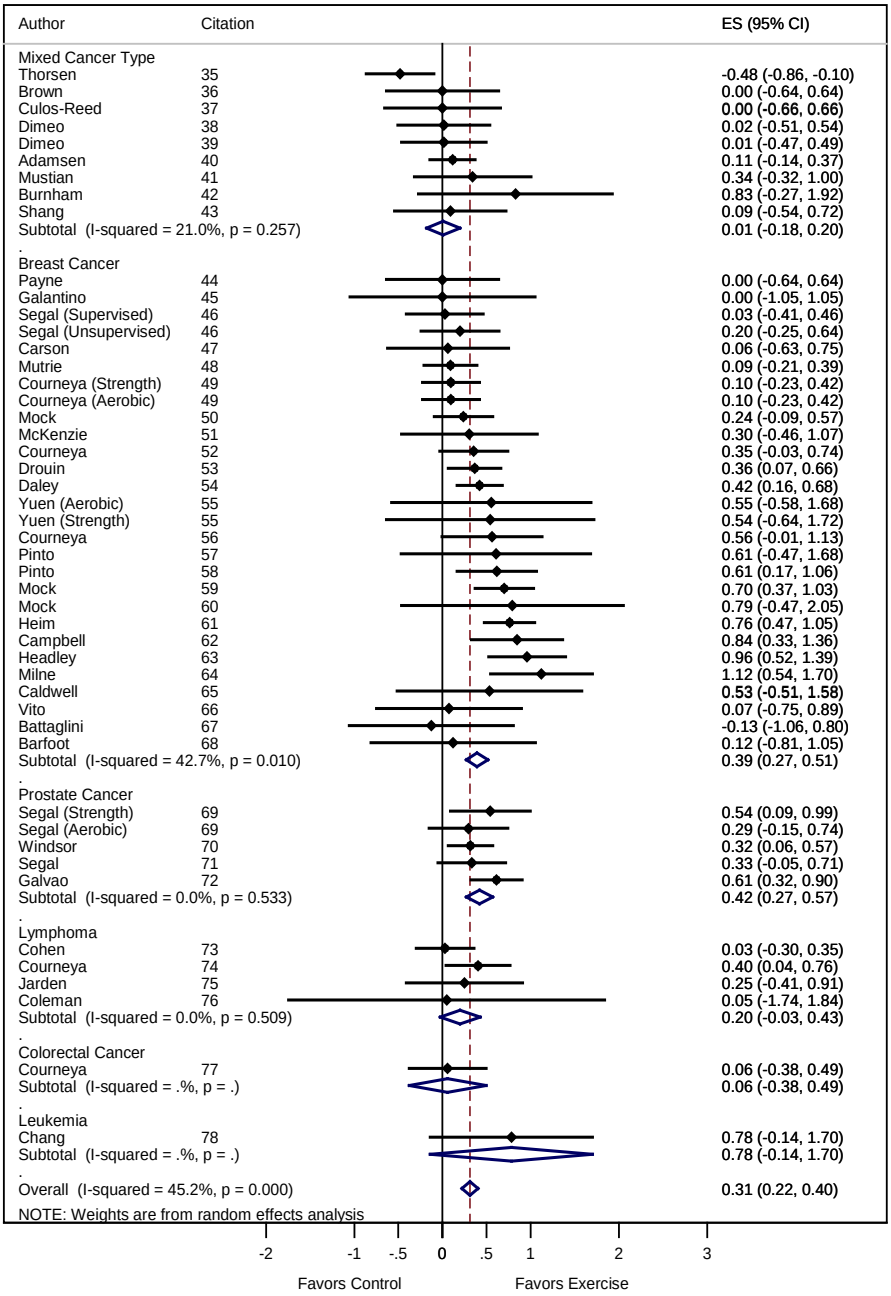
FACT, Functional assessment of cancer therapy. POMS, Profile of mood states. EORTC QOL-C30, European organization for research treatment center quality of life-care 30. METs, metabolic equivalent units. Percentages may not sum to 100% due to rounding error.

Table 2. Methodological quality of included studies by cancer type

Citation	Total	Study quality dimension										
		1	2	3	4	5	6	7	8	9	10	11
Thorsen (35)	7	+	+	-	+	-	-	-	+	+	+	+
Brown (36)	7	+	+	-	+	-	-	-	+	+	+	+
Culos-Reed (37)	7	+	+	-	+	-	-	-	+	+	+	+
Dimeo (38)	6	+	+	-	+	-	-	-	-	+	+	+
Dimeo (39)	7	+	+	-	+	-	-	-	+	+	+	+
Adamsen (40)	10	+	+	+	+	-	+	+	+	+	+	+
Mustain (41)	8	+	+	+	+	-	-	-	+	+	+	+
Burnham (42)	7	+	+	-	+	-	-	-	+	+	+	+
Shang (43)	7	+	+	-	+	-	-	-	+	+	+	+
Breast Cancer												
Payne (44)	5	+	+	-	+	-	-	-	+	+	-	-
Galantino (45)	4	+	+	-	-	-	-	-	+	-	-	+
Segal (46)	7	+	+	-	+	-	-	-	+	+	+	+
Carson (47)	7	+	+	-	+	-	-	-	+	+	+	+
Mutrie (48)	10	+	+	+	+	-	+	+	+	+	+	+
Courneya (49)	7	+	+	-	+	-	-	-	+	+	+	+
Mock (50)	7	+	+	-	+	-	-	-	+	+	+	+
McKenzie (51)	8	+	+	-	+	-	-	-	+	+	+	+
Courneya (52)	9	+	+	-	+	-	+	+	+	+	+	+
Drouin (53)	6	+	+	-	+	-	-	-	+	-	+	+
Daley (54)	7	+	+	-	+	-	-	-	+	+	+	+
Yuen (55)	6	+	+	-	+	-	-	-	+	-	+	+
Courneya (56)	8	+	+	-	+	-	-	+	+	-	+	+
Pinto (57)	6	+	+	-	+	-	-	-	+	-	+	+
Pinto (58)	5	+	+	-	-	-	-	-	+	-	+	+
Mock (61)	5	+	+	-	+	-	-	-	+	-	+	-
Heim (60)	6	+	+	-	+	-	-	-	+	-	+	+
Mock (61)	4	+	+	-	+	-	-	-	-	-	+	-
Campbell (62)	6	+	+	-	-	-	-	-	+	+	+	+
Headley (63)	3	+	+	-	-	-	-	-	+	-	-	-
Milne (64)	8	+	+	+	+	-	-	-	+	+	+	+
Caldwell (65)	7	+	+	-	+	-	-	-	+	+	+	+
Vito (66)	7	+	+	-	+	-	-	-	+	+	+	+
Battaglini (67)	8	+	+	-	+	-	-	+	+	+	+	+
Barfoot (68)	7	+	+	-	+	-	-	-	+	+	+	+
Prostate Cancer												
Segal (69)	6	+	+	-	+	-	-	-	-	+	+	+
Windsor (70)	6	+	+	-	+	-	-	-	+	-	+	+
Segal (71)	10	+	+	+	+	-	+	+	+	+	+	+
Galvao (72)	9	+	+	+	+	-	-	+	+	+	+	+
Lymphoma												
Cohen (73)	9	+	+	+	+	-	-	-	+	+	+	+
Courneya (74)	7	+	+	-	+	-	-	-	+	+	+	+
Jarden (75)	7	+	+	-	+	-	-	-	+	+	+	+
Coleman (76)	5	+	+	-	+	-	-	-	-	+	+	-
Colorectal												
Courneya (77)	7	+	+	-	+	-	-	+	+	+	+	+
Leukemia												
Chang (78)	6	+	+	-	+	-	-	-	+	-	+	+

1, eligibility criteria; 2, randomization; 3, concealed allocation; 4, baseline similarity of groups; 5, subject blinding; 6, therapist blinding; 7, assessor blinding; 8, outcome measure from >85% of subjects; 9, "intention to treat"; 10, between group statistical comparisons; 11, point & variability measure.

Figure 2. Forest plot of effect sizes gauging impact of exercise on CRF modulation by cancer type with random-effects means.



Brown JC, et al. 2011. *Cancer Epidemiology, Biomarkers & Prevention* Jan 2011;20:123-133.

Table 3. Weighted mean effect of exercise modulating CRF by type of cancer

		d_+ (95%CI)		Homogeneity of *d*'s		
Type of cancer	***k***	**Fixed-effects**	**Random-effects**	**Q**	**P**	**I^2 (95% CI)**
All cancers	44*	0.312 (0.249, 0.375)	0.310 (0.217, 0.403)	93.37	<.001	50% (30, 64)
Breast	25[†]	0.388 (0.303, 0.472)	0.391 (0.268, 0.514)	47.16	<.001	42% (10, 63)
Prostate	4[‡]	0.420 (0.270, 0.570)	0.420 (0.270, 0.570)	3.15	.533	0% (0, 96)
Lymphoma	4	0.199 (-0.025, 0.425)	0.199 (-0.025, 0.425)	2.32	.508	0% (0, 99)
Colorectal	1	0.057 (-0.469, 0.583)	…	…	…	…
Leukemia	1	0.779 (-0.141, 1.700)	…	…	…	…

Weighted mean effect size values (d_+) are positive when the exercise intervention was successful in reducing CRF compared to standard care. CRF, cancer-related fatigue. *k*, # of studies.

[a]44 studies provided a total of 48 effect sizes.

[b]25 studies provided a total of 28 effect sizes.

[c]4 studies provided a total of 5 effect sizes.

Table 4. Intervention characteristics related to CRF reduction for all cancer survivors, showing estimates at light and moderate levels of resistance exercise.

		Estimates of d_+ (95% *CI*)[b] Intensity of Resistance Exercise	
Study dimension	**Level[a]**	**Light (2.0 METs)**	**Moderate (6.0 METs)**
Use of theory	Absent	-0.034 (-0.207, 0.139)	0.361 (0.141, 0.582)
	Present	0.354 (0.177, 0.531)	0.749 (0.470, 1.029)
Age	39 years	0.160 (0.009, 0.311)	0.555 (0.319, 0.791)
	65 years	0.385 (0.205, 0.564)	0.780 (0.589, 0.971)
	70 years	0.428 (0.214, 0.643)	0.823 (0.612, 1.035)
Intervention quality	Highest quality (PEDro=10)	0.010 (-0.197, 0.217)	0.594 (0.310, 0.879)
	Mean quality (PEDro=6.8)	0.289 (0.165, 0.413)	0.684 (0.506, 0.862)
	Lowest quality (PEDro=3)	0.631 (0.363, 0.900)	0.794 (0.339, 1.249)

NOTE: Weighted mean effect size values (d_+) are positive when the exercise intervention was successful in reducing CRF compared to standard care. CRF, cancer-related fatigue. METs, metabolic equivalent of task.

[a]Levels represent values at the extreme observations of each moderator and for other values of interest within that range.

[b]d_+ and their 95% *CI* estimates statistically adjust for the presence of the moderators in the mixed-effects model, including the linear and quadratic trends for strength intensity, use of theory, age, and intervention quality, held constant at their means except for differences in strength intensity and the study dimension in question.

MET values were provided to demonstrate the emerging patterns among theory, age, and intervention quality with increasing resistance exercise intensity, representing light (2.0 MET) and moderate (6.0 MET) intensity.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009 Jul-Aug;59(4):225-49.

2. Crom DB, Hinds PS, Gattuso JS, Tyc V, Hudson MM. Creating the basis for a breast health program for female survivors of hodgkin disease using a participatory research approach. Oncol Nurs Forum. 2005 Nov 3;32(6):1131-41.

3. NCCN Clinical practice Guidelines in Oncology. Cancer-related fatigue. J Natl Compr Cancer Netw. 2009;1.

4. Schmitz KH, Courneya KS, Matthews C, et al. American college of sports medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010 Jul;42(7):1409-26.

5. Hofman M, Ryan JL, Figueroa-Moseley CD, Jean-Pierre P, Morrow GR. Cancer-related fatigue: The scale of the problem. Oncologist. 2007;12 Suppl 1:4-10.

6. Servaes P, Verhagen S, Bleijenberg G. Determinants of chronic fatigue in disease-free breast cancer patients: A cross-sectional study. Ann Oncol. 2002 Apr;13(4):589-98.

7. Dow KH, Ferrell BR, Leigh S, Ly J, Gulasekaram P. An evaluation of the quality of life among long-term survivors of breast cancer. Breast Cancer Res Treat. 1996;39(3):261-73.

8. Janda M, Gerstner N, Obermair A, et al. Quality of life changes during conformal radiation therapy for prostate carcinoma. Cancer. 2000 Sep 15;89(6):1322-8.

9. Ferrer, R.A., Huedo-Medina, T.B., Johnson, B.T., Ryan, S., Pescatello, L.S. Exercise interventions for cancer-surviviors: A meta-analysis of quality of life outcomes. Ann Behav Med. 2010 In Press.

10. Courneya KS, Friedenreich CM, Sela RA, Quinney HA, Rhodes RE, Handman M. The group psychotherapy and home-based physical exercise (group-hope) trial in cancer survivors: Physical fitness and quality of life outcomes. Psychooncology. 2003 Jun;12(4):357-74.

11. Kangas M, Bovbjerg DH, Montgomery GH. Cancer-related fatigue: A systematic and meta-analytic review of non-pharmacological therapies for cancer patients. Psychol Bull. 2008 Sep;134(5):700-41.

12. Velthuis MJ, Agasi-Idenburg SC, Aufdemkampe G, Wittink HM. The effect of physical exercise on cancer-related fatigue during cancer treatment: A meta-analysis of randomised controlled trials. Clin Oncol (R Coll Radiol). 2010 Jan 26.

13. Schmitz KH, Holtzman J, Courneya KS, Masse LC, Duval S, Kane R. Controlled physical activity trials in cancer survivors: A systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2005 Jul;14(7):1588-95.

14. Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: A systematic review and meta-analysis. J Cancer Surviv. 2010 Jan 6.

15. Cramp F, Daniel J. Exercise for the management of cancer-related fatigue in adults. Cochrane Database Syst Rev. 2008 Apr 16;(2)(2):CD006145.

16. Thompson, WR., Gordon, NF., Pescatello LS., editor. ACSM's guidelines for exercise testing and prescription. 8th ed. Lippincott, WIlliams & Wilkins; 2010.

17. Doyle C, Kushi LH, Byers T, et al. Nutrition and physical activity during and after cancer treatment: An american cancer society guide for informed choices. CA Cancer J Clin. 2006 Nov-Dec;56(6):323-53.

18. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the functional assessment of cancer therapy (FACT) measurement system. J Pain Symptom Manage. 1997 [cited 10 April 2010];13(2):63-74.

19. Piper BF, Dibble SL, Dodd MJ, Weiss MC, Slaughter RE, Paul SM. The revised piper fatigue scale: Psychometric evaluation in women with breast cancer. Oncol Nurs Forum. 1998 [cited 4 April 2010];25(4):677-84.

20. Baker F, Denniston M, Zabora J, Polland A, Dudley WN. A POMS short form for cancer patients: Psychometric and structural evaluation. Psychooncology. 2002 Jul-Aug;11(4):273-81.

21. Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: Use of the brief fatigue inventory. Cancer. 1999 [cited 10 April 2010];85(5):1186-96.

22. Locke DEC, Decker PA, Sloan JA, et al. Validation of single-item linear analog scale assessment of quality of life in neuro-oncology patients. J Pain Symptom Manage. 2007 [cited 10 April 2010];34(6):628-38.

23. Efficace F, Innominato PF, Bjarnason G, et al. Validation of patient's self-reported social functioning as an independent prognostic factor for survival in metastatic colorectal cancer patients: Results of an international study by the chronotherapy group of the european organisation for research and treatment of cancer. J Clin Oncol. 2008 Apr 20;26(12):2020-6.

24. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: An update of activity codes and MET intensities. Med Sci Sports Exerc. 2000 Sep;32(9 Suppl):S498-504.

25. Cohen J. Weighted kappa: Nominal scale agreement provision for scaled disagreement or partial credit. Psychol Bull. 1968 [cited 31 January 2010];70(4):213-20.

26. Bartko JJ. On various intraclass correlation reliability coefficients. Psychol Bull. 1976 [cited 27 February 2010];83(5):762-5.

27. Hedges LV, Olkin I. Statistical methods for meta-analysis. Orlando, FL: Academic Press Inc; 1985.

28. B.J. Becker. Handbook of applied multivariate statistics and mathematical modeling. In: H. E. A. Tinsley and S. D. Brown, editor. San Diego, CA.: Academic Press; 2000. p. 499-525.

29. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994 [cited 21 March 2010];50(4):1088-101.

30. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Br Med J. 1997 [cited 21 March 2010];315(7109):629-34.

31. Duval S, Tweedie R. A nonparametric ``trim and fill'' method of accounting for publication bias in meta-analysis. Journal of the American Statistical Association. 2000;95(449):89-98.

32. Mark W. Lipsey, David B. Wilson. Practical meta-analysis. Thousand Oaks, CA: SAGE; 2001.

33. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002 Jun 15;21(11):1539-58.

34. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods. 2006 Jun;11(2):193-206.

35. Thorsen L, Skovlund E, Stromme SB, Hornslien K, Dahl AA, Fossa SD. Effectiveness of physical activity on cardiorespiratory fitness and health-related quality of life in young and middle-aged cancer patients shortly after chemotherapy. J Clin Oncol. 2005 Apr 1;23(10):2378-88.

36. Brown P, Clark MM, Atherton P, et al. Will improvement in quality of life (QOL) impact fatigue in patients receiving radiation therapy for advanced cancer? Am J Clin Oncol. 2006 Feb;29(1):52-8.

37. Culos-Reed SN, Carlson LE, Daroux LM, Hately-Aldous S. A pilot study of yoga for breast cancer survivors: Physical and psychological benefits. Psychooncology. 2006;15(10):891-7.

38. Dimeo FC, Stieglitz RD, Novelli-Fischer U, Fetscher S, Keul J. Effects of physical activity on the fatigue and psychologic status of cancer patients during chemotherapy. Cancer. 1999;85(10):2273-7.

39. Dimeo FC, Thomas F, Raabe-Menssen C, Propper F, Mathias M. Effect of aerobic exercise and relaxation training on fatigue and physical performance of cancer patients after surgery. A randomised controlled trial. Support Care Cancer. 2004 Nov;12(11):774-9.

40. Adamsen L, Quist M, Andersen C. Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: Randomised controlled trial. . 2009;339:b3410.

41. Mustian KM, Peppone L, Darling TV, Palesh O, Heckler CE, Morrow GR. A 4-week home-based aerobic and resistance exercise program during radiation therapy: A pilot randomized clinical trial. J Support Oncol. 2009 Sep-Oct;7(5):158-67.

42. Burnham TR, Wilcox A. Effects of exercise on physiological and psychological variables in cancer survivors. Med Sci Sports Exerc. 2002;34(12):1863-7.

43. Shang J. Exercise adherence and contamination in a randomized control trial of a home-based walking program among patients receiving active cancer treatment. 2009.

44. Payne JK, Held J, Thorpe J, Shaw H. Effect of exercise on biomarkers, fatigue, sleep disturbances, and depressive symptoms in older women with breast cancer receiving hormonal therapy. Oncol Nurs Forum. 2008 Jul;35(4):635-42.

45. Galantino ML, Capito L, Kane RJ, Ottey N, Switzer S, Packel L. The effects of tai chi and walking on fatigue and body mass index in women living with breast cancer: A pilot study. Rehabilitation Oncology. 2003;21(1):17-22.

46. Segal R, Evans W, Johnson D, et al. Structured exercise improves physical functioning in women with stages I and II breast cancer: Results of a randomized controlled trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2001;19(3):657-65.

47. Carson JW, Carson KM, Porter LS, Keefe FJ, Seewaldt VL. Yoga of awareness program for menopausal symptoms in breast cancer survivors: Results from a randomized trial. Support Care Cancer. 2009 Oct;17(10):1301-9.

48. Mutrie N, Campbell AM, Whyte F, et al. Benefits of supervised group exercise programme for women being treated for early stage breast cancer: Pragmatic randomised controlled trial. BMJ. 2007 Mar 10;334(7592):517.

49. Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: A multicenter randomized controlled trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(28):4396-404.

50. Mock V, Frangakis C, Davidson NE, et al. Exercise manages fatigue during breast cancer treatment: A randomized controlled trial. Psychooncology. 2005;14(6):464-77.

51. McKenzie DC, Kalda AL. Effect of upper extremity exercise on secondary lymphedema in breast cancer patients: A pilot study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2003;21(3):463-6.

52. Courneya KS, Friedenreich CM, Sela RA, Quinney HA, Rhodes RE, Handman M. The group psychotherapy and home-based physical exercise (group-hope) trial in

cancer survivors: Physical fitness and quality of life outcomes. Psychooncology. 2003;12(4):357-74.

53. Drouin JS, Armstrong H, Krause S., Orr J, Birk TJ, Hryniuk WM. Effects of aerobic exercise training on peak aerobic capacity, fatigue, and psyhchological factors during radiation for breast cancer. Rehabilitation Oncology. 2005;1(23):11-7.

54. Daley AJ, Crank H, Saxton JM, Mutrie N, Coleman R, Roalfe A. Randomized trial of exercise therapy in women treated for breast cancer. J Clin Oncol. 2007 May 1;25(13):1713-21.

55. Yuen HK, Sword D. Home-based exercise to alleviate fatigue and improve functional capacity among breast cancer survivors. J Allied Health. 2007 Winter;36(4):e257-75.

56. Courneya KS, Mackey JR, Bell GJ, Jones LW, Field CJ, Fairey AS. Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: Cardiopulmonary and quality of life outcomes. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2003;21(9):1660-8.

57. Pinto BM, Clark MM, Maruyama NC, Feder SI. Psychological and fitness changes associated with exercise participation among women with breast cancer. Psychooncology. 2003;12(2):118-26.

58. Pinto BM, Frierson GM, Rabin C, Trunzo JJ, Marcus BH. Home-based physical activity intervention for breast cancer patients. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005;23(15):3577-87.

59. Mock V, Dow KH, Meares CJ, et al. Effects of exercise on fatigue, physical functioning, and emotional distress during radiation therapy for breast cancer. Oncol Nurs Forum. 1997 Jul;24(6):991-1000.

60. Heim ME, v d Malsburg ML, Niklas A. Randomized controlled trial of a structured training program in breast cancer patients with tumor-related chronic fatigue. Onkologie. 2007 Sep;30(8-9):429-34.

61. Mock V, Burke MB, Sheehan P, et al. A nursing rehabilitation program for women with breast cancer receiving adjuvant chemotherapy. Oncol Nurs Forum. 1994 Jun;21(5):899,907; discussion 908.

62. Campbell A, Mutrie N, White F, McGuire F, Kearney N. A pilot study of a supervised group exercise programme as a rehabilitation treatment for women with breast cancer receiving adjuvant treatment. Eur J Oncol Nurs. 2005 Mar;9(1):56-63.

63. Headley JA, Ownby KK, John LD. The effect of seated exercise on fatigue and quality of life in women with advanced breast cancer. Oncol Nurs Forum. 2004;31(5):977-83.

64. Milne HM, Wallman KE, Gordon S, Courneya KS. Impact of a combined resistance and aerobic exercise program on motivational variables in breast cancer survivors: A randomized controlled trial. Ann Behav Med. 2008 Oct;36(2):158-66.

65. Caldwell MG. The effects of an endurance exercise regime on cancer-related fatigue and physical performance in women with breast cancer. 2009.

66. Vito NL. The effects of a yoga intervention on physical and psychological functioning for breast cancer survivors. 2007.

67. Battaglini CLLG. A randomized study on the effects of a prescribed exercise intervention on lean mass and fatigue changes in breast cancer patients during treatment. 2004.

68. Barfoot DA. The effects of a resistance training protocol on changes in muscular strength and fatigue levels in breast cancer patients undergoing treatment. 2005.

69. Segal RJ, Reid RD, Courneya KS, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(3):344-51.

70. Windsor PM, Nicol KF, Potter J. A randomized, controlled trial of aerobic exercise for treatment-related fatigue in men receiving radical external beam radiotherapy for localized prostate carcinoma. Cancer. 2004;101(3):550-7.

71. Segal RJ, Reid RD, Courneya KS, et al. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. J Clin Oncol. 2003 May 1;21(9):1653-9.

72. Galvao DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: A randomized controlled trial. J Clin Oncol. 2010 Jan 10;28(2):340-7.

73. Cohen L, Warneke C, Fouladi RT, Rodriguez MA, Chaoul-Reich A. Psychological adjustment and sleep quality in a randomized trial of the effects of a tibetan yoga intervention in patients with lymphoma. Cancer. 2004;100(10):2253-60.

74. Courneya KS, Sellar CM, Stevinson C, et al. Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. . 2009 Sep 20;27(27):4605-12.

75. Jarden M, Baadsgaard MT, Hovgaard DJ, Boesen E, Adamsen L. A randomized trial on the effect of a multimodal intervention on physical capacity, functional performance and quality of life in adult patients undergoing allogeneic SCT. Bone Marrow Transplant. 2009 May;43(9):725-37.

76. Coleman EA, Coon S, Hall-Barrow J, Richards K, Gaylor D, Stewart B. Feasibility of exercise during treatment for multiple myeloma. Cancer Nurs. 2003;26(5):410-9.

77. Courneya KS, Friedenreich CM, Quinney HA, Fields AL, Jones LW, Fairey AS. A randomized trial of exercise and quality of life in colorectal cancer survivors. European journal of cancer care. 2003;12(4):347-57.

78. Chang PH, Lai YH, Shun SC, et al. Effects of a walking intervention on fatigue-related experiences of hospitalized acute myelogenous leukemia patients undergoing chemotherapy: A randomized controlled trial. J Pain Symptom Manage. 2008 May;35(5):524-34.

79. Prochaska JO, Velicer WF. The transtheoretical model of health behavior change. Am J Health Promot. 1997 Sep-Oct;12(1):38-48.

80. Jones LW, Courneya KS, Vallance JK, et al. Understanding the determinants of exercise intentions in multiple myeloma cancer survivors: An application of the theory of planned behavior. Cancer Nurs. 2006 May-Jun;29(3):167-75.

81. Marcus BH, Selby VC, Niaura RS, Rossi JS. Self-efficacy and the stages of exercise behavior change. Res Q Exerc Sport. 1992 Mar;63(1):60-6.

82. Roy, C., Andrews, H.A. The roy adaptation model. the definitive statement. Norwalk, CT.: Appleton & Lange; 1991.

83. Payne JK. A neuroendocrine-based regulatory fatigue model. Biol Res Nurs. 2004 [cited 5 April 2010];6(2):141-50.

84. Schaefer KM, Pond JB. Levine's conservation model as a guide to nursing practice. Nurs Sci Q. 1994 [cited 18 April 2010];7(2):53-4.

85. Ryan JL, Carroll JK, Ryan EP, Mustian KM, Fiscella K, Morrow GR. Mechanisms of cancer-related fatigue. Oncologist. 2007;12 Suppl 1:22-34.

86. Al-Majid S, Gray DP. A biobehavioral model for the study of exercise interventions in cancer-related fatigue. Biol Res Nurs. 2009 Apr;10(4):381-91.

87. Phillips SM, Tipton KD, Aarsland A, Wolf SE, Wolfe RR. Mixed muscle protein synthesis and breakdown after resistance exercise in humans. American Journal of Physiology - Endocrinology and Metabolism. 1997 [cited 25 July 2010];273(1 36-1):E99-E107.

88. Petersen AMW, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol. 2005 [cited 25 July 2010];98(4):1154-62.

89. Doherty TJ. Invited review: Aging and sarcopenia. J Appl Physiol. 2003 [cited 25 July 2010];95(4):1717-27.

90. Taylor NF, Dodd KJ, Damiano DL. Progressive resistance exercise in physical therapy: A summary of systematic reviews. Phys Ther. 2005 Nov;85(11):1208-23.

91. Galvao DA, Nosaka K, Taaffe DR, et al. Endocrine and immune responses to resistance training in prostate cancer patients. Prostate Cancer Prostatic Dis. 2008;11(2):160-5.

92. Courneya KS, Vallance JK, McNeely ML, Karvinen KH, Peddle CJ, Mackey JR. Exercise issues in older cancer survivors. Crit Rev Oncol Hematol. 2004 Sep;51(3):249-61.

93. Fishbein M. The role of theory in HIV prevention. AIDS Care - Psychological and Socio-Medical Aspects of AIDS/HIV. 2000 [cited 15 August 2010];12(3):273-8.

94. Prochaska JO, Velicer WF, Rossi JS, et al. Stages of change and decisional balance for 12 problem behaviors. Health Psychology. 1994 [cited 15 August 2010];13(1):39-46.

95. Jacobsen PB, Donovan KA, Vadaparampil ST, Small BJ. Systematic review and meta-analysis of psychological and activity-based interventions for cancer-related fatigue. Health Psychol. 2007 Nov;26(6):660-7.

96. Kuchinski AM, Reading M, Lash AA. Treatment-related fatigue and exercise in patients with cancer: A systematic review. Medsurg Nurs. 2009 May-Jun;18(3):174-80.

97. Lotfi-Jam K, Carey M, Jefford M, Schofield P, Charleson C, Aranda S. Nonpharmacologic strategies for managing common chemotherapy adverse effects: A systematic review. J Clin Oncol. 2008 Dec 1;26(34):5618-29.

98. Luctkar-Flude MF, Groll DL, Tranmer JE, Woodend K. Fatigue and physical activity in older adults with cancer: A systematic review of the literature. Cancer Nurs. 2007 Sep-Oct;30(5):E35-45.

99. Stevinson C, Lawlor DA, Fox KR. Exercise interventions for cancer patients: Systematic review of controlled trials. Cancer Causes Control. 2004 Dec;15(10):1035-56.

Supplementary (Online material only)

Search strategy. Systematic Search information

Figure 3. Funnel plot of effect size estimates

Table 5. Characteristics of included studies

Search strategy

Searches for studies concluded in February 2010 and utilized electronic databases including CINAHL (1981 to 2010), MEDLINE (1949 to 2010), Embase (1973 to 2010), and Scopus (1996 to 2010). OregonPDF in Health and Performance (1947 to 2010), Proquest Dissertations, and Theses (1980 and 2010) were also searched for unpublished literature including search words related to; 1) exercise, and 2) cancer and 3) fatigue. The following search strategy was utilized for this meta-analysis, using text and keyword and MESH terms in each database, with and RCT filter applied:

The databases PubMed, PsycINFO, CINAHL Plus, SPORTSdiscus, OregonPDF in Health and Performance, and ProQuest Theses and Dissertations were searched. We searched all databases using a Boolean search strategy [i.e., (cancer OR neoplas* OR tumor OR chemo* OR radiat* OR malign* OR carciniom*) AND (fatigue (fatig*) tired OR lethargic OR vitality OR weary OR exhaust* OR energy OR apathy OR lassitude OR weakness OR Drained OR sleepy OR sluggish) AND (exercise OR physical activity OR aerobic OR cardiovascular OR resistance OR strength OR muscular OR flexibility OR walking OR program OR interval OR sport OR fitness OR performance OR movement OR stretching OR tai chi OR yoga OR dance OR body OR composition)]. Journals focusing on cancer survivorship (*Breast Cancer Research and Treatment*, *Journal of Cancer Survivorship*, *Oncology Nursing Forum, Journal of Pain and Symptom Management* and the reference lists of included studies were also searched for

additional papers and previous meta-analyses(12-14, 95) and systematic reviews (11, 13-15, 95-99) were searched for additional literature that database searches may have missed.

Figure 3. Funnel plot of effect size estimates.

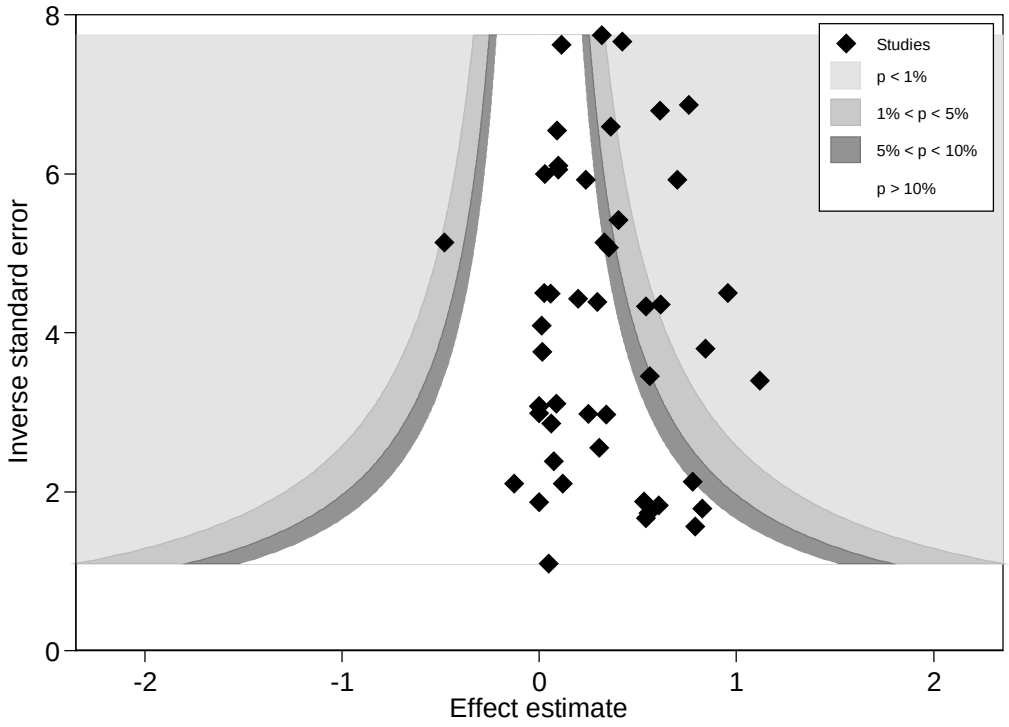


Table 5. Characteristics of included studies **(Online material only)**

Subject Characteristics				Exercise Characteristics					
Reference	**N**	**Type of Cancer**	**Type of Treatment**	**Frequency ($d \cdot wk^{-1}$)**	**Intensity**	**Time ($min \cdot d^{-1}$)**	**Type**	**Duration (wk)**	**CRF Measure**
Thorsen (35)	I=59 C=52	Lymphoma Breast Gynocologic	Chemotherapy	2	60-70% HR_{Max}	30	Walking Cyling Jogging	14	EORTC-QOL C30
Brown (36)	I=59 C=58	Mixed; Not-Specified	Radiation	1	N/A	90	Yoga Stretching	8	POMS
Culos-Reed (37)	I=20 C=18	Majority Breast; Others Not Specified	Not Specified	1	N/A	75	Yoga	7	POMS
Dimeo (38)	I=27 C=32	Breast Lymphoma Lung	Chemotherapy	7	30-50 RPM	30	Bed-Ergometer	12	POMS
Dimeo (39)	I=34 C=35	Lung Intestinal	Chemotherapy Radiation Surgery	5	80% HR_{Max}	30	Stationary Bike	3	EORTC-QOL C30
Adamsen (40)	I=135 C=134	21 Tumor Types	Chemotherapy	3	85-90% HR_{Max} 70-100% 1RM	90	Weights Stationary Biking	6	EORTC-QOL C30
Mustain (41)	I=19 C=19	Breast Prostate	Chemotherapy	3	60-70% HR Reserve	60	Walking Stretch Bands	4	BFI
Burnham (42)	I=6 C=12	Breast Colon	Chemotherapy Surgery	2	40-60% HR_{Max}	30	Treadmill Biking	10	LAS
Shang (43)	I=68 C=58	Breast Prostate Colon	Chemotherapy Radiaiton	4	50-70% HR_{Max}	30	Walking	13	PFS
				Breast					
Payne (44)	I=10 C=10	Breast	Hormone	4	Moderate Intensity	20	Walking	12	PFS
Galantino (45)	I=4 C=4	Breast	Chemotherapy Radiation	1	N/A	60	Tai Chi Walking	3	BFI
Segal (46)	I=42 I=40 C=41	Breast	Chemotherapy Radiation Surgery	3 5	50-60% V02 max (Supervised) 50-60% $V0_2$ max (Self-Directed)	30	Walking	26	SF-36

Carson (47)	I=16 C=20	Breast	Chemotherapy Surgery	1	N/A	120	Yoga	8	0-9 Scale
Mutrie (48)	I=101 C=102	Breast	Chemotherapy Radiation Surgery	3	50-75% HR_{max}	45	Walking Cycling Aerobics	12	FACT
Courneya (49)	I=78	Breast	Chemotherapy	3	70% $V0_2$ max	45	Cycle-Ergometer Treadmill Elliptical	17	FACT-A
	I=82 C=82				60-70% 1RM 2 Sets 8-12 Reps	45	Weight-Machines		
Mock (50)	I=60 C=59	Breast	Chemotherapy Radiation Surgery	5	Moderate Intensity	30	Walking	6	PFS
McKenzie (51)	I=7C=7	Breast	Chemotherapy Radiation Surgery	3	Ergometer: 25W Two Sets 10 reps	60	Arm-Ergometer Weight-Machines	8	SF-36
Courneya (52)	I=60 C=48	Breast	Chemotherapy Radiation	5	60-75 HR_{max}	30	Walking	10	FACT
Drouin (53)	I=13 C=8	Breast	Radiation	4	50-70% HR_{max}	45	Walking	8	PFS
Daley (54)	I=34 C=38	Breast	Chemotherapy Radiation Surgery	3	65-85% HR_{max}	50	Not-Specified	8	PFS
Yuen (55)	I=7	Breast	Chemotherapy Radiation Surgery	3	Moderate	30	Walking	12	PFS
	I=8				8-12 Reps (circuit)		Weight-Machines		
	C=7								
Courneya (56)	I=25 C=28	Breast	Chemotherapy Radiation	3	70-75% $V0_2$ max	45	Cycle-Ergometer	15	FACT-B
Pinto (57)	I=9 C=12	Breast	Chemotherapy Radiation Surgery	3	60-70% HR_{max}	50	Aerobic-Activities	12	POMS
Pinto (58)	I=43 C=43	Breast	Chemotherapy Radiation Surgery	5	55-65% HR_{max}	30	Walking Biking Swimming	12	POMS
Mock (61)	I=23 C=23	Breast	Chemotherapy Radiation Surgery	5	Self-Paced	30	Walking	6	PFS
Heim (60)	I=32 C=31	Breast	Chemotherapy Radiation Surgery Hormones	4	Not Specified	60	Walking Weight-Machines	12	FACT

Mock (61)	I=9 C=5	Breast	Chemotherapy Radiation Surgery	3	Not Specified	30	Walking	16	SAS
Campbell (62)	I=12 C=10	Breast	Chemotherapy Radiation	2	60-75% HR_{max}	45	Walking Cycling Aerobics	12	FACT-G
Headley (63)	I=16 C=16	Breast	Chemotherapy	3	Moderate Intensity	30	Not-Specified	16	FACT-F
Milne (64)	I=29 C=29	Breast	Chemotherapy Radiation Surgery	3	Moderate Intensity 2 sets 10-15 reps	60	Cycling Rowing Weights	12	FACT-B
Caldwell (65)	I=13 C=12	Breast	Chemotherapy Surgery	4	Light Intensity Light Resistance	30	Walking Resistance-Bands	12	SCFC (Schwartz Cancer)
Vito (66)	I=13 C=12	Breast	Chemotherapy Radiation	2	N/A	90	Yoga	8	FACT-B
Battaglini (67)	I=10 C=10	Breast	Radiation	2	Moderate Intensity 3 Sets 8-12 Reps	60	Treadmill Cycling Weights	15	PFS
Barfoot (68)	I=10 C=10	Breast	Chemotherapy Radiation	2	40-60% HR_{max} 2-3 Sets 6-12 Reps	60	Cycle-Ergometer Weights	14	PFS
Prostate									
Segal (69)	I=40 I=40 C=41	Prostate	Radiation	3	70-75% $V0_2$ max 60-70% 1RM 2 sets 8-12 reps	45	Cycling Weights	24	FACT-F
Windsor (70)	I=33 C=33	Prostate	Radiation Hormones	3	60-70% HR_{max}	30	Walking	8	BFI
Segal (71)	I=82 C=73	Prostate	Hormones	3	2 sets 8-12 reps	60	Weights	12	FACT-F
Galvao(72)	I=29 C=29	Prostate	Transplant	2	2-4 sets 6-12 reps	45	Weights	12	EORTC-QOL C30
Lymphoma									
Cohen (73)	I=20 C=19	Lymphoma	Chemotherapy Radiation	1	N/A	60	Yoga	7	BFI
Courneya (74)	I=60 C=62	Lymphoma	Chemotherapy Radiation	3	75% $V0_2$ max	45	Cycle-Ergometer	12	FACT-A
Jarden (75)	I=21	Lymphoma	Chemotherapy	5	50-75% HR_{max}	30	Cycle	5	EORTC-QOL

	C=21		Transplant						C30
Coleman (76)	I=14 C=10	Multiple Myeloma	Chemotherapy	3	N/A	20	Walking Cycling Stretch Bands	24	POMS
Colorectal									
Courneya (77)	I=69 C=33	Colorectal	Chemotherapy Surgery	4	65-75% HR_{max}	30	Walking	16	FACT-C
Leukemia									
Chang (78)	I=11 C=11	Leukemia	Chemotherapy	5	Moderate	12	Walking	3	BFI

Wk: week; min: minutes; HRmax : Maximum Heart Rate; HRR: Heart Rate Reserve; V02 max: maximum oxygen consumption; reps: repetition. FACT: Functional Assessment of Cancer Therapy; BFI: Brief Fatigue Index; POMS: Profile of Mood States; EORTC-QOL C-30: Quality of Life Compact 30; PFS: Piper Fatigue Scale; LAS/SAS: Linear/Symptom Analog Scale. I = n for intervention group; C = n for control group

Chapter 4 — Depression

The Efficacy of Exercise in Reducing Depression among Cancer Survivors: A Meta-Analysis

Justin C. Brown, MA[1]; Tania B. Huedo-Medina, PhD[1]; Blair T. Johnson, PhD[1]; Stacey M. Ryan, DPT[2]; Shannon M. Pescatello, BA[3]; Emily Moker, BS[1]; Jessica M. LaCroix, MS[1]; Rebecca A. Ferrer, PhD[4]; and Linda S. Pescatello, PhD[1]

[1]University of Connecticut, Storrs, CT
[2]M.D. Anderson Cancer Center, Houston, TX
[3]Western New England College, Springfield, MA
[4]National Cancer Institute, Rockville, MD

Correspondance and Reprints:
Justin C. Brown
Department of Kinesiology
University of Connecticut
Storrs, CT 06269-1110, USA.
Email: justin.brown@uconn.edu
Phone: (860)-486-2812
Fax: (860)-486-3149

Running title: Exercise and Depression: Meta-Analysis

Word count: 5,955

Total text pages: 21

Total references: 86

Total tables: 5

Total figures: 1

Financial Disclosures: None

Funding Source: University of Connecticut Research Advisory Council Foundation Grant # 433527 (PIs: Blair T. Johnson and Linda S. Pescatello)

Condensed Abstract: Exercise training provides an overall small reduction in depression among cancer survivors. Cancer survivors age 47–62 yr, those who had supervision, and those who engaged in higher amounts of aerobic exercise elicited the greatest reductions in depression.

Keywords: Physical activity, Behavior, Psychosocial, Quantitative Review.

Abstract

Introduction: The purpose of this meta-analysis was to examine the efficacy of exercise in reducing depression among cancer survivors. In addition, we examined the extent to which exercise dose and clinical characteristics of cancer survivors influenced the relationship between exercise and reductions in depression.

Methods: We conducted a systematic search identifying randomized controlled trials of exercise interventions among adult cancer survivors examining depression as an outcome. We calculated effect sizes for each study and performed weighted multiple regression moderator analysis.

Results: We identified 40 exercise interventions including 2,929 cancer survivors. Diverse groups of cancer survivors were examined in seven exercise interventions; breast cancer survivors were examined in 26; prostate cancer, leukemia, and lymphoma were examined in two; and colorectal cancer in one. Cancer survivors who completed an exercise intervention reduced depression more than controls, d_+=-0.13 (95% CI: -0.26, -0.01). Aerobic exercise reduced depression in dose response fashion (β=-0.24, p=0.03), a relationship evident in higher quality trials. Depression was reduced most when exercise sessions were supervised (β=0.26, p=0.01); and cancer survivors were between the ages of 47–62 yr (β=0.27, p=0.01).

Conclusion: Exercise training provides a small overall reduction in depression among cancer survivors but one that increased in dose-response fashion with aerobic exercise. Depression was reduced to the greatest degree among breast cancer survivors, among cancer survivors aged between 47–62 yr, or when exercise sessions were supervised.

Introduction

There are over 12 million cancer survivors in the US (1). Nearly 100% of all cancer survivors experience psychological and physical symptoms and side effects related to cancer or cancer treatment (2). Cancer survivors may experience fear of death, disease relapse, and body image changes (3) that may contribute to the depression experienced by up to 60% of cancer survivors (4) compared to 7% of the general US population (5). Depression associates with chemotherapy noncompliance (6, 7) and reduced 5 yr survival rates (8, 9). Therefore, management of depression among cancer survivors is of clinical importance. Exercise is an effective non-pharmacological therapy to reduce depression among healthy populations (10) with a moderate standardized mean reduction when compared to those who do not exercise. Exercise provides similar or larger reductions in depression among an array of clinical populations including those living with chronic obstructive pulmonary disease (11), human immunodeficiency virus (12), and coronary artery disease (13).

Accumulating evidence suggests exercise training after diagnosis of cancer may reduce the symptoms associated with cancer survivorship, improve quality of life and reduce cancer-related fatigue (14, 15). However, the efficacy of exercise to reduce depression is inconclusive (2). Some studies have demonstrated moderate to large reductions in depression as the result of exercise programs (16, 17), whereas others observe no such reductions (18, 19). Although a previous meta-analysis (20) quantified the heterogeneity of exercise interventions to reduce depression among cancer survivors and reported a moderate to large amount of heterogeneity (I^2=55%–76%), it did not examine moderator variables that could explain the heterogeneity in results.

Therefore, this meta-analysis examined the efficacy of exercise to reduce depression among cancer survivors and attempted to identify exercise prescription and clinical factors associated with the greatest reductions in depression. Identification of

characteristics moderating the magnitude of reduction in depression may aid clinicians in prescribing tailored exercise interventions to better manage depression among cancer survivors.

Methods

Inclusion Criteria

Studies were included if they: (1) utilized a randomized controlled design comparing an exercise intervention with a control group (i.e., no exercise program prescribed and instructions to maintain current activity levels or no exercise related information); (2) reported depression outcomes; and (3) targeted adults diagnosed with any type of cancer, regardless of stage of diagnosis or type or stage of treatment. Exercise interventions occurring in any setting, with or without supervision, were eligible.

Systematic Search [See supplementary material for systematic search strategy]

Coding and Reliability

Four independent, trained raters extracted information related to the study with high inter-rater reliability, mean Cohen's κ=0.90, for categorical variables, and mean intra-class correlation r=0.94 for continuous variables. Absolute intensity of exercise was coded using metabolic equivalent units (METs), where 1 MET represents sitting quietly (3.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$) and <3 METs, 3 to <6 METs, and ≥6 METs represent low, moderate, and vigorous intensity exercise, respectively (21). We calculated the weekly volume of aerobic exercise as the product of minutes of daily exercise and frequency of exercise sessions per week ($min \cdot wk^{-1}$). The Physiotherapy Evidence Database scale (PEDro) assessed methodological quality of the trials in terms of internal validity and statistical reporting (22).

Study Outcome and Effect Size Calculation

Assessment of depression levels among cancer survivors was a continuous outcome variable assessed as a component of a comprehensive psychological questionnaire with a depression subscale (23) or a questionnaire solely assessing depression levels (24-27) (Table 1). In order to standardize these differences across studies, the standardized mean difference effect size (*d*) was calculated to determine the difference in depression at follow-up between the exercise and control groups, correcting for small sample size bias and baseline depression levels (28, 29). For two group comparisons, *d* denotes the difference between the mean depression values of the control and exercise groups, divided by the pooled standard deviation (30). When more than one exercise group was provided (e.g., aerobic exercise and resistance exercise) we calculated multiple effect sizes. Subsequent sensitivity analysis examined the dependence between these effect sizes to confirm the weighted mean effect size of all exercise trials (d_+) was not influenced by an individual effect size (31). A negative *d* value indicated the exercise was efficacious in reducing depression compared to the control group.

Stata 11.1 (StataCorp, College Station, TX) with macros developed for meta-analysis (32) performed all statistical analyses. Prior to analysis, Begg's test (33) (z=-1.67, p=0.10), Egger's test (34) (t=-0.12, p=0.90), and the trim-and-fill method (35) identified no asymmetries in the effect size distribution suggestive of publication bias. Potential heterogeneity or between-study variance was calculated as Q and I^2 (and 95% CI) (36, 37). I^2 ranges from 0% to 100% with low values suggesting homogeneity and large values signifying heterogeneity. To explain variance in the effect size estimates—the relation between study level characteristics and the magnitude of effect size—a modified, weighted least squares regression was used with weights equal to the inverse variance of each exercise intervention effect size (viz., meta-regression). All statistical models pursued fixed effects assumptions. Statistically significant bivariate regression

analyses were integrated into a multi-moderator fixed effects regression to determine which variables could be eliminated and which explain unique between study variance. To reduce multicollinearity in multiple meta-regression models, all continuous variables were zero centered, and categorical variables were contrast coded (-1/+1). Two-sided statistical significance was $p<0.05$.

Results

Methodological Characteristics

Qualifying were 37 relevant randomized controlled exercise interventions (16-19, 38-70) (N=2,929) with a total of 40 comparisons (*k*=40) of exercise versus control conditions (Figure 1; Supplementary material describes each trial). Thirty-four studies provided one effect size, and three provided two effect sizes (19, 40, 48). The mean publication year of the exercise interventions was 2006±4.2. A majority of studies (70%) were conducted in North America. The mean PEDro score of the exercise interventions was 7.0±1.0 indicating high quality (22). Implementation of a theory of behavior change occurred in 20% of the exercise interventions (Table 1). Questionnaires assessing depression included the Center for Epidemiologic Studies-Depression (25) (40%), Profile of Mood States (23) (23%), Beck Depression Inventory (24) (18%), Hospital Anxiety and Depression Scale (26) (12%), and Symptom Assessment Scale (27) (7%).

[Insert Table 1 & Figure 1 here]

Cancer Survivor Characteristics

Cancer survivors participating in the exercise trials averaged 51.3±6.5 yr (range: 39–70). The majority of cancer survivors participating in the exercise interventions were white, non-Hispanic (n=2,255; 77%) women (n=2,548; 87%). Time since cancer diagnosis was 25.3±19.6 months (range: 2.8–73.0). Exercise interventions were more common during curative therapy with 29 of the 40 exercise interventions (73%) occurring during treatment (i.e., chemotherapy or radiation treatment). Diverse groups of cancer

survivors were examined in six exercise interventions (38-43), while breast cancer survivors were examined in 24 (16, 19, 44-65); prostate cancer (18, 66), leukemia (68, 69), and lymphoma (17, 70) in two; and colorectal cancer survivors in one (67).

Exercise Intervention Characteristics

The mean length of the 40 exercise interventions was 13.2±11.7 wk with a session frequency of 3.0±2.5 $d \cdot wk^{-1}$ for 49.1±27.1 $min \cdot session^{-1}$. Average weekly volume of all exercise was 129.4±64.9 $min \cdot wk^{-1}$. Exercise modalities included walking (*k*=16; 40%), stationary cycling (*k*=5; 13%), weight machines (*k*=2; 5%), resistance bands (*k*=3; 8%), and yoga (*k*=8; 20%). In addition, flexibility exercises were prescribed in 50% of the exercise interventions. The absolute intensity of exercise was 3.9±1.3 METs indicating they were of low (i.e., <3 METs) to moderate (i.e., $\geq$3 to <6 METs) intensity. A majority of exercise interventions (60%) were supervised.

The Influence of Exercise on Depression

Exercise provided a small overall reduction in depression compared to standard care among all types of cancer [*d*=-0.13 (95% CI: -0.26, -0.01)]. Subgroup analysis by cancer type revealed significant reductions in depression among breast cancer survivors [*d*=-0.17 (95% CI: -0.32, -0.02)], but no significant difference in depression among prostate, leukemia, lymphoma, and colorectal cancer survivors (Table 2). Collectively, the 40 effect sizes of the exercise interventions lacked homogeneity [I^2=55% (95% CI: 35–68), p<0.001], as did the analysis restricted to breast cancer survivors [I^2=59% (95% CI: 37–73), p<0.001; Table 2].

[Insert Table 2 here]

Moderators of the Influence of Exercise on Depression

Three moderators explained unique variance relating to the efficacy of exercise to reduce depression when entered in a multiple regression model. Weekly volume of aerobic exercise reduced depression in dose response fashion (β=-0.24, p=0.03), a

pattern that was more evident in higher quality trials. Depression was reduced most when exercise sessions were supervised (β=0.26, p=0.01); and cancer survivors were between 47–62 yr [(β=0.27, p=0.01); Table 3]. The following bivariate moderators ceased being statistically significant in the face of the former variables: (1) theory; (2) proportion of cancer survivors being non-Hispanic, white race; and (3) months since cancer diagnosis (Table 5, supplementary).

[Insert Table 3 here]

Discussion

This review found that exercise provided a small overall reduction in depression among cancer survivors, *d*=-0.13 (95% CI: -0.26, -0.01), but the amount of change varied widely across studies. We also attempted to elucidate the exercise dose and clinical characteristics modulating the overall reduction of depression among cancer survivors. The new and intriguing findings from these moderator analyses were depression reductions were influenced by age, supervision of exercise, and weekly volume of aerobic exercise. The largest reductions appeared among cancer survivors between 47–62 yr, when exercise was supervised, or as weekly volume of aerobic exercise increased. These trends retained significance in a model that included all factors simultaneously, suggesting each term has a unique impact in influencing depression levels.

Our analysis revealed exercise reduced depression among breast cancer survivors, *d*=-0.17 (95% CI: -0.32, -0.02), a pattern that confirms previous reports in the literature (71). We observed non-significant reductions in depression among prostate, colorectal, leukemia, and lymphoma survivors, but the lack of statistical significance among these types may be due in part to the small numbers of included studies and subsequent lowered statistical power to detect differences.

Depression reduction occurred in dose response fashion with aerobic exercise such that as weekly minutes of aerobic exercise increased so did reductions in depression, a finding observed in higher quality trials (Table 3). These trends are consistent with experimental evidence suggesting exercise reduces depression in dose response fashion among otherwise healthy populations (72). Consistent with our findings, the American College of Sports Medicine consensus statement in exercise and cancer survivorship suggests all cancer survivors strive to achieve a large volume of aerobic exercise of ≥150 $min \cdot wk^{-1}$ to maximize the health benefits (2). However, the clinical translation of advocating larger doses of weekly aerobic exercise may be an unrealistic initial exercise prescription for some cancer survivors for many reasons (e.g., previous sedentary behavior, constraints of the disease process itself, other comorbities) as well as more traditional barriers to exercise such as lack of time (73, 74). Accumulating large volumes of aerobic exercise should be progressive, increasing duration and frequency of exercise over weeks or months of exercise training as the course of the disease process allows and fitness increases (73, 75).

We found supervised exercise reduced depression more so than unsupervised exercise; consistent with improvements in quality of life (14) and fatigue reduction (76) among cancer survivors, and reducing depression among apparently healthy populations (77). Supervised exercise training is preferred over unsupervised exercise by breast and colon cancer survivors (78, 79), and provides opportunity to receive positive feedback and support, increasing compliance and associated mental and physical health benefits (80).

We found cancer survivors between the ages of 47–62 yr reduced depression more than <47 and >62 yr, respectively. The quadratic shape was unexpected as previous reports suggest a negative correlation between depression and age among cancer survivors (81, 82). Therefore, we hypothesized it would be younger cancer

survivors experiencing the greatest reductions in depression occurring in linear fashion. It is unclear why cancer survivors <47 yr did not experience exercise-induced reductions in depression. It is plausible the average weekly aerobic exercise volume performed (~130 min·wk^{-1}) was not a large enough dose of exercise to reduce depression among cancer survivors <47 yr. Functional capacity (i.e., $V0_{2peak}$) and age are negatively correlated (83). Thus, reducing depression among cancer survivors <47 yr may require a larger volume of aerobic exercise to elicit reductions in depression. Conversely, the lack of detecting a significant reduction in depression among cancer survivors >62 yr may be due in part to a floor effect (10). That is, older cancer experience less depression at baseline, and show smaller exercise-induced improvements in depression compared to those who are younger (84).

The findings from this meta-analysis provide additional insight to the physiology of depression. The therapeutic efficacy of monoamine oxidase inhibitors and tricyclic anti-depressant medications support the hypothesis of monoamine dysregulation as a mechanistic underpinning of depression (85). Anti-depressants act to increase circulating monoamines (86) and similar increases occur in response to acute and chronic aerobic exercise (87). Acute aerobic exercise increases noradrenaline, adrenaline, and serotonin above pre exercise levels (87, 88). Chronic aerobic exercise training increases noradrenaline, adrenaline, and serotonin levels above the levels elicited by an acute bout of aerobic exercise (87, 89). The higher concentrations of monoamines elicited in response to chronic aerobic exercise training support the use of chronic aerobic exercise training to reduce and manage depression (77). This supports our findings that accumulating larger weekly volumes of repeated bouts of aerobic exercise reduce depression in dose response fashion among cancer survivors. However, the monoamine hypothesis is one hypothesis of the etiology of depression. Continued research should investigate the complex physiology of depression and

exercise. In particular, identification of biomarker responses occurring with varying doses of aerobic exercise and their subsequent influence on depression.

Limitations

Despite our intention to include all types of cancer of any race, 26 of the 40 effect sizes (65%) targeted white, non-Hispanic, breast cancer survivors exclusively which has been a limitation of previous meta-analyses examining a variety of health-related outcomes among cancer survivors (14, 15, 20). The skewed number of exercise interventions among breast cancer survivors limits the generalizability of our findings to other types of cancer. This limitation should provide an impetus for researchers to continue investigating the effects of exercise among other cancer types.

Despite an overall rating of high methodological quality (7.0±1.0 of 11), we did note some consistent methodological weaknesses throughout the literature, such as inclusion of small sample sizes, inconsistent criterion with respect to study entry eligibility and baseline depression levels, and not following intent-to-treat analytic strategies.

Conclusion

In closing, we confirmed that exercise provides a small reduction in depression among cancer survivors, particularly among breast cancer survivors. Depression reduction occurred in dose response fashion with aerobic exercise. Larger reductions in depression also occurred with supervised exercise, and among cancer survivors 47–62 yr. Cancer survivors should strive to avoid inactivity; discuss the safety and feasibility of exercising with their medical care provider to optimize physical and psychological symptom management and improvement; and eventually aim to achieve larger weekly volumes of aerobic exercise of aerobic exercise if possible (2).

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011 Feb 4.

2. Schmitz KH, Courneya KS, Matthews C, et al. American college of sports medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010 Jul;42(7):1409-26.

3. Reich M, Lesur A, Perdrizet-Chevallier C. Depression, quality of life and breast cancer: A review of the literature. Breast Cancer Res Treat. 2008 [cited 18 December 2010];110(1):9-17.

4. Newport DJ, Nemeroff CB. Assessment and treatment of depression in the cancer patient. J Psychosom Res. 1998 Sep;45(3):215-37.

5. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatry. 2005 Jun;62(6):617-27.

6. Lebovits AH, Strain JJ, Schleifer SJ, Tanaka JS, Bhardwaj S, Messe MR. Patient noncompliance with self-administered chemotherapy. Cancer. 1990 Jan 1;65(1):17-22.

7. Gilbar O, De-Nour AK. Adjustment to illness and dropout of chemotherapy. J Psychosom Res. 1989;33(1):1-5.

8. Watson M, Haviland JS, Greer S, Davidson J, Bliss JM. Influence of psychological response on survival in breast cancer: A population-based cohort study. Lancet. 1999 [cited 18 December 2010];354(9187):1331-6.

9. Pasquini M, Biondi M. Depression in cancer patients: A critical review. Clinical Practice and Epidemiology in Mental Health. 2007 [cited 18 December 2010];3.

10. Conn VS. Depressive symptom outcomes of physical activity interventions: Meta-analysis findings. Ann Behav Med. 2010 May;39(2):128-38.

11. Coventry PA, Hind D. Comprehensive pulmonary rehabilitation for anxiety and depression in adults with chronic obstructive pulmonary disease: Systematic review and meta-analysis. J Psychosom Res. 2007 [cited 18 December 2010];63(5):551-65.

12. O'Brien K, Nixon S, Tynan AM, Glazier R. Aerobic exercise interventions for adults living with HIV/AIDS. Cochrane Database Syst Rev. 2010 Aug 4;(8)(8):CD001796.

13. Clark AM, Haykowsky M, Kryworuchko J, et al. A meta-analysis of randomized control trials of home-based secondary prevention programs for coronary artery disease. Eur J Cardiovasc Prev Rehabil. 2010 Jun;17(3):261-70.

14. Ferrer RA, Huedo-Medina TB, Johnson BT, Ryan S, Pescatello LS. Exercise interventions for cancer survivors: A meta-analysis of quality of life outcomes. Ann Behav Med. 2011 Feb;41(1):32-47.

15. Brown JC, Huedo-Medina TB, Pescatello LS, Pescatello SM, Ferrer RA, Johnson BT. Efficacy of exercise interventions in modulating cancer-related fatigue among adult cancer survivors: A meta-analysis. Cancer Epidemiol Biomarkers Prev. 2011 Jan;20(1):123-33.

16. Daley AJ, Crank H, Saxton JM, Mutrie N, Coleman R, Roalfe A. Randomized trial of exercise therapy in women treated for breast cancer. J Clin Oncol. 2007 May 1;25(13):1713-21.

17. Courneya KS, Sellar CM, Stevinson C, et al. Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. . 2009 Sep 20;27(27):4605-12.

18. Culos-Reed SN, Robinson JW, Lau H, et al. Physical activity for men receiving androgen deprivation therapy for prostate cancer: Benefits from a 16-week intervention. Support Care Cancer. 2010 May;18(5):591-9.

19. Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: A multicenter randomized controlled trial. J Clin Oncol. 2007 Oct 1;25(28):4396-404.

20. Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: A systematic review and meta-analysis. J Cancer Surviv. 2010 Jan 6;4(2):87-100.

21. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: An update of activity codes and MET intensities. Med Sci Sports Exerc. 2000 Sep;32(9 Suppl):S498-504.

22. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther. 2003 Aug;83(8):713-21.

23. Reddon JR, Marceau R, Holden RR. A confirmatory evaluation of the profile of mood states: Convergent and discriminant item validity. Journal of Psychopathology and Behavioral Assessment. 1985 [cited 26 January 2011];7(3):243-59.

24. Salkind MR. Beck depression inventory in general practice. J R Coll Gen Pract. 1969 [cited 26 January 2011];18(88):267-71.

25. Kohout FJ, Berkman LF, Evans DA, Cornoni-Huntley J. Two shorter forms of the CES-D (center for epidemiological studies depression) depression symptoms index. J Aging Health. 1993 May;5(2):179-93.

26. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983 [cited 26 January 2011];67(6):361-70.

27. Sutherland HJ, Walker P, Till JE. The development of a method for determining oncology patients' emotional distress using linear analogue scales. Cancer Nurs. 1988 [cited 26 January 2011];11(5):303-8.

28. Hedges LV, Olkin I. Statistical methods for meta-analysis. Orlando, FL: Academic Press Inc; 1985.

29. Becker BJ. Synthesizing standardized mean-change measures. Br J Math Stat Psychol. 1988 11;41(2):257-78.

30. Morris SB, DeShon RP. Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. Psychol Methods. 2002 03;7(1):105-25.

31. B.J. Becker. Handbook of applied multivariate statistics and mathematical modeling. In: H. E. A. Tinsley and S. D. Brown, editor. San Diego, CA.: Academic Press; 2000. p. 499-525.

32. Mark W. Lipsey, David B. Wilson. Practical meta-analysis. Thousand Oaks, CA: SAGE; 2001.

33. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994 [cited 21 March 2010];50(4):1088-101.

34. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Br Med J. 1997 [cited 21 March 2010];315(7109):629-34.

35. Duval S, Tweedie R. A nonparametric ``trim and fill'' method of accounting for publication bias in meta-analysis. Journal of the American Statistical Association. 2000;95(449):89-98.

36. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002 Jun 15;21(11):1539-58.

37. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods. 2006 Jun;11(2):193-206.

38. Burnham TR, Wilcox A. Effects of exercise on physiological and psychological variables in cancer survivors. Med Sci Sports Exerc. 2002;34(12):1863-7.

39. Dimeo FC, Stieglitz RD, Novelli-Fischer U, Fetscher S, Keul J. Effects of physical activity on the fatigue and psychologic status of cancer patients during chemotherapy. Cancer. 1999;85(10):2273-7.

40. Dodd MJ, Cho MH, Miaskowski C, et al. A randomized controlled trial of home-based exercise for cancer-related fatigue in women during and after chemotherapy with or without radiation therapy. Cancer Nurs. 2010 Jul-Aug;33(4):245-57.

41. Berglund G, Bolund C, Gustafsson UL, Sjoden PO. One-year follow-up of the 'starting again' group rehabilitation programme for cancer patients. Eur J Cancer. 1994;30A(12):1744-51.

42. Courneya KS, Friedenreich CM, Sela RA, Quinney HA, Rhodes RE, Handman M. The group psychotherapy and home-based physical exercise (group-hope) trial in cancer survivors: Physical fitness and quality of life outcomes. Psychooncology. 2003;12(4):357-74.

43. Thorsen L, Skovlund E, Stromme SB, Hornslien K, Dahl AA, Fossa SD. Effectiveness of physical activity on cardiorespiratory fitness and health-related quality of life in young and middle-aged cancer patients shortly after chemotherapy. J Clin Oncol. 2005 Apr 1;23(10):2378-88.

44. Culos-Reed SN, Carlson LE, Daroux LM, Hately-Aldous S. A pilot study of yoga for breast cancer survivors: Physical and psychological benefits. Psychooncology. 2006;15(10):891-7.

45. Rausch SM. Evaluating the psychosocial effects of two interventions, tai chi and spiritual growth groups, in women with breast cancer. 2007.

46. Ohira T, Schmitz KH, Ahmed RL, Yee D. Effects of weight training on quality of life in recent breast cancer survivors: The weight training for breast cancer survivors (WTBS) study. Cancer. 2006 May 1;106(9):2076-83.

47. Perna FM, Craft L, Freund KM, et al. The effect of a cognitive behavioral exercise intervention on clinical depression in a multiethnic sample of women with breast cancer: A randomized controlled trial. International Journal of Sport and Exercise Psychology. 2010 [cited 21 November 2010];8(1):36-47.

48. Lee SA, Kang JY, Kim YD, et al. Effects of a scapula-oriented shoulder exercise programme on upper limb dysfunction in breast cancer survivors: A randomized controlled pilot trial. Clin Rehabil. 2010 Jul;24(7):600-13.

49. Demark-Wahnefried W, Case LD, Blackwell K, et al. Results of a diet/exercise feasibility trial to prevent adverse body composition change in breast cancer patients on adjuvant chemotherapy. Clin Breast Cancer. 2008 Feb;8(1):70-9.

50. Targ EF, Levine EG. The efficacy of a mind-body-spirit group for women with breast cancer: A randomized controlled trial. Gen Hosp Psychiatry. 2002 Jul-Aug;24(4):238-48.

51. Mutrie N, Campbell AM, Whyte F, et al. Benefits of supervised group exercise programme for women being treated for early stage breast cancer: Pragmatic randomised controlled trial. BMJ. 2007 Mar 10;334(7592):517.

52. Latka RN, Alvarez-Reeves M, Cadmus L, Irwin ML. Adherence to a randomized controlled trial of aerobic exercise in breast cancer survivors: The yale exercise and survivorship study. J Cancer Surviv. 2009 Sep;3(3):148-57.

53. Patel SR. The effects of yoga on mood disturbance and pain in an underserved breast cancer population. 2004.

54. Vadiraja HS, Raghavendra RM, Nagarathna R, et al. Effects of a yoga program on cortisol rhythm and mood states in early breast cancer patients undergoing adjuvant radiotherapy: A randomized controlled trial. Integr Cancer Ther. 2009 Mar;8(1):37-46.

55. McClure MK, McClure RJ, Day R, Brufsky AM. Randomized controlled trial of the breast cancer recovery program for women with breast cancer-related lymphedema. Am J Occup Ther. 2010 Jan-Feb;64(1):59-72.

56. Pinto BM, Clark MM, Maruyama NC, Feder SI. Psychological and fitness changes associated with exercise participation among women with breast cancer. Psychooncology. 2003;12(2):118-26.

57. Mock V, Dow KH, Meares CJ, et al. Effects of exercise on fatigue, physical functioning, and emotional distress during radiation therapy for breast cancer. Oncol Nurs Forum. 1997 Jul;24(6):991-1000.

58. Danhauer SC, Mihalko SL, Russell GB, et al. Restorative yoga for women with breast cancer: Findings from a randomized pilot study. Psychooncology. 2009 Apr;18(4):360-8.

59. Cadmus LA, Salovey P, Yu H, Chung G, Kasl S, Irwin ML. Exercise and quality of life during and after treatment for breast cancer: Results of two randomized controlled trials. Psychooncology. 2009 Apr;18(4):343-52.

60. Drouin JS, Armstrong H, Krause S., Orr J, Birk TJ, Hryniuk WM. Effects of aerobic exercise training on peak aerobic capacity, fatigue, and psyhchological factors during radiation for breast cancer. Rehabilitation Oncology. 2005;1(23):11-7.

61. Chandwani KD, Thornton B, Perkins GH, et al. Yoga improves quality of life and benefit finding in women undergoing radiotherapy for breast cancer. J Soc Integr Oncol. 2010 Spring;8(2):43-55.

62. Vito NL. The effects of a yoga intervention on physical and psychological functioning for breast cancer survivors. 2007.

63. Payne JK, Held J, Thorpe J, Shaw H. Effect of exercise on biomarkers, fatigue, sleep disturbances, and depressive symptoms in older women with breast cancer receiving hormonal therapy. Oncol Nurs Forum. 2008 Jul;35(4):635-42.

64. Mock V, Burke MB, Sheehan P, et al. A nursing rehabilitation program for women with breast cancer receiving adjuvant chemotherapy. Oncol Nurs Forum. 1994 Jun;21(5):899,907; discussion 908.

65. Eyigor S, Karapolat H, Yesil H, Uslu R, Durmaz B. Effects of pilates exercises on functional capacity, flexibility, fatigue, depression and quality of life in female breast cancer patients: A randomized controlled study. Eur J Phys Rehabil Med. 2010 May 6;46(4):481-487.

66. Monga U, Garber SL, Thornby J, et al. Exercise prevents fatigue and improves quality of life in prostate cancer patients undergoing radiotherapy. Arch Phys Med Rehabil. 2007 Nov;88(11):1416-22.

67. Courneya KS, Friedenreich CM, Quinney HA, Fields AL, Jones LW, Fairey AS. A randomized trial of exercise and quality of life in colorectal cancer survivors. European journal of cancer care. 2003;12(4):347-57.

68. Jarden M, Nelausen K, Hovgaard D, Boesen E, Adamsen L. The effect of a multimodal intervention on treatment-related symptoms in patients undergoing hematopoietic stem cell transplantation: A randomized controlled trial. J Pain Symptom Manage. 2009 Aug;38(2):174-90.

69. Chang PH, Lai YH, Shun SC, et al. Effects of a walking intervention on fatigue-related experiences of hospitalized acute myelogenous leukemia patients undergoing chemotherapy: A randomized controlled trial. J Pain Symptom Manage. 2008 May;35(5):524-34.

70. Cohen L, Warneke C, Fouladi RT, Rodriguez MA, Chaoul-Reich A. Psychological adjustment and sleep quality in a randomized trial of the effects of a tibetan yoga intervention in patients with lymphoma. Cancer. 2004;100(10):2253-60.

71. Duijts SF, Faber MM, Oldenburg HS, van Beurden M, Aaronson NK. Effectiveness of behavioral techniques and physical exercise on psychosocial functioning and health-related quality of life in breast cancer patients and survivors-a meta-analysis. Psychooncology. 2011 Feb;20(2):115-26.

72. Dunn AL, Trivedi MH, Kampert JB, Clark CG, Chambliss HO. Exercise treatment for depression: Efficacy and dose response. Am J Prev Med. 2005 [cited 9 November 2010];28(1):1-8.

73. Thompson, WR., Gordon, NF., Pescatello LS., editor. ACSM's guidelines for exercise testing and prescription. 8th ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2010.

74. Schutzer KA, Graves BS. Barriers and motivations to exercise in older adults. Prev Med. 2004 [cited 17 April 2011];39(5):1056-61.

75. Jones LW, Eves ND, Peppercorn J. Pre-exercise screening and prescription guidelines for cancer patients. Lancet Oncol. 2010 Oct;11(10):914-6.

76. Velthuis MJ, Agasi-Idenburg SC, Aufdemkampe G, Wittink HM. The effect of physical exercise on cancer-related fatigue during cancer treatment: A meta-analysis of randomised controlled trials. Clin Oncol (R Coll Radiol). 2010 Jan 26;22(3):208-221.

77. Brosse AL, Sheets ES, Lett HS, Blumenthal JA. Exercise and the treatment of clinical depression in adults: Recent findings and future directions. Sports Med. 2002;32(12):741-60.

78. Spence RR, Heesch KC, Brown WJ. Colorectal cancer survivors' exercise experiences and preferences: Qualitative findings from an exercise rehabilitation programme immediately after chemotherapy. Eur J Cancer Care (Engl). 2011 Mar;20(2):257-66.

79. Whitehead S, Lavelle K. Older breast cancer survivors' views and preferences for physical activity. Qual Health Res. 2009 Jul;19(7):894-906.

80. Pedersen BK, Saltin B. Evidence for prescribing exercise as therapy in chronic disease. Scand J Med Sci Sports. 2006 Feb;16 Suppl 1:3-63.

81. Mor V, Allen S, Malin M. The psychosocial impact of cancer on older versus younger patients and their families. Cancer. 1994 Oct 1;74(7 Suppl):2118-27.

82. Mao JJ, Armstrong K, Bowman MA, Xie SX, Kadakia R, Farrar JT. Symptom burden among cancer survivors: Impact of age and comorbidity. J Am Board Fam Med. 2007 Sep-Oct;20(5):434-43.

83. Higginbotham MB, Morris KG, Williams RS, Coleman RE, Cobb FR. Physiologic basis for the age-related decline in aerobic work capacity. Am J Cardiol. 1986 Jun 1;57(15):1374-9.

84. Holland JC, Andersen B, Breitbart WS, et al. Distress management. J Natl Compr Canc Netw. 2010 Apr;8(4):448-85.

85. Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature. 2008 Oct 16;455(7215):894-902.

86. Berton O, Nestler EJ. New approaches to antidepressant drug discovery: Beyond monoamines. Nat Rev Neurosci. 2006 Feb;7(2):137-51.

87. Arida RM, Naffah-Mazzacoratti Mda G, Soares J, Cavalheiro EA. Monoamine responses to acute and chronic aerobic exercise in normotensive and hypertensive subjects. Sao Paulo Med J. 1998 Jan-Feb;116(1):1618-24.

88. Krum H, Conway EL, Howes LG. Acute effects of exercise on plasma lipids, noradrenaline levels and plasma volume. Clin Exp Pharmacol Physiol. 1991 Oct;18(10):697-701.

89. Mazzeo RS, Bender PR, Brooks GA, et al. Arterial catecholamine responses during exercise with acute and chronic high-altitude exposure. Am J Physiol. 1991 Oct;261(4 Pt 1):E419-24.

Table 1. Descriptive characteristics of included studies, subjects and exercise interventions by type of cancer (means ± SD, *k* or % where noted)

Descriptive Statistic	All Cancer	Breast	Prostate	Leukemia	Lymphoma
Study Characteristics					
Number of studies, *k*	40[a]	26[b]	2	2	2
Year of study	2006±4.2	2006±3.9	2008±2.1	2008±0.7	2006±3.5
Published in journal, *k*	34	21	2	2	2
PEDro quality	7.0±1.0	6.7±1.1	7.0±0.0	7.5±0.7	7.5±0.7
Subject Characteristics					
Total n (% total n)	2929 (100)	1796 (61)	121 (4)	66 (2)	161 (6)
Gender, n of women (% total n)	2548 (87)	1796 (100)	121 (0)	22 (33)	61 (38)
Ethnicity, n (% total n)					
White, non-Hispanic	2255 (77)	1437 (80)	–	–	–
African-American	498 (17)	296 (16)	–	–	–
Hispanic	88 (3)	54 (3)	–	–	–
Asian	59 (2)	18 (1)	–	–	–
Age, yr	51.3±6.5	50.9±4.7	68.5±1.2	45.2±8.6	52.1±1.5
Stage of treatment, *k*					
Currently treated	29	17	2	2	2
Previously treated	11	9	0	0	0
Time since diagnosis, mo	25.3±19.6	26.9±21.3	–	–	29.2±8.0
Exercise Intervention Characteristics					
Intervention length, wk	13.2±11.7	15.5±14.2	12.0±5.6	4.0±1.4	9.5±3.5
Length, min·session^{-1}	49.1±27.1	54.7±27.5	65.0±35.4	36.0±33.9	61.2±40.6
Frequency, session·wk^{-1}	3.0±2.5	2.8±1.3	2.0±1.4	5.0±0.0	2.0±1.4
Exercise volume, min·wk^{-1}	123.9±52.2	135.2±25.1	105.0±21.2	180.0±169.7	97.5±0.0
Aerobic intensity, MET	4.8±1.1	4.7±0.9	4.4±0.8	5.4±2.3	7.0±0.0
Strength intensity, MET	2.9±0.5	2.9±0.6	3.0±0.0	3.0±0.0	2.5±0.0
Neuromuscular, MET	2.5±0.0	2.5±0.0	–	–	2.5±0.0
Flexibility, *k*					
Included	20	13	2	1	1
Excluded	20	13	0	1	1
Supervision, *k*					
Supervised	24	19	2	2	2

Unsupervised	16	7	–	–	–
Use of theory, *k*					
None	32	21	2	2	1
Psychological	8	5	0	0	1
Depression Scale used, *k*					
CES-D	16	9	1	–	2
POMS	9	7	–	1	–
BDI	7	6	1	–	–
HADS	5	2	–	1	–
SAS	3	2	–	–	–

NOTE: Percentages may not sum to 100% due to rounding error.
CES-D, Center for Epidemiologic Studies Depression scale; POMS, Profile Of Mood States; BDI, Beck Depression Inventory; HADS, Hospital Anxiety and Depression Scale; SAS, Symptom Assessment Scale.
k, number of studies included.
MET, metabolic equivalent, 1MET = 3.5 ml $O_2 \cdot kg \cdot min^{-1}$.
[a] 37 studies provided 40 total effect size estimates
[b] 24 studies provided 26 total effect size estimates.

Table 2. Weighted mean effect of exercise modulating depression by type of cancer

		d_+ (95% CI)		Homogeneity of *d*s		
Type of Cancer	***k***	**Fixed-Effects**	**Random-Effects**	***Q***	**I^2 (95% CI)**	***P***
All Cancer	40[a]	-0.13 (-0.21, -0.06)	-0.13 (-0.26, -0.01)	86.13	55% (35, 68)	<0.001
Breast	26[b]	-0.19 (-0.28, -0.09)	-0.17 (-0.32, -0.02)	60.79	59% (37, 73)	<0.001
Prostate	2	-0.20 (-0.66, 0.25)	-0.20 (-0.82, 0.40)	0.00	0% (0, 100)	0.948
Leukemia	2	-0.22 (-0.73, 0.30)	-0.24 (-0.89, 0.40)	0.94	0% (0, 100)	0.332
Lymphoma	2	-0.35 (-0.67, -0.03)	-0.30 (-0.89, 0.29)	0.64	0% (0, 100)	0.424
Colorectal	1	-0.08 (-0.52, 0.35)	–	–	–	–

NOTE: Weighted mean effect size values (d_+) are negative when the exercise intervention was successful in reducing depression compare to standard care.

k, number of studies.

[a]37 studies provided 40 total effect size estimates.

[b]24 studies provided 26 total effect size estimates.

Table 3. Multi-moderator intervention characteristics related to depression change for all cancer survivors

Study dimension and level[a]			Adjusted[b] d_+ (95% CI)	β[c]	P
Accumulated weekly volume of aerobic exercise, min·wk[1] × PEDro methodological score	PEDro=5 (lower quality)	90 min·wk^{-1}	-0.29 (-0.54, 0.04)	-0.24[d]	0.03
		120 min·wk^{-1}	-0.19 (-0.40, 0.02)		
		150 min·wk^{-1}	-0.09 (-0.34, 0.14)		
		180 min·wk^{-1}	0.00 (-0.34, 0.34)		
	PEDro=10 (higher quality)	90 min·wk^{-1}	-0.07 (-0.42, 0.27)		
		120 min·wk^{-1}	-0.28 (-0.54, -0.02)		
		150 min·wk^{-1}	-0.49 (-0.77, -0.23)		
		180 min·wk^{-1}	-0.71 (-1.09, -0.33)		
Supervision of exercise		Unsupervised	-0.13 (-0.23, -0.04)	0.26	0.01
		Supervised	-0.36 (-0.55, -0.18)		
Age,[e] y (*Quadratic*)		40	0.16 (-0.08, 0.41)	0.27	0.01
		50	-0.20 (-0.30, -0.10)		
		60	-0.25 (-0.42, -0.08)		
		70	0.01 (-0.47, 0.56)		

NOTE: Weighted mean effect size values (d_+) are negative when the exercise intervention reduced depression compared to the control group. The regression equation is -0.2289–0.0164(age, y)+0.0016(age^2, y)+0.1117(supervised)–0.0993(PEDro)–0.0007(Min week aerobic exercise)–0.0021(PEDro×Min week aerobic exercise), where each continuous variable was zero-centered, and categorical variables were contrast coded (+1 vs -1).

[a]Levels represent values of interest of each moderator.

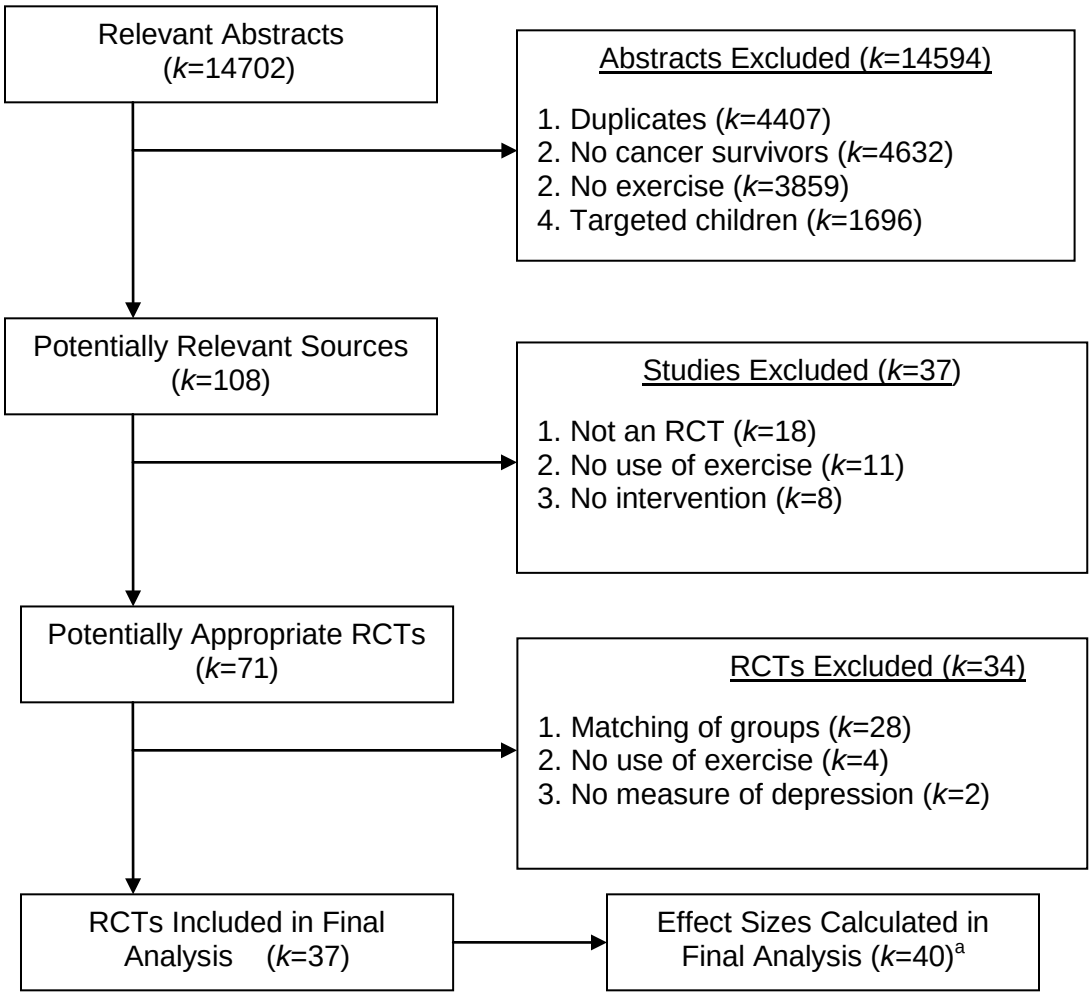
[b]d_+ and their 95% CI estimates statistically adjust for the presence of the rest of the moderators in the fixed-effects model, including weekly minutes of exercise × PEDro interaction and their independent linear terms, supervision of exercise, quadratic and linear trends for age, held constant at their means except for the study dimension in question.

[c]β values are standardized.

[d]β for interaction. Independent β: weekly aerobic volume, β = -0.09; PEDro methodological score, β = -0.28.

[e]Continuous quadratic trend including linear component.

Figure 1. Flow diagram of exercise intervention identification and selection



[a] Three studies provided two interventions, yielding two effect size calculations
RCT, Randomized controlled trial

Table and Figure titles and footnotes:

Table 2. Descriptive characteristics of included studies, subjects and exercise interventions by type of cancer (means ± SD, *k* or % where noted)

NOTE: Percentages may not sum to 100% due to rounding error.
CES-D, Center for Epidemiologic Studies Depression scale; POMS, Profile Of Mood States; BDI, Beck Depression Inventory; HADS, Hospital Anxiety and Depression Scale; SAS, Symptom Assessment Scale.
k, number of studies included.
MET, metabolic equivalent, 1MET = 3.5 ml $O_2 \cdot kg \cdot min^{-1}$.
[a] 37 studies provided 40 total effect size estimates
[b] 24 studies provided 26 total effect size estimates.

Table 2. Weighted mean effect of exercise modulating depression by type of cancer

NOTE: Weighted mean effect size values (d_+) are negative when the exercise intervention was successful in reducing
depression compare to standard care.
k, number of studies.
[a]37 studies provided 40 total effect size estimates.
[b]24 studies provided 26 total effect size estimates.

Table 3. Multi-moderator intervention characteristics related to depression change for all cancer survivors
NOTE: Weighted mean effect size values (d_+) are negative when the exercise intervention reduced depression compared to the control group. The regression equation is -0.2289 – 0.0164(age, yr) + 0.0016(age^2, y) + 0.1117(supervised) – 0.0993(PEDro) – 0.0007(Min week aerobic exercise) – 0.0021(PEDro × Min week aerobic exercise), where each continuous variable was zero-centered, and categorical variables were contrast coded (+1 vs -1).
[a]Levels represent values of interest of each moderator.
[b]d_+ and their 95% CI estimates statistically adjust for the presence of the rest of the moderators in the fixed-effects model, including

weekly minutes of exercise × PEDro interaction and their independent linear terms, supervision of exercise, quadratic and linear trends for age, held constant at their means except for the study dimension in question.

[c]β values are standardized.

[d]β for interaction. Independent β: weekly aerobic volume, β = -0.09; PEDro methodological score, β = -0.28.

[e]Quadratic trend including linear component.

Figure 1. Flow diagram of exercise intervention identification and selection

FOOTNOTE: [a] Three studies provided two interventions, yielding two effect size calculations

RCT, Randomized controlled trial

Systematic search strategy (Supplementary).

The databases PubMed, PsycINFO, CINAHL Plus, SPORTSdiscus, OregonPDF in Health and Performance, and ProQuest Theses and Dissertations were searched through Nov 18, 2010. We searched all databases using a Boolean search strategy [i.e., (cancer OR neoplas* OR tumor OR chemo* OR radiat* OR malign* OR carciniom*) AND (depress* OR anxiety OR anxious OR worried OR scared OR nervous OR cognitive OR biofeedback OR relaxation OR social support OR mind-body) AND (exercise OR physical activity OR aerobic OR cardiovascular OR resistance OR strength OR muscular OR flexibility OR walking OR program OR interval OR sport OR fitness OR performance OR movement OR stretching OR tai chi OR yoga OR dance OR body OR composition)]. Journals focusing on cancer survivorship (*Breast Cancer Research and Treatment*, *Journal of Cancer Survivorship*, *Oncology Nursing Forum, Journal of Pain and Symptom Management* and the reference lists of included studies were also searched for additional papers.

Table 4. Clinical, exercise and methodological characteristics of included studies. **Supplementary.**

First Author, Year, Reference	Clinical Characteristics		Exercise Characteristics					Methodological Characteristics	
	Sample Size	Type of Cancer	Freq ($d \cdot wk^{-1}$)	Intensity	Time ($min \cdot session^{-1}$)	Type	Duration (wk)	Depression Measure	PEDro Score
Mixed Cancer Diagnoses									
Burnham, 2002,(38)	I = 12 C = 6	Breast colon	3	40–60% HRR	30	Aerobic; treadmill, stationary cycle, stair climber	10	LASA	7
Dimeo, 1999,(39)	I = 27 C=32	Variety; solid tumors, lymphoma	7	50% HRR	30	Aerobic; supine biking ergometer	4	POMS	8
Dodd, 2010,(40)	I = 44 I (Delayed) = 36 C = 39	Breast Colorectal Ovarian	3–5	60–80% $V0_{2peak}$	20–30	Aerobic; walking, jogging, bicycling	52	CES-D	8
Berglund, 1994,(41)	I = 98 C = 101	Majority Breast cancer	2	n/a	60	n/a	7	HADS	7
Courneya, 2003,(42)	I = 60 C = 48	Breast Colon Ovarian Stomach Melanoma Hodgkin Non-Hodgkin's Brain Lung	3–5	65–75% HR_{max}	20–30	Aerobic; swimming, cycling	10	CES-D	8
Thorsen, 2005,(43)	I = 59 C = 52	Lymphoma Breast Gyne-cologic Testicular	2	60–70% HR_{max}	30	Aerobic; walking, cycling, jogging	14	HADS	8
Breast Cancer									
Daley, 2007,(16)	I = 34 C = 36	Breast	3	65–85% HR_{max}	50	n/a	8	BDI	8
Courneya, 2007,(19)	I (Aer) = 78 I (RET) = 82 C = 82	Breast	3	60–70% $V0_{2max}$ 2 Sets, 60–70%	15–45	Aerobic: cycle ergometer, treadmill, elliptical 9 strength	17	CES-D	7

First Author, Year, Reference	Clinical Characteristics		Exercise Characteristics					Methodological Characteristics	
	Sample Size	Type of Cancer	Freq ($d \cdot wk^{-1}$)	Intensity	Time ($min \cdot session^{-1}$)	Type	Duration (wk)	Depression Measure	PEDro Score
				predicted 1-RM		exercise			
Culos-Reed, 2006,(44)	I = 20 C = 18	Majority breast	1	n/a	75	Yoga	7	POMS	7
Rausch, 2007,(45)	I = 15 C = 8	Breast	1	n/a	90	Tai Chi	10	POMS	5
Ohira, 2006,(46)	I = 43 C = 43	Breast	2	Progressive resistance	60	Weight training	24	CES-D	6
Perna, 2010,(47)	I = 26 C = 25	Breast	3	Aerobic: 50–85% HR_{max} Weight training: 1 set, 12–15 reps	30	Aerobic; treadmill walking Weight training; weight belts	12	CES-D	9
Lee, 2010,(48)	I = 16 C = 18	Breast	1	Light (<40% 1-RM), elastic band, medicine ball exercise	40	Weight training of shoulder muscle groups	8	BDI	5
Demark-Wahnefried, 2008,(49)	I = 26 C = 29	Breast	≥3	Aerobic: walking Weight training: Light (<40% 1-RM)	≥30	Aerobic training; walking Weight training: elastic band, medicine ball exercise	12	HADS	6
Targ, 2002,(50)	I = 74 C = 60	Breast	1	n/a	90	Yoga	12	POMS	6
Mutrie, 2007,(51)	I =101 C =102	Breast	3	50–75% HR_{max}	45	Walking, cycling, aerobics, strength exercises	12	BDI	9

First Author, Year, Reference	Clinical Characteristics		Exercise Characteristics					Methodological Characteristics	
	Sample Size	Type of Cancer	Freq ($d \cdot wk^{-1}$)	Intensity	Time ($min \cdot session^{-1}$)	Type	Duration (wk)	Depression Measure	PEDro Score
Latka, 2009,(52)	I = 37 C = 38	Breast	5	60–80% HR_{max}	30	Walking	24	CES-D	7
Patel, 2004,(53)	I = 43 C = 19	Breast	1	n/a	90	Yoga	12	POMS	6
Vadiraja, 2009,(54)	I = 44 C = 44	Breast	3	n/a	60	Yoga	6	HADS	8
McClure, 2010,(55)	I = 16 C = 16	Breast	7	Low–moderate intensity	17	Arm flexibility exercise	17	BDI	6
Pinto, 2003,(56)	I = 12 C = 12	Breast	3	60–70% HR_{max}	50	Treadmill walking, arm cycling, stationary cycling, rowing	12	POMS	7
Mock, 1997,(57)	I = 22 C = 24	Breast	4–5	Self-paced	20–30	Walking	6	SAS	7
Danhauer, 2009,(58)	I = 13 C = 14	Breast	1	n/a	75	Yoga	10	CES-D	6
Cadmus, 2009,(59) **(IMPACT)**	I = 25 C =25	Breast	5	60–80% HR_{max}	30	Not-specified	24	CES-D	8
Drouin, 2005,(60)	I = 13 C = 8	Breast	5	50–70% HR_{max}	20–45	Treadmill walking	7	POMS	7
Chandwani, 2010,(61)	I = 30 C = 31	Breast	2	n/a	60	Yoga	6	CES-D	6
Vito, 2007,(62)	I =13 C = 12	Breast	2	n/a	90	Yoga	8	POMS	8
Payne, 2008,(63)	I =10 C = 10	Breast	4	Moderate intensity	20	Walking	12	CES-D	7
Mock, 1994,(64)	I = 9 C = 9	Breast	≥3	Self-paced	30	Walking	6	SAS	7

First Author, Year, Reference	Clinical Characteristics		Exercise Characteristics					Methodological Characteristics	
	Sample Size	Type of Cancer	Freq ($d \cdot wk^{-1}$)	Intensity	Time ($min \cdot session^{-1}$)	Type	Duration (wk)	Depression Measure	PEDro Score
Eyigor, 2010,(65)	I = 27 C = 25	Breast	3	n/a	20–30	Pilates	8	BDI	5
Prostate Cancer									
Culos-Reed, 2010,(18)	I = 53 C = 47	Prostate	3–5	moderate	60	Walking, resistance exercise	16	CES-D	7
Monga, 2007,(66)	I = 11 C = 10	Prostate	3	65% $HR_{reserve}$	30	Treadmill walking	8	BDI	7
Leukemia									
Jarden, 2009,(68)	I = 21 C = 21	Leukemia	1	50–75% HR_{max} 1–2 sets, 10–12 reps	60	Aerobic: Stationary cycling Resistance: Free weights, ankle weights	4–6	HADS	8
Chang, 2008,(69)	I = 11 C = 11	Leukemia	5	60–110 bpm	12	Walking	3	POMS	7
Lymphoma									
Courneya, 2009,(17)	I = 60 C = 62	Lymphoma	3	50–75% $V0_{2peak}$	20–45	Recumbent cycle ergometer	12	CES-D	8
Cohen, 2004,(70)	I = 20 C = 19	Lymphoma	1	n/a	60	Yoga	7	CES-D	7
Colorectal Cancer									
Courneya, 2003,(67)	I = 69 C = 33	Colorectal	3–5	65–75% HR_{max}	20–30	Walking	16	CES-D	9

NOTE: I, Intervention (exercise group); C, control group
CES-D, Center for Epidemiologic Studies Depression scale; POMS, Profile Of Mood States; BDI, Beck Depression Inventory; HADS, Hospital Anxiety and Depression Scale; SAS, Social Anxiety Scale.
HR_{max}, maximum heart rate; HRR, heart rate reserve; $V0_{2peak}$, maximal oxygen consumption ($ml \cdot kg \cdot min^{-1}$); bpm, beats per minute; 1-RM, one-repetition maximum

Table 5. Bivariate moderator intervention characteristics related to depression reduction for all cancer survivors. **Supplementary.**

Study dimension and level[a]		d_+ (95% *CI*)[c]	β[d]	P
Theory	None	-0.06 (-0.15, 0.03)	0.26	0.01
	Psychological	-0.26 (-0.39, -0.13)		
Supervision of exercise	Supervised	-0.22 (-0.32, -0.13)	0.37	0.002
	Non-supervised	0.07 (-0.06, 0.21)		
Non-Hispanic white, %	24	-0.34 (-0.52, -0.17)	0.06	0.01
	99	-0.92 (-1.55, -0.29)		
Time since diagnosis, mo	2.8	-0.17 (-0.29, -0.04)	0.35	0.02
	73.0	0.39 (-0.21, 1.00)		
Accumulated weekly volume of aerobic exercise, min·wk^{-1} × PEDro methodological score	PEDro = 5 × 90 min·wk^{-1}	-0.19 (-0.43, 0.06)	-0.25	0.03
	PEDro = 5 × 150 min·wk^{-1}	-0.02 (-0.26, 0.22)		
	PEDro = 10 × 90 min·wk^{-1}	0.05 (-0.24, 0.35)		
	PEDro = 10 × 150 min·wk^{-1}	-0.35 (-0.61, -0.08)		
Age[e], y	39	0.22 (-0.04, 0.47)	0.70	0.001
	51	-0.19 (-0.27, -0.10)		
	69	0.12 (-0.31, 0.54)		

NOTE: Weighted mean effect size values (d_+) are negative when the exercise intervention was successful in reducing depression compared to the control group.

[a]Levels represent values of interest of each moderator.

[b]*k*, For categorical variables, *k* denotes number of effect sizes in each group. For continuous variables, *k* denotes total observations.

[c]bivariate d_+ (95% *CI*) were calculated using fixed-effects models.

[d]β values are standardized.

[e]Quadratic trend including linear component.

Table and Figure titles and footnotes (Supplementary):

Table 4. (Supplementary Material) Clinical, exercise and methodological characteristics of included studies

NOTE: I, Intervention (exercise group); C, control group

CES-D, center for epidemiologic studies-depression; HADS, hospital anxiety & depression; POMS, profile of mood states; BDI, Beck depression inventory; SAS, system assessment scales (100-millimeter axis)

HR_{max}, maximum heart rate; HRR, heart rate reserve; $V0_{2peak}$, maximal oxygen consumption ($ml \cdot kg \cdot min^{-1}$); bpm, beats per minute; 1-RM, one-repetition maximum

Table 5. (Supplementary Material) Bivariate moderator intervention characteristics related to depression reduction for all cancer survivors

NOTE: Weighted mean effect size values (d_+) are negative when the exercise intervention was successful in reducing depression compared to the control group.

[a]Levels represent values of interest of each moderator.

[b]*k*, For categorical variables, *k* denotes number of effect sizes in each group. For continuous variables, *k* denotes total observations.

[c]bivariate d_+ (95% *CI*) were calculated using fixed-effects models.

[d]β values are standardized.

[e]Quadratic trend including linear component.

Chapter 5 – Discussion

This thesis includes two studies examining the efficacy of exercise on cancer-related fatigue (CRF) (1) and depression (2) among adult cancer survivors. In this concluding chapter, the specific aims and hypotheses of these studies along with the most relevant findings are reviewed. Then, the clinical significance and the translation of the findings into clinical practice regarding the Ex R_x among cancer survivors are discussed. Lastly, directions for future research and a concluding summary are provided.

Specific Aims & Hypotheses

Specific Aim 1: To meta-analyze the literature to determine the efficacy of exercise on reductions in CRF and depression among cancer survivors. **Hypothesis 1:** Cancer survivors engaging in exercise would demonstrate statistically significant reductions in CRF and depression compared to cancer survivors receiving standard care. Cancer survivors engaging in exercise experienced statistically significant reductions in CRF and depression when compared to cancer survivors receiving standard care.

Specific Aim 2: To meta-analyze the literature to examine the influence of the frequency, intensity, time and type (FITT) components of the Ex R_x on reductions in CRF and depression among cancer survivors. **Hypothesis 2:** FITT components of Ex R_x would modulate the magnitude of the reduction in CRF and depression among cancer survivors. The largest reductions in CRF occurred when cancer survivors performed resistance training (i.e., weight training). CRF reductions occurred in a dose response fashion with resistance exercise such that as intensity of resistance exercise increased, so did reductions in CRF. In contrast, the largest reductions in depression occurred when cancer survivors

performed aerobic exercise. Depression reduction occurred in dose-response fashion with aerobic exercise such that as weekly minutes of aerobic exercise increased, so did reductions in depression, a finding observed in higher quality trials. Moreover, larger reductions in depression occurred with supervised exercise.

Specific Aim 3: To meta-analyze the literature to examine the influence of patient clinical characteristics on reductions in CRF and depression among cancer survivors. **Hypothesis 3:** Clinical characteristics of cancer survivors would modulate the magnitude of the reduction in CRF and depression resulting from exercise. Subgroup analysis identified breast and prostate cancer survivors performing exercise significantly reduced CRF compared to breast and prostate cancer survivors receiving standard care. However, *only* breast cancer survivors performing exercise significantly reduced depression compared to other all types of cancer survivors receiving standard care.

Age moderated the magnitude of the exercise-induced reductions in CRF and depression. Interestingly, contrasting trends emerged with respect to age of cancer survivors performing exercise and the magnitude of CRF and depression reduction. Age of cancer survivors performing resistance exercise was positively correlated with CRF reduction such that older cancer survivors reduced their CRF levels to greater levels than younger cancer survivors. Whereas cancer survivors between the ages of 47–62 yr engaging in aerobic exercise reduced their depression levels to greater levels than those <47 or >62 yr.

Specific Aim 4: To meta-analyze the literature to examine the influence of the interactions among FITT components of Ex R_x and patient clinical characteristics

on reductions in CRF and depression among cancer survivors. **Hypothesis 4:** Interactions among FITT components of Ex R_x and patient clinical characteristics will modulate the magnitude of reduction in CRF and depression among cancer survivors. This hypothesis was not supported, as we identified no interactions among the Ex R_x FITT components and patient clinical characteristics on reductions in CRF and depression among cancer survivors.

Other findings

Exercise interventions using behavioral change strategies to develop and guide cancer survivors through the exercise intervention were more efficacious in reducing CRF than exercise interventions not developed or guided by a behavioral change model.

The magnitude of exercise-induced CRF reduction was moderated by the methodological quality of the exercise intervention assessed by the PEDro methodological score (3). There was a significant interaction between the PEDro methodological score and intensity of resistance exercise prescribed. Exercise interventions of lower methodological quality were efficacious in reducing CRF when they prescribed low or moderate intensity resistance exercise. Interventions of higher methodological quality were efficacious in reducing CRF only when they prescribed moderate-intensity resistance exercise.

There was a significant interaction between the PEDro methodological score and weekly volume of aerobic exercise. Exercise interventions of lower methodological quality were not efficacious in reducing depression at any weekly volume of aerobic exercise, whereas interventions of higher methodological quality were efficacious in reducing depression with larger weekly volumes of aerobic exercise.

Physiologic specificity of exercise and modulation of CRF and depression

The efficacy of exercise to reduce CRF and depression emerged to be modality (or type of exercise) specific. Resistance training reduced CRF in dose response fashion, whereas aerobic exercise reduced depression in dose response fashion. Despite the unknown etiology of CRF and depression among cancer survivors, several hypotheses are suggested (4, 5).

CRF associates with variety of physiologic alterations occurring with cancer and cancer treatment. These alterations include decreases in muscle mass and muscle strength, and marked increases in pro inflammatory cytokines, specifically interleukin-6 (IL-6), IL-1β, and tumor necrosis factor-α (TNF- α) (5). Interestingly, resistance exercise elicits increases in muscle mass, muscle strength, and a cascade of cytokine responses occurring in dose response fashion with exercise intensity among apparently healthy persons (6). During resistance exercise there is an up regulation of anti-inflammatory cytokines, specifically IL-6 and IL-10 (6, 7). This increase in anti-inflammatory cytokines results in subsequent down regulation of pro-inflammatory cytokines including TNF-α and IL-1β, postulated to result in diminished levels of CRF (5, 7). Appropriately, this meta-analysis found resistance training reduced CRF in dose response fashion, fully supporting the cytokine dysregulation hypothesis of CRF proposed by Al-Majid (5). Moderate intensity resistance training elicits similar cytokine responses in prostate cancer survivors resulting in diminished levels of CRF providing additional evidence for this hypothesis in a randomized controlled trial (8, 9).

The specific etiology of depression remains unclear despite 50 yr of investigation (10). Several hypotheses exist including monoamine imbalance, hypothalamic pituitary axis dysregulation, and depletion of β-endorphins in the brain (10, 11). Monoamine imbalance is the most widely proposed hypothesis

relating to depression. Monoamines (serotonin, noradrenaline, and dopamine) are critical to the efficacy of anti-depressant medication (10). The function of anti-depressants is to retard the rate of monoamine degradation in the body (10). This yields higher bioavailability of monoamines, subsequently increasing their concentration at synaptic junctions in the brain postulated to result in lower levels of depression (10). The physiologic response to anti-depressant medication is similar to that of aerobic exercise (10, 12); increasing the bioavailability of monoamines (12). Acute and chronic aerobic exercise increases monoamine concentrations above pre exercise levels, and above those achieved with heavy resistance training (13). This makes aerobic exercise an optimal modality to improve monoamine concentration among those with depression. An acute bout of aerobic exercise increases monoamine concentrations from pre exercise levels, and chronic aerobic exercise increases monoamine concentration from acute exercise levels (12). This monoamine response makes chronic aerobic exercise training an efficacious intervention for the management of depression. Appropriately, we found aerobic exercise reduced depression in dose response fashion; larger volumes of weekly aerobic exercise were more efficacious in reducing depression among cancer survivors. The finding that aerobic exercise in dose response was more efficacious than strength training to reduce depression supports the monoamine hypothesis proposed by others (10-12). A randomized controlled trial examining aerobic exercise and biomarkers associated with depression would provide additional evidence for this hypothesis.

Clinical significance of the findings and their translation into clinical practice

The current Ex R_x recommendations for cancer survivors suggest a general health fitness program focusing on accruing ≥150 $min \cdot wk^{-1}$ of aerobic exercise,

complimented with two days of resistance exercise, and flexibility training on days of non-exercise (14, 15). Ex R_x guidelines from the ACSM expert consensus for cancer survivors are consistent with the recommendations made in 2008 for physical activity among healthy Americans (16).

The current Ex R_x for cancer survivors was not developed and tailored for symptom management. Rather, the generic Ex R_x implements a broad range of modalities of light to moderate intensities, likely providing improvements in health related components of physical fitness including aerobic capacity, muscular strength and endurance, body composition, and flexibility, but providing no insight for symptom management. The current Ex R_x recommendations suggest a 'one size fits all' approach to exercise and symptom management. The expert panel did not provide symptom specific Ex R_x recommendations due to the heterogeneity of results in symptom improvements relating to the varying doses of exercise prescribed (14). The lack of evidence regarding symptom outcomes was a noted research gap warranting further investigation. The expert panel acknowledged, "The existent literature is insufficient to assist fitness professionals with the specifics required to ensure that cancer survivors receive safe and effective exercise prescriptions" (14).

This thesis provides support for the dose-response effects of exercise on CRF and depression. More importantly, the findings from this thesis provide evidence for hypothesis driven prospective randomized control trials to test the dose-response effect of exercise on CRF and depression. Evidence from future randomized trials may confirm the findings of this meta-analysis, suggesting refinement of the current Ex R_x based upon magnitude of symptoms experienced during and after treatment.

The findings of this meta-analysis indicate cancer survivors reporting CRF as their chief complaint may reap the largest benefits in CRF reduction by engaging in a progressive, supervised, strength training program, complimented by aerobic and flexibility exercises. Strength training should begin with little to no weight and progress as appropriate. Schmitz *et al.* (17, 18) demonstrated breast cancer survivors, with and at-risk for lymphedema, have been able to participate in slowly progressive weight training with no maximum intensity restrictions, including one repetition maximum testing (1-RM; the maximum amount of weight lifted one time). This trial used weighted Velcro straps or no weight at all for two sets of each exercise of 10 repetitions per set. After being able to perform two additional repetitions, for two sets, for two consecutive workouts, the resistance increased by the smallest possible increment. This indicates slowly progressive resistance training is safe for breast cancer survivors with and at risk for lymphedema, reduces limb swelling, reduces self-reported lymphedema symptoms, improves quality of life and body image, and reduces CRF.

Conversely, the findings of this meta-analysis suggest cancer survivors reporting depression as their chief complaint may reap the largest reductions in depression by engaging in a structured, supervised, aerobic exercise program with the primary goal of achieving large weekly volumes of aerobic exercise, complimented by strength and flexibility exercise. Breast cancer survivors accrued ≥150 $min \cdot wk^{-1}$ of aerobic treadmill exercise in 12 wk (19), and 225 $min \cdot wk^{-1}$ over 24 wk of training. Survivors performed 3–5 $d \cdot wk^{-1}$ treadmill walking for 15–20 $min \cdot d^{-1}$ with small weekly increments (i.e., 5–10 min) until 150 or 225 $min \cdot wk^{-1}$ was achieved (20). These trials provide a model for clinicians to follow when prescribing progressive aerobic exercise. However, accruing ≥150 $min \cdot wk^{-1}$ of aerobic exercise may take longer than 12 wk if pre-diagnosis physical activity

levels were low and other comorbidities exist (i.e., obesity). Jones *et al*. (21) provides a schematic to aid the clinician in identifying the appropriate dose of exercise to prescribe by assessing previous and current exercise levels of patients. The schematic provides the appropriate frequency, intensity, time, and type of exercise recommended by the current ACSM Ex R_x (4, 11). Clinicians and health fitness professionals should always weigh the risk to benefit ratio when prescribing larger or more intense doses of exercise to their patients and clients.

The ACSM expert panel acknowledged the interaction of age with exercise training is of special interest as many cancer survivors are older because they now living with rather than dying from cancer (14). We quantified the moderating effects of age and the exercise-induced reductions in CRF and depression. Cancer survivors reduced CRF to the greatest magnitude with increasing age, whereas cancer survivors age 47–62 yr reduced depression to the greatest magnitude (1, 2). Age modulates CRF and depression differently among different types of cancer survivors when performing exercise, suggesting age may be a characteristic considered when developing an Ex R_x for symptom management.

Future Research

This thesis provides continued evidence supporting the efficacy of exercise training among cancer survivors. However, many research questions remain. Other clinically relevant side effects of cancer or cancer treatment such as anxiety, nausea, and pain and their response to exercise training warrant continued investigation. Existent literature has examined the efficacy of exercise training among breast cancer survivors (22). Future research should investigate the safety and efficacy of exercise training on other common forms of cancer

including lung, colorectal, prostate, and ovarian cancers. Furthermore, a majority of cancer survivors participating in exercise training studies are Caucasian, non-Hispanic whites (14). Noted in the expert consensus statement (14), future research needs to examine the efficacy of exercise training among racial and ethnic minority groups as well as those of low socioeconomic status. Future trials should examine exercise training among cancer survivors presenting with co-morbidities such as cardiac conditions, obesity, metabolic, and bone disorders.

To verify our findings, a large, well-powered, randomized controlled trial examining the efficacy of the specific doses and modalities of exercise found to be efficacious in reducing CRF and depression among cancer survivors should be conducted. For example, a trial designed to test our findings relating to CRF reduction would employ a four arm randomized design with 42 subjects per arm (N=168). This sample would provide 80% power, and two-sided $\alpha = 0.05$ to detect a reduction in CRF. Participants would be randomized to one of four groups: 1) moderate intensity resistance training (60–80% 1-RM; 2 sets; 8–12 repetitions; 3 $d \cdot wk^{-1}$); 2) moderate intensity aerobic exercise (40–60% $V0_{2peak}$, 3 $d \cdot wk^{-1}$); 3) a combination of arms aerobic and strength exercise; or 4) placebo wait list control. This trial would compare different modalities of exercise to reduce CRF. Once the optimal modality of exercise is identified, other program variables manipulated in similarly designed trials might include frequency, intensity, and time of exercise. A similar randomized study design could also investigate depression as a primary outcome to elucidate efficacious modalities of exercise.

Conclusion

This meta-analysis examined the magnitude of the exercise induced reductions in CRF and depression among cancer survivors. Additionally, this thesis investigated the Ex R_x and clinical patient characteristics moderating the magnitude of the exercise induced responses in CRF and depression among cancer survivors. This thesis provides evidence that resistance training reduces CRF, and aerobic training reduces depression among cancer survivors. Both CRF and depression responding to exercise training in *dose response* fashion. This research highlights the importance of the continued development of symptom-specific Ex R_x among cancer survivors. The findings from this thesis provide a framework to begin tailoring the FITT components of the Ex R_x for symptom specific management of cancer survivors, whereas prior exercise interventions have prescribed a 'one size fits all' approach to exercise and symptom management. In accordance with current Ex R_x guidelines, all cancer survivors should strive to avoid inactivity if at all possible (14). Cancer survivors are encouraged to discuss the safety, feasibility, and efficacy of beginning an exercise program with their oncologist or primary care physician.

References

1. Brown JC, Huedo-Medina TB, Pescatello LS, Pescatello SM, Ferrer RA, Johnson BT. Efficacy of exercise interventions in modulating cancer-related fatigue among adult cancer survivors: A meta-analysis. Cancer Epidemiol Biomarkers Prev. 2011 Jan;20(1):123-33.

2. Brown JC, Huedo-Medina TB, Johnson BT, et al. The efficacy of exercise interventions on depression among cancer-survivors: A meta-analysis. Cancer. [In Review].

3. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther. 2003 Aug;83(8):713-21.

4. al-Majid S, McCarthy DO. Cancer-induced fatigue and skeletal muscle wasting: The role of exercise. Biol Res Nurs. 2001 Jan;2(3):186-97.

5. Al-Majid S, Gray DP. A biobehavioral model for the study of exercise interventions in cancer-related fatigue. Biol Res Nurs. 2009 Apr;10(4):381-91.

6. Izquierdo M, Ibanez J, Calbet JA, et al. Cytokine and hormone responses to resistance training. Eur J Appl Physiol. 2009 Nov;107(4):397-409.

7. Jager A, Sleijfer S, van der Rijt CC. The pathogenesis of cancer related fatigue: Could increased activity of pro-inflammatory cytokines be the common denominator? Eur J Cancer. 2008 Jan;44(2):175-81.

8. Galvao DA, Nosaka K, Taaffe DR, et al. Endocrine and immune responses to resistance training in prostate cancer patients. Prostate Cancer Prostatic Dis. 2008;11(2):160-5.

9. Galvao DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: A randomized controlled trial. J Clin Oncol. 2010 Jan 10;28(2):340-7.

10. Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature. 2008 Oct 16;455(7215):894-902.

11. Craft LL, Perna FM. The benefits of exercise for the clinically depressed. Prim Care Companion J Clin Psychiatry. 2004;6(3):104-11.

12. Arida RM, Naffah-Mazzacoratti Mda G, Soares J, Cavalheiro EA. Monoamine responses to acute and chronic aerobic exercise in normotensive and hypertensive subjects. Sao Paulo Med J. 1998 Jan-Feb;116(1):1618-24.

13. Raastad T, Glomsheller T, Bjoro T, Hallen J. Changes in human skeletal muscle contractility and hormone status during 2 weeks of heavy strength training. Eur J Appl Physiol. 2001 Jan-Feb;84(1-2):54-63.

14. Schmitz KH, Courneya KS, Matthews C, et al. American college of sports medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010 Jul;42(7):1409-26.

15. Thompson, WR., Gordon, NF., Pescatello LS., editor. ACSM's guidelines for exercise testing and prescription. 8th ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2010.

16. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: Updated recommendation for adults from the american college of sports medicine and the american heart association. Circulation. 2007 Aug 28;116(9):1081-93.

17. Schmitz KH, Ahmed RL, Troxel A, et al. Weight lifting in women with breast-cancer-related lymphedema. N Engl J Med. 2009 Aug 13;361(7):664-73.

18. Schmitz KH, Ahmed RL, Troxel AB, et al. Weight lifting for women at risk for breast cancer-related lymphedema: A randomized trial. JAMA. 2010 Dec 22;304(24):2699-705.

19. Irwin ML, Alvarez-Reeves M, Cadmus L, et al. Exercise improves body fat, lean mass, and bone mass in breast cancer survivors. Obesity (Silver Spring). 2009 Aug;17(8):1534-41.

20. Ballard-Barbash R, Hunsberger S, Alciati MH, et al. Physical activity, weight control, and breast cancer risk and survival: Clinical trial rationale and design considerations. J Natl Cancer Inst. 2009 May 6;101(9):630-43.

21. Jones LW, Eves ND, Peppercorn J. Pre-exercise screening and prescription guidelines for cancer patients. Lancet Oncol. 2010 Oct;11(10):914-6.

22. Ferrer RA, Huedo-Medina TB, Johnson BT, Ryan S, Pescatello LS. Exercise interventions for cancer survivors: A meta-analysis of quality of life outcomes. Ann Behav Med. 2011 Feb;41(1):32-47.

Appendix — Systematic Data Extraction Form

Exercise and Depression in Cancer Patients and Survivors

Study Selection Criteria

Studies must have an intervention intended to affect physical activity behavior in individuals who have been diagnosed with cancer (thus studies with no manipulation (or studies with a manipulation but in which researchers determined the manipulation was ineffective and separated the group for analysis based on self-selected exercise), studies with interventions intended to affect another behavior in cancer survivors, or interventions intended to affect behavior in relatives or friends of cancer survivors are excluded).

1. target adult (over age 18) cancer survivors (excluding studies that target pediatric and adolescent cancer survivors)
2. include an appropriate comparison (excluding studies with self-selected intervention/ control groups; does not exclude pre-test/ post-test design, studies that compare a pre-test control group measure to a post-test intervention group measure; non-equivalent control group designs or other designs that do not use randomization but have appropriate comparison data).
3. include non-independent data (excluding studies that are a re-analysis of data in studies already included in the analyses, and studies that use the same participants as studies already included in the analyses).
4. include appropriate quantitative dependent variables (depression, anxiety, physiological, and exercise adherence measures)
5. provide requisite statistical information to allow for calculation of effect size.

PHYSICAL ACTIVITY IN CANCER SURVIVORS META-ANALYSIS CODING FORM

24 May 2010

Note: Throughout, use "." to indicate missing information.

(V1) _____ **Coder** (Becky = 1, Blair = 2, Linda = 3, Stacey = 4, Justin = 5, Shannon = 6)

Study Information *(this page should be coded separately; complete the remainder coding pages later, once all information but methods have been removed from the folder)*

(V2) __ __ __ **Study ID #** Full APA citation:

(V3) __ __ __ __ **Publication year** (*consider this missing if unpublished)*

(V4) __ __ __ __ **Estimated year of data collection** (*earliest date for data collection or manuscript submission/publication; if unpublished and date unknown, use year manuscript was acquired; for dissertation or thesis, use year)*

(V5) _____ **Language of publication:**
1=English 3=German
2=French 4=other, specify:
_____

(V6) _____ **Source**:
1=journal 2=book 3=thesis/dissertation 4=conference paper 5=unpublished document
6=other published document; specify:
_____

(V7) _____ **Dominant theoretical perspective explicitly stated:**
1=Theory of Reasoned Action/Planned Behavior (*Fishbein, Ajzen, etc.)*
2=Social cognitive/Self-efficacy/Social learning (*Bandura, etc.*)
3=Transtheoretical Model (*"stages of change", Prochaska & DiClemente)*
4=Health Belief Model (HBM, *Rosenstock et al.)*
5=Information Motivation Behavioral Skills Model (IMB, *Fisher & Fisher)*
6=Protection-Motivation theory (*Rogers, etc.*)
7=Self-perception (or –persuasion)/Cognitive dissonance (*Aronson, Bem, Festinger cited, "hypocrisy" approaches)*
8=Social Action Theory (Ewart) 9=Social Diffusion (Rogers)
10=Conservation of Resources (Hobfall) 11=Payne Theoretical Model
12=Levine Conservation 13=Roy Adaptation Model

14= 5 A's of Exercise Adoption (ACSM) 15=Other, specify: _____

(V8) _____ **Type of clinical exercise recommendation followed/prescribed:**

1= National Comprehensive Cancer Network Recommendations (NCCN)

2= American College of Sports Medicine Exercise Rx for cancer survivors

3= American College of Sports Medicine Exercise Rx for (healthy)

4= Australian Association of Exercise and Sport Science Exercise (AAESS)

5= Other clinical recommendation; specify:_____

Sample Characteristics

(V9) **Notes on intervention within study relevant to coding (if more than one intervention in study)**

_____

(V10) _____ **Ethnicity reported?** 1 = yes; 0 = no

(V11) _____ Proportion White; if whole number available:_____
(V12) _____ Proportion Black; if whole number: _____
(V13) _____ Proportion Latino/Hispanic; if whole number: _____
(V14) _____ Proportion Caribbean; if whole number: _____
(V15) _____ Proportion Asian; if whole number: _____
(V16) _____ Proportion Mixed/other; if whole number: _____

(V17) _____ **Education reported?** 1 = yes; 0 = no

(V18) _____ Proportion high school only: _____

(V19) _____ Proportion college only: _____

(V20) _____ Proportion graduate school:_____

(V21) ___ **SES**
0 = Not given
1= Low
2 = Middle
3 = High

(V22) _____ **Region of sample**
1=American city: _____
2=other U.S. general region (*city not specified)*:
_____
3=Canada (city: _____)

4=Europe (city: _____)
5=South or Central America, Mexico, Caribbean (city: _____)
6=Africa (city: _____)
7=Asia (city: _____)
8=Australia (city: _____)

(V23) _____ **City size**
0=not given
1=rural (< 10 thousand people)
2=small (10 – 100 thousand people)
3=medium (100 thousand – 1 million people)
4=large (more than 1 million people)

(V24) ___ **Zip Code (US Only)** _____

(V25) ___ **City:** _____

(V26) _____ **Average age of sample** _____

(V27) _____ **SD for age** _____

(V28) _____ **Population**
1=school or college
2=community, not currently institutionalized; specify source (e.g., cancer clinic including University cancer treatment facilities)_____
_____
3=institutionalized; specify source (e.g., inpatient cancer treatment center; currently hospitalized):
_____
_____
0=not given

Risk Characteristics

(V29) _____ **Proportion of sample overweight**; if whole number:
_____

(V30) _____ **Average minutes of exercise at baseline:** _____

(V31) _____ **Type of cancer:**
1=breast
2=prostate
3=head and neck
4=colorectal
5=skin
6=leukemia
7=myeloma
8=lymphoma
9=gastrointestinal
10=lung
11=ovarian
12=pancreatic

13=bladder
14=endometrial
15=kidney/renal
16=appendix
17=cervical
18=testicular
19-brain
0=combination (list numbers): _____

(V32) _____ **Average Length since cancer diagnosis** (in months): _____

(V33) _____ **Proportion of participants in remission**

(V34) _____ **Treatment** (if more than one, indicate percentages)
0=none currently
1=chemotherapy
2=radiation
3=surgery
4=transplant
5=hormones
other (specify): _____

(V35) _____ **Proportion of participants under chemotherapy in the past**

(V36) _____ **Proportion of participants currently under chemotherapy**

(V37) _____ **Proportion of participants under radiation in the past**

(V38) _____ **Proportion of participants currently under chemotherapy**

(V39) _____ **Average length under treatment**

(V40) _____ **Average length under non treatment**

(V41) _____ **Proportion of the sample under drug treatment** (specify: _____)

(V42) _____ **Proportion of the sample with other diseases** (specify: _____)

(V43) _____ **Proportion of overweight sample**

(V44) _____ **Proportion of the sample under drug treatment** (specify: _____)

(V45) _____ **Proportion of smokers on the sample**

Design & Measurement

(V46) _____ **Recruitment method**
1=self-selected from community (via flyers, community centers, etc.)
2=recruited through clinical contact (cancer clinic, etc.)
3=recruited through hospital
4=other (specify): _____
0=not given

(V47) _____ **Type of control group used**
True control groups

1=random assignment of individuals to conditions
2=matching individuals on some variable (specify: _____), then random assignment
3=random assignment of some groups of individuals (e.g., classrooms)

Nonequivalent control groups (comparison group)

4=tried to ensure some comparability of the nonequivalent control group by: (*e.g., comparing on some var*):
_____
_____
5=the nonequivalence of comparison group was not addressed

(V48) _____ **Number of follow-ups:** _____
(V49) _____ **Interval of follow-ups:** _____
(V50) _____ **Scale used to measure depression:**
_____
(V51) _____ **Scale used to measure anxiety:**
_____

Control for social-desirability bias in self-report

(V52) _____ **Anonymity attempted** *(1 if unclear*)
1=no 2=yes 0=no measures self-report

(V53) _____ **Low reactivity of measure completion** *(1 if unclear*)
1=no; intervention and measurement staff were the same &/or face-to-face interviews used
2=yes; used different personnel for intervention and measurement, and measurement technique not highly reactive (written questionnaires used rather than oral responses)
0=no self report

Experimental (Intervention) Condition Details

(V54) _____ **Length of intervention in weeks:** _____
(V55) _____ **Aerobic/ Cardiovascular Activities** (in METS as defined in excel file)
(V56) _____ **Resistance/ Strength Activities** (in METS as defined in excel file)
(V57) _____ **Flexibility**
0=no
1=yes
(V58) _____ **Description of exercise based on report** (take description of exercise): _____
(V59) ____ **Structure of intervention**
1=incentive (e.g., payment based on sessions attended)
2=supervised (group exercise sessions provided)
3=unsupervised (education, etc. provided, but participants expected to exercise on own)

4=lifestyle activity

(V60) ____ **Intervention for weight loss or weight gain:**
1=loss
2=gain
3=neither

(V61) _____ **Type of intervention**
0=exercise only
1=exercise and diet
2=exercise and diet other (specify): _____
3=exercise and other (specify): _____

(V62) _____ **Level of intervention used in the study**
1=primarily one-on-one (e.g., individual counseling sessions; individuals each exposed to persuasive messages alone or in a group)
2=small group processes (interaction between leader and group, and group members)
3= small group processes (interaction among the group members, there is not leader)
4=single community (e.g., street studies with mix of media and face-to-face interventions)
5=multiple communities (e.g., mix of media and face-to-face interventions)

(V63) _____ **Number of experimental conditions for which effect sizes will each be calculate** *(if some experimental conditions in the study are omitted here, explain why they are excluded:* _____)

(V64) _____ **Number of DVs for which effect sizes will be calculated for each experimental condition**

Experimental condition _____ (*give label for condition, e.g., that used in the article)*

Intervention Details for INTERVENTION GROUP: (*use label from study):* _____

(V65) _____ **Number of sessions**
(V66) _____ **Number of minutes for each session;** if varies, report average; specify each: _____
(V67) _____ **Average size of participant group for a session**
(V68) _____ **Number of facilitators/experimenters <u>per group</u>**

(V69) _____ **<u>Training of session leaders or speakers</u>**
1=professionals—formal matriculation, licensing, or degree
2=paraprofessionals
3=peers
0=not given

(V70) _____ **Content of the intervention (NOT the measures) matched to sample**

0=no mention of elicitation research, focus groups to determine relevant issues for this population
1=mention of informal assessment of determining content through some kind of elicitation research, or pilot testing of content
2=systematic formal assessment of appropriate content—e.g., focus groups with content analyzed, or previous paper analyzing results of elicitation research
3=not reported

(V71) _____ **Number of participants who began study (in experimental group)**

(V72) _____ **Final N in experimental group (after attrition—use largest available)**

(V73) _____ **Number of participants who did not complete the study due to cancer-related mortality**

(V74) _____ **Number of participants who did not complete the study due to cancer-related illness/ complications**

(V75) _____ **Proportion of women in sample; if whole number available**: _____

CONTROL CONDITIONS: USE THE FOLLOWING SCHEME:

Codes for **control** conditions

1=wait-list/no treatment/no contact control group
2=exercise education only
3=irrelevant content (+/- education), matched for time/contact to experimental condition
4=brief form of experimental condition describe: _____
5=other kind of comparison condition; specify: _____

(V76) _____ Number of control/comparison groups in the study (*do not count any that are reasonably considered experimental conditions)*; describe each:

_____

_____

_____

(V77) _____ Number of participants n control group
(V78) _____ Final Control N (after attrition—use largest available at posttest)
(V79) _____ Number of participants who did not complete the study due to cancer-related mortality
(V80) _____ Number of participants who did not complete the study due to cancer-related illness/ complications
(V81) _.___ Proportion of women in sample; if whole number available: _____
(V82) _.___ **Proportion men in sample; if whole number: _____**

Criteria for selecting control groups for effect size calculations:
If control condition type 1 is available, use it; otherwise use group 2 to calculate effect sizes; all others should be considered as experimental conditions. If neither control type 1 or 2 is available, use the control condition corresponding to the lowest numerical value above (e.g., use 3 if available, otherwise 4, otherwise 5).

(V83) _____ Using the key above, list the code for the control group used in effect sizes

Content of Control Group (*in calculating time, do not include measurement completion time when possible)*

(V84) _____ **Number of sessions in control group**

(V85) _____ **Number of minutes for each session; if varies, report average (*estimate if necessary)*; specify each:**

_____

(V86) _____ **Average size of participant group for a session (*blank if no contact/wait list)***

(V87) _____ **Total minutes of exercise information (*estimate if necessary)***

(V88) _____ **Total minutes of non-exercise education presented (*estimated)***

---

1. **Eligibility criteria were specified**

   1 = Yes

   0 = No

2. **Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)**

   1 = Yes

   0 = No

3. **Allocation was concealed**

   1 = Yes

   0 = No

4. **The groups were similar at baseline regarding the most important prognostic indicators**

   1 = Yes

   0 = No

5. **There was blinding of all subjects**

   1 = Yes

   0 = No

6. **There was blinding of all therapists who administered the therapy**

   1 = Yes

   0 = No

7. **There was blinding of all assessors who measured at least one key outcome**

   1 = Yes

   0 = No

8. **Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups**

   1 = Yes

0 = No

9. **All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case,**
   data for at least one key outcome was analysed by "intention to treat"

   1 = Yes

   0 = No

10. **The results of between-group statistical comparisons are reported for at least one**
    key outcome

    1 = Yes

    0 = No

11. **The study provides both point measures and measures of variability for at**
    least one key outcome

    1 = Yes

    0=No