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THE DIFFERENTIAL EFFECTS OF EXERCISE ON CANCER-RELATED FATIGUE IN CANCER PATIENTS DURING AND FOLLOWING TREATMENT: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

by

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An abstract of a thesis submitted to the Faculty of the Rollins School of Public Health of Emory University in partial fulfillment of the requirements for the degree of

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ABSTRACT

The Differential Effects of Exercise on Cancer-Related Fatigue in Cancer Patients During And Following Treatment: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

by

TIMOTHY WILLIAM PUETZ

(Under the Direction of Carla J. Berg)

Exercise-induced improvements in cancer-related fatigue may be differentially moderated in patients during and following treatment. However, these effects have not been systematically reviewed. In accordance with PRISMA guidelines, the population effect size for exercise training on cancer-related fatigue during and following treatment was estimated and the extent to which the effect is differentiated across the time course of treatment and recovery was determined.

Articles published before August, 2011 were retrieved using Google Scholar, MEDLINE, PsychINFO, PubMed, and Web of Science databases. Seventy studies involving 4,881 cancer patients during or following treatment were selected. Articles included a cancer-related fatigue outcome measured at baseline and post-intervention and randomized allocation to an exercise or non-exercise comparison. Hedges' *d* effect sizes were computed, study quality was evaluated, and random effects models were used to estimate sampling error and population variance.

Exercise significantly reduced cancer-related fatigue by a mean effect size Δ (95%CI) of 0.32 (0.21, 0.43) and 0.38 (0.21, 0.54) during and following cancer treatment, respectively. During treatment, patients with lower baseline fatigue scores and higher exercise adherence rates realized the largest improvements. Following treatment, improvements were largest for trials with longer durations between completion of treatment and initiation of exercise, trials with shorter exercise program lengths, and trials using waitlist comparisons.

Exercise reduces cancer-related fatigue among patients during and following cancer treatment. These effects are differentially moderated over the time course of treatment and recovery. Exercise has a palliative effect in patients undergoing treatment and a recuperative effect following treatment.

INDEX WORDS: Cancer, Cancer-Related Fatigue, Exercise, Fatigue, Meta-Analysis, Physical Activity, Randomized Controlled Trial, Systematic Review

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DEDICATION

"Disease is war with the laws of our being, and all war, as a great general has said, is hell."
- Lewis G. Janes

To my brothers overseas, who taught me what it is to be a Soldier. It's funny when you fall out of cadence—that balanced, rhythmic flow of the march. You're lost for a moment in a stumble. When you finally catch yourself, there you are in Atlanta and your friends in Afghanistan. But we are Soldiers, we fight where we are told and we win where we fight. After all, Soldiers are nothing more than people who serve a cause greater than themselves. Though now we are fighting different battles, we will always be fighting the good fight. Rangers lead the way!

ACKNOWLEDGEMENTS

"Nine tenths of education is encouragement."
- Anatole France

What is the difference between school and life? In school, you're taught a lesson and then given a test. In life, you're given a test that teaches you a lesson. In either case, the only reason I've made it this far is because people smarter than I have been slipping me crib notes.

To my father, who has always been worth more than a hundred schoolmasters. I've had a hard life, but my hardships are nothing against the hardships that my father went through in order to get me to where I started. He taught me that no task set before us is above our strengths and no hardship is beyond our endurance. He made me believe that as long as we have faith in our cause and the unwavering tenacity to prevail, success will not be denied us. Because even on our darkest day, we just have to remember that is why we have tomorrows.

To my RSPH family, who proved to me – Men are from Mars. Women are from Venus. Computers are from hell. It is likely I will never really understand the latter two, but I do appreciate the dysfunctional family that held me together through the good and bad times of the research process. From the darkest days of final exams to the thrill of the thesis defense, they put new meaning into the expression "misery loves company." Thanks for being there to remind me we can alter our lives by altering our attitudes.

And finally to God, who has always found humor in my “plans” and has kept me humble in His revisions of my life’s aspirations. He never fails to remind me that life is not too different than research in that we spend a lot of time finding out what doesn’t work in order to find out what does. After all, isn’t it the little failures and setbacks that make the final answers worthwhile? Life is about learning. The tombstone is but a diploma.

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CHAPTER 1

INTRODUCTION

This thesis seeks to better understand the effect of exercise treatment on cancer-related fatigue (CRF) in cancer patients during and following treatment and determine whether selected variables of theoretical or practical importance moderate the effect. CRF is a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning and has been documented as a nearly universal symptom among cancer patients (Mock et al., 2000). Prevalence estimates suggest that approximately 50-90% of cancer patients undergoing cancer treatments experience fatigue (Campos, Hassan, Riechelmann, & Del Giglio, 2011). For a significant number of these patients, fatigue persists after treatment is completed (Hofman, Ryan, Figueroa-Moseley, Jean-Pierre, & Morrow, 2007).

Exercise has been proposed as an effective intervention to improve CRF in cancer patients both during and following treatment (Brown, et al., 2011; Velthuis, Agasi-Idenburg, Aufdemkampe, & Wittink, 2010). However, experimental trials examining the effects of exercise on CRF among cancer patients during and following treatment often report inconsistent results which are likely associated with weak research methodology and design (Cramp & Daniel, 2008; Schmitz, et al., 2010). A better understanding of the role of exercise in reducing CRF could contribute to enhancing quality of life as well as improving the treatment of fatigue across the time course of the disease and disease treatment.

Statement of the Problem

Pharmacological and non-pharmacological interventions have shown some efficacy for managing fatigue in patients both during and following treatment (Kangas, Bovbjerg, & Montgomery, 2008; Minton, Richardson, Sharpe, Hotopf, & Stone, 2008). Exercise has been proposed as an effective, non-pharmacologic intervention to promote psychological well-being during treatment and recovery (Duijts, Faber, Oldenburg, van Beurden, & Aaronson, 2011; Kangas, et al., 2008). The effects of exercise among patients during and following treatment have varied. There have been few large studies with adequate statistical power to guide practitioners in prescribing exercise for cancer patients over the time course of the disease. Methodological limitations including study design, poor selection of control groups, and low exercise adherence rates also have precluded meaningful interpretation of exercise effects (Cramp & Daniel, 2008; Schmitz, et al., 2010).

Previous narrative reviews have supported the efficacy of exercise on CRF symptoms (Dimeo, 2001; McNeely & Courneya, 2010; Watson & Mock 2004), but previous meta-analytic studies vary greatly in the reported magnitude of the effect. Of the three meta-analyses that have directly examined exercise effects on CRF, two have examined only patients during treatment (Velthuis et al., 2010) or only patients post-treatment (Brown et al., 2011), precluding direct examination of differential effects that may exist in patient groups during these two periods of time in disease treatment. Although the third meta-analysis allowed comparisons between patients during and following treatment, a moderator analysis was not conducted despite heterogeneity of effects (Cramp & Daniel, 2008). These issues have led not only to difficulties in

estimating the true effect of exercise interventions on CRF, but also to identifying potential differentiating effects in patients during these periods of treatment and recovery.

Subproblems

A systematic review and meta-analysis of randomized controlled trials is needed to:

(1) Quantify the magnitude and variability of the effect of exercise interventions on CRF in patients both during and following treatment.

(2) Determine the extent to which the effect is differentiated in patient groups during treatment and following treatment.

(3) Determine the extent to which the effect is moderated by selected variables of theoretical or practical importance (i.e., characteristics of study design, exercise interventions, and patient populations) in patients both during and following treatment.

Hypotheses

The following hypotheses will be addressed in the systematic review and meta-analysis of randomized, controlled trials:

(1) There will be a moderate-sized, positive effect of exercise interventions on CRF in patients both during and following treatment.

(2) The effect of exercise interventions on CRF will be differentiated in patient groups depending on whether it is implemented during or following treatment. Cancer patients participating in exercise conditions during treatment will maintain baseline-levels of CRF compared to control conditions that will have increases in CRF across the

intervention period. Cancer patients participating in exercise conditions following treatment will have reductions in CRF compared to control conditions that will maintain baseline-levels of CRF across the intervention period.

(3) The effect of exercise interventions on CRF will be heterogeneous and moderated by selected variables of theoretical or practical importance in cancer patients both during and following treatment.

Statistical Analysis

Meta-analytic procedures will be used to quantify the magnitude and variability of the effect of exercise interventions on CRF and to examine the extent to which the effect is moderated by selected variables of theoretical or practical importance including characteristics of study design, exercise interventions, and patient populations. A better understanding of the extant literature can be obtained by taking advantage of the strengths of meta-analysis. The advantages include uniform criteria for study selection, consistency in how research is summarized, quantitative precision, and avoidance of small sample bias by combining effects (Rosenthal, 1991). A macro (SPSS Inc., Chicago IL, version 19.0) will be used to calculate the aggregated mean effect size, the associated 95% confidence interval, and the sampling error variance using a random effects model (Lipsey & Wilson, 2001). The moderator variables will be entered into a weighted least squares multiple linear regression analysis to determine their independent effects ($p < 0.05$) on variation in effect size (Hedges & Olkin, 1985). Significant moderators in the regression analysis will be decomposed using a random effects model to compute effect sizes and 95% confidence intervals (Lipsey & Wilson, 2001).

Delimitations

The following delimitations will be placed on the systematic review and meta-analysis of randomized, controlled trials:

(1) This research will not attempt to examine the effects of exercise interventions on changes in CRF in terms of peripheral muscle physiology.

(2) This research will not attempt to examine the effect of a single bout of exercise on CRF.

(3) This research will not focus on health education or promotion interventions aimed at increasing physical activity in an attempt to reduce CRF.

Definitions of Terms

The following definitions of terms are presented to help provide clarity in understanding key constructs throughout the thesis:

Physical Activity. Physical activity is any bodily movement produced by skeletal muscle activation that results in energy expenditure (Caspersen, Powell, & Christenson, 1985).

Exercise. Exercise is planned, structured, repetitive bodily movements conducted for the purpose of improving or maintain one or more components of health or physical fitness (Caspersen, et al., 1985).

Acute Exercise. Acute exercise is a single, relatively short bout of exercise (Buckworth & Dishman, 2002).

Chronic Exercise. Chronic exercise is cumulative, acute bouts of exercise carried out repeatedly over time. It is often quantified in terms of frequency, intensity, duration, and mode (Buckworth & Dishman, 2002).

Fatigue. When operationalized as a multidimensional construct, fatigue is an overwhelming sustained sense of exhaustion and decreased capacity for physical and mental work (Piper, 1989).

Cancer-Related Fatigue. CRF is a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning (Mock et al., 2000).

Systematic Review. A systematic review is a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review. Statistical methods (i.e., meta-analysis) may or may not be used to analyze and summarize the results of the included studies (Moher et al., 2009).

Meta-Analysis. Meta-analysis refers to the use of statistical techniques in a systematic review to integrate the results of included studies (Moher et al., 2009).

Moderator. Moderation occurs in statistics when the direction and/or strength of the relationship between two variables are dependent on a third variable. The third variable is referred to as the moderator. The effect of a moderating variable is most often characterized statistically as an interaction (Baron & Kenny, 1986).

Moderator Analysis. Moderation analysis involves the use of linear multiple regression analysis or causal modeling to statistical quantify the effect of the interaction. In intervention studies, moderation analysis helps determine whether an intervention has a differential effect among subgroups that are defined by baseline characteristics. Thus, moderators provide useful information for treatment decisions and maximizing treatment effect (Baron & Kenny, 1986).

Abbreviations

The following abbreviations are presented to help provide clarity for these terms throughout the thesis:

ACSM is the abbreviation for the American College of Sports Medicine.

BFI is the abbreviation for the Brief Fatigue Inventory (Mendoza et al., 1999).

CRF is the abbreviation for Cancer-Related Fatigue.

EORTC QLQ-C30 is the abbreviation for the European Organization for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire (Aaronson et al., 1993).

FACT-F is the abbreviation for the Functional Assessment of Cancer Therapy Fatigue Subscale (Yellen, Cella, Webster, Blendowski, & Kaplan, 1997).

FSI is the abbreviation for the Fatigue Symptom Inventory (Hann, 1998).

ICD-10 is the abbreviation for the International Classification of Diseases, 10th Revision (World Health Organization, 2004).

LASA is the abbreviation for the Linear Analogue Self-Assessment Scale (Sutherland et al., 1988).

PFS is the abbreviation for the Piper Fatigue Scale (Piper et al., 1998).

MFI is the abbreviation for the Multidimensional Fatigue Inventory (Smets, Garssen, Bonke, & de Haes, 1995).

MOS SF-36 is the abbreviation for the Medical Outcomes Study 36-Item Short-Form Health Survey (Ware, 2000).

POMS is the abbreviation for the Profile of Moods States (POMS; McNair, Lorr, & Dropplemann, 1981),

Assumptions Regarding the Research

The following assumptions exist regarding the valid interpretation of the systematic review and meta-analysis of randomized, controlled trials:

(1) Randomized, controlled trials selected for analysis are of high enough quality in terms of research methodology and design to provide valid results for meta-analytic procedures.

(2) Valid and reliable interpretations of CRF can be drawn from self-report measures (e.g., FACT-F, MFI, PFS) and these measures are sensitive enough to detect changes associated with chronic exercise interventions.

(3) A minimum of three weeks of chronic exercise is a sufficient intervention period to show meaningful changes in CRF in cancer patients and survivors.

Overview & Organization

The remainder of this thesis will be organized into four chapters that will (1) provide a background for understanding and a rationale for examining the relationship between exercise and CRF in cancer patients during and following treatment, (2) describe the research methods for the systematic review and meta-analysis of randomized, controlled trials, (3) report the results of the systematic review and meta-analysis related to the magnitude of the effect and the extent to which the effect is moderated by selected variables of theoretical or practical importance, and (4) provide concluding comments and direction for future research as it relates to the examination of the effects of exercise on CRF in patients during and following cancer treatment.

CHAPTER 2

BACKGROUND

Early investigators of fatigue were challenged with the objective of developing an acceptable definition of fatigue and, at one point, declared "that the term fatigue be absolutely banished from precise scientific discussion" (Muscio, 1921, p. 45). The construct is further complicated when examined within the scope of CRF. Despite some reservation, fatigue has been acknowledged as a pervasive problem in cancer and cancer treatment that is well-deserving of serious scientific query in part because CRF has a significant negative impact on functionality and quality of life (Hofman, Ryan, Figueroa-Moseley, Jean-Pierre & Morrow, 2007). A better understanding of CRF ultimately could contribute to enhancing quality of life as well as improving the diagnosis and treatment of cancer patients.

Physical activity is a healthful behavior that can combat feelings of fatigue (O'Connor & Puetz, 2005; Puetz, 2006; Puetz, O'Connor, & Dishman, 2006). Randomized controlled trials of cancer patients currently undergoing and following active treatment have consistently documented these effects (Cramp & Daniel, 2008). However, surprisingly little empirical research has examined the differential effects of physical activity in cancer patients during and following treatment or the variables that may moderate the effect. Such information is important in developing proper treatment

interventions and clinicians should recognize these potential differences when prescribing exercise across the time course of the disease treatment and recovery.

This chapter provides a foundation for understanding the relationship between physical activity and CRF by (1) discussing the prevalence and social impact of CRF, (2) providing a brief history of exercise treatment and CRF, (3) outlining the conceptualization, operationalization, and measurement of physical activity and CRF, (4) exploring the time course of fatigue in cancer patients prior to, during, and following treatment, (5) examining the quality of the evidence investigating the impact of exercise interventions on CRF, and (6) discussing the proposed correlates and mechanisms of CRF. This information will provide a background for understanding and rationale for examining the relationship between exercise and CRF in cancer patients both during and following treatment.

Prevalence and Social Impact of Cancer and Cancer-Related Fatigue

The prevalence of both cancer and fatigue are of significant concern in medicine and public health. The issue becomes even more disconcerting when addressing the problem of CRF. The following section outlines the prevalence and social impact of cancer in the general population and then discusses the prevalence of CRF in cancer patients during and following treatment.

Prevalence and Social Impact of Cancer

Approximately 41 percent of men and women in the United States will be diagnosed with cancer during their lifetime. This statistic is slightly higher in men than women with one in two men and one in three women at risk for developing cancer,

respectively (Howlader et al., 2011). It is estimated that approximately 1.5 million men and women were diagnosed with and over 500,000 men and women died of cancer in 2010. The median age at diagnosis was 66 years with approximately 50 percent of all diagnoses occurring between 55 and 75 years of age. The age-adjusted incidence rate was 465 per 100,000 men and women per year. The median age at death was 73 years with approximately 55 percent of all deaths occurring between 65 and 85 years of age. The age-adjusted incidence rate was 184 per 100,000 men and women per year (Howlader et al., 2011). However, significant decrease in rates of cancer diagnosis and mortality has occurred over the last 10 years for men and women. The decrease in cancer incidence and mortality reflects progress in cancer prevention, early detection, and treatment. However, major challenges remain including increasing incidence rates and continued low survival for specific cancers such as brain and other nervous system cancers (Kohler et al., 2011).

Of the more than 1.5 million patients diagnosed with cancer every year in the United States, a typical family physician will have three or four patients each year who are given a new diagnosis of cancer (Kiernan & Frame, 1996). Having both primary care physicians and oncologists involved in both cancer treatment and follow-up produces the greatest level of medical care for cancer patients and survivors (Earle & Neville, 2004). However, less than 50 percent of cancer survivors are followed by an oncologist and primary care provider and 12 percent report no utilization of primary or secondary follow-up care. Discrepancies in the roles of primary and secondary care providers have resulted in the underuse of necessary care among cancer survivors (Grunfeld, Mant, Vessey, & Fitzpatrick, 1995; Earle & Neville, 2004).

Medicare payments for initial cancer treatment exceeded $6.7 billion in 2002 and have continued to grow over the last 10 years (Warren et al., 2008). The annual productivity cost from cancer mortality was approximately $115 billion in 2000 and is expected to exceed $147 billion by 2020. When including earnings lost due to care giving and household activity, these annual figures exceed $232 billion and $308 billion in the years 2000 and 2020, respectively (Bradley et al., 2008).

Prevalence of Cancer-Related Fatigue

CRF occurs both as a consequence of the cancer itself and as a side effect of cancer treatment. CRF is reported by approximately 40 percent of patients at diagnosis. Up to 80 percent of those treated with chemotherapy and 90 percent of patients treated with radiotherapy experience CRF (Hofman et al., 2007). CRF is the most prevalent and the most severe symptom reported by patients during treatment and is recognized as more distressing than pain, nausea, or depression. Approximately 20 percent of all cancer patients undergoing active treatment rate the intensity of fatigue as severe and over 30 percent report the frequency of fatigue as occurring every day (Curt, et al., 2000; Hickok, Morrow, Roscoe, Mustian, & Okunieff, 2005). CRF appears as a pervasive symptom across virtually all forms of cancer treatment (e.g., stem cell transplant, hormonal therapy) and cancer types with CRF affecting as high as 90 percent of patients with breast cancer and as low as 15 percent of patients with prostate cancer (Hofman et al., 2007).

For over one-third of cancer patients, CRF persists after treatment is completed (Hofman et al., 2007). Approximately 40 percent of cancer survivors have reported experiencing at least 2 weeks of fatigue in the previous month with over 33 percent of

cancer survivors reporting such experiences with fatigue despite having received their last treatment more than five years ago (Cella, Davis, Breitbart, & Curt, 2001). Over one-third of post-treatment cancer patients experience fatigue daily and 88 percent report fatigue significantly affects their ability to perform activities of daily living leading to over 75 percent of cancer survivors changing their employment status as a result of CRF (Curt et al., 2000). Only 64 percent of cancer patients return to work within 18 months of the start of cancer treatment with CRF levels at six months post-treatment predicting a patients' ability to return to work within this 18-month time period (Spelten et al., 2003). Despite the profound and pervasive effects of CRF on quality of life, approximately 50 percent of post-treatment cancer patients have not discussed treatment options with their oncologists and fewer than 30 percent of oncologists recommended any treatment for CRF (Vogelzang et al., 1997).

A Brief History of Cancer, Fatigue, and Exercise Treatment

Based on a steadily growing body of literature during the past 10 to 15 years, the relationship between exercise and CRF has emerged as a serious area of research in oncology. The ideas underlying this area of research, however, have a longer history. Early oncologists recognized symptoms of fatigue as "weakened vitality and enfeebled nerve power" in cancer patients related to both the disease and its treatments (Jones, 1911, pg. 19). These physicians focused on "build[ing] up the vitality of the patient at or near the normal health point" (pg. 50) realizing general health must be addressed before cancer can be improved through medicines and remedies that often "tear down the vitality of the patient…complicat[ing] the case and lessen[ing] chance of recovery" (Jones, 1911, p.267).

The tendency of cancer patients, especially those in the advanced stages of the disease, was to decrease physical activity. Exercise was a means to increase vitality and general health – the "very foundation of successful treatment of cancer" (Jones, 1911, pg. 68).

The early medical community recognized the preventative and palliative effects of exercise on cancer (Gibson, 1904; Hunt, 1860; Pope, 1855; Reyburn, 1906; Walshe, 1846). However, the conceptualization of fatigue as a physiological construct, as opposed to a psychological construct, remained a trend during the nineteenth century. It was not until the Italian physiologist Angelo Mosso (1846-1910) began to shift the focus of research from fatigue of the body to fatigue of the mind that the biopsychosocial conceptualization of fatigue became largely recognized in the field of medicine (Di Giulio, Daniele, & Tipton, 2005). Influenced by Mosso, clinicians began to make a sharp distinction between objective and subjective fatigue as the multi-dimensional nature of the construct became accepted in the medical community (Dearborn, 1902). These medical trends were embraced by oncologists and exercise was prescribed as a palliative treatment with which to treat both the "bodily health and mental tranquillity [sic] of the patient" (Hunt, 1860).

By the mid-1900s, many physicians – including oncologists – had adopted a holistic approach to fatigue in which both the physiological and psychological correlates of disease were considered. For example, Bartley and Chute (1947) recommended chronic fatigue research should examine the relative importance of multiple physical and psychological contributions to the feelings of fatigue. These recommendations were supported by clinical reports in which fatigue was identified as a chief complaint in most disease states such that physical and psychological disorders accounted for 20 and 80 percent of fatigue cases, respectively (Allen, 1944; Muncie, 1941). Cancer was the

primary diagnosis in approximately 10 percent of all physical disorders with a chief complaint of fatigue (Allen, 1944). Such clinical observations in chronic disease populations blurred the line between physical and psychological etiologies, suggesting that several biopsychosocial factors contributed to feelings of fatigue. As the conceptualization of feelings of fatigue continued to evolve, the clinical management of fatigue remained a continuous dose of light to moderate exercise (Allen, 1945; Wilber, 1949).

Today, fatigue remains a serious symptom that can severely impact quality of life in chronic disease populations including cancer patients during and following active treatment. Contemporary theories on exercise and CRF have changed little over the last century. Exercise is still considered an efficacious treatment for CRF during and after cancer treatment and the mechanism for the positive effects of exercise is likely an interaction among biopsychosocial variables (Dimeo, 2001; Watson & Mock, 2004; McNeely & Courneya, 2010). Unfortunately, the consistent recommendation of exercise in the clinical treatment of CRF has done little to move the research area of exercise and CRF forward. Against this historical background, serious scientific interest in the effects of exercise on CRF in the field of oncology remains in its infancy.

Conceptualization, Operationalization, and Measurement of Physical Activity and Cancer-Related Fatigue

The relationship between physical activity and CRF remains poorly understood partly because both physical activity and fatigue are difficult to define. The following section outlines the conceptualization and operationalization of physical activity and CRF and then discusses measurement issues related to this area of research.

Definition: What is Physical Activity?

The field of exercise science has distinctly conceptualized physical activity. Physical activity refers to any skeletal muscle activation resulting in energy expenditure beyond that of a resting level (Caspersen, Powell, & Christenson, 1985). This is operationalized through kilocalories (kcal) per unit of time. The term exercise is often used synonymously with physical activity; however, exercise is a subcategory of physical activity. Exercise refers to planned, structured, repetitive bodily movements conducted for the purpose of improving or maintaining one or more components of health or physical fitness (Caspersen et al., 1985). Exercise can be acute or chronic. Acute exercise refers to a single, relatively short bout of exercise. Chronic exercise refers to cumulative, acute bouts of exercise carried out repeatedly over time. Chronic exercise is often quantified in terms of frequency, intensity, duration, and mode (Buckworth & Dishman, 2002).

Definition: What is Cancer-Related Fatigue?

Unlike physical activity, an accepted and sufficiently accurate definition of fatigue remains elusive. The conceptualization of fatigue is further complicated when discussing CRF. Thus, it is important to delineate the nuances between fatigue and CRF.

Feelings of fatigue have been described as an aversive, non-specific, subjective experience that cannot currently be measured by objective methods (Ream & Richardson, 1996). Feelings of fatigue likely are multidimensional with emotional, behavioral, and cognitive components and refer to feelings of having a reduced capacity to complete mental or physical activities (O'Connor, 2004). This subjective mood state is a transient

feeling that people report experiencing ranging in duration from minutes to weeks to months that ultimately has an influence on thoughts and behaviors (Buckworth & Dishman, 2002). This reduced capacity to complete mental or physical activities is distinct from, but also often accompanies, other related moods, such as depression.

However, a number of other conceptualizations of fatigue have developed along dualistic (i.e., bidirectional) lines including acute and chronic fatigue, physiological and psychological fatigue, and central and peripheral fatigue. While dualistic approaches have proven to be popular, such definitions fail to capture the multidimensional components of fatigue (Shen, Barbera, & Shapiro, 2006). With no known biological markers and numerous proposed causes, the operationalization of fatigue through concrete indicators has failed to reflect the empirical reality of the construct.

CRF can be defined more specifically as a persistent, subjective sense of tiredness related to cancer and cancer treatment that interferes with usual functioning (Mock et al., 2000). It is characterized by feelings of tiredness, weakness, and lack of energy leading to a reduced capacity to complete activities of daily living, slowed physical recovery from tasks, and diminished concentration. CRF is distinct from the typical tiredness that most people experience as a result of normal daily life in that it is not relieved by rest or sleep, nor does it correspond to the patient's level of exertion (Hofman et al., 2007; Stasi, Abriani, Beccaglia, Terzoli, & Amadori, 2003). CRF is most often conceptualized as a subjective experience framed within a multi-dimensional context and assessed through diagnostic criteria, screening questionnaires, and self-report fatigue measures (Wagner & Cella, 2004).

Measuring Physical Activity and Cancer-Related Fatigue

Measurement is a twofold issue in research examining the relationship between physical activity and CRF. There is no single standard for measuring physical activity (Montoye, Kemper, Saris, & Washburn, 1996; Paffenbarger, Blair, Lee, & Hyde, 1993) or CRF (Stasi et al., 2003; Stone & Minton, 2008; Wagner & Cella, 2004). Thus, both the exposure and outcome variables must be assessed with imperfect measures. Establishing the validity of physical activity instruments has been a recognized, yet still unresolved, problem in exercise science research (LaPorte, Montoye, & Caspersen, 1985). However, the problem of establishing the validity of fatigue measures has only recently gained greater attention in the areas of medicine (Whitehead, 2009).

It is important to accurately measure physical activity because such measurement can help quantify the physiological responses that may directly or indirectly influence variables related to fatigue (Buckworth & Dishman, 2002). There are at least 30 methods for measuring physical activity, including direct and indirect calorimetry, physiologic markers (e.g., doubly labeled water), monitors (e.g., accelerometers), surveys (e.g., exercise recall), and direct observation. The selection of methods depends on the target population and level of sensitivity and specificity necessary to answer the research question (Casperson, 1989). Thus, it is important to address the difficulty in comparing results across studies without uniform assessment methods when discussing physical activity and exercise interventions.

Fatigue is a universal symptom not only associated with most acute and chronic illnesses, but also with normal health function and everyday life. Over 30 fatigue scales have proliferated the clinical and scientific community and no two scales have

operationalized the construct of fatigue exactly the same (Dittner, Wessely, & Brown, 2004; O'Connor, 2004). While some measure phenomenology, fatigue severity, or impact, many assess a mixture of all of these. There is no consensus about whether fatigue is best conceptualized as a symptom, a mood, an aspect of quality of life, or in some other way (O'Connor, 2004; Ream & Richardson, 1996). The choice of assessment ultimately depends on the conceptualization of fatigue, the clinical or research application, and the psychometric evidence to support interpretation of scores. Thus, fatigue research has been inundated with measures ranging widely in their ability to offer valid interpretation of the construct.

Oncologists have conceptualized CRF as both a subjective state and syndrome. As a subjective state the most appropriate way to measure CRF is psychometrically with self-report measures. There currently is a large and increasing number of self-report measures available to assess CRF in cancer patients and survivors (Minton & Stone, 2009); however, the most widely used and validated scales in this population include the Functional Assessment of Cancer Therapy Fatigue Subscale (FACT-F; Yellen, Cella, Webster, Blendowski, & Kaplan, 1997), Piper Fatigue Scale (PFS; Piper et al., 1998), Multidimensional Fatigue Inventory (MFI; Smets, Garssen, Bonke, & de Haes, 1995), Profile of Moods States (POMS; McNair, Lorr, & Dropplemann, 1981), Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36; Ware, 2000), and European Organization for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire (EORTC QLQ-C30; Aaronson et al., 1993). The choice of scale is dependent on the clinical and research application and the conceptualization of CRF as a unidimensional or multidimensional construct. A limitation of conceptualizing fatigue as a symptom in cancer

patients and survivors is that fatigue is also common in the general population; thus, interpretation of scores must consider the general prevalence of fatigue in the community.

An alternative approach is to conceptualize CRF as a syndrome and to define threshold criteria which need to be fulfilled before an individual can be considered to constitute a case of CRF. CRF syndrome has been included in the International Classification of Diseases 10th Revision (ICD-10; World Health Organization, 2004) with the goal of facilitating research and treatment planning through the availability of standardized diagnostic criteria (Cella, Peterman, Passik, Jacobson, & Breitbart, 1998). To meet the diagnosis for CRF syndrome, an individual should have experienced "significant fatigue, lack of energy, or an increased need to rest every day or nearly every day" for two weeks in the last month. In addition, cases should have experienced at least five out of nine other fatigue-related symptoms (e.g., diminished concentration) and the fatigue should have had a significant impact on functional abilities (Cella et al., 1998). These diagnostic criteria have been assessed in a number of clinical studies and have generally been found to be a reliable method to categorize patients (Cella, Davis, Breitbart, & Curt, 2001; Murphy, Alexander, & Stone, 2006; Sadler et al., 2002). A limitations of using diagnostic criteria is it is often too time-consuming and resource-intensive to be used in clinical assessment and often takes additional screening to identify patients with co-morbid psychiatric disorders.

Time Course of Cancer-Related Fatigue in Cancer Treatment and Recovery

CRF occurs both as a consequence of the cancer itself and as a side effect of cancer treatment. It is plausible that both the time course and contributing factors of fatigue may differ before, during, and after the initiation of cancer treatment. Understanding the

characteristics of CRF across the course of the disease can be helpful in the development of interventions to reduce fatigue in cancer patients during and following treatment. The following section outlines the time course of CRF before, during, and after the initiation of cancer treatment and examines potential predictors of fatigue during each stage of the disease and its treatment.

Fatigue from Diagnosis to the Initiation of Treatment

A paucity of research exists examining CRF in cancer patients prior to treatment. Most studies that have investigated CRF before the start of chemotherapy or radiotherapy treatment are confounded in that most patients are not treatment naive and have previously received treatments that could have contributed to CRF (e.g., Berger, Farr, Kuhn, Fischer, & Agrawal, 2007; Hickok et al., 2005). At least three quality of life studies have suggested that CRF may be problematic in treatment naive patients (Chimprich, 1999; Handy et al., 2002; Visser et al., 2006); however, none of these studies examined physical activity as a correlate of this effect. Research specifically aimed at examining physical activity and CRF in newly diagnosed cancer patients is lacking. This dearth of information is detrimental in the ability of clinicians to effectively prescribe exercise interventions as a means of mitigating CRF early in the disease process.

At least one study directly examined the prevalence and factors contributing to CRF in treatment naive cancer patients before the initiation of treatment (Goedendorp, Gielissen, Verhagen, Peters, & Bleijenberg, 2008). The investigators assessed 179 patients with various malignances before the start of treatment using the Checklist Individual Strength (CIS; Vercoulen et al., 1994, 1999) fatigue subscale and a single item

numeric rating scale ranging from zero "not physically active" to 10 "physically very active" for CRF and physical activity, respectively. Approximately 25 percent of the patients experienced severe fatigue before initiation of treatment with rates ranging as high as 28 percent for gastrointestinal cancer and as low as 14 percent for prostate cancer. Low levels of physical activity were significantly related to CRF prior to the initiation of cancer treatment. Despite the positive finding, results should be interpreted with caution because of the questionable validity of the physical activity and CRF measures.

Fatigue During Cancer Treatment

Fatigue is recognized as perhaps the most distressing symptom of cancer patients during active treatment (Hofman et al., 2007; Vogelzang et al., 1997). However, the time course of CRF during treatment and the possibility of CRF differences based on treatment modality still remain equivocal (Prue, Rankin, Allen, Gracey, & Cramp, 2006). This limitation is associated with the retrospective nature of most of the corpus of literature in this area. The few longitudinal studies that have examined the course of CRF in cancer patients receiving chemotherapy, radiation therapy, or a combination of both have found that CRF increases significantly over the course of the treatment (Greenburg, Sawicka, Eisenthal, & Ross, 1992; Greene, Nail, Fieler, Dudgeon, & Jones, 1994; Visser, Smets, Sprangers, & de Haes, 2000). This increase often plateaus around four weeks for radiotherapy (Greenburg et al., 1992); whereas, chemotherapy fatigue patterns tend to be greatest at the beginning of the cycle and decrease in the days following treatment (Greene et al., 1994). Combination therapies are more complicated in that a "response shift" during initial treatment may influence perceptions of fatigue during the second

treatment (Schwartz & Sprangers, 1999). Adaptations to increases in CRF have been recorded in cancer patients undergoing radiotherapy through retrospective self-reports in which the patients consistently rated CRF scores lower than those actually collected at baseline (Visser et al., 2000). It is unknown to what extent exercise interventions affect the time course of CRF during each of these cancer treatment modalities.

One study attempted to directly compare the characteristics and time course of CRF related to chemotherapy and radiotherapy during the active treatment period (Donovan et al., 2004). The investigators assessed 134 women with breast cancer receiving combination therapy (i.e., chemotherapy and radiotherapy) or radiotherapy alone using the Fatigue Symptom Inventory (FSI; Hann, 1998). Comparisons of CRF during initial treatment indicated that women who received chemotherapy reported greater fatigue severity than women receiving radiotherapy. Women not pre-treated with chemotherapy experienced increased fatigue over the course of radiotherapy suggesting a response shift in the perception of CRF for those women who received prior chemotherapy as part of their combination treatment. These results suggest that CRF differs as a function of the type and sequencing of treatment. Clinicians should recognize the differences in the time course of CRF related to specific treatment modalities. Future research should examine how exercise can be used as a palliative treatment for CRF during different types and sequencing of active cancer treatment.

Fatigue Following Cancer Treatment

For a significant number of cancer patients CRF remains after treatment is complete lasting months and sometimes years (Hofman et al., 2007). Cross-sectional studies support

that persistent fatigue is prevalent following cancer treatment, but few longitudinal studies have examined the incidence of CRF beyond the year after completion of treatment (Prue et al., 2006). A few studies have investigated CRF over longer periods of time in cancer patients post-treatment (i.e., two to 10 years), but none of these studies allowed for the examination of the extended time course of CRF following cancer treatment (e.g., Bower et al. 2006; Hjermstad, Fossa, Oldervall, Jacobsen, & Loge, 2005). Thus, there is limited research concerning both the time course of CRF in cancer patients beyond 12 months post-treatment and whether physical activity level may be probable predictors of persistent fatigue.

One longitudinal study attempted to examine the time course of CRF in post-treatment cancer patients over a two-year period and identify predictors of CRF during this time frame (Servaes, Gielissen, Verhagen, & Bleijenberg, 2007). One hundred and fifty disease-free breast cancer patients who were on average 29 months post-cancer treatment completed monthly fatigue questionnaires over a two-year period. A total of 121 of the 150 post-treatment cancer patients completed the study (i.e., 81 percent) with 101 of those individuals returning more than 20 of the monthly questionnaires (i.e., 83 percent). Approximately 25 percent of the survivors experienced persistent severe fatigue during the two-year observation period. This was a decrease with respect to the baseline assessment at which 38 percent of the survivors experienced severe fatigue. This suggests that CRF appears to decrease during the first three to four years following treatment, but remains in approximately one-quarter of cancer survivors. Higher CRF scores were significantly predicted by higher baseline fatigue and lower baseline physical functioning scores indirectly suggesting exercise interventions may be an effective

intervention in managing fatigue in this population. Future studies should utilize longitudinal designs to examine the impact of exercise intervention on CRF in cancer patients more than one-year post-active treatment.

Research on Exercise and Cancer-Related Fatigue

The body of research on exercise and CRF is not as extensive as that addressing the relationship between exercise and other related variables such as physical functioning and quality of life in cancer patients during and following treatment. Although there are some limitations in the research related to study design and instrumentation, the overall evidence for the effects of exercise on CRF generally is both positive and consistent (Cramp & Daniels, 2008; Watson & Mock, 2004). Epidemiological and experimental research that has addressed the relationship between exercise and CRF is described in the following sections.

Epidemiological Evidence

Population based studies show that physical inactivity is consistently associated with fatigue (Puetz, 2006). However, few epidemiological studies have directly examined the association between physical activity and CRF in cancer patients during and following treatment. A systematic narrative review examining the prevalence and patterns of CRF attempted to identify factors associated with fatigue during the time course of treatment and recovery (Prue et al., 2006). Fifteen of the epidemiological studies identified in the review concurrently measured physical activity or physical functioning and CRF. Five of the studies examined the relationship in cancer patients

during treatment (Berger & Farr, 1999; Berger & Higginbotham, 2000; Jacobsen et al., 1999; Roscoe et al., 2002; Stone, Richards, A'Hern, & Hardy, 2001), while the remaining 10 examined the relationship in cancer patients following treatment (Barstch, Weis, & Moser, 2003; Bower, Ganz, Aziz, & Fahey, 2002; Brown, McMillan, & Milroy, 2005; Dimeo et al., 2004; Hann, Jacobsen, Martin, Azzarello, & Greenberg, 1998; Okuyama et al., 2001; Servaes, van der Werf, Prins, Verhagen, & Bleigenberg, 2001; Servaes, Verhagen, & Bleigenberg, 2002a; Smets, et al., 1998; So, Dodgson, & Tai, 2003). All of the investigations of cancer patients both during and following treatment concluded that physical inactivity and poor physical functioning were related to increased CRF. However, these studies are limited by weaknesses in measurement and research design. Therefore interpretation of these population-based studies should take into consideration both measurement and research design limitations.

Although Prue et al. (2006) used rigorous methodology in selecting only well-validated multidimensional fatigue scales (e.g., FACT-F, PFS), the conceptualization of physical functioning as an equivalent to physical activity makes the interpretation of the results and final conclusions at very least suspect. Twelve of the 15 studies used physical functioning measures (Barstch et al., 2003; Bower et al., 2002, Brown, et al., 2005; Dimeo et al., 2004; Hann et al., 1998; Jacobsen et al., 1999; Okuyama et al., 2001; Servaes et al., 2001; Servaes et al., 2002a; Smets et al., 1998; So et al., 2003; Stone et al., 2001) while only three used actual physical activity measures (Berger & Farr, 1999; Berger & Higginbotham, 2000; Roscoe et al., 2002). This epidemiological evidence associated with physical functioning is difficult to interpret because the multidimensional characteristics of most physical functioning measures incorporate both fatigue and

physical activity items thus confounding the relationship by using fatigue as both a dependent and independent variable. Because these physical functioning measures do not have adequate convergent validity to support their interpretation of scores as measures of physical activity, it becomes difficult to conclude whether physical inactivity is, or is not, truly related to CRF. Thus, further empirical research is needed using well-validated measures of physical activity and CRF in population-based studies.

Inevitably there are limitations related to temporal sequence when discussing cross-sectional and prospective cohort designs, thus restricting what the study design can and cannot explain (Grimes & Schulz, 2002). Ten of the 15 studies presented in the Prue et al. (2006) review used cross-sectional design (Barstch et al., 2003; Bower et al., 2002; Brown et al., 2005; Dimeo et al., 2004; Hann et al., 1998; Okuyama et al., 2001; Servaes et al., 2000; Servaes et al., 2002a; Smets et al., 1998; So et al., 2003), while the remaining five studies used a prospective cohort design (Berger & Farr, 1999; Berger & Higginbotham, 2000; Jacobsen et al., 1999; Roscoe et al., 2000; Stone et al., 2001). Of the 10 cross-sectional studies, three used healthy population matched-controls (Brown et al., 2005; Hann et al., 1998; Smets et al., 1998). Because of the inherent weakness of cross sectional design to account for temporal changes, the effects associated with cross-sectional studies may be inflated compared to prospective cohort design. Despite the advantages of prospective cohort designs over cross-sectional studies, selection and confounding biases still exist with the prospective cohort design. These methodological limitations associated with the current state of evidence will remain until randomized, controlled trials are introduced into the literature.

Experimental Evidence

While experimental designs are often considered to be the most rigorous of all research designs, this is only the case if such a design is implemented well. Unfortunately, poor measurement and study design have limited experimental research in the area of exercise and CRF. This is often the due to knowledge gaps as oncologists with limited background in exercise science, or exercise scientists with limited background in oncology, attempt to conduct exercise and fatigue research in cancer patients and survivors (Buckworth & Dishman, 2002). Such issues regarding research design can be identified and addressed in quantitative reviews (i.e., meta-analyses) of randomized controlled trials.

Of three meta-analyses that have directly examined exercise effects on CRF, two have examined cancer patients only during treatment (Velthuis, Agasi-Idenburg, Aufdekampe, & Wittink, 2010) or only following treatment (Brown et al., 2011), precluding direct examination of differences between these groups over the time course of the disease and disease treatment. However, the third quantitative review allowed for comparisons between patients during and following treatment by examining both groups concurrently in the analysis (Cramp & Daniel, 2008). This meta-analysis provides the most compelling evidence for the differential effects of exercise on CRF in cancer patients and survivors.

Cramp and Daniel (2008) conducted a meta-analysis of 28 studies to examine the difference in the magnitude of effect in CRF following exercise treatment in cancer patients and survivors. There was a significant effect (ES, 95% CI) such that cancer patients following treatment (ES = -0.37; -0.55, -0.18) had a larger reduction in fatigue

than cancer patients during treatment (ES = -0.18; -0.32, -0.05). The survivor effects were similar to those of Brown et al. (2011), ES = 0.31, but those for cancer patients were significantly smaller than Velthuis et al. (2010), ES = 0.30. The primary limitation of the Cramp and Daniel (2008) meta-analysis was that a moderator analysis was not conducted. This limited the understanding of how characteristics of study design, exercise interventions, and patient populations may influence exercise efficacy in cancer during cancer treatment and recovery.

Cramp and Daniel (2008) did address several limitations of the included studies despite not providing quantitative evidence regarding the potential moderating effects of such limiting variables. The major limitations included (1) failing to target a more diverse sample of patients with regard to type of cancer diagnosis, (2) using both unidimensional and multidimensional CRF measures thus precluding direct comparisons between studies, (3) conducting studies with small sample sizes, poorly designed control conditions, and a lack of standardization of interventions to facilitate replication and increase internal validity, (4) using exercise interventions that did not meet the American College of Sports Medicine (ACSM) recommendations for physical activity, and (5) not controlling for or reporting issues of adherence and contamination in which control participants undertake exercise or the exercise group does not adhere to the program. These limitations should be addressed in future randomized controlled trials through more rigorous experimental research designs and in future quantitative reviews through a priori moderator analyses.

Cramp and Daniel (2008) provided some insight into differences in the magnitude of the effect between cancer patients during and following treatment, but the external

validity of the results were limited due to the heterogeneity of the effects and a lack of a moderator analysis. This weakness across meta-analytic reviews has made it difficult to interpret the effect of exercise on CRF across the time course of the disease. To date, only one randomized controlled trial has examined the effects of exercise on CRF across cancer pre-treatment, treatment, and recovery.

Evidence to support the positive effects of exercise on CRF across the time course of cancer treatment and recovery were presented in a randomized controlled trial examining the effect of a self-administered exercise intervention before, during, and after allogeneic hematopoietic stem cell transplantation (Wiskermann et al., 2011). One hundred and five cancer patients were randomly assigned to a partly self-administered exercise or social contact control condition. The exercise intervention consisted of three 20-40 minute light aerobic sessions and two full-body resistance training (i.e., 8-20 repetitions, 2-3 sets) sessions per week. Participants in the exercise group started exercising on an outpatient basis one to four weeks before hospital admission, continued during the inpatient period, and sustained the program until six to eight weeks after discharge from the hospital. The outpatient exercise period was self-directed at home; whereas, the inpatient exercise period was supervised twice weekly. The control group wore pedometers during the outpatient period to measure physical activity and received the same frequency of social contact as the exercise intervention during the inpatient period. Over the entire time course of cancer treatment and recovery from the initial medical checkup to the six- to eight-week follow-up, the exercise condition showed a 15 percent improvement in fatigue scores. The contact control condition showed a 28 percent deterioration in fatigue during the same time period.

This study effectively used research design to address the issue of differential effects of exercise across the time course of cancer treatment and recovery. Several important results from this study to support this were: (1) fatigue was reduced in the one- to four-week period following the medical check-up and prior to hospital admission for the exercise condition compared to the control condition, (2) fatigue was significantly mitigated at discharge from the hospital following cancer treatment in the exercise group compared to the control group in which fatigue actually increased, (3) fatigue was significantly reduced at the six- to eight-week follow-up in the exercise group compared to the control group to the extent that the exercise condition had scores significantly lower than baseline. These results support the conclusion that exercise has a palliative effect in patients undergoing cancer treatment and a recuperative effect in patients following treatment and clinicians should consider prescribing exercise at cancer diagnosis.

Proposed Correlates and Mechanisms of Cancer-Related Fatigue

Attempts to understand mechanisms of feelings of fatigue date to the early 20th century (Berrios, 1990). Researchers from this era concluded that, "Fatigue, which can be considered as a sort of poisoning, can alter the composition of the blood and biological homeostasis; however, we just feel it as a vague sensation of tiredness" (Mosso, 1903). The subjectivity and vagueness of feelings of fatigue still plague current attempts to uncover plausible mechanisms of CRF in cancer patients during and following active treatment. This section will attempt to provide an overview of the factors that are consistent correlates of CRF to include (1) direct effects of cancer, (2) treatment side-

effects, (3) comorbid medical conditions, (4) exacerbating comorbid symptoms, and (5) psychosocial factors. It will also summarize the neurobiological factors that have been proposed as possible mechanisms for fatigue.

Direct Effects of Cancer and Tumor Burden

Fatigue is recognized as the most common and distressing side effect of cancer treatment (Hofman et al., 2007). However, it is important to recognize that CRF may also occur as a consequence of the cancer itself. Fatigue is one of the first symptoms that cause individuals to seek medical care (Wang, 2008). Approximately 25 percent of cancer patients report significant fatigue prior to active treatment suggesting that fatigue may be related to changes occurring in the body in response to the malignancy itself (Goedendorp et al., 2008). Although disease and tumor-related variables show some correlation to CRF prior to and during treatment, no relationship has been found between variables related to the tumor and fatigue following treatment (Prue et al., 2006).

The direct effect of cancer and tumor burden on cancer-related fatigue is poorly understood. However, the physical impact exerted by the location of the tumor and host defense mechanisms are likely candidates related to symptoms of CRF prior to active treatment. The physical impact of tumor location on CRF can be illustrated through cancers affecting endocrine organs that control serotonin regulation resulting in depression, sleep disturbances, and reduced central nervous system afferent activity (Ryan et al., 2007; Wang, 2008). Host defense mechanisms related to the malignancy process can also affect symptoms of CRF through the neuromuscular changes associated with abnormal production of certain substrates (e.g., inflammatory cyctokines; Wang, 2008). In response

to malignant cancer, host immune systems issue an inflammatory response to the tumor. As a result increased levels of circulating cytokines (e.g., interleukins and tumor necrosis factor) are present that may inhibit energy metabolism or normal muscle function leading to increased CRF symptoms (Schubert et al., 2007; Wang, 2008).

Treatment Side-Effects

Although CRF is present prior to active treatment, CRF is dramatically increased following the initiation of cancer-related treatments (Servaes, Verhagen, & Bleijenberg, 2002b). Fatigue has been reported as a side effect of virtually all forms of cancer treatment including surgery, chemotherapy, radiotherapy, and biological response modification (Hofman et al., 2007; Servaes et al., 2002b; Wang, 2008). The literature consistently reports no relationship between CRF and treatment-related variables in patients either during or following cancer treatment (Prue et al., 2006). Differences in CRF have been indiscriminate of the type of surgery, type of therapy (i.e., chemo, radio, or hormone), or treatment characteristics such as dose or fractionation for radiotherapy or dose and regime for chemotherapy (Prue et al., 2006; Servaes et al., 2002b).

Immunologic and hematological alterations during active treatment have been identified as proposed mechanisms of CRF pathophysiology; however, the etiology of such treatment side-effects remains poorly understood. The relationship between physiological variables (e.g., hemoglobin, cytokines) and CRF remains equivocal in patients during treatment and appears to have no association in patients following treatment. However, psychological variables (e.g., anxiety, depression) appear to be highly correlated to CRF in patients both during and following treatment (Prue et al., 2006). This suggests that

psychosomatic mechanisms related to the physical response to treatment should be considered in CRF (Rubin, Cleare, & Hotopf, 2004; Wang, 2008).

Comorbid Medical Conditions

Comorbid medical conditions such as infection, malnutrition, and organ dysfunction could either cause or contribute to CRF (Wagner & Cella, 2004; Wang, 2008). Many of these comorbid medical conditions compound the physical and psychological symptoms associated with CRF leading to long-lasting effects on quality of life (Ryan et al., 2007). Two of the most common conditions include anemia and cachexia.

Anemia may occur as a result of either neoplastic disease or cancer treatment and is identified by the National Comprehensive Cancer Network (NCCN) as one of the treatable factors that may contribute to CRF (Mock et al., 2000). The cause of anemia associated with cancer is multifactorial and may be related to bleeding, hemolysis, bone marrow infiltration or nutritional deficiencies. The mechanism by which anemia might cause fatigue is unknown; however, hypoxia-related impairment of organ function has been suggested. This reduction in oxygen delivery to tissues can lead to a negative energy balance and presumably further lead to the symptoms of fatigue (Gutstein, 2001; Ryan et al., 2007).

Cachexia is a wasting disease affecting 50-85 percent of all cancer patients. It involves the loss of both adipose tissue and skeletal muscle mass leading to anorexia, weight loss, fatigue, and impaired function (Tisdale, 1997, 1999). The etiology of cancer cachexia is complex, but the metabolic and physiologic perturbations related to the progressive atrophy of muscle and tissue are likely moderated by inflammatory cytokines

(Tisdale, 2009). These processes lead to a negative energy balance which in turn affects symptoms of fatigue. It currently is not understood how a decreased energy supply could lead to the perception of fatigue (Gutstein, 2001).

Exacerbating Comorbid Symptoms

CRF often occurs as part of a cluster of symptoms to include pain, sleep disturbances, and deconditioning. The interaction of fatigue with these symptoms often leads to long-term reductions in quality of life (Ryan et al., 2007). Despite a paucity of research examining the relationship between pain and fatigue in cancer patients, the available studies have shown CRF was significantly associated with pain ratings in patients both during and following cancer treatment (Prue, et al. 2006; Servaes et al., 2002b). The relationship between sleep quality and CRF also is unambiguous in the literature. Sleep disturbances are consistently and strongly associated with higher levels of CRF in patients both during and following treatment. In fact, change in sleep patterns is among the most frequently mentioned symptoms to which patients attributed their fatigue (Prue et al., 2006; Servaes et al., 2002b). There is a strong relationship between CRF and deconditioning in patients both during and following treatment such that fatigue was found to be associated with less daytime physical activity (Prue et al., 2006; Searvaes et al., 2002b).

Interpreting the independent effects of comorbid symptoms on CRF is a difficult, but important, task if efficient and effective interventions are to be developed for patients both during and following cancer treatment. For example, one study found parameter estimates in patients newly diagnosed with cancer indicated that three-way interactions of pain, fatigue, and insomnia were statistically significant (Hoffman, Given, von Eye, Gift, &

Given, 2007). In addition, a study examining the effect of pain alleviation—via immediate and slow-release morphine—on the subjective symptom of fatigue in cancer patients found that pain was reduced, but the CRF remained unchanged suggesting that there may not be a direct association between the two constructs among cancer patients (Klepstad, Borchgrevink, & Kaasa, 2000). Such findings support the conclusion that the relationship between pain, sleep, and CRF is a complex and poorly understood phenomenon.

Psychosocial Factors

Emotional vulnerability and the endurance of heavy stress related to cancer or cancer treatment over prolonged periods of time may contribute to CRF. In fact, evidence suggests that 40% to 60% of the cases of fatigue in the general medical population are associated with psychiatric disorders (i.e., anxiety and depression) as opposed to organic causes (Reich, 1986). Therefore, the relationship between psychosocial factors like anxiety, depression, and coping behavior are important to address in relation to CRF. The majority of research has found a strong association between the presence of anxiety, depression, and CRF in cancer patients both during and following treatment (Prue et al., 2006; Servaes et al., 2002b). However, a handful of studies have identified an uncoupling of this relationship. For example, a correlation was reported between depression and CRF with a breast cancer group demonstrating significantly higher levels of fatigue than a matched group of participants with a benign breast problem; however, the two groups did not differ with respect to the amount of depression reported (Andrykowski, Curran, & Lightner, 1998). This suggests CRF likely has organic-related causes in addition to, but separate from, the psychosocial mechanisms related to anxiety and depression. Although

there is a limited research examining the relationship between coping and CRF, studies have shown that poor social support and environment are significantly related to CRF in patients during treatment; while, negative coping strategies such as catastrophizing events was significantly related to CRF in patients following cancer treatment (Prue, et al, 2006; Sevaes, et al, 2002b).

Bioneurological Mechanisms of Cancer-Related Fatigue

The brain has long been suspected as the primary driver of feelings of fatigue. It is now generally accepted that the brain controls mental, physiological, and behavioral processes. Brain functioning is controlled by genes, but social, developmental, and environmental factors can alter gene expression. These alterations in gene expression can induce changes in brain functioning and behavior (Dishman et al., 2006). Unclear is whether the origin of fatigue is in a particular brain structure, is the result of an integrative process involving a number of different brain regions, or is the result of electrophysiological synchronization of entire brain activity (St Clair Gibson et al., 2003). However, metabolic and neurochemical pathways within the central nervous system offer testable mechanisms that might help explain the effects of physical activity on feelings of fatigue.

The specific brain mechanisms that generate the sensation of fatigue are unknown, but monoamines, histamine, acetylcholine, glutamate and gamma-aminobutyric acid (GABA) mediated neurotransmission have been implicated (Demyttenaere, De Fruyt, & Stahl, 2005; Stahl, 2002; Stahl, Zhang, Damatarca, & Grady, 2003). There is evidence that physical activity can alter these neurotransmitters and neuromodulators (Dishman et al.,

2006). Understanding the neurotransmitters and neuromodulators involved in generating feelings of fatigue is important, but perhaps more important is examining how these chemical messengers regulate potentially malfunctioning neurological circuits or brain areas associated with mental and physical fatigue. For example, brain cortical areas (e.g., dorsolateral prefrontal cortex) and central nervous system components regulating motor functioning (e.g., striatum, cerebellum, spinal cord) could be reasonable candidates in mediating moods of mental and physical fatigue, respectively (Demyttenaere et al., 2005; Stahl et al., 2003).

Unfortunately, there has been very little use of the traditions and methods of biology, psychology, and neuroscience in the study of physical activity and CRF. Future research needs to incorporate the basics of neuroanatomy, neurophysiology, and psychopharmacology along with techniques of neuroscience to facilitate sound research on physical activity and CRF. The best strategy to employ in this course of research development is effective trans-disciplinary collaboration.

Conclusions

Exercise is a treatment that has promise for combating CRF in patients during and following treatment (Cramp & Daniel, 2008). Prevalence estimates suggest up to 90 percent of cancer patients undergoing cancer treatments experience fatigue (Campos et al., 2011). Approximately one-third of these patients' fatigue persists after treatment is completed (Hofman et al., 2007). Historically clinicians have recognized the physiological and psychological aspects of CRF and have consistently recommended exercise as a treatment. The subjective, multidimensional nature of CRF has made conceptualizing,

operationalizing, and measuring the construct difficult. This in conjunction with the imperfect measurement of physical activity has created some limitations in the area of exercise and CRF research. Despite such limitations, epidemiological evidence suggests that cancer patients both during and following treatment have an increased risk of CRF with physical inactivity and poor physical functioning (Prue et al., 2006). This population-based research has been substantiated with experimental evidence that shows exercise does reduce CRF across patients both during and following treatment (Brown et al., 2011; Cramp & Daniel, 2008; Velthuis et al., 2010). However, the quality of methodological rigor must continue to improve and evolve in a manner that incorporates biological, psychological, and psychosocial factors into CRF research. Future investigation can best meet these standards by incorporating interdisciplinary research into uncovering the biological mechanisms that contribute to improved feelings of fatigue across the time course of the disease and disease treatment.

CHAPTER 3

METHODS

The review protocol and extraction forms were designed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Moher, et al., 2009).

Data Sources and Searches

Electronic searches of publications published from January 1945 to August 2011 were located with searches of Google Scholar, MEDLINE, PsycInfo, PubMed, and Web of Science databases using the key words cancer, exercise, fatigue, physical activity, and randomized controlled trial. Supplemental searches of reference lists from retrieved articles were performed manually. The language of publication was not restricted.

Study Selection

Inclusion criteria were: (1) prospective, randomized, controlled trial design, (2) cancer patients currently undergoing treatment (e.g., chemotherapy, radiation therapy, hormone therapy) or cancer patients post-treatment, (3) randomized allocation to either an exercise intervention of at least three weeks or a comparison that lacked exercise, and (4) a CRF outcome measure assessed before and during and/or after exercise training (Table 3.1; Minton & Stone, 2009).

Table 3.1. Primary Dependent Measure of Fatigue Assessed in Studies

Studies of Patients During Cancer Treatment	
Name of Measure (Reference)	***Number of Studies***
Functional Assessment of Cancer Therapy: Fatigue scale (Yellen et al., 1997)	13
Piper Fatigue Scale (Piper et al., 1998)	9
Profile of Mood States: Fatigue subscale (McNair et al., 1992)	5
Brief Fatigue Inventory (Mendoza et al., 1999)	4
Medical Outcomes Survey Short Form-36: Vitality (Ware et al., 1992)	3
European Organization for Research & Treatment of Cancer Quality of Life Questionnaire-Core 30: Fatigue subscale (Aaronson et al., 1993)	2
Multidimensional Fatigue Inventory (Smets, et al., 1995)	2
Linear Analogue Self-Assessment Scale: Fatigue (Sutherland et al., 1988)	2
Fatigue Severity Scale (Krupp et al., 1989)	1
Pediatric Quality of Life Inventory: Multidimensional Fatigue Scale (Varni et al., 2002)	1
Schwartz Cancer Fatigue Scale (Schwartz, 1998)	1

Studies of Patients Following Cancer Treatment	
Name of Measure (Reference)	***Number of Studies***
Functional Assessment of Cancer Therapy: Fatigue scale (Yellen et al., 1997)	9
Piper Fatigue Scale (Piper et al., 1998)	3
Medical Outcomes Survey Short Form-36: Vitality (Ware et al., 1992)	3
European Organization for Research & Treatment of Cancer Quality of Life Questionnaire-Core 30: Fatigue subscale (Aaronson et al., 1993)	3
Profile of Mood States: Fatigue subscale (McNair et al., 1992)	2
Multidimensional Fatigue Inventory (Smets, et al., 1995)	2
Brief Fatigue Inventory (Mendoza et al., 1999)	1
Fatigue Impact Scale (Fisk et al., 1994)	1
Linear Analogue Self-Assessment Scale: Fatigue (Sutherland et al., 1988)	1
Author-developed categorical scale: Tiredness (Berglund et al., 1993)	1
Author-developed categorical scale: Fatigue (Carson et al., 2009)	1

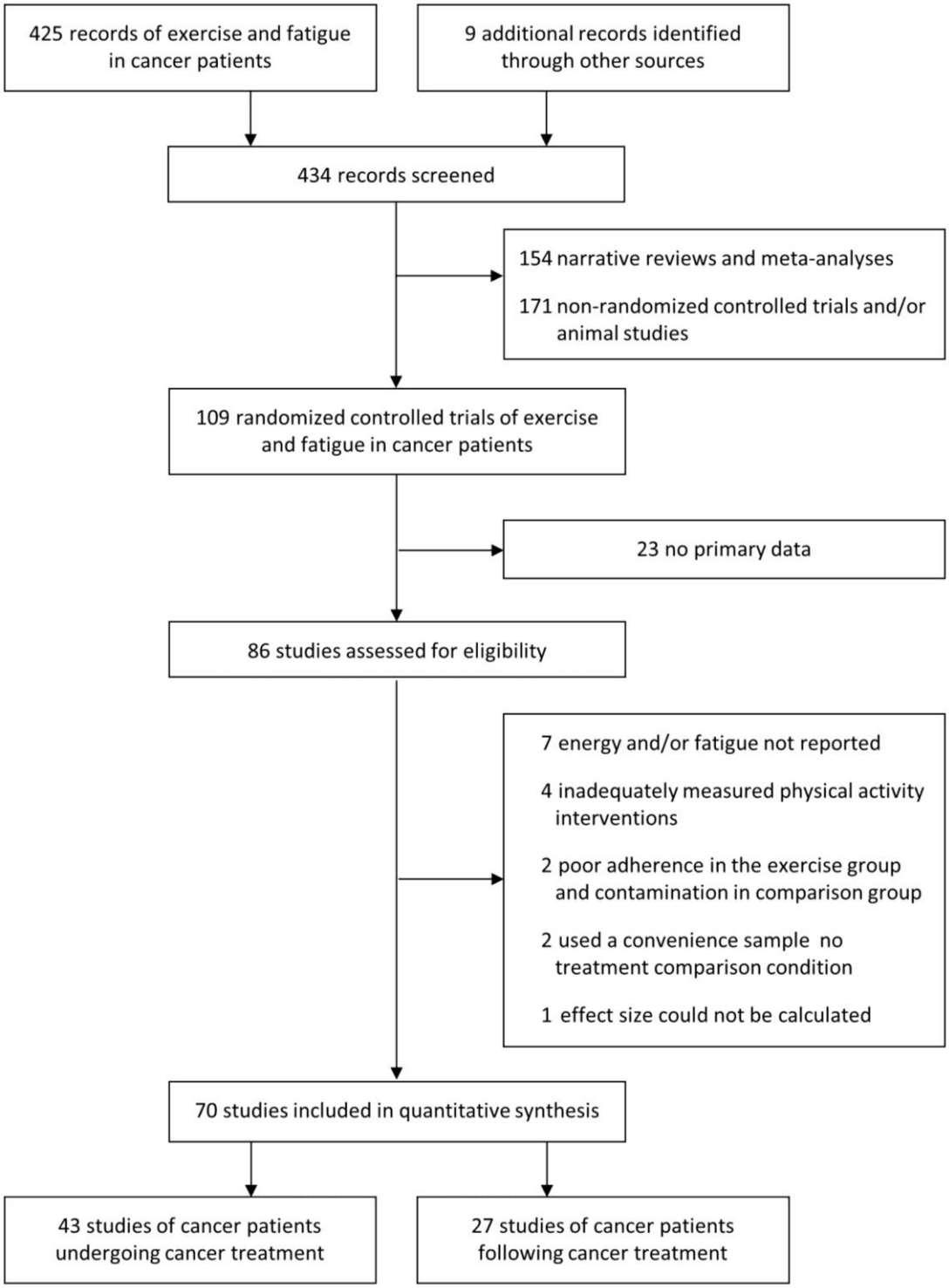
Exclusion criteria were: (1) compared exercise only with an active therapy (e.g., pharmacotherapy, another mode of exercise), (2) examined the effect of a single bout of exercise on CRF, and (c) focused on education or promotion interventions aimed at increasing physical activity but failed to show that physical activity levels were increased. A flowchart of study selection is presented in Figure 3.1.

Data Extraction and Quality Assessment

Data were independently extracted by the authors and discrepancies were resolved by consensus judgment. Authors of potentially eligible studies were contacted when necessary to resolve ambiguities in reported methods or results or for additional information.

Effect sizes were calculated by subtracting the mean change in the comparison condition from the mean change in the experimental condition and dividing the difference by the pooled standard deviation of pre-intervention scores (Hedges & Olkin, 1985). Effects sizes were adjusted using Hedges' small sample size bias correction and calculated so that decreases in CRF resulted in positive effect sizes (Hedges & Olkin, 1985). Multiple effects within a trial were averaged such that each trial contributed only one effect to analysis (Gleser & Olkin, 1994). When precise mean data were not reported, effect sizes were estimated (Rosenthal, 1991) from t tests (Headley, Ownby & John, 2004), exact p-values (McKenzie & Kalda, 2003; Carson, Carson, Porter, Keefe, & Seewaldt, 2009), or figures (Windsor, Nicol, & Potter, 2004; Brown et al., 2006; Hwang et al., 2008). For studies in which precise standard deviations were not reported (Crowley, 2003; MacVicar & Winningham, 1987; Mock et al., 1994; Mock et al., 1997), the standard deviation was drawn from published norms or the largest other study using the same measure.

Figure 3.1. Flowchart of Study Selection



Study Quality Assessment

The methodological quality of each study was assessed using a 15-item scale (one point per item for a maximum of 15; Detsky et al., 1992). The scale addressed randomization, sample selection, quality of outcome measures, and statistical analysis. Quality assessment scoring was performed independently by the authors and showed high concordance between the two raters (ICC [3,2] = 0.96, 95% CI = 0.89 to 0.98; Shrout & Fleiss, 1979). Using the Bland and Altman limits-of-agreement procedure, the average disagreement (mean, 95% CI) was close to zero (0.40, 0.10 to 0.70), suggesting no evidence for a systematic disagreement bias between the two reviewers (Altman & Bland, 1983; Bland & Altman, 1986). Quality scores were reported for each study for descriptive purposes, but were not used as weights or moderators in the analysis because of the potential disparity in results that depends on the specific quality scale employed (Juni, Witschi, Bloch, & Egger, 1999).

Data Synthesis and Analysis

Statistical analyses were initially performed based on an overall model examining both patients during treatment and patients post-treatment. Because analyses revealed differential effects among patients during and following treatment, separate regression models for patients during and patients post-treatment were developed and tested to better understand the effect of exercise on CRF over the time course of treatment and to identify variables that moderate the effect.

An SPSS macro (i.e., *MeanES*; SPSS version 19.0, SPSS Inc., Chicago, IL) was used to calculate the aggregated mean effect size delta (Δ), the associated 95% confidence

interval, and the sampling error variance according to a random effects model (Lipsey & Wilson, 2001). Random effects models were used to account for between-studies heterogeneity associated with both study-level sampling error and random effects variance (Lipsey & Wilson, 2001). In this model, each effect was weighted by the inverse of its variance and then reestimated after the random effects variance component was added (Hedges & Olkin, 1985). This procedure was used in all subsequent random effects analyses. Heterogeneity and consistency were evaluated with the Q statistic and the I^2 statistic, respectively (Higgins, Thompson, Deeks, & Altman, 2000). Because of the liberal estimate of heterogeneity associated with the Q statistic, heterogeneity was examined relative to observed variance and was indicated if the sampling error accounted for less than 75% of the observed variance (Hedges & Olkin, 1985). Publication bias was subjectively addressed by inspection of a funnel plot (Egger, Davey-Smith, Schneider, & Minder, 1997) on the outcome measure and quantified with the trim-and-fill method where bias is evidenced when $R_0 > 3$ (Duval & Tweetie, 2000). A fail-safe N_+ (i.e., how many new studies of mean effect zero would need to be added to the analysis to produce a significance level of 0.05) was calculated to estimate whether publication bias may be safely ignored in interpreting results (Rosenberg, 2005).

Primary Moderators and Analysis

To provide focused research hypotheses about variations in effect size over the course of cancer treatment, primary moderator variables were selected a priori for each model (i.e., overall, during treatment, and post-treatment) based on logical, theoretical, or prior empirical relation to CRF. With a small number of effects, inclusion of too many

variables could limit the valid interpretation of moderating effects by reducing statistical power (Hedges & Pigott, 2001; Hedges & Pigott, 2004). Three moderator variables were selected for the overall model: treatment status (i.e., patient currently undergoing treatment or patient post-treatment), percent fatigue reduction (i.e. the percent change in fatigue in the exercise group minus the percent change in fatigue in the control group), and the treatment status by percent fatigue reduction interaction. Three moderator variables were selected for the during treatment model: intervention adherence rate, baseline fatigue T-score, and the adherence by baseline fatigue score interaction. Three moderator variables were selected for the post-treatment model: time since cancer treatment, program length, and type of comparison (i.e., waitlist control or other comparison conditions).

Primary moderator variables for each model were included in a weighted least squares multiple linear regression analysis with maximum-likelihood estimation (Hedges & Olkin, 1985; Lipsey & Wilson, 2001). An SPSS macro (i.e., *MegaReg*; SPSS version 19.0, SPSS Inc., Chicago, IL) was used for the analyses which employed a random effects model to account for between-study heterogeneity associated with both study-level sampling error and random effects variance (Lipsey & Wilson, 2001). Each effect was weighted by the inverse of its variance and then recalculated with the random effects variance component added. Tests of the regression model *(*Q_R) and its residual error (Q_E) are reported. Significant categorical moderators in the regression analysis were decomposed using a random effects model to compute mean effect sizes and 95% confidence intervals (Lipsey & Wilson, 2001). The Johnson-Neyman procedure was conducted to identify the critical point in significant interactions of categorical and continuous variables in order to define regions of significance (Preacher, Curran, & Bauer, 2006).

Secondary Moderators and Analysis

Secondary moderator variables were selected for descriptive, univariate analyses based on a logical, theoretical, or prior empirical relation with CRF (Table 3.2). Mean effect sizes (Δ) and 95% confidence intervals (CIs) were computed for continuous and categorical variables using a random effects model to account for heterogeneity of moderator effects (Lipsey & Wilson, 2001).

Table 3.2. Definitions for Levels of Moderators

Effect Moderator	Levels
Demographics	
Treatment Status	**During Treatment:** individuals diagnosed with cancer currently undergoing active treatment (e.g., chemotherapy or radiation therapy) **Post-Treatment:** individuals diagnosed with cancer following the completion of active treatment (e.g., chemotherapy or radiation therapy)
Sex	**Male:** data from males only **Female:** data from females only **Mixed:** data from samples that combined females and males
Age	**Continuous variable:** Years
Baseline Fatigue Score	**Continuous variable:** T-scores
Time Since Post-Treatment	**Continuous variable:** Weeks
Exercise Intervention	
Exercise Frequency	**Continuous variable:** Days per week
Physical Activity Exposure	**Met guidelines:** intervention met Federal guidelines for vigorous (75 minutes vigorous intensity exercise per week) or moderate physical activity (150 minutes moderate intensity exercise per week) **Did not meet guidelines:** intervention did not meet moderate or vigorous physical activity recommendation or physical activity data were inadequately reported to determine whether recommendations were met
Exercise Session Duration	**Continuous variable:** Minutes

Table 3.2. Definitions for Levels of Moderators (cont.)

Effect Moderator	Levels
Exercise Mode	**Aerobic:** used exercise modes commonly described as aerobic (e.g., walking, jogging, cycling) only **Resistance:** used weight lifting only **Flexibility:** used a low intensity stretching program focused on increasing range of motion and was not explicitly classified as yoga **Yoga:** used yoga only **Mixed:** used a mix of aerobic exercise, weight lifting, and/or other modes of activity (e.g., yoga or recreational games)
Program Length	**Continuous variable:** Weeks
Program Setting	**Supervised:** exercise intervention was clinic- or community facility-based and allowed for direct supervision by investigators or fitness instructors **Self-Monitored:** exercise intervention was home-based and not directly supervised by investigators or fitness instructors
Adherence	**<80%:** study participants completed less than 80% of the specified exercise sessions **≥80%:** study participants complete greater than or equal to 80% of the specified exercise sessions **Not reported:** adherence rates were not reported
Fitness Change	**Increased fitness:** the confidence interval for Hedges' d effect size for fitness change did not include zero **No change:** the confidence interval for Hedges' d effect size for fitness change included zero **Not reported:** not enough information was reported to estimate whether the confidence interval for Hedge's d effect size for fitness change did or did not include zero
Study Characteristics	
Intervention Confound	**Yes:** the intervention consisted of both exercise treatment and one or more additional intervention components (e.g., education, counseling, pharmacotherapy) **No:** the intervention consisted of only an exercise treatment without the addition of additional intervention components (e.g., education, counseling, pharmacotherapy)

Table 3.2. Definitions for Levels of Moderators (cont.)

Effect Moderator	Levels
Physical Activity Controlled	**Yes:** the study inclusion/exclusion criteria placed a limitation on the physical activity level of the participant **No:** the study inclusion/exclusion criteria did not place a limitation on the physical activity level of the participant
Stratified Cancer Study	**Yes:** the study included only a defined sample of cancer patients (e.g., breast cancer or lung cancer or prostate cancer) **No:** the study included a mixed sample of cancer patients (e.g., breast, prostate, and lung cancer)
Percent Fatigue Reduction	**Yes:** the percent change in fatigue from baseline to post-intervention in the exercise group minus the percent change in fatigue from baseline to post-intervention in the control group was less than zero percent **No:** the percent change in fatigue from baseline to post-intervention in the exercise group minus the percent change in fatigue from baseline to post-intervention in the control group was greater than or equal to zero percent
Type of Comparison	**No Treatment:** the study used a no treatment control comparison condition **Usual Care:** the study used a usual care control comparison condition **Waitlist:** the study used a waitlist control comparison condition **Placebo:** the study used a placebo control comparison condition
Fatigue Measure	**FACT-F:** study used the Functional Assessment of Cancer Therapy-Fatigue scale **PFS:** study used the Piper Fatigue Scale **BFI:** study used the Brief Fatigue Inventory **SF-36:** study used the Short Form-36 Health Survey Questionnaire vitality scale **EORTC:** study used the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire fatigue scale **POMS:** study used the Profile of Mood States vigor and/or fatigue scale **MFI:** study used the Multidimensional Fatigue Inventory **Other**: used a fatigue measure not categorized above

CHAPTER 4

RESULTS

Characteristics of the trials included in the meta-analysis (Appendix B: References of Included Trials) and study quality assessment results are presented in Table 4.1. Examination of funnel plots and statistical test for funnel plot asymmetry suggested potential publication bias (Figures 4.1-4.3). The trim-and-fill analyses resulted in the imputation of five, four, and two studies to reach symmetry for the overall, during treatment, and post-treatment models, respectively. The fail-safe N+ was 1411, 487, and 212 for the overall, during treatment, and post-treatment models, respectively. These results suggest that any potential bias related to publication should not affect the interpretation of results (Sterne, Egger, & Smith, 2001).

Overall Model

Sixty-two of 70 (88.6%) effects were greater than zero. The distribution of the effects (Figure 4.4) was positively skewed (*g1*=1.26 [0.29]) and leptokurtic (*g2*=2.32 [0.57]). The mean effect size delta (95% CI) was 0.34 (k=70 [95% CI, 0.25-0.43]; *z*= 7.290, *P*< 0.001). The effect was heterogeneous ($Q_T(69)$= 143.49, *P*< 0.001). Sampling error accounted for 54.7% of the observed variance. The effect was moderately consistent across studies (I^2= 52.6%; 95% CI, 45.6% to 58.7%).

Table 4.1. Characteristics of Included Studies and Quality Assessment

	During Treatment (k = 43)	Post-Treatment (k = 27)
Total Sample (no.)	3,235	1,646
Age (mean years [SD])	52.0 [10.2]	55.0 [5.5]
Women (%)	68.0	87.0
Body Mass Index (mean [SD])	26.8 [2.2]	27.2 [1.8]
Aerobic Capacity (mean [SD])	21.1 [6.5]	24.2 [4.5]
Cancer Site (%)		
Blood	13.3	3.7
Brain	0.9	0.2
Breast	58.3	73.7
Colon	1.3	8.3
Gastrointestinal	2.6	0.9
Gynecological	1.3	3.7
Head & Neck	1.2	2.8
Lung	1.0	1.6
Prostate	18.0	0.3
Testicular	0.7	1.1
Other	1.5	3.7
Cancer Treatment		
Chemotherapy	58.9	38.2
Radiation	29.3	42.4
Hormone Therapy	11.9	19.4
Baseline Fatigue (mean T-score [SD])	50.3 [6.3]	41.4 [10.7]
Duration Post-Treatment (mean months [range])	N/A	16.3 [1.0-75.0]
Exercise Setting		
Home-Based (%)	37.0	29.6
Supervised (%)	63.0	70.4
Exercise Frequency (mean days/wk [SD])	3.4 [1.3]	2.9 [1.3]
Exercise Session Duration (mean min [SD])	42.3 [21.1]	49.6 [27.0]
Exercise Program Length (mean weeks [SD])	11.7 [6.9]	12.6 [6.5]
Exercise Intensity (mean % aerobic power [SD])	55.0 [14.4]	53.3 [10.9]
Retention Rate		
Exercise (median % [range])	89.0 [64.0-100]	86.5 [59.0-100]
Control (median % [range])	87.5 [50.0-100]	90.3 [60.0-100]
Adherence (mean % [range])	78.5 [58.0-100]	87.4 [34.0-98.0]
Study Quality (mean rating [SD])	10.9 [2.1]	11.1 [1.9]

Abbreviations: no. = number; SD = standard deviation; % = percentage; days/wk = days per week; min = minutes

Figure 4.1. Funnel Plot: Overall Model

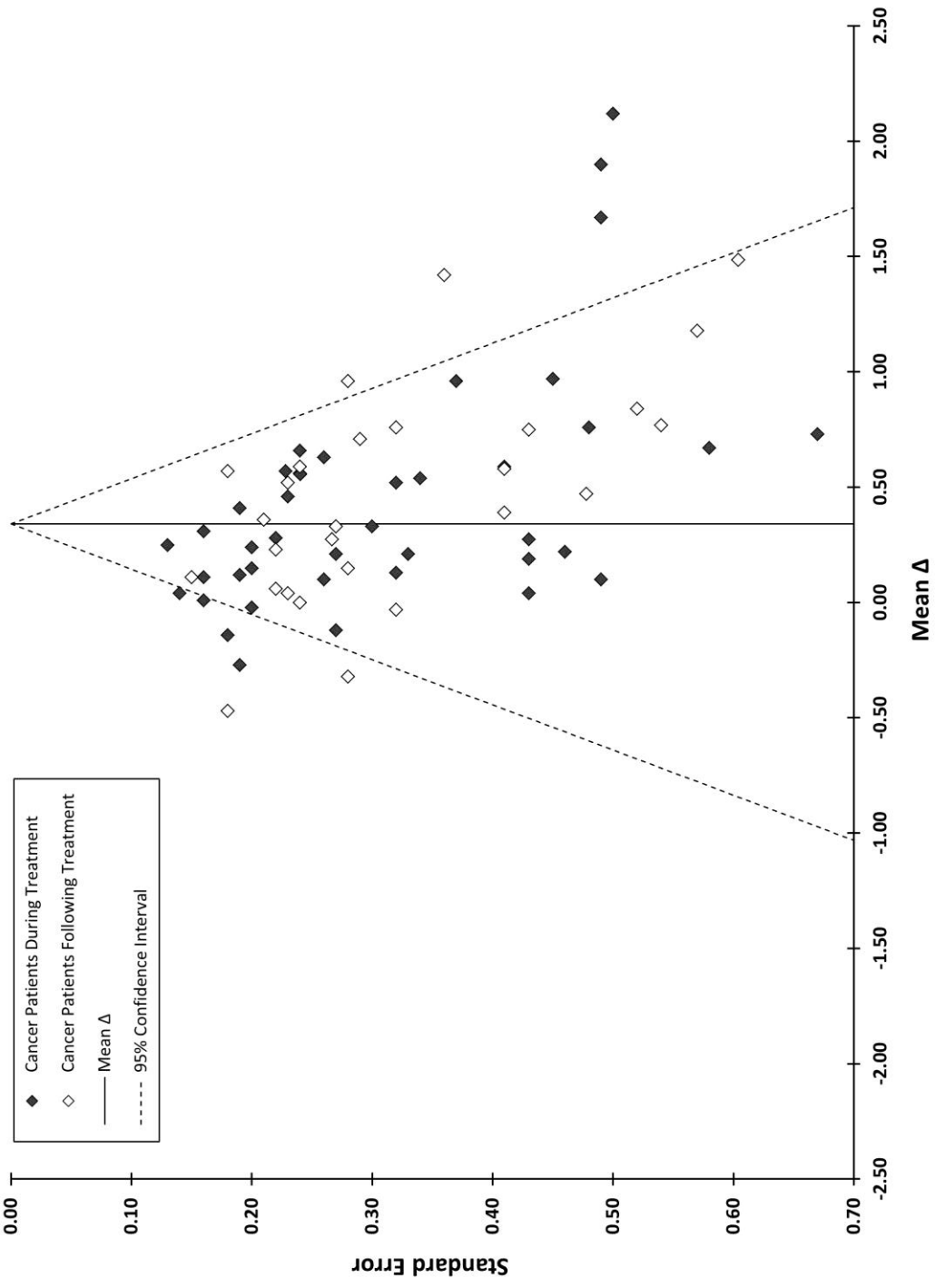


Figure 4.2. Funnel Plot: During Treatment Model

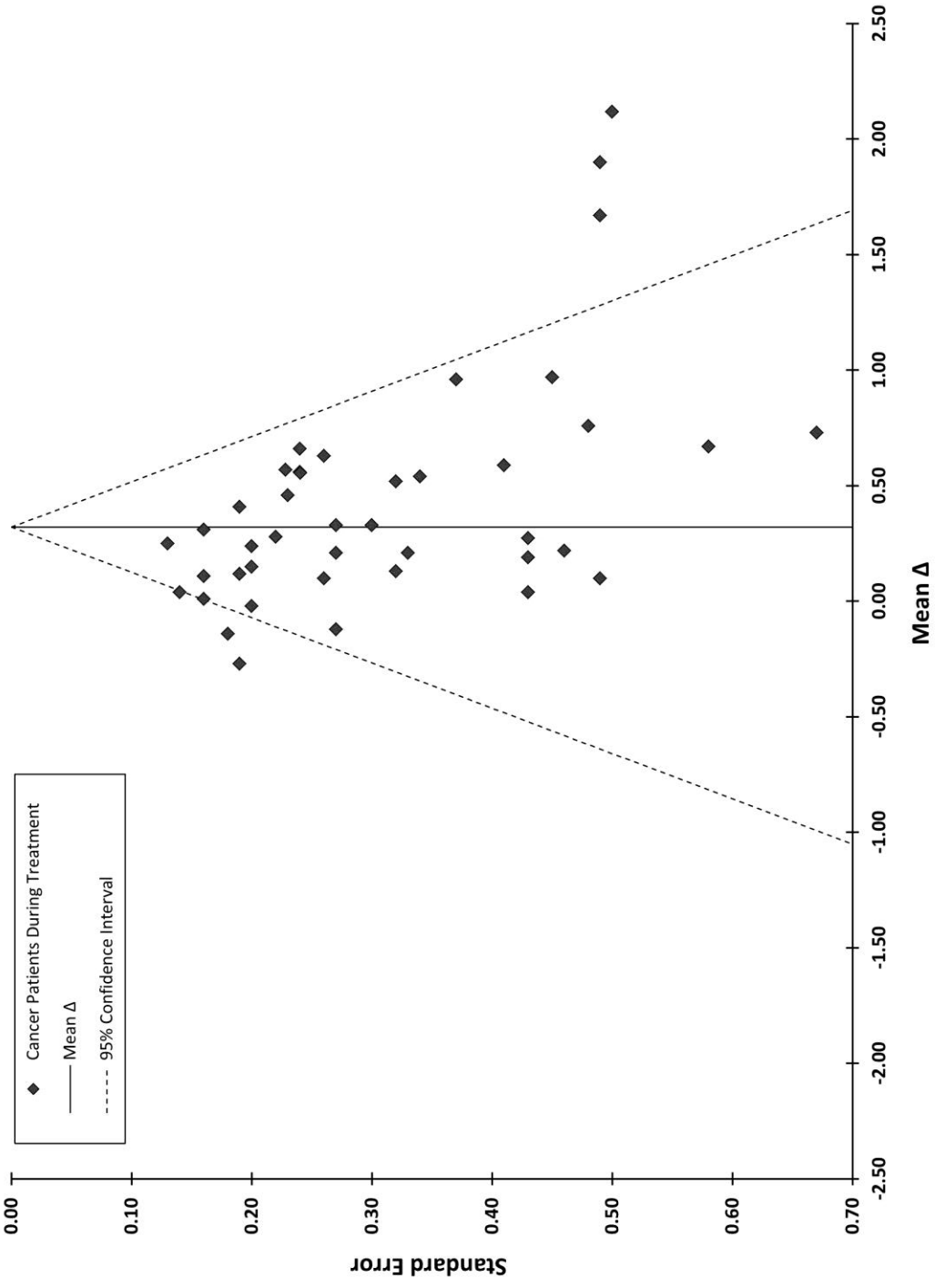


Figure 4.3. Funnel Plot: Post-Treatment Model

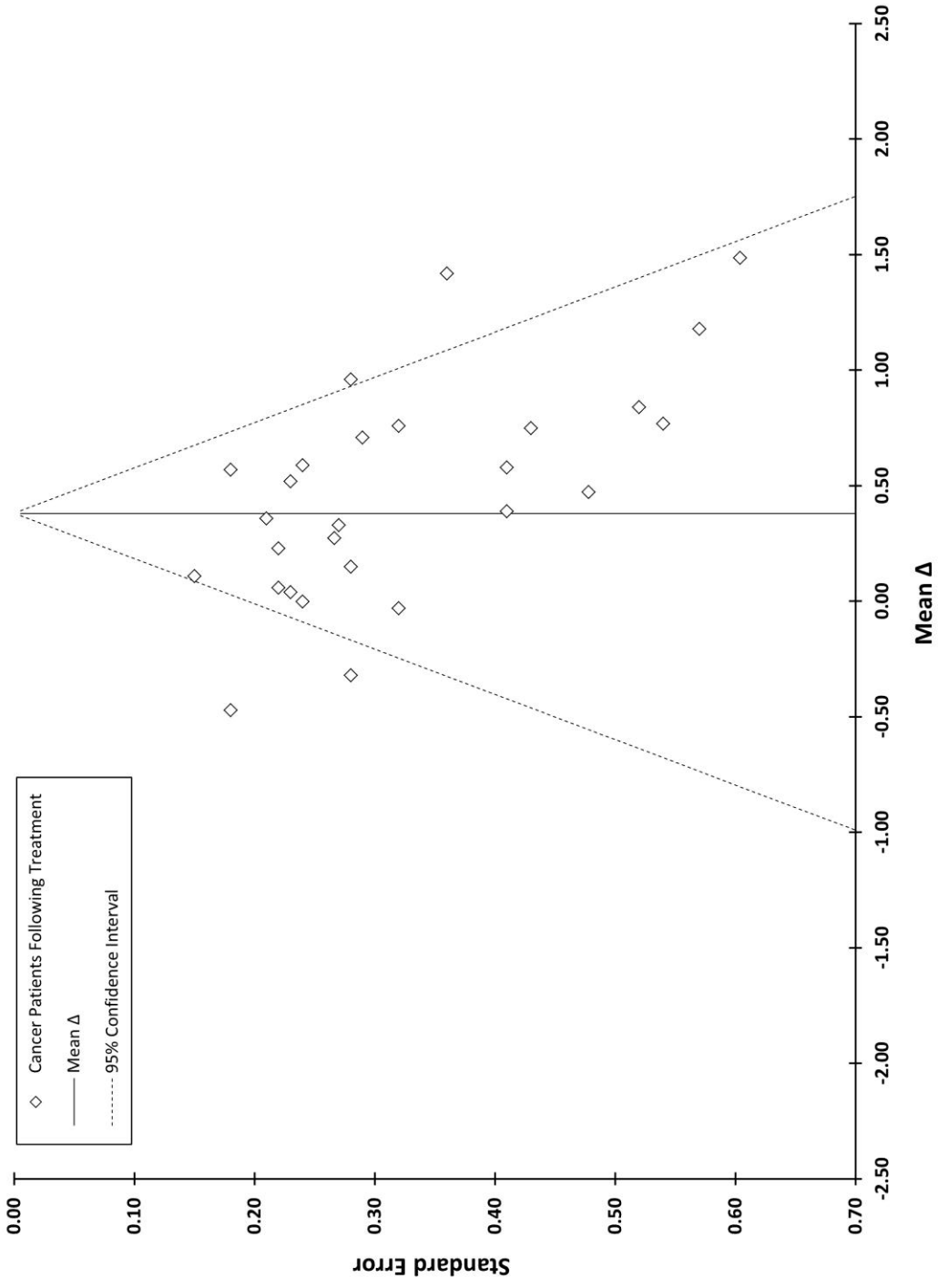
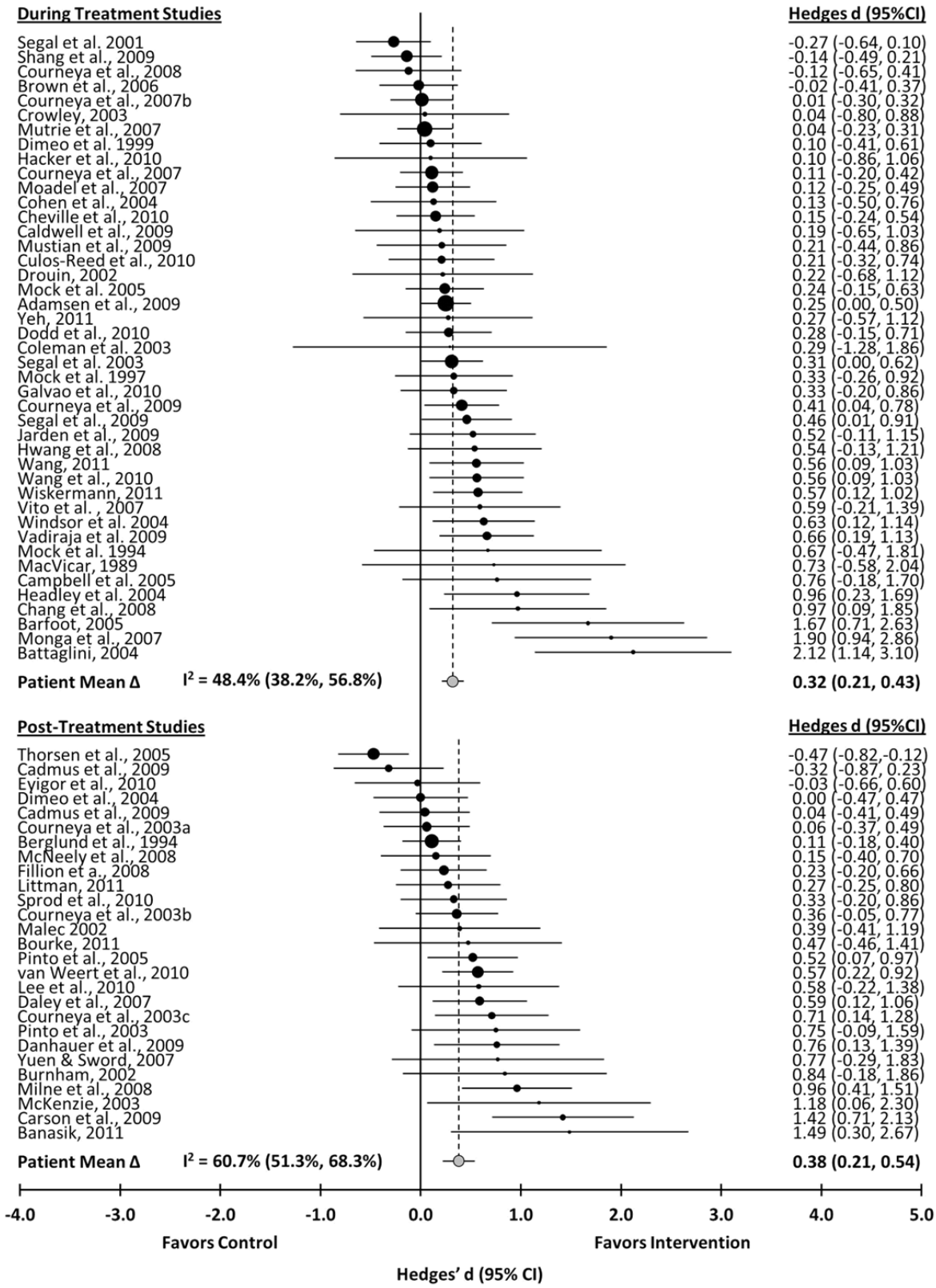


Figure 4.4. Forest Plot: Distribution of the Study Effects



Primary Moderator Analysis

The overall multiple regression model was significantly related to effect size ($Q_R(3)= 74.12$; $P< 0.0001$, $R^2 = 0.54$; $Q_E(63)= 63.03$, $P= 0.48$). The interaction of treatment status and percent fatigue reduction (Figure 4.5) was independently related to effect size ($\beta= 0.009$, $z= 2.96$, $P= 0.003$).

The Johnson-Neyman procedure yielded a critical point for percent fatigue reduction at -37.4% ($\beta= -0.19$, $t= 2.00$, $P= 0.05$). Figure 4.6 illustrates the differential effect of exercise and comparison conditions in cancer patients during and following treatment. Further decomposition revealed: (1) greater mitigation of CRF symptoms among exercise conditions (-4.2%) compared to comparison conditions in patients during treatment (29.1%) and, (2) larger reduction of CRF among exercise conditions (-20.5%) compared to comparison conditions in patients post-treatment (-1.3%). Because decomposition revealed differential effects among patients during and following treatment, regression models were developed and tested to examine differential effects of exercise on CRF in patients during treatment and patients post-cancer treatment.

Patients During Treatment

Thirty-nine of the 43 effects (94.3%) were greater than zero. The distribution of the effects (Figure 4.4) was positively skewed (*g1*= 1.84 [0.36]) and leptokurtic (*g2*= 3.98[0.71]). CRF symptoms were significantly reduced after exercise training ($\Delta= 0.32$ (0.21-0.43); $z= 5.74$, $P<0.001$). The effect was heterogeneous ($Q_T(42) = 79.44$, $P=0.004$). Sampling error accounted for 59.4% of the observed variance. The effect was moderately consistent across studies ($I^2= 48.4\%$; 95% CI, 38.2% to 56.8%).

Figure 4.5. Treatment Status x Percent Fatigue Reduction Interaction and Regions of Significance

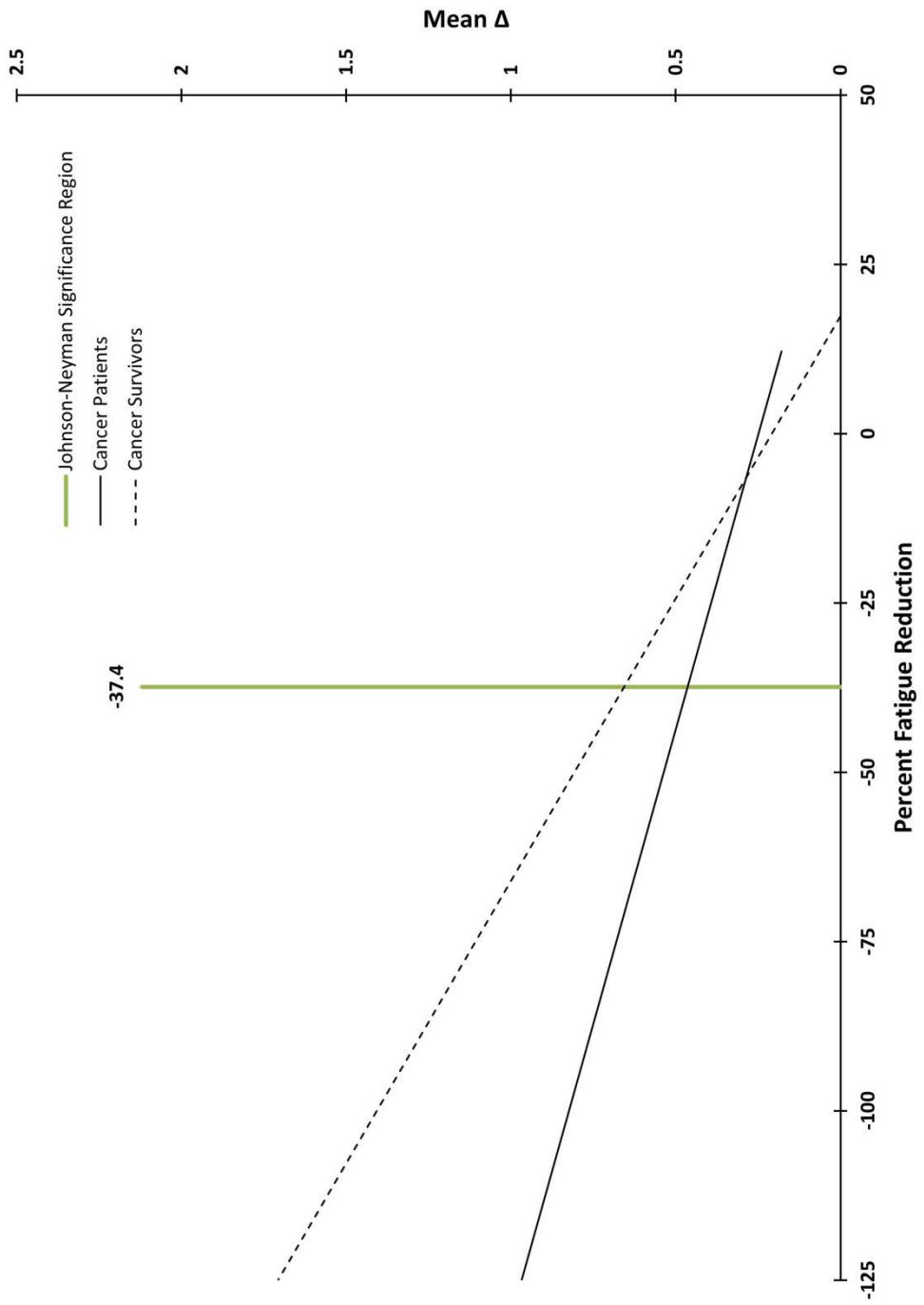
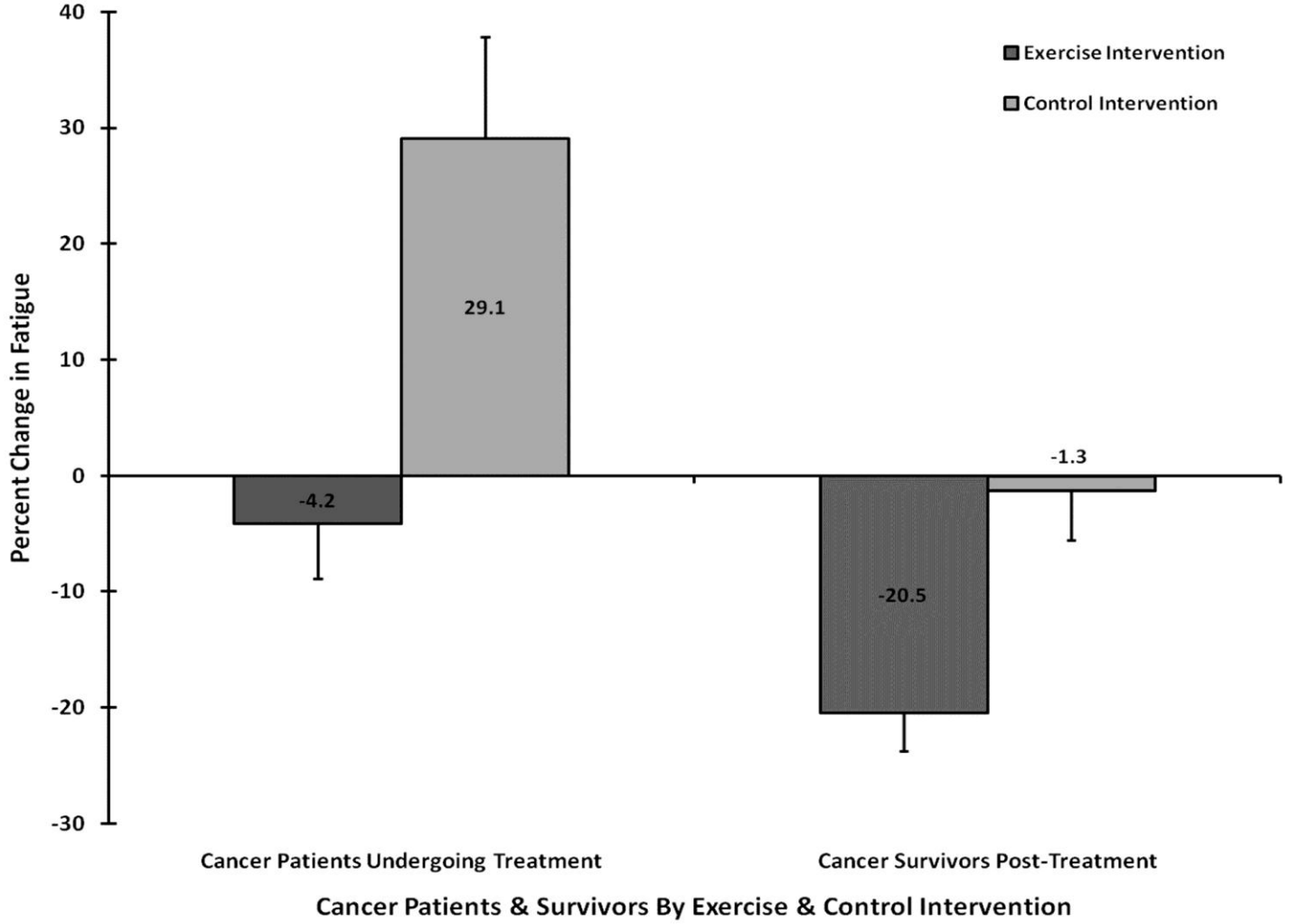


Figure 4.6. Treatment Status x Study Condition Interaction on Percent Change in Fatigue



Primary Moderator Analysis

The overall multiple regression model for patients was significantly related to effect size ($Q_R(3)= 22.09$; $p= 0.0001$, $R^2 = 0.45$; $Q_E(27)= 27.08$, $P= 0.46$). The interaction of baseline fatigue and exercise adherence (Figure 4.7) was independently related to effect size ($\beta= 0.19$, $z= 3.14$, $P= 0.002$).

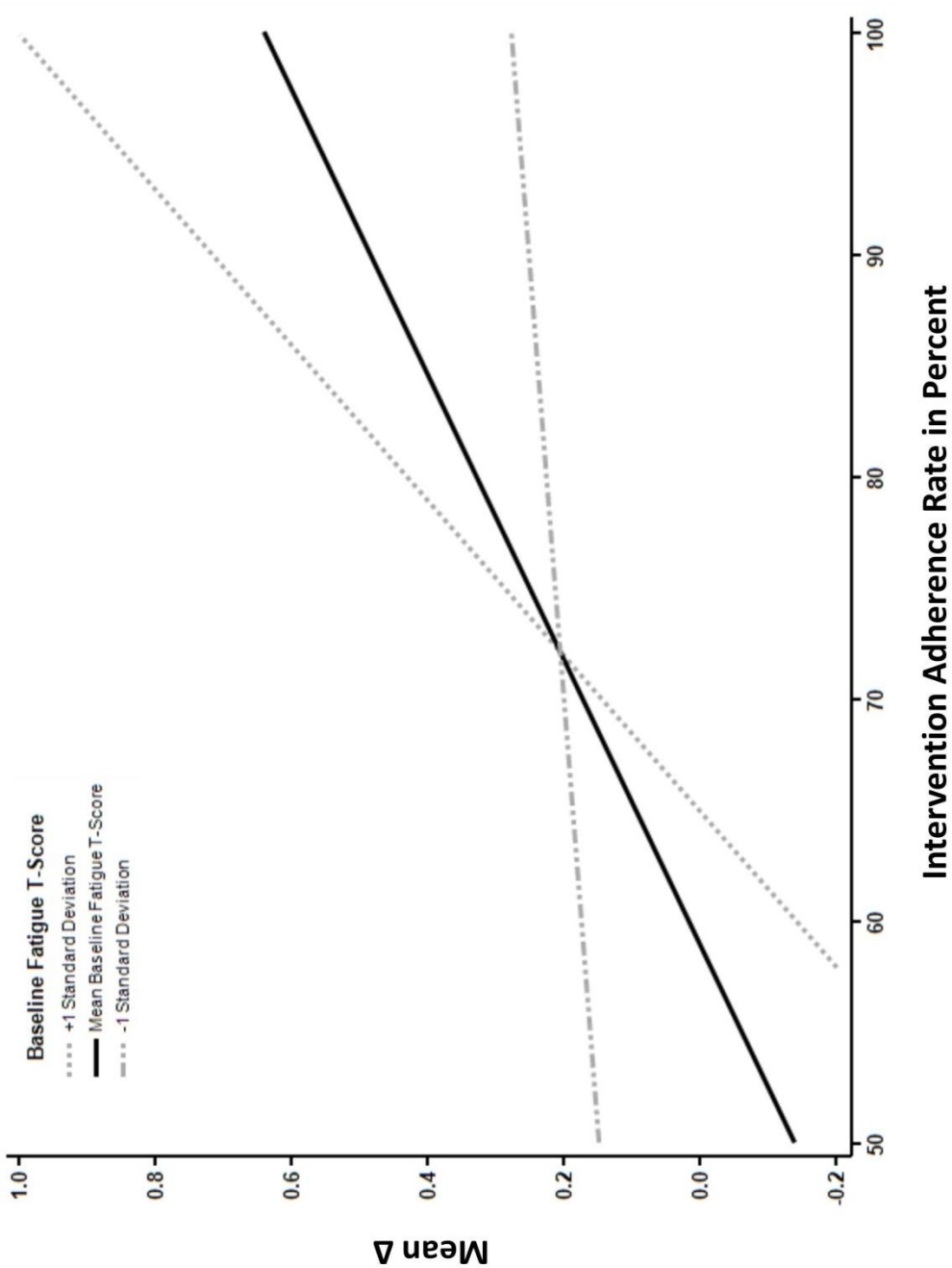
Patients Post-Treatment

Twenty-three of the 27 effects (94.3%) were greater than zero. The distribution of the effects (Figure 4.4) was positively skewed (*g1*= 0.27 [0.45]) and leptokurtic (*g2*= 0.06 [0.87]). Exercise training significantly improved CRF symptoms ($\Delta= 0.38$ (0.21-0.54); $z= 4.44$, $P< 0.0001$). The effect was heterogeneous ($Q_T(26) = 63.62$, $P= 0.0001$). Sampling error accounted for 46.8% of the observed variance. The effect was moderately consistent across studies ($I^2= 60.7\%$; 95% CI, 51.3% to 68.3%).

Primary Moderator Analysis

The overall multiple regression model for patients during treatment was significantly related to effect size ($Q_R(3)= 22.36$; $p= 0.0001$, $R^2= 0.50$; $Q_E(23)= 22.56$, $P= 0.49$). Post-treatment duration ($\beta= 0.01$, $z= 2.21$, $P= 0.0271$), exercise program length ($\beta= -0.03$, $z= -2.86$, $p= 0.0042$), and comparison condition ($\beta= 0.44$, $z= 3.90$, $p= 0.0013$) were independently related to effect size. Decomposition of the comparison condition variable showed that there was a larger effect (Δ, 95% CI) for studies that used a waitlist comparison condition ($\Delta= 0.66$, [95% CI, 0.42-0.90]) when contrasted with the average effect for other types of comparison conditions (i.e., no treatment, usual care, or placebo; $\Delta= 0.19$ [95% CI, 0.00-0.37]; $Q_B(1)= 9.74$, $P= 0.002$).

Figure 4.7. Baseline Fatigue T-Score x Exercise Adherence Interaction



Secondary Moderator Analyses

The number of effects (k), mean Δ effect size, 95% CI, and *p* value for each level of each moderator for the overall, during treatment, and post-treatment models are presented in Tables 4.2-4.4, respectively.

Table 4.2. Summary of Overall Univariate Moderator Analysis

Effect Moderator	Effects (k)	Δ or β	95% CI	p-value	I^2
Demographics					
Treatment Status					
During Treatment	43	0.3199	0.21, 0.43	0.0000	8.3%
Post-Treatment	27	0.3771	0.20, 0.40	0.0000	21.0%
Sex					
Male	6	0.5031	0.20, 0.81	0.0012	49.1%
Female	40	0.4325	0.30, 0.57	0.0000	23.2%
Mixed	24	0.1810	0.06, 0.30	0.0038	0.0%
Age	70	0.0082	-0.01, 0.02	0.1658	13.5%
Baseline Fatigue Score	62	0.0047	-0.01, 0.02	0.4291	10.0%
Time Since Post-Treatment	70	0.0048	-0.01, 0.01	0.1463	13.8%
Exercise Intervention					
Frequency	69	-0.0643	-0.13, 0.01	0.0736	12.4%
Physical Activity Exposure					
Met guidelines	24	0.2374	0.09, 0.38	0.0020	10.4%
Did not meet guidelines	46	0.3822	0.26, 0.50	0.0000	10.7%
Exercise Session Duration	64	0.0036	-0.00, 0.01	0.0791	11.6%
Exercise Mode					
Aerobic	24	0.3186	0.17, 0.47	0.0000	0.6%
Resistance	3	0.2561	-0.01, 0.52	0.0596	0.0%
Flexibility	3	0.2789	-0.21, 0.77	0.2624	66.3%
Yoga	8	0.5797	0.25, 0.91	0.0005	35.0%
Mixed	32	0.3352	0.19, 0.48	0.0000	19.9%
Program Length	67	-0.0127	-0.03, 0.00	0.0637	15.0%
Program Setting					
Supervised	46	0.3962	0.28, 0.51	0.0000	25.4%
Self-Monitored	24	0.2418	0.10, 0.38	0.0009	0.0%
Adherence					
< 80%	29	0.2624	0.13, 0.40	0.0001	5.3%
≥ 80%	25	0.4446	0.29, 0.60	0.0000	0.0%
Not reported	16	0.3241	0.12, 0.53	0.0018	53.5%

Table 4.2. Summary of Overall Model Univariate Moderator Analysis

Effect Moderator	Effects (k)	Δ or β	95% CI	p-value	I^2
Fitness Change					
Increased fitness	17	0.3368	0.16, 0.52	0.0003	15.0%
No change	27	0.3363	0.18, 0.50	0.0000	31.7%
Not reported	26	0.3546	0.21, 0.50	0.0000	0.0%
Study Characteristics					
Intervention Confound					
Yes	21	0.2951	0.17, 0.42	0.0000	0.0%
No	48	0.3678	0.24, 0.49	0.0000	24.7%
Physical Activity Controlled	17	0.2889	0.18, 0.40	0.0000	0.0%
Yes	53	0.3603	0.24, 0.48	0.0000	28.7%
No					
Stratified Cancer Study					
Yes	27	0.2518	0.12, 0.38	0.0002	0.0%
No	43	0.4142	0.29, 0.54	0.0000	21.7%
Percent Fatigue Reduction					
Yes	59	0.4245	0.33, 0.52	0.0000	12.7%
No	11	-0.0610	-0.21, 0.09	0.4300	0.0%
Type of Comparison					
No treatment	8	0.3061	0.02, 0.59	0.0336	70.0%
Usual care	39	0.2948	0.18, 0.42	0.0000	0.0%
Wait list	16	0.5101	0.32, 0.71	0.0000	8.9%
Placebo	7	0.2525	-0.03, 0.53	0.0745	9.0%
Fatigue Measure					
FACT-F	22	0.3509	0.20, 0.50	0.0000	0.0%
PFS	12	0.5197	0.27, 0.76	0.0000	60.8%
BFI	5	0.4177	0.04, 0.79	0.0283	4.0%
SF-36	6	0.0825	-0.21, 0.38	0.5819	33.5%
EORTC	5	0.1051	-0.24, 0.45	0.5507	54.0%
POMS	7	0.2677	-0.04, 0.57	0.0888	0.0%
MFI	4	0.4777	0.12, 0.83	0.0086	0.0%
Other	9	0.3971	0.13, 0.71	0.0046	4.7%

Table 4.3. Summary of Patients During Treatment Univariate Moderator Analysis

Effect Moderator	Effects (k)	Δ or β	95% CI	p-value	I^2
Demographics					
Treatment Status					
During Treatment	43	0.3199	0.21, 0.43	0.0000	48.4%
Sex					
Male	6	0.5031	0.20, 0.81	0.0012	51.2%
Female	22	0.3736	0.20, 0.55	0.0000	33.7%
Mixed	15	0.1964	0.07, 0.32	0.0022	0.0%
Age	42	0.0038	-0.01, 0.02	0.5407	16.3%
Baseline Fatigue Score	39	0.0267	0.01, 0.05	0.0070	24.2%
Exercise Intervention					
Frequency	43	-0.0435	-0.13, 0,04	0.3295	16.1%
Physical Activity Exposure					
Met guidelines	16	0.2504	0.08, 0.42	0.0041	26.6%
Did not meet guidelines	27	0.3512	0.21, 0.50	0.0000	12.6%
Exercise Session Duration	38	0.0017	-0.01, 0.01	0.5415	14.9%
Exercise Mode					
Aerobic	16	0.3099	0.10, 0.52	0.0039	79.6%
Resistance	2	0.2888	-0.02, 0.59	0.0632	NA
Flexibility	0	NA	NA	NA	NA
Yoga	4	0.3341	0.04, 0.63	0.0282	0.0%
Mixed	20	0.3207	0.16, 0.48	0.0001	22.5%
Program Length	40	-0.0100	-0.03, 0.01	0.2257	19.0%
Program Setting					
Supervised	27	0.3355	0.19, 0.48	0.0000	39.2%
Self-Monitored	16	0.2967	0.16, 0.44	0.0000	0.0%
Adherence					
< 80%	20	0.1897	0.04, 0.34	0.0123	0.0%
≥ 80%	15	0.4117	0.23, 0.59	0.0000	26.2%
Not reported	8	0.5906	0.27, 0.91	0.0002	61.6%

Table 4.3. Summary of Patients During Treatment Univariate Moderator Analysis

Effect Moderator	Effects (k)	Δ or β	95% CI	p-value	I^2
Fitness Change					
Increased fitness	10	0.4060	0.19, 0.63	0.0003	41.3%
No change	16	0.3288	0.09, 0.56	0.0064	43.3%
Not reported	17	0.2346	0.11, 0.36	0.0002	0.0%
Study Characteristics					
Intervention Confound					
Yes	14	0.2508	0.12, 0.38	0.0001	0.0%
No	29	0.3687	0.21, 0.53	0.0000	33.1%
Physical Activity Controlled					
Yes	12	0.2641	0.14, 0.39	0.0000	0.0%
No	31	0.3477	0.20, 0.50	0.0000	34.1%
Stratified Cancer Study					
Yes	16	0.2088	0.07, 0.34	0.0025	0.0%
No	27	0.4230	0.26, 0.59	0.0000	30.9%
Percent Fatigue Reduction					
Yes	35	0.4158	0.30, 0.53	0.0000	26.3%
No	8	-0.0354	-0.18, 0.11	0.630	0.0%
Type of comparison					
No treatment	4	0.9310	0.05, 10.81	0.0381	70.0%
Usual care	31	0.2979	0.18, 0.42	0.0000	0.0%
Wait list	5	0.2373	0.04, 0.44	0.0205	8.9%
Placebo	3	0.2704	-0.26, 0.80	0.3190	6.3%
Fatigue Measure					
FACT	13	0.2816	0.09, 0.47	0.0032	0.0%
PFS	9	0.4902	0.20, 0.78	0.0008	76.8%
BFI	4	0.4682	0.10, 0.83	0.0120	0.0%
SF-36	3	0.0932	-0.27, 0.45	0.6116	2.1%
EORTC	2	0.4991	-0.08, 1.08	0.0907	NA
POMS	5	0.1301	-0.53, 0.79	0.6971	NA
MFI	2	0.5766	0.03, 1.12	0.0385	NA
Other	5	0.2535	-0.03, 0.53	0.0754	0.0%

Table 4.4. Summary of Patients Post-Treatment Univariate Moderator Analysis

Effect Moderator	Effects (k)	Δ or β	95% CI	p-value	I^2
Demographics					
Treatment Status					
Post-Treatment	27	0.3771	0.20, 0.40	0.0000	60.7%
Sex					
Male	0	NA	NA	NA	NA
Female	18	0.5034	0.30, 0.71	0.0000	11.5%
Mixed	9	0.1625	-0.08, 0.41	0.1947	0.0%
Age	27	0.0278	-0.01, 0.06	0.0645	14.9%
Baseline Fatigue Score	23	-0.0075	-0.03, 0.01	0.4047	0.0%
Time Since Post-Treatment	27	0.0070	-0.01, 0.02	0.2858	11.2%
Exercise Intervention					
Frequency	26	-0.1008	-0.23, 0.03	0.1288	1.0%
Physical Activity Exposure	8	0.1955	-0.11, 0.50	0.2078	0.0%
Met guidelines	19	0.4317	0.23, 0.63	0.0000	4.8%
Did not meet guidelines					
Exercise Session Duration	26	0.0059	-0.01, 0.01	0.0758	1.1%
Exercise Mode					
Aerobic	8	0.3481	0.16, 0.53	0.0002	0.0%
Resistance	0	NA	NA	NA	NA
Flexibility	2	0.0858	-0.18, 0.35	0.5211	NA
Yoga	4	0.8905	0.31, 10.48	0.0029	51.9%
Mixed	12	0.3604	0.04, 0.68	0.0261	22.4%
Program Length	27	-0.0192	-0.04, 0.01	0.1293	5.7%
Program Setting					
Supervised	19	0.4927	0.30, 0.68	0.0000	1.2%
Self-Monitored	8	0.1329	-0.15, 0.42	0.3573	16.7%

Table 4.4. Summary of Patients Post-Treatment Univariate Moderator Analysis

Effect Moderator	Effects (k)	Δ or β	95% CI	p-value	I^2
Adherence					
< 80%	9	0.4408	0.17 0.71	0.0015	45.4%
≥ 80%	10	0.5037	0.23, 0.78	0.0004	0.0%
Not reported	8	0.1609	-0.12, 0.44	0.2626	23.7%
Fitness Change					
Increased fitness	7	0.2319	-0.09, 0.55	0.1591	23.0%
No change	11	0.3429	0.15, 0.54	0.0005	0.0%
Not reported	9	0.5540	0.19, 0.92	0.0027	15.0%
Study Characteristics					
Intervention Confound					
Yes	8	0.3927	0.10, 0.68	0.0076	16.7%
No	19	0.3707	0.15, 0.59	0.0011	6.2%
Activity Controlled					
Yes	5	0.3857	0.14, 0.63	0.0020	0.0%
No	22	0.3803	0.18, 0.58	0.0002	18.9%
Stratified Cancer Studies					
Yes	11	0.3437	0.07, 0.62	0.0148	11.0%
No	16	0.4058	0.19, 0.62	0.0002	6.5%
Percent Fatigue Reduction					
Yes	23	0.3632	0.17, 0.55	0.0001	0.0%
No	4	0.4643	0.04, 0.89	0.0336	80.0%
Type of Comparison					
No treatment	4	0.0418	-0.30, 0.39	0.8127	60.0%
Usual care	8	0.2446	-0.03, 0.52	0.0821	0.0%
Wait list	11	0.6652	0.42, 0.91	0.0000	13.3%
Placebo	4	0.2384	-0.11, 0.58	0.1761	0.0%
Fatigue Measure					
FACT-F	9	0.4943	0.21, 0.77	0.0006	0.0%
PFS	3	0.5190	0.16, 1.02	0.0430	0.0%
BFI	1	-0.0300	-0.90, 0.83	0.9459	NA
SF-36	3	0.0788	-0.43, 0.58	0.7594	73.9%
EORTC	3	-0.0798	-0.54, 0.38	0.7321	65.9%
POMS	2	0.5993	-0.01, 1.20	0.0515	NA
MFI	2	0.4094	-0.09, 0.91	0.1107	NA
Other	4	0.5637	0.12,1.00	0.0120	63.6%

CHAPTER 5

CONCLUSIONS

The cumulative evidence indicates that exercise training reduces CRF among patients both during and following treatment. The magnitude of the overall mean effect for cancer patients (Δ=0.32) and survivors (Δ=0.38) is comparable to the effect of: (1) exercise interventions on other mental health outcomes among cancer patients and survivors including depression (Duijts, Faber, Oldenburg, van Beurden, & Aaronson, 2011), anxiety (Speck, Courneya, Masse, Duval, & Schmitz, 2010), and quality of life (Duijts et al., 2011), (2) psychological interventions such as individual or group therapy on cancer-related fatigue (Kangas, Bovbjerg, & Montgomery, 2008), and (3) pharmacotherapy on cancer-related fatigue (Minton, Richardson, Sharpe, Hotopf, & Stone, 2008). Expressed as a binomial effect size (Rosenthal & Rubin, 1982), the effect of exercise training is equivalent to a clinical effect of 15.8% and 18.6% beyond chance among those patients involved in exercise interventions during and following treatment, respectively. The reduction in cancer-related fatigue found among exercising cancer patients and survivors is equivalent to a number needed to treat (Cook & Sackett, 1995) of approximately 3 (1.6 to 4.2) and 4 (2.0 to 15.7), respectively.

Although these results support previous reports of the efficacy of exercise interventions on CRF during and following active treatment, this is the first study to concurrently examine cancer patients during and following treatment and identify variables

that discriminately modify the effect in patients during specific points in the time course of the disease treatment and recovery. A better understanding of these moderating factors is important because it can help clinicians in timing the initiation of exercise interventions. It might also help identify patients vulnerable during these specific time periods such that the incorporation of other treatment modalities could be initiated in order alleviate CRF and/or maintain adherence to exercise programs.

Overall Model: Treatment Status x Percent Fatigue Reduction

Among the combined sample of patients undergoing treatment and patients post-treatment, CRF reductions varied according to an interaction between treatment status and percent reduction in CRF from baseline. For studies with larger percent reductions in CRF, the magnitude of the effect of exercise on CRF was greater among patients post-treatment compared with patients during treatment. However for studies with smaller percent reductions in CRF, patients during treatment realized a larger magnitude of effect of exercise on CRF than patients post-treatment. Exercise interventions appear to be effective in reducing CRF in patient both during and following treatment when percent reductions in fatigue fall below -37.4%. For studies having percent fatigue reductions above -37.4%, there was insufficient evidence to conclude whether exercise was helpful in reducing CRF.

The interaction is likely related to the differential responses to exercise and control conditions in patients during and following treatment. CRF symptoms are mitigated in patients participating in an exercise intervention during treatment compared to comparison interventions (-4.2% vs. 29.1%); whereas, CRF symptoms are reduced in patients participating in exercise post-treatment compared to comparison intervention (-20.5% vs.

-1.3%). These findings suggest exercise has a palliative effect in patients during cancer treatment and a recuperative effect in patients following treatment. This evidence should assist clinicians when prescribing exercise treatment to these groups.

Patients During Treatment: Baseline Fatigue x Exercise Adherence Interaction

Improvement in CRF for patients during treatment varied according to the patient's baseline CRF scores and exercise adherence rates. The largest improvements were realized by patients with lower baseline CRF scores and higher intervention adherence rates. This finding should be interpreted with caution. It is plausible that cancer patients with lower levels of CRF were able to tolerate exercise to a greater extent than those with higher levels of CRF during cancer treatment and therefore experienced greater protective effectives. However, baseline fatigue severity was not associated with exercise adherence rates in a previous study of breast cancer patients receiving chemotherapy. In that study, as the amount of exercise exposure increased the intensity of CRF decreased across all baseline levels of CRF (Schwartz, Mori, Gao, Nail, & King, 2001). CRF also was not a significant predictor of exercise adherence in a randomized controlled trial of breast cancer patients undergoing chemotherapy; however, aerobic fitness (i.e., $\dot{V}O_{2peak}$) was a significant predictor of adherence in the study (Courneya et al., 2008). This cumulative evidence suggests that CRF during cancer treatment is likely maintained at pre-treatment levels through the palliative effects of exercise. The present findings also suggest the recommendation of exercise before cancer treatment to increase fitness which may mediate the CRF and adherence relationship.

Patients Post-Treatment: Post-treatment Duration, Exercise Program Length, & Comparison Condition

In cancer patients following treatment, greater effects were seen for longer durations between the completion of treatment and the initiation of an exercise program, exercise interventions with shorter program length, and trials using waitlist comparisons. Unlike in patients undergoing treatment, CRF is a significant predictor of exercise adherence in patients following treatment (Courneya et al., 2004a). Exercise levels among cancer patients decrease from pre-diagnosis to active treatment and then slowly increase from active treatment to post-treatment, but usually not to pre-diagnostic levels (Courneya & Friedenreich, 1997). Thus, a longer post-treatment duration will increase the natural progression towards exercise in cancer patients following treatment (Pinto, Trunzo, Reiss, & Shiu, 2002).

Exercise program length also could be related to this phenomenon. Larger effects associated with shorter exercise intervention programs may be related to the reduction in CRF symptoms that naturally occurs over time in control groups and/or with the exercise contamination effects seen in longer clinical trials (Courneya, Friedenreich, Sela, Quinney, & Rhodes, 2002; Courneya, et al., 2004b; Courneya et al., 2010). Baseline exercise stage of change and past exercise are predictors of exercise contamination in comparison groups (Courneya et al., 2002; Courneya, et al., 2004b; Courneya et al., 2010). Unlike other types of comparison conditions, waitlist controls may provide a viable active treatment in post-treatment cancer patients' natural progression towards exercise such that it serves as a pre-contemplation or contemplation stage in the Transtheoretical Model of Behavior Change (Prochaska & Marcus, 1994). In any case, clinicians should prescribe exercise at cancer

diagnosis to attempt to mitigate the deleterious effects of active treatment that reduce the physical activity levels of patients post-treatment which ultimately compound CRF.

Limitations

Limitations in the quality and reporting of the included trials are notable. Many studies lacked adequate information regarding features of the exercise intervention (i.e., frequency, intensity, duration, mode, energy expenditure), appropriateness of comparison conditions, and underreporting of adherence rates, concomitant medication use, and cancer-sites. Only 51 of the 70 articles were rated at or above a score of 10 on a 15-point quality assessment scale (Median=11; Range=5.0 to 15.0), suggesting that over 25% of the studies included in the analysis were of a lower quality and may have led to an overestimation of effect. The lack of consistency observed in study quality is disappointing, as is the fact that approximately 10% of the included trials did not include a well-validated CRF outcome (Minton & Stone, 2009). These findings reiterate the importance of adoption of and compliance with reporting guidelines to improve the quality of future trials in this field (Schmitz et al., 2010).

Implications for Future Research

A better understanding of the effects of exercise on CRF may be achieved through well-designed randomized, controlled trials which examine how biological, psychological, and psychosocial aspects of exercise contribute to improved CRF across the time course of the disease and disease treatment. To date, only one randomized controlled trial has examined the effects of exercise on CRF from diagnosis, through hospital admission and

treatment, and into post-treatment follow-up (Wiskermann et al., 2011). Future randomized, controlled trials should: (1) seek to more fully characterize the features of the exercise stimulus (i.e., frequency, intensity, session duration, program length, mode); (2) examine exercise effects on specific neurobiological and psychological outcome measures of CRF; (3) examine the degree of overlap and/or independence of the effect of physical activity on CRF and other important mood states including anxiety, depression, and quality of life; and, (4) investigate the mechanistic similarities, interactions, and differences among different exercise training paradigms, psychosocial interventions, and pharmacological treatments employed to reduce CRF. Such investigations will help define the appropriate exercise prescription across the time course of cancer treatment and recovery, and offer important insight into the biopsychosocial mechanisms of CRF.

Conclusions

Exercise interventions reduce CRF among patients both undergoing active treatment and following active treatment, but these effects are differentially moderated in patients over the time course of treatment and recovery. Exercise has a palliative effect in patients undergoing cancer treatment and a restorative effect in patients following treatment. These findings provide evidence to prescribe exercise during and following treatment as a potentially low-risk, adjuvant therapy for cancer-related fatigue. However, the timing of such treatment should consider patient and intervention characteristics. Clinicians should recognize the differential effects of exercise on CRF when prescribing exercise treatment to patients during and following treatment.

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APPENDICES

APPENDIX A

CANCER META-ANALYSIS CODING SHEET

CANCER META-ANALYSIS CODING SHEET

I. General Information

Author(s): _____

Title: _____

Coder: 1 = Puetz
2 = Other

Year: _____

II. Design Characteristics

Type: 1 = Pre-Experimental: One-group pretest-posttest design
2 = Experimental: No treatment control
3 = Experimental: Usual care control
4 = Experimental: Placebo control
5 = Other

Total Sample Size: _____

Group Sample Size:

Group/Condition	Size	Age (SD)	% Female
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

Age Reported: 1 = Yes
2 = No

Age: 1 = Youth
2 = Adults
3 = Elderly
4 = Combined

Mean Age: _____

SD of Age: _____

Sex of Respondents: 1 = Male
2 = Female
3 = Mixed
4 = Not Reported

II. Design Characteristics Cont.

Percent Female: _____

General Characteristics of Cancer Site (%):

1=Lung	____	2=Brain	____	3=Hodgkin's	____
4=Pancreas	____	5=Lymphoma	____	6=Liver	____
7=Head & Neck	____	8=Breast	____	9=Leukemia	____
10=Melanoma	____	11=Colon	____	12=Prostate	____
13=Gynecological	____	14=Testicular	____	15=Other	____

General Characteristics of Cancer Treatment (%):

1=Hormone Alone	_____	2=Radiation Alone	_____	3=Chemo Alone	_____
4=Radiation Alone	_____	5=Chemo & Hormone	_____	6=Chemo & Radiation	_____
7=Hormone, Radiation & Chemo	_____	8=Other	_____		

Fitness Level:
1 = $VO2_{max}$
2 = METs
3 = Other Specify: _____

Mean Fitness Level: _____

SD of Fitness Level: _____

III. Exercise Characteristics

Mode:
1 = Aerobic
2 = Anaerobic
3 = Resistance Training
4 = Combination
5 = Other Specify: _____

III. Exercise Characteristics Cont.

Confounding Rehabilitation:
1 = Health Education
2 = Relaxation Therapy
3 = Psychological Counseling
4 = Other Specify: _____

Duration:
1 = Reported
2 = Not Reported

Group/Condition	Measure	Duration (SD)
_____	_____	_____
_____	_____	_____
_____	_____	_____

Relative Intensity:
1 = Reported
2 = Not Reported

Group/Condition	Measure	Intensity (SD)
_____	_____	_____
_____	_____	_____
_____	_____	_____

Absolute Intensity:
1 = Reported
2 = Not Reported

Group/Condition	Measure	Intensity (SD)
_____	_____	_____
_____	_____	_____
_____	_____	_____

Frequency:
1 = Reported
2 = Not Reported

Group/Condition	Measure	Frequency (SD)
_____	_____	_____
_____	_____	_____
_____	_____	_____

IV. Psychological Measures

Energy/Fatigue Measure:
1 = FACT
2 = POMS
3 = SF-36
4 = Other Specify: _____

Energy/Fatigue Baseline:	Measure	Raw Score	T-Score
	_____	_____	_____
	_____	_____	_____
	_____	_____	_____

Depression Measure:
1 = FACT
2 = POMS
3 = BDI
4 = Other Specify: _____

Depression Baseline:	Measure	Measure	Measure
	_____	_____	_____
	_____	_____	_____
	_____	_____	_____

Anxiety Measure:
1 = FACT
2 = POMS
3 = STAI
4 = Other Specify: _____

Anxiety Baseline:	Measure	Measure	Measure
	_____	_____	_____
	_____	_____	_____
	_____	_____	_____

Pain Measure:
1 = FACT
2 = SF-36
3 = VAS
4 = Other Specify: _____

Pain Baseline:	Measure	Measure	Measure
	_____	_____	_____
	_____	_____	_____
	_____	_____	_____

V. Subject Retention & Compliance

Subject Retention:
1 = Reported
2 = Not Reported

Subject Retention Rates:	Group/Condition	Starting Number	Ending Number
	_____	_____	_____
	_____	_____	_____
	_____	_____	_____
	_____	_____	_____

Subject Compliance:
1 = Reported
2 = Not Reported

Subject Compliance Rates:	Group/Condition	Percent Attended
	_____	_____
	_____	_____
	_____	_____
	_____	_____

VI. Results

Energy/Fatigue:	Group/Condition	Baseline	Mid-Intervention	Post-Intervention	Follow-Up
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
	_____	_____	_____	_____	_____
	_____	_____	_____	_____	_____
	_____	_____	_____	_____	_____
	_____	_____	_____	_____	_____

Depression:	Group/Condition	Baseline	Mid-Intervention	Post-Intervention	Follow-Up
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
	_____	_____	_____	_____	_____
	_____	_____	_____	_____	_____
	_____	_____	_____	_____	_____
	_____	_____	_____	_____	_____

VI. Results Cont.

Anxiety:	Group/Condition	Baseline	Mid-Intervention	Post-Intervention	Follow-Up
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
	_____	_____	_____	_____	_____
	_____	_____	_____	_____	_____
	_____	_____	_____	_____	_____
	_____	_____	_____	_____	_____

Pain:	Group/Condition	Baseline	Mid-Intervention	Post-Intervention	Follow-Up
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
	_____	_____	_____	_____	_____
	_____	_____	_____	_____	_____
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VII. Other Comments

Describe completely any test statistics that may be converted into an effect size:

Other Comments:

APPENDIX B

REFERENCES OF INCLUDED TRIALS

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Cancer Patients

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