8-1-2010

Effects of a high-intensity resistance training program on muscular strength, muscular endurance, and psychological measures in cancer survivors

Jessica M. Weiderspon
University of Northern Colorado

UNIVERSITY OF NORTHERN COLORADO

Greeley, Colorado

The Graduate School

THE EFFECTS OF A HIGH-INTENSITY RESISTANCE TRAINING PROGRAM ON MUSCULAR STRENGTH, MUSCULAR ENDURANCE, AND PSYCHOLOGICAL MEASURES IN CANCER SURVIVORS

A Thesis
Submitted in Partial Fulfillment
of the Requirements for the Degree of
Master of Science

Jessica M. Weiderspon

College of Natural and Health Sciences
School of Sport and Exercise Science
Exercise Science

August, 2010

This Thesis by: Jessica M. Weiderspon

Entitled: *The Effects of a High-Intensity Resistance Training Program on Muscular Strength, Muscular Endurance, and Psychological Measures in Cancer Survivors*

has been approved as meeting the requirements for the Degree of Master of Science in the College of Natural and Health Sciences in The School of Sport and Exercise Science, Concentration of Exercise Science

Accepted by the Thesis Committee:

____

Carole Schneider, Ph. D., Chair

____

David Hydock, Ph. D., Committee Member

Accepted by the Graduate School

____

Robbyn R. Wacker, Ph. D.
Assistant Vice President for Research
Dean of the Graduate School & International Admissions

ABSTRACT

Weiderspon, Jessica M. *The Effects of a High-Intensity Resistance Training Program on Muscular Strength, Muscular Endurance, and Psychological Measures in Cancer Survivors* Unpublished Master of Science, University of Northern Colorado, 2010.

Cancer can be characterized as an uncontrolled growth and spread of irregular cells in the body. Approximately 559,880 Americans die from cancer every year, however an estimated 562,340 Americans are anticipated to survive from cancer. With greater advances in treatment and increased survival rates, rehabilitation of normal life functioning becomes a large priority for cancer survivors. It has been found that exercise improves physiological and psychological factors in cancer survivors, although the most advantageous mode, duration, or intensity has not been determined. Aerobic and mixed interventions (aerobic, resistance, flexibility) have been studied in depth but a pure resistance training program has not been evaluated. The purpose of this study was to examine the effects of two resistance training protocols, (low and high intensities, as compared to a flexibility only control group) on muscular strength, muscular endurance, fatigue, quality of life, and depression following a four week training intervention. Nine participants were randomly separated into one of three groups (n=3), a high intensity group (HIRT), a low intensity group (LIRT), and a flexibility control group (FLEX). All groups improved in total body strength by 15%, 23%, and 46% in FLEX, LIRT, and HIRT, respectively. Significant differences were seen between the HIRT group and the FLEX group in total strength ($p=0.005$). Total fatigue was reduced in both the FLEX and LIRT groups by 31.21% and 47.61%, respectively. All groups saw a dramatic decrease in depression following the exercise interventions, with the largest decrease occurring in the HIRT group (-70.45%). Each group improved in QOL, with the LIRT group having the greatest increase (+23.18%; $p=0.04$). Both low and high resistance training appears to be well-tolerated and effective in improving quality of life and depression in cancer survivors, although high-intensity resistance training produces greater results in regards to muscular strength and endurance.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER I

INTRODUCTION

Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells. If the spread is not controlled, it can result in death. Cancer is caused by both internal and external factors that act together to initiate and promote carcinogenesis. The costs of cancer from direct medical costs, indirect morbidity cost (loss of productivity due to illness), and indirect mortality (cost of loss of productivity due to premature death) are $93.2 billion, $18.8 billion, and $116.1 billion, respectively. This brings the total cost of cancer to $228.1 billion. The lifetime probability of developing cancer is 43.89%, or 1 in 2, in males, and 37.35%, or 1 in 3, in females. There were 292,540 cancer deaths in males and 269,800 in females estimated in 2009, making cancer the second leading cause of death in the United States, representing 559,880 deaths or 23.1% of all deaths this year. About 562,340 Americans are expected to survive from cancer this year, and the 5-year survival rate has increased to 66% from 1975-2004, which is an increase from the 50% survival rate in 1975-1977 (American Cancer Society, 2009). The improvement in survival rates reflects progress in diagnosing certain cancers, the earlier stage of detection, and the developments in treatment. With greater advances in survival rates and treatment, rehabilitation of normal life functioning becomes a large priority for cancer survivors.

The most common treatments for cancer include surgery, chemotherapy, and radiation therapy. Surgery is a treatment for cancer that removes all or part of the cancer.

Chemotherapy is considered systemic therapy, or the treatment of cancer with drugs that affect both healthy and cancerous cells. Radiation therapy is the use of radiation to damage or destroy cancer cells. Radiation in high doses kills cancer cells or keeps them from growing and producing more cancer cells by disrupting the way they grow and divide (Mayo Clinic Staff, 2009). Hormone therapy, either through suppression or inhibition of specific hormones, has become a common and useful treatment for endocrine-responsive cancer in past years.

Oncology treatment side effects can occur any time after treatment, ranging from immediately following treatment to years afterwards. Side effects can include: cytotoxicity, prolonged bleeding, suppression of immune function, susceptibility to secondary infection, lymphedema, osteoporosis, and weight gain. Psychological side effects that often occur long term include: chronic fatigue, depression, worry, fear, sexual dysfunction, and decreased overall quality of life (Hayes, Rowbottom, Davies, Parker, & Bashford, 2003; Mayo Clinic Staff, 2009; Ohira, Schmitz, Ahmed, & Yee, 2006). Hayes et al. (2003) speculated that if cancer patients are experiencing intense feelings of unhappiness, that it could activate the hypothalamus pituitary-adrenal axis, which may in turn lead to immune suppression, an increase in susceptibility to infection, and enhance the risk of cancer recurrence and secondary disease. Androgen-deprivation therapy, a type of hormone therapy used to treat prostate cancer, has specifically been found to elicit adverse side-effects that may be easily attenuated by exercise. The side effects include: reduced muscle strength, reduced lean and bone mass, increased fat mass, increased risk of fractures, unfavorable lipid profile, decreased quality of life, and depression compromising physical and physiological function (Galvao, Nosaka, Taaffe, Spry, Kristjanson, McGuigan, et al., 2006; Galvao, Taaffe, Spry, & Newton, 2007).

A recent meta-analysis of all exercise regimens for the treatment of cancer and cancer treatment-related side-effects (McNeely, Campbell, Rowe, Klassen, Mackey & Courneya, 2006) found that regular physical exercise has been shown to counteract these adverse side effects by improving patients' health status. The general, post training effects have demonstrated an increase in cardiopulmonary function, muscle strength, lean body mass, bone mineral density, quality of life, and a decrease in chronic fatigue and depression (De Backer, Schep, Backx, Vreugdenhil, & Kuipers, 2009; Ohira et al., 2006; Schneider, Hsieh, Sprod, Carter, & Hayward, 2007a; Schneider, Hsieh, Sprod, Carter, & Hayward, 2007b). While a large amount of research is available regarding aerobic training and mixed protocols (aerobic, resistance training, and flexibility), little research has looked exclusively at resistance training. In fact, most protocols with cancer survivors that claim to study resistance training actually use aerobic or interval training in part (Adamsen, Midtgaard, Rorth, Borregaard, Andersen, Quist, et al., 2003; De Backer, Vreugdenhil, Nijziel, Kester, Van Breda, & Schep, 2008). There is copious knowledge that moderate-intensity resistance training, as part of an exercise intervention, improves physiological and psychological outcomes; however few studies have examined high intensity resistance training. This research in itself is limited, therefore, the purpose of this study was to examine the effects of high intensity resistance training on muscular strength, muscular endurance, fatigue, depression, and quality of life in cancer survivors.

Statement of Purpose

To examine the effects of two resistance training protocols, (low and high intensities, as compared to a stretching only control group) on fatigue, quality of life, depression, and muscular strength and endurance following a four week training period.

Significance of Study

Recent studies have shown that exercise can have significant positive effects on fatigue in cancer patients and cancer survivors. Some studies have found that simply increasing physical activity, regardless of the mode, will decrease levels of fatigue (Escalante & Manzullo, 2009; Meeske, Smith, Alfano, McGregor, McTiernan, Baumgartner et al., 2007; Schwartz, Mori, Gao, Nail, & King, 2000). Others have found that aerobic exercise and mixed protocols attenuate fatigue (Hanna, Avila, Meteer, Nicholas, & Kaminsky, 2008; Oldervoll, Kaasa, Hjermstad, Lund, & Loge, 2004; Schneider et al., 2007b). Only one study has exclusively evaluated the effects of resistance training on fatigue (Winters-Stone, Bennett, Nail, & Schwartz, 2008). Similarly, physical activity in itself has been found to help levels of QOL in cancer survivors (Blanchard, Baker, Denniston, Courneya, Hann, Gesme et al., 2003; Courneya, Karvinen, Campbell, Pearcey, Dundas, Capstick et al., 2005). Aerobic interventions have been studied in depth and appear to greatly improve QOL in cancer survivors (Cadmus, Salovey, Yu, Chung, Kasl, & Irwin, 2009; Courneya, Friedenreich, et al., 2003; Courneya, Mackey, et al., 2003). Additionally, mixed protocols and those focusing primarily on resistance training have improved QOL (De Backer, Van Breda, Vreugdenhil, Nijziel, Kester, & Schep, 2007; Ohira et al., 2006; Segal et al., 2003.)

Unlike the improvements in fatigue and quality of life, depression appears to be less affected by aerobic and mixed exercise interventions. For example, Schneider et al. (2007b) showed reduced depression following a mixed intervention, Courneya, Freidenreich, et al. (2003) found boderline significant improvements in depression. Additionally, Cadmus et al. (2009) showed that depression was entirely unaffected by exercise.

Cancer cachexia, or muscle wasting, is a common side-effect of cancer and cancer treatments leading to poor prognosis and treatment limitations. Decreases in muscle tissue and weakness have been linked to decreased quality of life and increased fatigue (Stewart, Skipworth, & Fearon, 2006). There is considerable evidence that resistance training, particularly at a high-intensity, can attenuate many of the mechanisms that contribute to muscle wasting (Al-Majid & McCarthy, 2001; Tisdale, 2002).

Immune function plays an invaluable role during and following cancer treatment, therefore any action that could affect the immune system negatively should be avoided. It has been demonstrated that high-intensity aerobic training can negatively affect the immune system (Hayes et al., 2003; McTiernan, 2004), however high-intensity strength training has not been studied. Some mixed protocols in cancer survivors showed no significant changes after the intervention, positive or negative, leading the researchers to suggest the protocols may have lacked sufficient intensity to induce results (Galvao et al., 2006; Galvao et al., 2008; Nieman et al., 1995).

Finally, pure high-intensity resistance training protocols have been used in the elderly and in patients with chronic diseases, such as coronary artery disease, congestive heart failure, and type II Diabetes and have been found to be beneficial and well tolerated

(Ades et al., 2003; Dunstan, Daly, Owen, Jolley, DeCourten, Shaw et al., 2002; Seynnes et al., 2004; Volaklis, Konstantinos, Tokmakidis, & Savvas, 2005).

To date, there are no studies which have investigated the effects of a high-intensity resistance training intervention on muscular function and phsychological outcomes, despite the knowledge that high-intensity resistance training can attenuate muscle wasting and may prove beneficial to the immune function. High intensity resistance training has been well tolerated in the eldery and in other special populations, and needs to be evaluated in cancer survivors.

CHAPTER II

REVIEW OF LITERATURE

Introduction

It has been shown that exercise improves both physiological and psychological function in cancer survivors. Most protocols have, however, been either unclear in their precise methodology or have used mixed (aerobic, resistance, and flexibility) interventions, which makes it difficult to know which mode/intensity of the exercise has improved function. Resistance training has been studied extensively in several populations and has been found to improve muscular strength, muscular endurance, attenuate muscle wasting, decrease fatigue, reduce depression, and improve quality of life (Ades et al., 2003; Al-Majid & McCarthy, 2001; De Backer et al., 2007; Dunstan et al., 2002; Ohira et al., 2006; Kraemer & Ratamess, 2004; Seynnes et al., 2004; Segal, et al., 2003; Tisdale, 2002; Winters-Stone et al. 2008). Consequently, this literature review seeks to elaborate on resistance training and its effects on fatigue, quality of life, depression, and muscular strength and endurance, as well its effects on muscle wasting in relation to low and high intensity resistance training programs. A section has also been included to investigate resistance training programs and their effect and tolerance in other special populations, in hopes of directing future studies with cancer survivors.

Fatigue in Cancer Survivors

Chronic fatigue is one of the most deleterious side effects of both cancer and cancer-treatments. Fatigue may be defined as a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning. Fatigue is the most frequently reported symptom by cancer survivors and many of these survivors perceive fatigue as the most distressing symptom associated with their illness because it imposes limitations on their daily activity level. In fact, it has been reported that up to 30% of cancer survivors report a loss of energy even years after they complete treatment. (Escalante & Manzullo, 2009). Specifically, fatigue afflicts up to 96% of patients receiving chemotherapy, 78% of patients receiving radiation therapy, and up to 80% of patients with advanced malignancies (Al-Majid & McCarthy, 2001). One study of just under 2,000 breast cancer survivors found that 66.1% experienced moderate-to-severe fatigue. The fatigue was strongly correlated with depression (r=0.455, P<0.001) and was negatively associated with health-related quality of life (Kim, Son, Hwang, Han, Yang, Lee et al., 2008). The cause of fatigue in long-term cancer survivors that are disease free has not been fully elucidated, but may be because of persistent activation of the immune system or to late treatment effects on major organ systems.

It has been suggested that exercise has the strongest evidence supporting its effectiveness among nonpharmacologic interventions for managing fatigue. In fact, a recent meta-analyses of 28 different studies, found that exercise was statistically more effective than the control in reducing fatigue, both during and after cancer treatment (Escalante & Manzullo, 2009). Likewise, a greater physical activity level has been found to decrease the levels of fatigue experienced. Meeske et al. (2007) found that out of the 1,183 breast cancer survivors studied, 41% experienced moderate-to-severe fatigue and that the fatigue was associated with pain, cognitive problems, weight gain, and physical inactivity. To further assess the relationship between fatigue and exercise levels, a regression analyses was performed. Four hours or more of exercise per week was associated with a statistically significant reduction in fatigue (β-coefficient = 0.43. P=0.04). In fact, subjects who performed 4 or more hours of physical activity per week had a nearly 50% reduction in fatigue risk. Similar results have been found for subjects undergoing chemotherapy as well. A study examining the relationship between exercise and fatigue over the first two cycles of chemotherapy found that fatigue was significantly reduced on the days the subjects exercised and that the longer the subjects exercised, the less fatigue was felt (up to >60 minutes) (Schwartz et al., 2000).

Exercise interventions using both aerobic and mixed (aerobic, resistance training, and flexibility) protocols have demonstrated improvements in fatigue as a result of the exercise. Oldervoll et al. (2004) found that total fatigue was reduced by 43.7%, physical fatigue was reduced by 43.6%, and mental fatigue was reduced by 44% after 20 weeks of aerobic exercise training (P<0.001). A study of 96 breast cancer survivors undergoing various clinical treatments of surgery, chemotherapy, radiation therapy, and combinations of each demonstrated significant reduction in behavioral (4.68 ± 2.62 to 2.68 ± 2.38), affective (5.27 ± 2.54 to 3.58 ± 2.66), sensory (5.48 ± 2.26 to 3.80 ± 2.19), cognitive/mood (4.93 ± 2.18 to 3.72 ± 2.06) (P<0.05) and total fatigue (5.00 ± 2.10 to 3.37 ± 2.08) after a 6-month mixed exercise intervention (Schneider et al., 2007b). Another study using low-to-moderate intensity mixed training found that cancer survivors, after exercise, reported significantly less fatigue on the Piper Fatigue Scale (mean = 3.56) compared to the before levels of fatigue (mean = 4.81, P<0.05) (Hanna et al., 2008).

Very little research has been done examining the effects of resistance training on fatigue or on resistance exercise in cancer survivors in general. Instead, aerobic exercise has been given the most attention. A study by Winters-Stone et al., (2008) examined correlations between fatigue, aerobic fitness levels, muscular strength, body composition, and total physical activity levels after a two-hour physiological and psychological assessment. Fatigue was significantly correlated with all independent variables, with the exception of aerobic fitness, leading the authors to suggest that aerobic training may not be as beneficial on fatigue as once thought. Fatigue was found to increase with a greater percentage of body fat, more adjuvant treatments, poorer lower-extremity strength, less physical activity, and if diagnosed at a lower age. In regression analysis, lower-extremity muscular strength and physical activity levels were significant independent predictors of fatigue. In fact, lower-extremity strength was inversely related to fatigue and accounted for 15.1% ($P<0.01$) of the variance in fatigue scores. Similarly, physical activity was also inversely related to fatigue and accounted for 7.3% ($P<0.03$) of the variance in fatigue scores (Winters-Stone et al., 2008). This research sheds new light on the importance of a resistance training intervention in the management of cancer and cancer-related side effects.

Quality of Life in Cancer Survivors

As with fatigue, quality of life appears to be improved in cancer survivors who exercise. A survey mailed to 386 endometrial cancer survivors found that 70% of the subjects were not meeting public exercise guidelines and that 72% were overweight or obese (Courneya, et al., 2005). The endometrial cancer survivors who met public exercise guidelines had significantly better quality of life than survivors not meeting the guidelines. Subjects meeting guidelines showed QOL values of 157.2 ± 22.2 on the Functional Assessment of Cancer Therapy-Anemia scale versus those not meeting guidelines with lower scores of 144.9 ± 26.2 ($P<0.001$). Likewise, a similar study with surveys sent out to 352 cancer survivors found that cancer survivors who currently exercised three times per week had significantly higher QOL than those who did not exercise ($\beta=0.24$, $P<0.01$). Also, the current absolute amount of exercise each survivor described explained 1% ($P<0.05$) of the variance in QOL, while the change in exercise amount from diagnosis until the time of the survey explained an additional 7% ($P<0.01$). The authors suggested that while it appears that exercise improves quality of life, perhaps the greatest changes occur following diagnosis and exercise onset, and in cancer survivors who adopt exercise after being sedentary (Blanchard, et al., 2003).

Aerobic exercise has been shown to increase QOL in cancer survivors. A study of 52 post-menopausal breast cancer survivors who were randomly assigned to a control or cardiovascular exercise group, found exercise to increase QOL values by 9.1 points, compared with only a 0.3 point increase in the control group ($P<0.001$) (Courneya, Mackey, et al., 2003). This intervention consisted of cycling for 35 minutes, three times per week at an intensity of 70%-75% $VO2_{max}$. Another aerobic intervention with recently resected colorectal cancer survivors receiving adjuvant therapy found that moderate intensity cardiovascular exercise at 65%-75% HR_{max} and home-based training resulted in increased QOL (Courney, Freidenreich et al., 2003). This protocol had a very high contamination of the control group due to outside exercise, leading the researchers to compare subjects of both groups who increased physical fitness (as measured by a submaximal aerobic test) to those who decreased physical fitness. QOL was found to increase by 4.3 points in those who improved cardiovascular fitness and decrease by 2.2 points in subjects who decreased fitness level (*P*=0.038). This research is not supported by findings from Cadmus et al. (2009) who found that after a 6-month cardiovascular exercise regimen at 60-80% of HR_{max}, QOL measures were not improved in 75 breast cancer survivors after the intervention.

A mixed regimen, using individualized exercise prescriptions for aerobic, resistance, and flexibility training based on subjects' fitness assessments has been found to significantly improve quality of life measures in cancer survivors following treatment. This moderate-intensity intervention improved quality of life by 7.2% (*P*=0.006), while concomitantly improving muscular strength and endurance. Similarly, a resistance training protocol at 60%-70% of 1-repetition maximum, three times a week was found to significantly improve health-related QOL in men receiving androgen-deprivation therapy (Segal et al., 2003). This trend in increased muscular fitness correlating to increased quality of life was best observed following a 6-month randomized, controlled exercise intervention in 86 cancer survivors (Ohira et al., 2006). Physical and psychosocial quality of life scores were found to improve in the exercise group (+1.2%; *P*=0.006 and 2.5%; *P*=0.02, respectively.) In fact, increases in upper body strength was correlated with improvements in physical QOL (*r*=0.32; *P*<0.01) and psychosocial QOL (*r*=0.30; *P*<0.01).

Recently resistance training protocols have been used in hopes of improving quality of life in cancer survivors. De Backer et al. (2007) studied the effects of an 18 week exercise intervention primarily consisting of resistance training. After the protocol, all measures of quality of life improved (*P*<0.01). Physical QOL increased by

17%, emotional QOL increased by 28.3%, global health state increased by 20%, and cognitive fatigue increased by 9.1%. The authors found that muscular strength correlated significantly with physical functioning QOL both before and after the intervention, suggesting an increase in muscular strength will augment quality of life. The same authors sought to evaluate the follow-up effects of this exercise protocol one year later. They found that the increases in quality of life remained unchanged, however the values were not statistically different from the control group. The researchers suggested that perhaps a ceiling effect is reached in cancer survivors long after treatment, and although limitations may still exist, survivors may be relatively satisfied with life and score high on quality of life outcomes. Regardless, resistance training does appear to create the same positive effect on QOL, but far sooner than spontaneous remission.

Depression in Cancer Survivors

The improvement in depression following an exercise intervention has not been observed to the same extent as other psychological measures. The aforementioned study by Schneider et al. (2007b) found a significant decrease in depression of -25.6% (P=0.013) after the individualized exercise intervention, while borderline significant differences were seen between groups by Courneya, Freidenreich, et al. (2003). Depression was seen to decrease by 2.4 points in the group which increased in fitness, but only increased by 1.7 points in the group which decreased fitness (p=0.055). Depression was not significantly altered in a 6-month,cardiovascular program that met twice per week at an intensity of 60%-80% HR_{max} (Cadmus et al., 2009) or in a resistance training regimen, also meeting twice a week for 6-months (Ohira et al., 2006). More studies need to be done to specifically understand the relationship between exercise (type and intensity) on depression in cancer survivors.

Cancer Cachexia

Cancer can result in a complex metabolic state leading to muscle wasting. This progressive wasting is characterized by both a loss in adipose tissue and muscle mass, causing uncontrollable weight loss. The increased weight loss can limit the effects of cancer treatments, causing decreased responsiveness and/or dose-limiting toxicities. Skeletal muscle wasting occurs due to perturbations in muscle protein metabolism including: decreased muscle protein synthesis, increased muscle protein degradation, or a combination. Decreased protein synthesis is affected by increased angiotensin II activity, increased proteolysis-inducing factors, decreased mTOR and $P70^{S6k}$ protein kinases, and decreased physical activity (Tisdale 2002). Increased protein degradation is influenced by increased calpain system activity, increased ubiquitin-proteasome pathway activity, and an increased production of pro-inflammatory cytokines. It has been speculated that progressive resistance training may attenuate some of these mechanisms (Al-Majid & McCarthy, 2001).

Cachexia is one of the most common effects of cancer and is characterized by an involuntary loss of >5% pre-morbid weight in a six month period from both adipose and protein stores (DeWys, Becc, Lavin, Band, Bennet, Bertino et al., 1980). Cancer-related cachexia is associated more closely with particular types of cancer, primarily those of the gastrointestinal tract and lung (Bossola, Pacelli, Tortorelli, & Doglietto, 2007; DeWys et al., 1980). Cachexia accounts for about 20% of cancer deaths (Tisdale, 2002) and contributes to decreased responsiveness to cancer treatments, such as radiation and chemotherapy. Cancer-related cachexia can also cause severe dose-limiting toxicities which lead to poor prognosis and increased morbidity and mortality. (Andreyev, Norman, Oates, & Cunningham, 1998). Because muscle mass and cross-sectional area are directly proportional to muscular strength, r=0.76 (Jones, Rutherford, & Parker, 1989), muscle wasting contributes to weakness. This has been found to reduce functional ability and, most importantly, decreased quality of life (Stewart et al., 2006). Cachexia, unlike starvation in which fat is lost while lean body mass is preserved, causes severe weight loss from both compartments (Tisdale, 2002). Fearon (1992) found that lung cancer patients who lost 30% of their pre-illness body mass, had a 75% decrease in skeletal muscle protein and an 85% decrease in total body fat. Reiterating the complex metabolic changes that occur with cachexia and the large role protein metabolism plays, it has been found that the liver mass is increased due to the metabolic recycling, degradation, and synthesis of lean muscle as well as visceral protein during cachexia. This is different than starvation, as the liver mass decreases to offset the equal losses in both skeletal muscle and organ protein (Tisdale, 2002).

Progressive resistance training (PRT) is any type of strength training where the stimulus is progressively increased to promote greater resistance and muscle force over time (Al-Majid & Waters, 2008). Because of this constant increase in stimulus PRT stimulates muscle synthesis and will subsequently lead to increases in strength, functional ability, and quality of life (Stewart et al., 2006). It has also been found that PRT increases the rate of protein synthesis by increasing mTOR and $p70^{S6k}$. An acute bout of low-intensity resistance exercise—combined with blood flow restriction— performed at 20% of 1 repetition maximum in the vastus lateralis resulted in $p70^{S6k}$ phosphorylation and a 3-fold downstream activation of mTOR compared to both exercised—without blood flow restriction— and non-exercised groups. This in turn caused a 46% increase in muscle protein synthesis in the exercised, blood flow restricted group ($P < .05$). The authors suggested that their aim with this approach of blood flow restriction was to "mimic" higher exercise intensities, of >70% 1-RM, which have already been shown to increase the phosphorylation of $p70^{S6k}$ and increase protein synthesis (Fujita, Abe, Drummond, Cadenas, Dreyer, Sato et al., 2007). PRT has also been found to release the pro-inflammatory cytokine interleukin-6 which, when released in skeletal muscle as opposed to in a tumor, creates a cascade effect attenuating tumor-necrosis alpha and interleukin-1. In these ways, increasing muscle contractile activity, increasing protein synthesis, and lessening the affect of pro-inflammatory cytokines, PRT can limit muscle wasting in cachexia.

Physiological Alterations and Exercise Dose

The immune system is a complex organization of numerous cells and cell types with the overall function of ridding the body of malignant cells and pathogenic agents. In regards to cancer, the immune cells primarily responsible for recognizing and killing tumor cells are the natural killer cells, cytotoxic T lymphocytes, and the cells of the monocyte-macrophage system (Nieman, Nehlsen-Cannarella, & Markoff, 1990). Natural killer cells are very responsive to exercise and it has been found that their circulating numbers increase by 150-300% after exercise (Nieman, 1994). In sedentary subjects, regular exercise training significantly enhanced the resting levels of natural killer cells (Nieman et al., 1990). In addition to the potential increase in natural killer cells after exercise in cancer survivors, it has also been suggested that for site-specific cancers, exercise may be of great benefit. With colon cancer, exercise may decrease risk by shortening the transit time within the intestine, thereby decreasing contact between the potential carcinogens and healthy tissue. Hormones play an important role in male and female reproductive caners and exercise has been found to alter the levels of these hormones, potentially decreasing the risk (Lee, 1995).

McTiernan (2004) found that the relationship between exercise and immune function follows a “J” shaped curve with the lowest risk of compromised immune system among individuals who undertake regular moderate exercise. This is important when designing programs for those with weakened immune systems, such as cancer survivors undergoing treatment. Similar to the “J” curve, there is growing recognition that both acute and chronic exercise can modulate immune function, depending on factors such as duration, mode, and intensity, forming the “inverted ‘U’ theory”. This theory similarly states that moderate exercise may enhance immune function, whereas both heavy exercise or a sedentary lifestyle may attenuate the immune response leading to poorer immune function (Hayes et al., 2003). It is important to note that both the “J” curve and “inverted ‘U’ theory” seem to occur only with aerobic exercise, however resistance training has yet to be studied significantly.

Natural killer cells are responsible for destroying tumor cells and any increase would be of benefit. A 7-month, moderate intensity, aerobic protocol was found to increase natural killer cell activity at rest compared with baseline values pre exercise training (Nieman et al. 1995). As stated previously, the monocyte-macrophage system is an important part of immune function in cancer patients. Monocytes are cells that are produced in the bone marrow, stored briefly, and then released into tissues or specialized vessels where they mature into macrophages. In a healthy population, it has been found that high-intensity aerobic training over several consecutive days may decrease the number of these cells by more than 50% (Woods, Davis, Mayer, Ghaffer, & Pate, 1993). In regards to moderate intensity exercise, a 6-month exercise regimen consisting of mixed aerobic and resistance training in breast cancer patients receiving chemotherapy was found to increase lymphocyte activation of T-helper cells significantly compared to controls (Hutnick, Williams, Kraemer, Ortega-Smith, Dixon, Bleznak et al., 2005). In healthy subjects, a high-intensity, acute bout of aerobic exercise was found to increase circulating levels of T-helper cells by 50%-100% (Nieman, 1994). A mixed exercise intervention of aerobic and resistance training at 70%-90% HR_{max} and 8-20 RM respectively, for 3 months had no effect on the number of T-cells. The researchers suggested that the lack of statistical significance indicated the exercise intervention had no effect on immune function and the intensity may not have been of sufficient magnitude to induce a positive effect (Hayes et al., 2003). This evidence suggests a moderate intensity mixed protocol can be well tolerated in cancer patients receiving adjuvant treatment, but that a high-intensity approach may prove beneficial and merits study.

Several studies have appeared to have no effect on immune function. In a study by Galvao et al. (2006) substantial improvements were seen in muscular strength, muscular endurance, muscular thickness, and body composition after the exercise intervention, with no changes in hormonal and immune function. Similarly, an 8-week mixed exercise program for 60 minutes in breast cancer patients, three times per week, did not show any differences in white blood cell subset numbers, natural killer cell number, and natural killer cell activity compared with sedentary controls (Nieman et al., 1995). Contrastingly, a home-based 16-week, mixed protocol in breast cancer survivors was associated with a near-significant decrease in insulin levels and waist circumference. It has been speculated that the relationship between physical activity and breast cancer prognosis may be mediated by changes in insulin levels and body fat levels (Ligibel, Campbell, Partridge, Chen, Salinardi, Chen et al., 2008). Lowered insulin levels may decrease the likelihood of secondary diseases and increase prognosis. Perhaps, the home-based regimen did not reach the necessary intensity to deliver significant and meaningful findings. A high-intensity resistance training protocol at 6-RM in cancer patients receiving treatment for 20 weeks resulted in no significant effects on resting levels of inflammatory markers and serum hormones (Galvao et al., 2008). Acute trainings, however, resulted in increased serum growth hormone levels (3.7 ± 0.8 ng ml^{-1}), dehydroepiandrosterone (DHEA) (2.1 ±0.3 ng ml^{-1}), interleukin-6 (62.6 ± 0.5 pg ml^{-1}), tumor necrosis factor-α (1.8 ± 0.2 pg ml^{-1}), and differential blood leukocyte counts of hemoglobin and white blood cells from base ($P<0.05$). The authors noted this was a similar response to exercise as occurs in healthy individuals and concluded that the high-intensity resistance training did not affect the cancer treatment. This suggests that a supervised, high-intensity intervention needs to be evaluated further in cancer survivors.

Effects of Moderate and High Intensity Training on Muscular Strength and Endurance

It is well known that resistance training elicits gains in muscular strength, muscular endurance, and power (Kraemer & Ratamess, 2004). In healthy, college-aged women both a 3-8 RM and a less intense 8-12 RM resistance training program elicited gains in muscular hypertrophy, strength, and power. Of import, the researchers found that the most intense loading range of 3-8 RM did appear to demonstrate the most significant increases in the aforementioned variables, however the 8-12 RM protocol was statistically ($P<0.05$) as effective in stimulating improvements, and may be better tolerated in cancer survivors. It is well known that in healthy adult subjects lifting at a high intensity is most beneficial for improving muscular strength and hypertrophy because the maximal number of motor units is recruited (Kraemer & Ratamess, 2004). Additionally, high intensity weight training is beneficial in preventing further bone loss in patients at risk for osteoporosis, such as in postmenopausal breast cancer survivors (De Backer et al., 2009). To further clarify intensity, an algebraic equation (y= -2.8371x + 102.7; where y = % 1RM and x = RM) can be used to convert percent 1-repetition max to the amount of a certain repetition max lifted. Therefore, 100% 1-RM is equivalent to 1RM, 97% 1-RM equals 3-RM, 86% 1-RM equals 6-RM, and 69% 1-RM equals 12-RM. In relation to strength training, intensity is a relative term.

> "Intensity can be defined as the *effort* or how difficult the training stimulus or exercise is. A resting muscle represents minimal intensity, whereas momentary muscular fatigue (failure) in the concentric portion of an exercise performed in strict form represents high intensity." Therefore, "the RM indicates that the muscle has reached a point of fatigue or failure in which the force-generating capacity falls below the required force to shorten the muscle against the imposed resistance. At this point, the progressive recruitment of muscle fiber motor units has occurred and the muscle is at high intensity. Thus high intensity can be reached by performing a few repetitions (3-6) with a heavier resistance or several repetitions (8-12) with a lighter resistance" (American College of Sports Medicine, 2009).

Among cancer patients and survivors, high intensity strength training has been defined as working within the range of 60%-85% 1-RM. (De Backer et al., 2007; Galvao et al., 2006; McNeely, Parliament, Seikaly, Jha, Magee, Haykowsky et al., 2008; Segal et al., 2003).

Most exercise interventions in cancer survivors use a mixed approach, consisting of aerobic, resistance, and flexibility training. One-hundred and thirty-five breast and prostate cancer survivors underwent an individualized and personalized mixed, exercise intervention. This protocol was based upon each clients' fitness assessment data and personal goals. Following the treatment, cancer survivors showed significant (P=0.006) improvements in upper-body muscular endurance, increasing 46.6%, and improvements in lower-body muscular endurance of 67.1%. Core muscular endurance increased by 32.5%, and as stated previously, the psychological measures of depression and quality of life were also improved (Schneider et al., 2007a). The researchers suggested that this moderate-intensity individualized prescriptive approach is both a safe and effective means to augment muscular function and improve quality of life in cancer survivors.

Only a few studies have researched the effects of high-intensity resistance training in cancer survivors. Segal et al. (2003) used a 12 week total-body resistance training protocol at 60%-70% 1-RM for 2 sets, 3 times per week in men receiving androgen deprivation therapy. At the end of the intervention, submaximal strength increased by 42% and 32% for the chest press and leg press, respectively (P<0.05). A 20 week total body resistance training program at 12-6 RM (≈70-85% 1-RM) in prostate cancer survivors resulted in substantial improvements in muscular strength, endurance, and thickness. A 41% increase in upper body strength and a 96.3% in lower body strength was seen after the intervention (P<0.0001). Lower body endurance was also improved by 56.3% (P<0.001) (Galvao et al., 2006). Another study, (McNeely et al., 2008) sought to compare the effects of a moderate-to-high resistance training protocol to a low intensity, standard therapeutic exercise protocol commonly used in cancer rehabilitation programs. They found the moderate-to-high program to be superior for improving shoulder pain and disability as well as muscular strength. Upper extremity strength and upper extremity endurance increased by 10.8 kg ($P<0.001$) and +194 repetitions ($P=0.039$) respectively in 52 head and neck cancer survivors assigned to the resistance training program. The authors noted that in this population, pain is a major predictor of quality of life, and that a lifting load of 60-70% 1-RM 2-3 times per week was not high enough to induce further pain or discomfort, but rather was able to alleviate it. Recently an exercise intervention using primarily high-intensity resistance training with periods of moderate-to-high interval training was evaluated on 57 cancer patients for 18 weeks. The resistance training used a loading range of 65-80% 1-RM for the first 12 weeks then switched to muscular endurance training at 35-40% 1-RM for the last 6 weeks. The reason for the change was unclear and would undoubtedly skew the results. After the intervention, the patients exhibited significant improvements in strength with large effect sizes of 1.32 to 2.68. Lunge strength increased by 105% ($P<0.01$) and pull over strength increased 93% ($P<0.01$) after the 18 weeks. As stated previously, this protocol was also able to significantly improve QOL and the increases in muscular strength were correlated with the improvements in QOL (De Backer et al., 2007). The improvements seen in strength were still significantly higher than controls a year after the intervention (De Backer et al., 2008) suggesting possible long-term improvements with resistance training.

The highest load seen in cancer rehabilitation was used in a mixed protocol involving massage, relaxation, aerobic, and resistance training at an intensity of 85%-95% of 1-RM for 45 minutes. This protocol was well received by all patients undergoing chemotherapy with an adherence rate of 85.2%, and even developed a waiting list

(Adamsen et al., 2003). After the intervention, strength increased by 32.5%, specifically the chest press improved by 19.2%, the pull-down by 20%, and the leg press by 44% ($P<0.0001$). The authors suggested that this level of training was well tolerated and induced significant positive effects mainly due to the restorative nature of the massage and relaxation part of the intervention.

High Intensity Strength Training in Elderly & Patients with Chronic Disease

A purely high-intensity resistance training protocol has not yet been evaluated in cancer survivors. Most protocols have some other form of intervention included (aerobic training, interval training, flexibility, relaxation, etc.) Many researchers have concern that the intensity is too great and that the protocol is not appropriately individualized for cancer survivors to reap real benefits. Others however have suggested that an intensity ranging from 50-80% 1-RM, 3 times per week is the optimal guideline for resistance exercise (Galvao et al., 2007). High-intensity resistance training regimens, however, have been evaluated in patients with other chronic diseases such as coronary artery disease, congestive heart failure, and type II diabetes with great success. A study by Ades et al. (2003) using 65-88 year old, female patients suffering from coronary artery disease, found that a 6-month resistance training intervention at 80% 1-RM resulted in significant increases in physical function and functional performance. The subjects increased distance during a weighted, 6 minute walk by 15% or from 1172 ± 383 ft to 1343 ± 379 ft ($P<0.01$). Leg strength also increased from 66 ± 21 kg to 78 ± 24 kg and upper-body strength improved from 41 ± 18 kg to 66 ± 21 kg ($P<0.05$). The authors pointed out that the rating of perceived exertion for the exercise regimen reached 14-20 RPE, or “maximal exertion” on the Original Borg Scale and was well tolerated in elderly women, suffering from CAD. Augmenting these findings in patients with CAD, Volaklis et al. (2005) suggested that resistance training at 80% 1-RM is tolerated haemodynamically and clinically in patients with advanced heart failure and is considered a safe and effective training mode. Similarly, a 6-month resistance program, with a loading range of 75-85% 1-RM, was effective and well-tolerated by older patients (60-80 years) with type 2 diabetes. Importantly, the researchers found that the program was effective in improving glycemic control and muscular strength. The subjects showed a three-fold decrease in HbA 1c (glycated hemoglobin) and improved glucose tolerance (Dunstan et al., 2002).

Another study using elderly male subjects (mean age 81.5 years) sought to test the efficacy of a high-intensity (80% 1-RM) and a low-intensity (40% 1-RM) resistance training regimen versus a sedentary control group. The assessors measured leg extensor maximal strength, endurance, and functional performance as assessed by a 6-minute loaded walk. After the interventions, the high-intensity (HI) group had significantly greater gains in strength, endurance, and functional ability as compared with the low-intensity (LI) group. Strength increased by 57.3 ± 4.8% in the group versus only a 36.6 ± 5.9% increase in the LI group (*P*=0.001). Similarly muscular endurance improved by 284.6 ± 73.5% versus 117 ± 33.1% in the HI group (*P*=0.008). The authors concluded a strong dose-response relationship between resistance training intensity and strength gains and between strength gains and functional improvements after training. Low-intensity resistance training may not be sufficient to achieve optimal improvements of functional performance; high-intensity training appears to be just as safe, but is more effective physiologically and functionally (Seynnes et al., 2004).

Summary

Chronic fatigue is the most frequently reported symptom by cancer survivors and often the most distressing. Exercise has been found to be the most effective treatment intervention both during and after cancer treatment. Mixed protocols, using aerobic, resistance, and flexibility training, have reported significant reductions in total fatigue (Meeske et al., 2007; Schwartz et al., 2000; Schneider et al., 2007b). Very little research has been done assessing the role resistance training may play on fatigue levels. However recent studies have concluded that muscular strength is inversely related to levels of fatigue (Winters-Stone et al., 2008), and protocols aimed towards strength gains may be the most effective in attenuating chronic fatigue.

Increased physical activity, in any mode, seems to be effective in improving quality of life. Aerobic protocols, protocols adopting a mixed regimen (aerobic, resistance, and flexibility), and resistance training have all significantly enhanced levels of QOL (Ohira et al., 2006; Segal et al., 2003). As with fatigue, quality of life appears to be related to muscular strength, suggesting an increase in strength will augment QOL (Courneya et al., 2005).

Levels of depression do not appear to be as affected by exercise as other psychological measures. Both aerobic and resistance training protocols have failed to significantly alter levels of depression post exercise (Cadmus et al., 2009; Courneya, Freidenreich, et al., 2003). More research is needed to further elucidate these findings.

Cancer-related cachexia is a common and deleterious effect of cancer and can limit treatment and increase the risk of mortality and morbidity. Cachexia occurs due to decreased muscle protein synthesis, increased muscle protein degradation, or a combination of both. Resistance training has been found to attenuate these processes, improving muscular hypertrophy and improving strength (Al-Majid & Waters, 2008; Tisdale, 2002).

Preserving and augmenting immune function is an invaluable part of cancer rehabilitation. It has been observed that the relationship between exercise and immune function follows a "J" shaped curve with the lowest risk of compromising the immune system in the individuals who undertake regular moderate exercise. Likewise, factors such as duration, mode, and intensity appear to have the greatest effect (Hayes, 2003). Moderate aerobic exercise and a moderate intensity mixed protocol both have been found to improve immune function in cancer survivors, while high-intensity aerobic exercise in healthy subjects appears to inhibit function. Contrastingly, a mixed exercise intervention had no effect on immune function (Galvao D. A., et al., 2006; Galvao D. A., et al., 2008). More research is needed on the appropriate mode, duration, and intensity to improve immune function.

Resistance training has been found to increase muscular strength, muscular endurance, and power. It appears that the higher the intensity of training, the greater the strength and endurance gains (Folland & Williams, 2007). High intensity training has been defined simply as reaching muscular failure, regardless of the load and number of repetitions. However, most research among cancer survivors defines high-intensity resistance training as working within the range of 60%-85% 1-RM. All moderate and high intensity resistance training programs have resulted in increased muscular strength and/or muscular endurance. One study sought to compare low and high-intensity strength training, and found greater significant improvements in the high-intensity group as compared to the low-intensity group (McNeely et al., 2008). Additional research is needed to understand the effects of a high-intensity resistance training protocol.

High-intensity resistance training has not been fully evaluated in cancer survivors. However, high-intensity resistance training has been studied in the elderly and patients with chronic diseases such as coronary artery disease, congestive heart failure, and type II diabetes with success (Ades et al., 2003; Volaklis et al., 2005). High-intensity interventions of 75-85% 1-RM have been well-tolerated and have significantly improved muscular strength, muscular endurance, and functional ability in these populations.

CHAPTER III

METHODOLOGY

Experimental Design

The purpose of this study was to investigate the effects of a 4-week high-intensity resistance training exercise intervention (HIRT) at 75%-85% estimated 1-RM on physiological and psychological measures in cancer survivors following treatment with chemotherapy and/or radiation. This was compared with a low-intensity resistance training regimen (LIRT) at 35%- 45% of 1-RM normally found in rehabilitation facilities (Schneider et al., 2007a) and a flexibility (FLEX) control group. Cancer survivors followed a 4-week resistance training regimen conducted by trained Cancer Exercise Specialists, starting no earlier than 6-weeks post completion of chemotherapy or radiation. An initial screening, physical assessment, and psychological assessment were conducted on each subject in the study, and any subject presenting with serious co-morbidity were excluded. Post physical and psychological assessments were obtained following the 4-week protocols. The initial and post assessments were used to assess muscular strength, muscular endurance, fatigue, depression, and quality of life.

Participants

Nine cancer survivors were recruited for participation in this study. Cancer survivors referred from the local medical community were screened through the Rocky Mountain Cancer Rehabilitation Institute (RMCRI) at the University of Northern Colorado to determine participation eligibility. Inclusion criteria consisted of (1) diagnosed with cancer, (2) not undergoing any type of chemotherapy or radiation therapy, (3) at least 18 years of age, (4) currently exercising less than 20 minutes per day, two days per week, (5) no serious co-morbidity, and (6) cleared by physician to exercise. Eligible and willing participants were randomly assigned to participate in one of the 4-week exercise interventions or in the flexibility control group. Random assignment of participants to the exercise interventions occurred after initial physical and psychological assessments. Three slips of paper with "Exercise 1" (HIRT) written on them, three slips with "Exercise 2" (LIRT), and three slips of paper with "Exercise 3" (FLEX) written on them were placed in an opaque container. The participants drew a piece of paper from the container, assigning them to either the flexibility group or to one of the exercise intervention groups. Participants in all groups were informed of the nature of the exercise training and that the training will take place at RMCRI under the supervision of a Certified Cancer Exercise Specialist. Initial and post physical assessments were used to establish the appropriate weight to be lifted to achieve either high or low intensity. Throughout the 4 weeks muscular strength will be reassessed using the estimated 1-RM protocol when needed or when subjects' ratings of perceived exertion no longer met the intensity requirements, thus reestablishing the weight to be lifted and ensuring the appropriate intensity. After each participant had a clear understanding of the study and protocols, they received a copy of the informed consent (see Appendix A), approved by the University of Northern Colorado Institutional Review Board (see Appendix B).

Preliminary Paperwork

Upon entry into RMCRI and before inclusion into the study, participants were given questionnaires to complete, including a cancer history, medical history, and lifestyle/activity evaluation. For measurement of psychological parameters, participants were given the Piper Fatigue Scale, the Beck Depression Inventory, and the Ferrans and Powers Quality of Life Index Cancer Version III to be filled out pre-assessment. The cancer and medical histories were used to establish the date of cancer diagnosis, the cancer stage, treatments used, pre-existing conditions, and limitations or considerations relevant to prescribing exercise. The lifestyle/activity evaluation was used to assess lifestyle choices such as tobacco use, fluctuations in body weight, and preferred modes of physical activity. The answers given for the psychological measures were discussed and clarified during the pre-assessment. Participants in all groups completed initial and post physical and psychological assessments at RMCRI. A heart rate monitor (Polar Inc., Lake Success, NY) was worn throughout the assessment to monitor heart rate and heart responses to exercise. Blood pressure and oxygen saturation were also monitored during the protocol. Height, weight, muscular strength, and muscular endurance were assessed. The muscular strength measurement was used to individualize the exercise intervention and ensure appropriate intensities (35%-45% or 75%-85% of 1-RM). Muscular strength was measured using an estimated-l-repetition maximum (1-RM) test. The Brzycki equation was used to estimate the 1-RM from the actual weight lifted and the number of repetitions lifted {1-RM = weight lifted (lb) 1 [1.0278 — (reps to fatigue x 0.0278)]}. This equation can be used for any combination of submaximal weights and repetitions to fatigue, providing that the repetitions to fatigue do not exceed 10 (Brzycki, 1993). The estimated 1-RM weight lifted was compared with age and gender norms. Muscular endurance was measured using a push-up test. Subjects were instructed to lie prone on a mat with their legs together and hands pointing forward under the shoulders. The subjects were instructed to push up from the mat by fully extending the elbows and by using either the toes (for males) or the knees (for females) as the pivot point. Subjects returned to the down position and performed as many consecutive repetitions as possible. The maximal number of completed push-ups were recorded and compared with age and gender based population norms. Fatigue was measured using the Piper Fatigue Inventory which assesses total cancer related fatigue and specifically the subscales of behavioral, affective, sensory, cognitive, and/or mood. These subscales comprise 22 points with the average score of each representing total fatigue. The range of possible scores for each subscale as well as total fatigue could range from 0 to 10. A score of 0 indicates that the cancer survivor has no fatigue; scores ranging from 1 to 3 are indicative of mild fatigue; scores 4 to 6 suggest moderate fatigue; and scores of 7 or greater indicate severe fatigue (Piper et al., 1998).

Depression was measured using the Beck Depression Inventory which is a 21-question index with scores ranging from 0 to 63; 0 being no depression and >40 being extreme depression (Salkind, 1969).

Quality of Life was measured, before and after the exercise interventions, using the Ferrans and Powers Quality of Life Index Cancer Version III. This is a 66-question index that assesses social, psychological, family, and health satisfaction. A higher total score and higher scores on the social, psychological, family, and health subscales indicate greater satisfaction. This instrument has an internal reliability of a=0.95 and a validity of r = 0.80 (Ferrans & Powers, 1985).

Exercise Intervention & Flexibility Control Group

Participants attended supervised exercise sessions three non-consecutive days per week for 4 weeks. The resistance training sessions lasted sixty minutes and consisted of a 10-minute cardiovascular warm-up on a treadmill or cycle ergometer at a low intensity, 45 minutes of high or low intensity resistance training, and 5 minutes of stretching. The flexibility sessions lasted sixty minutes and consisted of a 10-minute cardiovascular warm-up on a treadmill or cycle ergometer at a low intensity and 50 minutes of flexibility training. The HIRT sessions consisted of 3 sets of 10 repetitions to failure at 75%-85% of estimated 1-RM. The LIRT sessions consisted of 3 sets of 10 repetitions at 35%-45% of estimated 1-RM. Exercises included: leg press, leg curl, leg extension, seated chest press, seated row, lat-pulldown, and shoulder press. All exercises were completed on the Cybex® Eagle Single Station Pin Selection Series TM. The FLEX sessions consisted of dynamic, static, and proprioceptive neuromuscular function (PNF) stretching. Prior to each exercise session, a Certified Cancer Exercise Specialist askrf each subject a series of questions to elucidate any changes in medication, recurrence of cancer, health considerations, and if there was any pain or soreness as a result of the previous sessions. This information was used to evaluate subjects' ability to remain in the study and to adjust weight lifted within the desired intensity ranges. To ensure the desired intensities were being met throughout the four weeks of training, the subjects' rating of perceived exertion (RPE) using the modified 0-10 Borg RPE scale was ascertained. If RPE was lower than 7 in the HIRT group, weight was added slowly until the RPE increased. If the RPE was greater than 4 in the LIRT group, then weight was slowly decreased until the appropriate RPE was acquired. The RPE was maintained at the 1-3 range in the FLEX group. The subjects in all groups were asked to refrain from any additional physical activity, apart from normal living, during this time.

Statistical Analysis

A one-way analysis of variance (ANOVA) was used to determine if there was a significant difference between any of the groups in muscular strength, muscular endurance, fatigue, QOL, and depression between each group. Paired t-tests with equal variance were used to determine where the differences occurred. To analyze the combined changes in all psychological measures (fatigue, QOL, and depression), a one-way analysis of variance (ANOVA) was used to determine if there was a significant difference between any of the groups' percent changes. Tukey's post-hoc test was used to examine any difference between groups. A Pearson correlation was used to determine if there was a correlation between muscular strength and all other variables. Paired t-tests were used to determine if there was a significant difference between pre and post measures in each subject after exercise intervention. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS, Chicago, IL). For all of the statistical analyses the significance level was set at $\alpha = 0.5$.

CHAPTER IV

RESULTS

Participant Characteristics

Participant characteristics are shown in Table I. The study included 9 cancer survivors (3 males; 6 females) with a mean age of 54.2 ± 12.6 years. Cancer diagnosis included anal/rectal, breast, colon, esophageal, hairy cell leukemia, and pancreatic among the subjects. Of the 9 survivors, 8 completed the intervention, while 1 subject withdrew due to cancer recurrence. No significant differences were observed in weight, height, and age between the groups.

An analysis of the correlation between the time delay from the last cancer treatment (radiation, chemotherapy, and/or surgery) to the start of the exercise training and initial 1-RM yielded no significant correlation. Figure 1.

Table 1

Participant Characteristics

Group	*n*	Weight (lb)			Height (inches)			Age (years)		
FLEX	5	128.7	±	17.2	65.3	±	2.5	53.3	±	14.3
LIRT	5	189.0	±	62.4	67.5	±	3.5	54.7	±	18.0
HIRT	4	151.0	±	21.0	66.8	±	2.0	54.7	±	10.0

Values are means ± standard error; n, number of subjects; FLEX, flexibility training; LIRT, low-intensity resistance training; HIRT, high-intensity resistance training.

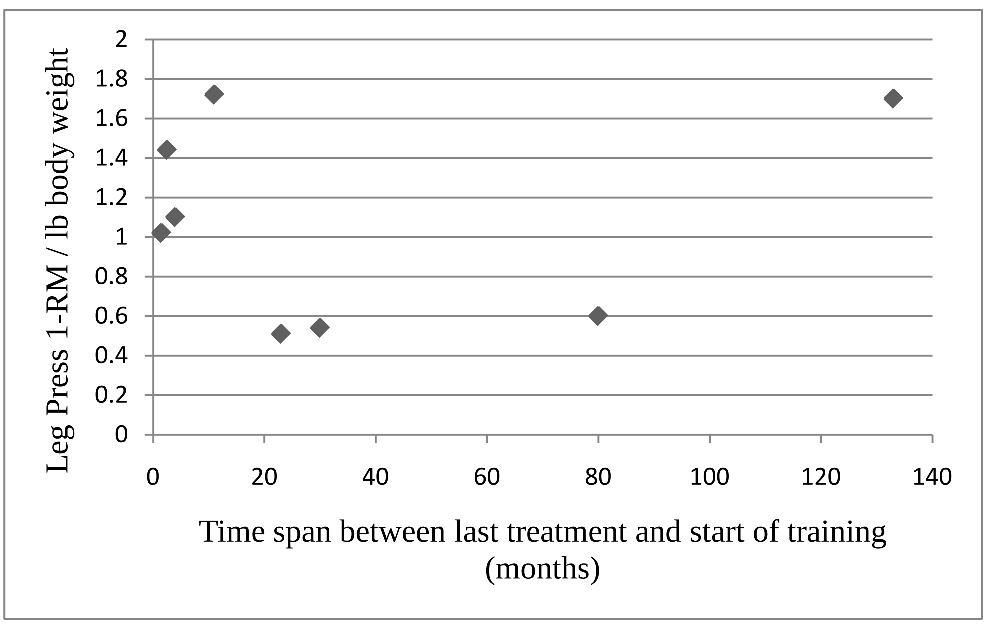

Figure 1. Leg Press Strength in Relationship to Time since Final Treatment

Strength Changes after Exercise Intervention

Strength changes after the exercise intervention in the FLEX group are shown in Table II. All exercises revealed a positive increase in strength pre to post, save the chest press, although none were significantly altered. The largest increase in the FLEX group occurred in the leg press, with an increase of 28.13% pre to post training. Strength in all exercises in the LIRT group improved following the intervention, although none yielded significance. See Table III. The chest press exercise improved by 40.48%. Strength appeared to be most affected in the HIRT group with all exercises revealing improvement in strength pre to post. See Table IV. The largest improvements occurred in the shoulder press (+70.83%), the leg press (+53.57%), and the seated row (+42.59%; $P<0.05$), the latter being significantly altered.

Table 2

Strength Changes with Exercise Interventions: FLEX Group

Strength exercise (1-RM / lb Body Weight)	*n*	Pre	Post	Percent Change	P-value
Lat-Pulldown	3	0.72 ± 0.27	0.82 ± 0.35	13.89	0.20
Shoulder Press	3	0.37 ± 0.28	0.41 ± 0.32	10.81	0.18
Chest Press	2	0.81 ± 0.71	0.63 ± 0.54	-22.22	0.77
Seated Row	3	0.57 ± 0.23	0.67 ± 0.30	17.54	0.17
Leg Press	3	1.28 ± 0.38	1.64 ± 0.53	28.13	0.12
Leg Extension	3	0.78 ± 0.28	0.90 ± 0.35	15.38	0.14
Leg Curl	3	0.66 ± 0.23	0.77 ± 0.27	16.67	0.13

Values are means ± standard error; n, number of subjects;

Table 3

Strength Changes with Exercise Interventions: LIRT Group

Strength exercise (1-RM / lb Body Weight)	*n*	Pre	Post	Percent Change	P-value
Lat-Pulldown	3	0.49 ± 0.14	0.62 ± 0.31	26.53	0.33
Shoulder Press	3	0.21 ± 0.07	0.24 ± 0.23	14.29	0.82
Chest Press	3	0.42 ± 0.35	0.59 ± 0.53	40.48	0.24
Seated Row	3	0.45 ± 0.23	0.54 ± 0.32	20.00	0.22
Leg Press	3	0.85 ± 0.51	1.15 ± 0.93	35.29	0.33
Leg Extension	3	0.43 ± 0.01	0.52 ± 0.14	20.93	0.37
Leg Curl	3	0.44 ± 0.06	0.56 ± 0.14	27.27	0.21

Values are means ± standard error; n, number of subjects;

Table 4

Strength Changes with Exercise Interventions: HIRT Group

Strength exercise (1-RM / lb Body Weight)	*n*	Pre	Post	Percent Change	P-value
Lat-Pulldown	2	0.82 ± 0.59	0.84 ± 0.55	2.44	0.50
Shoulder Press	2	0.24 ± 0.16	0.41 ± 0.16	70.83	0.41
Chest Press	2	0.49 ± 0.44	0.60 ± 0.36	22.45	0.31
Seated Row	2	0.54 ± 0.48	0.77 ± 0.50	42.59	0.04[a]
Leg Press	2	1.12 ± 0.82	1.72 ± 0.98	53.57	0.12
Leg Extension	2	0.76 ± 0.62	0.85 ± 0.59	11.84	0.14
Leg Curl	2	0.57 ± 0.34	0.67 ± 0.34	17.54	0.80

Values are means ± standard error; n, number of subjects.

[a] $P<0.05$

All three groups saw an increase in total upper and lower body strength after the exercise interventions. The HIRT group had the largest increase in both upper body strength (+53.8%) and lower body strength (+35.9%). The LIRT group had an increase in upper and lower body strength (21.3% and 24.4%, respectively), and the FLEX group had an increase in both upper and lower body strength (11.7%, 20.0%, respectively). There was a significant difference between FLEX and HIRT when comparing upper body strength pre to post training (12% versus 54%; $p=.01$). See Figure 2.

All of the groups had an increase in total strength percent change. The FLEX group increased their overall strength by 15%, the LIRT group by 23%, and the HIRT by 46%. There was a significant increase between HIRT and FLEX (15% versus 46%; $p<.005$), and there was a near significance between LIRT and HIRT (23% versus 46%; $p=.08$).

The strength training exercise interventions increased muscular endurance in the HIRT (+190.00%) and the LIRT (+3.03%), while the FLEX group showed no changes in muscular endurance. There was a significant difference between HIRT and FLEX and between HIRT and LIRT ($p=.05$).

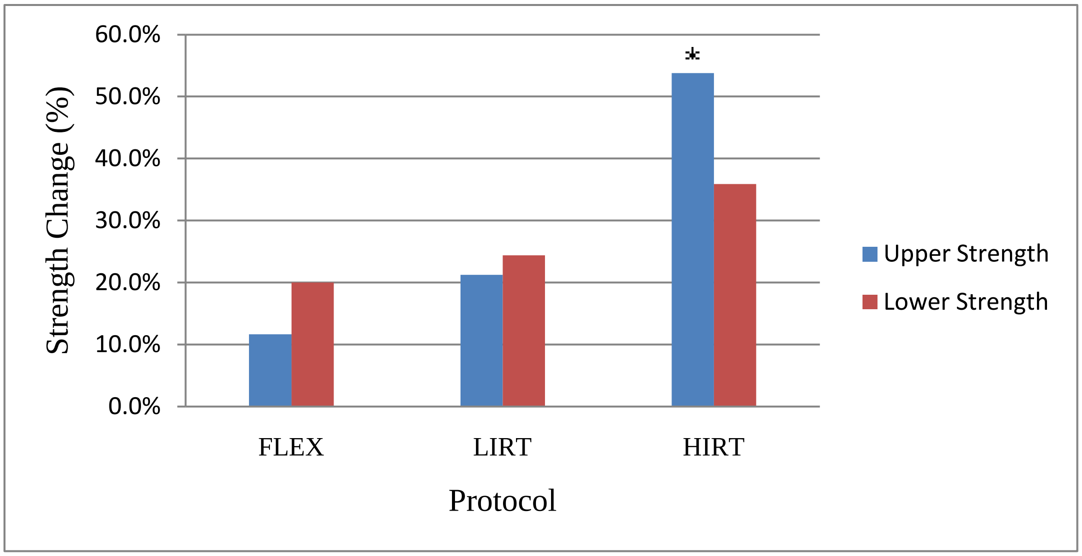

Figure 2. Percent Change in Strength after Exercise Training

** P<0.05, significantly different than FLEX*

Psychological Changes after Exercise Intervention

Each groups' psychological pre to post measures are shown in Tables V, VI, and VII. The percent change in psychological measures after exercise training are shown in Figure 3. The exercise interventions showed an overall decrease in total fatigue (-28.2%), an overall increase in QOL (+14.48%), and an overall decrease in depression (-58.25%).

Table 5

Psychological Changes with Exercise Interventions: FLEX Group

Psychological Measure	*n*	Pre	Post	Percent Change	P-value
Total Fatigue	3	6.66 ± 0.59	4.52 ± 0.58	-31.21	0.09
Quality of Life	3	20.48 ± 2.45	22.0 ± 2.00	8.99	0.47
Depression	3	12.67 ± 2.40	5.67 ± 0.33	-50.60	0.11

Values are means ± standard error; n, number of subjects.

Table 6

Psychological Changes with Exercise Interventions: LIRT Group

Psychological Measure	*n*	Pre	Post	Percent Change	P-value
Total Fatigue	3	4.79 ± 1.41	3.12 ± 1.60	-47.61	0.07
Quality of Life	3	19.18 ± 1.76	23.69 ± 2.57	23.18	0.04[a]
Depression	3	8.33 ± 1.20	3.33 ± 1.45	-57.78	0.13

Values are means ± standard error; n, number of subjects.

[a] $P<0.05$

Table 7

Psychological Changes with Exercise Interventions: HIRT Group

Psychological Measure	*n*	Pre	Post	Percent Change	P-value
Total Fatigue	2	4.65 ± 3.65	2.91 ± 1.31	5.42	0.59
Quality of Life	2	16.65 ± 5.45	18.22 ± 5.86	9.66	0.16
Depression	2	12.50 ± 9.50	6.50 ± 6.50	-70.45	0.30

Values are means ± standard error; n, number of subjects.

All groups had decreases in total fatigue, except the HIRT group. The HIRT group had an increase of 5.42%. The LIRT had a decrease of 47.61%, and the FLEX group's total fatigue score decreased by 31.21%, and approached significance (*p=0.09*). There was a significant difference in total fatigue between the LIRT and HIRT group (*p=0.02*). Each group revealed increases in QOL; FLEX increased by 8.99%, the HIRT group by 9.66%, and the LIRT group had the greatest significant increase of 23.18% (*p=0.04*). All groups show a dramatic decrease in depression after the exercise interventions; the largest decrease was seen in the HIRT group, which reduced their depression scores by 70.45%. The FLEX group had a 50.60% decrease in depression, and the LIRT group had a 57.78% decrease.

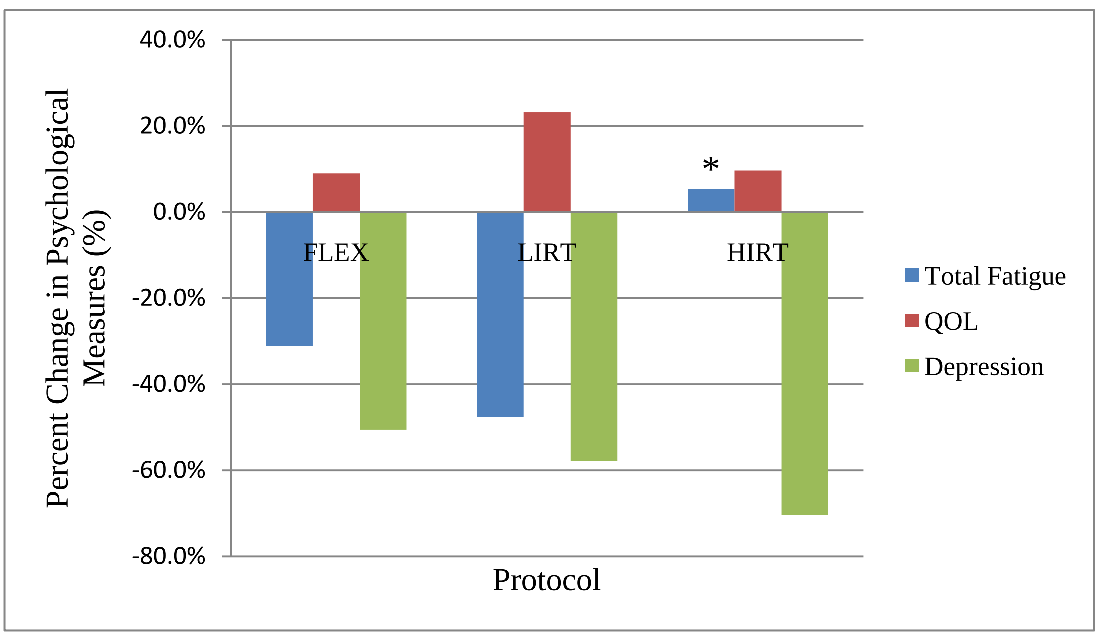

Figure 3. Percent Change in Psychological Measures after Exercise Training

* *P<0.05,* significantly different than LIRT

A Pearson correlation between muscular strength of the lat pull-down and seated row revealed an inverse relationship between strength and depression (r=0.53 for each). See Figure 4.

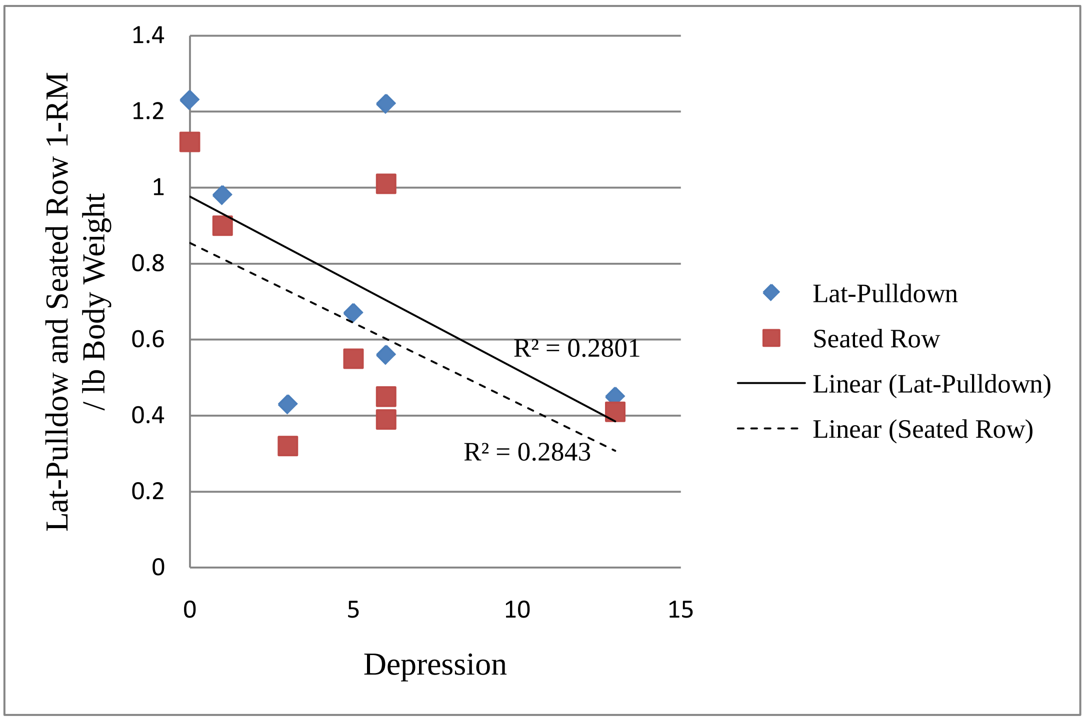

Figure 4. Correlation between Muscular Strength and Depression

CHAPTER V

DISCUSSION

A pure resistance training exercise intervention has not yet been evaluated in cancer survivors following treatment. The purpose of this study was to investigate the changes that might occur with a high-intensity resistance training protocol and compare this with an established (Schneider, Dennehy, & Carter, 2003) low-intensity resistance training protocol and a flexibility-based control group.

The three eldest subjects were spread evenly between the three groups, therefore no one group's results could be attributed to the age of the subjects. Regardless, research has shown that there is no doubt that older adults undergo skeletal muscle hypertrophy and improve in strength in response to resistance training (Folland & Williams, 2007), although the absolute increase is smaller than when compared to young adults. One study using similar methodology as our study, tested the difference between two resistance training regimens [low-intensity (LI) at 40% 1-RM and high-intensity (HI) at 80% 1-RM], against a sedentary control group for 10 weeks in healthy, older subjects. Strength and endurance increased significantly in the HI and LI groups (35.40% and 25.77%, respectively) as compared with no change in the control. Changes in HI were significantly different than those observed in the LI group ($p<0.001$). This agrees with the findings of our study as total strength improved in the FLEX, LIRT, and HIRT groups by 15%, 23%, and 46%, respectively. There was a linear increase in total strength, with each group near doubling its strength gains from the previous group. This suggests the greater the training intensity, the greater the increases, which supports research by Folland and Williams (2007) who found strength gains and hypertrophic responses are dependent on training load. To further illustrate this point, the MET values for each group were assessed using the Compendium of Physical Activity (Ainsworth, Haskell, Leon, Jacobs, Montoye, Sallis, et al., 1993). The FLEX group was estimated at 2.5 METS, the LIRT group at 3 METS, and the HIRT group at 6 METS. These values show the same doubling, linear increase as the gains in strength.

It is important to note that the HIRT group was the only group which increased in intensity during the 4 week protocol. If the subjects' rating of perceived exertion fell below a rating of 7 during an exercise, the load was increased so the subjects fatigued by the 10^{th} repetition. This was unique to this group, as the FLEX protocol never changed, and the opposite procedure was undertaken with the LIRT group. After the exercise intensity was set at 35%-45% 1-RM in this group, the weight was lowered at some points due to subjects reporting an RPE of greater than 4. Because of this methodological difference, the HIRT group was the only group which experienced muscular stress continuously.

In the present study, high-intensity training yielded larger increases in upper body muscular strength as compared to both LIRT and FLEX groups, the latter being significant ($p=0.01$), which agrees with other literature suggesting a greater hypertrophic response to resistance training in upper body musculature as compared with lower extremity muscles in previously untrained individuals (Folland & Williams, 2007).

It has been well noted that neurological adaptations contribute to the muscular changes in strength and performance during the first 6-8 weeks of resistance training

(Folland & Williams, 2007; Julien, Marie, & Alain, 2005), while the changes following this period are due to muscular adaptations such as hypertrophy. A study by Julien at al. (2005) found that during the first 4 weeks of training in healthy subjects, the increase in voluntary strength could be ascribed to an increase in neural activation occurring at the spinal and/or supraspinal level. A training regimen lasting more than 6 weeks appears to be effective to induce morphological changes in muscle. Since our exercise intervention was 4 weeks in length, we can conclude that neural adaptations account for the initial increases in strength and endurance. These neural adaptations are essentially changes in coordination and learning that facilitate improved recruitment and activation of the involved muscles (Folland & Williams, 2007), therefore some of the increases in strength can be explained by how well each subject learned and became acclimated to the exercises. This could explain differences in recruitment between subjects who have weight trained previously in life and subjects who have never used a weight machine. This protocol needs to be tested beyond 8 weeks, to analyze the muscular adaptations that will likely occur.

It has been shown that any type of physical activity can decrease fatigue in cancer survivors (Escalante & Manzullo, 2009; Meeske et al., 2007; Winters-Stone et al, 2008). In fact, participating in at least 4 hours of physical activity a week had a nearly 50% reduction rate in fatigue (Meeske et al., 2007). Our study provided the subjects with 3 hours of exercise per week and fatigue decreased in both the LIRT and FLEX groups. Perhaps increasing the duration of this protocol, either by session length or number of sessions would provide greater reductions in fatigue.

Interestingly, fatigue in cancer survivors has been found to increase in those who have poor lower-body strength. In a study by Winters-Stone et al. (2008), lower-extremity strength was inversely related to fatigue and accounted for 15.1% ($P<0.01$) of the variance in fatigue scores. As mentioned previously, all three groups were successful at improving lower body strength. It is important to note that although the HIRT group improved by 35.9% in lower body strength, it failed to decrease in levels of fatigue. This result may not be entirely accurate, as it appears the HIRT group contained an outlier with regards to fatigue and contained the smallest number of subjects (n=2). Although both subjects improved in lower body strength, one subject decreased in fatigue by 49% (the second largest decline in the study), while the other subject increased in fatigue by 60% (the only increase). If an increase in lower body strength has been seen to attenuate fatigue, the improvements in the simple and very low intensity FLEX group may be valuable in the rehabilitation of cancer survivors, the elderly, frail, or injury prone subjects.

Of all the psychological measures tested in our study, depression was the most affected. This is concurrent with another study which tested a high-intensity resistance training protocol (80%1-RM), and a low-intensity resistance training protocol (20% 1-RM), against standard care (SC) in healthy patients with depression (Singh et al., 2005). A 50% reduction was achieved in 61% of the high-intensity group, 29% of the low-intensity group, and only 21% of the SC ($p=0.03$). Strength gain was directly associated with reduction in depressive symptoms ($r=0.40$; $p=0.004$). This agreed with our findings as depression decreased by 70.45% in HIRT, 57.78% in LIRT, and 50.60% in FLEX. Depression was inversely associated with strength gains ($r=0.53$).

It has been shown that flexibility shows similar results as various cardiovascular programs when it comes to increasing lower body strength and physical function in healthy, older adults. Misic et al. (2009) compared a cardiovascular regimen at 75% $HR_{reserve}$ against a FLEX protocol similar to ours. Both groups improved significantly in lower body strength by 21-65% ($p<0.05$), as well as in physical function ($p<0.05$). They concluded that sedentary older adults achieve similar improvements in strength and physical function with either cardiovascular or FLEX training, with the latter being related to improvements in leg strength. Our study with cancer survivors found lower average improvements in lower body strength in the FLEX group (20%), however one subject improved by 50%. It is interesting to note that the average difference between the FLEX group and LIRT group in lower body strength only differed by 4.4%. FLEX appeared to be equally as effective as lower-intensity resistance training in our study and equally as effective as moderate intensity cardiovascular training in the aforementioned study.

Our study was the first to compare a flexibility program to two resistance training regimens in cancer survivors. This program was chosen to represent a control group, however it has been suggested that gentler physical activities such as stretching or Yoga may help promote regular participation, especially in chronic disease populations (Culos-Reed, Carlson, Daroux, & Hately-Aldousa, 2006). Culos-Reed et al. (2006) demonstrated this by using a modified yoga program that was very similar to our FLEX group in breast cancer survivors. They found that the stretching group increased their QOL values by 17.46% from pre to post ($p<0.01$) while the control group only increased by 0.7%, with a significant difference between the two groups ($p<0.01$). Depression scores did not differ significantly between the two groups. Our study showed an improvement in QOL in the FLEX group, but it was not significant compared to the other two groups. In fact, the LIRT group was the only group to improve significantly ($p=0.04$). This suggests that a FLEX group may provide better psychological benefits, but this may not be as effective as resistance training. Regardless, our FLEX group may not have been an appropriate control.

As stated previously, it must be noted that our FLEX group did affect muscular strength, muscular endurance, and psychological measures in the 4 weeks of our study. These changes were not as great as the other two groups, however it may be safe to assume FLEX training has merit and may not be a suitable control group for many studies. This type of training if it does cause positive effects will increase the risk of type II error in a study. However, if subjects in the control group are not offered an attractive intervention, we believe that withdrawal in the control group could bias the result of the study. Therefore the activity in the control group must be perceived as relevant to the subjects in order to keep them compliant.

Conclusion

It is apparent that HIRT is the most effective protocol for improving muscular strength and endurance in cancer survivors. Many other studies have found a correlation between increased muscular strength and improved fatigue, QOL, and depression. This study lacked the sample size and length to fully evaluate these trends. Strength did appear to be inversely correlated with reductions in depression, supporting the role of high-intensity resistance training in managing this deleterious side effect. Only the LIRT group significantly altered QOL, although all three protocols experienced improvement.

Both FLEX and LIRT decreased levels of fatigue, however the HIRT group appeared to contain an outlier. All three protocols appear to have merit and more research must be done to understand what role each intervention may play in cancer rehabilitation.

Future Research

The subject size and length of the protocol are the largest limitations to the present study. A protocol of 8-12 weeks is adequate to show the muscular adaptations that occur with training and this length may be necessary to demonstrate the effects of a high-intensity resistance training protocol. High-intensity resistance training can be quantified as reaching muscular failure (American College of Sports Medicine, 2009), therefore any protocol which causes this can be considered high-intensity training. Some subjects may not enjoy or may find heavy lifting (>75% 1-RM) difficult. A protocol that involves lighter weight with higher repetitions to failure should be tested.

In the present study, it should be noted that the flexibility group had results not anticipated in a control group. This type of protocol may prove of great benefit to subjects who cannot, or do not want to participate in traditional exercise, as well as cancer survivors who are in treatment or immediately following treatment.

REFERENCES

Adamsen, L., Midtgaard, J., Rorth, M., Borregaard, N., Andersen, C., Quist, M., et al. (2003). Feasibility, physical capacity, and health benefits of a multidimensional exercise program for cancer patients undergoing chemotherapy. *Support Care Cancer , 11*, 707-716.

Ades, P. A., Savage, M. E., Cress, M., Brochu, M., Lee, N. M., & Poehlman, E. T. (2003). Resistance training on physical performance in disabled older female cardiac patients. *Medicine and Science in Sports and Exercise , 35* (8), 1265-1270.

Ainsworth, B. E., Haskell, W. L., Leon, A. S., Jacobs, D. R., Montoye, H. J., Sallis, J. F., et al. (1993). Compendium of physical activities: Classification of energy costs of human physical activities. *Medicine and Science in Sports and Exercise , 25*, 71-80.

Al-Majid, S., & McCarthy, D. O. (2001). Cancer-induced fatigue and skeletal muscle wasting: the role of exercise. *Biological Research for Nursing , 2* (3), 186-197.

Al-Majid, S., & Waters, H. (2008). The biological mechanisms of cancer-related skeletal muscle wasting: the role of progressive resistance exercise. *Biological Research for Nursing , 10* (1), 7-20.

American Cancer Society. (2009). *Cancer Facts & Figures 2009.* Atlanta, GA.

American College of Sports Medicine. (2009). *ACSM's Guidelines For Exercise Testing and Prescription* (Eighth ed.). Baltimore, Maryland: Lippincott Williams & Williams.

Andreyev, H. J., Norman, A. R., Oates, J., & Cunningham, D. (1998). Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastronintestinal malignancies? *European Journal of Cancer , 34*, 503-509.

Blanchard, C. M., Baker, F., Denniston, M. M., Courneya, K. S., Hann, D. M., Gesme, D. H., et al. (2003). Is absolute amount or change in exercise more associated with quality of life in adult cancer survivors? *Preventative Medicine , 37*, 389-395.

Cadmus, L. A., Salovey, P., Yu, H., Chung, G., Kasl, S., & Irwin, M. L. (2009). Exercise and quality of life during and after treatment for breast cancer: results of two randomized controlled trials. *Psycho-Oncology , 18*, 343-352.

Courneya, K. S., Friedenreich, C. M., Quinney, H. A., Fields, A. L., Jones, L. W., & Fairey, A. S. (2003). A randomized trial of exercise and quality of life in colorectal cancer survivors. *European Journal of Cancer Care , 12*, 347-357.

Courneya, K. S., Karvinen, K. H., Campbell, K. L., Pearcey, R. G., Dundas, G., Capstick, V., et al. (2005). Associations among exercise, body weight, and quality of life in a population based sample of endometrial cancer survivors. *Gynecologic Oncology , 97* (2), 422-430.

Courneya, K. S., Mackey, J. R., Bell, G. J., Jones, L. W., Field, C. J., & Fairey, A. S. (2003). Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. *Journal of Clinical Oncology , 21* (9), 1660-1668.

Culos-Reed, N. S., Carlson, L. E., Daroux, L. M., & Hately-Aldousa, S. (2006). Pilot study of yoga for breast cancer survivors: physical and psychological benefits. *Psycho-Oncology , 15*, 891-897.

De Backer, I. C., Schep, G., Backx, F. J., Vreugdenhil, G., & Kuipers, H. (2009). Resistance training in cancer survivors: a systematic review. *International Journal of Sports Medicine , 30*, 703-712.

De Backer, I. C., Van Breda, E., Vreugdenhil, A., Nijziel, M. R., Kester, A. D., & Schep, G. (2007). High-intensity strength training improves quality of life in cancer survivors. *Acta Oncologica , 46*, 1143-1151.

De Backer, I. C., Vreugdenhil, G., Nijziel, M. R., Kester, A. D., Van Breda, E., & Schep, G. (2008). Long-term follow-up after cancer rehabilitation using high-intensity resistance training: persistent improvement of physical performance and quality of life. *British Journal of Cancer , 99*, 30-36.

DeWys, W. D., Becc, C., Lavin, P. T., Band, P. R., Bennet, J. M., Bertino, J. R., et al. (1980). Prognostic effect of weight loss prior to chemotherapy in cancer patients. *American Journal of Medicine , 69*, 491-497.

Dunstan, D. W., Daly, R. M., Owen, N., Jolley, D., De Courten, M., Shaw, J., et al. (2002). High-intensity resistance training improves glycemic control in older patients with type 2 diabetes. *Diabetes Care , 25* (10), 1729-1736.

Escalante, C. P., & Manzullo, E. F. (2009). Cancer-related fatigue: the approach and treatment. *Journal of General Internal Medicine , 24* ((Suppl 2)), 412-416.

Fearon, K. C. (1992). The Sir David Medical Lecture 1991. The mechanisms and treatment of weight loss in caner. *Proc Nutr Soc*, *51* (2), 251-265.

Folland, J. P., & Williams, A. G. (2007). The adaptations to strength training: morphological and neurological contributions to increased strength. *Sports Medicine , 37* (2), 145-168.

Fujita, M., Abe, T., Drummond, T., Cadenas, J. G., Dreyer, H. C., Sato, Y., et al. (2007). Blood flow restriction during low-intenstiy resistance exercise increases S6K1 phosphorylation and muscle protein synthesis. *Journal of Applied Physiology , 103*, 903-910.

Galvao, D. A., Nosaka, K., Taaffe, D. R., Peake, J., Spry, N., Suzuki, K., et al. (2008). Endocrine and immune responses to resistance training in prostate cancer patients. *Prostate Cancer and Prostatic Diseases , 11*, 160-165.

Galvao, D. A., Nosaka, K., Taaffe, D. R., Spry, N., Kristjanson, L. J., McGuigan, M. R., et al. (2006). Resistance training and reduction of treatment side effects in prostate cancer patients. *Medicine and Science in Sports and Exercise , 38* (12), 2045-2052.

Galvao, D. A., Taaffe, D. R., Spry, N., & Newton, R. U. (2007). Exercise can prevent and even reverse adverse effects of androgen suppression treatment in men with prostate cancer. *Prostate Cancer and Prostatic Disease , 10*, 340-346.

Hanna, L. R., Avila, P. F., Meteer, J. D., Nicholas, D. R., & Kaminsky, L. A. (2008). The effects of a comprehensive exercise program on physical function, fatigue, and mood in patients with various types of cancer. *Oncology Nursing Forum , 35* (3), 461-468.

Hayes, S. C., Rowbottom, D., Davies, P. S., Parker, T. W., & Bashford, J. (2003). Immunological changes after cancer treatment and participation in an exercise program. *Medicine and Science in Sports and Exercise , 35* (1), 2-9.

Hutnick, N. A., Williams, N. L., Kraemer, W. J., Ortega-Smith, E., Dixon, R. H., Bleznak, A. D., et al. (2005). Exercise and lymphocyte activation following chemotherapy for breast cancer. *Medicine and Science in Sports and Exercise, 37* (11), 1827-1835.

Jones, E. G., Rutherford, O. M., & Parker, D. F. (1989). Physiological changes in skeletal muscle as a result of strength training. *Quarterly Journal of Experimental Physiology , 74*, 233-256.

Julien, G., Marie, G., & Alain, M. (2005). Neural and muscular changes after 4 and 8 weeks of electromyostimulation training. *Computer Methods in Biomechanics and Biomedical Engineering , 8*, 119-120.

Kim, S. H., Son, H. B., Hwang, S. Y., Han, W., Yang, J., Lee, S., et al. (2008). Fatigue and depression in disease-free breast cancer survivors: prevalence, correlates, and associate with quality of life. *Journal of Pain and Symptom Management , 35* (6), 644-655.

Kraemer, W. J., & Ratamess, N. A. (2004). Fundamentals of resistance training: progression and exercise prescription. *Medicine and Science in Sports and Exercise , 36* (4), 674-688.

Krogh, J., Petersen, L., Timmermann, M., Saltin, B., & Nordentoft, M. (2007). Design paper: the DEMO trial: a randomized, parallel-group observer-blinded clinical trial of aerobic versus non-aerobic versus relaxation training for patients with light to moderate depression. *Contemporary Clinical Trials , 28*, 79-89.

Lee, I.-M. (1995). Exercise and physical health: cancer and immune function. *Research Quarterly for Exercise and Sport , 66* (4), 286-291.

Ligibel, J. A., Campbell, N., Partridge, A., Chen, W. Y., Salinardi, T., Chen, H., et al. (2008). Impact of a mixed strength and endurance exercise intervention on insulin levels in breast cancer survivors. *Journal of Clinical Oncology , 26* (6), 907-912.

Mayo Clinic Staff. (2009). *Cancer survivors: managing late effects of cancer treatment.* Mayo Foundation for Medical Educationa and Research.

McNeely, M. L., Campbell, K. L., Rowe, B. H., Klassen, T. P., Mackey, J. R., & Courney, K. S. (2006). Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. *Canadian Medical Association Journal, 175* (1), 34-41.

McNeely, M. L., Parliament, M. B., Seikaly, H., Jha, N., Magee, D. J., Haykowsky, M. J., et al. (2008). Effect of exercise on upper extremity pain and dysfunction in head and neck cancer survivors. *Cancer , 113*, 214-222.

McTiernan, A., (2004). Physical activity after cancer: physiologic outcomes. *Cancer Investigation*, *22* (1), 68-81.

Meeske, K., Smith, A. W., Alfano, C. M., McGregor, B. A., McTiernan, A., Baumgartner, K. B., et al. (2007). Fatigue and breast cancer survivors two to five years post diagnosis: a HEAL study report. *Quality of Life Research , 16* (6), 947-960.

Misic, M. M., Valentine, R. J., Rosengren, K. S., Woods, J. A., & Evans, E. M. (2009). Impact of training modality on strength and physical function in older adults. *Gerontology , 55*, 411-416.

Moadel, A. B., Shah, C., Wylie-Rosett, J., Harris, M. S., Patel, S. R., Hall, C. B., et al. (2007). Randomized controlled trial of Yoga among a multiethnic sample of breast cancer patients: effects on quality of life. *Journal of Clinical Oncology , 25,* 4387-4395.

Nieman, D. C. (1994). Exercise, upper respiratory infection, and the immune system. *Medicine and Science in Sports and Exercise , 26,* 128-139.

Nieman, D. C., Cook, V. D., Henson, D. A., Suttles, J., Rejeski, W. J., Ribisl, P. M., et al. (1995). Moderate exericse training and natural killer cell cytotoxic activity in breast cancer patients. *Journal of International Sports , 16* (5), 224-337.

Nieman, D. C., Nehlsen-Cannarella, S. L., & Markoff, P. A. (1990). The effects of moderate exercise training on natural killer cells and acute respiratory infection. *International Journal of Sports Medicine , 11,* 467-473.

Ohira, T., Schmitz, K. H., Ahmed, R. L., & Yee, D. (2006). Effects of Weight Training on Quality of Life in Recent Breast Cancer Survivors. *Cancer , 106,* 2076-2083.

Oldervoll, L. M., Kaasa, S., Hjermstad, M. J., Lund, J. A. & Loge, J. H. (2004). Physical exercise results in the improved subjective well-being of a few or is effective rehabilitation for all cancer patients? *European Journal of Cancer, 40,* 1951-1962.

Piper, B. F., Dibble, S.L., Dodd, M. J., Weiss, M. C., Slaughter, R.E., Paul, S.M. (1998). The revised Piper Fatigue Scale: psychometric evaluation in women with breast cancer. *Oncology Nursing Forum*, *25,* 677-684.

Salkind, M. R. (1969). Beck depression inventory in general practice. *Coll Gen Pract, 18,* 267-271.

Schneider, C. M., Dennehy, C. A., & Carter, S. D. (2003). *Exercise and Cancer Recovery.* Champaign, IL: Human Kinetics.

Schneider, C. M., Hsieh, C. C., Sprod, L. K., Carter, S. D., & Hayward, R. (2007a). Cancer Treatment-Induced Alterations in Muscular Fitness and Quality of Life: the Role of Exercise Training. *Annals of Oncology , 18* (12), 1957-1962.

Schneider, C. M., Hsieh, C. C., Sprod, L. K., Carter, S. D., & Hayward, R. (2007b). Effects of supervised exercise training on cardiopulmonary function and fatigue in breast cancer survivors during and after treatment. *Cancer , 110* (4), 918-925.

Schwartz, A. I., Mori, M., Gao, R., Nail, L. M., & King, M. E. (2000). Exercise reduces daily fatiguein women with breast cancer receiving chemotherapy. *Medicine and Science in Sports and Exercise , 33* (5), 719-723.

Segal, R. J., Reid, R. D., Courneya, K. S., Malone, S. C., Parliament, M. B., Scott, C. G., et al. (2003). Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *Journal of Clinical Oncology , 21*, 1653-1659.

Seynnes, O., Singh, M. A., Hue, O., Pras, P., Legros, P., & Bernard, P. L. (2004). Physiological and functional responses to low-moderate verus high-intensity progressive resistance training in frail elders. *The Journals of Gerontology , 59* (5), M503-M509.

Singh, N. A., Stavrinos, T. M., Scarbek, Y., Galambos, G., Liber, C., Singh, M. A., et al. (2005). A randomized controlled trial of high versus low intensity weight training versus general practioner care for clinical depression in older adults. *The Journals of Gerontology , 60A* (6), 768-776.

Stewart, G. D., Skipworth, R. J., & Fearon, K. C. (2006). Cancer cachexia and fatigue. *Clinical Medicine , 6*, 140-143.

Tisdale, M. J. (2002). Cachexia in cancer patients. *Nature Publishing Group , 2*, 862-871.

Volaklis, Konstantinos, A., Tokmakidis, & Savvas, P. (2005). Resistance exercise training in patients with heart failure. *Sports Medicine* , *35* (12), 1085-1103.

Winters-Stone, K. M., Bennett, J. A., Nail, L., & Schwartz, A. (2008). Stength, physical activity, and age predict fatigue in older breast cancer survivors. *Oncology Nursing Forum* , *35* (5), 815-821.

Woods, J. A., Davis, J. M., Mayer, E. P., Ghaffer, A., & Pate, R. R. (1993). Exercise increases inflammatory macrophage cytotoxicity. *Journal of Applied Physiology, 75*, 879-886.

APPENDIX A

INFORMED CONSENT FOR PARTICIPATION IN RESEARCH

Informed Consent for Participation in Research

<u>Project Title</u>:

The Effects of a High-Intensity, Resistance Training Program on Muscular Strength, Muscular Endurance, and Psychological Measures in Cancer Survivors

Rocky Mountain Cancer Rehabilitation Institute
Jessica Weiderspon, B.S. Head Researcher
Jessica.weiderspon@unco.edu
Chris Repka, M.S., Clinical Coordinator
Chris.repka@unco.edu
Carole M. Schneider, Ph.D., Director

You are being asked to participate in a research study collecting information to assess the effect of an exercise program on muscular strength, muscular endurance, fatigue, quality of life, and depression following cancer treatment. The Rocky Mountain Cancer Rehabilitation Institute (RMCRI) supports the practice of protection of human subjects participating in research. The following information is provided for you to decide whether you choose to participate in the present study. You should be aware that even if you agree to participate, you are free to withdraw at any time without affecting your opportunities in other projects offered by the Institute.

This project involves exercise in the form of resistance training, at either a low-intensity or a high-intensity, and flexibility training. Resistance training, also known as strength training, is a type of exercise which causes the muscles to contract against an external resistance such as on a weight machine. Measurement of muscular strength will be assessed using an estimated 1-repetition max test. Measurement of muscular endurance will be measured using a push-up test. Measurement of oxygen consumption on a motor-driven treadmill will assess your cardiorespiratory capacity. The pulmonary function test requires maximum exhalation into a sterile mouthpiece. Heart rate, blood pressure, height, weight, and circumference measurements are also taken. Forms to be completed include cancer history, medical history, cardiovascular risk profile, lifestyle/activity questionnaire, quality of life scores, and fatigue and depression scales. Assessments will take place at RMCRI and take approximately 2 hours to complete. Following the assessment of your muscular strength and muscular endurance the results will be analyzed and an exercise prescription written.

You will be randomly selected to be a part of either of the three exercise protocols, and all have merit. Following the 12 week period of exercise intervention, you will have the opportunity to participate in any of the three training interventions or the standard RMCRI protocol at no cost. A great benefit for participating in this study is exercise training with trained Cancer Exercise Specialists. Additionally, each participant will be provided a summary of his or her exercise data at the beginning and the end of the project period with a clear and concise exercise intensity recommendation based upon the exercise assessment results. There is no compensation for participating in this study.

The resistance training interventions will include 1 hour training sessions 3 days per week with trained Cancer Exercise Specialists. Every four weeks, for a total of three tests, excluding the pre and post assessments, muscular strength will be reevaluated in the resistance training participants. This will ensure those selected are continually lifting at the appropriate intensity. On these three occasions, the resistance training participants will arrive 15 minutes earlier than normal, and after a 10-minute cardiovascular warm-up, will complete the estimated 1-RM protocol in all muscle groups used. The exercise protocol will follow. The flexibility intervention will include 40 minute sessions 3 days per week with trained Cancer Exercise Specialists.

This study will run under the supervision of the RMCRI director, RMCRI Clinical Coordinator, and lead investigator, but other persons will be associated with or assist in the data collection. The obtained data may be used in reports or publications but your identity will not be associated with such reports. A number will be used as your identification and your medical and exercise information kept in a locked file cabinet available only to the lead investigator. Confidentiality will only be broken if our assessment reveals that you are severely depressed or if you indicate you are a threat to yourself or to others, at which time you will be referred through our ancillary services for psychological counseling.

This research should not result in physical injury; however, physical injury may occur. Additionally, the VO_{2peak} fitness test used to assess your cardiorespiratory capacity can be uncomfortable. The duration of the discomfort is short. If you are injured as a result of this study, you will treated in the usual manner and charges billed to your insurance/self. The study will not pay for health care costs.

Participation is voluntary. You may decide not to participate in this study and if you begin participation you may still decide to stop and withdraw at any time. Your decision will be respected and will not result in loss of benefits to which you are otherwise entitled. Having read the above and having had an opportunity to ask any questions, please sign below if you would like to participate in this research. A copy of this form will be given to you to retain for future reference. If you have any concerns about your selection or treatment as a research participant, please contact the Office of Sponsored Programs, Kepner Hall, University of Northern Colorado Greeley, CO 80639; 970-351-2161.

______________________________ ________________________________

Participant Name DATE **Signature of Researcher DATE**

______________________________ ___________________________________

Signature of Subject Agreeing to Participate. By signing this consent you certify you are at least 18 years of age. **Signature of Medical Director DATE**

APPENDIX B

INSTITUTIONAL REVIEW BOARD APPROVAL

STUDENT'S COPY

UNIVERSITY of NORTHERN COLORADO
Institutional Review Board (IRB)

January 15, 2010

TO: Heather Helm
APCE

FROM: Gary Heise, Co-Chair GDH
UNC Institutional Review Board

RE: Expedited Review of Proposal, *Effects of a High-Intensity, Resistance Training Program on Muscular Strength, Muscular Endurance, and Psychological Measures in Cancer Survivors,* submitted by Jessica M. Weiderspon (Research Advisor: Carole Schneider)

First Consultant: The above proposal is being submitted to you for an expedited review. Please review the proposal in light of the Committee's charge and direct requests for changes directly to the researcher or researcher's advisor. If you have any unresolved concerns, please contact Gary Heise, School of Sport and Exercise Science, Campus Box 39, (x1738). When you are ready to recommend approval, sign this form and return to me.

I recommend approval as is. Heather Helm 2.15.10
Signature of First Consultant Date

The above referenced prospectus has been reviewed for compliance with HHS guidelines for ethical principles in human subjects research. The decision of the Institutional Review Board is that the project is approved as proposed for a period of one year: 18 FEB 2010 to 18 FEB 2011.

Gary D. Heise 18 FEB 2010
Gary Heise, Co-Chair Date
as revised

Comments: