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Effects of a Twelve Week Aerobic and Strength Training Intervention on Chemotherapy-Induced Peripheral Neuropathy

Sherilyn M. Sommerville

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UNIVERSITY OF NORTHERN COLORADO

Greeley, Colorado

The Graduate School

EFFECTS OF A TWELVE WEEK AEROBIC AND
STRENGTH TRAINING INTERVENTION ON
CHEMOTHERAPY-INDUCED
PERIPHERAL NEUROPATHY

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

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

May 2016

This Thesis by: Sherilyn M. Sommerville

Entitled: *Effects Of A Twelve Week Aerobic Training And Strength Training Intervention On Chemotherapy-Induced Peripheral Neuropathy*

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

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ABSTRACT

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Chemotherapy is one of the most effective cancer treatments to date; however, it has the potential to produce debilitating life-long side effects. Chemotherapy-induced peripheral neuropathy is a side effect caused by toxic chemotherapy agents that deteriorate the peripheral nerves of the body. Research has suggested that aerobic and strength training may be able to alleviate some of the symptoms associated with chemotherapy-induced peripheral neuropathy. Some of the benefits of both aerobic and strength training include increasing blood and nutrient flow to the peripheral nerves, which could help restore sensation and alleviate the some symptoms of chemotherapy-induced peripheral neuropathy. However, to our knowledge, there is little research evaluating the effects of an aerobic and strength-training intervention on chemotherapy-induced peripheral neuropathy. **Purpose:** The purpose of this study was to examine the effects of a 12-week aerobic and strength training intervention on the symptoms of chemotherapy-induced peripheral neuropathy. **Methods:** Ten participants (aged 48-76) participated in a 12-week exercise intervention and completed a pre-, mid-, and post-4.17/1g Semmes Weinstein Monofilament Test and 5.07/10g Semmes Weinstein Monofilament Test. A comprehensive physical assessment was completed before and after the 12-week intervention. **Results:** Wilk's Lambda Multivariate analysis of variance

revealed significant ($p < 0.05$) changes from pre-, mid-, and post- 4.17/1g Semmes Weinstein Monofilament Test scores. However, there were no significant ($p < 0.05$) results detected with the 5.07 Semmes Weinstein Monofilament test. Paired samples t-tests revealed significant ($p < 0.05$) differences between aerobic and several strength tests from pre- to post-assessment. Several psychological scores improved significantly ($p < 0.05$) as well from pre- to post- assessment. **Conclusion:** Significant improvements were observed for the 4.17/1g Semmes Weinstein Monofilament test following a 12-week aerobic and strength training intervention for subjects experiencing chemotherapy-induced peripheral neuropathy. These results suggest that aerobic and strength training may contribute to a reduction in chemotherapy-induced peripheral neuropathy.

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CHAPTER I

INTRODUCTION

The American Cancer Society estimates that there were 14.5 million Americans living with cancer in 2014 (American Cancer Society, 2015). Every year cancer rates continue to increase even with advances in modern medicine. The most common treatments for cancer include surgery, chemotherapy, radiation therapy, and hormone therapy. When diagnosed with cancer, chemotherapy is one of the effective forms of treatment that can prolong survival (Malik & Stillman, 2008). There are numerous types and combinations of chemotherapy treatments available; however, they all have the potential of producing debilitating side effects.

One of the major side effects of chemotherapy treatments is chemotherapy-induced peripheral neuropathy (CIPN). Thirty to forty percent of all patients receiving chemotherapy will experience CIPN, which is a type of peripheral neuropathy that is caused by certain chemotherapy agents (Pignataro & Swisher, 2010). Peripheral neuropathy is defined as any damage that occurs to the peripheral nerves and enables them to function properly. Neuropathic symptoms include pain, numbness, tingling, decreased motor function, weakness, and any type of paresthesia or dysesthesia (Kluding et al., 2012; Pignataro & Swisher, 2010; Hausheer, Schilsky, Bain, Berghorn, & Lieberman, 2006; Kochman, Carnegie, & Burke, 2002). Several theories have suggested how chemotherapy causes neuropathy. Specifically with platinum drugs, such as cisplatin

or carboplatin, pre-mature cell apoptosis may be occurring (Argyriou, Bruna, Marmioli, & Cavaletti, 2012). It has been theorized that taxane chemotherapy drugs interfere with the microtubules of the mitotic spindle, which in turn interferes with axonal transport, thereby affecting the somatosensory neurons and causing destruction of distal nerve endings (Argyriou et al., 2012). Taxane chemotherapy has also been shown to disrupt Schwann cells, which leads to many issues within the axonal membranes, and can disrupt the myelination of the axon terminals (Quasthoff & Hartung, 2002; Persohn et al., 2005; Wickham, 2007). Platinum chemotherapies such as cisplatin, carboplatin, and oxaliplatin, have been shown to disrupt the cytoplasmic and nuclear components of an axon and disrupt axonal transport ultimately (Wickham, 2007). The exact cause behind CIPN is still unknown; however, exercise may be a viable method to alleviate the symptoms.

Within the past ten years, exercise has shown to benefit cancer patients tremendously and reduce cancer-related side effects (Hsieh et al., 2008; Schneider, Hsieh, Sprod, Carter, & Hayward, 2007a; Schneider, Hsieh, Sprod, Carter, & Hayward, 2007b). Major cancer-related side effects include toxicities to major organ systems in the body along with fatigue, psychological issues, lymphedema, pain, body image problems, depression, anxiety, and sleep disturbances (Schneider et al., 2007a; Schneider et al., 2007b; Schneider, Dennehy, & Carter, 2003). Some of the toxicities that present include immune system toxicity, cardiovascular toxicity, pulmonary toxicity, gastrointestinal toxicity, hepatic toxicity, neuroendocrine toxicity, nephrotoxicity, and dermatological toxicity (Schneider et al., 2003). Exercise has been shown to improve the cardiovascular system, respiratory system, metabolic system, neuromuscular system, and endocrine system (Schneider et al., 2003). When cancer patients exercise, they may also experience

a reduction in chemotherapy-related side effects. However, very few studies have been conducted to examine the effects of exercise on CIPN.

Previous research has theorized that strength training and aerobic training may help alleviate CIPN (Kluding et al., 2012; Toftagen, Visovsky, & Berry, 2012). Kluding et al., (2012) found significant evidence that an aerobic and strength training intervention helped to reduce the pain and symptoms associated with diabetic peripheral neuropathy. Symptoms of CIPN are assessed in a variety of ways. Nerve conduction tests, Semmes Weinstein monofilament tests (SWMT), and the Michigan Neuropathy Screening Instrument (MNSI) are common ways to assess CIPN currently. However, there is no gold standard for assessing CIPN. Research has shown SWMT can be a beneficial instrument to assess CIPN over time using a composite score (Tan, 2010; Feng, Schlösser, & Sumpio, 2009; Kamei et al., 2005; Lee et al., 2003; Kochman et al., 2002; Olaleye, Perkins, & Bril, 2001; Kumar et al., 1991). To date, no studies have evaluated the effects of an aerobic and strength training exercise intervention on CIPN.

Statement of Purpose

The purpose of this study was to examine the effects of a 12-week aerobic and strength training intervention on the symptoms of chemotherapy-induced peripheral neuropathy.

Research Hypothesis

- H Participants who are experiencing CIPN and participating in the strength training and aerobic training intervention will show improvements in CIPN symptoms. Potential improvements would translate to lower CIPN composite assessment scores.

Significance of Study

Patients who have received chemotherapy treatment can potentially develop CIPN as a life-long side effect, which could lead to an overall decrease in quality of life if left untreated (Kluding et al., 2012; Pignataro & Swisher, 2010; Hausheer et al., 2006; Kochman et al., 2002). CIPN can decrease the quality of life for many patients and inhibit them from activities of daily living. Exercise has already shown to reduce chemotherapy-related side effects for other major toxicities, and may potentially reduce CIPN symptoms (Schneider et al., 2007a; Schneider et al., 2003; Kluding et al., 2012; Tofthagen et al., 2012). To date no research exists that evaluates the effects of strength training and aerobic training on the severity of CIPN. If in fact, exercise training regimens that include both aerobic and resistance components can alleviate CIPN, such interventions should be considered for all cancer patients experiencing peripheral neuropathies.

CHAPTER II

REVIEW OF LITERATURE

Chemotherapy-Induced Peripheral Neuropathy

Chemotherapy-Induced Peripheral Neuropathy can be described as damage to the peripheral nerves as a result of exposure to chemotherapy toxic agents. Every chemotherapeutic drug is unique and each drug can potentially damage peripheral nerves differently. Platinum drugs, taxanes, epothilones, vinca alkaloids, bortezomib, and thalidomide are the most common chemotherapeutic agents that cause CIPN (Wolf, Barton, Kottschade, Grothey, & Loprinzi, 2008; Hausheer et al., 2006). These toxic agents affect both small and large fiber axons (Wolf et al., 2008; Schloss et al., 2013; Kluding et al., 2012). Small fibre axons are unmyelinated and are responsible for sensing temperature and pain (Wolf et al., 2008; Schloss et al., 2013), while large fibre axons are myelinated and are responsible for sensing position, vibration, and motor control (Wolf et al., 2008; Schloss et al., 2013). While these drugs are unable to cross the blood brain barrier (Schloss et al., 2013) the peripheral nervous system does not have a protective barrier and it is susceptible to these agents.

At the cellular level, platinum drugs may alter the DNA of peripheral nerve cells by causing an overproduction of cyclin D1 expression and hyper-phosphorylation of the retinoblastoma gene, which can lead to apoptosis or ultimately peripheral neuropathy

(Argyriou et al., 2012). Another possibility is that there could be a disruption in mitochondrial function within the cells, which causes oxidative stress and triggers neuronal apoptosis (Argyriou et al., 2012). Some platinum agents, specifically oxaliplatin, have been hypothesized to cause CIPN due to chelation of calcium from neural membranes (Hausheer et al., 2006). These could be possible mechanisms explaining CIPN with platinum based chemotherapy.

Another major chemotherapy drug group, the taxane, causes a disruption in the microtubules of the mitotic spindle, which interferes with axonal transport in the axons as well as the soma of somatosensory neurons (Argyriou et al., 2012). It has also been observed that taxane drugs initiate death of the peripheral nerves, starting from the distal nerve endings and ultimately causing a disturbance of cytoplasmic flow within the neuron itself (Quasthoff & Hartung, 2002; Argyriou et al., 2012). Taxanes also have deleterious effects on excitability of sensory and motor nerves due to an axonal membrane leak and a non-specific ion influx (Quasthoff & Hartung 2002). In order for a membrane to depolarize correctly, the correct exchange of sodium and potassium must occur across the membrane. If ions are crossing the membrane in a disorderly fashion, problems may arise with message and cell signaling. Like taxane drugs, epothilones have a similar effect on the neuron. Epothilones have been found to cause polymerization of the tubulin in microtubules in the absence of guanosine triphosphate, which is needed in a healthy cell to polymerize (Argyriou et al., 2012). The preformed tubulin is then put into depolymerizing conditions, which ultimately lead to the destruction of the microtubules (Argyriou et al., 2012).

The vinca alkaloids group of chemotherapy drugs includes vinblastine, vincristine, vinorelbine, and vinese drugs (Hausheer et al., 2006). Vinca alkaloids ultimately lead to cell death due to an arrest of dividing cells during the metaphase stage of development (Argyriou et al., 2012). The vinca alkaloids cause alterations in the neuronal cytoskeleton due to binding on the intracellular tubulin, which leads to alterations in axonal transport, buildup of neurofilaments in the cell bodies and proximal axons, and accumulation of axoplasmic organelles and vesicles (Quasthoff & Hartung 2002; Argyriou et al., 2012). There is also a reduction in myelin thickness and shortening of inter-nodal length that occurs (Argyriou et al., 2012).

The pathogenesis of bortezomib and thalidomide are still unknown to researchers. Theories suggest that bortezomib interferes with transcription, nuclear processing, nuclear transport, and cytoplasmic translation of mRNA's in dorsal root ganglion neurons. This can ultimately affect the signaling cascade within the neuron and can lead to cytotoxicity (Hausheer et al., 2006). Thalidomide is hypothesized to causes angiogenesis inhibition, immunomodulation, and cytokine modulation (Argyriou et al., 2012). By inhibiting angiogenesis, the formation of new blood vessels, the body may be depriving itself of blood circulation starting with the peripheries first. Also, immunomodulation may be beneficial for some patients with cancer because it allows medical professionals to essentially modify the immune system, but it may be detrimental to the peripheral nerves. However, much research still needs to be performed to clearly understand the effects of thalidomide and bortezomib.

Symptoms of Chemotherapy-Induced Peripheral Neuropathy

The symptoms for CIPN are similar and have found to be dose-dependent across all chemotherapy drugs (Schloss et al., 2014; Wolf et al., 2008; Quasthoff & Hartung 2002). This infers that higher cumulative doses of chemotherapy may result in longer and more severe CIPN. This is detrimental to the patient because if the CIPN escalates, it can cause secession of the chemotherapy. Also, different chemotherapy drugs will elicit different symptoms of CIPN. Many CIPN patients complain of a “glove-and-stocking” feeling and distribution (Schloss et al., 2013). This can be best described as the patient feeling as if they are always wearing gloves and socks on their hands or feet. CIPN can also present as numbness, tingling, pain, decreased motor function, weakness, and any type of paresthesia or dysesthesia (Kluding et al., 2012; Hausheer et al., 2006; Kochman et al., 2002). Another symptom of CIPN is the inability to sense temperature (Wilkes, 2007). It ultimately leads to a diminished quality of life, chronic discomfort, reduced physical activity, reduced dexterity, and in some cases ulceration, which can lead to amputation (Schloss et al., 2014; Speck et al., 2012; Feng et al., 2009; Lee et al., 2003; Kumar et al., 1991).

Chemotherapy-Induced Peripheral Neuropathy Testing

Currently there is no gold standard for the testing of CIPN. However, the Semmes Weinstein Monofilament Test (SWMT) has been shown to be a beneficial instrument for the testing of all peripheral neuropathy (Tan, 2010; Feng et al., 2009; Kamei et al., 2005; Lee et al., 2003; Kochman et al., 2002; Olaleye et al., 2001; Kumar et al., 1991). The SWMT consists of several different nylon monofilaments of varying gauges and forces.

The monofilament is applied to the surface of the skin and force is applied until the monofilament bends. The monofilament will buckle at a set force, which helps control for variability between tests and is reproducible (Feng et al., 2009; Kumar et al., 1991).

These monofilaments can measure the subject's cutaneous pressure perception threshold (Kumar et al., 1991). The 5.07/10 g SWMT is the most commonly used monofilament by clinicians and researchers, as the inability to sense this gauge suggests the loss of protective sensation and an increased risk of foot ulceration (Feng et al., 2009; Tan, 2010; Lee et al., 2003; Olaleye et al., 2001; Kamei et al., 2005; Leonard, Farooqi, & Myers, 2004; Kumar et al., 1991). The 5.07/10g SWMT has been validated against nerve conduction tests and vibration perception threshold tests, and were all found to be correlated with each other (Feng et al., 2009; Kamei et al., 2005; Lee et al., 2003; Olaleye et al., 2001; Kumar et al., 1991). The 4.17/1g SWMT is commonly used alongside the 5.07/10g SWMT due to its ability to detect a diminishing protective sensation (Lee et al., 2003; Callahan, Hunter, & Mackin, 1995; Kumar et al., 1991). The 4.17/1g SWMT may be useful in the early detection of peripheral neuropathy. Due to the fact that very little research regarding CIPN has been conducted, many of the studies examined pertained to diabetic peripheral neuropathy. Therefore, these findings may be relevant for diabetic peripheral neuropathy, but CIPN may be more responsive to other testing instruments.

Similarly to the testing modality, there is no agreement over which sites and how many sites on the hands and feet should be tested. The first, third, and fifth metatarsal head have consistently been shown to be positive indicators of peripheral neuropathy, and have a 94% accuracy of identifying peripheral neuropathy (Tan, 2010; Lee et al., 2003).

The peripheral nerves that lie within the foot branch through the foot and include: 1)

medial plantar nerves which innervate the first through third metatarsal head along the medial plantar aspect of the foot; 2) the lateral plantar nerve which innervates the fourth and fifth metatarsals along the lateral plantar aspect of the foot; 3) the saphenous nerve which innervates the arch of the foot; 4) the sural nerve which innervates the most lateral aspect of the foot; 5) the tibial nerve which innervates the calcaneus; 6) the deep peroneal nerve which innervates the majority of the dorsal surface of the foot; and 7) the deep peroneal nerve which innervates the dorsal surface of the foot in-between the first and second metatarsals (Tortora & Derrickson, 2009). In the hand: 1) the median nerve innervates the palmar surface of the first, second, third, and half of the fourth phalanges and metacarpals, 2) the ulnar nerve innervates half of the fourth phalange and metacarpal., as well as the fifth phalange and metacarpal, and 3) the radial nerve innervates the most lateral aspect of the first metacarpal (Tortora & Derrickson, 2009).

Strength and Aerobic Training Benefits in Chemotherapy-Induced Peripheral Neuropathy

There is very little research regarding the effects of strength and aerobic training on peripheral neuropathy. Some studies have shown that exercise can improve balance, improve gait patterns, and decrease the risk of falls in neuropathic patients, yet neuropathic symptoms were not assessed over time (Toftagen et al., 2012). One study did find that a 10-week exercise intervention improved a selected measure of peripheral nerve function (Kluding et al., 2012). Kluding et al., (2012) designed a 10-week exercise program consisting of aerobic and strength training exercises. The aerobic exercise was kept at a moderate level, 50%-70% of VO_2 reserve, and strength training was performed at a moderate range as well; rate of perceived exertion (RPE) of 7-8 out of 10 on the

modified Borg scale. Health professionals monitored the exercise and results were based on the Michigan Neuropathy Screening Instrument (MNSI). The MNSI is a survey conducted by a health professional that includes a lengthy physical assessment and a medical history section. However, this study presented major limitations including short intervention duration, small sample size, lack of a control group, and limited knowledge of CIPN (Kluding et al., 2012). Along with the cellular level disruptions chemotherapy agents can cause, they may also induce sensory or motor neuropathy by activating mitochondrial and vascular dysfunction (Toftagen et al., 2012). However, research has supported the assumption that exercise stimulates endoneurial blood flow and mitochondrial protein synthesis and glycolysis which both have the ability to generate energy (Toftagen et al., 2012). Aerobic exercise specifically has been shown to enhance axon regeneration after peripheral nerve injury (Sabatier, Redmon, Schwartz, & English, 2008). This could be due to an up regulation in neurotropic factors that occur with exercise and increased neuronal activity (Sabatier et al., 2008). Neurotropic factors are responsible for growth and maintenance of neurons within the body (Widmaier, Raff, & Strang, 2006). Strength exercise has also been thought to enhance nerve re-innervation (Wilkes, 2007). Exercise could ultimately increase the supply of blood, oxygen, and other essential nutrients to the mitochondria, and then to the peripheral nerves, which could result in fewer neuropathic symptoms (Toftagen et al., 2012). Benefits of exercise on peripheral nerve damage have not received much attention in research. The lack of research in this area demonstrates a need for studies investigating the beneficial effects of exercise on CIPN.

CHAPTER III

METHODS

Experimental Design

The purpose of this study was to examine the effects of a 12-week aerobic and strength training intervention on the symptoms of chemotherapy-induced peripheral neuropathy. This study consisted of a pre-to-posttest design. Pre and post physical assessments were conducted on each participant to establish whether a training effect and if any physiological improvements occurred. The pre and post assessments consisted of a neuropathy screening, physiological screenings, and psychological screenings. Baseline measurements were gathered prior to and following each individual exercise intervention. A peripheral neuropathy screening was performed prior to the intervention, at 6 weeks, and at 12-weeks to evaluate changes in chemotherapy-induced peripheral neuropathy (CIPN) symptoms.

Preliminary Paperwork

Before entering the RMCRI program and inclusion into the study, each participant was asked to complete questionnaires and surveys, which included a medical history, cancer history, and a lifestyle and activity evaluation. The cancer and medical history established pertinent information about cancer diagnosis, cancer stage, past and current treatments, pre-existing conditions, and limitations and considerations for exercise. The lifestyle and activity evaluation was administered to help establish lifestyle choices, such

as previous and current activity levels, tobacco use, alcohol use, and fluctuations in body weight. Psychological measures were evaluated using the Beck Depression Inventory (Salkind, 1969), the Piper Fatigue Scale (Piper et al., 1998), and the Ferrans and Powers Quality of Life Index Cancer Version III (Ferrans & Powers, 1985). Each participant was asked to complete surveys and questionnaires prior to each pre-and-post assessment.

Participants

Fifteen participants were recruited for this study. Each cancer patient was referred to the Rocky Mountain Cancer Rehabilitation Institute (RMCRI) from the local medical community. Patients were then screened for the cancer exercise rehabilitation program through RMCRI at the University of Northern Colorado to establish eligibility for the study. The inclusion criteria for this study consisted of: 1) must be at least 18 years of age; 2) have been diagnosed with cancer; 3) have received chemotherapy treatment for cancer in the past or currently be undergoing chemotherapy treatment; 4) must have been experiencing self-reported neuropathy in either hands or feet; 5) have had no serious co-morbidities such as diabetes; and 6) been cleared by a physician for exercise. Exclusion criteria for this study consisted of: 1) diagnosis of Type I or Type II diabetes; 2) past or present alcohol abuse or substance abuse; 3) history of central nervous system dysfunction prior to a cancer diagnosis; or 4) currently receiving pharmacological interventions for CIPN or other forms of intervention for the management of CIPN. Participants who met these criteria and were willing to participate were assigned to a specific training phase and exercise intervention following the initial assessment. The participants were informed of the nature of the exercise intervention and that they would be trained by a certified Cancer Exercise Specialist at RMCRI. To obtain

the appropriate weights and intensities, the initial assessment values were used. After the participants were informed and understood the study and the protocols, they signed a copy of the informed consent, which was approved by the University of Northern Colorado Institutional Review Board (see Appendix 1). As per the directions on the informed consent, a copy was also made available for them to keep.

Assessment

Physiological measurements were evaluated during the initial and post assessment. These measures included balance, cardiovascular endurance, pulmonary function, body composition, functional movement, flexibility, and muscular strength and endurance. During both the pre and post assessments, a heart rate monitor (Polar, Inc. Lake Success, NY) was worn by each participant at all times to monitor heart rate response to exercise. Blood pressure and oxygen saturation were also measured at the beginning and end of the assessment with a sphygmomanometer and pulse oximeter, respectively.

Cardiovascular Assessment

Cardiovascular endurance was evaluated using RMCRI's VO_{2peak} treadmill test. This protocol has been found to be more accurate and appropriate for cancer survivors due to the sensitivity of the population (Shackelford, Brown, Lalonde, Hydock, & Schneider, 2012). The objective of the test is to allow the participant to reach self-perceived maximal exhaustion or fatigue, and the highest measurement of oxygen consumption was recorded. For RMCRI's treadmill protocol, heart rate and oxygen saturation were recorded and obtained at the end of each minute/stage, blood pressure and RPE was obtained and recorded at the end of each third minute, and speed and/or grade

increased at the end of each minute. Termination of the test occurred when the participant reached volitional fatigue, asked to stop, or the Cancer Exercise Specialist felt the test needed to be terminated due predetermined termination criteria. The criteria for terminating the VO_{2peak} test included: drop in systolic blood pressure of more than 10 mmHg, heart rate does not increase with increased intensity, diastolic blood pressure fluctuates more than 10 mmHg from baseline, or oxygen saturation dropped below 80 on the pulse oximeter (Arena, 2014). The time in which VO_{2peak} was established was recorded in standard and decimal form, as well as whether the participant was running or walking and if handrails were used. VO_2 values were obtained utilizing ACSM metabolic equations.

Strength and Muscular Endurance

Strength was assessed using the estimated 1-repetition maximum test along with the Brzycki equation (Brzycki, 1993). This information allowed the Cancer Exercise Specialist to write an accurate exercise prescription and progress the participant appropriately. Muscular endurance was evaluated using the handgrip test (Mathiowetz, Weber, Volland, & Kashman, 1984), core/plank test, and the chair squat test, which indicated the level of muscular fatigue the participant experienced. These tests also helped to indicate which muscle groups would need more endurance training through the intervention.

Estimated 1-Repetition Max Assessment. Muscular strength was estimated via the Brzycki equation using an estimated 1-repetition max (est. 1-RM) test. The exercises assessed were the latissimus dorsi (lat) pull-down, shoulder press, chest press, seated row, leg press, leg extension, and leg curl using Cybex Eagle weight resistance machines

(Cybex International., Inc., Medway, MA). The researchers demonstrated how to perform each exercise and the seat was adjusted to an estimate of proper fit for the participant. With an appropriate weight, the participant was instructed to perform five warm-up repetitions. Next, a starting weight was selected and each participant was asked to perform repetitions until told to stop. If a participant reached ten repetitions, the set was stopped automatically. An RPE was asked of the participant after every set and then the weight was adjusted accordingly. If ten repetitions were reached during the second set, the participant would move on to another machine and then repeat the same machine later during the assessment.

Handgrip Strength Assessment. Handgrip strength was evaluated using a handgrip dynamometer (Takei Scientific Instruments Co., LTD., Niigata City, Japan). The handgrip size was adjusted accordingly for the participant. The participant was then instructed to hold the dynamometer by his or her side with the dial facing away from the body, and to squeeze the dynamometer as hard as possible without moving the arm. Three trials were administered for each hand, alternating hands after every attempt, and then the highest values were recorded.

Core Muscular Endurance Assessment. Core muscular endurance was assessed using the plank test. For the plank test, the participant began in a neutral position on his or her hands and knees. Each participant was then instructed to assume the plank position, with his or her forearms on the floor in front of him or her, while keeping his or her hips in line with his or her spine and were asked to hold the position as long as possible to a maximum of 60 seconds. The time was recorded and a score was assigned.

Chair Squat Test. For the chair squat test, the researchers showed the participant the proper form for doing a squat onto a chair. A chair was then positioned behind the participant and the participant was instructed to cross his or her arms and squat down into the chair so that their buttocks touched the seat for a brief moment, and then return to standing. The participant was instructed to perform as many squats as possible until fatigue or until 50 repetitions were completed. Values were then recorded.

Chemotherapy-Induced Peripheral Neuropathy Assessment

Chemotherapy-Induced Peripheral Neuropathy (CIPN) was evaluated in each participant to look for changes prior to and after the 12-week intervention of strength, aerobic and flexibility training. CIPN was evaluated using the Semmes-Weinstein Monofilament Test (SWMT) (Feng, Schlösser, & Sumpio, 2011; Tan, 2010; Feng et al., 2009; Kamei et al., 2005; Leonard et al., 2004; Lee et al., 2003; Kochman et al., 2002; Olaleye et al., 2001; Mueller, 1996; Kumar et al., 1991; Grunfield, 1988). A total of ten sites were evaluated using the 5.07/10g monofilament and the 4.17/1 monofilament on both the feet and hands of the participant, depending on the location of the neuropathy. The ten sites used to assess the foot were the dorsal mid-foot, the medial and lateral mid-foot, the calcaneus, and the plantar aspect of the foot, including the first, third, and fifth digits, as well as the first, third, and fifth metatarsal heads (Figure 1). Both the 4.17 and 5.07 monofilament have been suggested to be used to identify patients at risk with peripheral neuropathy (Lee et al., 2003; Mueller, 1996; Kumar et al., 1991). The tests were performed bilaterally. Participants who had self-reported symptoms of CIPN in the feet were instructed to lie supine, with their toes pointing up, and were blindfolded. The researcher instructed the participant to say “yes” when the participant felt the

monofilament. The researcher did not inform the participant when the monofilament would be applied to the skin and the sites were randomly tested. The filament was pressed slowly onto the test site and then bowed for 1.5 seconds. The participant was instructed to respond, “Yes,” whenever the participant recognized that he or she was being touched by the filament and on which side of the body. Participants who could not detect the 4.17 or 5.07 monofilament on a specific site were classified as having a loss of protective sensation in that specific site. To assess for neuropathy of the hand, a ten-site method was used. The sites were: (1) the medial surface of the palm, (2) first medial metacarpal head, (3-5) first, third, and fifth metacarpophalangeal joint, (6-8) first, third, and fifth distal phalanx head, and (9-10) the third and fifth distal metacarpal head (Van Brakel et al., 2003; Nunes, de Oliveira, Aruin, & dos Santos, 2012). (Figure 2). The same monofilaments were used for the hand test as for the foot test. For this test, the participant was instructed to lie supine, extend his or her arm out laterally, palm face up, and were blindfolded. Participants were also blinded to the test in that they were not able to watch the test being performed on them. The test would then be administered the same way as the foot assessment and one insensate site would put the participant at risk for neuropathy (Tan, 2010). Quick application and bouncing of the filament were avoided. To help ensure accuracy, the same two evaluators were used for every SWMT test. Using a conservative approach for this study, it was best thought to include a site pertaining to each nerve that runs through either the hand or foot. Also, because there is no clear evidence on how to score a SWMT, any one insensate site was considered to be an indication of neuropathy (Tan, 2010).

Phase Training of Cancer Rehabilitation

The exercise intervention took place at the Rocky Mountain Cancer Rehabilitation Institute (RMCRI) on the University of Northern Colorado (UNC) campus in Greeley, Colorado. RMCRI is a nationally recognized cancer rehabilitation center that maintains consistent referrals of cancer patients who experience treatment-related side effects. Physiological data was recorded by UNC graduate and undergraduate students in the exercise physiology department. RMCRI utilizes a Phase training system to confirm that the five basic principles of exercise are being met. These five principles include overload, specificity, individuality, diminishing return, and reversibility. The Phase system allows for individuality of each participant based on stage of cancer, treatment types, and time since treatment. It also allows for progression at appropriate intensities according to the individual.

The RMCRI phase program consists of four Phases. Phase One consists of participants who are receiving treatment during the exercise intervention. The main goal of this Phase is to attenuate the deleterious effects of chemotherapy and radiation treatments. The participants who are in this Phase may not see improvement, but there should not be any declination in initial values. The exercise intensity established for this phase is 30-45% of a participant's heart rate reserve (HRR) and est. 1-RM. Cardiovascular and muscular improvement might only be 0-5% for this phase, and participants should be reporting RPE values from 1-3. The participant remains in Phase One until he or she has fully completed his or her treatment regimen.

Phase Two of the training program is intended for participants who have graduated from Phase One, participants who have had only surgical and/or hormonal

treatment, or participants who are new to the RMCRI program and have not undergone chemotherapy or radiation. The goal of Phase Two is to build a foundational base of exercise using corrective and functional training. The training intensity established for this phase is 40%-60% of the participant's HRR and est. 1-RM, and the participant should be reporting RPE's of 3-6. Cardiovascular and muscular improvement for this Phase may increase by 10-20%. The time duration of this phase is 12 weeks.

Phase Three of RMCRI's phase training program is intended for participants who have graduated from Phase Two. The goal of this phase is to continue to improve physiological and psychological variables beyond baseline measures and should be able to progress to functional health or become "apparently healthy." Another goal of this Phase is to instruct the participant how to exercise without the help of a trainer and for the participant to become knowledgeable about exercises. The exercise intensity established for this phase is considered moderate-to-high at 60%-85% of the participant's HRR and est. 1-RM. Cardiovascular improvements may increase by 5-15% for this phase, while muscular improvements may improve by 30-50%. The period for this Phase is three months.

Phase Four of RMCRI's phase program is for participants who have graduated from Phase Three and could be considered "apparently healthy." The goal of this phase is to continue improving physiological and psychological measures. The exercise intensity established for this phase is 65%-95% of a participant's HRR and est. 1-RM, and the timeline is limitless for this Phase. Clients who are in this Phase are now healthy and knowledgeable enough to exercise on their own, in a group model, or continue with one-on-one training. Cardiovascular and muscular improvements should be greater than

5% increments for this phase. For the purpose of this study, only participants in Phases One and Two will be used.

Exercise Intervention

The aerobic portion of the intervention was conducted on a treadmill (Trackmaster, city etc. or MedTrack CR60, city etc.), cycle ergometer (Life Cycle 8500, city etc.; Life Cycle 9500E, city etc.; SciFit, city), and/or NuStep (Biodex), Aerobic exercise was performed for 20 minutes between 30% and 60% of the participant's HRR depending on the Phase of the RMCRI program the participant was enrolled into. Each participant was prescribed to either maintain his or her cardiovascular and muscular strength baseline measures or increase from 5%-20% also depending on his or her phase.

The muscular strength portion of the intervention was conducted with free weights, Cybex Fitness Machines, and/or body weight. The muscular strength intervention was also performed at 30% to 60% of the participant's est. 1-RM depending on the Phase of the RMCRI program the participant was assigned. The participant either maintained muscular strength or increased it by 10%-50%. This portion of the intervention lasted 30 minutes. During the muscular strength training intervention, balance was also included. In order to incorporate balance, the participant may have been asked to perform an exercise on a stability ball, BOSU, foam pad, or textured balance pods.

The flexibility portion of the intervention lasted ten minutes in length and was conducted at the end of the training session. Any muscle groups used during the strength portion of the training intervention were stretched accordingly and ranges of motion stretches were included. Stretches were also done in accordance with the participant's

NASM squat test results. Equipment that may have been used for stretching included rope pulleys, a ROM wheel harnessed to the wall, ropes, or gliding disks.

Statistical Analysis

Preliminary descriptive and data frequency analyses were run to represent the raw data visually. A power analysis was run initially to determine appropriate sample size. A Wilk's Lambda multivariate analysis of variance (MANOVA) test was run on the pre, mid, and post CIPN assessment scores to evaluate any changes due to the exercise intervention. Individual MANOVA's were run for the 4.17 and 5.07 monofilament tests. A paired sample T-test was run on physiological assessment pre- and post- data and psychological assessment data to evaluate any changes due to the exercise intervention. Data was analyzed using statistical software (SPSS, 20). Significance was set at $p < 0.05$.

CHAPTER IV

RESULTS

Participant Characteristics

Participant characteristics are shown in Table 1. For the purpose of this observation, this study included 10 participants (6 females, 4 males). Ten out of thirteen eligible participants completed the 12-week exercise intervention along with pre-, mid-, and post- assessments. Two subjects that were not able to complete the study dropped out for personal reasons and one subject passed away during the study. Each participant that completed the training study was able to complete 36 sessions. If a participant had to cancel a session for personal reasons, there were no more than 10 days between the next training sessions in order to sustain training effects. All participants completed pre-, mid- and post- assessments. Cancer Exercise Specialists at the Rocky Mountain Cancer Rehabilitation Institute conducted the physical and psychological assessments. In addition, during the year and a half that this study took place, there were a total of two different assessors for the CIPN portion of the assessment.

Table 1

Participant Characteristics

<i>N</i>	Weight (pounds)	Height (inches)	Age (years)
12	171 ± 46	66 ± 4	62 ± 7

Note: Values are means ± standard deviation; N, number of participants

Chemotherapy-Induced Peripheral Neuropathy Changes after Intervention

The Wilk's Lambda Multivariate Test showed significant ($P < .05$) effects between all three levels for the 4.17 SWMT. Mauchly's test of sphericity did not show significance ($p > .05$) of variance between groups. Results are presented in Table 2 below. Figure 1 also shows a negative trend of the SWMT 4.17 cumulative scores over time. For the 5.07 SWMT, the Wilks Lambda Multivariate test showed no significant effects ($p > .05$) due to training. Mauchly's test of sphericity did not show significance ($p < .05$) of variance between groups. Statistical results are presented in Table 2 below. Figure 2 shows a partial negative trend of SWMT 5.07 cumulative scores below.

Table 2

SWMT Significant Differences

	<i>p</i> value	Mauchly's Test of Sphericity
SWMT 4.17	.025	.576
SWMT 5.07	.060	.957

Note: Significant difference for SWMT 4.17 pre- to mid- to post; no significant differences were found for SWMT 5.07 tests pre- to mid- to post-; SWMT, Semmes Weinstein Monofilament Test; *significantly different at $p < .05$.

SWMT 4.17 Cumulative Scores Over Time

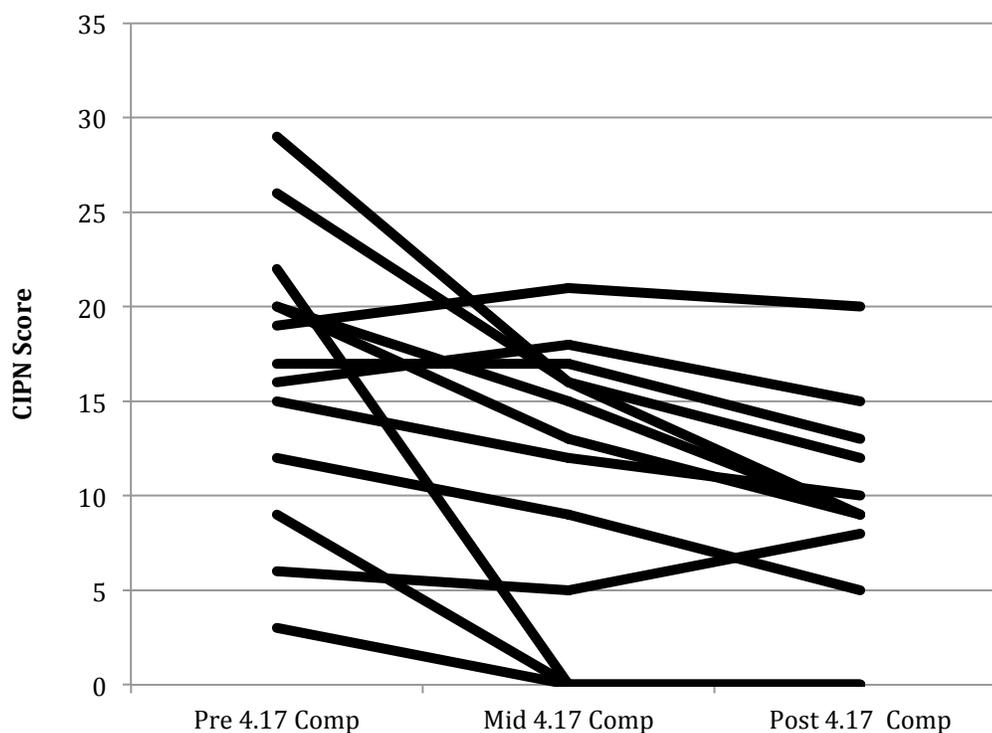


Figure 1. 4.17 Semmes Weinstein Monofilament Scores Over Time. Values are composite scores from each participant; Average, average score on CIPN assessment; linear trend line is based on average scores; CIPN, chemotherapy-induced peripheral neuropathy;

SWMT 5.07 Cumulative Scores Over Time

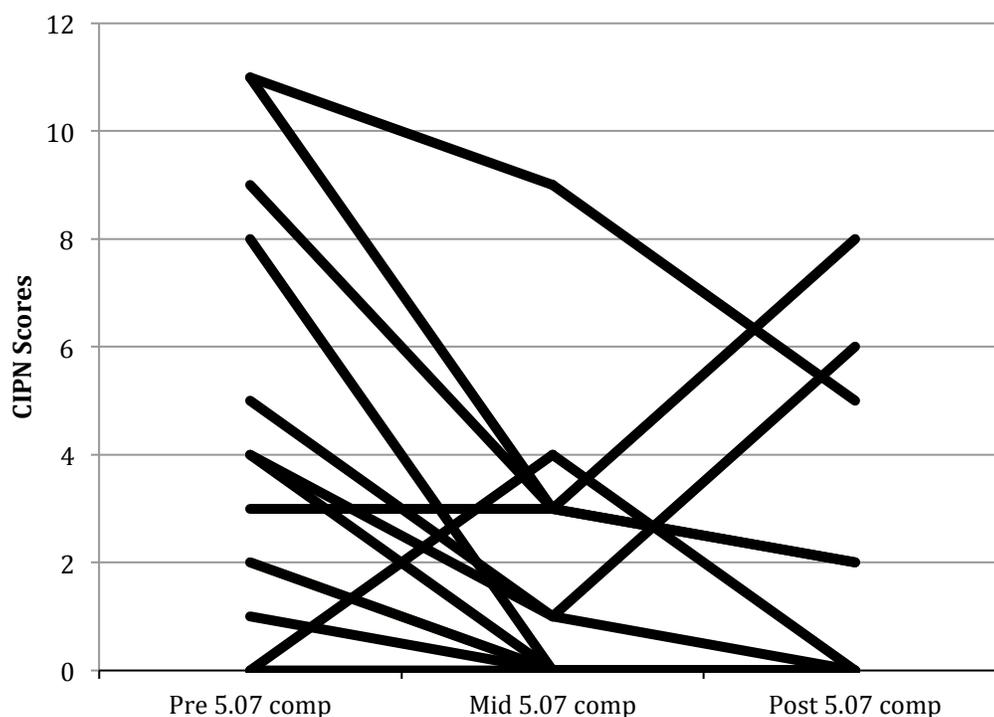


Figure 2. 5.07 Semmes Weinstein Monofilament Scores Over Time. Values are composite scores from each participant; Average, average score on CIPN assessment; linear trend line is based on average scores; CIPN, chemotherapy-induced peripheral neuropathy;

Strength Changes after Exercise Intervention

Paired Sample T-Tests showed some significant ($p < .05$) changes in strength pre to post assessment. Results for all strength assessments pre- to post are presented in Table 3 below. Latissimus pull-down, shoulder press, chest press, leg curl, and leg press all showed significant changes. Row and leg extension did not show significant changes. Functional strength showed some significant ($p < .05$) changes in strength pre to post. Results for functional strength assessments pre- to post- are presented in Table 4 below.

Both right and left hand grip tests showed significant changes; however, the chair test and plank test did not show significant changes.

Table 3

Strength Vales Pre- and Post- Intervention

Exercise	Pre (pounds)	Post (pounds)	<i>p</i> value
Latissimus Pull down	89 ± 35	100 ± 28	.021*
Shoulder Press	40 ± 19	54 ± 23	.014*
Chest Press	64 ± 28	84 ± 38	.000*
Row	71 ± 26	92 ± 34	.141
Leg Curl	79 ± 28	99 ± 23	.030*
Leg Extension	83 ± 41	111 ± 46	.085
Leg Press	158 ± 45	206 ± 64	.002*

Note: Weights are means ± standard deviation in pounds; *significance set at $p < .05$.

Table 4

Functional Strength Values Pre- and Post- Intervention

Exercise	Pre	Post	<i>p</i> value
Chair Test (reps)	20 ± 14	28 reps ± 10	.148
Plank Test (reps)	41 ± 23	48 sec ± 20	.450
Handgrip R (kg)	22 ± 10	27 kg ± 12	.000*
Handgrip L (kg)	21 ± 11	24 kg ± 11	.003*

Note: Values are means ± standard deviation; Reps, repetitions; sec, seconds; kg, kilograms; *significantly different at $p < .05$.

Aerobic Changes after Exercise Intervention

There were significant ($p < .05$) main effects observed for Paired T-Test analysis for VO_{2peak} . Aerobic physiological changes from pre- to post- training assessments are displayed in Table 5.

Table 5

VO_{2peak} Pre- and Post- Intervention

	Pre	Post	<i>p</i> value
VO _{2peak}	19.07 ± 3.4	24.1 ± 7.7	.014*

Note: All values are ml/kg/min⁻¹; Values are means + standard deviation; *significantly different at *p* < .05.

CHAPTER V

DISCUSSION

The Wilk's Lambda Multivariate test was able to also show significant differences between pre- and post- data for VO_{2peak} , strength values, and functional strength values. It was expected that significant differences would be present between the pre and post assessments. In fact, VO_{2peak} increased significantly due to the aerobic exercise intervention. All strength values increased significantly with the exception of the 1-RM row, 1-RM leg extension, chair squat test, and plank test. This indicates that exercise adaptations did occur and the reduction in CIPN symptoms could be related to the exercise adaptations. It could also be concluded from the results that exercise had a beneficial effect on CIPN symptoms. Research has supported the assumption that exercise stimulates endoneurial blood flow and mitochondrial protein synthesis and glycolysis which both have the ability to generate energy (Toftagen et al., 2012). Exercise could ultimately increase the supply of blood, oxygen, and other essential nutrients to the mitochondria, and then to the peripheral nerves, which could result in fewer neuropathic symptoms (Toftagen et al., 2012). Exercise also has been suggested to enhance nerve re-innervation as well as an increase in neurotropic factors within the peripheral nerves (Wilkes, 2007; Sabatier et al., 2008). Both of these have the possibility of regenerating nerve endings, and the current study suggests that these theories may

possibly be accurate. In addition, the theory that exercise can benefit peripheral nerve damage is in agreement with Sabatier et al., 2008 and Kluding et. al., 2012.

The reduction in 4.17 SWMT scores from pre- to post- and symptoms supports the theory that exercise could serve as an alternative form of treatment in the management of CIPN. However, it is unknown from this study whether or not the aerobic exercise, strength training, or combination of the two was more beneficial. Since both aerobic and strength training have been shown to improve side effects of cancer treatments, the researchers did not want to disadvantage any participants by only having them participate in one modality. Further research will need to be conducted to determine if one modality has a greater effect than the other on CIPN symptoms. However, for the purpose of this study, the combination of the two suggested the greatest benefit in reduction of CIPN symptoms.

Future research should also include analyzing different modalities that could increase blood flow and peripheral vasodilation to the nerves, such as laser treatments or heat treatments. However, patients who experience CIPN can have difficulty in sensing temperature in the affected areas (Wolf et al., 2008; Wilkes, 2007). Some subjects may sense temperatures as extremes, and some subjects may not feel any temperature change at all. What would be warm to an apparently healthy person may present as a burning sensation to a person experiencing CIPN. Also, if the temperature is too hot, the subject may not be able to sense that it is too hot. Thus, temperature would have to be closely monitored.

Another explanation to the reduction in 4.17/1g SWMT scores is a cessation of treatment. All of the subjects were no longer receiving their chemotherapy treatments. As

stated earlier, CIPN is dose dependent, indicating that once a subject stops receiving treatment, his or her symptoms may disappear. This is not always the case, however, as each subject is different. In order to control for this, future research will need to include a control group.

The Wilk's Lambda Multivariate test was able to show significant differences between pre-, mid-, and post- CIPN assessment scores for the 4.17/1g SWMT but not for the 5.07/10g SWMT. These two tests differ in that the 4.17/1g SWMT is used to detect a diminishing protective sensation and the 5.07/10g SWMT is used to detect the loss of protective sensation (Feng et al., 2009; Tan, 2010; Lee et al., 2003; Olaleye et al., 2001; Kamei et al., 2005; Leonard et al., 2004; Kumar et al., 1991; Lee et al., 2003; Callahan et al., 1995; Kumar et al., 1991). Thus, the 4.17/1g SWMT detects for the onset of neuropathy, while the 5.07/10g SWMT detects for a more progressive form of neuropathy. Paresthesia and numbness are sometimes considered earlier signs of neuropathy because the sensory neurons and axons that transmit these signals are unmyelinated, so they are affected sooner than myelinated fibers by the chemotherapy agents (Malik & Stillman, 2008). As CIPN progresses, all sensation would cease in the hands and feet (Malik & Stillman, 2008). This could suggest that the subjects from this study were still in the early stages of CIPN, which would indicate why the 5.07/10g SWMT did not significantly report changes in CIPN. The 4.17/1g SWMT may be more useful in the early detection of peripheral neuropathy and may be more useful for detecting CIPN. All of the subjects had patient reported symptoms of CIPN prior to entry into the study. However, some subjects were still sensate to the 5.07/10g SWMT, but were insensate to the 4.17/1g SWMT. It is possible that some patients with CIPN did not

have complete loss of protective sensation; thus, they could still feel the 5.07/10g SWMT. Thus, if a patient reports he or she is feeling signs of neuropathy, it is possible he or she would still be sensate to the 5.07/10g monofilament. It could conclude that all the subjects were only experiencing a diminished loss of protective sensation and CIPN is more likely to be diminishing in sensation rather than a total loss of protective sensation. This could also conclude that 4.17g/1g monofilament is a more accurate measurement for CIPN because it tests for the diminished sensation rather than total loss.

The 5.07/10g SWMT test did not present with significant differences from pre- to mid- to post- CIPN assessment scores. This could be mainly due to the fact that current research supports the 5.07/10g SWMT for diabetic peripheral neuropathy, but not for CIPN. Since the cellular mechanisms between the two conditions are different, the caliber of symptoms may also be different. The general symptoms between the two are similar; however, DPN is speculated to be caused by a metabolic issue, while CIPN is said to be caused by toxic agents (Schloss et al., 2013; Kluding et al., 2012; Wolf et al., 2008; Balducci et al., 2006). The results from the current study are not in agreement with current research (Feng et al., 2009; Tan, 2010; Lee et al., 2003; Olaleye et al., 2001; Kumar et al., 1991). However, many of these studies were assessing the use of the 5.07/10g SWMT on diabetic peripheral neuropathy. The 5.07/10g SWMT may not be a useful assessment tool for CIPN and needs further research. DPN is due to a hyperglycemic environment, ultimately (Head, 2006). DPN can be possibly resolved by maintaining glycemic control (Singh, Armstrong, & Lipsky, 2005; Kluding et al., 2012; Braunstein, 2001). CIPN is due to a toxic agent damaging part of the nerve and impairment in the repair mechanisms (Head, 2006). CIPN can be reversible over time

(Quasthoff & Hartung 2002). Currently, the only alleviating agent for CIPN is cessation of chemotherapy treatment (Hausheer et al., 2006; Quasthoff & Hartung 2002; Wilkes, 2007). However, this is not always an option for many people who are receiving chemotherapy. Some studies have found vitamins to be helpful, but nothing that demonstrated substantial efficacy (Hausheer et al., 2006; Quasthoff & Hartung 2002; Speck et al., 2012). The results from the current study suggest that exercise could be beneficial in alleviating symptoms of CIPN.

The results of this study indicate that exercise may be an effective and safe treatment in the management of CIPN symptoms. Prior research has examined the effects of vitamins on CIPN symptoms, but no conclusive results were obtained. Heat therapy could also be beneficial for patients with CIPN; however, there is a higher risk factor for burns or injury due to the nature of the symptoms of CIPN. Not only could exercise alleviate CIPN symptoms, but it has shown improvement for other side effects that could develop due to chemotherapy treatments as well.

Conclusion

To our knowledge, there has been very little research on the effects of aerobic training and strength training on CIPN symptoms. Results from the current study reported significant differences between pre-, mid-, and post- 4.17 SWMT CIPN assessment scores, as well as other important outcomes occurred. First, aerobic and strength training were beneficial to paresthesia symptoms associated with CIPN. Exercise has the ability to increase blood flow and nutrient flow to peripheral nerves, which could help repair any damage that occurred (Toftthagen et al., 2012; Sabatier et al., 2008; Wilkes, 2007; Kluding et al., 2012). Second, the 4.17/1g SWMT may be a more appropriate instrument

for assessing neuropathy in cancer patients than other calibers of the SWMT. All of the subjects assessed had patient-reported symptoms of neuropathy; however, the 5.07/10g SWMT, which previous research supported, did not significantly detect changes in CIPN score. More research and validation is needed for this theory. Lastly, exercise should be included in any post-cancer treatment rehab because it can attenuate many side effects of treatment. Along with being beneficial for the symptom management of CIPN, it can also lessen fatigue and depression, increase VO_{2peak} , and increase whole body strength. Previous studies have documented exercise as beneficial to anyone who is combating cancer treatments, but to date, there is not much research examining the effects of aerobic and strength training on CIPN.

Limitations

Although the need for more research in this area was a strong point for this study, several limitations did occur. The small sample size was a major limitation to this study. The original power analysis suggested a sample size of fifteen participants. However, due to Cancer Exercise Specialist availability and scheduling, RMCRI was not able to accept as many new patients as preferred. Time frame was also a limitation to this study. CIPN was only assessed over a 12-week period. Many participants still had some symptoms of CIPN at the end of their intervention. A major limitation to this study was the lack of a control group. Since research has shown to benefit patients who are receiving cancer treatment, the researchers did not want to disadvantage some in order to create a control group. It is also known that CIPN is dose-dependent. This means that if a subject were to terminate his or her chemotherapy, it is possible that CIPN symptoms would start to disappear without the help of an exercise protocol. Future research will need to include a

control group to test for this assumption. A longer time period is needed to further evaluate the effects of exercise. Along with time frame, another limitation is when the patient stopped receiving his or her chemotherapy treatment. Since CIPN is dose dependent, it is possible that a patient's symptoms will gradually start to lessen after he or she receives his or her final dose of chemotherapy. Another major limitation was the lack of knowledge. There is very little research regarding CIPN and exercise to date. Due to this, researchers had to rely on information regarding diabetic peripheral neuropathy. However, the two conditions are similar, but the mechanism of onset is different; thus, treatment and management may be different as well. More research needs to be conducted within this area of cancer research.

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APPENDIX A
INSTITUTIONAL REVIEW
BOARD APPROVAL



Institutional Review Board

DATE: March 31, 2015

TO: Reid Hayward, PhD
FROM: University of Northern Colorado (UNCO) IRB

PROJECT TITLE: [573297-3] Exercise Interventions to Attenuate the Negative Side-Effects of Cancer Treatments

SUBMISSION TYPE: Continuing Review/Progress Report

ACTION: APPROVED

APPROVAL DATE: March 27, 2015

EXPIRATION DATE: March 27, 2016

REVIEW TYPE: Expedited Review

Thank you for your submission of Continuing Review/Progress Report materials for this project. The University of Northern Colorado (UNCO) IRB has APPROVED your submission. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on applicable federal regulations.

Please remember that informed consent is a process beginning with a description of the project and insurance of participant understanding. Informed consent must continue throughout the project via a dialogue between the researcher and research participant. Federal regulations require that each participant receives a copy of the consent document.

Please note that any revision to previously approved materials must be approved by this committee prior to initiation. Please use the appropriate revision forms for this procedure.

All UNANTICIPATED PROBLEMS involving risks to subjects or others and SERIOUS and UNEXPECTED adverse events must be reported promptly to this office.

All NON-COMPLIANCE issues or COMPLAINTS regarding this project must be reported promptly to this office.

Based on the risks, this project requires continuing review by this committee on an annual basis. Please use the appropriate forms for this procedure. Your documentation for continuing review must be received with sufficient time for review and continued approval before the expiration date of March 27, 2016.

Please note that all research records must be retained for a minimum of three years after the completion of the project.

If you have any questions, please contact Sherry May at 970-351-1910 or Sherry.May@unco.edu. Please include your project title and reference number in all correspondence with this committee.

Dr. Hayward and colleagues -

Thank you for the clear and thorough IRB continuation review application. Please add a place for participants to initial the first page of the two-page consent form (i.e., Page 1 of 2 _____ please initial) given that the signatures are on page 2 per IRB guidelines. This small revision does not need to be submitted for subsequent review.

Best wishes with your continued, valuable research at the Rocky Mountain Cancer Rehabilitation Institute and please don't ever hesitate to contact me with any IRB-related questions or concerns.

Sincerely,

Dr. Megan Stellino, UNC IRB Co-Chair

This letter has been electronically signed in accordance with all applicable regulations, and a copy is retained within University of Northern Colorado (UNCO) IRB's records.

APPENDIX B
INFORMED CONSENT



Name _____ Date _____

INFORMED CONSENT

CAROLE M. SCHNEIDER, PH.D.

REID HAYWARD, PH.D.

KURT DALLOW, M.D.



BEN NIGHTHORSE
CAMPBELL CENTER

19TH STREET & 10TH AVENUE

CAMPUS BOX 6

GREELEY, CO 80639

PHONE 970-351-1876

FAX 970-351-1720

The RMCRI and the School of Sport and Exercise Science support the practice of protection of human subjects participating in research. The following information is provided for you to decide whether you wish 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 opportunities for participation in other projects offered by this department.

This project is involved with the assessment of your cardiovascular endurance, muscular strength and endurance, range of motion, and body composition. Measuring oxygen consumption on a motor-driven treadmill will assess your cardiorespiratory capacity. Assessment of muscular strength and endurance will occur through the use of weights, dumbbells, a handgrip dynamometer, and abdominal crunches. Flexibility and range of motion are measured by an instrument called a goniometer and by the sit-and-reach test. The pulmonary function test requires maximum exhalation into a sterile mouthpiece. Skinfold calipers are used to measure body composition (body fat percentage). 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, and fatigue and psychological tests such as depression scales, quality of life, fatigue and cognitive functioning. Blood will be drawn with your permission pre exercise and following your exercise intervention.

Once all of the tests are completed, the results will be analyzed and an exercise prescription written. The expected benefits associated with your participation in this program include information regarding your level of physical fitness and recommended fitness and lifestyle changes necessary to improve the quality of your life.

The project will be under the direction of the RMCRI Director and Clinical Coordinator but other persons will be associated or assist with the data collection. Your participation is solicited, although strictly voluntary. The obtained data may be used in reports or publications but your identity will not be associated with such reports.

This research should not result in physical injury, however, some soreness may occur and some of the fitness tests can be uncomfortable. Additionally, with the blood draws you may feel temporary discomfort. The duration of the discomfort is short. Please give your consent with full knowledge of the nature and purpose of the procedures, the benefits that you may expect, and the discomforts and/or risks which may be encountered. We appreciate your assistance. You will be given a copy of this consent form.

"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".

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

Signature of Researcher

Date

Signature of Physician

Date

9/9/2011



APPENDIX C

ROCKY MOUNTAIN CANCER
REHABILITATION INSTITUTE
TREADMILL PROTOCOL

Stage	Speed (mph)	Grade (%)	Time Corresponding with VO ₂ Peak Calculation	Estimated VO ₂ Peak (mL/kg/min)		Estimated VO ₂ Peak (Handrails)	
0	1.0	0	1:00-1:59	6.2 (walk)		6.2 (walk)	
1	1.5	0	2:00-2:59	7.5 (walk)		7.5 (walk)	
2	2.0	0	3:00-3:59	8.9 (walk)		8.9 (walk)	
3	2.5	0	4:00-4:59	10.2 (walk)		10.2 (walk)	
4	2.5	2	5:00-5:59	12.6 (walk)		12.1 (walk)	
5	3.0	2	6:00-6:59	14.4 (walk)		13.4 (walk)	
6	3.3	3	7:00-7:59	17.1 (walk)		15.2 (walk)	
7	3.4	4	8:00-8:59	19.2(walk)		16.6 (walk)	
8	3.5	5	9:00-9:59	21.3(walk)		18.1 (walk)	
9	3.6	6	10:00-10:59	28.0 (run)	23.6 (walk)	22.8 (run)	19.7 (walk)
10	3.7	7	11:00-11:59	29.6 (run)	25.9 (walk)	23.9 (run)	21.3 (walk)
11	3.8	8	12:00-12:59	31.2 (run)	28.3 (walk)	25.0 (run)	23.0 (walk)
12	3.9	9	13:00-13:59	32.9 (run)	30.9 (walk)	26.1 (run)	24.8 (walk)
13	4.0	10	14:00-14:59	34.6 (run)	33.5 (walk)	27.3 (run)	26.6 (walk)
14	4.1	11	15:00-15:59	36.4 (run)	36.2 (walk)	28.6 (run)	28.5 (walk)
15	4.2	12	16:00-16:59	38.2 (run)	39.1 (walk)	29.8 (run)	30.4 (walk)
16	4.3	13	17:00-17:59	40.0 (run)	42.0 (walk)	31.1 (run)	32.5 (walk)
17	4.4	14	18:00-18:59	41.9 (run)	45.0 (walk)	32.4 (run)	34.6 (walk)
18	4.5	15	19:00-19:51	43.9 (run)	48.1 (walk)	33.8 (run)	36.7 (walk)
19	4.6	16	20:00-20:59	45.9 (run)	51.3 (walk)	35.2 (run)	39.0 (walk)
20	4.7	17	21:00	48.0 (run)	54.6 (walk)	36.6 (run)	41.2 (walk)

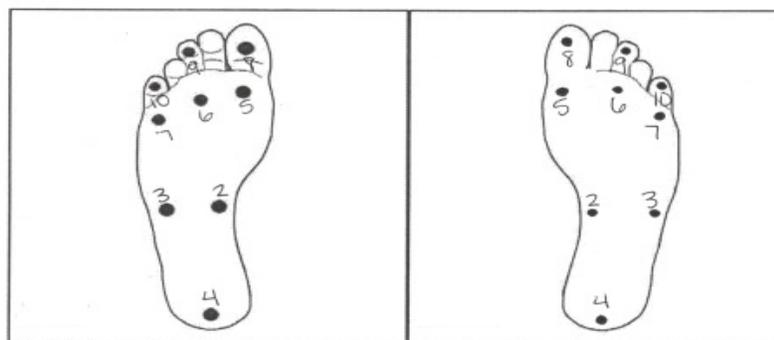
APPENDIX D**CHEMOTHERAPY-INDUCED
PERIPHERAL NEUROPATHY
DATA COLLECTION SHEET**

Id #: _____ CIPN Score _____
 Initials: _____ R Foot: _____ L Foot: _____
 5.07 4.17 R Hand: _____ L Hand: _____

Foot Sites

Right

Left



| Top of foot: _____

| Top of foot: _____

Hand Sites

