THE THERAPEUTIC EFFECTS OF A HIGH VELOCITY RESISTANCE TRAINING INTERVENTION FOR CHEMOTHERAPY INDUCED POLYNEUROPATHY

by

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In memory of Joan Boyer and Michael Gleeson

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Mariah Elizabeth Gleeson

ABSTRACT

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Chemotherapy induced polyneuropathy, also referred to as chemotherapy induced peripheral neuropathy (CIPN) is a dose dependent, neurotoxicity from known neuropathic agents, such as taxanes, platinums, and vinca alkaloids, causing damage to the peripheral nervous system which sends signals between the central nervous system and the body. CIPN can present as sensory, motor, or autonomic symptoms, such as paresthesia, hyperpathia, hypoesthesia, muscle weakness, balance impairments, orthostatic hypotension, or altered sexual function. Currently, there are no standard treatment or standard prevention methods for CIPN. The purpose of this case series was to assess the therapeutic effects of a high velocity resistance training (HVRT), or power training, in women diagnosed and treated for cancer, who presented with CIPN by measuring balance, functional performance, neuropathy, quality of life (QoL), and an inflammatory biomarker (c-reactive protein [CRP]). The HVRT consisted of 24 exercise sessions over 12 weeks including upper and lower extremity movements. The intensity prescribed was 30-60% one repetition maximum for upper extremity, and 0-60% one repetition maximum for lower extremity exercises. Findings demonstrate the feasibility

of designing and implementing a HVRT intervention to potentially attenuate CIPN symptoms. Moreover, HVRT may improve in balance, functional performance, and QoL outcomes. Although the CRP results increased, the values remained within normal limits (*Quest Diagnostics,* n.d.), thus lifestyle modifications are needed. This study provides encouraging evidence for a future HVRT intervention pilot study modulating CIPN symptoms. Assessments such as balance, functional performance, and inflammatory markers should be measured prior and throughout treatment in persons receiving known neuropathic agents to better establish baseline values. Further research is needed to enable clinicians to provide comprehensive and effective treatment plans for persons with neuropathy, subsequently improving QoL.

TABLE OF CONTENTS

TABLE OF CONTENTS—Continued

TABLE OF CONTENTS—Continued

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

1RM	1 Repetition Maximum
6MWT	6 Minute Walk Test
ADLs	Activities of Daily Living
AE	Aerobic Exercise
ANS	Autonomic Nervous System
BT	Balance Training
BNB	Blood Nerve Barrier
BBB	Blood Brain Barrier
CRP	C-Reactive Protein
CVF	Cardiovascular Fitness
CNS	Central Nervous System
CIPN	Chemotherapy induced peripheral neuropathy
ACSM	American College of Sports Medicine
CRC	Colorectal
DRG	Dorsal Root Ganglia
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ CIPN 20	European Organization of Research and Treatment of Cancer Quality of Life Questionnaire-CIPN
EDGE	Evaluation Database to Guide Effectiveness
5xSTS	Five Times Sit to Stand

5RM	Five-Repetition Maximum
FAB	Fullerton Advanced Balance Scale
FACT/GOG-Ntx	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity
GGT-Reha	Gleichgewichtstest
HIIT	High Intensity Interval Training
HVRT	High Velocity Resistance Training
ICC	Intraclass Correlation Coefficient
IG	Intervention Group
MCID	Minimal Clinically Important Difference
MDC	Minimal Detectable Change
mCTSIB	modified Clinical Test of Sensory Integration and Balance
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCA	National Strength and Conditioning Association
NCT	Nerve Conduction Tests
NCV	Nerve Conduction Velocity
OIPN	Oxaliplatin-Induced Peripheral Neuropathy
PROs	Patient Reported Outcomes
RPE	Rate of Perceived Exertion
PNS	Peripheral Nervous System
QoL	Quality of Life

ROS	Reactive Oxygen Species
RT	Resistance Training
ST	Sensorimotor Training
TUG	Timed Up and Go
TNS	Total Neuropathy Score
TNSc	TNS Clinical
TNSr	TNS Reduced
UC	Usual Care
VPT	Vibration Perception Threshold

CHAPTER ONE

INTRODUCTION

1.1 Introduction and Significance

Chemotherapy induced polyneuropathy, also referred to as chemotherapy induced peripheral neuropathy (CIPN), is a dose dependent neurotoxicity from known neuropathic agents, such as taxanes, platinums, or vinca alkaloids, that damage the peripheral nervous system (PNS). The PNS sends signals between the central nervous system and the body (Desforges, 2022). CIPN can present as sensory, motor, or autonomic symptoms which can occur dependent on the agent administered and the cumulative dose (Cioroiu, 2017; Zajączkowska, 2019). Sensory symptoms are the most commonly reported, develop first, and can be accompanied by motor and autonomic symptoms (Zajączkowska, 2019). Sensory symptoms can present as paresthesia, hyperpathia, or hypoesthesia. Motor symptoms can include muscle weakness, balance impairments, and/or gait impairment. Autonomic symptoms occur in 1% of patients, and can present as orthostatic hypotension, altered sexual function, or urinary dysfunction (Zajączkowska, 2019). The highest CIPN prevalence (70%-100%) occurs in patients who receive platinum-based agents, followed by taxanes (11%-87%), and lastly vinca alkaloids (up to 20%) (Banach, 2017). CIPN occurs in 68% of patients after the first month of chemotherapy administration, 60% of patients after the third month, and persists in 30% of patients at six months or more after treatment completion (Seretny, 2014). Risk factors for neuropathy can include cumulative dose, presence of neuropathy

at baseline, advancing age, co-morbid diabetes, and smoking history (Cioroiu, 2017, Zajączkowska, 2019).

Though the exact CIPN pathophysiology is not fully elucidated, previous research supports the relation among inflammation and neuropathy development, and neuropathic persistent pain (Zajączkowska, 2019). It can be speculated that neurotoxic chemotherapeutic agents such as taxanes, platinums, and vinca alkaloids, increase oxidative stress (Zajączkowska, 2019). Oxidative stress can be characterized as an excessive production in reactive oxygen species in cells and tissues subsequently causing molecular imbalance and damage, such as DNA and protein damage (Hussain, 2016). Evidence supports oxidative stress playing a pathogenic role resulting in an increase in inflammation and inflammatory diseases, thus, clinically can present as CIPN (Zajączkowska, 2019).

Inflammation can be characterized as an increase in pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and c-reactive protein (CRP) (Hussain, 2016). High inflammatory levels are associated with many chronic diseases such as autoimmune, cardiovascular, metabolic disease, and relevant to this project, cancers (Furman, 2019). Risk factors for high inflammatory levels are associated with low physical activity levels, high body mass index, chronic stress, poor diet intake, smoking, poor sleep, alcohol consumption, and exposures to toxins (Furman, 2019). Exercise is a promising nonpharmacological approach that modulates oxidative stress and reduces inflammation (Khosravi, 2019).

In response to muscular contraction, inflammatory mediators and cytokines are produced, expressed, and released as myokines (Barbalho, 2020). Exercise induced

myokines mediate communication between skeletal muscles and other organs and further demonstrate a wide array of paracrine, endocrine, and autocrine effects (Severinsen, 2020). There are several hundred types of myokines identified to date, and the most widely studied is IL-6. Although previously mentioned as pro-inflammatory, IL-6 demonstrates both pro and anti-inflammatory properties, and exercise induced IL-6 has demonstrated an inhibition to inflammatory cytokine production, and further stimulate anti-inflammatory effects (Severinsen, 2020). Myokines regulate several processes associated with cancer cachexia, sarcopenia, and physical frailty (Barbalho, 2020). Cancer cachexia is identified as ongoing loss of skeletal muscle mass that may or may not be accompanied by loss of adipose tissue (Anjanappa, 2020). Cancer cachexia is caused by a combination of dietary related changes to cancer treatments, increased protein catabolism, and inflammation (Anjanappa, 2020). Sarcopenia can be characterized as loss of skeletal muscle mass associated with aging, whereas physical frailty can be characterized as a multisystem impairment associated with aging (Anjanappa, 2020). Of note, cancer cachexia, sarcopenia, and physical frailty are interrelated (Gingrich, 2019). Though inflammatory levels are higher in cancer cachexia (Anjanappa, 2020).

Recent reviews have demonstrated that resistance training (RT) is highly effective for improving many properties such as, strength, physical function, body composition, and reducing inflammation in persons with a cancer diagnosis (Khosravi, 2019; Champ, 2023). RT can be defined as various types of exercises performed against an external load performed with a specific number of sets, repetitions, and progressions as well as a

fitness goal per the American College of Sports Medicine (ACSM) (2018). Therefore, RT interventions are needed in cancer populations.

However, it is important to note type II skeletal muscle fibers, or fast twitch fibers, are primarily responsible for producing power (El Hadouchi, 2022). Power is the product of force and velocity, and the ability to produce power at a lower external resistance is critical for success with daily functional tasks, such as rising from a chair, climbing the stairs, and recovering from loss of balance (El Hadouchi, 2022). Research suggests that type II skeletal muscle fibers are more likely to atrophy under cancer cachexia and sarcopenic conditions than type I fibers, or slow twitch muscle fibers (Miljkovic, 2015) and collectively contributes to physical frailty (Miljkovic, 2015). Thus, training for power in persons with a cancer diagnosis may be of critical importance (Miljkovic, 2015; El Hadouchi, 2022). High velocity resistance training (HVRT), also referred to as power training, differs from traditional RT due to the requirement of lifting lighter loads (30-60% of their one repetition maximum (1RM)) and fast concentric movements and 2-3 second eccentric contractions. Whereas RT for strength or hypertrophy is characterized by lifts of heavier loads ($\geq$ 67% 1RM) at constant velocities (Fragala, 2019).

Currently, there are no standard intervention methods for treating CIPN symptoms (Brown, 2019; Loprinzi, 2020). There is a need for a feasible and efficacious exercise training prescription in persons who are experiencing polyneuropathy. The purpose of this dissertation was to:

1. Review the current literature on resistance interventions for CIPN in persons diagnosed with cancer in relation to quality of life (QoL), balance, strength, aerobic capacity, and inflammatory biomarker outcomes.

2. Apply a HVRT, or power training, intervention in women who have had a diagnosis of cancer and are reporting CIPN post treatment to target muscle power, balance, and functional performance.
3. Assess the therapeutic response of RT on an inflammatory biomarker, c-reactive protein (CRP), a secondary measure of neuropathy.

To acknowledge the first aim, a literature review was conducted relative to resistance, or resistance and aerobic exercise (AE) combination interventions for persons with CIPN, as well as a second review of the effect of RT on inflammatory biomarkers. The literature review demonstrated feasibility in use of resistance, or resistance and AE combination training intervention studies to attenuate CIPN symptoms, increase strength, improve balance, aerobic capacity, and QoL outcomes, as well as modulate inflammatory biomarkers. However, overall studies lacked consistency among CIPN measures used, included heterogenous samples (e.g., patient baseline co-morbidities, neuropathy at baseline, inflammatory levels, cancer diagnosis, treatment type, cumulative dose, and timing intervention), and a wide range of exercise prescriptions (e.g., frequency, duration, modality), making it challenging to draw firm conclusions for clinical use (Streckmann, 2014; McCrary, 2019; Dhawan, 2020; Kleckner, 2018; Chen, 2020; Zimmer 2018; Vollmers, 2018; Muller, 2021).

To address the gaps in the literature, a HVRT intervention was designed and implemented in persons who were diagnosed with cancer and reported CIPN symptoms, measuring balance, functional performance, neuropathy, QoL, and CRP outcomes. HVRT is a specific exercise prescription tailored to train for muscular power, thus enhancing balance and functional performance (McKinnon, 2017). This type of exercise

has previously demonstrated significant functional improvements in older adults (Balachandran, 2022). The multi-joint movements such as upper extremity push and pull, and lower extremity resistance exercises were selected based on the following: efficiency of exercises, equipment availability, time commitment per session, and practicality (Paoli, 2017).

Furthermore, HVRT provided relevance to women for various reasons:

1. Physical inactivity is more prevalent among women than men, and participation in physical activity decreases as women age.

2. Women's exercise studies are less extensively studied compared to men's.

3. Women are more likely to report barriers to exercise such as self-efficacy and outcome expectancies.

4. Research suggests that participation in a comprehensive physical activity intervention tailored to address women's needs can facilitate an increase in physical activity (Costello, 2014; Edwards, 2016).

To the author's knowledge, no evidence currently exists with respect to HVRT being utilized as an intervention for persons diagnosed and treated for cancer. Additionally, the study assessed the inflammatory response to RT, a secondary measure for CIPN. The inflammatory biomarker, CRP, was selected as the outcome measure based on abundant biomarker evidence in previous research, accessibility, and reasonable cost to obtain via bloodwork sampling (Winters-Stone, 2018; Van Vulpen, 2018; Fragala, 2019; Schulz, 2022).

Although there is a wide array of pathologies that contribute toward neuropathy development, research suggests that endothelial dysfunction may be a critical contributor

(Maiuolo, 2019). Vascular endothelium is the first point of contact for chemotherapy administration, causing direct endothelial toxicity (Mclaughlin, 2021); moreover, evidence supports the relation between impaired endothelial cells and peripheral neuropathies (Maiuolo, 2019). Research suggests that an accumulation of reactive oxygen species, endothelial cell apoptosis, and an increase in pro-inflammatory cytokines contribute toward biochemical and functional changes in the blood nerve barrier, thus representing early stages of peripheral nerve damage (Maiuolo, 2019). The anti-inflammatory responses from RT have demonstrated to improve antioxidant capacity and activity, protect against oxidative stress and induce suppression of inflammation, which collectively may contribute to neuropathy improvements (Longobucco, 2022). It is hypothesized that a HVRT intervention in CIPN will improve balance, functional performance, and neuropathy outcomes, and decrease the level of CRP.

1.2 Organization of Dissertation

This dissertation is divided into five chapters. A review of the literature is provided in Chapter 2 (resistance, or resistance and AE combination training on CIPN, QoL, balance, muscular strength, aerobic capacity, and inflammation). A case series of a RT intervention for persons diagnosed and treated for cancer and reporting CIPN symptoms is presented in Chapter 3. An overarching discussion and conclusion are presented in Chapters 4 and 5, respectively.

CHAPTER TWO

LITERATURE REVIEW

2.1 Background and Statistics

Cancer is the second leading cause of death in the United States, and in 2024 there will be an estimated two million new cancer cases diagnosed (Siegel, 2024). Encouragingly, advancements in early detection and medical treatment regimens perpetuate a rise in survival rates (Siegel, 2024). A common adverse effect among persons receiving cancer therapies, however, is chemotherapy induced polyneuropathy, also referred to as chemotherapy induced peripheral neuropathy (CIPN) (Zajączkowska, 2019). CIPN is defined as damage to the axons in the peripheral nervous system and is dependent on treatment type and cumulative medication dose (Zajączkowska, 2019). Moreover, up to 70% of patients receiving chemotherapy, specifically agents such as taxanes, platinums, or vinca alkaloids, report CIPN symptoms (Sałat, 2020). While CIPN prevalence decreases over time for many, at least 30% of patients experience symptoms six months or later after completing treatment (van de Graaf, 2023). Sensory symptoms can present as numbness, tingling, burning of the distal extremities, whereas motor symptoms can include muscular weakness possibly resulting in balance impairments (Zajączkowska, 2019). Risk factors for neuropathy can include cumulative dose, presence of neuropathy at baseline, advancing age, co-morbid diabetes, and smoking history (Cioroiu, 2017, Zajączkowska, 2019).

Though the exact CIPN pathophysiology is not fully elucidated, previous research supports the relation among inflammation and neuropathy development, and neuropathic

persistent pain (Zajączkowska, 2019). It can be speculated that neurotoxic chemotherapeutic agents such as taxanes, platinums, and vinca alkaloids, increase oxidative stress (Zajączkowska, 2019). Oxidative stress can be characterized as an excessive production in reactive oxygen species in cells and tissues subsequently causing molecular imbalance and damage such as DNA and protein damage (Hussain, 2016). Evidence supports oxidative stress playing a pathogenic role in an increase in inflammation and inflammatory diseases, thus, clinically can present as CIPN (Zajączkowska, 2019).

Inflammatory biomarkers are measurable characteristics found in the body and can be used to provide early evidence of a therapeutic responses from stimuli (Calliff, 2018). Inflammation can be characterized as an increase in pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and c-reactive protein (CRP) (Hussain, 2016). High inflammatory levels are associated with many chronic diseases such as autoimmune, cardiovascular, metabolic disease, and relevant to this project, cancers (Furman, 2019). Risk factors for high inflammatory levels are associated with low physical activity levels, high body mass index, chronic stress, poor diet intake, smoking, poor sleep, alcohol consumption, and exposures to toxins (Furman, 2019).

Exercise is a promising nonpharmacological approach that modulates oxidative stress and reduces inflammation (Khosravi, 2019), and has demonstrated to reduce inflammatory markers, such as TNF-α, and CRP in persons with a cancer diagnosis (Khosravi, 2019). In response to muscular contraction, inflammatory mediators and cytokines are produced, expressed, and released as myokines (Barbalho, 2020). Exercise induced myokines mediate communication between skeletal muscles and other organs

and further demonstrate a wide array of paracrine, endocrine, and autocrine effects (Severinsen, 2020). There are several hundred types of myokines identified to date, and the most widely studied is IL-6. Although previously mentioned as pro-inflammatory, IL-6 demonstrates both pro and anti-inflammatory properties, and exercise induced IL-6 has demonstrated to inhibit inflammatory cytokine production, and further stimulate anti-inflammatory effects (Severinsen, 2020).

There are no standard measurements to quantify CIPN symptoms (Brown, 2019; Loprinzi, 2020). The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), an instrument used to document adverse events in clinical or laboratory settings, is the most common CIPN measure; however, it does not capture clinical changes over time (Colvin, 2019). The NCI-CTCAE grades CIPN on a scale of one to five, from asymptomatic to death (*National Cancer Institute: NCI GUIDELINES FOR INVESTIGATORS: ADVERSE EVENT REPORTING REQUIREMENTS FOR DCTD (CTEP AND CIP) INDs AND IDEs*. (n.d.)). Quantitative measures (e.g., vibration perception threshold (VPT), pinprick sensitivity, and nerve conduction tests (NCT)) are objective tools used to assess CIPN and have demonstrated an increase in diagnostic sensitivity (McCrary, 2017). Although the NCT is the gold standard measure for persons with diabetic polyneuropathy, the NCT requires specialized training and equipment, and is not feasible in all clinical settings (McCrary, 2017; Shibata, 2019). CIPN patient reported outcomes (PROs) have gained popularity due to relevance, sensitivity, and correlation with objective measures; however, PROs are not regularly administered due to the lack of consensus regarding best available measure (McCrary, 2017).

Currently, there are no standard prevention interventions or treatments to manage CIPN (Brown, 2019; Loprinzi, 2020). Research has demonstrated that exercise training interventions in persons with CIPN were safe and feasible in attenuating CIPN symptoms (Kanzawa-Lee, 2020). Though there is paucity in the literature regarding resistance training (RT) interventions in CIPN due to heterogenous interventions implemented. RT can be defined as various types of exercises performed against an external load performed with a specific number of sets, repetitions, and progressions as well as a fitness goal, per American College of Sports Medicine (ACSM) (2018). Therefore, the purpose of this review was to examine the effects of RT, or resistance and aerobic exercise (AE) combination, in CIPN populations, on CIPN related symptoms, muscular strength, balance, aerobic capacity, and inflammatory biomarkers.

2.2 Methods

Two separate searches were conducted. The first search was performed to establish methods and gaps in the exercise interventions in the current CIPN literature. The search included PubMed, CINAHL, and Embase databases. The keywords for PubMed and CINAHL included "Chemotherapy Induced Peripheral Neuropathy or Chemotherapy Induced Polyneuropathy" AND "Malignant Neoplasms or Cancer" AND "Exercise or Resistance Training or Strength Training." The keywords for Embase included "chemotherapy induced peripheral neuropathy" AND "resistance training" AND "cancer." Studies were included if published in the English language between 2014-2024. A total of 322 studies were initially identified. After removing duplicates, abstract only, systematic reviews and meta-analyses, and lack of RT interventions, a total of 10 (Bland, 2019; Chen, 2020; Dhawan, 2020; Kleckner, 2018; McCrary, 2019; Muller, 2021;

Vollmers, 2018; Zimmer, 2018; Hatlevoll, 2021; Streckmann, 2014) were identified, and among the 10 studies, seven (Bland, 2019; Dhawan, 2020; Kleckner, 2018; Muller, 2021; Vollmers, 2018; Zimmer, 2018; Streckmann, 2014) were randomized controlled trials. **Appendix A** presents Literature Review - Neuropathy.

The second search was conducted after data collection to identify supportive literature based on the project's findings, High Velocity Resistance Training Intervention in Chemotherapy Induced Polyneuropathy for Women Presenting with Chemotherapy Induced Polyneuropathy. The databases included PubMed, CINAHL, and Embase and the keywords used were "inflammatory markers" or "CRP" AND "cancer induced peripheral neuropathy" or "cancer" AND "resistance exercise." Studies were included if published in the English language and between 2014-2024. A total of 2,388 studies were initially identified. After removing duplicates, abstract only, systematic reviews and meta-analyses, and articles with no RT interventions, a total of 10 studies were identified (Hiensch, 2021; Cormie, 2016; De Jesus Leite, 2021; Hagstrom, 2016; Van Vulpen, 2018; Schulz, 2022; Winters-Stone, 2018; De Paulo, 2018; Ricci, 2018; Grote, 2016). Thus, a total of 20 studies were included in this review. **Appendix B** presents Literature Review - Inflammation.

Results and Discussion

2.3 Chemotherapy Induced Polyneuropathy Quantitative Assessments

Six studies used quantitative assessments to measure CIPN, and suggest that RT, or RT, balance training (BT), and AE combination may improve CIPN symptoms in persons with a cancer diagnosis receiving treatment and after treatment completion. Five quantitative assessments were identified as CIPN measurements including: the NCI-

CTCAE, VPT, pinprick, nerve conduction velocity (NCV) and Total Neuropathy Score (TNS) (Chen, 2020; Bland, 2019; Streckmann, 2014; McCrary 2019; Dhawan, 2020; Muller; 2021). Chen et al. (2020) assessed CIPN using the NCI-CTCAE, an instrument used to document adverse events in clinical and laboratory settings (inter-rater reliability weighted kappa (κ) Cohen coefficients > 0.7) (Cheng, 2020), and VPT using a 128-Hertz (Hz) tuning fork (reliability κ=0.42 (0.15 to 0.70)) (McIllhatton, 2021) during a 3-month TheraBand (yellow resistance) intervention in persons diagnosed with colorectal cancer (CRC) that were receiving platinum-based chemotherapy (Chen, 2020; *National Cancer Institute: NCI GUIDELINES FOR INVESTIGATORS: ADVERSE EVENT REPORTING REQUIREMENTS FOR DCTD (CTEP AND CIP) INDs AND IDEs*. (n.d.)). Participants demonstrated a gradual increase in CIPN symptoms over the course of the intervention. Furthermore, researchers found no change in CIPN symptoms using the VPT (Chen, 2020). VPT quantifies vibration sense in diabetic neuropathy, vibration sense is impaired in large fiber neuropathy (Nolte, 2020). Bland et al. (2019) assessed VPT using a 128-Hz tuning fork, and pinprick sensitivity (reliability κ=0.45 (0.22 to 0.69)) (McIllhatton, 2021), which also tests sensation fibers, during an exercise intervention in persons with a breast cancer diagnosis. Participants were randomized into two groups, either during (immediate exercise group) or after (delayed exercise group) taxane based chemotherapy treatment, and prescribed a RT, balance training (BT), and AE intervention for 8-12 weeks (Bland, 2019). Bland et al. (2019) found no significant difference between groups at the end of treatment (Bland, 2019). In contrast, Streckmann et al. (2014) also assessed VPT using a graduated tuning fork (κ=0.68, 95% confidence interval (CI): 0.41–0.95, $p < 0.01$) (Lanting, 2020) during a combined RT, AE, and balance training (BT)

intervention for 36 weeks in persons with a lymphoma cancer diagnosis receiving (unspecified) chemotherapy or immunotherapy treatment (Streckmann, 2014). Streckmann et al. (2014) demonstrated sensation incidence was lower in the intervention group (IG); furthermore, the IG demonstrated 87% of symptoms diminished, whereas no change in the control group (CG) after the intervention (Streckmann, 2014). The discrepant results are perhaps related to patient co-morbidities, neuropathy at the time of intervention, cancer treatment regimens received (e.g., treatment type, cumulative dose), heterogenous exercise prescriptions (e.g., frequency, duration, modality), and timing of intervention. Further research is needed to further assess VPT on CIPN symptoms during RT interventions.

Three studies (McCrary 2019; Dhawan, 2020; Muller; 2021) used variations of NCV assessments, that measured how fast electrical impulses travel through the nerves and can be used to detect nerve damage (Walsh, 2015). Literature has demonstrated sensitivity and specificity in NCV assessments persons with polyneuropathy in the peroneal nerves (sensitivity of 94% (95% CI 71–100%), specificity of 91% (95% CI 82–96%)) and sural nerves (sensitivity of 100% (95% CI 80–100%), specificity of 42% (95% CI 31–54%) (Kelmenson, 2018). In all three studies (McCrary 2019; Dhawan, 2020; Muller; 2021), no change in NCV was demonstrated. Dhawan et al. (2020) prescribed a muscle strengthening and BT intervention, consisting of lower and upper extremity body weight exercises, and BT exercises for 10 weeks duration, in persons with a cancer diagnosis (ovarian, cervical, lung, and head and neck diagnosis) receiving taxanes and platinum-based chemotherapy (Dhawan, 2020). McCrary et al. (2019) prescribed a RT, BT, and AE intervention with upper and lower extremity push/pull movements and BT

exercises during an eight-week intervention in persons with a cancer diagnosis (breast, CRC, ovarian, endometrial, appendix, lymphoma, myeloma, urothelial diagnosis) at least three months post treatment from known neuropathic agents (McCrary 2019). McCrary et al. (2019) measured exercise intensity using Borg Rate of Perceived Exertion (RPE) on a scale 6-20. Participants were encouraged to exercise at 13-15 RPE. The Borg RPE is defined as how hard a person perceives they are working during exercise (Lopes, 2022). Lastly, Muller et al. (2021) prescribed a RT (machine and home-based exercises) or BT intervention, 20-week duration in persons with a cancer diagnosis (breast, pancreatic, prostate, stomach, head and neck, colon, brain, ovarian, CRC, lung and bronchus, cervix, and bladder diagnosis) who were receiving known neuropathic agents at the time of intervention (Muller; 2021). No change was demonstrated using the NCV assessments (McCrary 2019; Dhawan, 2020; Muller; 2021). This is perhaps related to heterogenous samples (e.g., including more than one diagnosis, patient co-morbidities, neuropathy at baseline, types of treatments regimens received, and cumulative dose), time since treatment completion, heterogenous exercise prescriptions (e.g., frequency, duration, modality), and timing of intervention (e.g., during treatment or post treatment).

Furthermore, McCrary et al. (2019) and Muller et al. (2021) used modified versions of the TNS, a reliable (interrater reliability, 0.94; intra-rater reliability, 0.97) instrument and previously developed for persons with diabetic polyneuropathy (Wampler, 2006), which measures motor, sensory, and autonomic symptoms. This team also assessed VPT as a quantitative assessment (McCrary, 2017; McCrary, 2019; Muller, 2021). McCrary et al. (2019) found significant improvements in the IG group using the TNS clinical (TNSc), exclusively clinically based, whereas Muller et al. (2021) found

significant increases in all groups using the TNS reduced (TNSr) without VPT, but with the neurophysiological investigation of peripheral nerves, and small changes in the TNSc assessments (McCrary, 2019; Muller, 2021).

The discrepancy in the quantitative assessment results is perhaps related to the wide array of measures used and heterogenous patient characteristics e.g., patient baseline co-morbidities, neuropathy at the time of intervention, cancer diagnosis, type of treatments received and cumulative dose, and time since treatment completion. Additionally, variations of exercise interventions prescribed, e.g., frequency, duration, modality, and timing of intervention (e.g., during treatment or post treatment). Further research is needed to quantify neuropathy symptoms over time in persons receiving known neuropathic agents.

2.4 Chemotherapy Induced Polyneuropathy Patient Reported Outcomes

Ten studies utilized a variation of PRO's, during a RT, or RT, BT, and AE combination, and suggest that CIPN symptoms remain unchanged or improve in persons with a cancer diagnosis who are receiving known neuropathic agents, or who had completed treatment at the time the exercise intervention. Four self-report assessments were identified including the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (EORTC QLQ C30), EORTC Quality of Life Questionnaire-CIPN twenty-item scale (EORTC QLQ CIPN 20), Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity (FACT/GOG-Ntx), and a self-report 1-10 scale (McCrary, 2019; Muller, 2021; Dhawan, 2020; Streckmann, 2014; Chen, 2020; Hatlevoll, 2021; Bland, 2019; Vollmers, 2018; Zimmer, 2018; Kleckner, 2018). The EORTC is a self-report assessment which can be

administered to measure CIPN symptoms and QoL outcomes. The EORTC QLQ CIPN 20 measures CIPN related symptoms and has demonstrated high psychometric properties (Cheng, 2020). Whereas the EORTC QLQ C30 measures cancer related functional health, symptom burden, and health related QoL and has demonstrated good evidence of content validity (Cocks, 2023). The FACT/GOG-Ntx emphasizes the following QoL domains of physical, social, emotional, functional wellbeing, and neurotoxicity subscales (Cronbach's alpha coefficients of the FACT/GOG-Ntx subscale 0.82–0.89) (Beijers, 2014; Cheng, 2020).

Four studies used the EORTC QLQ CIPN 20 or the EORTC QLQ C30 to assess QoL and demonstrated discrepant results. EORTC QLQ CIPN 20: McCrary et al. (2019) utilized the EORTC QLQ CIPN 20 and a QoL self-report assessment and found significant improvements in CIPN symptoms during a RT, BT, and AE intervention. The intervention consisted of upper and lower extremity push/pull movements and BT exercises during the three times per week for eight weeks intervention in persons with a cancer diagnosis (breast, CRC, ovarian, endometrial, appendix, lymphoma, myeloma, or urothelial diagnosis) at least three months post treatment from known neuropathic agents (McCrary, 2019). In contrast, Muller et al. (2021), also used the EORTC QLQ CIPN 20 and found no change between groups (RT, BT, or usual care (UC)) in persons with a cancer diagnosis (breast, pancreatic, prostate, stomach, head and neck, colon, brain, ovarian, CRC, lung and bronchus, cervix, or bladder diagnosis) who were receiving known neuropathic agents at the time of intervention; moreover, symptoms persisted in all groups at the six month follow up (Muller, 2021).

EORTC QLQ C30: Dhawan et al. (2020) assessed neuropathic pain scores in persons with a cancer diagnosis (ovarian, cervical, lung, and head and neck diagnosis) receiving taxanes and platinum-based chemotherapy using the EORTC QLQ C30 during a muscle strengthening and BT intervention, and found significant reductions in neuropathy pain (Dhawan, 2020). Lastly, Streckmann et al. (2014) used the EORTC QLQ C30 during an RT, BT, and AE intervention for 36 weeks in persons diagnosed with lymphoma cancer receiving (unspecified) chemotherapy or immunotherapy treatment, and despite significant intergroup difference within the first 12 weeks, there were no QoL differences between groups at the end of the intervention (Streckmann, 2014). The reason for discrepancy in results is perhaps related to heterogenous samples (e.g., patient baseline co-morbidities, neuropathy at baseline, including more than one diagnosis, treatment type, and cumulative dose), time since treatment completion, heterogenous exercise prescriptions (e.g., frequency, duration, modality), and timing of intervention implementation.

Four studies used both the EORTC QLQ CIPN 20 and the EORTC QLQ C30 to assess QoL, furthermore, demonstrated discrepant results. Chen et al. (2020) demonstrated that sensory symptoms gradually increased throughout treatment in persons diagnosed with CRC that were receiving platinum-based chemotherapy using the EORTC QLQ CIPN20; furthermore, the EORTC QLQ C30 demonstrated no changes CIPN symptoms (Chen, 2020). Hatlevoll et al. (2021) also assessed CIPN during a RT, BT, and AE, 24-week intervention in persons diagnosed and treated for CRC, receiving (IV) fluorouracil/calcium folinate or oral capecitabine in combination with IV oxaliplatin. Hatlevoll et al. (2021) demonstrated an increase in CIPN symptoms from baseline using

both EORTC QLQ C30 and EORTC QLQ CIPN 20 (Hatlevoll, 2021). Bland et al. (2019) conducted an intervention in persons diagnosed with breast cancer. Participants were randomized into the immediate exercise group (before receiving taxane treatment), or delayed exercise group (after taxane treatment completion). Furthermore, demonstrated that the immediate exercise group demonstrated a higher QoL using EORTC QLQ C30 than delayed exercise group after treatment; however, there were no significant differences in EORTC QLQ CIPN 20 between groups at any point during the intervention (Bland, 2019). Vollmers et al. (2018) assessed a physical training and sensorimotor exercise training program twice per week in persons diagnosed with breast cancer receiving taxane based chemotherapy treatment and continued the intervention for six weeks after chemotherapy termination and found no significant improvements in EORTC QLQ CIPN 20 and EORTC QLQ C30 (Vollmers, 2018). The discrepant results are perhaps related to patient co-morbidities, neuropathy at baseline, treatment type, cumulative dose, timing of intervention implementation as well as prescribing various exercise interventions (e.g., frequency, duration, modality).

Zimmer et al. (2018) assessed CIPN utilizing the FACT/GOG -NTX during an eight-week RT, BT, and AE intervention in stage IV CRC receiving chemotherapy regimens such as leucovorin calcium (folinic acid), fluorouracil, and irinotecan hydrochloride (FOLFIRI), leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin (FOLFOX), Capecitabine, or targeted therapies such as Bevacizumab, Regorafenib, or Trastuzumab. The study demonstrated that neuropathic symptoms remained stable in the IG when compared to the CG, while CIPN worsened in the CG from pre-test to follow up (Zimmer, 2018).

Kleckner et al. (2018) measured patient reported CIPN symptoms on a 1-10 symptom severity scale, reliability and validity have been previously demonstrated in similar scales (Mendoza, 2013), during a six week at home unsupervised daily walking (60-85% Heart Rate Reserve (HRR)) and theraband exercise program in persons with a cancer diagnosis (breast, lymphoma, colon, lung, and other - non specified diagnosis, stages I-IV) receiving taxanes, platinums, vinca alkaloids, or a combination treatment. Kleckner et al. (2018) demonstrated a decrease in symptoms of hot/cold in hands/feet, and numbness/tingling in the IG compared to a CG. It is also worth noting participants who reported a reduction in CIPN symptoms from the exercise intervention were of older age, male, or had breast cancer (Kleckner, 2018).

Previous research lacks consistency in CIPN and QoL outcomes, and in RT or resistance and AE combination interventions. This is perhaps due to heterogenous samples e.g., patient baseline co-morbidities, neuropathy at the time of intervention, cancer diagnosis, type of treatments received, cumulative dose, time since treatment completion, and variations of exercise interventions prescribed, e.g., frequency, duration, modality. Despite a broad range of CIPN assessments available, clinicians and researchers should consider clinic feasibility for the most optimal measure to use. Nevertheless, a standard CIPN measure is needed for clinical and research application.

2.5 Muscular Strength

Three studies were found to measure muscular strength (Vollmers, 2018; Zimmer, 2018; Chen, 2020), and research suggests RT, or RT, BT, and AE combination may improve strength outcomes in persons with a cancer diagnosis who are receiving treatment at the time of intervention. Two studies used one repetition maximum (1RM),

the gold standard measurement for muscular strength (Grgic, 2020), whereas one study assessed handgrip strength. Chen et al. (2020) measured muscle strength using 1RM during a 4.5-month intervention that consisted of lower extremity exercises using a yellow resistance theraband (3-4.3 lb.) three times per week for 30-35 minutes in persons diagnosed and treated for CRC. Participants were recruited at the third cycle of chemotherapy treatment (three months duration). Significant strength improvements in lower extremity 1RM outcomes measures were reported (Chen, 2020). Zimmer et al. (2018) measured strength using an estimated 1RM in the bench press, lat pull down, and leg press. The eight-week intervention included RT, BT, and AE two times per week for 60 minutes. The participants for this intervention were persons diagnosed with stage IV CRC receiving chemotherapy regimens such as leucovorin calcium (folinic acid), fluorouracil, and irinotecan hydrochloride (FOLFIRI), leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin (FOLFOX), Capecitabine, or targeted therapies such as Bevacizumab, Regorafenib, or Trastuzumab. This study demonstrated a significant difference in strength between groups from baseline to end of intervention and from baseline to four week follow up (Zimmer, 2018). Vollmers et al. (2018) utilized hand dynamometry to measure handgrip strength in persons with a breast cancer diagnosis receiving taxane based chemotherapy treatment and continued the intervention for six weeks after chemotherapy termination. The intervention protocol consisted of sensorimotor training (ST) - static and dynamic balance, and RT for the upper and lower extremities (six exercises for two sets of 20 repetitions at an RPE of 13-15 for two times per week) during treatment. Results included significant loss of handgrip strength in the CG compared to a slight improvement in the IG (Vollmers, 2018). Although research has

reported some promising strength outcomes, studies lacked exercise adherence due to treatment complications, structured exercise progressions and additionally, prescribed heterogenous exercise prescriptions (e.g., frequency, duration, modality). Future work should focus on tailoring intensities based on administration of cancer therapies and provide strength goals with individualized and safe exercise intensities and progressions.

2.6 Static and Dynamic Balance

Four studies assessed balance outcomes during a RT, or RT, BT, and AE combination, to determine exercise impact on static and dynamic balance in persons with a cancer diagnosis who were receiving treatment, or who were post treatment at the time of the exercise intervention. Static balance can be characterized as the ability to maintain upright posture with minimal movement, whereas dynamic balance can be characterized as the ability to maintain upright posture while moving (Gottlieb, 2023). Three studies used instruments to quantify static and dynamic balance, whereas one study assessed only static balance. Muller et al. (2021) measured center of pressure with a force plate during a RT, ST, or usual care group in persons who were receiving known neuropathic agents at the time of intervention. A force plate is the gold standard measurement for postural balance assessment (Clark, 2018) that can quantify the center of pressure, an indirect measure of postural sway. An increase in postural sway is associated with balance impairments and increase risk for falls (Fino, 2019). The RT intervention consisted of two times per week for 45 minutes on machines, and one time per week for 15 minutes home-based training with a 70-80% of the participants' 1RM. Muller et al. (2021) ST intervention consisted of 35 minutes of various balance exercises three times per week and found significant increase in center of pressure in bipedal eyes closed measure in all

groups (RT, ST, and UC) (Muller, 2021). Vollmers et al. (2018) measured static balance and dynamic balance in persons with a breast cancer diagnosis receiving taxane based chemotherapy treatment and continued the intervention for six weeks after chemotherapy termination. Static balance was assessed using a posturometry, a diagnostic tool that measures fall risk by evaluating sway area, and dynamic balance using the Fullerton Advanced Balance (FAB) Scale - a reliable (intraclass correlation coefficient (ICC) = 0.98) and valid ($P < 0.001$) 10 item assessment for static and dynamic balance (Huang, 2019). The intervention protocol consisted of physical training - six exercises for the upper and lower extremities, 20 repetitions, 13-15 RPE, as well as sensorimotor exercises two times per week throughout the taxane based chemotherapy treatment and continued intervention for six weeks after chemotherapy termination (Vollmers, 2018). The IG demonstrated significant improvements in bipedal stance over time, and significant smaller postural sway during monopedal stance after the six week follow up; furthermore, significant differences in dynamic balance FAB Scale scores were found in the IG (Vollmers, 2018). McCrary et al. (2019) measured static balance using a Swaymeter, a reliable measurement (ICC=0.654 to 0.944) for quantifying static balance (Sturnieks, 2011), and the 5xSTS, a reliable tool (ICC=0.937, $p < 0.001$) to measure extremity strength and dynamic balance for individuals with balance impairments (Muñoz-Bermejo, 2021). The protocol consisted of RT, AE, and BT intervention (RPE 13-15) three times per week for eight weeks in persons with mixed cancer diagnoses (breast, CRC, ovarian, endometrial, appendix, lymphoma, myeloma, urothelial) at least three months post treatment from known neuropathic agents. Results in the IG demonstrated that static balance eyes open, on stable and unstable surfaces significantly

improved, whereas static balance eyes closed on stable and unstable surfaces demonstrated no change. Furthermore, the IG demonstrated an improved 5xSTS (McCrary, 2019). Lastly, Zimmer et al. (2018) used the GGT-Reha, or the Balance Test in English translation. The GGT-Reha is a 28-task static and dynamic balance test, with three intervals increasing in difficulty with each interval. The intervention consisted of a RT, AE, and BT intervention in stage IV CRC receiving chemotherapy regimens, and found no change in simple static (less challenging and complex tasks) or dynamic balance. However, significant improvements was demonstrated in advanced static (more challenging and complex tasks) outcomes (Zimmer, 2018).

Despite discrepancies in balance outcomes, three studies found significant changes in balance over time (Vollmers, 2018; Zimmer 2018; McCrary, 2019). This is perhaps due to participant baseline characteristics (e.g., co-morbidities, neuropathy at the time of intervention, balance at baseline), treatment type, cumulative dose, time since treatment completion, heterogenous exercise prescriptions (e.g., frequency, duration, modality), implementing interventions after treatment completion, and participants likely to avoid treatment related adverse effects e.g., nausea, generalized weakness, fatigue. Previous research suggests that RT, or a combination of training modalities may improve postural balance in persons with CIPN (Vollmers, 2018; Zimmer 2018; McCrary, 2019). Balance assessments should be implemented early and throughout treatment to establish the patient's baseline, and identify declines in persons with CIPN, which will guide clinicians to an appropriate exercise prescription.

2.7 Aerobic Capacity

Three out of ten studies measured aerobic capacity (Zimmer, 2018; McCrary, 2019; Chen, 2020) in which all utilized the 6MWT, suggesting that RT, or combinations may improve aerobic capacity in persons with a cancer diagnosis who were receiving treatment, or post treatment at the time of intervention. The submaximal 6MWT measures the maximum distance covered in six minutes, exhibits good psychometric properties and reliability (ICC=0.93 (0.86-0.97)) and validity (r=0.67) in oncology populations, and has been extensively used in persons diagnosed with a breast cancer to assess functional capacity (Fisher, 2015). Cardiovascular fitness (CVF) is a strong predictor for morbidity and mortality among healthy and cancer populations (Schmid, 2015; Imboden, 2018). The maximal oxygen consumption, or VO2 max assessment, is the gold standard for measuring CVF and capacity for physical function (Bonikowske, 2024). Though the VO2 max is the gold standard for CVF assessment, performing exercise to near exhaustion may pose difficulties for novice exercisers, older populations, and less motivated participants, thus participants may cease testing prior to reaching their VO2 max, leading to inaccuracy in outcomes (Poole, 2017). Submaximal measures such as the 6 Minute Walk Test (6MWT), are more practical in clinical settings. McCrary et al. (2019), and Chen et al. (2020), both demonstrated a significant increase in distance, whereas Zimmer et al. found no change between groups (Zimmer, 2018; McCrary, 2019; Chen, 2020). McCrary et al. (2019) prescribed a RT, BT, and AE intervention with upper and lower extremity push/pull movements and BT exercises during an eight-week intervention in persons with a cancer diagnosis (breast, CRC, ovarian, endometrial, appendix, lymphoma, myeloma, urothelial diagnosis) at least three months post treatment

from known neuropathic agents (McCrary 2019). McCrary et al. (2019) measured exercise intensity using Borg Rate of Perceived Exertion (RPE) on a scale 6-20. Chen et al. (2020) prescribed a 4.5-month intervention that consisted of lower extremity exercises using a yellow resistance theraband (3-4.3 lb.) three times per week for 30-35 minutes in persons diagnosed and treated for CRC. Participants were recruited at the third cycle of chemotherapy treatment (three months duration). Lastly, Zimmer et al. prescribed an eight-week intervention included RT, BT, and AE two times per week for 60 minutes. The participants for this intervention were persons diagnosed with stage IV CRC receiving chemotherapy regimens such as leucovorin calcium (folinic acid), fluorouracil, and irinotecan hydrochloride (FOLFIRI), leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin (FOLFOX), Capecitabine, or targeted therapies such as Bevacizumab, Regorafenib, or Trastuzumab (Zimmer, 2018).

An increase in 6MWT is perhaps due to the patient's co-morbidities, neuropathy at the time of intervention, baseline aerobic capacity, cancer treatment regiments received (e.g., treatment type, cumulative dose), time since treatment completion, and heterogenous exercise prescriptions (e.g., frequency, duration, modality). Cancer treatments, such as chemotherapy, is associated with cardiotoxicities and cardiorespiratory impairments; thus, it may impact cardiovascular assessment outcomes, and status at baseline if measured after chemotherapy has been administered. (Truong, 2014; Hughes, 2018). Establishing functional assessments and encouraging aerobic interventions may minimize cardiotoxicities and cardiorespiratory impairments in persons diagnosed with cancer.

2.8 Inflammatory Biomarkers

Strong evidence supports anti-inflammatory effects from exercise subsequently improving overall health and reducing all-cause mortality (Scheffer, 2020), though there are discrepant results in RT interventions in cancer populations. Three inflammatory biomarkers including CRP, IL-6, and TNF-α were the most common biomarkers assessed (De Paulo, 2018; De Jesus Leite, 2021; Van Vulpen, 2018; Cormie, 2016; Grote, 2016; Winters-Stone, 2018; Schulz, 2022; Ricci, 2018; Hagstrom, 2016).

Ten studies measured the therapeutic effects of RT, or RT and AE combination on inflammatory biomarkers (Hagstrom, 2016; Cormie, 2016; Grote, 2016; Van Vulpen, 2018; Winters-Stone, 2018; De Paulo, 2018; Ricci, 2018; Hiensch, 2021; De Jesus Leite, 2021; Schulz, 2022). Eight studies included only persons diagnosed with breast cancer (Hagstrom, 2016; Cormie, 2016; Winters-Stone, 2018; Van Vulpen, 2018; De Paulo, 2018; De Jesus Leite, 2021; Hiensch, 2021; Schulz, 2022), whereas two studies included more than one cancer diagnosis (Ricci, 2018; Grote, 2016). Ricci et al. (2018) included breast, CRC, myeloma/lymphoma, gynecologic, thyroid, prostate, skin, and lung diagnoses. Grote et al. (2016) included breast, ovarian, CRC, Hodgkin lymphoma, and lung diagnoses. Four studies implemented an exercise intervention during cancer treatment (Hiensch, 2021; Schulz, 2022; Van Vulpen, 2018; De Paulo, 2018), and six studies implemented an exercise intervention post treatment (Cormie, 2016; De Jesus Leite, 2021; Hagstrom, 2016; Winters-Stone, 2018; Grote, 2016; Ricci, 2018).

Regarding inflammatory biomarker outcomes, five studies demonstrated either an increase or no change in biomarkers in women with a breast cancer diagnosis (De Paulo, 2018; De Jesus Leite, 2021; Van Vulpen, 2018; Heinsch, 2021; Cormie, 2016). Four out

of the five studies implemented an exercise intervention in women diagnosed with breast cancer during cancer treatment (De Paulo 2018; Van Vulpen 2018; Hiensch 2021; De Jesus Leite 2021). De Paulo et al. (2018) assessed inflammatory marker, CRP, during a RT and AE intervention three times per week for 13 weeks in persons receiving aromatase inhibitor therapy. Van Vulpen et al. (2018) prescribed a RT or RT and AE intervention two times per week for 12-18 weeks in persons during chemotherapy treatment, measuring IL-6, interleukin-1 receptor antagonist, and IL-6/ interleukin-1 receptor antagonist ratio. Hiensch et al. (2021) prescribed a RT high intensity interval training (HIIT) (70-80% 1RM) and AE HIIT two times per week for 16 weeks during chemotherapy. Heinisch et al. (2021) measured the following biomarkers IL-1 alpha, Interferon beta, IL-2, IL-5, IL-13, IL-21, IL-33, IL-35, and IL-12 receptor subunit beta 1. De Jesus Leite et al. (2021) prescribed RT of upper and lower extremity exercises 60-85% 1RM for three times per week for 12 weeks in persons diagnosed with breast cancer receiving tamoxifen hormonal therapy, measuring IL-4, IL-6, IL-10, IL-17, TNF-α (De Jesus Leite, 2021). Whereas Cormie et al. (2016) assessed acute inflammatory effects (24 hours) in persons diagnosed with breast cancer, post treatment, and presented with lymphedema. Cormie et al. (2016) implemented a low, medium, and high intensity RT intervention of upper and lower extremities, 55-85% 1RM intensity and demonstrated no significant changes in biomarkers (CRP, IL-6, TNF) (Cormie, 2016).

In contrast, five studies demonstrated a decrease or no change in inflammatory outcomes in persons with a cancer diagnosis receiving treatment or who were post treatment at the time of intervention. Winters-Stone et al. (2018) and Schulz et al. (2022) demonstrated a decrease in CRP measures, though the remaining inflammatory

biomarkers (IL-1β, IL-6, TNF-α) remained unchanged (Winters-Stone, 2018; Schulz, 2022). Winters-Stone prescribed a RT of upper and lower extremity exercises at 60-80% 1RM and AE intervention three times per week for 12 months, in persons diagnosed with breast cancer post treatment (Winters-Stone, 2018). Whereas Schulz et al. (2022) measured high-sensitivity C-reactive protein (hs-CRP) during a HIIT training in persons diagnosed with breast cancer either during or after treatment. Schulz et al. prescribed a HIIT at 85-100% VO2 peak and strength intervention (upper and lower extremity exercises up to 60-80% 1RM) two times per week for 12 weeks (Schulz, 2022). Furthermore, both Ricci et al. and Grote et al. demonstrated a decrease in CRP outcomes. Both studies prescribed a RT and AE intervention post cancer treatment in samples consisting of more than one diagnosis (Grote, 2016; Ricci, 2018). Lastly, Hagstrom et al. (2016) demonstrated a significantly lower expression of TNF-α on their natural killer cells after a RT in persons with a history of breast cancer diagnosis, were post treatment, with upper and lower extremity exercises at 80% 8RM intensity three times per week for 16 weeks (Hagstrom, 2016).

It is worth noting the variations of exercise interventions prescribed e.g., frequency, duration, modality used in study design. Additionally, heterogenous populations and numerous confounders that contributed toward systemic inflammation were observed e.g., patient baseline co-morbidities, inflammatory levels, lifestyle factors (e.g., physical activity levels, chronic stress, poor diet intake, smoking, poor sleep, alcohol consumption), cancer diagnosis, type of treatments received, cumulative dose, and time since treatment completion (Furman, 2019). Cancer chemotherapy agents are complex, vary among drug class, cumulative dose, frequency, and duration. This myriad perhaps

accounts for some of the discrepant results in RT on biomarkers. Thus, extensive research is needed to assess the therapeutic response of RT on inflammatory markers in relation to CIPN symptoms.

2.9 Conclusion

Adverse effects from neurotoxic chemotherapeutic agents can present as declines in muscle strength, balance impairments, increase risk for falls, and increase in inflammatory biomarkers, collectively contributing toward a decrease in QoL. Currently there are no standard prevention or treatment methods for CIPN (Brown, 2019; Loprinzi, 2020). Several RT, or RT and AE combination interventional studies have shown the feasibility in attenuating CIPN symptoms, increasing strength, aerobic capacity, balance, QoL outcomes, and modulating inflammatory biomarkers (Streckmann, 2014; McCrary, 2019; Dhawan, 2020; Kleckner, 2018; Chen, 2020; Zimmer 2018; Vollmers, 2018; Muller, 2021; Winters-Stone, 2018; Schulz, 2022; Ricci, 2018; Grote, 2016). However, overall studies lacked consistency among CIPN measures used, included heterogenous samples (e.g., patient baseline co-morbidities, neuropathy at the time of intervention, inflammatory levels, cancer diagnosis, treatment type, cumulative dose), time since treatment completion, heterogenous exercise prescriptions (e.g., frequency, duration, modality), and timing of intervention (e.g., during treatment or post treatment) (Streckmann, 2014; McCrary, 2019; Dhawan, 2020; Kleckner, 2018; Chen, 2020; Zimmer 2018; Vollmers, 2018; Muller, 2021). Future research should consider measuring balance outcomes in relation to the specific exercise modalities prescribed, implement RT programs with individualized intensities and progressions, and assess minimum exercise dose response requirements that can attenuate CIPN symptoms. Furthermore, assessment

of inflammatory responses to resistance exercise programs and CIPN symptoms should also be a priority for research in this domain.

CHAPTER THREE

CASE SERIES

3.1 Background

In the United States, there were an estimated two million new cancer cases in 2024 (Siegel, 2024). Treatment advancements are improving survival rates, specifically, 5-year survival rates of 69% among white people and 65% among black people for all diagnoses in 2013-2019 (Siegel, 2024). However, the impact on overall survival rate is multifactorial, and positively associated with treatment advancements, cancer screening/early detection and treatment, age at diagnosis, and stage of diagnosis (Siegel, 2024). Cancer survivors are at an increased risk for the development of chronic diseases, such as cardiovascular disease, diabetes, and osteoporosis (Zullig, 2022). Also compounding complexity are medical treatment related adverse effects occurring in an estimated 86% of patients, many of which may persist long after treatment completion (Pearce, 2017). One adverse effect this study will highlight is chemotherapy induced polyneuropathy, also referred to as chemotherapy induced peripheral neuropathy, or CIPN.

3.2 Chemotherapy Induced Polyneuropathy Statistics and Symptoms

CIPN is a dose dependent neurotoxicity caused by known neuropathic agents, taxanes, platinums, vinca alkaloids, thalidomide, bortezomibs, and epothilones, that induce damage to the nervous system structure (Banach, 2017). CIPN occurs in 68% of patients diagnosed with cancer after receiving the first month of chemotherapy and can persist in 30% of patients six months after completing treatment (Seretny, 2014). In very

rare cases, chemotherapy, radiation therapies, or surgical interventions can lead to phrenic nerve neuropathy and diaphragm dysfunction (Rosado, 2014). Typically, patients are asymptomatic, though may experience an increase in dyspnea in supine position. Furthermore, individuals with phrenic nerve neuropathy have an increased risk for experiencing sleep-disorder breathing (Norton, 2020). Though thalidomide, bortezomib, and epothilones induce neuropathy, this study will primarily focus on taxanes, platinums, and vinca alkaloids because they are found to precipitate the highest toxicities and result in an increased CIPN prevalence. The highest CIPN prevalence (70%-100%) occurs in patients who receive platinum-based agents, followed by taxanes (11%-87%), and lastly vinca alkaloids (up to 20%) (Banach, 2017). Symptoms can present as sensory, motor, or autonomic and negatively impact quality of life (QoL) in many survivors/persons living with and beyond cancer (Zajączkowska, 2019). Sensory symptoms are the most common, develop first, and can be accompanied by motor and autonomic symptoms (Seretny, 2014). Sensory symptoms typically occur in the feet first; however, both hands and feet are affected (Starobova, 2017) and can present as paresthesia, hyperpathia, or hypoesthesia (Cioroiu, 2017). Motor symptoms include muscle weakness, balance impairments, and gait impairments (Winters-Stone, 2017). Autonomic symptoms occur in 1% of patients, and can present as orthostatic hypotension, altered sexual function, or urinary dysfunction (Cioroiu, 2017; Starobova, 2017). Risk factors for developing CIPN symptoms include cumulative dose, neuropathy at baseline, older age, co-morbid diabetes, and smoking history (Cioroiu, 2017). The effects of chemotherapy on the nervous system are multifactorial and complex.

3.3 Nervous System

The nervous system has two parts: the central nervous system (CNS), which includes the brain and spinal cord, and the peripheral nervous system (PNS), encompassing the nerves outside the brain and spinal cord (Thau, 2022). The brain is composed of nervous tissue, and controls movement, sensation, thoughts, memory, and speech (Thau, 2022). The spinal cord is located within the vertebral column that sends motor commands from the brain to the peripheral body, additionally relays sensory information from the sensory organs to the brain (Thau, 2022). The PNS can be divided into the somatic and autonomic nervous systems (*SEER Training Modules,* n.d.). The somatic nervous system supplies motor impulses to the skeletal muscles, whereas the autonomic nervous system (ANS) operates smooth skeletal muscles, heart, and other organs (*SEER Training Modules,* n.d.). The ANS can further be divided into the sympathetic and parasympathetic nervous system (*SEER Training Modules,* n.d.). The sympathetic nervous system sends "fight or flight" responses in stressful situations, while the parasympathetic is responsible for "rest and digest" conditions (*SEER Training Modules,* n.d.). It is important to recognize that the CNS is protected by the blood-brain barrier (BBB). This barrier protects the CNS from toxic substances, regulates the passage of biological substances, and is responsible for maintaining the homeostasis of the brain microenvironment (Daneman, 2015). The PNS is not protected by the BBB, thus is more susceptible to damage and diseases (Grisold, 2021). Chemotherapeutic agents damage PNS structures and, depending on the individual compound, cause a variety of neuropathies: large and small fiber, sensory or motor, demyelinating and axonal, cranial, and autonomic (Cioroiu, 2017). The exact CIPN pathophysiology mechanism has not

been fully elucidated, however previous research supports the relation among inflammation, neuropathy development, and neuropathic persistent pain (Zajączkowska, 2019). Furthermore, these effects vary among the different classes of drugs, combination effects of drugs, cumulative dose, and patients baseline co-morbidities (Cioroiu, 2017).

3.3.1 Platinum Pathophysiology

Platinum-based chemotherapies (e.g., oxaliplatin, cisplatin and carboplatin) are commonly used to treat solid tumors. Oxaliplatins are used for the treatment of digestive tract tumors (advanced colorectal, esophageal, stomach, liver, and pancreatic cancers); whereas cisplatin and carboplatin are used for the treatment of other types of tumors (small-cell lung cancer, testicular, ovarian, brain, uterine and bladder cancers) (Zajączkowska, 2019). Research has demonstrated acute oxaliplatin-induced peripheral neuropathy (OIPN) can precipitate cold-related paresthesias of the hands and feet, a unique feature for OIPN, occurring in 65-98% of patients within hours of infusion, lasting for five to seven days after the first cycle (Zajączkowska, 2019); moreover, symptoms were still reported > 21 days after cycle 12 (Zajączkowska, 2019). Chronic symptoms have been demonstrated as sensory, axonal neuropathy, with stocking and glove distribution, that involves feet and hands, starting distally and moving proximally. This occurs in 26-46% of patients at 12 months follow up after termination of treatment (Beijers, 2014). Sensory neurons of the dorsal root ganglia (DRG) are the primary anatomical structures affected by platinum agents; therefore, patients present with positive sensory neuropathy symptoms (Staff, 2019). The DRG is located outside the CNS and not protected by the blood brain barrier (BBB). Though the exact pathophysiology is not fully elucidated, current research has highlighted the following

molecular mechanisms contributing toward the development of platinum induced neuropathy as platinum:

1. Binds directly to DNA, prohibiting DNA replication and RNA transcription, resulting in cell apoptosis (Dasari, 2014).

2. Binds to mitochondrial DNA, forming DNA adducts, impairing the replication and transcription, leading to decrease in cellular metabolism and an increase in production of reactive oxygen species (ROS) and oxidative stress (Zajączkowska, 2019).

3. Affects ion channels (Na+, K+, Transient Receptor Potential), resulting in the hyperexcitability of peripheral neurons (Zajączkowska, 2019).

4. Activates glia cells, thus causes activation and attraction of immune cells, and a release and elevation of pro-inflammatory cytokines, resulting in nociceptor sensitization and hyperexcitability of peripheral neurons (Zajączkowska, 2019).

3.3.2 Taxane Pathophysiology

Another class of neurotoxic chemotherapeutic agents are taxane-based chemotherapies (e.g., Paclitaxel, Docetaxel, and Cabazitaxel). Paclitaxel is used for breast cancer, non-small cell lung cancer (NSCLC), and ovarian cancer. Docetaxel is used for breast, prostate, stomach, head and neck cancers, and NSCLC, and Cabazitaxel is used for prostate cancers (Zajączkowska, 2019). Taxane neuropathy is sensory dominant, affecting small diameter sensory fibers, and can present clinically as paresthesia, hypoesthesia, dysesthesias, altered proprioception and loss of dexterity in the toes and fingers; however, other localizations are possible. Motor and autonomic symptoms are infrequent but may also develop (Zajączkowska, 2019). Taxane symptoms can occur within the first two months of treatment, can persist up to one to three years,

are likely to progress, and can worsen after cessation of treatment (Eckhoff, 2015; Jordan, 2020).

The molecular mechanisms that have been proposed to explain the development of taxane induced neuropathy include the fact that taxanes:

1. Cause microtubule disruption, impairing axonal transport, subsequently leading to Wallerian degeneration.

2. Induce mitochondrial damage, contributing toward increased production of ROS. Mitochondrial damage can also result in damage of enzymes, proteins, and lipids, as well as the dysregulation of calcium homeostasis within neurons. This leads to apoptotic changes and demyelination of peripheral nerves, ultimately impacting the excitability of peripheral neurons (Zajączkowska, 2019).

3. Activates microglia and astrocytes which leads to the activation of attraction and activation of immune cells and to the release and elevation of pro-inflammatory cytokines (interleukins and chemokines). This process results in the nociceptor sensitization and hyperexcitability of peripheral neurons and may lead to nociceptor sensitization and the development of neuroinflammation (Zajączkowska, 2019).

3.3.3 Vinca Alkaloid Pathophysiology

Vinca alkaloid-based chemotherapies are commonly used for NSCLC (vincristine), including Hodgkin and non–Hodgkin lymphoma, breast, testicular germ (Zajączkowska, 2019). In adults who receive vinca alkaloids, up to 20% report sensory neuropathy, and 17.5% report motor neuropathy (Burgess, 2021). Symptoms associated with vinca alkaloids include pain in the hands and feet, muscle weakness including wrist extensors and dorsiflexors as well as cramping (Zajączkowska, 2019). Vinca alkaloids do

not cross the BBB; however, they act on the cell body of the peripheral nerves inducing sensorimotor neuropathy.

The molecular mechanisms that have been proposed to explain the development of vinca alkaloid induced neuropathy as vinca alkaloids:

1. Affect the large axons and DRG neurons, causing myelin sheath damage and impairment, Wallerian degeneration, altered activity of ion channels, and ultimately hyperexcitability of peripheral neurons.

2. Attract and activate immune cells, causing a release and elevation of pro-inflammatory cytokines, resulting in neuroinflammation.

3. Inhibit polymerization into microtubules, impairing axon transport and inducing distal neuropathy, altering the excitability of peripheral neurons (Zajączkowska, 2019).

In summary, it can be speculated that neurotoxic chemotherapeutic agents such as taxanes, platinums, and vinca alkaloids, increase oxidative stress (Zajączkowska, 2019). Oxidative stress can be characterized as an excessive production in ROS in cells and tissues subsequently causing molecular imbalance and damage such as DNA and protein damage (Hussain, 2016). Evidence supports oxidative stress playing a pathogenic role in an increase in inflammation and inflammatory diseases, thus, clinically can present as CIPN (Zajączkowska, 2019).

3.4 Chemotherapy Induced Polyneuropathy Measurements

Measures utilized to identify CIPN include patient reported outcomes, composite scoring systems, and QoL outcomes (Park, 2019; Burgess, 2021). The most common tool used in this review to measure CIPN is the 5-point rating The National Cancer Institute

Common Terminology Criteria for Adverse Events (NCI-CTCAE), which primarily focuses on interference with activities of daily living (ADLs), and grades both motor and sensory neuropathy as follows: asymptomatic (grade 1), moderate with intervention indicated (grade 2), severe (grade 3), life threatening (grade 4), and death (grade 5) (*National Cancer Institute: NCI GUIDELINES FOR INVESTIGATORS: ADVERSE EVENT REPORTING REQUIREMENTS FOR DCTD (CTEP AND CIP) INDs AND IDEs*. (n.d.)). The NCI-CTCAE is subjective, and patient reported, and does not capture clinical changes over time (Colvin, 2019). Considering CIPN is progressive and dose-dependent, this is a major limitation. Composite scoring systems include the Total Neuropathy Score (TNS), which is a 10-item tool that comprises a physical examination, vibration perception threshold, and nerve conduction test (Park, 2019). The TNS a reliable (interrater reliability, 0.94; intra-rater reliability, 0.97) measure in patients with diabetic neuropathy evaluating sensory, motor, and autonomic symptoms (Wampler, 2006). Additionally, the TNS assesses a semi-quantitative sensory examination of the vibration perception threshold inclusive of neurophysiological examination. Two modified versions of the TNS exist: the Total Neuropathy Score reduced (TNSr) which does not include vibration perception threshold, and Total Neuropathy Score clinical (TNSc) which does not include nerve conduction assessment (Park, 2019). The Functional Assessment of Cancer Therapy-Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx), a functional and QoL assessment, has been demonstrated to correlate with the TNSr and TNSc (Park, 2019). The FACT/GOG-Ntx subscale domains measure physical, social, emotional, and functional wellbeing. Furthermore, it demonstrates reliability, validity, sensitivity to change and responsiveness (Cronbach's alpha

coefficients of the FACT/GOG-Ntx subscale 0.82–0.89**)** to evaluate CIPN in persons with a cancer diagnosis (Cheng, 2020).

3.5 Resistance Training

It is well established that exercise training (e.g., resistance, aerobic, or a combination) stimulates anti-inflammatory signals that modulate inflammation (Gonzalo-Encabo, 2021). In response to muscular contraction, inflammatory mediators and cytokines are produced, expressed, and released as myokines. Exercise induced myokines mediate communication between skeletal muscles and other organs and further demonstrate a wide array of paracrine, endocrine, and autocrine effects. There are several hundred types of myokines identified to date, and the most widely studied is Interleukin-6 (IL-6) which inhibits pro-inflammatory cytokine production, and further stimulates anti-inflammatory effects (Severinsen, 2020). Myokines regulate several processes associated with cancer cachexia, sarcopenia, and physical frailty (Barbalho, 2020). Cancer cachexia is identified as ongoing loss of skeletal muscle mass that may or may not be accompanied by loss of adipose tissue (Anjanappa, 2020). Cancer cachexia is caused by a combination of dietary related changes to cancer treatments, increased protein catabolism, and inflammation (Anjanappa, 2020). Sarcopenia can be characterized as loss of skeletal muscle mass associated with aging, whereas physical frailty can be characterized as a multisystem impairment associated with aging (Anjanappa, 2020). Of note, cancer cachexia, sarcopenia, and physical frailty are interrelated (Gingrich, 2019). Though inflammatory levels are higher in cancer cachexia (Anjanappa, 2020).

Previous research supports resistance training (RT) modulating inflammatory biomarkers in cancer populations (Winters-Stone, 2018; Schulz, 2022; Ricci, 2018;

Grote, 2016). RT can be defined as various types of exercises performed against an external load performed with a specific number of sets, repetitions, and progressions as well as a fitness goal per the American College of Sports Medicine (ACSM) (2018). However, the effects of RT on inflammatory markers are discrepant due to heterogenous populations, and contributing confounders associated with inflammatory levels (Winters-Stone, 2018; Schulz, 2022; Ricci, 2018; Grote, 2016). Thus, assessing the therapeutic response of RT on inflammatory markers, a secondary measure for CIPN, could assist clinicians with symptom prevention and mitigation.

Type II skeletal muscle fibers, or fast twitch fibers, are primarily responsible for producing power (El Hadouchi, 2022). Power is the product of force and velocity, and the ability to produce power at a lower external resistance is critical for success with daily functional tasks, such as rising from a chair, climbing the stairs, and recovering from loss of balance (El Hadouchi, 2022). Research suggests that type II skeletal muscle fibers are more likely to atrophy under cancer cachexia and sarcopenic conditions than type I fibers, or slow twitch muscle fibers (Miljkovic, 2015) and collectively they contribute to physical frailty (Miljkovic, 2015). Thus, training for power in persons with a cancer diagnosis may be of critical importance (Miljkovic, 2015; El Hadouchi, 2022).

High velocity resistance training (HVRT), also referred to as power training, differs from traditional RT due to the requirement of lifting lighter loads (30-60% of their one repetition maximum (1RM)) and fast concentric movements and 2-3 seconds eccentric contractions. Whereas RT for strength or hypertrophy is characterized by lifts of heavier loads ($\geq$ 67% 1RM) at constant velocities (Fragala, 2019). Evidence supports exercise interventions in CIPN populations; however, current research data has remained

inconclusive due to heterogenous populations, CIPN measurements, specific exercise modalities prescribed, and intervention timing (e.g., post treatment, during treatment, or combination) (Streckmann, 2014; McCrary, 2019; Dhawan, 2020; Kleckner, 2018). Previous studies have shown the feasibility of HVRT interventions, demonstrating significant functional performance improvements in older, deconditioned populations, and may be clinically relevant for neuromuscular improvements (El Hadouchi, 2022).

3.6 Significance

Currently, there are no standard treatment methods for CIPN (Tamburin, 2021). Previous CIPN literature has demonstrated the feasibility of RT, or a combination of RT and AE in attenuating CIPN symptoms, improving balance, increasing muscle strength, and improving QoL outcomes (McCrary, 2019; Vollmers, 2018; Streckmann, 2014). However, overall studies lacked consistency among CIPN measures used, included heterogenous samples (e.g., patient baseline co-morbidities, neuropathy at the time of intervention, inflammatory levels, cancer diagnosis, treatment type, cumulative dose, and timing intervention), and prescribed a wide range of exercise prescriptions (e.g., frequency, duration, modality), making it challenging to draw firm conclusions for clinical use (Streckmann, 2014; McCrary, 2019; Dhawan, 2020; Kleckner, 2018; Chen, 2020; Zimmer 2018; Vollmers, 2018; Muller, 2021). Future research should include homogenous samples with specific inclusion criteria, and measure balance outcomes in relation to the specific exercise modalities prescribed, intensities, and progressions. Thus, these steps can further assist clinicians in prescribing individualized intensities exercise for persons who present with CIPN. To address the gaps in the previous literature, this case series implemented a specific exercise prescription to target muscle power, balance,

and functional performance. Additionally, case series study assessed the inflammatory biomarker, c-reactive protein (CRP), a secondary measure for neuropathy, to further assess the therapeutic response of the HVRT intervention.

This study provides meaningful impact in women for various reasons:

1. Physical inactivity is more prevalent among women than men, and participation in physical activity decreases as women age.

2. Women's exercise studies are less extensively studied compared to men's.

3. Women are more likely to report barriers to exercise such as self-efficacy and outcome expectancies.

4. Research suggests that participation in a comprehensive physical activity intervention tailored to address women's needs can facilitate an increase in physical activity (Costello, 2014; Edwards, 2016).

The purpose of this case series was to measure the therapeutic effects of a HVRT program in women with a cancer diagnosis who report experiencing CIPN across balance, functional performance, neuropathy, QoL, and CRP. It is hypothesized that a HVRT intervention in women diagnosed with cancer who report experiencing CIPN will improve balance, functional performance, and neuropathy outcomes, and decrease CRP levels.

3.7 Methods

This intervention was a prospective case series conducted in women with a cancer diagnosis who reported CIPN and were at least three months post cancer treatment completion. A single group study was designed, with pre and post measures performed before and after the exercise intervention. The timeline included a pretest measurement

visit, pretest blood draw, orientation session, repetition maximum session, 24 exercise sessions, post-test measurement visit, and post-test blood draw. The study duration took approximately 17-22 weeks (approximately four to five months) for each participant to complete. **Table 1** presents the study's timeline. The study protocols were approved by Oakland University's Institutional Review Board (IRB #: IRB-FY2022-211), research procedures took place at Oakland University Human Health Building (OU HHB), and blood draws were completed at Any Lab in Rochester Hills, Michigan.

Table 1 - Study Timeline

Session #	0	1-2	3	4	5-28	29, 30
Activity	Consent	Pre-Test, Bloodwork	Familiarization Session	Repetition Max Session	Exercise Intervention (24 sessions)	Post-Test, Bloodwork
Location	Your Desired Location, Time	OU HHB Any Lab, Rochester, MI	OU HHB	OU HHB	OU HHB	OU HHB Any Lab, Rochester, MI
Duration	10 min.	1.5 hr.	30 min.	1 hr.	1hr./session	1.5 hr.

Abbreviations: OU HHB - Oakland University Human Health Building

Women in the Detroit Metropolitan area were recruited to participate in the study via word of mouth, group announcements, flyers, and social media. Locations included multiple clinics, cancer support groups, and events. Potential participants were screened for participation either in person, by telephone, or by zoom. Inclusion criteria included women with a history of non-metastatic cancer, completed medical treatment (30 days - eight years post treatment), received known neuropathic agents - taxanes, platinums, vinca alkaloids or a combination, presented with CIPN symptoms, aged 18-84 years old, participated in less than 150 minutes of physical activity per week, and absent of current

injury. Participants were required to receive medical clearance prior to participating. Exclusion criteria were women with stage IV diagnosis, received cancer treatment at the time of the exercise intervention, possessed musculoskeletal injuries at the time of the intervention, and women who were pregnant. All eligible participants were informed of the study purpose, potential risks and benefits, study procedures, time commitments, option to withdraw at any time, and voluntary nature of study participation prior to signing the informed consent, which was obtained from all participants prior to data collection. Data analysis included descriptive statistics and comparative analysis.

Measurements included medical history, fall history, waist circumference, balance, functional performance, and CIPN assessment. Two balance assessments were utilized including the force plate and the Fullerton Advanced Balance (FAB) Scale. The force plate is the gold standard measurement for static balance (Clark, 2018). The Balance Tracking System (BTrackS) modified Clinical Test of Sensory Integration and Balance (mCTSIB) is a portable force plate that measures static balance (Goble, 2019). The mCTSIB is a reliable measure (Intra-class correlation coefficient (ICC) (0.47-0.79)) and assessed sensory feedback during upright posture, measuring the standard, proprioceptive, vision, and vestibular contributions toward balance. The assessment was performed with the participant standing on the force plate with their feet shoulder width apart, and hands on hips. There were four, 30 second trials with 10 seconds between each trial while the participant is standing on force plate, eyes open (standard), standing on the force plate, eyes closed (proprioception), standing on foam, eyes open (vision), and standing on foam, eyes closed (vestibular) (Goble, 2019).

The second balance assessment, FAB Scale, was composed of static and dynamic assessments. The FAB Scale assessment included standing with feet together, eyes closed; reaching forward toward an object; turning in a full circle; stepping up and over; tandem walking; standing on one leg; standing on foam, eyes closed; two footed jump; walking with head turns; and reactive postural control. Each assessment was scored zero to four, with four being the highest (Rose, 2006). This measure has a breast cancer Evaluation Database to Guide Effectiveness (EDGE) Task Force rating of 4, which has demonstrated high psychometric properties for reliability, validity, and data for interpretation (Huang, 2019) (FAB ICC = 0.98, r=0.581). The EDGE Task Force provides a comprehensive list of outcome measurements that can be applied to cancer populations based on specific diagnoses aiming to facilitate evidence-based practice in clinic and research settings (Miale, 2013), and further assists professionals in effective assessment and prescription of treatment plans to improve patient outcomes.

Functional Performance was measured via two tests, the Six Minute Walk Test (6MWT) and the Timed Up and Go (TUG). The 6MWT measured the maximum distance a person can walk in six minutes, on a hard flat surface. This test has been demonstrated to measure exercise tolerance in cardiac patients; however, it has been widely accepted as a clinically useful functional capacity measure in cancer populations (Fisher, 2015). Moreover, the 6MWT has been demonstrated to measure functional improvements over time (Fisher, 2015). Gait speed was assessed using the TUG. The TUG started with the participant seated in an armchair with back and arms against the chair. The participant was asked to stand up, walk three meters, turn around, walk back and sit back down in the chair. The TUG was measured in seconds, time started when the tester said “go,” and

stopped when the participants glutes touched the seat. The TUG is a significant predictor of functional performance and dependency (Fisher, 2015). Within the cancer population, this test is also used to measure mobility and postural control. Both functional performance assessments, 6MWT (ICC=0.93, r=0.67) and TUG (r=0.90, r=0.85) , have a breast cancer EDGE rating of '4' for functional performance (Fisher, 2015).

The Semmes Weinstein Monofilament (SWM) test was used to measure CIPN. Monofilament sizes 4.17 (1.4 gram), 5.07 (10 gram), and 6.1 (100 gram) were used to assess neuropathy. Monofilament 5.07 (10 gram) has previously demonstrated reliability (k = 0.61) (McIllhatton, 2021). The SWM is a non-invasive, low cost, rapid, easy application measurement, and is clinically used to assess diabetic neuropathy (Craig, 2014). This test was performed with shoes and socks off, and eyes closed. The assessment was first demonstrated on the participants forearm, then the participant is asked to say "yes," every time they felt the monofilament, regardless of how lightly they perceived the touch. The monofilament was placed at a 90-degree angle to the skin, pushed into the skin until bent to 1cm, and then released at a rate of 1-3 seconds. This assessment was repeated randomly on the surfaces of the hallux, 3rd and 5th toes, and the plantar surfaces of the same three toes metatarsal heads (Richardson, 2021). Neuropathy was determined by the inability to detect the monofilament at one or more sites of each foot (Hicks, 2022).

The self-report FACT/GOG- Ntx, was also used to measure QoL and neuropathy outcomes. This assessment has a breast cancer EDGE rating of '4' for CIPN (alpha > 0.7) (Hile, 2015).

Inflammatory biomarker, CRP, was measured. Venous blood samples were drawn by a registered nurse and analyzed at Any Lab Test Now ®. Participants were not required to fast prior to blood draw. Samples were taken as part of the pretest measurements, and at least 48 hours after the last day of their exercise training session.

The exercise intervention - HVRT - The exercise intervention included one orientation session, and a five-repetition maximum (5RM) testing session per ACSM protocol with 48-hours in between sessions (Ploutz-Synder, 2001). The orientation session included instruction on the following exercises: bench press, latissimus pull down, back squat, overhead press, bent row, and lunge per National Strength and Conditioning (NSCA) guidelines. Regarding the bench press, the participants were instructed to maintain the five-point body contact position, 1. head in neutral on the bench, 2. shoulders and upper back even on bench, 3. glutes on bench, and 4. right foot and 5. left foot on the floor. The barbell was lowered, touched the chest, then the elbows extended back to starting position. For the latissimus pull down, the participants were instructed to grab the bar slightly wider than shoulder width, to pull the bar to their chest, then extended their elbows back to starting position. For the back squat, the participants were instructed to squat to a depth where the mid-thigh was parallel to the floor, while maintaining the torso 35 to 45 degrees from vertical, then extending the knees and hips back to upright position. For the overhead press, the participants were instructed to start with the dumbbells at the anterior deltoids, elbows extended overhead, then returned to starting position. For the bent row, the participants were instructed to bend at the torso parallel to the floor, pulling the dumbbells to the upper abdomen with the elbows remaining upwards and shoulder blades together. For the lunge, the participates were

instructed to take a large step forward, lowering the hips while maintaining the thigh parallel to the floor and maintaining the torso in an upright position, then pushing through the heel to return to starting position. The 5RM per ACSM protocol, started with five to eight sub-maximal repetitions. The investigators determined the 5RM within four trials, with three to five minutes of rest between trials was sufficient for this study. The weight for the initial trial was selected within perceived capacity (~50-70% repetition maximum). Resistance was progressively increased 5-10% for upper extremity and 10-20% for lower extremity from a previous successful attempt until the participant could not complete the selected repetitions. The final weight was recorded as multiple repetition max, and the participants estimated 1RM was calculated.

The multi-joint movements such as upper extremity push and pull, and lower extremity resistance exercises were selected based on the following: efficiency of exercises, equipment availability, time commitment per session, and practicality (Paoli, 2017). The training protocol was designed per NSCA (2021) guidelines and to further facilitate the Physical Activity Guidelines for Americans physical activity recommendations (150 minutes of moderate physical activity per week). The intervention included 24 sessions over 15 weeks (20 weeks maximum) to complete. All exercise sessions consisted of the following: 5-10 minute warm up of the choice of treadmill, rowing machine, or cycle, at light to moderate intensity using Borg's 0-10 Rate of Perceived Exertion (RPE) scale ratings of two to three. The Borg RPE is the participant's perception of how hard they are exerting themselves during exercise (Lopes, 2022). Resistance exercises followed next and consisted of a bench press, latissimus pull down, back squat, overhead press, bent row, lunge, abdominal plank, and ball slams, with a RPE

of at least four. Standard or regression exercises were performed, tailored to the participant, and dependent on their skill level. The completion of the session involved a 5-10-minute cooldown with their choice of a treadmill, rowing machine, or cycle, and stretch, at an intensity of two to three RPE. The frequency included two days/week, and intensity ranged between 30-60% of 1RM for upper extremity exercises, and 0 (or body weight) -60%, of 1RM for lower extremity exercises. The type of exercise prescribed was HVRT (fast concentric contractions, 2-3 seconds eccentric contractions), for 60 minutes/session. Exercises were performed for three sets of at least 8-12 repetitions, and the abdominal plank held for at least 10 seconds. Time was increased as strength and technique improved, time ended when the participant could no longer hold with correct technique. Progressions were instructed with a gradual increase in intensity and complexity of the prescribed exercises. Rest periods included two to three minutes for multi joint, high intensity exercises, and one to two minutes for assisted, low intensity exercises. The specific exercises and variations prescribed, HVRT, or power training, were individualized with specific fitness goals of improving balance and functional performance using compound movements to increase the efficiency of the workout. Participants were also encouraged to engage in physical activity on non-intervention days. **Table 2** presents the standard or regression resistance exercises performed.

Table 2 - Standard and Regression Resistance Exercises

Standard	Regression
Back squat	Box squat, leg press
Bench press	Machine press
Bent row	Add wrist strap
Lunge	With support (e.g., chair)
Press	Resistance bands (resistance band was fixed at the shoulder with one arm, while the working arm performed the press)
Lat pull	Add wrist strap
Ball slams	Decrease weight
Abdominal Plank	Abdominal plank on knees

3.8 Results

Three women consented to participate in the study.

Case Presentation 1 - A 62-yr-old woman, with no known co-morbidities (height=170.2 cm, body mass=66.2 kg, body mass index (BMI)=22.9 kg/m^2, and 20 months postdiagnosis) with a history of a diagnosis and treatment for stage III breast cancer. Her treatment consisted of lumpectomy, mastectomy, four adjuvant treatments of doxorubicin and cyclophosphamide (AC), three months of paclitaxel (Taxol), and she received 28 radiotherapy treatments. The participant reported balance impairments and experienced one fall within the last six months, which resulted in an upper extremity injury.

Case Presentation 2 - A 60-yr-old woman, with obesity (height=54.9 cm, body mass=77.1 kg., BMI=32.1 kg/m^2, 72 months postdiagnosis) and a history of diagnosis and treatment for stage IIIb colon cancer. Her treatment consisted of right partial resection of the colon, six months of adjuvant treatments consisting of leucovorin calcium (folinic acid), fluorouracil, and irinotecan hydrochloride (FOLFIRI) and Oxaliplatin (Eloxatin). The participant reported no falls within the last six months.

Case Presentation 3 - A 55-yr-old woman, with no known co-morbidities (height=67.6 cm, body mass=74.8 kg, BMI=26.6 kg/m2, 3 months postdiagnosis) and a history of diagnosis and treatment for stage Ib breast cancer. Her treatment consisted of five months of neoadjuvant treatments of Trastuzumab, Pertuzumab, carboplatin, Docetaxel (Herceptin, Perjeta, Paraplatin, Taxotere), double mastectomy, three months of adjuvant treatments of Trastuzumab emtansine (Kadcyla) and radiation, and five months of Trastuzumab and Pertuzumab (Herceptin and Perjeta). **Table 3** presents participant characteristics.

Table 3 - Participant Characteristics

Participant	Age	Cancer diagnosis	Height (cm)	Weight (kg)	BMI (kg/m^2)	Time since treatment completion (months)
1	62	Breast III	165	66	24.3	20
2	60	Colon IIIb	152	77	33.2	72
3	55	Breast Ib	162	75	28.3	3

Abbreviations: BMI - Body Mass Index

A total of three participants consented to participate:

Participant 1 completed 24/24 exercise sessions.

Participant 2 completed 5/24 exercise sessions, declined to further participate in the exercise intervention, but completed post-test measures. It is important to note, that she did not meet the required number of exercise intervention sessions, and there were approximately eight weeks between the last exercise session and posttest measures.

Participant 3 also discontinued early due to personal reasons and completed 14/24 exercise sessions.

For participants 1 and 3, posttest measures were performed at least 48-72 hours after the last exercise session. The average number of visits for the three participants was 14.3. There were no adverse events reported by the participants.

3.8.1 Balance and Functional Performance

Participant 1 showed improvements in BTrackS mCTSIB proprioception, vision, vestibular, and composite score (sum scores in cm.) measures, and a decrease in the standard measure. Participant 2 had small increase in standard measure, and a decrease in proprioception and vision results. The vestibular and composite score results are not available due to participant 2 declining to participate in vestibular assessment. Participant 3 demonstrated improvements in the standard measures and a decline in vision measures, whereas proprioception, vestibular, and composite measures demonstrated no change**.** **Table 4** presents the participants results for the BTrackS mCTSIB.

Table 4 - BTrackS mCTSIB

Participant	Standard (cm),%	Proprioception (cm),%	Vision (cm),%	Vestibular (cm),%	Composite (cm),%
1 (pre-test)	15, 53%	46, 2%	60, 2%	72, 33%	193, 11%
1 (post-test)	22, 14%	30, 19%	34, 29%	65, 43%	151, 29%
2 (pre-test)	29, 3%	36,9%	31, 37%	-	-
2 (post-test)	25, 8%	52, 1%	74, 1%	-	-
3 (pre-test)	18,31%	32, 13%	28,49%	94,15%	172, 18%
3 (post-test)	16, 46%	33, 12%	33, 31%	94, 15%	176, 17%

Abbreviations: Balance Tracking System (BTrackS) modified Clinical Test of Sensory Integration and Balance (mCTSIB). The left column presents the path length in

centimeters (cm), and the right column is the participants percentile rank in comparison to healthy adults of the same sex.

Participant 1 demonstrated improvements in the FAB Scale, 6MWT, and TUG. Participant 2 showed no change in the FAB Scale and 6MWT, and an increase in TUG time. Participant 3 demonstrated improvements in FAB Scale, 6MWT, and TUG. Participant 1 and 3 demonstrated minimal detectable change (MDC) in the FAB Scale, and minimal clinically important difference (MCID) in 6MWT. Furthermore, participant 3 demonstrated MDC changes in TUG results. MDC is the smallest amount of change detected and corresponds with change in ability, and MCID is the smallest amount of change deemed important by clinicians (Huang, 2019). The FAB Scale MDC is 1.36-point change, 6MWT MCID is a 14-30.5-meter change, and TUG MDC is 0.95s change (Huang, 2019; Bohannon, 2016).

3.8.2 Neuropathy

Participant 1 baseline neuropathy scores demonstrated an inability to feel sensation in five locations with 4.17 (1.4-gram) SWM, one location with 5.07 (10-gram) SWM, and one location with 6.1 (100-gram) SWM. At follow up, participant 1 demonstrated inability to feel sensation in two locations with 4.17 (1.4-gram). Furthermore, participant 1 reported similar improvements in the right hand, and complete resolution of numbness in the left hand. Participant 2 baseline neuropathy scores demonstrated inability to feel sensation in 10 locations with 4.17 (1.4-gram) SWM, five locations with 5.07 (10-gram) SWM, and three locations with 6.1 (100-gram) SWM. At follow up, participant 2 demonstrated inability to feel sensation in two locations with 4.17 (1.4-gram) SWM, two locations with 10-gram SWM, and one location with 6.1

(100-gram) SWM. Participant 3 baseline neuropathy scores demonstrated inability to feel sensation in five locations with 4.17 (1.4-gram) SWM. At follow up, participant 3 demonstrated inability to feel sensation in two locations with 4.17 (1.4-gram) SWM.

3.8.3 Quality of Life

Participant 1 demonstrated improvements in QoL composite results, and MCID improvements in the neurotoxicity subscale. The FACT/GOG-Ntx neurotoxicity sub score MCID is 1.38 and 3.68 change (Cheng, 2020). Whereas participant 2 and 3 QoL composite results decreased. Participant 2 neurotoxicity subscale results decreased, whereas participant 3 neurotoxicity subscale results remained the same.

3.8.4 Inflammation

CRP increased in participant 1 and 3. CRP reference range < 8 mg/L. (*Quest Diagnostics*, n.d.). **Table 5** presents a summary of the participants results.

Table 5 - Results

Participant	1		2		3	
Number of intervention visits	24/24		5/24		14/24	
	Baseline	Post-Test	Baseline	Post-Test	Baseline	Post-Test
FAB Scale	32/40	37/40	16/40	16/40	29/40	39/40
6MWT (m)	450	480	300	305	370	470
TUG (s)	7.98	7.76	9.85	11.38	9.68	7.31
QoL	127/152	138/152	107/152	94/152	124/152	117/152
CRP (mg/L)	0.9	3.1	0.2	-	4.4	6.6

Abbreviations: FAB Scale - Fullerton Advanced Balance (FAB) Scale, 6MWT - Six Minute Walk Test, TUG - Timed Up and Go, QoL - Quality of Life, CRP - C-reactive protein

3.9 Discussion

The purpose of this case series was to measure the therapeutic effects of a HVRT intervention in balance, functional performance, neuropathy, QoL, and CRP, in three women diagnosed and treated for cancer presenting with CIPN. It was hypothesized that a HVRT intervention in CIPN will improve balance, functional performance, and neuropathy outcomes, and decrease CRP levels. The current findings demonstrate the feasibility in a HVRT intervention in attenuating CIPN symptomology and suggest HVRT provides improvements in balance, functional performance, neuropathy, and QoL outcomes.

With respect to balance results, participant 1 demonstrated improvements, participant 2 demonstrated declines, and participant 3 demonstrated no change. The balance improvements were consistent with McCrary et al. (2019) balance outcomes. McCrary et al. (2019) prescribed a resistance, aerobic, and balance training intervention with upper and lower extremity push/pull movements and balance exercises during an eight-week intervention in persons with a cancer diagnosis (breast, CRC, ovarian, endometrial, appendix, lymphoma, myeloma, urothelial diagnosis) at least three months post treatment from known neuropathic agents (McCrary 2019). McCrary et al. (2019) measured exercise intensity using Borg RPE on a scale 6-20. Participants were encouraged to exercise at 13-15 RPE. Regarding functional performance, two out of three participants had clinically meaningful improvements in the FAB Scale and 6MWT, furthermore one of these participants had clinically meaningful improvements in TUG results. Lastly, one participant's FAB Scale and 6MWT remained unchanged and had an increase in TUG time. The functional performance improvements were consistent again

with previous research conducted persons with CIPN who were post treatment (McCrary, 2019). The discrepancies in the balance and functional performance results could be related to the design of the RT prescription specifically targeting functional performance and not addressing static balance training, as well as lack of adherence to the exercise intervention (Aartolahti, 2015). The potential reason for improvement in balance and functional performance are perhaps related to the specificity of exercise prescription, neural adaptations, and progressions (Hughes, 2018; Walker, 2021; Duchateau, 2021). Neural adaptations, especially in anaerobic training modalities, depend on optimal neural recruitment for performance, and an increased neural drive is important for maximizing muscular power (Hughes, 2018; Walker, 2021). Neural adaptions in anaerobic training include increased agonist muscle recruitment (increased involvement of major muscles during exercise), increased neural firing rates, improved neuron synchronization, and reduced inhibitory mechanisms (Hughes, 2018; Walker, 2021). Progressions provided modifications over time based on individual status (Fragala, 2019). It is worth noting, that in order to maintain muscle strength gains, an increase in external demands on the neural muscular system is required (Duchateau, 2021). HVRT with progressions appears to be a relevant exercise prescription in individuals with CIPN for maintaining activities of daily living (ADLs) for this reason.

All participants demonstrated improvements in neuropathy symptoms in their feet. Furthermore, participant 1 reported improvement in the right hand, and complete resolution of numbness in the left hand. This suggests that neuropathy improvements can also be related to participant's neuropathy at baseline, lifestyle factors that influence inflammation (e.g., physical activity levels, chronic stress, diet intake, smoking, poor

sleep, alcohol consumption), treatment type, cumulative dose, and time since treatment completion. The neuropathy results were consistent with previous research in post treatment CIPN populations in resistance, aerobic and balance training interventions (McCrary, 2019). One participant demonstrated improvements in QoL results whereas two participants demonstrated a decrease in their QoL results. The most compliant participant had both improvements in CIPN and QoL results. A retrospective cross-sectional study supports exercise training in persons with a breast cancer diagnosis to significantly reduce CIPN symptoms in a dose dependent manner regardless of chemotherapy type (Saint, 2023). Furthermore, exercise training has demonstrated to improve health related QoL outcomes in persons with a cancer diagnosis (Campbell, 2019).

The CIPN symptom improvements are perhaps related to the therapeutic response to HVRT (Longobucco, 2022). Although there is a wide array of pathologies that contribute toward neuropathy development, it can be speculated that endothelial dysfunction may be a critical contributor (Maiuolo, 2019). Vascular endothelium is the first point of contact for chemotherapy administration, causing direct endothelial toxicity (Mclaughlin, 2021); moreover, evidence supports the relation between impaired endothelial cells and the presence of polyneuropathies. At the CNS level, the BBB ensures extracellular brain fluids and plasma homeostasis, whereas, at the PNS level, this process is controlled by the blood nerve barrier (BNB). The BNB restricts exogenous substances and maintains homeostasis of the nervous tissues adjacent to the endothelium (Maiuolo, 2019). Research suggests that an accumulation of ROS, endothelial cell apoptosis, and an increase in pro-inflammatory cytokines contribute toward biochemical

and functional changes in the BNB, thus represent early stages of peripheral nerve damage (Maiuolo, 2019). The anti-inflammatory responses from RT have demonstrated to improve antioxidant capacity and activity, furthermore, protect against oxidative stress and induce suppression of inflammation, collectively which may contribute to neuropathy improvements (Longobucco, 2022). Though the inflammatory biomarker, CRP, increased in the post measurement for two participants, the values remained within normal limits (< 8.0 mg/L) (*Quest Diagnostics,* n.d.). The reason for discrepancy in the CRP results is likely multifactorial and risk factors associated with high inflammatory levels include other chronic diseases, physical activity level, and lifestyle factors such as diet, thus lifestyle modifications are imperative for prevention and maintenance of inflammation (Furman, 2019).

Despite the promising findings, limitations exist within this study. The first limitation was slow participant accrual. Specific challenges associated with accrual included:

1. Complex inclusion criteria that initially included only breast cancer diagnoses which was later expanded to all cancer diagnoses who received neurotoxic chemotherapeutic agents.

2. Lack of interest in exercise, physician's and participant's general unfamiliarity with RT and its benefits.

3. Lack of and delay in obtaining physician referral.

4. Overall participant time commitment and geographical barriers. Potential participants expressed interest, however, could not commit time and feasibly commute to

research site. Despite the protocol supported by ACSM guidelines, the time commitment of the intervention may have been a barrier.

Further limitations include lack of control group, timeframe variability between assessments and intervention start and end, long term follow-up data was not collected, and practice effect, indicating participants familiarity with measures at post-test may have contributed to improved results. Strengths of this study included the use of a force plate, a gold standard measurement for static balance, reliable and valid measures dynamic balance, functional performance, and QoL measures, and implementation of a participant specific exercise prescription with progressions. Although the case series results are not generalizable, the study data provides is encouraging evidence for a future HVRT intervention pilot study modulating CIPN symptoms. Further investigation is needed to determine the dose response requirements to attenuate CIPN symptoms. Additionally, future research should include both men and women with multiple cancer diagnosis, consider multiple institution collaboration with multiple locations to optimize accrual potential, improve convenience and access, and study design should incorporate lifestyle interventions for inflammation prevention and maintenance.

3.10 Conclusion

This study measured the therapeutic effects of a HVRT protocol in women with CIPN consequences to balance, functional performance, neuropathy, QoL, and inflammatory biomarker CRP. The current findings demonstrate that HVRT may provide improvements in balance, functional performance, neuropathy, and QoL outcomes in CIPN. This study presents clinical relevance by demonstrating baseline values are imperative. Assessments such as balance, functional performance, and inflammatory

markers should be measured prior to and throughout treatment in persons receiving known neuropathic agents to establish better baseline values that would guide clinicians to provide comprehensive and effective treatment plans for persons with neuropathy and subsequently improve QoL and functional outcomes. A HVRT intervention is a feasible exercise prescription that can be applied to persons with CIPN. Lastly, lifestyle modifications are needed for inflammation prevention and maintenance to reduce incidence and progression of chronic diseases such as cancers. Acknowledgements: American Physical Therapy Association Michigan, International Organization for Health, Sports, and Kinesiology, David Kunnath - Any Lab, Rochester MI, St. Paul's Cancer Support Group.

CHAPTER FOUR

DISCUSSION

4.1 Summary

This dissertation contains a current literature review of resistance training (RT), or RT and aerobic exercise (AE) combination interventions for persons with chemotherapy induced polyneuropathy, also referred to as chemotherapy induced peripheral neuropathy (CIPN), and a case series comprised of a RT intervention for persons with CIPN. Currently there are no standard interventions to prevent or treat CIPN sequalae (Brown, 2019; Loprinzi, 2020). The literature review aimed to examine methods, and gaps in RT, or RT and AE combination studies, and furthermore, examine the effects of RT on inflammatory biomarker outcomes in cancer populations. The current literature highlights the feasibility of RT, or RT and AE combination training interventions in attenuating CIPN symptoms, increasing strength gains, aerobic capacity, balance, quality of life (QoL) outcomes, and modulating inflammatory biomarkers (Streckmann, 2014; McCrary, 2019; Dhawan, 2020; Kleckner, 2018; Chen, 2020; Zimmer 2018; Vollmers, 2018; Muller, 2021; Winters-Stone, 2018; Schulz, 2022; Ricci, 2018; Grote, 2016). Despite promising findings, overall studies lacked consistency among CIPN measures used, included heterogenous samples (e.g., patient baseline co-morbidities, neuropathy at the time of intervention, inflammatory levels, cancer diagnosis, treatment type, cumulative dose, and timing intervention), and prescribed a range of exercise prescriptions (e.g., frequency, duration, modality), making it challenging to draw firm

conclusions for clinical use (Streckmann, 2014; McCrary, 2019; Dhawan, 2020; Kleckner, 2018; Chen, 2020; Zimmer 2018; Vollmers, 2018; Muller, 2021).

To address the current gaps, a research project was designed and implemented to evaluate the therapeutic effects of a high velocity resistance training (HVRT) intervention in women presenting with CIPN. The project's findings demonstrate the potential feasibility of a HVRT intervention attenuating CIPN symptoms, and, moreover, suggest this intervention may provide clinically meaningful improvements in balance, functional performance, and QoL outcomes in the sample population.

Two out of three participants demonstrated improvements in balance as well as clinically meaningful improvements in functional performance results - Fullerton Advanced Balance (FAB) Scale, Timed Up and Go (TUG), and 6 Minute Walk Test (6MWT), whereas one participant had no change in both balance and functional performance results (FAB Scale, TUG, and 6MWT). The balance and functional performance improvements were consistent with previous research examining exercise interventions in CIPN samples (McCrary, 2019). McCrary et al. (2019) prescribed a resistance, aerobic, and balance training intervention with upper and lower extremity push/pull movements and balance exercises during an eight-week intervention in persons with a cancer diagnosis (breast, CRC, ovarian, endometrial, appendix, lymphoma, myeloma, urothelial diagnosis) at least three months post treatment from known neuropathic agents (McCrary 2019). McCrary et al. (2019) measured exercise intensity using Borg Rate of Perceived Exertion (RPE) on a scale 6-20. Participants were encouraged to exercise at 13-15 RPE. The discrepancies in the balance and functional performance results could be related to the design of the RT prescription specifically

targeting functional performance and not addressing static balance training, as well as lack of adherence to the exercise intervention (Aartolahti, 2015). The potential reason for improvement in balance and functional performance are perhaps related to the specificity of exercise prescription, neural adaptations, and progressions (Hughes, 2018; Walker, 2021; Duchateau, 2021). Neural adaptations, especially in anaerobic training modalities, depend on optimal neural recruitment for performance, and an increased neural drive is important for maximizing muscular power. Neural adaptions in anaerobic training include increased agonist muscle recruitment (increased involvement of major muscles during exercise), increased neural firing rates, improved neuron synchronization, and reduced inhibitory mechanisms (Hughes, 2018; Walker, 2021). Progressions provided modifications over time based on individual performance status (Fragala, 2019). It is worth noting, that in order to maintain muscle strength gains, an increase in external demands on the neural muscular system is required (Duchateau, 2021). HVRT with progressions appears to be a more relevant exercise prescription in individuals with CIPN for maintaining activities of daily living (ADLs) for this reason. All participants demonstrated improvements in neuropathy symptoms in their feet. Furthermore, participant 1 reported improvement in the right hand, and complete resolution of numbness in the left hand. This suggests that neuropathy improvements are perhaps related to participant baseline co-morbidities, neuropathy at baseline, lifestyle factors that influence inflammation (e.g., physical activity levels, chronic stress, diet intake, smoking, poor sleep, alcohol consumption), treatment type, cumulative dose, and time since treatment completion. The neuropathy results were consistent again with McCrary et al.'s (2019) RT, AE, and balance training for CIPN symptoms post treatment (McCrary,

2019). One participant demonstrated improvements in QoL results whereas two participants demonstrated a decrease in their QoL outcomes. Notably, the most compliant participant had both increased CIPN improvements as well as improvements in QoL results. Previous research supports exercise training in persons living beyond cancer to improve CIPN symptoms and enhance QoL (Saint, 2023; Campbell, 2019).

The CIPN symptom improvements are perhaps related to the therapeutic response to resistance exercise (Longobucco, 2022). Although there is a wide array of pathologies that contribute toward neuropathy development, it can be speculated that endothelial dysfunction may be a critical contributor (Maiuolo, 2019). Vascular endothelium is the first point of contact for chemotherapy administration, causing direct endothelial toxicity (Mclaughlin, 2021); moreover, evidence supports the relation between impaired endothelial cells and polyneuropathies. At the central nervous system, the blood brain barrier ensures extracellular brain fluids and plasma homeostasis, whereas, at the peripheral nervous system, this process is controlled by the blood nerve barrier (BNB). The BNB restricts exogenous substances and maintains homeostasis of the nervous tissues adjacent to the endothelium (Maiuolo, 2019). Research suggests that an accumulation of reactive oxygen species, endothelial cell apoptosis, and an increase in pro-inflammatory cytokines contribute toward biochemical and functional changes in the BNB, thus represent early stages of peripheral nerve damage (Maiuolo, 2019). The anti-inflammatory responses from RT have demonstrated to improve antioxidant capacity and activity, furthermore, protect against oxidative stress and induce suppression of inflammation, collectively which may contribute to neuropathy improvements (Longobucco, 2022). Though the inflammatory biomarker, CRP, increased in the post

measurement for two participants, the values remained within normal limits (< 8.0 mg/L) (*Quest Diagnostics,* n.d.). The reason for discrepancy in the CRP results are likely multifactorial. Inflammatory levels are dependent on cancer stage, (e.g., higher CRP levels (> 10 ug/ml) are associated with advanced stage), treatments received, cumulative dose, and time since treatment completion (Hart, 2020; Bower, 2022; Cioroiu, 2017). Risk factors associated with high inflammatory levels are other chronic diseases, physical activity level, lifestyle factors, such as sleep, nutrition, stress, and more, thus lifestyle modifications are imperative for prevention and management of inflammation.

Despite the promising findings, limitations within this study included first and foremost low participant accrual. Specific challenges associated with accrual included:

1. Complex inclusion criteria that initially included only breast cancer diagnoses which was later expanded to all cancer diagnoses who received neurotoxic chemotherapeutic agents.

2. Lack of interest in exercise, physician's and participant's general unfamiliarity with RT and it's benefits.

3. Lack of and delay in obtaining physician referral.

4. Overall participant time commitment and geographical barriers. Potential participants expressed interest, however, could not commit time and feasibly commute to research site. Despite the protocol supported by American College of Sports Medicine (ACSM) guidelines, the time commitment of the intervention may have been a barrier.

Further limitations include no control group, timeframe variability between assessments and intervention start and end, long term follow-up data was not collected, and practice effect, indicating participants familiarity with measures at post-test may

contribute to improved results. Strengths of this study included the use of a force plate, a gold standard measurement for static balance, reliable and valid measures dynamic balance, functional performance, and QoL measures, and implementation of a participant specific exercise prescription with progressions. Although these case series results are not generalizable, the data this study provides is encouraging evidence for a future HVRT intervention pilot study modulating CIPN symptoms. Further investigation is needed to determine the dose response requirements to attenuate CIPN symptoms. Additionally, future studies should include both men and women with multiple cancer diagnosis and consider multiple institution collaboration with multiple locations to optimize accrual potential, improve convenience and access, and study design should incorporate lifestyle interventions for inflammation prevention and maintenance.

CHAPTER FIVE

CONCLUSION

5.1 Future Directions

This study measured the therapeutic effects of a high velocity resistance training (HVRT) intervention in female cancer survivors with chemotherapy induced polyneuropathy, also referred to as chemotherapy induced peripheral neuropathy (CIPN) consequences to balance, functional performance, neuropathy, quality of life (QoL), and inflammatory biomarker c-reactive protein (CRP). The study's findings demonstrated the feasibility of a HVRT intervention attenuating CIPN symptoms, and moreover, suggest this intervention may provide clinically meaningful improvements in balance, functional performance, and QoL outcomes in the sample population. Further research is needed in other cancer diagnoses, neurotoxic treatment type, cumulative dose, and time since exposure; moreover, providing assessment and intervention at multiple sites/institutions is recommended to increase participant accrual potential due to perceived limitations with participant accrual for this project. Also, assessment of specific dose response requirements to attenuate persons with CIPN symptoms needs to be explored. Additionally, more research is needed to examine the therapeutic response of resistance training on inflammatory biomarkers concerning cancer-related adverse effects.

This study presents clinical relevance by demonstrating baseline values are imperative. Assessments such as balance, functional performance, and inflammatory markers should be measured prior to and throughout treatment in persons receiving known neuropathic agents to establish better baseline values that would guide clinicians

to provide comprehensive and effective treatment plans for persons with neuropathy and subsequently improve QoL and functional outcomes. A HVRT intervention is a feasible exercise prescription that can be applied to persons with CIPN. Lastly, lifestyle modifications are needed for inflammation prevention and maintenance to reduce incidence and progression of chronic diseases such as cancers. Acknowledgements: American Physical Therapy Association Michigan, International Organization for Health, Sports, and Kinesiology, David Kunnath - Any Lab, Rochester MI, St. Paul's Cancer Support Group.

APPENDICES

APPENDIX A

Table 6. Literature Review - Neuropathy 1 of 6

Author	Sample	Frequency	Intensity	Type	Measures	Results
Bland, 2019	Breast I-III IE: 1 wk. before first taxane cycle and ended 2-3 wk. after last cycle DE: started 2-3 wk. after last taxane cycle	3x/wk. multimodal and 2x/wk. home-based AE, 8-12 wk. total duration 40-60 sessions	RT-1 x 10 at 50% 1RM, progressing to 2 x 10-12 at 65% 1RM. BT-single leg stance on stable and unstable surfaces AE-50-75% HRR	RT, BT, AE,	EORTC QLQ CIPN 20 EORTC QLQ C30 Tuning fork, Pinprick	EORTC QLQ CIPN 20 - no difference between groups at any point in time in scores EORTC QLQ C30 - QoL increased in DE and maintained in IE. No significant different between groups at follow up Tuning fork, Pinprick - no significant difference at end of treatment between groups

Table 6. Literature Review - Neuropathy Continued 2 of 6

Author	Sample	Frequency	Intensity	Type	Measures	Results
Chen, 2020	CRC II-IV during treatment	3x/wk., 30-35 min., 3 months 12 wk. 36 sessions	RT-TheraBand :yellow	RT	CTCAE EORTC QLQ CIPN 20 EORTC QLQ C30 Tuning fork Motor-manual resistance 1RM 6MWT Tandem, unilateral stance	CTCAE, EORTC QLQ CIPN 20 - gradual CIPN increase over time. Autonomic - gradual decrease over time EORTC QLQ C30 - no change Tuning fork - no change Motor - manual resistance - no change 1RM - significant improvements 6MWT - significant improvements Tandem, unilateral stance - no change
Dhawan, 2020	Mixed diagnosis during treatment	30 min./daily 10 wk., 50 sessions	RT-UE, LE body weight exercises BT-balance exercises	RT, BT	CIPNAT Nerve conduction velocity Leeds Assessment neuropathic symptoms and signs EORTC QLQ C30	CIPNAT - no change Nerve conduction velocity - no change Leeds Assessment neuropathic symptoms and signs - no change EORTC QLQ C30 - significant reduction in functional, symptom, and global health sub scores

Table 6. Literature Review - Neuropathy Continued 3 of 6

Author	Sample	Frequency	Intensity	Type	Measures	Results
Hatlevoll, 2021	CRC II-IV during treatment	2x/wk., 60 min./ session, 12-14 wk. duration, 24-28 sessions	RT-UE, LE RT-1-3 sets x 8-12 reps, RPE 12-16, BT- exercises on various surfaces AE- treadmill walking	RT, BT, AE	EORTC QLQ C30 EORTC QLQ CIPN20 Physical Fatigue Mental Fatigue	EORTC QLQ C30, EORTC QLQ CIPN20 - CIPN increased Physical Fatigue - decreased 1 point Mental Fatigue - increased
Kleckner, 2018	Mixed diagnosis I-IV during treatment	Daily, 6 wk., 42 sessions	RT- TheraBand: red, green, blue, UE, LE (max 4 x 15), RPE 3-5 AE- walking 60-85% HRR, increasing steps 5-20% /wk.	RT, AE	Patient reported CIPN symptoms	Patient reported CIPN symptoms (scale 1-10) - decrease in symptoms of hot/cold in hands/feet (P=.045), and numbness/tingling in IG compared to CG.

Table 6. Literature Review - Neuropathy Continued 4 of 6

Author	Sample	Frequency	Intensity	Type	Measures	Results
McCrary, 2019	Mixed diagnosis post treatment	3x/wk., 60 min., 8 wk., 24 sessions	RT-2 sets of each exercise w/ TheraBand, machines, dumbbells. UE, LE RPE 13-15 BT-balance exercises AE-RPE 13-15	RT, BT, AE	TNSc EORTC CIPN20 CIPN-R-ODS 6MWT 5xSTS Static balance with Swaymeter CMAPs CSAPs nerve conduction	TNSc - significant improvements EORTC CIPN20 - significant improvements CIPN-R-ODS - significantly reduced 6MWT - significantly increased 5xST - improved Static balance with Swaymeter - significant improvements in eyes open, stable and unstable. No change in eyes closed, stable and unstable CMAPs, CSAPs, nerve conduction - no change
Muller, 2021	Mixed diagnosis I-IV during treatment	RT-3x/wk. ST- 3x/wk., 35 min.; 20 wk., ~40 session	RT- 2x/wk., 45 min.(Machines), 1x/wk., 15 min. (Home based exercise)70-80% 1RM	RT, ST	TNSr TNSc CMAP, SNAP EORTC CIPN 15 EORTC QLQ C30 COP	TNSr - significant increase in all groups TNSc - small change, no significant difference CMAP, SNAP - no change EORTC CIPN 15 - no significant difference between groups during intervention EORTC QLQ C30 - no significant difference COP - significant increase - all groups

Table 6. Literature Review - Neuropathy Continued 5 of 6

Author	Sample	Frequency	Intensity	Type	Measures	Results
Streckmann, 2014	Lymphoma I-IV during treatment	2x/wk. 1hr./ session 36 wk., 72 sessions		RT, BT, AE	EORTC QLQ C30 Tuning fork Static balance - force plate Dynamic balance	EORTC QLQ C30 - significant intergroup difference at 12wk. No difference at end of intervention Tuning fork- incidence lower in IG group, 87% symptoms diminished in IG, 0% CG Static balance - monopedal - IG reduced sway path % while CG declined, no significant difference b/w groups in static bipedal blind or baseline comparison. Dynamic - monopedal - IG reduced sway path % while CG declined perturbation - IG significantly reduced in bipedal, monopedal, CG increased sway

Table 6. Literature Review - Neuropathy Continued 6 of 6

Author	Sample	Frequency	Intensity	Type	Measures	Results
Vollmers, 2018	Breast during treatment	2x/wk. during treatment	RT- UE, LE, 20 reps, RPE 13-15	Physical Training, BT	Sway area FAB HGS Chair rising test EORTC QLQ CIPN 20 EORTC QLQ C30	Sway area - significant improvements in bipedal, significant smaller sway in monopedal FAB - significant differences in scores HGS - significant loss in HGS compared to CG - slight improvement Chair rising test - no significant changes EORTC QLQ CIPN 20, EORTC QLQ C30 - no significant changes
Zimmer, 2018	CRC IV during treatment	2x/wk., 60 min., 8 wk., 16 sessions	RT-UE, LE 2 x 8-12 reps, at 60-80% 1RM; Borg CR10 Scale level 6 AE RPE 12-13	RT, BT, AE	FACT GOG NTX GGT-Reha (balance) h1RM 6MWT	FACT GOG NTX - PWB, FWB, NTX significant differences over time, CIPN remained stable in IG GGT-Reha (balance) - no statistical significance in simple static or dynamic, statistical significance in advanced static h1RM - significant difference in muscle groups in baseline to T2 6MWT - no statistical significance

Resistance training and chemotherapy induced polyneuropathy literature review results by author, participant characteristics, frequency, intensity, type of intervention, measures, and results. Abbreviations: 1RM - One Repetition Maximum, 5xSTS – Five Times Sit to Stand, 6MWT - Six Minute Walk Test, AE - Aerobic Exercise, BT - Balance Training, CG - Control Group, CIPN-R-ODS - Rasch-Built Overall Disability, CIPNAT - Chemotherapy-Induced Peripheral Neuropathy Assessment Tool, CMAPS - Compound Motor Action Potentials, COP - Center of Pressure, CRC - Colorectal, CSAP - Sensory Action Potentials, CTCAE - Common Terminology Criteria for Adverse Events, DE - Delayed Exercise, EORTC QLQ CIPN 20 - European Organization of Research and Treatment of Cancer Quality of Life Questionnaire-CIPN, EORTC QLQ-C30 - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, FAB - Fullerton Advanced Balance Scale, FACT/GOG-Ntx - Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity, FWB - Functional Wellbeing, GGT-Reha - Gleichgewichtstest, h1rm - Hypothetic One Repetition Maximum, HGS - Handgrip Strength, HRR - Heart Rate Reserve, IE - Immediate Exercise, IG - Intervention Group, LE - Lower Extremity, PWB - Physical Wellbeing, PWB - Physical Wellbeing, RPE - Rate Of Perceived Exertion, RT - Resistance Training, ST - Sensorimotor Training, TNSc - Total Neuropathy Score Clinical, UE Upper - Extremity

APPENDICES

APPENDIX B

Table 7. Literature Review - Inflammation 1 of 2

Author	Sample	Intervention	Measure	Results
Cormie, 2016	BC I-IV during and post treatment	Low, medium, high load RT, UE exercises RM 55-85% Acute effects (24 hr.)	CRP, IL6, TNF	No significant changes in biomarkers in all three exercises
De Jesus Leite, 2021	BC 0-IIIa during treatment	RT 60-85% RM UE, LE exercises 3x/wk., 12 wk.	IL-4, IL-6, IL-10, IL17, IFN-γ, TNF-α	IL-6 had significant increase IL-17 decreased
De Paulo, 2018	BCS during aromatase therapy	RT + AE, CG 3x/wk., 36wk	CRP	No differences in CRP between groups
Grote, 2016	>1 diagnosis post treatment	RT + AE AE HR 40-80% HRR AE, circuit RT (UE, LE), core, flexibility, cool down 3x/wk., 13wk.	CRP	Positive relation among decrease in waist circumference a decrease in CRP
Hagstrom, 2016	BC I-IIIa post treatment	RT 80% RM UE, LE 3x/wk., 16 wk.	CRP, IL-6, IL-10, TNF-α	No changes in biomarkers
Hiensch, 2021	BC I-IIIa during treatment	RT HIIT, AE HIIT, UC AE HIIT-moderate to high intensity AE RT HIIT-RT + AE, RT 70-80% RM 2x/wk., 16wk.	IL-1a, IL-2,IL-5, IL-13, IL-21, IL-33, IL-35,	All groups had increase in pro-inflammatory cytokines IL-6 significantly less pronounced after RT HIIT compared to UC No difference between AT HIIT and UC

Table 7. Literature Review - Inflammation 2 of 2

Author	Sample	Intervention	Measure	Results
Ricci, 2018	>1 diagnosis post treatment	RT + AE AE-35-85% HRR RT-per ACSM 3x/wk., 26 wk.	CRP	CRP lower in TST group compared to 1-4 and 5+yr
Schulz, 2022	BC I-III during or post treatment	HIIT endurance and strength, CG HIIT endurance-50, 85-100%VO2 peak Strength-UE, LE 50% RM, up to 60-80% RM. RPE 12-14 2x/wk., 12 sessions	hsCRP,	hsCRP decreased in IG POST intervention, no significant differences at 12- or 24-month f/u compared to PRE CG hsCRP did not differ at any time points
Van Vulpen, 2018	BC during treatment	RT, RT + AE RT 2x/wk., 12 wk. RT+AE 2x/wk., 18 wk.	IL6, L-1ra and IL6/IL-1ra ratio	Significant increase in IL-6 in all groups
Winters-Stone, 2018	BC 0-IIIc post treatment	RT + AE, CG 3x/wk., 12 months 60-80% 1RM UE, LE	IL1B, IL6, TNFa, CRP	RT had decreases in CRP. No significant group difference between RT and CG for other biomarkers

Resistance training and inflammation literature review results by author, participant characteristics, intervention, measures, and results. Abbreviations: AE - Aerobic Exercise, BC - Breast Cancer, BCS - Breast Cancer Survivors, CG - Control Group, CRP - C-Reactive Protein, HIIT - High Intensity Interval Training, HR - Heart Rate, HRR - Heart Rate Reserve, HsCRP - High Sensitivity C-Reactive Protein, IL - Interleukin, LE - Lower Extremity, RM - Repetition Maximum, RT - Resistance Training, TNF-α -Tumor Necrosis Factor Alpha, TST - Time Since Treatment, UC - Usual Care, UE - Upper Extremity

APPENDICES

APPENDIX C

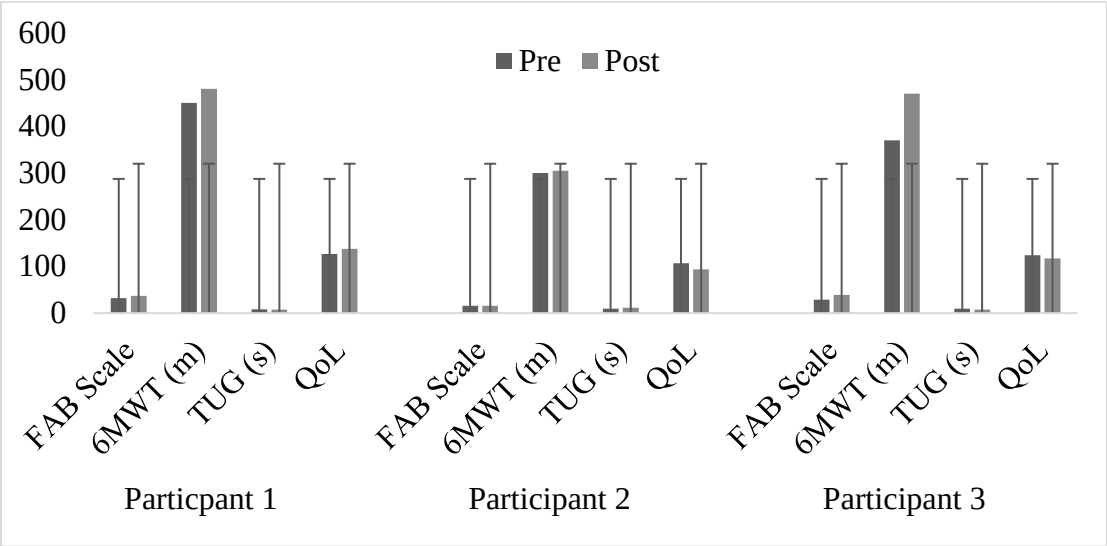

Figure 1. Participant Results - Static and Dynamic Balance, Quality of Life

Abbreviations: FAB Scale - Fullerton Advanced Balance (FAB) Scale, 6MWT - Six Minute Walk Test, TUG - Timed Up and Go, QoL - Quality of Life

APPENDICES

APPENDIX D

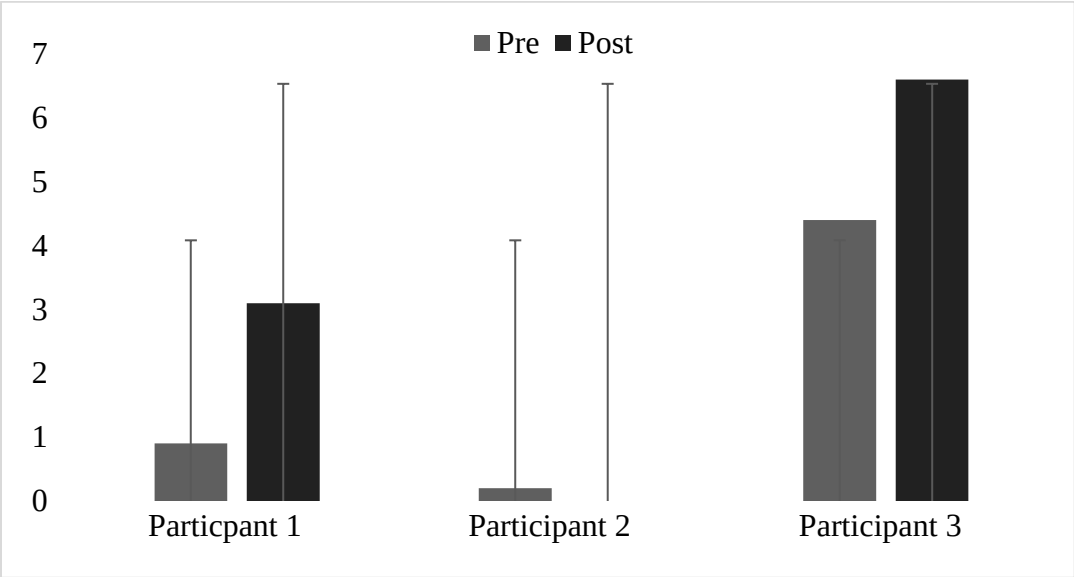

Figure 2. Participant Results - C Reactive Protein (mg/L)

APPENDICES

APPENDIX E

Exercise Images

Figure 3. Bench Press

Figure 4. Overhead Press

Figure 5. Bent Row

Figure 6. Latissimus Pull Down

Figure 7. Back Squat

Figure 8. Lunge

Figure 9. Abdominal Plank

Figure 10. Ball Slams

Figure 10. Continued Ball Slams

REFERENCES

Aartolahti, E., Tolppanen, A. M., Lönnroos, E., Hartikainen, S., & Häkkinen, A. (2015). Health condition and physical function as predictors of adherence in long-term strength and balance training among community-dwelling older adults. *Archives of gerontology and geriatrics*, *61*(3), 452–457. https://doi.org/10.1016/j.archger.2015.06.016

American College of Sports Medicine, Riebe, D., Ehrman, J. K., Liguori, G., & Magal, M. (Eds.). (2018). *ACSM's guidelines for exercise testing and prescription* (Tenth edition). Wolters Kluwer.

Anjanappa, M., Corden, M., Green, A., Roberts, D., Hoskin, P., McWilliam, A., & Choudhury, A. (2020). Sarcopenia in cancer: Risking more than muscle loss. *Technical innovations & patient support in radiation oncology*, *16*, 50–57. https://doi.org/10.1016/j.tipsro.2020.10.001

Balachandran, A. T., Steele, J., Angielczyk, D., Belio, M., Schoenfeld, B. J., Quiles, N., Askin, N., & Abou-Setta, A. M. (2022). Comparison of Power Training vs Traditional Strength Training on Physical Function in Older Adults: A Systematic Review and Meta-analysis. *JAMA network open*, *5*(5), e2211623. https://doi.org/10.1001/jamanetworkopen.2022.11623

Banach, M., Juranek, J. K., & Zygulska, A. L. (2017). Chemotherapy-induced neuropathies—A growing problem for patients and health care providers. *Brain and Behavior*, *7*(1), e00558. https://doi.org/10.1002/brb3.558

Barbalho, S. M., Flato, U. A. P., Tofano, R. J., Goulart, R. A., Guiguer, E. L., Detregiachi, C. R. P., Buchaim, D. V., Araújo, A. C., Buchaim, R. L., Reina, F. T. R., Biteli, P., Reina, D. O. B. R., & Bechara, M. D. (2020). Physical Exercise and Myokines: Relationships with Sarcopenia and Cardiovascular Complications. *International journal of molecular sciences*, *21*(10), 3607. https://doi.org/10.3390/ijms21103607

Beijers, A. J. M., Mols, F., & Vreugdenhil, G. (2014). A systematic review on chronic oxaliplatin-induced peripheral neuropathy and the relation with oxaliplatin administration. *Supportive Care in Cancer*, *22*(7), 1999–2007. https://doi.org/10.1007/s00520-014-2242-z

Bland, K. A., Kirkham, A. A., Bovard, J., Shenkier, T., Zucker, D., McKenzie, D. C., Davis, M. K., Gelmon, K. A., & Campbell, K. L. (2019). Effect of Exercise on Taxane Chemotherapy–Induced Peripheral Neuropathy in Women with Breast Cancer: A Randomized Controlled Trial. *Clinical Breast Cancer*, *19*(6), 411–422. https://doi.org/10.1016/j.clbc.2019.05.013

Bonikowske, A. R., Taylor, J. L., Larson, K. F., Hardwick, J., Ozemek, C., Harber, M. P., Kaminsky, L. A., Arena, R., & Lavie, C. J. (2024). Evaluating current assessment techniques of cardiorespiratory fitness. *Expert Review of Cardiovascular Therapy*, 1–11. https://doi.org/10.1080/14779072.2024.2363393

Bower, J. E., Ganz, P. A., Irwin, M. R., Cole, S. W., Carroll, J., Kuhlman, K. R., Petersen, L., Garet, D., Asher, A., Hurvitz, S. A., & Crespi, C. M. (2022). Acute and Chronic Effects of Adjuvant Therapy on Inflammatory Markers in Breast Cancer Patients. *JNCI cancer spectrum*, *6*(4), pkac052. https://doi.org/10.1093/jncics/pkac052

Brown, T. J., Sedhom, R., & Gupta, A. (2019). Chemotherapy-Induced Peripheral Neuropathy. *JAMA Oncology*, *5*(5), 750. https://doi.org/10.1001/jamaoncol.2018.6771

Burgess, J., Ferdousi, M., Gosal, D., Boon, C., Matsumoto, K., Marshall, A., Mak, T., Marshall, A., Frank, B., Malik, R. A., & Alam, U. (2021). Chemotherapy-Induced Peripheral Neuropathy: Epidemiology, Pathomechanisms and Treatment. *Oncology and Therapy*, *9*(2), 385–450. https://doi.org/10.1007/s40487-021-00168-y

Campbell, K. L., Winters-Stone, K. M., Wiskemann, J., May, A. M., Schwartz, A. L., Courneya, K. S., Zucker, D. S., Matthews, C. E., Ligibel, J. A., Gerber, L. H., Morris, G. S., Patel, A. V., Hue, T. F., Perna, F. M., & Schmitz, K. H. (2019). Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Medicine & Science in Sports & Exercise*, *51*(11), 2375–2390. https://doi.org/10.1249/MSS.0000000000002116

Champ, C. E., Carpenter, D. J., Diaz, A. K., Rosenberg, J., Ackerson, B. G., & Hyde, P. N. (2023). Resistance Training for Patients with Cancer: A Conceptual Framework for Maximizing Strength, Power, Functional Mobility, and Body Composition to Optimize Health and Outcomes. *Sports medicine (Auckland, N.Z.)*, *53*(1), 75–89. https://doi.org/10.1007/s40279-022-01759-z

Chen, S.-C., Huang, H.-P., Huang, W.-S., Lin, Y.-C., Chu, T.-P., Beaton, R. D., & Jane, S.-W. (2020). Non-randomized preliminary study of an education and elastic-band resistance exercise program on severity of neuropathy, physical function, muscle strength and endurance & quality of life in colorectal cancer patients experiencing oxaliplatin-induced peripheral neuropathy. *European Journal of Oncology Nursing*, *49*, 101834. https://doi.org/10.1016/j.ejon.2020.101834

Cheng, H. L., Lopez, V., Lam, S. C., Leung, A. K. T., Li, Y. C., Wong, K. H., Au, J. S. K., Sundar, R., Chan, A., De Ng, T. R., Suen, L. K. P., Chan, C. W., Yorke, J., & Molassiotis, A. (2020). Psychometric testing of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group—Neurotoxicity (FACT/GOG-Ntx) subscale in a longitudinal study of cancer patients treated with

chemotherapy. *Health and Quality of Life Outcomes*, *18*(1), 246. https://doi.org/10.1186/s12955-020-01493-y

Cioroiu, C., & Weimer, L. H. (2017). Update on Chemotherapy-Induced Peripheral Neuropathy. *Current Neurology and Neuroscience Reports*, *17*(6), 47. https://doi.org/10.1007/s11910-017-0757-7

Clark, R. A., Mentiplay, B. F., Pua, Y.-H., & Bower, K. J. (2018). Reliability and validity of the Wii Balance Board for assessment of standing balance: A systematic review. *Gait & Posture*, *61*, 40–54. https://doi.org/10.1016/j.gaitpost.2017.12.022

Cocks, K., Wells, J. R., Johnson, C., Schmidt, H., Koller, M., Oerlemans, S., Velikova, G., Pinto, M., Tomaszewski, K. A., Aaronson, N. K., Exall, E., Finbow, C., Fitzsimmons, D., Grant, L., Groenvold, M., Tolley, C., Wheelwright, S., & Bottomley, A. (2023). Content validity of the EORTC quality of life questionnaire QLQ-C30 for use in cancer. *European Journal of Cancer*, *178*, 128–138. https://doi.org/10.1016/j.ejca.2022.10.026

Colvin L. A. (2019). Chemotherapy-induced peripheral neuropathy: where are we now?. *Pain*, *160 Suppl 1*(Suppl 1), S1–S10. https://doi.org/10.1097/j.pain.0000000000001540

Cormie, P., Singh, B., Hayes, S., Peake, J. M., Galvão, D. A., Taaffe, D. R., Spry, N., Nosaka, K., Cornish, B., Schmitz, K. H., & Newton, R. U. (2016). Acute Inflammatory Response to Low-, Moderate-, and High-Load Resistance Exercise in Women with Breast Cancer–Related Lymphedema. *Integrative Cancer Therapies*, *15*(3), 308–317. https://doi.org/10.1177/1534735415617283

Costello, J. T., Bieuzen, F., & Bleakley, C. M. (2014). Where are all the female participants in Sports and Exercise Medicine research?. *European journal of sport science*, *14*(8), 847–851. https://doi.org/10.1080/17461391.2014.911354

Craig, A. B., Strauss, M. B., Daniller, A., & Miller, S. S. (2014). Foot sensation testing in the patient with diabetes: introduction of the quick & easy assessment tool. *Wounds : a compendium of clinical research and practice*, *26*(8), 221–231.

Daneman, R., & Prat, A. (2015). The blood-brain barrier. *Cold Spring Harbor perspectives in biology*, *7*(1), a020412. https://doi.org/10.1101/cshperspect.a020412

Dasari, S., & Bernard Tchounwou, P. (2014). Cisplatin in cancer therapy: Molecular mechanisms of action. *European Journal of Pharmacology*, *740*, 364–378. https://doi.org/10.1016/j.ejphar.2014.07.025

De Jesus Leite, M. A. F., Mariano, I. M., Dechichi, J. G. C., Giolo, J. S., Gonçalves, Á. D. C., & Puga, G. M. (2021). Exercise training and detraining effects on body

composition, muscle strength and lipid, inflammatory and oxidative markers in breast cancer survivors under tamoxifen treatment. *Life Sciences*, *284*, 119924. https://doi.org/10.1016/j.lfs.2021.119924

De Paulo, T. R. S., Winters-Stone, K. M., Viezel, J., Rossi, F. E., Simões, R. R., Tosello, G., & Freitas, I. F. (2018). Effects of resistance plus aerobic training on body composition and metabolic markers in older breast cancer survivors undergoing aromatase inhibitor therapy. *Experimental Gerontology*, *111*, 210–217. https://doi.org/10.1016/j.exger.2018.07.022

Desforges, A. D., Hebert, C. M., Spence, A. L., Reid, B., Dhaibar, H. A., Cruz-Topete, D., Cornett, E. M., Kaye, A. D., Urits, I., & Viswanath, O. (2022). Treatment and diagnosis of chemotherapy-induced peripheral neuropathy: An update. *Biomedicine & Pharmacotherapy*, *147*, 112671. https://doi.org/10.1016/j.biopha.2022.112671

Dhawan, S., Andrews, R., Kumar, L., Wadhwa, S., & Shukla, G. (2020). A Randomized Controlled Trial to Assess the Effectiveness of Muscle Strengthening and Balancing Exercises on Chemotherapy-Induced Peripheral Neuropathic Pain and Quality of Life Among Cancer Patients. *Cancer Nursing*, *43*(4), 269–280. https://doi.org/10.1097/NCC.0000000000000693

Duchateau, J., Stragier, S., Baudry, S., & Carpentier, A. (2021). Strength Training: In Search of Optimal Strategies to Maximize Neuromuscular Performance. *Exercise and Sport Sciences Reviews*, *49*(1), 2–14. https://doi.org/10.1249/JES.0000000000000234

Eckhoff, L., Knoop, As., Jensen, Mb., & Ewertz, M. (2015). Persistence of docetaxel-induced neuropathy and impact on quality of life among breast cancer survivors. *European Journal of Cancer*, *51*(3), 292–300. https://doi.org/10.1016/j.ejca.2014.11.024

Edwards, E. S., & Sackett, S. C. (2016). Psychosocial Variables Related to Why Women are Less Active than Men and Related Health Implications. *Clinical medicine insights. Women's health*, *9*(Suppl 1), 47–56. https://doi.org/10.4137/CMWH.S34668

El Hadouchi, M., Kiers, H., De Vries, R., Veenhof, C., & Van Dieën, J. (2022). Effectiveness of power training compared to strength training in older adults: A systematic review and meta-analysis. *European Review of Aging and Physical Activity*, *19*(1), 18. https://doi.org/10.1186/s11556-022-00297-x

Fino, P. C., Horak, F. B., El-Gohary, M., Guidarelli, C., Medysky, M. E., Nagle, S. J., & Winters-Stone, K. M. (2019). Postural sway, falls, and self-reported neuropathy in aging female cancer survivors. *Gait & posture*, *69*, 136–142. https://doi.org/10.1016/j.gaitpost.2019.01.025

Fisher, M., Lee, J., Davies, C., Geyer, H., Colon, G., & Pfalzer, P. (2015). *Oncology Section EDGE Task Force on Breast Cancer Outcomes: A Systematic Review of Outcome Measures for Functional Mobility*.

Fragala, M. S., Cadore, E. L., Dorgo, S., Izquierdo, M., Kraemer, W. J., Peterson, M. D., & Ryan, E. D. (2019). Resistance Training for Older Adults: Position Statement from the National Strength and Conditioning Association. *Journal of Strength and Conditioning Research*, *33*(8), 2019–2052. https://doi.org/10.1519/JSC.0000000000003230

Furman, D., Campisi, J., Verdin, E., Carrera-Bastos, P., Targ, S., Franceschi, C., Ferrucci, L., Gilroy, D. W., Fasano, A., Miller, G. W., Miller, A. H., Mantovani, A., Weyand, C. M., Barzilai, N., Goronzy, J. J., Rando, T. A., Effros, R. B., Lucia, A., Kleinstreuer, N., & Slavich, G. M. (2019). Chronic inflammation in the etiology of disease across the life span. *Nature medicine*, *25*(12), 1822–1832. https://doi.org/10.1038/s41591-019-0675-0

Gingrich, A., Volkert, D., Kiesswetter, E., Thomanek, M., Bach, S., Sieber, C. C., & Zopf, Y. (2019). Prevalence and overlap of sarcopenia, frailty, cachexia and malnutrition in older medical inpatients. *BMC geriatrics*, *19*(1), 120. https://doi.org/10.1186/s12877-019-1115-1

Goble, D. J., Brar, H., Brown, E. C., Marks, C. R., & Baweja, H. S. (2019). Normative data for the Balance Tracking System modified Clinical Test of Sensory Integration and Balance protocol. *Medical devices (Auckland, N.Z.)*, *12*, 183–191. https://doi.org/10.2147/MDER.S206530

Gonzalo-Encabo, P., Maldonado, G., Valadés, D., Ferragut, C., & Pérez-López, A. (2021). The Role of Exercise Training on Low-Grade Systemic Inflammation in Adults with Overweight and Obesity: A Systematic Review. *International Journal of Environmental Research and Public Health*, *18*(24), 13258. https://doi.org/10.3390/ijerph182413258

Gottlieb, U., Hoffman, J. R., & Springer, S. (2023). Dynamic postural control in individuals with and without chronic ankle instability-do the modified star-excursion balance test and jump-landing stabilization have the same control mechanism?. *Physical therapy in sport : official journal of the Association of Chartered Physiotherapists in Sports Medicine*, *60*, 104–111. https://doi.org/10.1016/j.ptsp.2023.01.011

Grgic, J., Lazinica, B., Schoenfeld, B. J., & Pedisic, Z. (2020). Test–Retest Reliability of the One-Repetition Maximum (1RM) Strength Assessment: A Systematic Review. *Sports Medicine - Open*, *6*(1), 31. https://doi.org/10.1186/s40798-020-00260-z

Grisold, W., & Carozzi, V. (2021). Toxicity in Peripheral Nerves: An Overview. *Toxics*, *9*(9), 218. https://doi.org/10.3390/toxics9090218

Grote, S., Almstedt, H., & Tarleton, H. (2016). Cardiometabolic Health Among Cancer Survivors: A 13-Week Pilot Study of a Combined Aerobic and Resistance Training Program. *Oncology Nursing Forum*, *43*(3), 306–315. https://doi.org/10.1188/16.ONF.306-315

Hagstrom, A. D., Marshall, P. W. M., Lonsdale, C., Papalia, S., Cheema, B. S., Toben, C., Baune, B. T., Fiatarone Singh, M. A., & Green, S. (2016). The effect of resistance training on markers of immune function and inflammation in previously sedentary women recovering from breast cancer: A randomized controlled trial. *Breast Cancer Research and Treatment*, *155*(3), 471–482. https://doi.org/10.1007/s10549-016-3688-0

Hart, P. C., Rajab, I. M., Alebraheem, M., & Potempa, L. A. (2020). C-Reactive Protein and Cancer-Diagnostic and Therapeutic Insights. *Frontiers in immunology*, *11*, 595835. https://doi.org/10.3389/fimmu.2020.595835

Hatlevoll, I., Oldervoll, L. M., Wibe, A., Stene, G. B., Stafne, S. N., & Hofsli, E. (2021). Physical exercise during adjuvant chemotherapy for colorectal cancer—A non-randomized feasibility study. *Supportive Care in Cancer*, *29*(6), 2993–3008. https://doi.org/10.1007/s00520-020-05789-z

Hicks, C. W., Wang, D., Schneider, A. L. C., Johansen, M. C., Gottesman, R. F., Matsushita, K., Coresh, J., Windham, B. G., & Selvin, E. (2022). Associations of Peripheral Neuropathy Defined by Monofilament Insensitivity with Mild Cognitive Impairment and Dementia in Older Adults. *Dementia and geriatric cognitive disorders*, *51*(2), 150–158. https://doi.org/10.1159/000523762

Hiensch, A. E., Mijwel, S., Bargiela, D., Wengström, Y., May, A. M., & Rundqvist, H. (2021). Inflammation Mediates Exercise Effects on Fatigue in Patients with Breast Cancer. *Medicine & Science in Sports & Exercise*, *53*(3), 496–504. https://doi.org/10.1249/MSS.0000000000002490

Hile, E., Levangie, P., Ryans, K., & Gilchrist, L. (2015). Oncology section task force on breast cancer outcomes: clinical measures of chemotherapy-induced peripheral neuropathy—a systematic review. *Rehabilitation Oncology*, *33*(3), 32-41.

Huang, M. H., Hile, E., Croarkin, E., Wampler-Kuhn, M., Blackwood, J., Colon, G., & Pfalzer, L. A. (2019). Academy of Oncologic Physical Therapy EDGE Task Force: A Systematic Review of Measures of Balance in Adult Cancer Survivors. *Rehabilitation Oncology*, *37*(3), 92–103. https://doi.org/10.1097/01.REO.0000000000000177

Hughes, D. C., Ellefsen, S., & Baar, K. (2018). Adaptations to Endurance and Strength Training. *Cold Spring Harbor Perspectives in Medicine*, *8*(6), a029769. https://doi.org/10.1101/cshperspect.a029769

Hussain, T., Tan, B., Yin, Y., Blachier, F., Tossou, M. C., & Rahu, N. (2016). Oxidative Stress and Inflammation: What Polyphenols Can Do for Us?. *Oxidative medicine and cellular longevity*, *2016*, 7432797. https://doi.org/10.1155/2016/7432797

Imboden, M. T., Harber, M. P., Whaley, M. H., Finch, W. H., Bishop, D. L., & Kaminsky, L. A. (2018). Cardiorespiratory Fitness and Mortality in Healthy Men and Women. *Journal of the American College of Cardiology*, *72*(19), 2283–2292. https://doi.org/10.1016/j.jacc.2018.08.2166

Jordan, B., Margulies, A., Cardoso, F., Cavaletti, G., Haugnes, H. S., Jahn, P., Le Rhun, E., Preusser, M., Scotté, F., Taphoorn, M. J. B., & Jordan, K. (2020). Systemic anticancer therapy-induced peripheral and central neurotoxicity: ESMO–EONS–EANO Clinical Practice Guidelines for diagnosis, prevention, treatment and follow-up. *Annals of Oncology*, *31*(10), 1306–1319. https://doi.org/10.1016/j.annonc.2020.07.003

Kanzawa-Lee, G. A., Larson, J. L., Resnicow, K., & Smith, E. M. L. (2020). Exercise Effects on Chemotherapy-Induced Peripheral Neuropathy: A Comprehensive Integrative Review. *Cancer nursing*, *43*(3), E172–E185. https://doi.org/10.1097/NCC.0000000000000801

Kelmenson, D. A., Quan, D., & Moss, M. (2018). What is the diagnostic accuracy of single nerve conduction studies and muscle ultrasound to identify critical illness polyneuromyopathy: a prospective cohort study. *Critical care (London, England)*, *22*(1), 342. https://doi.org/10.1186/s13054-018-2281-9

Khosravi, N., Stoner, L., Farajivafa, V., & Hanson, E. D. (2019). Exercise training, circulating cytokine levels and immune function in cancer survivors: A meta-analysis. *Brain, behavior, and immunity*, *81*, 92–104. https://doi.org/10.1016/j.bbi.2019.08.187

Kleckner, I. R., Kamen, C., Gewandter, J. S., Mohile, N. A., Heckler, C. E., Culakova, E., Fung, C., Janelsins, M. C., Asare, M., Lin, P.-J., Reddy, P. S., Giguere, J., Berenberg, J., Kesler, S. R., & Mustian, K. M. (2018). Effects of exercise during chemotherapy on chemotherapy-induced peripheral neuropathy: A multicenter, randomized controlled trial. *Supportive Care in Cancer*, *26*(4), 1019–1028. https://doi.org/10.1007/s00520-017-4013-0

Lanting, S. M., Spink, M. J., Tehan, P. E., Vickers, S., Casey, S. L., & Chuter, V. H. (2020). Non-invasive assessment of vibration perception and protective sensation in people with diabetes mellitus: inter- and intra-rater reliability. *Journal of foot and ankle research*, *13*, 3. https://doi.org/10.1186/s13047-020-0371-9

Longobucco, Y., Masini, A., Marini, S., Barone, G., Fimognari, C., Bragonzoni, L., Dallolio, L., & Maffei, F. (2022). Exercise and Oxidative Stress Biomarkers among Adult with Cancer: A Systematic Review. *Oxidative medicine and cellular longevity*, *2022*, 2097318. https://doi.org/10.1155/2022/2097318

Lopes, T. R., Pereira, H. M., & Silva, B. M. (2022). Perceived Exertion: Revisiting the History and Updating the Neurophysiology and the Practical Applications. *International Journal of Environmental Research and Public Health*, *19*(21), 14439. https://doi.org/10.3390/ijerph192114439

Loprinzi, C. L., Lacchetti, C., Bleeker, J., Cavaletti, G., Chauhan, C., Hertz, D. L., Kelley, M. R., Lavino, A., Lustberg, M. B., Paice, J. A., Schneider, B. P., Lavoie Smith, E. M., Smith, M. L., Smith, T. J., Wagner-Johnston, N., & Hershman, D. L. (2020). Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update. *Journal of Clinical Oncology*, *38*(28), 3325–3348. https://doi.org/10.1200/JCO.20.01399

Maiuolo, J., Gliozzi, M., Musolino, V., Carresi, C., Nucera, S., Macrì, R., Scicchitano, M., Bosco, F., Scarano, F., Ruga, S., Zito, M. C., Oppedisano, F., Mollace, R., Paone, S., Palma, E., Muscoli, C., & Mollace, V. (2019). The Role of Endothelial Dysfunction in Peripheral Blood Nerve Barrier: Molecular Mechanisms and Pathophysiological Implications. *International Journal of Molecular Sciences*, *20*(12), 3022. https://doi.org/10.3390/ijms20123022

McCrary, J. M., Goldstein, D., Boyle, F., Cox, K., Grimison, P., Kiernan, M. C., Krishnan, A. V., Lewis, C. R., Webber, K., Baron-Hay, S., Horvath, L., & Park, S. B. (2017). Optimal clinical assessment strategies for chemotherapy-induced peripheral neuropathy (CIPN): A systematic review and Delphi survey. *Supportive Care in Cancer*, *25*(11), 3485–3493. https://doi.org/10.1007/s00520-017-3772-y

McCrary, J. M., Goldstein, D., Sandler, C. X., Barry, B. K., Marthick, M., Timmins, H. C., Li, T., Horvath, L., Grimison, P., & Park, S. B. (2019). Exercise-based rehabilitation for cancer survivors with chemotherapy-induced peripheral neuropathy. *Supportive Care in Cancer*, *27*(10), 3849–3857. https://doi.org/10.1007/s00520-019-04680-w

McIllhatton, A., Lanting, S., Lambkin, D., Leigh, L., Casey, S., & Chuter, V. (2021). Reliability of recommended non-invasive chairside screening tests for diabetes-related peripheral neuropathy: a systematic review with meta-analyses. *BMJ open diabetes research & care*, *9*(2), e002528. https://doi.org/10.1136/bmjdrc-2021-002528

McKinnon, N. B., Connelly, D. M., Rice, C. L., Hunter, S. W., & Doherty, T. J. (2017). Neuromuscular contributions to the age-related reduction in muscle power:

Mechanisms and potential role of high velocity power training. *Ageing research reviews*, *35*, 147–154. https://doi.org/10.1016/j.arr.2016.09.003

Mclaughlin, M., Florida-James, G., & Ross, M. (2021). Breast cancer chemotherapy vascular toxicity: A review of mediating mechanisms and exercise as a potential therapeutic. *Vascular Biology*, *3*(1), R106–R120. https://doi.org/10.1530/VB-21-0013

Mendoza, T. R., Zhao, F., Cleeland, C. S., Wagner, L. I., Patrick-Miller, L. J., & Fisch, M. J. (2013). The validity and utility of the M. D. Anderson Symptom Inventory in patients with breast cancer: evidence from the symptom outcomes and practice patterns data from the eastern cooperative oncology group. *Clinical breast cancer*, *13*(5), 325–334. https://doi.org/10.1016/j.clbc.2013.02.014

Miale, S., Harrington, S., & Kendig, T. (2013). Oncology Section Task Force on Breast Cancer Outcomes: Clinical Measures of Upper Extremity Function: *Rehabilitation Oncology*, *31*(1), 27–34. https://doi.org/10.1097/01893697-201331010-00006

Miljkovic, N., Lim, J. Y., Miljkovic, I., & Frontera, W. R. (2015). Aging of skeletal muscle fibers. *Annals of rehabilitation medicine*, *39*(2), 155–162. https://doi.org/10.5535/arm.2015.39.2.155

Muller, J., Weiler, M., Schneeweiss, A., Haag, G. M., Steindorf, K., Wick, W., & Wiskemann, J. (2021). Preventive effect of sensorimotor exercise and resistance training on chemotherapy-induced peripheral neuropathy: A randomised-controlled trial. *British Journal of Cancer*, *125*(7), 955–965. https://doi.org/10.1038/s41416-021-01471-1

Muñoz-Bermejo, L., Adsuar, J. C., Mendoza-Muñoz, M., Barrios-Fernández, S., Garcia-Gordillo, M. A., Pérez-Gómez, J., & Carlos-Vivas, J. (2021). Test-Retest Reliability of Five Times Sit to Stand Test (FTSST) in Adults: A Systematic Review and Meta-Analysis. *Biology*, *10*(6), 510. https://doi.org/10.3390/biology10060510

National Cancer Institute: NCI GUIDELINES FOR INVESTIGATORS: ADVERSE EVENT REPORTING REQUIREMENTS FOR DCTD (CTEP AND CIP) INDs AND IDEs. (n.d.). https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/aeguidelines.pdf

Nolte, S., Van Londen, M., Elting, J. W. J., De Greef, B. T. A., Kuks, J. B. M., Faber, C. G., Nolte, I. M., Groen, R. J. M., Bakker, S. J. L., Groothof, D., Lesman-Leegte, I., Berger, S. P., & Drost, G. (2020). Vibration threshold in non-diabetic subjects. *PLOS ONE*, *15*(10), e0237733. https://doi.org/10.1371/journal.pone.0237733

Norton, M., Alkurashi, A. K., Hasan Albitar, H. A., Almodallal, Y., & Iyer, V. N. (2020). A rare case of chemotherapy induced phrenic neuropathy. *Respiratory medicine case reports*, *30*, 101117. https://doi.org/10.1016/j.rmcr.2020.101117

Paoli, A., Gentil, P., Moro, T., Marcolin, G., & Bianco, A. (2017). Resistance Training with Single vs. Multi-joint Exercises at Equal Total Load Volume: Effects on Body Composition, Cardiorespiratory Fitness, and Muscle Strength. *Frontiers in physiology*, *8*, 1105. https://doi.org/10.3389/fphys.2017.01105

Park, S. B., Alberti, P., Kolb, N. A., Gewandter, J. S., Schenone, A., & Argyriou, A. A. (2019). Overview and critical revision of clinical assessment tools in chemotherapy-induced peripheral neurotoxicity. *Journal of the Peripheral Nervous System*, *24*(S2). https://doi.org/10.1111/jns.12333

Poole, D. C., & Jones, A. M. (2017). Measurement of the maximum oxygen uptake $\dot{V}o_{2max}$: $\dot{V}o_{2peak}$ is no longer acceptable. *Journal of applied physiology (Bethesda, Md. : 1985)*, *122*(4), 997–1002. https://doi.org/10.1152/japplphysiol.01063.2016

Quest Diagnostics.
(n.d.). https://jdos.nicholsinstitute.com/dos/Medfusion/test/999535/?k=CRP

Ricci, J. M., Flores, V., Kuroyama, I., Asher, A., & Tarleton, H. P. (2018). Pilot Study of Dose–Response Effects of Exercise on Change in C-Reactive Protein, Cortisol, and Health-Related Quality of Life Among Cancer Survivors. *BioResearch Open Access*, *7*(1), 52–62. https://doi.org/10.1089/biores.2018.0003

Richardson, C., Borgeson, J., & Van Harrison, R. (2021). How to Use a Monofilament to Test for Foot Neuropathy. In *Management of Type 2 Diabetes Mellitus*.

Rosado, E., Amanakis, E., Sperl, D., & Sorantin, E. (2014). Unilateral phrenic nerve neuropathy as an early sign of recurrent mediastinal Hodgkin's disease. *EURORAD: Radiological Case Database*.

Rose, D. J., Lucchese, N., & Wiersma, L. D. (2006). Development of a Multidimensional Balance Scale for Use with Functionally Independent Older Adults. *Archives of Physical Medicine and Rehabilitation*, *87*(11), 1478–1485. https://doi.org/10.1016/j.apmr.2006.07.263

Sałat, K. (2020). Chemotherapy-induced peripheral neuropathy: Part 1—current state of knowledge and perspectives for pharmacotherapy. *Pharmacological Reports*, *72*(3), 486–507. https://doi.org/10.1007/s43440-020-00109-y

Scheffer, D. D. L., & Latini, A. (2020). Exercise-induced immune system response: Anti-inflammatory status on peripheral and central organs. *Biochimica et biophysica acta. Molecular basis of disease*, *1866*(10), 165823. https://doi.org/10.1016/j.bbadis.2020.165823

Schmid, D., & Leitzmann, M. F. (2015). Cardiorespiratory fitness as predictor of cancer mortality: A systematic review and meta-analysis. *Annals of Oncology*, *26*(2), 272–278. https://doi.org/10.1093/annonc/mdu250

Schulz, S. V. W., Schumann, U., Otto, S., Kirsten, J., Treff, G., Janni, W., Huober, J., Leinert, E., Steinacker, J. M., & Bizjak, D. A. (2022). Two-year follow-up after a six-week high-intensity training intervention study with breast cancer patients: Physiological, psychological and immunological differences. *Disability and Rehabilitation*, *44*(17), 4813–4820. https://doi.org/10.1080/09638288.2021.1921861

SEER Training Modules, The Peripheral Nervous System. (n.d.). U. S. National Institutes of Health, National Cancer Institute. https://training.seer.cancer.gov/anatomy/nervous/organization/pns.html

Seretny, M., Currie, G. L., Sena, E. S., Ramnarine, S., Grant, R., MacLeod, M. R., Colvin, L. A., & Fallon, M. (2014). Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Pain*, *155*(12), 2461–2470. https://doi.org/10.1016/j.pain.2014.09.020

Severinsen, M. C. K., & Pedersen, B. K. (2020). Muscle–Organ Crosstalk: The Emerging Roles of Myokines. *Endocrine Reviews*, *41*(4), 594–609. https://doi.org/10.1210/endrev/bnaa016

Shibata, Y., Himeno, T., Kamiya, T., Tani, H., Nakayama, T., Kojima, C., Sugiura-Roth, Y., Naito, E., Kondo, M., Tsunekawa, S., Kato, Y., Nakamura, J., & Kamiya, H. (2019). Validity and reliability of a point-of-care nerve conduction device in diabetes patients. *Journal of Diabetes Investigation*, *10*(5), 1291–1298. https://doi.org/10.1111/jdi.13007

Siegel, R. L., Giaquinto, A. N., & Jemal, A. (2024). Cancer statistics, 2024. *CA: A Cancer Journal for Clinicians*, *74*(1), 12–49. https://doi.org/10.3322/caac.21820

Staff, N. P., Cavaletti, G., Islam, B., Lustberg, M., Psimaras, D., & Tamburin, S. (2019). Platinum-induced peripheral neurotoxicity: From pathogenesis to treatment. *Journal of the Peripheral Nervous System*, *24*(S2). https://doi.org/10.1111/jns.12335

Starobova, H., & Vetter, I. (2017). Pathophysiology of Chemotherapy-Induced Peripheral Neuropathy. *Frontiers in Molecular Neuroscience*, *10*, 174. https://doi.org/10.3389/fnmol.2017.00174

Streckmann, F., Kneis, S., Leifert, J. A., Baumann, F. T., Kleber, M., Ihorst, G., Herich, L., Grüssinger, V., Gollhofer, A., & Bertz, H. (2014). Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing

therapy. *Annals of Oncology*, *25*(2), 493–499. https://doi.org/10.1093/annonc/mdt568

Sturnieks, D. L., Arnold, R., & Lord, S. R. (2011). Validity and reliability of the Swaymeter device for measuring postural sway. *BMC geriatrics*, *11*, 63. https://doi.org/10.1186/1471-2318-11-63

Thau, L., Reddy, V., & Singh, P. (2022). *Anatomy, Central Nervous System*.

Truong, J., Yan, A. T., Cramarossa, G., & Chan, K. K. W. (2014). Chemotherapy-Induced Cardiotoxicity: Detection, Prevention, and Management. *Canadian Journal of Cardiology*, *30*(8), 869–878. https://doi.org/10.1016/j.cjca.2014.04.029

van de Graaf, D. L., Engelen, V., de Boer, A., Vreugdenhil, G., Smeets, T., van der Lee, M. L., Trompetter, H. R., & Mols, F. (2023). Experiences of cancer survivors with chemotherapy-induced peripheral neuropathy in the Netherlands: symptoms, daily limitations, involvement of healthcare professionals, and social support. *Journal of cancer survivorship : research and practice*, 10.1007/s11764-023-01402-4. Advance online publication. https://doi.org/10.1007/s11764-023-01402-4

Van Vulpen, J. K., Schmidt, M. E., Velthuis, M. J., Wiskemann, J., Schneeweiss, A., Vermeulen, R. C. H., Habermann, N., Ulrich, C. M., Peeters, P. H. M., Van Der Wall, E., May, A. M., & Steindorf, K. (2018). Effects of physical exercise on markers of inflammation in breast cancer patients during adjuvant chemotherapy. *Breast Cancer Research and Treatment*, *168*(2), 421–431. https://doi.org/10.1007/s10549-017-4608-7

Vollmers, P. L., Mundhenke, C., Maass, N., Bauerschlag, D., Kratzenstein, S., Röcken, C., & Schmidt, T. (2018). Evaluation of the effects of sensorimotor exercise on physical and psychological parameters in breast cancer patients undergoing neurotoxic chemotherapy. *Journal of Cancer Research and Clinical Oncology*, *144*(9), 1785–1792. https://doi.org/10.1007/s00432-018-2686-5

Walker S. (2021). Evidence of resistance training-induced neural adaptation in older adults. *Experimental gerontology*, *151*, 111408. https://doi.org/10.1016/j.exger.2021.111408

Walsh, M. E., Sloane, L. B., Fischer, K. E., Austad, S. N., Richardson, A., & Van Remmen, H. (2015). Use of Nerve Conduction Velocity to Assess Peripheral Nerve Health in Aging Mice. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *70*(11), 1312–1319. https://doi.org/10.1093/gerona/glu208

Wampler, M., Miaskowski, C., Hamel, K., Byl, N., Rugo, H., & Topp, K. (2006). *The Modified Total Neuropathy Score: A Clinically Feasible and Valid Measure of*

Taxane-Induced Peripheral Neuropathy in Women with Breast Cancer. https://www.researchgate.net/profile/Kimberly-Topp-2/publication/242577865_The_Modified_Total_Neuropathy_Score_A_Clinically_Feasible_and_Valid_Measure_of_Taxane-Induced_Peripheral_Neuropathy_in_Women_With_Breast_Cancer/links/53dfe6300cf27a7b8307a578/The-Modified-Total-Neuropathy-Score-A-Clinically-Feasible-and-Valid-Measure-of-Taxane-Induced-Peripheral-Neuropathy-in-Women-With-Breast-Cancer.pdf

Winters-Stone, K. M., Horak, F., Jacobs, P. G., Trubowitz, P., Dieckmann, N. F., Stoyles, S., & Faithfull, S. (2017). Falls, Functioning, and Disability Among Women with Persistent Symptoms of Chemotherapy-Induced Peripheral Neuropathy. *Journal of Clinical Oncology*, *35*(23), 2604–2612. https://doi.org/10.1200/JCO.2016.71.3552

Winters-Stone, K. M., Wood, L. J., Stoyles, S., & Dieckmann, N. F. (2018). The Effects of Resistance Exercise on Biomarkers of Breast Cancer Prognosis: A Pooled Analysis of Three Randomized Trials. *Cancer Epidemiology, Biomarkers & Prevention*, *27*(2), 146–153. https://doi.org/10.1158/1055-9965.EPI-17-0766

Zajączkowska, R., Kocot-Kępska, M., Leppert, W., Wrzosek, A., Mika, J., & Wordliczek, J. (2019). Mechanisms of Chemotherapy-Induced Peripheral Neuropathy. *International Journal of Molecular Sciences*, *20*(6), 1451. https://doi.org/10.3390/ijms20061451

Zimmer, P., Trebing, S., Timmers-Trebing, U., Schenk, A., Paust, R., Bloch, W., Rudolph, R., Streckmann, F., & Baumann, F. T. (2018). Eight-week, multimodal exercise counteracts a progress of chemotherapy-induced peripheral neuropathy and improves balance and strength in metastasized colorectal cancer patients: A randomized controlled trial. *Supportive Care in Cancer*, *26*(2), 615–624. https://doi.org/10.1007/s00520-017-3875-5