Exercise to Reduce Chemotherapy-Induced Peripheral Neuropathy: A Pilot RCT

by

Grace A. Kanzawa-Lee

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Nursing)
in the University of Michigan
2020

Doctoral Committee:

Professor Ellen Lavoie Smith, Chair
Professor Janet L. Larson
Research Professor Robert J. Ploutz-Snyder
Professor Kenneth Resnicow

Grace A. Kanzawa-Lee

ORCID iD: 0000-0003-1522-638X

DEDICATION

This dissertation is dedicated to my mentor, husband, family, and the people who gave their time to participate in this study.

ACKNOWLEDGMENTS

This dissertation was written by Grace A. Kanzawa-Lee, with extensive contributions by Dr. Ellen Smith and the committee, research assistants Athena Lievense and Lauren Kavanagh, and clinical support by Dr. John Krauss and Heidi Deininger.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

FIGURE

LIST OF ABBREVIATIONS

$\bar{X}_{\Delta}$	Difference in Means between Groups
CI	Confidence Interval
CIPN	Chemotherapy-Induced Peripheral Neuropathy
CIPN20	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy Scale
COI	Conflict of Interest
CVI	Content Validity Index
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
FOLFIRINOX	Folinic Acid (leucovorin), Irinotecan, and Oxaliplatin
FOLFOX	Folinic Acid (leucovorin), Fluorouracil (5FU), and Oxaliplatin
GI	Gastrointestinal
ICC	Intra-class Correlation Coefficient
ITT	Intention to Treat Analysis
MET	Motivational Enhancement Therapy
MICE	Multivariate Imputation by Chained Equations
mTNS©	Modified Total Neuropathy Score
MVPA	Moderate to Vigorous Physical Activity
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NRS	Numeric Rating Scale
OIPN	Oxaliplatin-Induced Peripheral Neuropathy
PA	Physical Activity
PAD	Peripheral Arterial Disease
PF	Physical Function
PN	Peripheral Neuropathy
PRO	Patient-Reported Outcome (measure)

RPE	Rating of Perceived Exertion
QLQ	Quality of Life Questionnaire
QOL	Quality of Life
RCT	Randomized Controlled Trial
SCT	Social Cognitive Theory
SD	Standard Deviation
SDT	Self-Determination Theory
SMART	Specific, Measurable, Action-Oriented, Realistic, and Time-Based
TNS©	Total Neuropathy Score
TOUS	Theory of Unpleasant Symptoms

ABSTRACT

Background: Oxaliplatin-induced peripheral neuropathy (OIPN) occurs in 85-95% of patients receiving FOLFOX or FOLFIRINOX, oxaliplatin-based chemotherapy for invasive gastrointestinal (GI) cancers. Persistent OIPN can impair long-term quality of life (QOL). No OIPN cures are known. Aerobic physical activity (PA) may reduce OIPN by enhancing circulation and re-distributing neurotoxic oxaliplatin away from vulnerable neurons. However, no trials have evaluated solely aerobic exercise for OIPN. This dissertation reports the results of a 1) literature review on exercise for chemotherapy-induced peripheral neuropathy, and 2) pilot randomized controlled trial (RCT) of brisk walking for OIPN in FOLFOX/FOLFIRINOX-receiving GI cancer survivors. The "MI-Walk Intervention"—an eight-week motivational enhancement therapy (MET)- home-based aerobic walking intervention—was tested in this study.

Purpose: The RCT aims were to explore the 1) effect of the MI-Walk Intervention on eight-week OIPN severity and QOL compared to PA education alone, and 2) intervention feasibility among patients receiving FOLFOX/FOLFIRINOX. The primary hypothesis was that the intervention participants would report less severe OIPN and higher QOL at eight weeks than participants who received PA education alone.

Methods: Recruitment of 60 GI cancer patients from two cancer clinics occurred at the second FOLFOX/FOLFIRINOX visit. All participants received PA education and regular phone assessments of intervention-related adverse events (the control condition). Half (n=30) received

the MI-Walk Intervention, which included theory-based motivational supports (e.g., a Fitbit Charge 2, three MET sessions, and goals worksheets). Ongoing peer support was encouraged via peer email, phone, and walking groups. Self-report surveys of OIPN (primary outcome) and QOL were administered pre-and post-intervention. Feasibility, including intervention acceptability survey scores, were also explored. Intergroup differences at eight weeks were explored using multiple imputation for intention-to-treat linear regression analyses. Linear mixed model regression was used to evaluate intergroup differences in PA. Randomization was stratified by clinic and diabetes diagnosis.

Results: The enrollment and completion rates were 62% ($N = 57$) and 87%, respectively. The intervention compared to the control condition had no effect on sensory OIPN (mean difference [$\bar{X}_{\Delta}$] = -0.01; $p > .99$), motor OIPN ($\bar{X}_{\Delta} = 2.39$; $p = .17$) and QOL ($\bar{X}_{\Delta} = -1.43$; $p > .99$). Eight-week sensory ($\bar{X} = 11.48 \pm 0.38$) and motor OIPN severities ($\bar{X} = 7.48 \pm 0.36$) both increased from baseline ($p \leq .01$) but were mild. The intervention group's Fitbit-measured weekly minutes of aerobic PA increased from baseline to eight weeks ($\bar{X}_{\Delta} = 17.39$; $p = .03$). However, self-reported PA increases over time were slightly higher on average in the control than the intervention group ($\bar{X}_{\Delta} = -24.02$; $p = .30$). Satisfaction with the intervention was high ($\bar{X} = 4.32 \pm 0.9$), but overall acceptability scores were low ($\bar{X} = 47.91 \pm 11.45$); the Fitbit and MET were rated most helpful in encouraging walking; the email and walking groups were unhelpful. No adverse events were noted.

Conclusions: This study failed to detect significant beneficial effects of aerobic walking on OPIN, however small sample size and notable PA increases in the control group suggest that further research is necessary in order to replicate or refute our null findings among GI cancer survivors receiving FOLFOX/FOLFIRINOX. Although OIPN severities increased (indicating

aerobic exercise may not completely prevent OIPN), they were mild at eight weeks. Some intervention components were “unhelpful.” Studies are needed to identify the most helpful intervention components to tailor interventions for individuals receiving FOLFOX/FOLFIRINOX.

CHAPTER I

Introduction

Over 1.7 million individuals will be diagnosed with cancer in 2019 in the United States (American Cancer Society 2019a). Colorectal cancer is the second most commonly diagnosed cancer worldwide (World Health Organization and International Agency for Research on Cancer 2012) and third most common in the United States (American Cancer Society 2019a). Over half of the new cases of gastrointestinal (GI) cancer are distant or metastasized (stage II-IV) (National Cancer Institute 2016), necessitating more aggressive therapy including neurotoxic chemotherapy (American Cancer Society 2019b). Various neurotoxic chemotherapy drugs, including taxanes (paclitaxel and docetaxel), platinums (cisplatin, oxaliplatin, and carboplatin), vinca alkaloids (vincristine and vinblastine), proteasome inhibitors (bortezomib), and thalidomide, have known antitumor benefits. However, these drugs may cause life-altering chemotherapy-induced peripheral neuropathy (CIPN). This dissertation focuses specifically on CIPN that is caused by oxaliplatin, a mainstay chemotherapy treatment for many GI cancers.

Statement of the Problem

About 85%-95% of patients who receive FOLFOX or FOLFIRINOX—standard chemotherapy regimens for stage II-III GI cancers—develop a type of CIPN called oxaliplatin-induced peripheral neuropathy (OIPN). The FOLFOX and FOLFIRINOX regimens contain oxaliplatin (85 mg/m^2) administered every other week for 16-24 weeks, resulting in a cumulative

dose of 680-1,020 mg/m^2 (André, Boni, and Navarro 2009; Choi et al. 2019; Drott et al. 2016; Meyers et al. 2017).

The hallmark symptoms of OIPN common among all types of CIPN include numbness, tingling, and neuropathic (e.g., burning, freezing, and shock-like) pain. These symptoms are generally preceded by unique acute OIPN symptoms, including muscle cramps, and cold sensitivity in the face, throat, hands, and feet (Carozzi, Canta, and Chiorazzi 2015; Jaggi and Singh 2012; S. B. Park et al. 2013). The severity of OIPN increases with increasing cumulative oxaliplatin dosages (Pachman et al. 2015, 2016); and acute OIPN predicts long-term OIPN severity and associated-deficits (Argyriou et al. 2013; Beijers et al. 2015; Loprinzi et al. 2014; Pachman et al. 2015, 2016; Ventzel et al. 2015; Ventzel, Madsen, et al. 2016).

Eventually, FOLFOX and FOLFIRINOX may cause irreversible neuronal damage and permanent OIPN sensory and motor deficits (Ahmed Hussein Zedan et al. 2014). Up to 11 years after chemotherapy completion, 20-75% of patients still report OIPN symptoms, and impaired balance, physical function (Mols et al. 2013; S. B. Park et al. 2013; Ventzel et al. 2015), and quality of life (QOL) (Kidwell et al. 2012; Mols et al. 2013; Soveri et al. 2019; Speck et al. 2012; Tofthagen 2010b, 2010a; Tofthagen et al. 2013; Tofthagen, McAllister, and McMillan 2011). Individuals with OIPN commonly report difficulty with daily tasks, such as buttoning shirts or climbing stairs (Bakitas 2007; Monfort et al. 2016; Speck et al. 2012; Tofthagen 2010b, 2010a). These deficits may lead to a sense of a loss of purpose and ability to engage in usual work and leisure activities, leading to social isolation and frustration (Boehmke and Dickerson 2005; Exposito Vizcaino et al. 2018; Tofthagen, McAllister, and McMillan 2011; Zanville et al. 2016).

There are no known effective curative treatments or preventive agents for OIPN (Hershman et al. 2014); thus, OIPN is the primary dose-limiting factor of oxaliplatin-based

regimens (Beijers et al. 2015; Ventzel et al. 2015). Current practices to address OIPN include altering the chemotherapy regimen and using drugs often used to treat other neuropathic pain conditions (e.g., tricyclic antidepressants, gabapentin, amitriptyline, baclofen, and ketamine) (Argyriou et al. 2013; Guido Cavaletti 2014; Majithia et al. 2016). However, over 80 trials have tested these drugs and other therapies and found that only duloxetine (Smith et al., 2013) is effective for treating existing OIPN (Hershman et al. 2014; Lee et al. 2019; Majithia et al. 2016).

Exercise may be an effective intervention for OIPN (Henke et al. 2014; McCrary et al. 2019; Streckmann, Kneis, et al. 2014; Wonders 2014; Zimmer et al. 2018). Specifically, aerobic exercise practiced at least 10 minutes per day, two to five days per week, at moderate-intensity (Borg Rating of Exertion of 12 to 14), for at least six to eight weeks may be a consistently effective intervention for OIPN (Henke et al. 2014; Kleckner et al. 2018; Streckmann, Kneis, et al. 2014; Wonders 2014; Zimmer et al. 2018). Mechanistically, aerobic exercise may target OIPN's main proposed pathophysiologic mechanism: oxidative stress-induced neuronal apoptosis (Carozzi, Marmiroli, and Cavaletti 2010; Imai et al. 2017). Aerobic exercise may reduce oxaliplatin-induced oxidative stress by increasing circulation and sweeping oxaliplatin away from vulnerable neurons such as the dorsal root ganglia where it is known to accumulate (Ashor et al. 2015; Azizbeigi et al. 2015; Di Cesare Mannelli et al. 2012; Chang et al. 2015; Gomez-Cabrera et al. 2015; Karimi and Roshan 2013; Jong-Hwan Park et al. 2013; Schaun et al. 2011; Tofthagen, Visovsky, and Hopgood 2013; Zhou et al. 2016).

However, no trials have been designed specifically to evaluate the effects of aerobic exercise on OIPN (Brayall et al. 2018; Duregon et al. 2018; Jung, Rein, and Fuchs 2018). All the trials tested multimodal exercise interventions, and only one trial focused on OIPN independent of other types of CIPN (Zimmer et al. 2018). Fundamentally, many trials have lacked control for

key confounding factors such as type, dosage, and prior receipt of neurotoxic chemotherapy, and CIPN-influencing comorbidities.

Purpose

The purpose of this prospective, randomized, controlled, pilot experiment was to evaluate the effect of an aerobic walking intervention for OIPN in GI cancer patients receiving FOLFOX or FOLFIRINOX. The primary objective was to evaluate the effect of the "MI-Walk Intervention"—an eight-week motivational enhancement therapy- and home-based aerobic walking intervention—on OIPN severity at eight weeks, compared to physical activity (PA) education alone. Intervention feasibility (including fidelity and acceptability) and secondary outcomes were also evaluated, including the effects on eight-week QOL and physical and emotional function.

Theoretical Framework

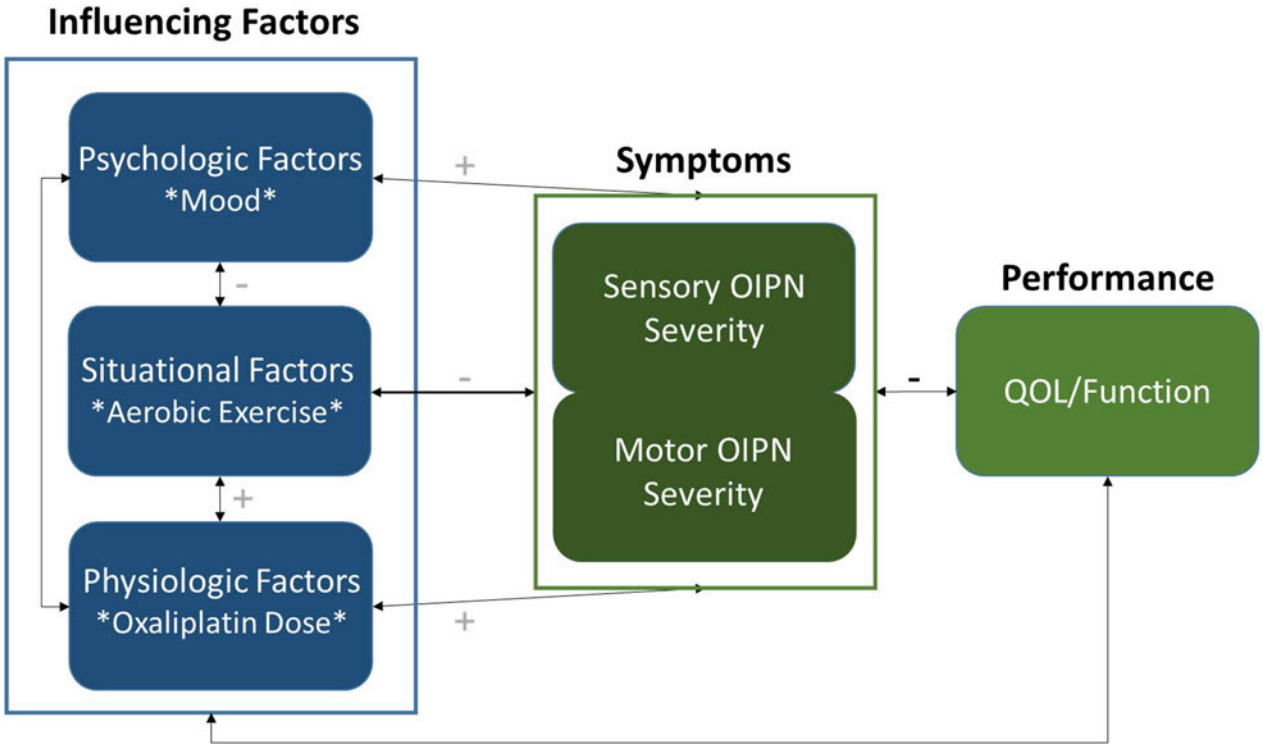
The Theory of Unpleasant Symptoms (TOUS) provided the overall framework for the study (Lenz et al. 1997). The Social Cognitive Theory (SCT) (Bandura, 1986, 2004; Rogers et al., 2004, 2005; Stacey, James, Chapman, Courneya, & Lubans, 2015) and Self-Determination Theory (SDT) (Deci & Ryan, 1985; Ryan, 1991, 1995) were merged and provided the framework for the aerobic exercise ("MI-Walk") intervention.

The Theory of Unpleasant Symptoms

Figure I.1—the study theoretical model—depicts the relationships among the key study variables—aerobic exercise (independent), OIPN severity (primary dependent), total oxaliplatin dose (covariate), mood (covariate), and QOL/function (secondary dependent). These variables were deduced from the TOUS constructs: influencing factors, symptoms, and performance (Lenz et al. 1997). The eligibility criteria were also informed by the TOUS.

Figure I.1

Theoretical Model of Exercise to Reduce Oxaliplatin-Induced Peripheral Neuropathy



Note. The theoretical model was deduced from the Theory of Unpleasant Symptoms (Lenz et al. 1997).
Abbreviations. OIPN, oxaliplatin-induced peripheral neuropathy; QOL, quality of life.

Symptoms. The main symptom of focus in the theoretical model and dissertation is OIPN; however, other cancer treatment-related symptoms may cluster and interact with OIPN: fatigue, pain, sleep disturbance, anxiety, and depression (Berger 2010; Binkley et al. 2012; El-Shami et al. 2015; Fernandez et al. 2015; Kamath 2012; Knoerl, Chornoby, and Smith 2018, 2019; Mols et al. 2013; Pachman et al. 2012; Skerman, Yates, and Battistutta 2012). Evidence suggests these symptoms may share pathophysiologic pathways such as inflammation (Beijers et al. 2015; Berger 2010; Binkley et al. 2012; El-Shami et al. 2015; Hong, Tian, and Wu 2014; H.-J. Kim et al. 2012; Pachman et al. 2012; Skerman, Yates, and

Battistutta 2012). These symptoms were evaluated indirectly using a cancer-related QOL survey and may be explored in future secondary cluster analyses.

Performance. Performance in patients with OIPN refers to the physical and subsequently emotional function and QOL outcomes of the symptom experience (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). Specifically, OIPN may impair QOL by affecting various functional domains, including physical (Bakitas, 2007; Monfort et al., 2016; Speck et al., 2012; Tofthagen, 2010a, 2010b) and emotional function (Boehmke & Dickerson, 2005; Exposito Vizcaino, Casanova-Molla, Escoda, Galan, & Miro, 2016; Tofthagen, McMillan, & Kip, 2011; Zanville et al., 2016). Performance feeds back to the influencing factors. For example, OIPN-induced QOL and functional impairments lead to oxaliplatin dose reductions in about 70% of patients (Andre et al. 2004; Huang et al. 2015; Ventzel, Madsen, et al. 2016). Various functional domains of and global QOL are key performance outcomes of this study.

Influencing factors. Situational, physiological, and psychological influencing factors interact and influence OIPN. Situational factors encompass culture and lifestyle behaviors (social environmental factors), and climate and geographical location (physical environmental factors) that influence symptom perception and expression. Lifestyle behaviors including aerobic exercise are conceptualized as social situational factors in the TOUS and in the study's theoretical model. Aerobic exercise may moderate OIPN through its physiological and psychological effects (e.g., improving blood circulation and mood). Environmental factors such as cold weather may exacerbate OIPN (Tofthagen, McAllister, and McMillan 2011). Thus, aerobic exercise was a key situational OIPN influencing factor evaluated in this study; the winter and summer seasonal temperature variation during the study emphasized the importance of the controlled trial design.

Physiological influencing factors of OIPN include type, dosage, and prior receipt of neurotoxic chemotherapy, age, body mass index, concomitant neuropathic pain drugs and supplements, smoking status, and pre-existing peripheral neuropathy (measured in the study); comorbidities such as diabetes, HIV, peripheral vascular disease, vitamin B deficiency, and alcohol dependence (exclusion criteria in the study); and genes (Beijers et al. 2015; E. I. Chen et al. 2015; M.-Y. Chen et al. 2011; Hershman et al. 2016; Kleckner et al. 2018; S. B. Park et al. 2013; Petrovchich et al. 2019; Seretny et al. 2014; Terrazzino et al. 2015; Ahmed H Zedan and Vilholm 2014). Further, OIPN may be influenced indirectly by factors associated with aerobic exercise. Obesity may be associated with lower levels of moderate to vigorous physical activity (MVPA) (van Putten et al. 2016) and lower adherence to vigorous aerobic exercise interventions (Courneya, Segal, et al. 2014). Additionally, impaired mobility, comorbidity, and cancer treatment-related symptoms such as fatigue, insomnia, and depression have commonly been cited as barriers to MVPA (Courneya et al., 2005; Fernandez et al., 2015; Hawkes et al., 2013; Henriksson, Arving, Johansson, Igelstrom, & Nordin, 2016; Kamath, 2012; Mikkelsen, Nielsen, Vinther, Lund, & Jarden, 2019). Mixed evidence suggests that older age may predict lower levels of PA (van Putten et al. 2016) or higher adherence (Courneya, Segal, et al. 2014) and response to exercise interventions for OIPN (Kleckner et al. 2016). Due to the pilot nature of our study, genetic factors were not evaluated but oxaliplatin dose was surveyed as a covariate in the study.

Finally, psychological factors—more specifically, mood, and SCT/SDT constructs—may directly and indirectly influence OIPN. The direct potential neurobiological link among anxiety, depression, and OIPN, is described above in the symptoms section. Additionally, mood may indirectly affect OIPN via associations with aerobic exercise (Ekkekakis, Parfitt,

& Petruzzello, 2011; Hawkes et al., 2013; Henriksson, Arving, Johansson, Igelstrom, & Nordin, 2016; Kwan & Bryan, 2010; Mas, Quantin, & Ninot, 2015; Morielli et al., 2016; Shang, Wenzel, Krumm, Griffith, & Stewart, 2012; Williams et al., 2008). For example, anxiety and depressive mood disorders are common after cancer diagnosis and predict less immediate PA behavior (Liao et al. 2016; Liao, Shonkoff, and Dunton 2015; Mata et al. 2012; Shang et al. 2012). Mood was measured in the study using the emotional functioning subscale of the European Organisation for Research and Treatment of Cancer QLQ 30-Item Questionnaire. This subscale has been shown to predict response to chronic CIPN treatment (Smith et al., 2015). Despite the inconsistent terminology, the emotional functioning subscale items refer to mood (a chronic, event-independent, affective state), not emotion (an acute, high-intensity, real-time emotional experiences induced by a specific event) and affect (a non-cognitively processed neurophysiological feeling) (Ekkekakis, 2013). Self-efficacy—a SCT construct—to manage OIPN (e.g., beliefs in pain control) may negatively moderate OIPN severity (Knoerl et al. 2018). The remaining psychological factors derived from the SCT and SDT that informed the MI-Walk Intervention are described below.

The Social Cognitive and Self-Determination Theories

Several key constructs of the SCT and SDT (e.g., self-efficacy, autonomous motivation, and perceived social support) form the basis of the MI-Walk Intervention. The propositions and their application to the study are described below.

The Social Cognitive Theory (Bandura, 1986, 2004)**.** Knowledge; self-efficacy (perceived ability to perform a task and overcome barriers to performing the task); goals; physical, psychological, and material outcome expectations; and perceived physical, social, and situational facilitators and impediments determine one's engagement in aerobic exercise.

Self-efficacy is a key construct proposed to influence behavior directly and indirectly through the other constructs. Personal task-specific skills and prior accomplishments (mastery) may be the greatest contributing factor toward self-efficacy. Additionally, self-efficacy may be drawn from inspiration from observing influential role models' task-specific successes (vicarious experience), affirmation and encouragement from a trusted source (verbal persuasion), and less interpretation of physiological and affective barriers as indicators of incapability (physiological and affective states) (Bandura 1977; B. J. Zimmerman 2000).

The Self-Determination Theory (Deci and Ryan 1985; Ryan 1995; Ryan and Deci 2000). The SDT suggests that three basic psychological needs drive motivation: competency (akin to self-efficacy), autonomy (perceived internal volitional control over one's behavior and outcomes), and relatedness (social belongingness). These needs are akin to the four sources of self-efficacy: mastery (task-specific competence), vicarious influences (relatedness), verbal persuasion (competence and relatedness), and physiological and affective states (competence and autonomy). Motivation may be either intrinsic (derived from inherent pleasure in a behavior or the challenge and novelty of the behavior) or extrinsic (controlled motivation resulting from external or self-evaluative pressures or integrated regulation-derived: identification and integration of aerobic exercise's importance with personal beliefs and value). Further, autonomous motivation—intrinsic and integrated-regulated extrinsic motivation—is proposed to be a key mediator of behavior change.

***Integration of the behavioral theories for exercise in cancer survivors*.** Self-efficacy as outlined in the SCT, and autonomous motivation, a key variable in the SDT, may act synergistically and/or through distinct mechanisms to influence one's effort, persistence, emotional health (Ekkekakis, Lind, and Vazou 2010; B. J. Zimmerman 2000), and aerobic

exercise performance (E. I. Chen et al. 2015; Hartman et al. 2013; Hershman et al. 2016; Van Hoecke et al. 2013; Janssen et al. 2014; Knittle et al. 2015; Ryan and Deci 2000; Seretny et al. 2014; Slovinec D'Angelo et al. 2014; Teixeira et al. 2015). Self-efficacy and mastery-bolstering self-regulation techniques may be particularly important in establishing short term exercise behaviors among chronic illness populations (Anderson-Bill, Winett, and Wojcik 2011; Ashford, Edmunds, and French 2010; Ayotte, Margrett, and Hicks-Patrick 2010; Bandura 2004; Hawkes et al. 2013; Knittle et al. 2015; Phillips and McAuley 2013; Slovinec D'Angelo et al. 2014; Swenson, Nissen, and Henly 2010; S. M. White, Wojcicki, and McAuley 2012). Further, cancer survivors who have previously reported fears of exercise injury, lack of confidence in physical abilities, and perceived limitations from ageing may particularly benefit from self-efficacy support (Henriksson et al. 2016; Mas, Quantin, and Ninot 2015).

Autonomous motivation may moderate the influences of cancer survivor-reported barriers—loss of meaning, lack of motivation, coddling from friends and family, and fatigue—on ultimate exercise engagement (Courneya et al. 2005; Henriksson et al. 2016; Mas, Quantin, and Ninot 2015; Morielli, Usmani, Boule, Severin, et al. 2016). Some evidence suggests autonomous motivation predicts exercise behavior more strongly than self-efficacy (Littlecott et al. 2014) and may be the critical mediator between self-efficacy and long term exercise (Rothman et al. 2004; Sweet et al. 2009; H. E. Tulloch, Reid, and Fortier 2007).

Finally, social networks—linked to vicarious experience (SCT), and relatedness (SDT)—may be another key exercise-promoting factor (Anderson-Bill, Winett, and Wojcik 2011; Van Hoecke et al. 2013; Janssen et al. 2014; Rogers et al. 2005). Low- to no-cost group walking/exercise in malls and other indoor facilities may also improve exercise adherence, given

the evidence that suggests cold weather and exercise facility accessibility influence lower adherence to aerobic exercise interventions (Chou et al. 2017; Courneya, Segal, et al. 2014).

Application of the behavioral theories to the MI-Walk Intervention. The MI-Walk Intervention employed motivational interviewing to bolster autonomous motivation, relatedness, and self-efficacy/competence through verbal persuasion (i.e., affirmation) (Hawkes et al. 2013; Spencer and Wheeler 2016; Swenson, Nissen, and Henly 2010). Additional autonomous motivation-facilitating techniques were also used: if-then implementation statements and SMART (specific, measurable, action-oriented, realistic, and time-based) goals (Apodaca and Longabaugh 2009; Miller and Rose 2009; Resnicow and McMaster 2012; Webber, Tate, and Quintiliani 2008; Ziegelmann et al. 2007). Further, Fitbits, exercise logs, and progress summaries were used to promote sense of mastery/competence (Cadmus et al. 2009; Hawkes et al. 2013; Mock et al. 2005; Swenson, Nissen, and Henly 2010). The progress summaries targeted vicarious experience by providing individuals' PA levels in comparison to their peers and facilitate self-efficacy (Ashford, Edmunds, and French 2010). Additionally, survivor exercise testimonies targeted vicarious experience/competence and an email group and weekly walking events targeted relatedness (Mas, Quantin, and Ninot 2015; Mock et al. 2005; Rogers et al. 2005). Finally, cancer treatment and exercise education were provided to support the last source of self-efficacy: adaptive perceived physiological and affective states (Hawkes et al. 2013; Mock et al. 2005; Spencer and Wheeler 2016; Swenson, Nissen, and Henly 2010).

Self-efficacy, autonomous motivation, and perceived social support were not formally evaluated in this study due to its pilot nature and focus on testing the efficacy of aerobic walking on OIPN. However, participants were asked during the motivational interviewing

sessions to rate their perceived level of importance and confidence in performing aerobic exercise during cancer treatment. Although not described in the dissertation, this data may be explored post-hoc.

Specific Aims and Hypotheses

The specific aims and hypotheses were to:

Aim 1: Evaluate the effect of the MI-Walk Intervention on OIPN severity at eight weeks compared to PA education alone.

Hypothesis: Participants who received the MI-Walk Intervention would exhibit less severe OIPN at eight weeks than participants who received PA education alone.

Aim 2: Evaluate the effect of the MI-Walk Intervention on QOL and function at eight weeks compared to PA education alone.

Hypothesis: Participants who received the MI-Walk Intervention would report higher QOL and physical and emotional function at eight weeks than participants who received PA education alone.

Aim 3: Evaluate the feasibility of the MI-Walk Intervention.

Research Questions: Among patients receiving FOLFOX, 1) how acceptable was the intervention? 2) what percent of patients enrolled in, completed, and adhered to the intervention? 3) what participant characteristics were associated with intervention uptake, completion, and acceptability and attained levels of MVPA? 4) What, if any, adverse events would result from the MI-Walk Intervention?

Summary

This chapter introduced the scope of the problem associated with CIPN, and aerobic exercise to potentially, non-pharmacologically prevent and/or ameliorate OIPN, a type of CIPN. It also described the formation of the theoretical framework for the study, based on the TOUS (Lenz et al. 1997), SCT (Bandura, 1986, 2004; Rogers et al., 2004, 2005; Stacey et al., 2015), SDT (Deci & Ryan, 1985; Ryan, 1991, 1995), and empirical evidence. Further, the specific aims and hypotheses of the proposed study were presented. The following chapter (Chapter II) will comprehensively outline the literature regarding the evidence supporting exercise as a treatment for various types of CIPN, including OIPN. Chapters III and IV will present the results of the dual-site pilot randomized-controlled study of the MI-Walk Intervention compared to PA education alone among GI cancer survivors who were actively receiving FOLFOX or FOLFIRINOX.

Specifically, in Chapter III, results that address Aims one and two of this dissertation research are presented: effects of the MI-Walk Intervention on OIPN and QOL at eight weeks, compared to PA education alone. In Chapter IV, findings addressing Aim three are presented: the feasibility of the MI-Walk Intervention, including study enrollment and attrition rates, and intervention acceptability, uptake, and fidelity; and participant PA trends. The participant characteristics associated with completion and acceptability of the intervention as well as MVPA levels were also explored. Chapter V will close the dissertation with a summary of the results, remaining gaps in the literature, future directions, and clinical implications of the dissertation findings.

References

American Cancer Society. (2019a). *Cancer facts & figures 2019*. Atlanta. Retrieved from https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf

American Cancer Society. (2019b). *Cancer treatment and survivorship facts & figures 2019-2021*. Atlanta. Retrieved from https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer-treatment-and-survivorship-facts-and-figures/cancer-treatment-and-survivorship-facts-and-figures-2019-2021.pdf

Anderson-Bill, E. S., Winett, R. A., & Wojcik, J. R. (2011). Social cognitive determinants of nutrition and physical activity among web-health users enrolling in an online intervention: The influence of social support, self efficacy, outcomes expectations, and self-regulation. *Journal of Medical Internet Research*, *13*(1), 147–162. https://doi.org/10.2196/jmir.1551

Andre, T., Boni, C., Mounedji-Boudiaf, L., Navarro, M., Tabernero, J., Hickish, T., … de Gramont, A. (2004). Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *The New England Journal of Medicine*, *350*(23), 2343–2351. https://doi.org/10.1056/NEJMoa032709

André, T., Boni, C., & Navarro, M. (2009). Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol*, *27*(19), 3109–3116. https://doi.org/10.1200/JCO.2008.20.6771

Apodaca, T. R., & Longabaugh, R. (2009). Mechanisms of change in motivational interviewing: A review and preliminary evaluation of the evidence. *Addiction*, *104*(5), 705–715. https://doi.org/10.1111/j.1360-0443.2009.02527.x

Argyriou, A. A., Cavaletti, G., Briani, C., Velasco, R., Bruna, J., Campagnolo, M., … Kalofonos, H. P. (2013). Clinical pattern and associations of oxaliplatin acute neurotoxicity: A prospective study in 170 patients with colorectal cancer. *Cancer*, *119*(2), 438–444. Retrieved from http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L52110114

Ashford, S., Edmunds, J., & French, D. P. (2010). What is the best way to change self-efficacy to promote lifestyle and recreational physical activity? A systematic review with meta-analysis. *Br J Health Psychol*, *15*. https://doi.org/10.1348/135910709X461752

Ashor, A. W., Lara, J., Siervo, M., Celis-Morales, C., Oggioni, C., Jakovljevic, D. G., & Mathers,

J. C. (2015). Exercise modalities and endothelial function: A systematic review and dose-response meta-analysis of randomized controlled trials. *Sports Medicine*, *45*(2), 279–296. Journal Article, Meta-Analysis, Research Support, Non-U.S. Gov't, Review. https://doi.org/10.1007/s40279-014-0272-9

Ayotte, B. J., Margrett, J. A., & Hicks-Patrick, J. (2010). Physical activity in middle-aged and young-old adults: The roles of self-efficacy, barriers, outcome expectancies, self-regulatory behaviors and social support. *Journal of Health Psychology*, *15*(2), 173–185. https://doi.org/10.1177/1359105309342283

Azizbeigi, K., Azarbayjani, M. A., Atashak, S., & Stannard, S. R. (2015). Effect of moderate and high resistance training intensity on indices of inflammatory and oxidative stress. *Research in Sports Medicine (Print)*, *23*(1), 73–87. https://doi.org/10.1080/15438627.2014.975807

Bakitas, M. A. (2007). Background noise: The experience of chemotherapy-induced peripheral neuropathy. *Nursing Research*, *56*(5), 323–331. https://doi.org/10.1097/01.NNR.0000289503.22414.79

Bandura, A. (1977). Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev*, *84*. https://doi.org/10.1037/0033-295X.84.2.191

Bandura, A. (1986). *Social Foundations of Thought and Action: A Social Cognitive Theory.* Englewood Cliffs, NJ: Prentice Hall Inc.

Bandura, A. (2004). Health Promotion by Social Cognitive Means. *Health Education & Behavior*, *31*(2), 143–164. https://doi.org/10.1177/1090198104263660

Beijers, A. J. M., Mols, F., Tjan-Heijnen, V. C. G., Faber, C. G., van de Poll-Franse, L. V, & Vreugdenhil, G. (2015). Peripheral neuropathy in colorectal cancer survivors: The influence of oxaliplatin administration. Results from the population-based PROFILES registry. *Acta Oncologica*, *54*(4), 463–469. https://doi.org/10.3109/0284186X.2014.980912

Berger, A. M. A. M. (2010). Fatigue and other variables during adjuvant chemotherapy for colon and rectal cancer. *Oncology Nursing Forum*, *37*(6), E359–E369. https://doi.org/10.1188/10.ONF.E359-E369

Binkley, J. M., Harris, S. R., Levangie, P. K., Pearl, M., Guglielmino, J., Kraus, V., & Rowden, D. (2012). Patient perspectives on breast cancer treatment side effects and the prospective surveillance model for physical rehabilitation for women with breast cancer. *Cancer*, *118*(8 Suppl), 2207–2216. https://doi.org/10.1002/cncr.27469

Boehmke, M. M., & Dickerson, S. S. (2005). Symptom, symptom experiences, and symptom

distress encountered by women with breast cancer undergoing current treatment modalities. *Cancer Nursing*, *28*(5), 382–389.

Brayall, P., Donlon, E., Doyle, L., Leiby, R., & Violette, K. (2018). Physical therapy-based interventions improve balance, function, symptoms, and quality of life in patients with chemotherapy-induced peripheral neuropathy: A systematic review. *Rehabilitation Oncology*, *36*(3), 161–166. https://doi.org/10.1097/01.REO.0000000000000111

Cadmus, L. A., Salovey, P., Yu, H., Chung, G., Kasl, S., & Irwin, M. L. (2009). Exercise and quality of life during and after treatment for breast cancer: Results of two randomized controlled trials. *Psycho-Oncology*, *18*(4), 343–352. https://doi.org/10.1002/pon.1525

Carozzi, V. A., Canta, A., & Chiorazzi, A. (2015). Chemotherapy-induced peripheral neuropathy: What do we know about mechanisms? *Neuroscience Letters*, *596*, 90–107. https://doi.org/10.1016/j.neulet.2014.10.014

Carozzi, V. A., Marmiroli, P., & Cavaletti, G. (2010). The role of oxidative stress and anti-oxidant treatment in platinum-induced peripheral neurotoxicity. *Current Cancer Drug Targets*, *10*(7), 670–682.

Cavaletti, G. (2014). Chemotherapy-induced peripheral neurotoxicity (CIPN): What we need and what we know. *Journal of the Peripheral Nervous System*, *19*(2), 66–76. https://doi.org/10.1111/jns5.12073

Chang, C.-F., Chang, C.-C., Hwang, S.-L., & Chen, M.-Y. (2015). Effects of Buerger exercise combined health-promoting program on peripheral neurovasculopathy among community residents at high risk for diabetic foot ulceration. *Worldviews on Evidence-Based Nursing*, *12*(3), 145–153. https://doi.org/10.1111/wvn.12091

Chen, E. I., Crew, K. D., Trivedi, M., Awad, D., Maurer, M., Kalinsky, K., … Hershman, D. L. (2015). Identifying Predictors of Taxane-Induced Peripheral Neuropathy Using Mass Spectrometry-Based Proteomics Technology. *PloS One*, *10*(12), e0145816. https://doi.org/10.1371/journal.pone.0145816

Chen, M.-Y., Huang, W.-C., Peng, Y.-S., Guo, J.-S., Chen, C.-P., Jong, M.-C., & Lin, H.-C. (2011). Effectiveness of a health promotion programme for farmers and fishermen with type-2 diabetes in Taiwan. *Journal of Advanced Nursing*, *67*(9), 2060–2067. https://doi.org/10.1111/j.1365-2648.2011.05678.x

Choi, J. G., Nipp, R. D., Tramontano, A., Ali, A., Zhan, T., Pandharipande, P., … Hur, C. (2019). Neoadjuvant FOLFIRINOX for patients with borderline resectable or locally advanced pancreatic cancer: Results of a decision analysis. *The Oncologist*, *24*(7), 945–954. https://doi.org/10.1634/theoncologist.2018-0114

Chou, Y.-J., Lai, Y.-H., Lin, B.-R., Liang, J.-T., & Shun, S.-C. (2017). Factors influencing amount of weekly exercise time in colorectal cancer survivors. *Cancer Nursing*, *40*(3), 201–208. https://doi.org/10.1097/NCC.0000000000000383

Courneya, K. S., Friedenreich, C. M., Quinney, H. A., Fields, A. L. A., Jones, L. W., Vallance, J. K. H., & Fairey, A. S. (2005). A longitudinal study of exercise barriers in colorectal cancer survivors participating in a randomized controlled trial. *Annals of Behavioral Medicine*, *29*(2), 147–153. https://doi.org/10.1207/s15324796abm2902_9

Courneya, K. S., Segal, R. J., Gelmon, K., Mackey, J. R., Friedenreich, C. M., Yasui, Y., … McKenzie, D. C. (2014). Predictors of adherence to different types and doses of supervised exercise during breast cancer chemotherapy. *The International Journal of Behavioral Nutrition and Physical Activity*, *11*, 85. https://doi.org/10.1186/s12966-014-0085-0

Deci, E. L., & Ryan, R. M. (1985). *Intrinsic Motivation and Self-Determination in Human Behavior* (1st ed.). New York: Plenum Press. https://doi.org/10.2307/2070638

Deci, E. L., & Ryan, R. M. (1990). A motivational approach to self: Integration in personality. *Nebr Symp Motiv*, *38*, 237–288.

Di Cesare Mannelli, L., Zanardelli, M., Failli, P., & Ghelardini, C. (2012). Oxaliplatin-induced neuropathy: Oxidative stress as pathological mechanism. Protective effect of silibinin. *The Journal of Pain*, *13*(3), 276–284. https://doi.org/10.1016/j.jpain.2011.11.009

Drott, J., Starkhammar, H., Kjellgren, K., & Bertero, C. (2016). The trajectory of neurotoxic side effects' impact on daily life: A qualitative study. *Supportive Care in Cancer*, *24*(8), 3455–3461. https://doi.org/10.1007/s00520-016-3179-1

Duregon, F., Vendramin, B., Bullo, V., Gobbo, S., Cugusi, L., Di Blasio, A., … Ermolao, A. (2018). Effects of exercise on cancer patients suffering chemotherapy-induced peripheral neuropathy undergoing treatment: A systematic review. *Critical Reviews in Oncology/Hematology*, *121*(November 2017), 90–100. https://doi.org/10.1016/j.critrevonc.2017.11.002

Ekkekakis, P. (2013). *The Measurement of Affect, Mood, and Emotion: A Guide for Health-Behavioral Research*. New York, NY, US: Cambridge University Press.

Ekkekakis, P., Lind, E., & Vazou, S. (2010). Affective responses to increasing levels of exercise intensity in normal-weight, overweight, and obese middle-aged women. *Obesity*, *18*(1), 79–85. https://doi.org/10.1038/oby.2009.204

Ekkekakis, P., Parfitt, G., & Petruzzello, S. J. (2011). The pleasure and displeasure people feel when they exercise at different intensities: Decennial update and progress towards a

tripartite rationale for exercise intensity prescription. *Sports Medicine*, *41*(8), 641–671. https://doi.org/10.2165/11590680-000000000-00000

El-Shami, K., Oeffinger, K. C., Erb, N. L., Willis, A., Bretsch, J. K., Pratt-Chapman, M. L., … Cowens-Alvarado, R. L. (2015). American Cancer Society colorectal cancer survivorship care guidelines. *CA Cancer Journal for Clinicians*, *65*(6), 427–455. https://doi.org/10.3322/caac.21286

Exposito Vizcaino, S., Casanova-Molla, J., Escoda, L., Galan, S., & Miro, J. (2018). Neuropathic pain in cancer patients treated with bortezomib. *Neurologia*, *33*(1), 28–34. https://doi.org/10.1016/j.nrl.2016.05.008

Fernandez, S., Franklin, J., Amlani, N., DeMilleVille, C., Lawson, D., & Smith, J. (2015). Physical activity and cancer: A cross-sectional study on the barriers and facilitators to exercise during cancer treatment. *Canadian Oncology Nursing Journal*, *25*(1), 37–48.

Gomez-Cabrera, M. C., Salvador-Pascual, A., Cabo, H., Ferrando, B., & Vina, J. (2015). Redox modulation of mitochondriogenesis in exercise. Does antioxidant supplementation blunt the benefits of exercise training? *Free Radical Biology & Medicine*, *86*, 37–46. https://doi.org/10.1016/j.freeradbiomed.2015.04.006

Hartman, J. E., Boezen, H. M., de Greef, M. H., & Ten Hacken, N. H. (2013). Physical and psychosocial factors associated with physical activity in patients with chronic obstructive pulmonary disease. *Archives of Physical Medicine and Rehabilitation*, *94*(12), 2396-2402.e7. https://doi.org/10.1016/j.apmr.2013.06.029

Hawkes, A. L., Chambers, S. K., Pakenham, K. I., Patrao, T. A., Baade, P. D., Lynch, B. M., … Courneya, K. S. (2013). Effects of a telephone-delivered multiple health behavior change intervention (CanChange) on health and behavioral outcomes in survivors of colorectal cancer: A randomized controlled trial. *Journal of Clinical Oncology*, *31*(18), 2313–2321. https://doi.org/10.1200/JCO.2012.45.5873

Henke, C. C., Cabri, J., Fricke, L., Pankow, W., Kandilakis, G., Feyer, P. C., & de Wit, M. (2014). Strength and endurance training in the treatment of lung cancer patients in stages IIIA/IIIB/IV. *Supportive Care in Cancer*, *22*(1), 95–101. https://doi.org/10.1007/s00520-013-1925-1

Henriksson, A., Arving, C., Johansson, B., Igelstrom, H., & Nordin, K. (2016). Perceived barriers to and facilitators of being physically active during adjuvant cancer treatment. *Patient Education and Counseling*, *99*(7), 1220–1226. https://doi.org/10.1016/j.pec.2016.01.019

Hershman, D. L., Lacchetti, C., Dworkin, R. H., Lavoie Smith, E. M., Bleeker, J., Cavaletti, G., … Loprinzi, C. L. (2014). Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical

Oncology clinical practice guideline. *Journal of Clinical Oncology*, *32*(18), 1941–1967. https://doi.org/10.1200/JCO.2013.54.0914

Hershman, D. L., Till, C., Wright, J. D., Awad, D., Ramsey, S. D., Barlow, W. E., … Unger, J. (2016). Comorbidities and risk of chemotherapy-induced peripheral neuropathy among participants 65 years or older in southwest oncology group clinical trials. *Journal of Clinical Oncology*, *34*(25), 3014–3022. https://doi.org/10.1200/JCO.2015.66.2346

Hong, J. S., Tian, J., & Wu, L. H. (2014). The influence of chemotherapy-induced neurotoxicity on psychological distress and sleep disturbance in cancer patients. *Current Oncology*, *21*(4), 174–180. https://doi.org/10.3747/co.21.1984

Huang, J.-S., Wu, C.-L., Fan, C.-W., Chen, W.-H., Yeh, K.-Y., & Chang, P.-H. (2015). Intravenous glutamine appears to reduce the severity of symptomatic platinum-induced neuropathy: A prospective randomized study. *Journal of Chemotherapy*, *27*(4), 235–240. Retrieved from http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L605188640

Imai, S., Koyanagi, M., Azimi, Z., Nakazato, Y., Matsumoto, M., Ogihara, T., … Matsubara, K. (2017). Taxanes and platinum derivatives impair Schwann cells via distinct mechanisms. *Scientific Reports*, *7*(1), 5947. https://doi.org/10.1038/s41598-017-05784-1

Jaggi, A. S., & Singh, N. (2012). Mechanisms in cancer-chemotherapeutic drugs-induced peripheral neuropathy. *Toxicology*, *291*(1–3), 1–9. https://doi.org/10.1016/j.tox.2011.10.019

Janssen, I., Dugan, S. A., Karavolos, K., Lynch, E. B., & Powell, L. H. (2014). Correlates of 15-year maintenance of physical activity in middle-aged women. *International Journal of Behavioral Medicine*, *21*(3), 511–518. https://doi.org/10.1007/s12529-013-9324-z

Jung, M., Rein, N., & Fuchs, B. (2018). Physical therapy for chemotherapy-induced peripheral neuropathy in pediatric oncology. *Physikalische Medizin Rehabilitationsmedizin Kurortmedizin*, *28*(1), 46–52. https://doi.org/10.1055/s-0043-124644

Kamath, J. (2012). Cancer-related fatigue, inflammation and thyrotropin-releasing hormone. *Current Aging Science*, *5*(3), 195–202.

Karimi, N., & Roshan, V. D. (2013). Change in adiponectin and oxidative stress after modifiable lifestyle interventions in breast cancer cases. *Asian Pacific Journal of Cancer Prevention*, *14*(5), 2845–2850.

Kidwell, K. M., Yothers, G., Ganz, P. A., Land, S. R., Ko, C. Y., Cecchini, R. S., … Wolmark, N. (2012). Long-term neurotoxicity effects of oxaliplatin added to fluorouracil and

leucovorin as adjuvant therapy for colon cancer: Results from National Surgical Adjuvant Breast and Bowel Project trials C-07 and LTS-01. *Cancer*, *118*(22), 5614–5622. https://doi.org/10.1002/cncr.27593

Kim, H.-J., Barsevick, A. M., Fang, C. Y., & Miaskowski, C. (2012). Common biological pathways underlying the psychoneurological symptom cluster in cancer patients. *Cancer Nursing*, *35*(6), E1–E20. https://doi.org/10.1097/NCC.0b013e318233a811

Kleckner, I. R., Kamen, C., Gewandter, J. S., Mohile, N. A., Heckler, C. E., Culakova, E., … Musian, 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

Kleckner, I. R., Kamen, C. S., Peppone, L. J., Janelsins, M. C., Asare, M., Heckler, C. E., … Mustian, K. M. (2016). A URCC NCORP nationwide randomized controlled trial investigating the effect of exercise on chemotherapy-induced peripheral neuropathy in 314 cancer patients. *Journal of Clinical Oncology*, *34*. Retrieved from http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L611752704

Knittle, K., De Gucht, V., Hurkmans, E., Peeters, A., Ronday, K., Maes, S., & Vlieland, T. V. (2015). Targeting motivation and self-regulation to increase physical activity among patients with rheumatoid arthritis: a randomised controlled trial. *Clinical Rheumatology*, *34*(2), 231–238. https://doi.org/10.1007/s10067-013-2425-x

Knoerl, R., Chornoby, Z., & Smith, E. M. L. (2018). Estimating the frequency, severity, and clustering of SPADE symptoms in chronic painful chemotherapy-induced peripheral neuropathy. *Pain Management Nursing*, *19*(4), 354–365. https://doi.org/10.1016/j.pmn.2018.01.001

Knoerl, R., Chornoby, Z., & Smith, E. M. L. (2019). Corrigendum to 'Estimating the frequency, severity, and clustering of SPADE symptoms in chronic painful chemotherapy-induced peripheral neuropathy' Pain Management Nursing 2018;19(4):354-365. *Pain Management Nursing*, *20*(1), 88. https://doi.org/10.1016/j.pmn.2018.12.010

Knoerl, R., Smith, E. M. L., Barton, D. L., Williams, D. A., Holden, J. E., Krauss, J. C., & LaVasseur, B. (2018). Self-guided online cognitive behavioral strategies for chemotherapy-induced peripheral neuropathy: A multicenter, pilot, randomized, wait-list controlled trial. *The Journal of Pain : Official Journal of the American Pain Society*, *19*(4), 382–394. https://doi.org/10.1016/j.jpain.2017.11.009

Kwan, B. M., & Bryan, A. (2010). In-task and post-task affective response to exercise: translating exercise intentions into behaviour. *British Journal of Health Psychology*,

15(Pt 1), 115–131. https://doi.org/10.1348/135910709X433267

Lee, D., Kanzawa-Lee, G., Knoerl, R., Wyatt, G., & Smith, E. (2019). Characterization of internal validity threats to Phase III clinical trials for chemotherapy-induced peripheral neuropathy management: A systematic review. In *Oncology Nursing Forum* (Vol. 46). ONCOLOGY NURSING SOC 125 ENTERPRISE DR, PITTSBURGH, PA 15275 USA.

Lenz, E. R., Pugh, L. C., Milligan, R. A., Gift, A., & Suppe, F. (1997). The middle-range theory of unpleasant symptoms: An update. *Advances in Nursing Science*, *19*(3), 14–27.

Liao, Y., Chou, C.-P., Huh, J., Leventhal, A., & Dunton, G. (2016). Examining acute bi-directional relationships between affect, physical feeling states, and physical activity in free-living situations using electronic ecological momentary assessment. *Journal of Behavioral Medicine*. https://doi.org/10.1007/s10865-016-9808-9

Liao, Y., Shonkoff, E. T., & Dunton, G. F. (2015). The Acute Relationships Between Affect, Physical Feeling States, and Physical Activity in Daily Life: A Review of Current Evidence. *Frontiers in Psychology*, *6*, 1975. https://doi.org/10.3389/fpsyg.2015.01975

Littlecott, H. J., Moore, G. F., Moore, L., & Murphy, S. (2014). Psychosocial mediators of change in physical activity in the Welsh national exercise referral scheme: Secondary analysis of a randomised controlled trial. *The International Journal of Behavioral Nutrition and Physical Activity*, *11*, 109. https://doi.org/10.1186/s12966-014-0109-9

Loprinzi, C. L., Qin, R., Dakhil, S. R., Fehrenbacher, L., Flynn, K. A., Atherton, P., … Grothey, A. (2014). Phase III randomized, placebo-controlled, double-blind study of intravenous calcium and magnesium to prevent oxaliplatin-induced sensory neurotoxicity (N08CB/Alliance). *Journal of Clinical Oncology*, *32*(10), 997–1005. https://doi.org/10.1200/JCO.2013.52.0536

Majithia, N., Temkin, S. M., Ruddy, K. J., Beutler, A. S., Hershman, D. L., & Loprinzi, C. L. (2016). National Cancer Institute-supported chemotherapy-induced peripheral neuropathy trials: Outcomes and lessons. *Supportive Care in Cancer*, *24*(3), 1439–1447. https://doi.org/10.1007/s00520-015-3063-4

Mas, S., Quantin, X., & Ninot, G. (2015). Barriers to, and facilitators of physical activity in patients receiving chemotherapy for lung cancer: An exploratory study. *Journal of Palliative Care*, *31*(2), 89–96. Retrieved from https://www.scopus.com/inward/record.uri?eid=2-s2.0-84937859700&partnerID=40&md5=660e8d75227723bc158f1c91cb3aa42e

Mata, J., Thompson, R. J., Jaeggi, S. M., Buschkuehl, M., Jonides, J., & Gotlib, I. H. (2012). Walk on the bright side: physical activity and affect in major depressive disorder. *Journal of Abnormal Psychology*, *121*(2), 297–308. https://doi.org/10.1037/a0023533

McCrary, J. M., Goldstein, D., Sandler, C. X., Barry, B. K., Marthick, M., Timmins, H. C., … Park, S. B. (2019). Exercise-based rehabilitation for cancer survivors with chemotherapy-induced peripheral neuropathy. *Supportive Care in Cancer*. https://doi.org/10.1007/s00520-019-04680-w

Meyers, B. M., Cosby, R., Quereshy, F., & Jonker, D. (2017). Adjuvant chemotherapy for stage II and III colon cancer following complete resection: A cancer care ontario systematic review. *Clinical Oncology*, *29*(7), 459–465. https://doi.org/10.1016/j.clon.2017.03.001

Mikkelsen, M. K., Nielsen, D. L., Vinther, A., Lund, C. M., & Jarden, M. (2019). Attitudes towards physical activity and exercise in older patients with advanced cancer during oncological treatment - A qualitative interview study. *European Oncology Nursing*, *41*, 16–23. https://doi.org/10.1016/j.ejon.2019.04.005

Miller, W. R., & Rose, G. S. (2009). Toward a theory of motivational interviewing. *The American Psychologist*, *64*(6), 527–537. https://doi.org/10.1037/a0016830

Mock, V., Frangakis, C., Davidson, N. E., Ropka, M. E., Pickett, M., Poniatowski, B., … McCorkle, R. (2005). Exercise manages fatigue during breast cancer treatment: A randomized controlled trial. *Psycho-Oncology*, *14*(6), 464–477. https://doi.org/10.1002/pon.863

Mols, F., Beijers, T., Lemmens, V., van den Hurk, C. J., Vreugdenhil, G., & van de Poll-Franse, L. V. (2013). Chemotherapy-induced neuropathy and its association with quality of life among 2- to 11-year colorectal cancer survivors: Results from the population-based PROFILES registry. *Journal of Clinical Oncology*, *31*(21), 2699–2707. https://doi.org/10.1200/JCO.2013.49.1514

Monfort, S. M., Pan, X., Patrick, R., Singaravelu, J., Loprinzi, C. L., Lustberg, M. B., & Chaudhari, A. M. W. (2016). Natural history of postural instability in breast cancer patients treated with taxane-based chemotherapy: A pilot study. *Gait & Posture*, *48*, 237–242. https://doi.org/10.1016/j.gaitpost.2016.06.011

Morielli, A. R., Usmani, N., Boule, N. G., Severin, D., Tankel, K., Nijjar, T., … Courneya, K. S. (2016). Exercise motivation in rectal cancer patients during and after neoadjuvant chemoradiotherapy. *Supportive Care in Cancer*, *24*(7), 2919–2926. https://doi.org/10.1007/s00520-016-3110-9

National Cancer Institute. (2016). *SEER Cancer Statistics Review, 1975-2013*. Bethesda, MD. Retrieved from http://seer.cancer.gov/csr/1975_2013/

Pachman, D. R., Barton, D. L., Swetz, K. M., & Loprinzi, C. L. (2012). Troublesome symptoms in cancer survivors: Fatigue, insomnia, neuropathy, and pain. *Journal of Clinical Oncology*, *30*(30), 3687–3696. https://doi.org/10.1200/JCO.2012.41.7238

Pachman, D. R., Qin, R., Seisler, D. K., Smith, E. M. L., Beutler, A. S., Ta, L. E., … Loprinzi, C. L. (2015). Clinical course of oxaliplatin-induced neuropathy: Results from the randomized phase III trial N08CB (Alliance). *Journal of Clinical Oncology*, *33*(30), 3416–3422. https://doi.org/10.1200/JCO.2014.58.8533

Pachman, D. R., Qin, R., Seisler, D., Smith, E. M. L., Kaggal, S., Novotny, P., … Loprinzi, C. L. (2016). Comparison of oxaliplatin and paclitaxel-induced neuropathy (Alliance A151505). *Supportive Care in Cancer*, *24*(12), 5059–5068. https://doi.org/10.1007/s00520-016-3373-1

Park, J.-H., Miyashita, M., Takahashi, M., Kawanishi, N., Bae, S.-R., Kim, H.-S., … Nakamura, Y. (2013). Effects of low-volume walking programme and vitamin E supplementation on oxidative damage and health-related variables in healthy older adults. *Nutrition & Metabolism*, *10*(1), 38. https://doi.org/10.1186/1743-7075-10-38

Park, S. B., Goldstein, D., Krishnan, A. V, Lin, C. S.-Y., Friedlander, M. L., Cassidy, J., … Kiernan, M. C. (2013). Chemotherapy-induced peripheral neurotoxicity: A critical analysis. *Cancer Journal for Clinicians*, *63*(6), 419–437. https://doi.org/10.3322/caac.21204

Petrovchich, I., Kober, K. M., Wagner, L., Paul, S. M., Abrams, G., Chesney, M. A., … Miaskowski, C. (2019). Deleterious effects of higher body mass index on subjective and objective measures of chemotherapy-induced peripheral neuropathy in cancer survivors. *Journal of Pain and Symptom Management*, *58*(2), 252–263. https://doi.org/10.1016/j.jpainsymman.2019.04.029

Phillips, S. M., & McAuley, E. (2013). Social cognitive influences on physical activity participation in long-term breast cancer survivors. *Psycho-Oncology*, *22*(4), 783–791. https://doi.org/10.1002/pon.3074

Resnicow, K., & McMaster, F. (2012). Motivational interviewing: Moving from why to how with autonomy support. *International Journal of Behavioral Nutrition and Physical Activity*, *9*(1), 19. https://doi.org/10.1186/1479-5868-9-19

Rogers, L. Q., Matevey, C., Hopkins-Price, P., Shah, P., Dunnington, G., & Courneya, K. S. (2004). Exploring social cognitive theory constructs for promoting exercise among breast cancer patients. *Cancer Nursing*, *27*(6), 462–473. Retrieved from http://proxy.lib.umich.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=ccm&AN=106599684&site=ehost-live&scope=site

Rogers, L. Q., Shah, P., Dunnington, G., Greive, A., Shanmugham, A., Dawson, B., & Courneya, K. S. (2005). Social cognitive theory and physical activity during breast cancer treatment. *Oncology Nursing Forum*, *32*(4), 807–815. https://doi.org/10.1188/05.ONF.807-815

Rothman, A. J., Baldwin, A. S., Hertel, A. W., & Fuglestad, P. T. (2004). Disentangling behavioral initiation and behavioral maintenance. *Handbook of Self-Regulation. Research, Theory, and Applications; Guilford Press: New York, NY, USA*, 130–148.

Ryan, R. M. (1995). Psychological needs and the facilitation of integrative processes. *Journal of Personality*, *63*(3), 397–427.

Ryan, R. M., & Deci, E. L. (2000). Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. *The American Psychologist*, *55*(1), 68–78.

Schaun, M. I., Dipp, T., Rossato, J. da S., Wilhelm, E. N., Pinto, R., Rech, A., … Reischak-Oliveira, A. (2011). The effects of periodized concurrent and aerobic training on oxidative stress parameters, endothelial function and immune response in sedentary male individuals of middle age. *Cell Biochemistry and Function*, *29*(7), 534–542. https://doi.org/10.1002/cbf.1781

Seretny, M., Currie, G. L., Sena, E. S., Ramnarine, S., Grant, R., MacLeod, M. R., … 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

Shang, J., Wenzel, J., Krumm, S., Griffith, K., & Stewart, K. (2012). Who will drop out and who will drop in: Exercise adherence in a randomized clinical trial among patients receiving active cancer treatment. *Cancer Nursing*, *35*(4), 312–322. https://doi.org/10.1097/NCC.0b013e318236a3b3

Skerman, H. M., Yates, P. M., & Battistutta, D. (2012). Cancer-related symptom clusters for symptom management in outpatients after commencing adjuvant chemotherapy, at 6 months, and 12 months. *Supportive Care in Cancer*, *20*(1), 95–105. https://doi.org/10.1007/s00520-010-1070-z

Slovinec D'Angelo, M. E., Pelletier, L. G., Reid, R. D., & Huta, V. (2014). The roles of self-efficacy and motivation in the prediction of short- and long-term adherence to exercise among patients with coronary heart disease. *Health Psychology : Official Journal of the Division of Health Psychology, American Psychological Association*, *33*(11), 1344–1353. https://doi.org/10.1037/hea0000094

Smith, E. M. L., Pang, H., Cirrincione, C., Al, E., Fleishman, S., Paskett, E. D., … Shapiro, C. L. (2013). Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: A randomized clinical trial. *JAMA*, *309*(13), 1359–1367. https://doi.org/10.1001/jama.2013.2813

Smith, E. M. L., Pang, H., Ye, C., Cirrincione, C., Fleishman, S., Paskett, E. D. D., … Shapiro,

C. L. L. (2017). Predictors of duloxetine response in patients with oxaliplatin-induced painful chemotherapy-induced peripheral neuropathy (CIPN): A secondary analysis of randomised controlled trial - CALGB/alliance 170601. *European Journal of Cancer Care*, *26*(2), e12421. https://doi.org/10.1111/ecc.12421

Soveri, L. M., Lamminmäki, A., Hänninen, U. A., Karhunen, M., Bono, P., & Osterlund, P. (2019). Long-term neuropathy and quality of life in colorectal cancer patients treated with oxaliplatin containing adjuvant chemotherapy. *Acta Oncologica*, *58*(4), 398–406. https://doi.org/10.1080/0284186X.2018.1556804

Speck, R. M., DeMichele, A., Farrar, J. T., Hennessy, S., Mao, J. J., Stineman, M. G., & Barg, F. K. (2012). Scope of symptoms and self-management strategies for chemotherapy-induced peripheral neuropathy in breast cancer patients. *Supportive Care in Cancer*, *20*(10), 2433–2439. https://doi.org/10.1007/s00520-011-1365-8

Spencer, J. C., & Wheeler, S. B. (2016). A systematic review of motivational interviewing interventions in cancer patients and survivors. *Patient Education and Counseling*, *99*(7), 1099–1105. https://doi.org/10.1016/j.pec.2016.02.003

Stacey, F. G., James, E. L., Chapman, K., Courneya, K. S., & Lubans, D. R. (2015). A systematic review and meta-analysis of social cognitive theory-based physical activity and/or nutrition behavior change interventions for cancer survivors. *Journal of Cancer Survivorship*, *9*(2), 305–338. https://doi.org/10.1007/s11764-014-0413-z

Streckmann, F., Kneis, S., Leifert, J. A., Baumann, F. T., Kleber, M., Ihorst, G., … 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

Sweet, S. N., Fortier, M. S., Guerin, E., Tulloch, H., Sigal, R. J., Kenny, G. P., & Reid, R. D. (2009). Understanding physical activity in adults with type 2 diabetes after completing an exercise intervention trial: A mediation model of self-efficacy and autonomous motivation. *Psychology, Health & Medicine*, *14*(4), 419–429. https://doi.org/10.1080/13548500903111806

Swenson, K. K., Nissen, M. J., & Henly, S. J. (2010). Physical activity in women receiving chemotherapy for breast cancer: Adherence to a walking intervention. *Oncology Nursing Forum*, *37*(3), 321–330. https://doi.org/10.1188/10.ONF.321-330

Teixeira, P. J., Carraca, E. V, Marques, M. M., Rutter, H., Oppert, J.-M., De Bourdeaudhuij, I., … Brug, J. (2015). Successful behavior change in obesity interventions in adults: A systematic review of self-regulation mediators. *BMC Medicine*, *13*, 84. https://doi.org/10.1186/s12916-015-0323-6

Terrazzino, S., Argyriou, A. A., Cargnin, S., Antonacopoulou, A. G., Briani, C., Bruna, J., … Cavaletti, G. (2015). Genetic determinants of chronic oxaliplatin-induced peripheral neurotoxicity: a genome-wide study replication and meta-analysis. *Journal of the Peripheral Nervous System : JPNS*, *20*(1), 15–23. https://doi.org/10.1111/jns.12110

Tofthagen, C. S. (2010a). Patient perceptions associated with chemotherapy-induced peripheral neuropathy. *Clinical Journal of Oncology Nursing*, *14*(3), E22-8. https://doi.org/10.1188/10.CJON.E22-E28

Tofthagen, C. S. (2010b). Surviving chemotherapy for colon cancer and living with the consequences. *Journal of Palliative Medicine*, *13*(11), 1389–1391. https://doi.org/10.1089/jpm.2010.0124

Tofthagen, C. S., Donovan, K. A., Morgan, M. A., Shibata, D., & Yeh, Y. (2013). Oxaliplatin-induced peripheral neuropathy's effects on health-related quality of life of colorectal cancer survivors. *Supportive Care in Cancer*, *21*(12), 3307–3313. https://doi.org/10.1007/s00520-013-1905-5

Tofthagen, C. S., McAllister, R. D., & McMillan, S. C. (2011). Peripheral neuropathy in patients with colorectal cancer receiving oxaliplatin. *Clinical Journal of Oncology Nursing*, *15*(2), 182–188. https://doi.org/10.1188/11.CJON.182-188

Tofthagen, C. S., McMillan, S. C., & Kip, K. E. (2011). Development and psychometric evaluation of the chemotherapy-induced peripheral neuropathy assessment tool. *Cancer Nursing*, *34*(4), E10-20. https://doi.org/10.1097/NCC.0b013e31820251de

Tofthagen, C. S., Visovsky, C. M., & Hopgood, R. (2013). Chemotherapy-induced peripheral neuropathy: An algorithm to guide nursing management. *Clinical Journal of Oncology Nursing*, *17*(2), 138–144. https://doi.org/10.1188/13.CJON.138-144

Tulloch, H. E., Reid, R., & Fortier, M. (2007). Personal and environmental determinants of exercise in patients with coronary artery disease: Evaluating a social-cognitive model. *Journal of Cardiopulmonary Rehabilitation and Prevention*, *27*(5), 341.

Van Hoecke, A.-S., Delecluse, C., Opdenacker, J., Lipkens, L., Martien, S., & Boen, F. (2013). Long-term effectiveness and mediators of a need-supportive physical activity coaching among Flemish sedentary employees. *Health Promotion International*, *28*(3), 407–417. https://doi.org/10.1093/heapro/das025

van Putten, M., Husson, O., Mols, F., Luyer, M. D. P., van de Poll-Franse, L. V, & Ezendam, N. P. M. (2016). Correlates of physical activity among colorectal cancer survivors: Results from the longitudinal population-based profiles registry. *Supportive Care in Cancer*, *24*(2), 573–583. https://doi.org/10.1007/s00520-015-2816-4

Ventzel, L., Madsen, C. S., Jensen, A. B., Jensen, A. R., Jensen, T. S., & Finnerup, N. B. (2015). Assessment of acute oxaliplatin-induced cold allodynia: a pilot study. *Acta Neurologica Scandinavica*. https://doi.org/10.1111/ane.12443

Ventzel, L., Madsen, C. S., Jensen, A. B., Jensen, A. R., Jensen, T. S., & Finnerup, N. B. (2016). Assessment of acute oxaliplatin-induced cold allodynia: A pilot study. *Acta Neurologica Scandinavica*, *133*(2), 152–155. https://doi.org/10.1111/ane.12443

Webber, K. H., Tate, D. F., & Quintiliani, L. M. (2008). Motivational interviewing in internet groups: A pilot study for weight loss. *Journal of the American Dietetic Association*, *108*(6), 1029–1032. https://doi.org/10.1016/j.jada.2008.03.005

White, S. M., Wojcicki, T. R., & McAuley, E. (2012). Social cognitive influences on physical activity behavior in middle-aged and older adults. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *67*(1), 18–26. https://doi.org/10.1093/geronb/gbr064

Williams, D. M., Dunsiger, S., Ciccolo, J. T., Lewis, B. A., Albrecht, A. E., & Marcus, B. H. (2008). Acute affective response to a moderate-intensity exercise stimulus predicts physical activity participation 6 and 12 months later. *Psychology of Sport and Exercise*, *9*(3), 231–245. https://doi.org/10.1016/j.psychsport.2007.04.002

Wonders, K. Y. (2014). The effect of supervised exercise training on symptoms of chemotherapy-induced peripheral neuropathy. *Int J Phys Med Rehabil*, *2*(4), 1–5.

World Health Organization, & International Agency for Research on Cancer. (2012). All cancers (excluding non-melanoma skin cancer) estimated incidence, mortality and prevalence worldwide in 2012. Retrieved January 4, 2017, from http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx

Zanville, N. R., Nudelman, K. N. H., Smith, D. J., Von Ah, D., McDonald, B. C., Champion, V. L., & Saykin, A. J. (2016). Evaluating the impact of chemotherapy-induced peripheral neuropathy symptoms (CIPN-sx) on perceived ability to work in breast cancer survivors during the first year post-treatment. *Supportive Care in Cancer*, *24*(11), 4779–4789. https://doi.org/10.1007/s00520-016-3329-5

Zedan, Ahmed H, & Vilholm, O. J. (2014). Chemotherapy-induced polyneuropathy: Major agents and assessment by questionnaires. *Basic & Clinical Pharmacology & Toxicology*, *115*(2), 193–200. https://doi.org/10.1111/bcpt.12262

Zedan, Ahmed Hussein, Hansen, T. F., Fex Svenningsen, A., & Vilholm, O. J. (2014). Oxaliplatin-induced neuropathy in colorectal cancer: Many questions with few answers. *Clinical Colorectal Cancer*, *13*(2), 73–80. https://doi.org/10.1016/j.clcc.2013.11.004

Zhou, W., Liu, G., Yang, S., Mi, B., & Ye, S. (2016). Low-intensity treadmill exercise promotes rat dorsal wound healing. *Journal of Huazhong University of Science and Technology*, *36*(1), 121–126. https://doi.org/10.1007/s11596-016-1553-3

Ziegelmann, J. P., Luszczynska, A., Lippke, S., & Schwarzer, R. (2007). Are goal intentions or implementation intentions better predictors of health behavior? A longitudinal study in orthopedic rehabilitation. *Rehabilitation Psychology*, *52*(1), 97–102. https://doi.org/10.1037/0090-5550.52.1.97

Zimmer, P., Trebing, S., Timmers-Trebing, U., Schenk, A., Paust, R., Bloch, W., … 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

Zimmerman, B. J. (2000). Self-efficacy: An essential motive to learn. *Contemporary Educational Psychology*, *25*(1), 82–91. https://doi.org/10.1006/ceps.1999.1016

CHAPTER II

Review of the Literature

Chemotherapy-induced peripheral neuropathy (CIPN) is among the most prevalent and debilitating side effects of cancer treatment. Approximately 60% of cancer survivors develop CIPN from neurotoxic chemotherapies, such as taxanes (paclitaxel, docetaxel), platinums (oxaliplatin, cisplatin, carboplatin), vinca alkaloids (vincristine, vinblastine, vinorelbine), bortezomib, and anti-angiogenesis agents (thalidomide, lenalidomide) (Banach, Juranek, and Zygulska 2017; Ventzel, Jensen, et al. 2016). These chemotherapies can damage the peripheral sensory, motor, and autonomic nerves and lead to CIPN manifestations: most commonly numbness, tingling, burning or shooting pain, extremity weakness, and loss of proprioception and deep tendon reflexes. Long-term pain and sensorimotor deficits associated with CIPN increase risk for falls and impair physical function and quality of life (QOL) (Bakitas 2007; Tofthagen et al. 2013). Thus, CIPN is a primary dose-limiting factor for patients who are receiving neurotoxic chemotherapy for the treatment of their cancer (Beijers et al. 2015).

Currently, there are no evidence-based preventive or curative treatments for CIPN (Hershman et al. 2014; Majithia et al. 2016); however, some studies suggest exercise may be beneficial for other types of peripheral neuropathy (Quigley et al., 2014b, 2014a) and in treating other cancer-treatment-associated symptoms: pain, fatigue, mood, emotional distress, sleep disturbance, balance, and decreased QOL (Mustian et al. 2009; van Waart et al. 2015). Large observational trials have also shown links between higher physical activity levels and less severe

CIPN (Greenlee et al. 2017; Mols et al. 2015). Exercise may attenuate CIPN through its influence on blood circulation/oxidative stress (Marcelino et al. 2013; Marques-Aleixo et al. 2012), inflammation (Y.-W. Chen et al. 2014; S. B. Jones et al. 2013; Yoon et al. 2015), pain-inhibiting neurotransmitters (Bobinski et al. 2015), endogenous opioids (Stagg et al. 2011), growth factors (Molteni et al. 2004), neuroplasticity (Taube, Gruber, et al. 2007), and coping and symptom interaction mechanisms (Cooper, Kluding, and Wright 2016; Courneya 2014; Peddle, Au, and Courneya 2008). Although exercise is recommended for cancer survivors (Buffart et al. 2014), little is known about specific exercise prescriptions' effectiveness in reducing CIPN and feasibility among individuals who have received neurotoxic chemotherapy.

Purpose

The purpose of this integrative review was to synthesize research literature published since 2006, reporting the effects of exercise interventions on CIPN and other relevant outcomes among previously or currently neurotoxic chemotherapy-receiving people of all age groups. In this population, the specific aims were to (a) investigate the effects of exercise and physical therapy on CIPN severity and related outcomes, (b) identify the exercise type, delivery mode, and dosage associated with superior participant adherence rates, and effects on CIPN, and (c) explore feasibility, including the rates and influencing factors of exercise intervention trial enrollment and completion, and adverse events. This review will add to the existing systematic reviews (Brayall et al. 2018; Duregon et al. 2018; Jung, Rein, and Fuchs 2018) by providing critical appraisal and numerical synthesis of the most recent literature to identify patterns among the sample characteristics; exercise types, dosages, and delivery settings; and CIPN and other relevant outcomes.

Methods

PubMed, CINAHL, Scopus, PsycINFO, and SportDiscus were searched for all trials and meta-analyses that evaluated the effects of exercise on CIPN. Two re-iterations of the full search were conducted: first between May and November 2016 to evaluate the literature published from 2006 to 2017, then in April 2019 to evaluate the literature published from 2017 to 2019. The authors preliminarily reviewed all literature published since database inception before conducting the full search and had identified that only the studies published since 2006 had evaluated peripheral neuropathy outcomes of exercise. Article references, ScienceDirect recommendations, PEDro, and select journals and grey-literature databases were hand-searched, including American College of Sports Medicine's, Health & Fitness Journal, Advances in Physiotherapy, Human Kinetics and Neurology journals, clinicaltrials.gov, opengrey.eu, ProQuest Dissertations and Theses, and eric.edu.gov. The following keywords were used to find relevant studies: exercise, physical activity, physical therapy, physiotherapy, peripheral neuropathy, polyneuropathy, and neurotoxicity.

Inclusion and Exclusion Criteria

Articles were considered if they met all of the following inclusion criteria 1) randomized controlled trial (RCT), meta-analysis, or quasi-experimental (QE) design, 2) published within 2006 to 2019, 3) human subjects of any age, 4) most (≥ 50%) participants had received or were receiving neurotoxic chemotherapy, 5) at least 10 participants, 6) tested exercise interventions, including physical therapy and exercise counseling, 7) measured CIPN outcomes, and 8) published in English. Articles were excluded if they 1) were an abstract or protocol only, 2) tested passive exercise interventions (e.g., whole-body vibration, passive range of motion,

splinting), and 3) tested concurrent non-exercise physiological interventions (e.g. drugs, supplements, transcutaneous electrical nerve stimulation).

Data Abstraction and Measurement Strategy

The following information was abstracted from the studies: 1) study design; 2) sample size; 3) sample characteristics (neuropathy and cancer type and grade/stage, age, gender, body mass index (BMI), and fitness/activity level); 4) intervention characteristics—type, prescribed dose and intensity, duration, and delivery settings; 5) control condition; 6) CIPN and related outcomes; 7) long-term post-intervention outcomes; 8) intervention adherence; 9) enrollment and completion rates; 10) reasons for participation refusal or discontinuation; and 8) adverse effects.

Analysis/Quality Appraisal Methods

All *n*s refer to the number of *studies* being quantified/described. Descriptive analyses were used to describe the sample and intervention characteristics. Multi-arm trials that lacked a true control condition (e.g., evaluated side-by-side physical interventions, or compared the intervention only to healthy controls) were analyzed as pre-posttest QE studies. Those classified as mixed sample studies included participants with mixed cancer types; and/or who were receiving various chemotherapy regimens. In cases where, the articles only provided ranges (and no means), the average of that range was used in this review's descriptive analysis (e.g., 40 minutes per day was used in the analysis for prescriptions of 30-50 min per day).

Regarding the exercise type, studies of functional and sensorimotor training were grouped in with balance training due to the similarity in their methods and intentions. One intervention focused on elastic band training and increasing step counts was categorized as an aerobic+strength training intervention.

The efficacy of the interventions on/among various outcomes and populations were evaluated based on the percentage of studies that showed clinically (≥ 30% difference) (Farrar et al. 2001) and statistically ($p \leq .05$) significant effects for each outcome. Effect sizes were considered in the synthesized outcome discussion if provided by the studies. This review only presents results on outcomes that were evaluated in at least three studies. Two studies—from which only pre-posttest results were gleanable in active neurotoxic chemotherapy-receiving individuals with no baseline CIPN—were excluded from the dichotomous quantification of outcomes (1, significant improvement; 0, no improvement), because they had no room for improvement. Description and further explanation for the exclusion of these studies are provided in the Outcome measures and results section.

Critical appraisal. The articles were critically appraised by the primary author using the CONSORT checklist.(Schulz et al. 2011) The author categorized studies as having a low or moderate risk of bias if the study met key CONSORT criteria and did not present with other critical confounding factors. No studies met 100% of the criteria; thus, the in-depth critical appraisal and results from all eligible studies are described below.

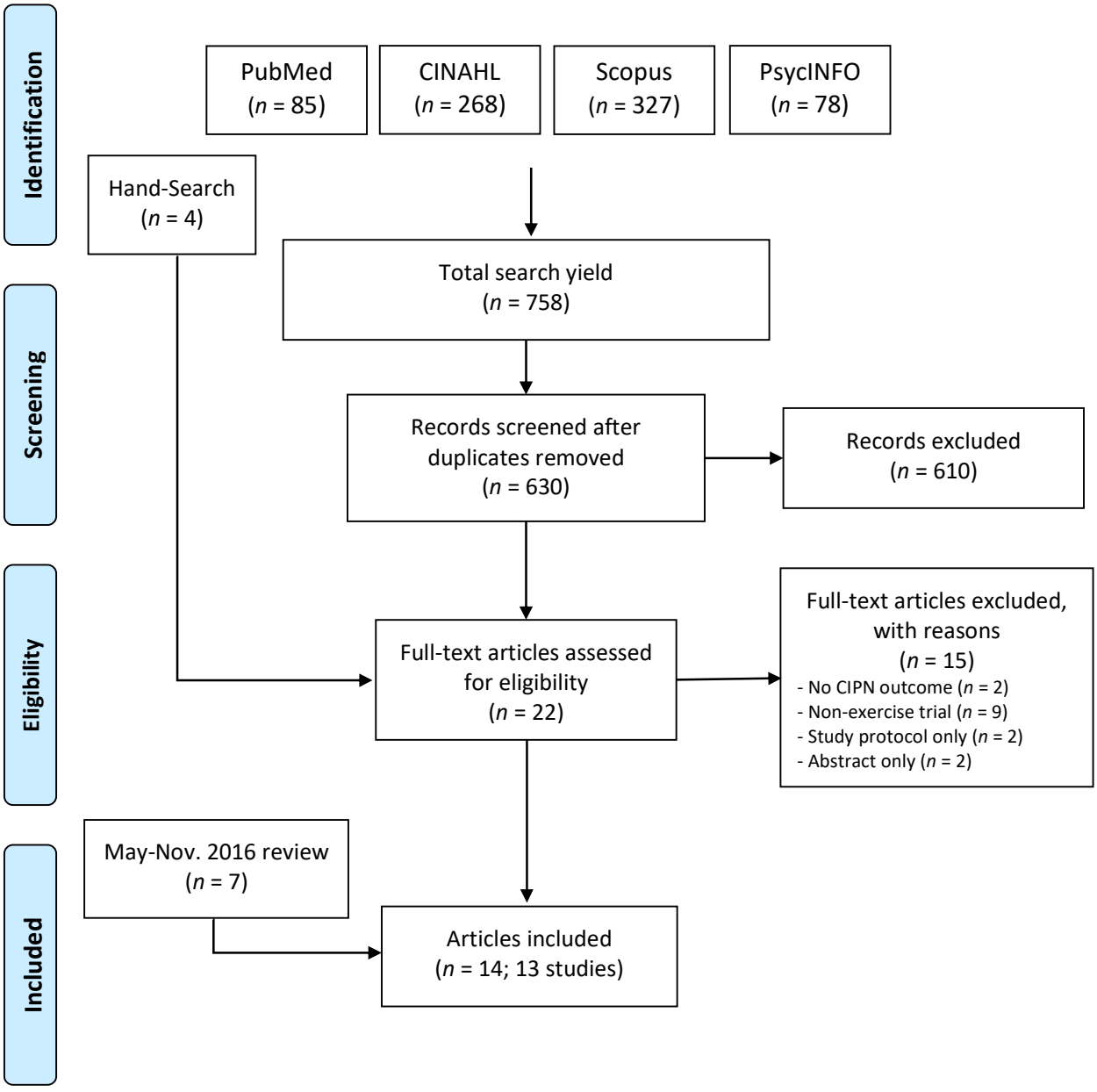
Results

Figure II.1 is a flowchart of the literature search. The search yielded 758 results from the databases and 4 from hand-searching. Studies were mostly excluded because they did not evaluate a CIPN outcome or did not test an active exercise intervention. Ultimately, 13 studies (7 RCTs (Dhawan et al. 2019; Henke et al. 2014; Kleckner et al. 2018; Streckmann et al. 2018; Streckmann, Kneis, et al. 2014; Vollmers et al. 2018; Zimmer et al. 2018) and 6 QE studies (Clark, Cortese-Jimenez, and Cohen 2012; Courneya et al. 2013; Courneya, McKenzie, et al.

2014; Fernandes and Kumar 2016; McCrary et al. 2019; Mizrahi et al. 2015; Wonders 2014)) remained and are summarized in Table II.1.

Figure II.1

Flow Chart of the Literature Search



Abbreviations: CIPN, peripheral neuropathy

Table II.1

Exercise Trials for Chemotherapy-Induced Peripheral Neuropathy Published 2006-2019

Author & Year	Exercise Type	Design & Sample	Intervention[b]	Outcomes & Significant Results
Courneya (2013; 2014)	**Aerobic** vs **Combined**	3-arm RT Taxanes[a] No baseline CIPN (*N* = 301)	Intervention: 3 days/week; 16-32 weeks (duration of chemo); vigorous intensity; clinic 1. STAN – Standard Aerobic; 75-90 min/week (25-30 min/day); 55-75% VO_{2peak} 2. HIGH – High-Dose Aerobic; 150-180 min/week (50-60 min/day); 55-75% VO_{2peak} 3. COMB – Aerobic + Strength; 150-180 min/week (25-30 min/day aerobic at 55-75% VO_{2peak}; 8 strength tasks, 2 sets of 10-12 reps each, 60-75% 1RPM)	Measurement Timepoints: Baseline (chemo start); 1/3 & 2/3 mid-chemo; post-intervention (3-4 weeks post-chemo); and 6, 12, & 24 months post-chemo Pre-Post Test Results: CIPN (FACT-Taxane$^{v\ all\ groups}$), Pain (SF-36$^{\wedge\ HIGH;\ -\ STAN}$), Physical Function & QOL (SF-36$^{v\ all\ groups}$), Fitness (lower body$^{\wedge\ COMB}$, upper body$^{\wedge\ STAN\ \&\ COMB}$, $VO_{2peak}{}^{v\ all\ groups}$), Other Sx (FACT$^{v\ all\ groups}$) Key Inter-Group Results: HIGH beneficial for pain and better at blunting the worsening in VO_{2peak} compared to COMB. COMB-induced strength improvements significantly > STAN & HIGH.
Fernandes (2016)	**Balance**	P-QE Chemo type NR Established CIPN (*N* = 25)	Intervention: 3 weeks in clinic Balance - 60 min/week (7 tasks; 2-3 sets of 10 reps → 12 min/day; 5 days/week);	Measurement Timepoints: Baseline & 3 weeks Results: CIPN (mTNS©^), Balance (BBS^)
Streckmann (2018)	**Balance**	4-arm RCT Mixed chemo types Established CIPN (*N* = 40)	Intervention: 6 weeks in clinic Balance - 23 min/week (4 tasks; 3 sets of 20 s → 11-12 min/day; 2 days/week) Comparison: Whole Body Vibration Control 1: No intervention; patients with CIPN Control 2: No intervention; healthy age/gender-matched	Measurement Timepoints: Baseline & 6 weeks Results: CIPN (tendon reflexes^, vibration sensitivity^, light touch perception$^{n\ d}$, proprioception$^{n\ d}$, LE strength$^{n\ d}$, FACT/GOG-NTX$^{n\ d}$, NCS$^{n\ d}$)
Henke (2014)	**Combined** (Aerobic + Strength)	RCT Platinums[a] Mild-no baseline CIPN (*N* = 29)	Intervention: Over 3 chemo cycles (9-12 weeks) in clinic Aerobic - 40 min/week (8 min/day, 5 days/week); moderate intensity (55-70% $HR_{reserve}$) Strength – 4 tasks; 3 sets of 10 reps; 50% $reps_{max}$ Control: Conventional Physiotherapy	Measurement Timepoints: Baseline & post-intervention (after 3 cycles of chemo) Results: CIPN & Pain (QLQ-C30/LC-13 PN item^), Physical Function (Barthel Index^) & QOL (QLQ-C30/LC-13$^{n\ d}$), Fitness (6MWT^, stair walking^, Modified Borg Scale^, and muscle strength^)

Kleckner (2018)	**Combined** (Aerobic + Strength)	RCT No baseline CIPN (*N* = 355)	Intervention: 6 weeks at home Aerobic – Increase mean daily step count 5-20% each week Strength – 10-14 tasks; max 4 sets of 15 reps; RPE 3-5 (3 progressive resistance elastic bands provided) Control: No exercise	Measurement Timepoints: Baseline (pre-chemo) & 6 weeks Results: CIPN (0-10 NRS^)
Wonders (2014)	**Combined** (Aerobic + Strength)	P-QE Taxane or vinorelbine[a] Baseline CIPN present (*N* = 38)	Intervention: 12 weeks in clinic; 2 days/week Aerobic – 50 min/week (20-30 min/day); moderate intensity (40-60% VO_{2max}) Strength 2-3 sets of 10-12 reps	Measurement Timepoints: Baseline & 12 weeks Results: CIPN (Leeds Assessment of Neuropathic Symptoms and Signs^), Physical Function (flexibility[n d]), QOL (McGill QOL^), Fitness (VO2max^, Parital Curl-Up Test^, Handgrip Dynamometer[n d])
Dhawan (2019)	**Combined** (Strength + Balance)	RCT Paclitaxel/carboplatin[a] Baseline CIPN present (*N* = 46)	Intervention: 10 weeks at home; 7 days/week Strength – 8 tasks (20 min lying and sitting tasks); light intensity (body weight only) Balance – 4 tasks (10 min) Control: Usual Care	Measurement Timepoints: Baseline & 10 weeks Results: CIPN (CIPNAT^, NCS[NR]), Pain (Leeds Assessment of Neuropathic Symptoms and Signs^), QOL (QLQ-C30^)
Vollmers (2018)	**Combined** (Strength + Balance)	RCT Paclitaxel[a] Unclear baseline CIPN presence (*N* = 36)	Intervention: Duration and through 6 weeks post completion of chemo in clinic; 2 days/week Strength – 6 tasks (2 sets of 20 reps); moderate intensity (RPE 13-15) Balance – no dose specified Control: Pamphlet about physical activity & cancer	Measurement Timepoints: Baseline (pre-chemo) & post-intervention (6 weeks post-chemo completion) Results: CIPN (EORTC QLQ CIPN20[n d]), QOL (QLQ-C30[n d], EORTC-BR23[n d]), Balance (Posturometry sway area^, Fullerton Advanced Balance Scale PRO^), Fitness (Hand dynamometer^, Chair Rising Test[n d])
McCrary (2019)	**Combined** (Aerobic + Strength + Balance)	P-QE Mixed chemo types Established CIPN (*N* = 29)	Intervention: 8 weeks in home & clinic; 3 days/week Aerobic - 60 min/week (20 min/day); moderate intensity (RPE 13-15) Strength – 4 tasks (2 sets/task → 20 min/day) Balance – 4 tasks (2 sets of 15-30s or 8 reps/task → 20 min/day)	Measurement Timepoints: Baseline (pre-control period), pre-intervention (8 weeks), & post-intervention (16 weeks) Results: CIPN (TNSc^, EORTC QLQ CIPN20^, NCS[n d]), Physical Function (6MWT^, CIPN-R-ODS^), QOL (SF-36^), Balance (Swaymeter^), Fitness (5-time sit-to-stand^)

Mizrahi (2015)[a]	**Combined** (Aerobic + Strength + Balance)	P-QE Paclitaxel/carboplatin[a] Baseline CIPN present (*N* = 21)	Intervention: 12 weeks at home; 3-4 days/week; 90 min/week (10-30 min/day) Aerobic – light-moderate intensity (55-70% HR_{max}) Strength – 3 sets of 10 reps; light-moderate intensity (RPE 11-14) Balance – For those with severe CIPN or balance issues only	Measurement Timepoints: Baseline, 12 weeks (post-intervention), & 24 weeks Results: CIPN (FACT/GOG-NTX[n d]); Physical Function (30 s sit-to-stand test^, SF-36^), QOL (FACT-O^); Balance (Single-leg balance test^); Fitness (10 rep max test^, submaximal aerobic capacity test[n d]); Physical Activity Behavior (IPAQ^); Fatigue (SPHERE^); Other measures (PSQI^, anthropometric measures[n d])
Streckmann (2014)	**Combined** (Aerobic + Strength + Balance)	RCT Mixed chemo types[a] Unclear baseline CIPN presence (*N* = 61)	Intervention: 36 weeks in clinic; 2 days/week Aerobic – 20-60 min/week (10-30 min/day); vigorous intensity (60-80% HR_{max}) Strength – 4 tasks (5 min/day); vigorous intensity (max force for 1 minute) Balance – 4 tasks (3 sets of 20 s → 10 min/day)	Measurement Timepoints: Baseline (pre-chemo); 12, 24, & 36 weeks Results: CIPN (Vibration sensitivity^), Pain (QLQ-C30 pain item[n d]), QOL (QLQ-C30[n d]), Balance (force plate^), Fitness (Incremental Step Test^, lactic threshold^)
Zimmer (2018)	**Combined** (Aerobic + Strength + Balance)	RCT Oxaliplatin[a] Baseline CIPN present (*N* = 30)	Intervention: 8 weeks in clinic; 2 days/week Aerobic – 20 min/week (10 min/day); moderate intensity (60-70% HRmax) Strength – 5 tasks (2 sets of 8-12 reps → 20 min/day); moderate intensity (60-80% 1RM) Balance – 4 tasks (15 min/day) Control: Waitlist	Measurement Timepoints: Baseline, post-intervention (8 weeks), & 12 weeks Results: CIPN (FACT/GOG-TOI^, NTX^); Balance (Gleichgewichtstest^); Strength (hypothetical 1RM^); Endurance (6MWT[n d])
Clark (2012)	**Yoga**	4-arm RT Platinums Established CIPN (*N* = 26)	Intervention: 6 weeks in clinic; group-based Yoga - 60 min/week (60 min/day, 1 day/week); low intensity Comparison: Reiki or meditation Control: Education	Measurement Timepoints: Baseline & 6 weeks Results: CIPN (FACT/GOG-Ntx[n d]), QOL (FACT/GOG-Ntx[n d], BSI[n d], Mindful Attention Awareness Scale[n d])

Abbreviations. ^, significant result in favor of the intervention; [v], significant result in opposition of the intervention; [n d], no difference in the outcome; 6MWT, Six Minute Walk Test; 1RM, one repetition max; BBS, Berg Balance Scale; BR23, Breast Cancer Module; BSI, Brief Symptom Inventory; CIPN, chemotherapy-induced peripheral neuropathy; CIPN20, chemotherapy-induced peripheral neuropathy module; CIPNAT, CIPN Assessment Tool; CIPN-R-ODS, CIPN Rasch Built Overall Disability Score; EORTC, European Organisation for Research and Treatment of Cancer; FACT, Functional Assessment of Cancer Therapies; FACT-O, FACT Ovarian Cancer module; GOG-Ntx, Gynecologic Oncology Group Neurotoxicity Scale; IPAQ, International Physical Activity Questionnaire; LC-13, lung cancer module; LE, lower-extremity; max, maximum; MFI, Multidimensional Fatigue Inventory; mTNS©, Modified Total Neuropathy Score; NCS, nerve conduction studies; NR, not reported; NRS, Numerical Rating Scale 0-10; PSQI, Pittsburgh Sleep Quality Index, PN, peripheral neuropathy; rep, repetitions; PRO, patient-reported outcome; QE, quasi-experiment; QLQ-C30, Quality of Life survey; QOL, quality of life; RCT, randomized controlled trial; RPE, rating of perceived exertion; RT, randomized trial; SF-36, Medical Outcome Study Short Form 36; SPHERE, Somatic and Psychological Health Report questionnaire; Sx, symptoms; TNSc, Total Neuropathy Score-Clinical; TOI, Trial of Outcome Index.

[a]Active treatment. Unless otherwise specified, the interventions were conducted individually (i.e., not in groups).

Table II.2 presents the critical appraisal results of the studies' risks of scientific bias. CIPN was the primary outcome in five studies (Dhawan et al. 2019; McCrary et al. 2019; Streckmann et al. 2018; Wonders 2014; Zimmer et al. 2018). All but 2 studies (McCrary et al. 2019; Streckmann et al. 2018) had a high risk of bias. The first study rated to have a moderate risk of bias by McCrary et al. (2019) tested an aerobic+strength+balance training intervention. The second "moderate-risk" study by Streckmann et al. (2018) tested a sensorimotor (balance) training intervention. The strengths of these "moderate-risk" studies included employment of both clinical and patient-reported outcome (PRO) measures to assess CIPN as the primary outcome and enrollment of individuals who had established clinically- and patient report-confirmed chronic CIPN. Despite small sample sizes ($N = 40$ split into 4 groups (Streckmann et al. 2018), and $N = 29$ (McCrary et al. 2019)), both studies found significant CIPN benefits.

However, both the McCrary et al. (2019) and Streckmann et al. (2018) studies had significant limitations. The McCrary et al. QE study lacked report of the qualification and blinding of the individual who performed the clinical CIPN assessments (McCrary et al. 2019). The Streckmann et al. study lacked report of inter-rater reliability for the CIPN clinical assessments (Streckmann et al. 2018). Instead of using a validated measure like the Total Neuropathy Score (TNS©) (Guido Cavaletti et al. 2006; Chaudhry et al. 1994; Cornblath et al. 1999), clinical signs of CIPN (e.g., tendon reflexes) were evaluated separately without clear use of an established, reproducible, grading rubric (Streckmann et al. 2018). Finally, their PRO neuropathic pain (PainDETECT) data is likely unreliable due to missing data (likely from individuals who had no pain per the authors) (Streckmann et al. 2018).

Table II.2

Risk of Scientific Bias of the Studies

Author & Year	Met Criteria (+)											Bias Risk
	CIPN Primary Outcome[a]	RCT[b]	Concealed Allocation[b]	Power ≥ 80%	Appropriate Sample[b,c]	Similar Groups[b]	Blinded[b,d]	Valid Measures[b]	Attrition ≤ 20%	ITT	No COIs	
McCrary (2019)	+	--	N/A	+	+	N/A	?	+	+	--	+	Mod
Streckmann (2018)	+	+	+	--	+	+	+	+	+	+	+	Mod
Zimmer (2018)	+	+	+	+	+	+	--	+	+	+	+	High[e]
Dhawan (2019)	+	+	+	+	+	--	?	--	+	+	+	High
Wonders (2014)	+	--	N/A	?	+	N/A	--	--	+	--	?	High
Clark (2012)	--	+	+	--	+	+	?	+	+	+	+	High[e]
Courneya (2013; 2014)	--	+	+	+	--	+	--	--	+	+	+	High
Fernandes (2016)	--	--	N/A	--	+	N/A	--	+	?	?	--	High
Henke (2014)	--	+	+	--	--	--	?	--	--	--	+	High
Kleckner (2018)	--	+	+	+	+	+	--	--	+	?	+	High
Mizrahi (2015)	--	--	N/A	--	--	N/A	--	+	--	--	+	High
Streckmann (2014)	--	+	+	--	--	+	+	+	+	+	+	High
Vollmers (2018)	--	+	+	?	+	--	?	+	+	--	+	High

Abbreviations. +, criteria met; --, criteria not met; ?, unclear whether the criteria was met; CIPN, chemotherapy-induced peripheral neuropathy; COI, conflict of interest; ITT, intention-to-treat analysis; Mod, moderate; PRO, patient-reported outcome; RCT, randomized controlled trial.

[a]The study had to meet this criteria to be categorized "low" risk of bias;

[b]The study had to meet this criteria to be categorized "mod" risk of bias.

[c]All participants had and/or were at risk for developing CIPN; patients with other types of peripheral neuropathy and/or who were receiving other neurotoxic drugs were excluded; and no potential critical selection bias (e.g., enrollment rate ≥50%; all accessible eligible patients were offered the chance to participate (e.g., no physician referrals of just the "pleasant" or "compliant" patients); no significant differences between participants who enrolled and did not enroll in, or were analyzed vs. withdrew from the study).

[d]Studies needed to report assessor blinding to be considered moderate; and assessor and interventionist blinding to be considered low risk of bias. Lack of assessor blinding was disregarded if the CIPN outcome was a PRO.

[e]Study considered to have a higher risk of bias, due to additional critical confounding factors in the study.

Most other studies lacked assessor blinding (Clark, Cortese-Jimenez, and Cohen 2012; Courneya et al. 2013; Courneya, McKenzie, et al. 2014; Dhawan et al. 2019; Fernandes and Kumar 2016; Henke et al. 2014; Kleckner et al. 2018; McCrary et al. 2019; Mizrahi et al. 2015; Vollmers et al. 2018; Wonders 2014; Zimmer et al. 2018) and sufficient power (Clark, Cortese-Jimenez, and Cohen 2012; Fernandes and Kumar 2016; Henke et al. 2014; Mizrahi et al. 2015; Streckmann et al. 2018; Streckmann, Kneis, et al. 2014; Vollmers et al. 2018; Wonders 2014). Few studies utilized either a strong PRO (Clark, Cortese-Jimenez, and Cohen 2012; Vollmers et al. 2018; Zimmer et al. 2018) or clinical assessment (Fernandes and Kumar 2016) CIPN measure; even fewer used both a strong PRO and clinical assessment CIPN measure (Dhawan et al. 2019; McCrary et al. 2019; Streckmann et al. 2018). No studies of CIPN as a secondary/exploratory outcome reported error rate adjustment to avoid the risk of statistical fishing bias (Clark, Cortese-Jimenez, and Cohen 2012; Courneya et al. 2013; Courneya, McKenzie, et al. 2014; Fernandes and Kumar 2016; Henke et al. 2014; Kleckner et al. 2018; Mizrahi et al. 2015; Streckmann, Kneis, et al. 2014; Vollmers et al. 2018). All 13 studies lacked control for potential confounding factors, including peripheral neuropathy-related comorbidities (e.g., diabetes, peripheral arterial disease, and vitamin B deficiency); heterogeneity of the sample in CIPN presence, severity, and stability at baseline; chemotherapy status, regimen, and duration; and other psychological mediators/moderators (e.g., mood). Further, all the studies lacked report of or control for the participants' intervention adherence and/or outside exercise/physical activity.

Sample Characteristics

The study sample sizes referenced above ranged from 21 to 355 participants. Average participant age was 55.6 (*range* = 18- 81) years (n = 12); BMI, 25.62 kg/m2 (n = 7); and percent male, 27% (n = 12). All studies were conducted in adults, whose physical activity or fitness was

generally below average. Study participants had stage I to IV (mostly breast) cancer; and had received (Clark, Cortese-Jimenez, and Cohen 2012; Fernandes and Kumar 2016; McCrary et al. 2019; Streckmann et al. 2018) or were actively receiving (Courneya et al. 2013; Dhawan et al. 2019; Henke et al. 2014; Kleckner et al. 2018; Mizrahi et al. 2015; Streckmann, Kneis, et al. 2014; Vollmers et al. 2018; Wonders 2014; Zimmer et al. 2018) primarily taxane- (Courneya et al. 2013; Courneya, McKenzie, et al. 2014; Dhawan et al. 2019; Vollmers et al. 2018; Wonders 2014) or platinum-based (Clark, Cortese-Jimenez, and Cohen 2012; Henke et al. 2014; Zimmer et al. 2018), or mixed types of chemotherapy (Kleckner et al. 2018; McCrary et al. 2019; Mizrahi et al. 2015; Streckmann et al. 2018; Streckmann, Kneis, et al. 2014). Few studies focused on one type of cancer and chemotherapy (Courneya et al. 2013; Courneya, McKenzie, et al. 2014; Henke et al. 2014; Mizrahi et al. 2015; Streckmann, Kneis, et al. 2014; Vollmers et al. 2018; Zimmer et al. 2018). Baseline CIPN was chronic and moderate-severe (n = 4) (Clark, Cortese-Jimenez, and Cohen 2012; Fernandes and Kumar 2016; McCrary et al. 2019; Streckmann et al. 2018), absent/mild (n = 3) (Courneya et al. 2013; Courneya, McKenzie, et al. 2014; Kleckner et al. 2018; Vollmers et al. 2018), or mixed/acute/unclearly specified (n = 5) (Dhawan et al. 2019; Henke et al. 2014; Mizrahi et al. 2015; Streckmann, Kneis, et al. 2014; Wonders 2014; Zimmer et al. 2018).

Exercise Interventions

Six different types of exercise were tested in the 13 studies: yoga (Clark, Cortese-Jimenez, and Cohen 2012), and exercise with aerobic (n = 7) (Courneya et al. 2013; Courneya, McKenzie, et al. 2014; Henke et al. 2014; Kleckner et al. 2018; McCrary et al. 2019; Mizrahi et al. 2015; Streckmann, Kneis, et al. 2014; Wonders 2014; Zimmer et al. 2018), strength (n = 9) (Courneya et al. 2013; Courneya, McKenzie, et al. 2014; Dhawan et al. 2019; Henke et al. 2014;

Kleckner et al. 2018; McCrary et al. 2019; Mizrahi et al. 2015; Streckmann, Kneis, et al. 2014; Vollmers et al. 2018; Wonders 2014; Zimmer et al. 2018), and balance (n = 7) training components (Dhawan et al. 2019; Fernandes and Kumar 2016; McCrary et al. 2019; Mizrahi et al. 2015; Streckmann et al. 2018; Streckmann, Kneis, et al. 2014; Vollmers et al. 2018; Zimmer et al. 2018). The interventions in all but three—one yoga (Clark, Cortese-Jimenez, and Cohen 2012), and two balance training alone (Fernandes and Kumar 2016; Streckmann et al. 2018)—studies were multimodal: varied combinations of aerobic, strength, and balance training. Aerobic+strength (Courneya et al. 2013; Courneya, McKenzie, et al. 2014; Henke et al. 2014; Kleckner et al. 2018; Wonders 2014), and aerobic+strength+balance (McCrary et al. 2019; Mizrahi et al. 2015; Streckmann, Kneis, et al. 2014; Zimmer et al. 2018) exercises were the most common interventions.

Dosages. The mean exercise prescription characteristics included 107.61 (23-210) minutes per week, over 3.42 (1-7) days per week, for a duration of 11.68 (3-36) weeks. Seven interventions encouraged moderate- to vigorous-intensity (50%-80% heart rate maximum/reserve, 40%-75% VO_{2peak}, or Borg rating of perceived exertion [RPE] of 13-15) exercise (Courneya et al. 2013; Courneya, McKenzie, et al. 2014; Henke et al. 2014; McCrary et al. 2019; Streckmann, Kneis, et al. 2014; Vollmers et al. 2018; Wonders 2014; Zimmer et al. 2018).

The most common aerobic exercise dosages prescribed were 20 to 30 minutes per session of moderate- to vigorous-intensity physical activity, two to five days per week. The total prescribed weekly doses (20-165 min per week) and durations (6-36 weeks) of the aerobic interventions varied. The strength training dosages ranged from 4 strength training tasks (3 sets of 10 repetitions per task) (Henke et al. 2014) to 14 tasks (4 sets of 15 repetitions per task)

(Kleckner et al. 2018) performed at light to moderate-intensity two to seven days per week (Courneya et al. 2013; Courneya, McKenzie, et al. 2014; Dhawan et al. 2019; Henke et al. 2014; Kleckner et al. 2018; McCrary et al. 2019; Streckmann, Kneis, et al. 2014; Vollmers et al. 2018; Wonders 2014; Zimmer et al. 2018). Balance training sessions were most commonly 10 to 12 minutes in duration (Dhawan et al. 2019; Fernandes and Kumar 2016; Streckmann et al. 2018; Streckmann, Kneis, et al. 2014) and involved four (Dhawan et al. 2019; McCrary et al. 2019; Streckmann et al. 2018; Streckmann, Kneis, et al. 2014; Zimmer et al. 2018), 15- to 30-second (McCrary et al. 2019; Streckmann et al. 2018; Streckmann, Kneis, et al. 2014) balance training tasks repeated two to three times each (Fernandes and Kumar 2016; McCrary et al. 2019; Streckmann et al. 2018; Streckmann, Kneis, et al. 2014; Zimmer et al. 2018).

Delivery setting. All but four studies (Dhawan et al. 2019; Kleckner et al. 2018; McCrary et al. 2019; Mizrahi et al. 2015) were conducted in a clinical setting. One intervention was delivered by group (Clark, Cortese-Jimenez, and Cohen 2012).

Control Conditions

The most common control conditions were no exercise/usual care (Dhawan et al. 2019; Henke et al. 2014; Kleckner et al. 2018; Streckmann et al. 2018; Streckmann, Kneis, et al. 2014) or health education (Clark, Cortese-Jimenez, and Cohen 2012; Vollmers et al. 2018). One four-arm study evaluated a balance training intervention compared to whole body vibration, no intervention, and age- and gender-matched healthy controls (Streckmann et al. 2018); and another four-arm study evaluated yoga compared to reiki, meditation, or health education (Clark, Cortese-Jimenez, and Cohen 2012). One three-arm study evaluated three exercise interventions alone (Courneya et al. 2013; Courneya, McKenzie, et al. 2014).

Outcome Measures and Results

Table II.3 contains a list of the most common outcome variables evaluated, the *n* that evaluated that outcome, and the percentage of studies that showed outcome improvement. Balance, fitness, and CIPN outcomes improved most consistently. Given the dichotomous quantification (improvement or no improvement) in the tables, two pre-posttest QE studies of individuals in active neurotoxic chemotherapy treatment without baseline CIPN were excluded, because the participants had no room for improvement (Courneya et al. 2013; Mizrahi et al. 2015).

Table II.3

Outcomes Measured and Frequency of Positive Effects in the Studies

Outcome Variable	All Studies (N=11)[a]	
	Frequency (*n*)	Positive Effects[b] (*n* [%])
CIPN	11	9 (82)
Pain	4	2 (50)
Balance	6	6 (100)
PF	3	2 (67)
QOL	8	4 (50)
Fitness	6	6 (100)
Other symptoms[c]	3	2 (67)

Abbreviations. CIPN, chemotherapy-induced peripheral neuropathy; PF, physical function; QOL, quality of life.
[a]The results from two pre-posttest quasi-experiments in individuals actively receiving neurotoxic chemotherapy could not be interpreted dichotomously, and thus, excluded from this table.[40,44,45]
[b]A study was considered to have demonstrated positive effects if the intervention was statistically significantly ($p \leq .05$) beneficial for the outcome pre-posttest or between groups.
[c]Other symptom outcomes included fatigue, cognitive impairment, endocrine symptoms, and hemoptysis.

CIPN outcomes. Table II.4 lists the n and percentage of studies that demonstrated statistically significant ($p < .05$) outcome improvement by sample characteristic. Five (83%) studies demonstrated clinically significant (≥ 30%) intervention group-favoring *intergroup* differences in PRO-surveyed (Dhawan et al. 2019; Henke et al. 2014; Kleckner et al. 2018; Zimmer et al. 2018) and clinically assessed CIPN (Streckmann, Kneis, et al. 2014) among patients with (Dhawan et al. 2019; Streckmann, Kneis, et al. 2014) and without baseline CIPN

(Henke et al. 2014; Kleckner et al. 2018; Zimmer et al. 2018). Clinically significant pre-post-intervention CIPN improvements were also demonstrated, using clinical assessments (Fernandes and Kumar 2016; Streckmann et al. 2018) and PRO surveys (Dhawan et al. 2019; Streckmann et al. 2018) in patients with baseline CIPN (Dhawan et al. 2019; Fernandes and Kumar 2016; Streckmann et al. 2018). Although not clinically significant, two studies showed moderate statistically significant improvements in CIPN, measured by the TNS©-Clinical version (24.29% improvement; $p = .001$) (McCrary et al. 2019), European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) CIPN20 module (27.17% improvement; $p < .001$) (McCrary et al. 2019), and Leeds assessment of neuropathic symptoms and signs (no effect size reported) (Wonders 2014). Nerve conduction studies—often considered a diagnostic tool for peripheral neuropathy—did not detect significant effects, even though clinical assessment and PRO surveys of CIPN did (Dhawan et al. 2019; McCrary et al. 2019; Streckmann et al. 2018). One study among individuals with baseline chronic CIPN, showed that clinically assessed CIPN values recovered to a level that matched healthy age- and gender-matched controls after the intervention (Streckmann et al. 2018).

Table II.4

Synthesis of Outcomes by Sample Characteristic (n = 11)[a]

Population	*n* Studies	Positive Effects						Adherence Rate	Completion Rate
		CIPN	Pain	PF	QOL	Balance	Fitness		
Chemotherapy Type		(n_+ [%])[b]	(n_+/n_{mo} [%])[b]					*Mean (*n*)*	
Taxane-primary[c]	3	2 (67)	1/1 (100)	0/1	2/3 (67)	1/1 (100)	2/2 (100)	67.5 (*n*=1)	89.4 (*n*=3)
Platinums	3	2 (67)	1/1 (100)	1/1 (100)	0/2	1/1 (100)	2/2 (100)	88.3 (*n*=1)	71.7 (*n*=3)
Mixed or Not Reported	5	5 (100)	0/2	1/1 (100)	2/3 (67)	4/4 (100)	2/2 (100)	75 (*n*=3)	89 (*n*=4)
Chemotherapy Status									
Active	7	6 (86)	2/3 (67)	1/2 (50)	3/5 (60)	3/3 (100)	5/5 (100)	74.5 (*n*=4)	83.8 (*n*=7)
Completed	4	3 (75)	0/1	1/1 (100)	1/3 (33)	3/3 (100)	1/1 (100)	83.1 (*n*=1)	84.2 (*n*=3)
CIPN Status at Baseline									
Little-None	2	1 (50)	--	--	0/1	1/1 (100)	1/1 (100)	77 (*n*=1)	84.1 (*n*=2)
Some with acute CIPN	5	4 (100)	1/2 (50)	1/2 (50)	2/3 (67)	2/2 (100)	4/4 (100)	76.7 (*n*=2)	81.8 (*n*=4)
Established moderate-severe CIPN	4	3 (75)	0/1	1/1 (100)	1/3 (33)	3/3 (100)	1/1 (100)	83.1 (*n*=1)	84.2 (*n*=3)
Sample Sizes									
< 30	4	3 (75)	1/1 (100)	2/2 (100)	1/3 (33)	2/2 (100)	2/2 (100)	83.1 (*n*=1)	72.7 (*n*=3)
30-50	5	4 (80)	1/2 (50)	0/1	2/4 (50)	3/3 (100)	3/3 (100)	77.9 (*n*=2)	89.1 (*n*=5)
> 50	2	2 (100)	0/1	--	1/1 (100)	1/1 (100)	1/1 (100)	71 (*n*=2)	87.8 (*n*=2)

Abbreviations. --, no study measured the specified outcome; CIPN, chemotherapy-induced peripheral neuropathy; PA, physical activity; PF, physical function; QOL, quality of life.

[a]The results from two pre-posttest quasi-experiments in individuals actively receiving neurotoxic chemotherapy could not be interpreted dichotomously, and thus, excluded from this table.[40,44,45]

[b](n_+/n_{mo} [%]) = *n* positive studies over n studies that measured the specified outcome.

[c]Two of these studies evaluated patients received carboplatin or vinorelbine in addition to paclitaxel.

Among individuals actively receiving chemotherapy, those with acute baseline CIPN showed no progression (Mizrahi et al. 2015; Zimmer et al. 2018) or significant improvement of CIPN ($p < .05$) (Dhawan et al. 2019; Wonders 2014); but those with no baseline CIPN demonstrated significant development/worsening of CIPN over time (Courneya et al. 2013; Henke et al. 2014; Kleckner et al. 2018). Regardless of baseline CIPN status, intergroup outcomes were often better in the intervention than the control groups in individuals receiving chemotherapy (Dhawan et al. 2019; Henke et al. 2014; Kleckner et al. 2018; Streckmann, Kneis, et al. 2014; Zimmer et al. 2018).

Table II.5 lists the n and percentage of studies that demonstrated statistically significant outcome improvement by exercise intervention characteristic. Statistically significant CIPN benefits were found in all studies of home-based interventions (Dhawan et al. 2019; Kleckner et al. 2018; McCrary et al. 2019); and those with an aerobic exercise component (Henke et al. 2014; McCrary et al. 2019; Streckmann, Kneis, et al. 2014; Vollmers et al. 2018; Wonders 2014; Zimmer et al. 2018), dosages, ≥ 100 minutes per week of exercise (Dhawan et al. 2019; Kleckner et al. 2018; McCrary et al. 2019; Streckmann, Kneis, et al. 2014; Zimmer et al. 2018), and/or durations of eight to 12 weeks (Dhawan et al. 2019; Henke et al. 2014; McCrary et al. 2019; Wonders 2014; Zimmer et al. 2018). All interventions with only balance training led to large clinically significant improvements in established CIPN (Fernandes and Kumar 2016; Streckmann et al. 2018). However, some studies of clinic-based interventions (Fernandes and Kumar 2016; Henke et al. 2014; Streckmann et al. 2018; Streckmann, Kneis, et al. 2014; Wonders 2014; Zimmer et al. 2018); and those of doses less than 100 (as low as 22.66) minutes per week also demonstrated statistically significant CIPN benefits (Fernandes and Kumar 2016; Henke et al. 2014; Streckmann et al. 2018; Wonders 2014). Finally, balance training for as low as

three weeks (Fernandes and Kumar 2016) and aerobic+strength training for as low as six weeks in duration resulted in statistically significant CIPN benefits (Kleckner et al. 2018).

Focusing on the eight aerobic intervention studies, moderate-large intergroup (Henke et al. 2014; Kleckner et al. 2018; Streckmann, Kneis, et al. 2014; Zimmer et al. 2018) and small pre-posttest (McCrary et al. 2019; Zimmer et al. 2018) CIPN benefits—measured by PRO (Henke et al. 2014; Kleckner et al. 2018; McCrary et al. 2019; Wonders 2014; Zimmer et al. 2018) and clinical assessments (McCrary et al. 2019; Streckmann, Kneis, et al. 2014)—were demonstrated among patients mostly in active treatment with various neurotoxic chemotherapy types (Henke et al. 2014; Kleckner et al. 2018; Streckmann, Kneis, et al. 2014; Wonders 2014; Zimmer et al. 2018). The interventions that led to large intervention-favoring CIPN benefits (40%-141% difference between groups) all were of moderate-vigorous intensity (55%-70% of heart rate reserve or 60%-80% of heart rate maximum). The one home, step-count prescription-based intervention led to moderate intervention-favoring CIPN benefits (34% difference) between groups (Kleckner et al. 2018). Various doses (20-60 minutes per week; 8-30 minutes per day), frequencies (2-5 days per week), and durations (6-36 weeks) of aerobic exercise led to moderate-large clinically significant benefits. No studies tested (in comparison to a control condition) an aerobic exercise dose greater than 60 minutes per week. Of note, one study that had no control condition found no differences in FACT-Taxane-measured CIPN outcomes between prescriptions of 25 to 30 minutes and 50 to 60 minutes per day of vigorous-intensity aerobic exercise three days per week throughout chemotherapy (over 16-32 weeks) (Courneya et al. 2013; Courneya, McKenzie, et al. 2014).

Table II.5

Synthesis of the Outcomes by Exercise Intervention Characteristic (n = 11)[a]

Exercise	n Papers	Positive Effects						Adherence Rate	Completion Rate
		CIPN	Pain	PF	QOL	Balance	Fitness		
Type[c]		(n_+ [%])[b]	(n_+/n_{mo} [%])[b]					*Mean (n)*	
Aerobic Component	6	6 (100)	1/2 (50)	2/3 (67)	3/4 (75)	3/3 (100)	5/5 (100)	78.8 (*n*=3)	84.49 (*n*=5)
Strength Component	8	7 (88)	2/3 (67)	2/3 (67)	4/6 (67)	4/4 (100)	6/6 (100)	76 (*n*=4)	83.6 (*n*=7)
Balance Component	7	6 (86)	1/3 (33)	1/1 (100)	3/5 (20)	6/6 (100)	4/4 (100)	80.3 (*n*=5)	87.7 (*n*=6)
Yoga	1	0	--	--	0/1	--	--	--	72 (*n*=1)
Balance Alone	2	2 (100)	0/1	--	0/1	2/2 (100)	--	--	97.5 (*n*=1)
Aerobic+Strength	3	3 (100)	1/1 (100)	1/2 (50)	1/2 (50)	--	2/2 (100)	--	78.2 (*n*=2)
Strength+Balance	2	1 (50)	1/1 (100)	--	1/2 (50)	1/1 (100)	1/1 (100)	67.5 (*n*=1)	87.4 (*n*=2)
Aerobic+Strength+Balance	3	3 (100)	0/1	1/1 (100)	2/2 (100)	3/3 (100)	3/3 (100)	78.8 (*n*=3)	84.6 (*n*=3)
Duration[d]									
< 8 weeks	4	3/4 (75)	0/1	--	0/2	2/2 (100)	--	--	84.9 (*n*=2)
8-12 weeks	5	5 (100)	2/2 (100)	2/3 (67)	3/4 (75)	2/2 (100)	4/4 (100)	79.6 (*n*=3)	82.1 (*n*=5)
> 12 weeks	2	1/2 (50)	0/1	--	1/2 (50)	2/2 (100)	2/2 (100)	65 (*n*=1)	87.4 (*n*=2)
Per Week Dose (min/week)									
< 100 min/week	5	4 (80)	1/2 (50)	1/2 (75)	1/4 (25)	2/2 (100)	2/2 (100)	--	81.5 (*n*=4)
100-120 min/week	2	2 (100)	0/1	--	1/1 (100)	2/2 (100)	2/2 (100)	76.7 (*n*=2)	85.5 (*n*=2)
> 120 min/week	3	3 (100)	1/1 (100)	1/1 (100)	2/2 (100)	1/1 (100)	1/1 (100)	75.9 (*n*=3)	86.2 (*n*=3)
Not Reported	1	0	--	--	0/1	1/1 (100)	1/1 (100)	--	83.7 (*n*=1)
Frequency									
1-2 days/week	6	4 (67)	0/2	0/1	2/5 (40)	4/4 (100)	4/4 (100)	76.7 (*n*=2)	86.3 (*n*=6)
≥ 3 days/week	5	5 (100)	2/2 (100)	2/2 (100)	2/3 (67)	2/2 (100)	2/2 (100)	75.9 (*n*=3)	80.4 (*n*=4)
Intensity									
Light	5	4 (80)	1/2 (50)	--	1/3 (33)	2/2 (100)	--	72.3 (*n*=2)	86.3 (*n*=4)
Moderate-Vigorous	6	5 (83)	1/2 (50)	2/3 (67)	3/5 (60)	4/4 (100)	6/6 (100)	78.8 (*n*=3)	82.3 (*n*=6)
Setting									
Home	2	2 (100)	1/1 (100)	--	1/1 (100)	--	--	72.3 (*n*=2)	87.8 (*n*=2)
Clinic	7	6 (86)	1/3 (33)	1/2 (50)	2/6 (33)	5/5 (100)	5/5 (100)	76.7 (*n*=2)	84.8 (*n*=6)
Both Home/Clinic	1	1 (100)	--	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	83.1 (*n*=1)	82.9 (*n*=1)

Abbreviations. --, no study measured the specified outcome; CIPN, chemotherapy-induced peripheral neuropathy; PF, physical function.

[a]The results from two pre-posttest quasi-experiments in individuals actively receiving neurotoxic chemotherapy could not be interpreted dichotomously, and thus, excluded from this table.[40,44,45]

[b]n_+/n_{mo} [*%*]) = *n* positive studies over *n* studies that measured the specified outcome.

[c]One 3-arm study tested and therefore is counted as both an aerobic alone and strength alone intervention study.

[d]Some intervention durations varied based on the chemotherapy regimen; these studies are accounted for in the duration category that best fits the sample studied.

Finally, the two studies with a moderate risk of bias showed small-moderate (19%-35%) statistically significant pre-post-posttest benefits. Specifically, aerobic+strength+balance and solely balance training alleviated established moderate-severe clinical signs and symptoms of CIPN, measured by the TNSc© and CIPN20 (McCrary et al. 2019), and deep tendon reflexes and vibration sensibility (Streckmann et al. 2018). Specifically the QE study (N = 29) suggested that 8 weeks of individualized combined home- and clinic-based moderate-vigorous aerobic+strength+balance training (60 minutes per day, 3 days per week) may alleviate CIPN, and improve physical function, balance, and QOL in individuals with breast, colorectal, ovarian, and other cancers who have completed paclitaxel, oxaliplatin, or other types of neurotoxic chemotherapy treatment (McCrary et al. 2019). The 4-arm RCT (N = 40) showed that six weeks of clinic-based sensorimotor training (2 days per week; < 30 minutes per week) may effectively treat chronic CIPN in individuals one to five years post-taxane- platinum-, or vinca alkaloid-treatment; it may restore tendon reflexes and vibration sensibility to normal levels exhibited by age- and gender-matched healthy controls. Brief sensorimotor training may also improve balance and subjective CIPN; however, a higher dose may be required to induce significant benefit.

Other key outcomes. Balance and fitness improved significantly in all the studies, regardless of exercise type, dosage, or setting, but pain, physical function, and QOL improvement varied. Higher weekly doses (> 100 minutes) and frequencies (≥ 3 days) resulted in more consistent holistic outcome benefits.

Long-term outcomes. Two studies reported long-term follow-up one month (Zimmer et al. 2018) and 3 months (Mizrahi et al. 2015) post-intervention completion. Eight weeks of clinic-based moderate-vigorous aerobic+strength+balance training (60 minutes twice weekly) led to sustained improvements in subjective CIPN and objectively-measured balance and strength at

one-month follow-up in colorectal cancer survivors receiving oxaliplatin; the control group simultaneously exhibited declines in all the outcomes (Zimmer et al. 2018). The other study did not provide meaningful long-term follow-up results because it lacked intent-to-treat analysis and only had three-month follow-up data on 12 (40%) participants who complied with the intervention and had no medical complications (Mizrahi et al. 2015).

Adherence and completion rates. Eleven studies reported outcome assessment completion rates ranging from 70% (Mizrahi et al. 2015) to 99% (Courneya et al. 2013; Courneya, McKenzie, et al. 2014). Seven studies reported adherence rates (65% (Streckmann, Kneis, et al. 2014)-88.3% (Zimmer et al. 2018)), defined as the percent of intervention sessions attended or time completed (Courneya et al. 2013; Courneya, McKenzie, et al. 2014; McCrary et al. 2019; Zimmer et al. 2018); or percent of participants who met a specified exercise dose/criteria (Dhawan et al. 2019; Kleckner et al. 2018; Mizrahi et al. 2015; Streckmann, Kneis, et al. 2014). Participants adhered to 64 to 120 (*SD*s = 17-39) minutes per week of moderate-vigorous intensity aerobic exercise (65.2%-68.4% VO_{2peak}) in a clinic-supervised setting (Courneya et al. 2013; Courneya, McKenzie, et al. 2014) and 196 (*SD* = 138) minutes per week of aerobic+strength+balance exercise self-reported in a home-based setting (Mizrahi et al. 2015). Participants averaged 4,820 steps per day in another home-based aerobic+strength training study (Kleckner et al. 2018). These adherence levels were all obtained from patients in active chemotherapy treatment.

The studies with the lowest adherence rates were conducted in individuals actively receiving treatment (Dhawan et al. 2019; Kleckner et al. 2018; Mizrahi et al. 2015; Streckmann, Kneis, et al. 2014); two studies also had high standards for their definition of adherence: percent that averaged ≥120 (Streckmann, Kneis, et al. 2014) or 150 minutes per week of exercise

(Dhawan et al. 2019). The studies with the lowest completion rates evaluated low dosage/intensity interventions and small sample sizes (Clark, Cortese-Jimenez, and Cohen 2012; Henke et al. 2014; Mizrahi et al. 2015), lacked rigor (Clark, Cortese-Jimenez, and Cohen 2012; Mizrahi et al. 2015), and/or were conducted in stage III to IV cancer survivors receiving treatment (Henke et al. 2014; Mizrahi et al. 2015). The primary reasons reported by participants for study discontinuation included loss of interest/unknown reasons (20%-100%), medical complications (11%-100%), noncompliance (5%-59%), death (11%-35%), and time concerns (33%). One study reported that three (33%) of the patients who withdrew did so due to chemotherapy side effects (Mizrahi et al. 2015). No other patterns were found between the intervention characteristics and adherence or completion rates.

The studies with an adherence and completion rate ≥ 80% (Courneya et al. 2013; Courneya, McKenzie, et al. 2014; McCrary et al. 2019; Zimmer et al. 2018) tested clinic-based aerobic, balance, and multimodal training interventions performed two to three days per week. The intervention and sample characteristics were otherwise heterogenous in these studies.

Enrollment rates. On average, 53.16% (*range* = 33%-76.3%) of patients enrolled out of the 233 (*range* = 48-728) mean patients approached for the studies (Courneya et al. 2013; Courneya, McKenzie, et al. 2014; Dhawan et al. 2019; Kleckner et al. 2018; McCrary et al. 2019; Mizrahi et al. 2015; Streckmann, Kneis, et al. 2014; Vollmers et al. 2018). Recruitment occurred over a mean period of 28.89 (*range* = 6-84) months and most often in clinics or hospital settings (Courneya et al. 2013; Courneya, McKenzie, et al. 2014; Dhawan et al. 2019; Henke et al. 2014; Kleckner et al. 2018; McCrary et al. 2019; Mizrahi et al. 2015; Streckmann, Kneis, et al. 2014; Vollmers et al. 2018; Zimmer et al. 2018). The oncologists usually referred potentially eligible patients. All the studies with enrollment rates below 55% had attempted to

recruit patients pre- and/or shortly after chemotherapy initiation (Courneya et al. 2013; Courneya, McKenzie, et al. 2014; Kleckner et al. 2018; Streckmann, Kneis, et al. 2014; Vollmers et al. 2018). However, the 2 studies with the highest enrollment rates (63% (Mizrahi et al. 2015) and 76.3% (Dhawan et al. 2019)) recruited participants midway through chemotherapy treatment. The top reasons for declining participation (and the % of patients who cited the reason) included lack of interest or response (15%-100%), living too far away/transportation issues (11%-54%; highest in supervised intervention studies), time concerns (22%-28%), and medical complications (6%-28%). One study reported that 6.02% of patients refused participation due to chemotherapy side effects (Courneya et al. 2013; Courneya, McKenzie, et al. 2014).

Adverse effects. No exercise adverse effects were found (Courneya et al. 2013; Courneya, McKenzie, et al. 2014; Dhawan et al. 2019; Mizrahi et al. 2015; Streckmann et al. 2018; Streckmann, Kneis, et al. 2014; Zimmer et al. 2018). However, nearly half of the studies lacked report about adverse effects.

Discussion

This integrative review identified 13 clinical trials that reported the effects of an exercise or physical therapy intervention on CIPN and other key outcomes. The following key findings emerged:

- All the studies had a moderate-high risk of bias and were conducted in adults.
- CIPN, balance, and fitness improved consistently after the exercise interventions.
- All the aerobic exercise-containing interventions led to significant CIPN benefits; however, no studies have tested just aerobic exercise to reduce CIPN.

- Adherence, completion, and enrollment rates were the lowest among patients who were just starting chemotherapy treatment.
- The samples and intervention types, dosages, and delivery settings were otherwise highly heterogeneous.

These findings are consistent with prior systematic reviews of exercise interventions among patients with CIPN (Brayall et al. 2018; Duregon et al. 2018; Jung, Rein, and Fuchs 2018). The general consensus is that exercise may lead to improvements in balance, fitness, and CIPN among adults with and/or at risk for CIPN; however, the evidence is limited in abundance and quality. Further, the current studies have been too heterogeneous to identify the most effective exercise prescriptions to target CIPN (Brayall et al. 2018). One review highlighted the importance of balance training for reducing CIPN but ultimately proposed that moderate-intensity aerobic+strength+balance training (2-5 days per week; ≤ 60 minutes per session) for at least 36 weeks may be most beneficial for individuals receiving neurotoxic chemotherapy (Duregon et al. 2018).

This integrative review supports the value of combined aerobic+strength+balance training (≥ 100 minutes; ≥ 3 days per week) for individuals with CIPN (Dhawan et al. 2019; Kleckner et al. 2018; McCrary et al. 2019; Streckmann, Kneis, et al. 2014; Zimmer et al. 2018); however, this review found that interventions eight to 12 weeks in duration led to the most consistent (Dhawan et al. 2019; Henke et al. 2014; McCrary et al. 2019; Wonders 2014; Zimmer et al. 2018) and potentially sustainable CIPN benefits (Zimmer et al. 2018).

Further, this review's numerical evidence suggests that aerobic exercise is a key modality to reduce CIPN (Henke et al. 2014; Kleckner et al. 2018; McCrary et al. 2019; Streckmann, Kneis, et al. 2014; Wonders 2014; Zimmer et al. 2018), particularly during active neurotoxic

chemotherapy treatment (Henke et al. 2014; Kleckner et al. 2018; Streckmann, Kneis, et al. 2014; Wonders 2014; Zimmer et al. 2018). Various aerobic exercise doses (20-60 minutes per week; 8-30 minutes per day), frequencies (2-5 days per week), intensities (Borg RPE 11-15; 40%-80% VO_{2peak}, HR_{max}, or $HR_{reserve}$), and durations (6-36 weeks) were beneficial. However, no studies have tested the effects of aerobic exercise alone and/or in doses ≥ 60 minutes per week on CIPN, compared to control.

Overall, few studies have tested unimodal, national guideline prescription-compliant, and home- and group-based exercise interventions for CIPN. Sole aerobic exercise and balance training interventions appear most promising for CIPN, but no studies have evaluated their individual long-term effects on acute, chronic, and painful CIPN at various dosages. Finally, only three studies tested a home-based intervention—all of which showed improved CIPN outcomes (Dhawan et al. 2019; Kleckner et al. 2018; Mizrahi et al. 2015)—and one study tested a group-based intervention (yoga) (Clark, Cortese-Jimenez, and Cohen 2012).

Patterns between adherence, completion, and enrollment rates; and CIPN outcomes and sample characteristics were difficult to identify. Seven studies reported variable exercise adherence rates (65%-88.3%) based on variable definitions of adherence (Courneya et al. 2013; Courneya, McKenzie, et al. 2014; Dhawan et al. 2019; Kleckner et al. 2018; McCrary et al. 2019; Mizrahi et al. 2015; Streckmann, Kneis, et al. 2014; Zimmer et al. 2018); 6 studies reported adverse effects data.(Courneya et al. 2013; Courneya, McKenzie, et al. 2014; Dhawan et al. 2019; Mizrahi et al. 2015; Streckmann et al. 2018; Streckmann, Kneis, et al. 2014; Zimmer et al. 2018) No studies comprehensively described the recruitment process (e.g., timing, location, and medium); however, the studies that recruited patients before and/or just after beginning chemotherapy treatment exhibited the lowest enrollment, completion, and adherence rates. Lack

of interest/personal reasons, living far away/transportation issues especially in supervised intervention studies, and time concerns were also common reasons for declining participation. Few studies employed strong CIPN assessment methods. No studies rigorously controlled for peripheral neuropathy-related comorbidities (e.g., diabetes); potential mediating or moderating psychological confounders (e.g., mood); intervention adherence; outside physical activity (in non-home-physical activity-based interventions); and sample heterogeneity in baseline CIPN presence, severity, and stability, and chemotherapy status, regimen, and duration. Lastly, few studies reported key participant characteristics (e.g., baseline BMI, physical activity level, and motivational traits) that could have biased participant enrollment, completion, and benefit from the exercise interventions.

Limitations

Definitive conclusions about the most effective intervention types and dosages cannot be drawn from this review, because a small number of studies with moderate-high risk of bias have been published, and the tested interventions were highly heterogeneous. These review findings can only be used to inform future studies among adults, given that no studies in this review had evaluated pediatric populations. Additionally, the study samples may not fully represent the population of patients with or at risk for CIPN, because some study samples were mixed and included some participants who were and some that were not receiving/had not received any *neurotoxic* chemotherapy. For example, some participants in the Courneya et al. (2013) study received non-neurotoxic regimens (e.g., Adriamycin and Doxorubicin) and some received paclitaxel or other neurotoxic chemotherapies. Finally, one author primarily reviewed and synthesized the literature; however, the co-authors were consulted to develop the eligibility criteria and settle confusion regarding the inclusion of questionable articles.

Conclusions and Recommendations for Further Research

Considering the findings and limitations of this review along with prior systematic reviews of exercise for CIPN, the following can be concluded:

- Exercise, particularly aerobic exercise and balance training are promising preventive interventions and treatments for CIPN and should be further investigated individually.
- Higher quality studies are needed to provide more definitive results on the effects of specific exercise types, dosages, and delivery methods on specific types of CIPN.
- Studies are needed to evaluate the effects of exercise on CIPN among children.

No cures or preventive interventions for CIPN have been found.(Hershman et al. 2014; Majithia et al. 2016) Yet, preliminary empirical evidence suggests that exercise may be effective in preventing and treating CIPN. Thus, research is needed to evaluate the mechanisms that mediate the protective *or* treatment effects of specific exercise types—first focusing on aerobic and balance training—on CIPN in homogeneous samples. Homogeneous samples would consist of individuals receiving a uniform neurotoxic drug class, dose, and schedule who participate in the study at a similar time in relation to chemotherapy treatment. For example, influence from coasting effects may be avoided by enrolling all participants at least 6 months after they have completed neurotoxic chemotherapy treatment. Prior studies have also lacked control (through eligibility criteria or statistics) for potential confounding factors: baseline peripheral neuropathy severity and related comorbidities, use of medications intended to reduce peripheral neuropathy (e.g., duloxetine), cumulative chemotherapy dose received, and outside physical activity levels.

Secondly, studies are needed to evaluate the feasibility of specific exercise prescriptions in patients with or at risk for developing CIPN. Report of participants' baseline BMI, physical activity level, and motivational traits in future studies will contribute to the understanding of the

best individualized exercise prescriptions for specific populations. Further, studies are needed to evaluate the interactions among the exercise prescription; participant adherence; changes in outside physical activity and lifestyle; and CIPN outcomes. Finally, future studies should test and compare the efficacy and feasibility (e.g., cost/labor effectiveness) of home- and group-based interventions versus standard individually supervised, in-clinic interventions.

Implications for Practice

CIPN is among the most common, debilitating, and treatment-resistant side effects of neurotoxic chemotherapy. However, a growing body of evidence has shown that appropriately prescribed exercise is safe, feasible, and a potentially effective intervention for patients with CIPN (Courneya 2014; Courneya et al. 2003; Henke et al. 2014; Streckmann, Kneis, et al. 2014; Streckmann, Zopf, et al. 2014). Various exercise types and dosages and increased physical activity have demonstrated broad benefits at every stage of cancer survivorship (Courneya, McKenzie, et al. 2014; Fernandes and Kumar 2016; Henke et al. 2014; Streckmann, Kneis, et al. 2014; Zimmer et al. 2018); however, identifying exercise *prescriptions* to utilize as non-pharmacological symptom treatment requires rigorous research. This review highlights the importance of critically evaluating the literature before using the findings. Ultimately, the practice implications that can be drawn from the current studies of exercise for CIPN is limited, because all but two studies had critical limitations.

However, nurses can encourage and educate cancer survivors about the safety and importance (particularly in bolstering balance and fitness, and possibly alleviating symptoms) of exercise throughout cancer survivorship. Patients in active chemotherapy treatment with baseline CIPN and poorer functional status may require additional support to promote adherence to exercise programs. Although no definitive conclusions can be made about exercise as a treatment

for CIPN, nurses can empower patients to promote their own well-being by staying physically active.

References

Bakitas, M. A. (2007). Background noise: The experience of chemotherapy-induced peripheral neuropathy. *Nursing Research*, *56*(5), 323–331. https://doi.org/10.1097/01.NNR.0000289503.22414.79

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

Beijers, A. J. M., Mols, F., Tjan-Heijnen, V. C. G., Faber, C. G., van de Poll-Franse, L. V, & Vreugdenhil, G. (2015). Peripheral neuropathy in colorectal cancer survivors: The influence of oxaliplatin administration. Results from the population-based PROFILES registry. *Acta Oncologica*, *54*(4), 463–469. https://doi.org/10.3109/0284186X.2014.980912

Bobinski, F., Ferreira, T. A. A., Cordova, M. M., Dombrowski, P. A., da Cunha, C., Santo, C. C. do E., … Santos, A. R. S. (2015). Role of brainstem serotonin in analgesia produced by low-intensity exercise on neuropathic pain after sciatic nerve injury in mice. *Pain*, *156*(12), 2595–2606. https://doi.org/10.1097/j.pain.0000000000000372

Brayall, P., Donlon, E., Doyle, L., Leiby, R., & Violette, K. (2018). Physical therapy-based interventions improve balance, function, symptoms, and quality of life in patients with chemotherapy-induced peripheral neuropathy: A systematic review. *Rehabilitation Oncology*, *36*(3), 161–166. https://doi.org/10.1097/01.REO.0000000000000111

Buffart, L. M., Galvão, D. A., Brug, J., Chinapaw, M. J. M., & Newton, R. U. (2014). Evidence-based physical activity guidelines for cancer survivors: Current guidelines, knowledge gaps and future research directions. *Cancer Treatment Reviews*, *40*(2), 327–340. https://doi.org/10.1016/j.ctrv.2013.06.007

Cavaletti, G., Jann, S., Pace, A., Plasmati, R., Siciliano, G., Briani, C., … Giussani, G. (2006). Multi-center assessment of the Total Neuropathy Score for chemotherapy-induced peripheral neurotoxicity. *Journal of the Peripheral Nervous System : JPNS*, *11*(2), 135–141. https://doi.org/10.1111/j.1085-9489.2006.00078.x

Chaudhry, V., Rowinsky, E. K., Sartorius, S. E., Donehower, R. C., & Cornblath, D. R. (1994).

Peripheral neuropathy from taxol and cisplatin combination chemotherapy: Clinical and electrophysiological studies. *Annals of Neurology*, *35*(3), 304–311. https://doi.org/10.1002/ana.410350310

Chen, Y.-W., Tzeng, J.-I., Lin, M.-F., Hung, C.-H., & Wang, J.-J. (2014). Forced treadmill running suppresses postincisional pain and inhibits upregulation of substance P and cytokines in rat dorsal root ganglion. *The Journal of Pain*, *15*(8), 827–834. https://doi.org/10.1016/j.jpain.2014.04.010

Clark, P. G., Cortese-Jimenez, G., & Cohen, E. (2012). Effects of Reiki, Yoga, or Meditation on the physical and psychological symptoms of chemotherapy-induced peripheral neuropathy: A randomized pilot study. *Journal of Evidence-Based Complementary & Alternative Medicine*, *17*(3), 161-171 11p. https://doi.org/10.1177/2156587212450175

Cooper, M. A., Kluding, P. M., & Wright, D. E. (2016). Emerging relationships between exercise, sensory nerves, and neuropathic pain. *Frontiers in Neuroscience*, *10*, 372. https://doi.org/10.3389/fnins.2016.00372

Cornblath, D. R., Chaudhry, V., Carter, K., Lee, D., Seysedadr, M., Miernicki, M., & Joh, T. (1999). Total neuropathy score: Validation and reliability study. *Neurology*, *53*(8), 1660–1664.

Courneya, K. S. (2014). A multicenter randomized trial of the effects of exercise dose and type on psychosocial distress in breast cancer patients undergoing chemotherapy. *Cancer Epidemiology, Biomarkers & Prevention*, *23*(5), 857–864. https://doi.org/10.1158/1055-9965.EPI-13-1163

Courneya, K. S., Friedenreich, C. M., Quinney, H. A., Fields, A. L. A., Jones, L. W., & Fairey, A. S. (2003). A randomized trial of exercise and quality of life in colorectal cancer survivors. *European Journal of Cancer Care*, *12*(4), 347–357. https://doi.org/10.1046/j.1365-2354.2003.00437.x

Courneya, K. S., McKenzie, D. C., Mackey, J. R., Gelmon, K., Friedenreich, C. M., Yasui, Y., … Segal, R. J. (2013). Effects of exercise dose and type during breast cancer chemotherapy: Multicenter randomized trial. *Journal of the National Cancer Institute*, *105*(23), 1821–1832. https://doi.org/10.1093/jnci/djt297

Courneya, K. S., McKenzie, D. C., Mackey, J. R., Gelmon, K., Friedenreich, C. M., Yasui, Y., … Segal, R. J. (2014). Subgroup effects in a randomised trial of different types and doses of exercise during breast cancer chemotherapy. *British Journal of Cancer*, *111*(9), 1718–1725. https://doi.org/10.1038/bjc.2014.466

Dhawan, S., Andrews, R., Kumar, L., Wadhwa, S., & Shukla, G. (2019). 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*. https://doi.org/10.1097/NCC.0000000000000693

Duregon, F., Vendramin, B., Bullo, V., Gobbo, S., Cugusi, L., Di Blasio, A., … Ermolao, A. (2018). Effects of exercise on cancer patients suffering chemotherapy-induced peripheral neuropathy undergoing treatment: A systematic review. *Critical Reviews in Oncology/Hematology*, *121*(November 2017), 90–100. https://doi.org/10.1016/j.critrevonc.2017.11.002

Farrar, J. T., Young, J. P. J., LaMoreaux, L., Werth, J. L., & Poole, R. M. (2001). Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*, *94*(2), 149–158.

Fernandes, J., & Kumar, S. (2016). Effect of lower limb closed kinematic chain exercises on balance in patients with chemotherapy-induced peripheral neuropathy: A pilot study. *International Journal of Rehabilitation Research*. https://doi.org/10.1097/MRR.0000000000000196

Greenlee, H., Hershman, D. L., Shi, Z., Kwan, M. L., Ergas, I. J., Roh, J. M., & Kushi, L. H. (2017). BMI, lifestyle factors and taxane-induced neuropathy in breast cancer patients: The pathways study. *Journal of the National Cancer Institute*, *109*(2). https://doi.org/10.1093/jnci/djw206

Henke, C. C., Cabri, J., Fricke, L., Pankow, W., Kandilakis, G., Feyer, P. C., & de Wit, M. (2014). Strength and endurance training in the treatment of lung cancer patients in stages IIIA/IIIB/IV. *Supportive Care in Cancer*, *22*(1), 95–101. https://doi.org/10.1007/s00520-013-1925-1

Hershman, D. L., Lacchetti, C., Dworkin, R. H., Lavoie Smith, E. M., Bleeker, J., Cavaletti, G.,

… Loprinzi, C. L. (2014). Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *Journal of Clinical Oncology*, *32*(18), 1941–1967. https://doi.org/10.1200/JCO.2013.54.0914

Jones, S. B., Thomas, G. A., Hesselsweet, S. D., Alvarez-Reeves, M., Yu, H., & Irwin, M. L. (2013). Effect of exercise on markers of inflammation in breast cancer survivors: The Yale exercise and survivorship study. *Cancer Prevention Research*, *6*(2), 109–118. https://doi.org/10.1158/1940-6207.CAPR-12-0278

Jung, M., Rein, N., & Fuchs, B. (2018). Physical therapy for chemotherapy-induced peripheral neuropathy in pediatric oncology. *Physikalische Medizin Rehabilitationsmedizin Kurortmedizin*, *28*(1), 46–52. https://doi.org/10.1055/s-0043-124644

Kleckner, I. R., Kamen, C., Gewandter, J. S., Mohile, N. A., Heckler, C. E., Culakova, E., … Musian, 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

Majithia, N., Temkin, S. M., Ruddy, K. J., Beutler, A. S., Hershman, D. L., & Loprinzi, C. L. (2016). National Cancer Institute-supported chemotherapy-induced peripheral neuropathy trials: Outcomes and lessons. *Supportive Care in Cancer*, *24*(3), 1439–1447. https://doi.org/10.1007/s00520-015-3063-4

Marcelino, T. B., Longoni, A., Kudo, K. Y., Stone, V., Rech, A., de Assis, A. M., … Matte, C. (2013). Evidences that maternal swimming exercise improves antioxidant defenses and induces mitochondrial biogenesis in the brain of young Wistar rats. *Neuroscience*, *246*, 28–39. https://doi.org/10.1016/j.neuroscience.2013.04.043

Marques-Aleixo, I., Oliveira, P. J., Moreira, P. I., Magalhaes, J., & Ascensao, A. (2012). Physical exercise as a possible strategy for brain protection: Evidence from mitochondrial-mediated mechanisms. *Progress in Neurobiology*, *99*(2), 149–162. https://doi.org/10.1016/j.pneurobio.2012.08.002

McCrary, J. M., Goldstein, D., Sandler, C. X., Barry, B. K., Marthick, M., Timmins, H. C., … Park, S. B. (2019). Exercise-based rehabilitation for cancer survivors with chemotherapy-

induced peripheral neuropathy. *Supportive Care in Cancer*. https://doi.org/10.1007/s00520-019-04680-w

Mizrahi, D., Broderick, C., Friedlander, M., Ryan, M., Harrison, M., Pumpa, K., & Naumann, F. (2015). An exercise intervention during chemotherapy for women with recurrent ovarian cancer: A feasibility study. *International Journal of Gynecological Cancer*, *25*(6), 985–992. https://doi.org/10.1097/IGC.0000000000000460

Mols, F., Beijers, A. J. M., Vreugdenhil, G., Verhulst, A., Schep, G., & Husson, O. (2015). Chemotherapy-induced peripheral neuropathy, physical activity and health-related quality of life among colorectal cancer survivors from the PROFILES registry. *Journal of Cancer Survivorship*, *9*(3), 512–522. https://doi.org/10.1007/s11764-015-0427-1

Molteni, R., Zheng, J.-Q., Ying, Z., Gomez-Pinilla, F., & Twiss, J. L. (2004). Voluntary exercise increases axonal regeneration from sensory neurons. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(22), 8473–8478. https://doi.org/10.1073/pnas.0401443101

Mustian, K. M., Sprod, L. K., Palesh, O. G., Peppone, L. J., Janelsins, M. C., Mohile, S. G., & Carroll, J. (2009). Exercise for the management of side effects and quality of life among cancer survivors. *Current Sports Medicine Reports*, *8*(6), 325–330. https://doi.org/10.1249/JSR.0b013e3181c22324

Peddle, C. J., Au, H.-J., & Courneya, K. S. (2008). Associations between exercise, quality of life, and fatigue in colorectal cancer survivors. *Diseases of the Colon and Rectum*, *51*(8), 1242–1248. https://doi.org/10.1007/s10350-008-9324-2

Quigley, P. A., Bulat, T., Schulz, B., Friedman, Y., Hart-Hughes, S., Richardson, J. K., & Barnett, S. (2014a). Erratum. Exercise interventions, gait, and balance in older subjects with distal symmetric polyneuropathy: A three-group randomized clinical trial. *American Journal of Physical Medicine & Rehabilitation*, *95*(12), 1108. Retrieved from http://proxy.lib.umich.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=sph&AN=99766218&site=ehost-live&scope=site

Quigley, P. A., Bulat, T., Schulz, B., Friedman, Y., Hart-Hughes, S., Richardson, J. K., & Barnett, S. (2014b). Exercise interventions, gait, and balance in older subjects with distal

symmetric polyneuropathy: A three-group randomized clinical trial. *American Journal of Physical Medicine & Rehabilitation*, *93*(1), 1-12 12p. https://doi.org/10.1097/PHM.0000000000000052

Schulz, Altman, Moher, & Group, C. (2011). CONSORT 2010 checklist of information to include when reporting a randomised trial. Retrieved from www.consort-statement.org

Stagg, N. J., Mata, H. P., Ibrahim, M. M., Henriksen, E. J., Porreca, F., Vanderah, T. W., & Philip Malan, T. J. (2011). Regular exercise reverses sensory hypersensitivity in a rat neuropathic pain model: Role of endogenous opioids. *Anesthesiology*, *114*(4), 940–948. https://doi.org/10.1097/ALN.0b013e318210f880

Streckmann, F., Kneis, S., Leifert, J. A., Baumann, F. T., Kleber, M., Ihorst, G., … 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

Streckmann, F., Lehmann, H. C., Balke, M., Schenk, A., Oberste, M., Heller, A., … Baumann, F. T. (2018). Sensorimotor training and whole-body vibration training have the potential to reduce motor and sensory symptoms of chemotherapy-induced peripheral neuropathy-A randomized controlled pilot trial. *Supportive Care in Cancer*. https://doi.org/10.1007/s00520-018-4531-4

Streckmann, F., Zopf, E. M., Lehmann, H. C., May, K., Rizza, J., Zimmer, P., … Baumann, F. T. (2014). Exercise intervention studies in patients with peripheral neuropathy: A systematic review. *Sports Medicine*, *44*(9), 1289–1304. https://doi.org/10.1007/s40279-014-0207-5

Taube, W., Gruber, M., Beck, S., Faist, M., Gollhofer, A., & Schubert, M. (2007). Cortical and spinal adaptations induced by balance training: Correlation between stance stability and corticospinal activation. *Acta Physiologica*, *189*(4), 347–358. https://doi.org/10.1111/j.1365-201X.2007.01665.x

Tofthagen, C. S., Donovan, K. A., Morgan, M. A., Shibata, D., & Yeh, Y. (2013). Oxaliplatin-induced peripheral neuropathy's effects on health-related quality of life of colorectal cancer survivors. *Supportive Care in Cancer*, *21*(12), 3307–3313. https://doi.org/10.1007/s00520-013-1905-5

van Waart, H., Stuiver, M. M., van Harten, W. H., Geleijn, E., Kieffer, J. M., Buffart, L. M., … Aaronson, N. K. (2015). Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: Results of the PACES randomized clinical trial. *Journal of Clinical Oncology*, *33*(17), 1918–1927. https://doi.org/10.1200/JCO.2014.59.1081

Ventzel, L., Jensen, A. B., Jensen, A. R., Jensen, T. S., & Finnerup, N. B. (2016). Chemotherapy-induced pain and neuropathy: A prospective study in patients treated with adjuvant oxaliplatin or docetaxel. *Pain*, *157*(3), 560–568. https://doi.org/10.1097/j.pain.0000000000000404

Vollmers, P. L., Mundhenke, C., Maass, N., Bauerschlag, D., Kratzenstein, S., Rocken, 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

Wonders, K. Y. (2014). The effect of supervised exercise training on symptoms of chemotherapy-induced peripheral neuropathy. *Int J Phys Med Rehabil*, *2*(4), 1–5.

Yoon, H., Thakur, V., Isham, D., Fayad, M., & Chattopadhyay, M. (2015). Moderate exercise training attenuates inflammatory mediators in DRG of Type 1 diabetic rats. *Experimental Neurology*, *267*, 107–114. https://doi.org/10.1016/j.expneurol.2015.03.006

Zimmer, P., Trebing, S., Timmers-Trebing, U., Schenk, A., Paust, R., Bloch, W., … 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

CHAPTER III

The Effects of Exercise on Chemotherapy-Induced Peripheral Neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is a prevalent side effect of neurotoxic chemotherapy that can lead to ongoing discomfort and functional impairments during and after the completion of cancer treatment. Broadly, about 60% of individuals with various types of cancer develop CIPN from frontline neurotoxic chemotherapies, such as platinum compounds, taxanes, vinca alkaloids, proteasome inhibitors, antiangiogenesis agents, epothilones, ifosfamide and gemcitabine. Some types of neurotoxic chemotherapy such as oxaliplatin—a standard platinum-based chemotherapy for invasive gastrointestinal (GI) cancer—can cause CIPN in 85% to 95% of individuals (Andre et al., 2004; Argyriou, Bruna, Marmiroli, & Cavaletti, 2012; Argyriou et al., 2013; Beijers et al., 2015; Ventzel, Madsen, et al., 2016).

The acute manifestations of oxaliplatin-induced peripheral neuropathy (OIPN) include cramps, tingling, and cold sensitivity in the face, throat, and bilateral hands and feet (Drott et al., 2019). Additionally, patients may exhibit pre-clinical signs of OIPN including loss of deep tendon reflexes and proprioception. As OIPN progresses, patients may begin to report cumulative OIPN symptoms: persistent numbness, neuropathic pain, and weakness in the bilateral hands and feet that progress up the extremities. Autonomic OIPN signs (e.g., orthostatic hypotension and constipation) are uncommon (Carozzi, Canta, & Chiorazzi, 2015; Dermitzakis et al., 2016; Giannoccaro et al., 2011; Nazir et al., 2017; Simon, Danso, Alberico, Basch, & Bennett, 2017; Stratogianni et al., 2012). Individuals with OIPN have a two times higher risk for falls than

cancer survivors without OIPN due to impaired proprioception, balance, and strength (Bao et al., 2016; Kolb et al., 2016; Winters-Stone et al., 2017). Cancer survivors with OIPN also report difficulty with simple tasks, such as typing, grasping items from the refrigerator, and buttoning a shirt. These impairments can be distressing and reduce individuals' quality of life (QOL) and ability to function in their usual roles (Exposito Vizcaino, Casanova-Molla, Escoda, Galan, & Miro, 2018; Monfort et al., 2016; Speck et al., 2012; Tofthagen, 2010b, 2010a; Tofthagen, McAllister, & McMillan, 2011; Zanville et al., 2016).

Although most individuals develop some degree of OIPN during oxaliplatin treatment, the individuals at the highest risk for developing persistent and severe OIPN include those with baseline peripheral neuropathy (e.g., diabetic neuropathy) (de la Morena Barrio et al., 2015; Hershman et al., 2016; Kawakami et al., 2012; Saad, Tafani, Psimaras, & Ricard, 2014; Seretny et al., 2014) and a history of prior cancer treatment (Argyriou et al., 2012; Lewis et al., 2015; Velasco et al., 2010). Additionally, higher oxaliplatin cumulative dose is the dominant direct predictor of OIPN chronicity and severity (Argyriou et al., 2012; Beijers et al., 2015; Miltenburg & Boogerd, 2014; Seretny et al., 2014; Velasco et al., 2014; Ventzel, Jensen, Jensen, Jensen, & Finnerup, 2016). With each cycle of chemotherapy, acute OIPN becomes more severe and the risk of chronic OIPN increases (Argyriou et al., 2012, 2013; Beijers et al., 2015; Krishnan & Park, 2014; Loprinzi et al., 2014; Miltenburg & Boogerd, 2014; Pachman et al., 2015, 2016; Seretny et al., 2014; Velasco et al., 2014; Ventzel, Jensen, et al., 2016; Ventzel, Madsen, et al., 2016). Other risk factors for OIPN include co-administration of other neurotoxic drugs and malnutrition (Staff & Windebank, 2014); obesity (Cox-Martin et al., 2017; Shahriari-Ahmadi, Fahimi, Payandeh, & Sadeghi, 2015; Song et al., 2017); older age (Cox-Martin et al., 2017; Hershman et al., 2016; Song et al., 2017); genetic predisposition (Kerckhove et al., 2017); and

lifestyle behaviors, including physical inactivity, smoking, and alcohol use disorder (Brydoy et al., 2009; Greenlee et al., 2017; Mols et al., 2015; Saad et al., 2014; Seretny et al., 2014).

No preventative therapies for OIPN are known; the primary treatment for OIPN is oxaliplatin dosage reduction or cessation. However, burgeoning evidence suggests that exercise may help to reduce OIPN (Dhawan, Andrews, Kumar, Wadhwa, & Shukla, 2019; Fernandes & Kumar, 2016; Henke et al., 2014; Kleckner et al., 2018; McCrary et al., 2019; Streckmann et al., 2014, 2018; Wonders, 2014; Zimmer et al., 2018). Three randomized controlled trials (RCT) (Henke et al., 2014; Streckmann et al., 2014; Zimmer et al., 2018) and two quasi-experiments (McCrary et al., 2019; Wonders, 2014) suggest that aerobic exercise may be key in both preventing and treating OIPN. Specifically, the most abundant evidence supports that in-clinic and home-based moderate to vigorous aerobic exercise (50%-70% of maximum heart rate; 10 to 30 minutes per day, two to three days per week, over eight to 12 weeks) combined with strength and/or balance training, may reduce OIPN during and after completing chemotherapy treatment (Henke et al., 2014; McCrary et al., 2019; Streckmann et al., 2014; Wonders, 2014; Zimmer et al., 2018). One secondary data analysis of an RCT also showed that a six-week home-based light step-count prescribed physical activity (PA) and elastic band strength training intervention led to better CIPN outcomes among individuals in active taxane and platinum-based chemotherapy treatment (Kleckner et al., 2018).

Aerobic exercise may target and reduce OIPN through multiple mechanisms. Some evidence suggests that oxaliplatin primarily causes OIPN by pooling around and inducing oxidative stress, inflammation, and apoptosis of vulnerable peripheral nerves. Aerobic exercise may reduce OIPN (i.e., neurotoxicity) by improving blood circulation and reducing oxaliplatin concentration around vulnerable nerves. Additionally, aerobic exercise may directly reduce

oxidative stress and inflammation (Azizbeigi, Azarbayjani, Atashak, & Stannard, 2015; Chang, Chang, Hwang, & Chen, 2015; Di Cesare Mannelli, Zanardelli, Failli, & Ghelardini, 2012; Gomez-Cabrera, Salvador-Pascual, Cabo, Ferrando, & Vina, 2015; L. W. Jones et al., 2014; Karimi & Roshan, 2013; Park et al., 2013; Schaun et al., 2011; Tofthagen, Visovsky, & Hopgood, 2013; Zhou, Liu, Yang, Mi, & Ye, 2016). Finally, aerobic exercise may relieve symptom distress associated with OIPN by bolstering mood (Courneya, 2014; Thraen-Borowski, Trentham-Dietz, Edwards, Koltyn, & Colbert, 2013) and reducing co-occurring symptoms such as fatigue, insomnia, pain, anxiety, and depression (Berger, 2010; Binkley et al., 2012; El-Shami et al., 2015; Knoerl, Chornoby, & Smith, 2018, 2019; Mols et al., 2013; Pachman, Barton, Swetz, & Loprinzi, 2012; Skerman, Yates, & Battistutta, 2012).

Altogether, the studies that have evaluated the effects of exercise on OIPN and other types of CIPN have had critical limitations: most commonly small sample sizes, heterogeneous samples of mixed CIPN types, and lack of strong CIPN measures and control for CIPN-influencing factors. Few studies have evaluated home-based exercise, and no studies isolated aerobic exercise to evaluate its unique impact on one type of CIPN such as OIPN.

Purpose and Design

The purpose of this pilot study was to explore the efficacy of eight weeks of home-based moderate-intensity aerobic exercise (i.e., brisk walking) for OIPN in GI cancer survivors receiving active neurotoxic treatment. Specifically, the aims of this dual-site, prospective, randomized, controlled, pilot study were to evaluate the effect of an eight-week home-based brisk walking (the "MI-Walk") intervention, on 1) OIPN severity and 2) QOL at eight weeks, compared to PA education alone in oxaliplatin-receiving GI cancer survivors. The primary hypothesis was that patients in the MI-Walk Intervention would have less severe sensory OIPN

than patients in control group at eight weeks, controlling for received oxaliplatin dose and baseline sensory OIPN. Motor OIPN severity, global QOL, and individual QOL domains (i.e., physical and emotional function) were explored as secondary outcomes. Additionally, mood was explored as a covariate in the models. Finally, dose response—association between moderate to vigorous PA (MVPA) and the outcomes—were explored.

Methods

Sixty adults (at least 18 years of age) with stage II-IV colon, rectal, colorectal, pancreatic, ileal, and esophageal cancers were recruited to the study at their second cycle of FOLFOX or FOLFIRINOX (two oxaliplatin-based chemotherapy regimens). Convenience sampling was used to identify participants that met the additional following eligibility criteria, based on their electronic medical records, and medical oncologist- and self-report. The institutional review board at both recruitment sites approved the study and all participants gave informed consent.

Inclusion Criteria

Participants were eligible for the study if they were 1) scheduled to receive at least 6 cycles of FOLFOX or FOLFIRINOX, 2) had a Karnofsky Performance Status ≥ 80% or an Eastern Cooperative Oncology Group (ECOG) Status zero to one; and 6) voluntarily consented to participate in all intervention components.

Exclusion Criteria

Individuals were excluded if they had 1) exercise- or mobility-limiting cardiovascular, pulmonary, musculoskeletal, or psychological disease, 2) a major surgical procedure scheduled during the eight-week study time period, 3) self-reported pre-existing peripheral neuropathy (potentially due to diabetes, central nervous system malignancy, vitamin deficiency, heredity, nerve compression injury, non-surgically corrected carpal tunnel disease, or alcohol dependence),

and 5) a prognosis of less than three months. Baseline peripheral neuropathy was screened by in-person interview (e.g., "do you have numbness or tingling in your hands or feet?") and using the primary outcome measure (CIPN20 survey); participants with a CIPN20 sensory subscale score ≥ 25 ("a little" sensory neuropathy on the transformed scale) were considered ineligible due to baseline peripheral neuropathy and were excluded from the analysis. Pregnancy and inability to read or speak English were additional exclusion criteria.

Intervention and Control Condition

Participants were stratified by diabetes status and recruitment site then randomized in a 1:1 ratio to receive either the PA education control condition or the eight-week MI-Walk Intervention. The same interventionist (the first author) provided the education and guided participants through the MI-Walk Intervention. The control group at each site solely received the *Physical Activity and the Cancer Patient* pamphlet (American Cancer Society, 2014) and verbal reinforcement of safety precautions surrounding, tips for maintaining, and the benefits and recommended levels of PA during and after cancer treatment. Telephone follow-up (to assess for adverse events) occurred at one, two, four, and six weeks.

The MI-Walk Intervention. In addition to the PA education, participants in the intervention group received a tailored progressive walking plan, three motivational enhancement therapy (MET) sessions, and tools described below to encourage home-based aerobic walking. The progressive walking plan goal by eight weeks was for participants to meet or exceed the national aerobic PA guidelines: at least 150 minutes of MVPA per week (American Cancer Society, 2014; Schmitz et al., 2010; U.S. Department of Health and Human Services, 2018). Walking was generally prescribed in progressive dosages of 10 to 60 minutes, three to five days

per week, at moderate intensity defined as Borg rating of perceived exertion between 12 and 14 (Borg, 1998).

The MET sessions—motivational interviewing and worksheets to write exercise goals and barrier-addressing "if-then implementation intention" statements—occurred in-person at intervention initiation and by telephone two and four weeks later. The "if-then implementation intention" statement worksheet encouraged participants to identify their major exercise barrier(s) and create a plan to address it/them. For example, if a participant's major barrier was forgetting to walk, their intention statement could be "if it is six PM on Saturday, then I will walk for 10 minutes."

The intervention group participants also received additional tools, including a Fitbit Charge 2, tailored progressive walking plan, exercise diary, progress summary at two and four weeks, supplemental cancer treatment and exercise educational pamphlet, and written patient testimony about staying physically active during oxaliplatin treatment. Additionally, the intervention participants were added to an email group and invited to weekly group walking events with the other intervention group participants. They received one weekly scripted motivational message and were encouraged to engage in email discussion.

Measurement

Participants completed the outcome measure surveys electronically on a tablet at the baseline and eight-week timepoints. Baseline assessments occurred at the participants' second infusion visit. The eight weeks assessments occurred at the sixth infusion visit or whichever visit coincided with the eight-week timepoint. A one-week leeway was permitted in cases when a chemotherapy visit was re-scheduled. All assessments occurred at least two weeks after the prior dose of chemotherapy. A blinded assessor administered the eight-week surveys to 75% of the

participants at eight weeks; the interventionist provided the eight-week surveys to 25% of the participants due to limited personnel.

OIPN. The European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-Chemotherapy-Induced Peripheral Neuropathy 20-item supplement (CIPN20) (Postma et al., 2005) was used to measure the primary outcome. It is a patient-reported outcome that assesses three domains of CIPN symptoms: sensory (9 items), motor (8 items) and autonomic function (3 items). Each item was rated on a scale from 1 ("not at all") to 4 ("very much"). The mean of each subscale score was linearly transformed to a 0 to 100 scale (higher scores represented worse CIPN severity). Evidence supports the internal consistency reliability among the sensory (Cronbach's α coefficient = 0.82-0.88), motor (α coefficient = 0.73-0.88), and autonomic (α = 0.76-0.78) items (Lavoie Smith et al., 2013; Postma et al., 2005). Factor analysis has supported the construct validity of the sensory and motor subscales (Lavoie Smith et al., 2013). Excellent content validity has been demonstrated by cognitive interviews with patients, and review by five oncology practitioners and scientists (*CVI* = 0.80) (Smith et al., 2017). The CIPN20 has demonstrated responsiveness to change (cohen's *d range* = 0.32-0.69) (Smith et al., 2018) in the context of chronic stable CIPN (Alberti et al., 2014; Cavaletti et al., 2013; Knoerl et al., 2017; Lavoie Smith et al., 2013; Postma et al., 2005; Smith et al., 2018). Finally, the electronic tool has demonstrated excellent mode equivalence with the paper-pencil CIPN20 (*ICC range* >0.91) (Knoerl et al., 2017).

QOL. The EORTC QLQ-Core 30-item (C30) survey was used to assess QOL. It is a 30-item patient-reported measure of cancer-specific QOL. The EORTC QLQ-C30 contains five multi-item functional scales measuring physical (5 items) and emotional function (4 items); and role, cognitive, and social function (2 items each). The survey also contains a fatigue (3-item),

pain (2-item), and nausea and vomiting (2-item) symptom and global health/QOL scale (2 items); and several individual symptom items. Participants rated the degree to which each item applied to them during the past week using a four-point Likert scale (1, not at all; 4, very much). The average of the item scores gives a raw subscale score, and all raw subscale and single-item scores are transformed to a 0 to 100 scale. Higher scores indicate that a concept applies more strongly to an individual. For example, a higher score on the emotional functioning scale indicates higher emotional functioning, but a higher symptom score indicates more severe symptoms. The EORTC QLQ-C30 and its individual subscales have demonstrated strong internal consistency reliability ($\alpha = 0.74\text{-}0.85$); and group-contrasting validity ($p \leq .02$; grouped by ECOG performance status) globally in adults receiving cancer treatment (Aaronson et al., 1993; Cankurtaran et al., 2007; Li, Lin, Qiu, Gao, & Xu, 2014; Nicklasson & Bergman, 2007; Niezgoda & Pater, 1993; Osoba et al., 1994; Ringdal & Ringdal, 1993; Sherman et al., 2000). Evidence supports its convergent validity with other common QOL (e.g., the 36-Item Short Form Health Survey) and mood (e.g., Hospital Anxiety and Depression Scale) measures ($r = .24\text{-}.77$) (Cankurtaran et al., 2007; Li et al., 2014; Ringdal & Ringdal, 1993; Rodrigues et al., 2017; Sherman et al., 2000; Snyder et al., 2014).

Fitbit-measured physical activity. In the MI-Walk group, the Fitbit Charge 2 was used to measure PA trends over the eight weeks. Total (light to vigorous) PA and MVPA were quantified as the minutes of PA performed at or above 1.1 and 3 metabolic equivalent of tasks, respectively (American Cancer Society, 2014; Fitbit, 2019; U.S. Department of Health and Human Services, 2018). Step count per day was also collected.

Intervention participants continuously wore the Fitbit over the eight weeks. The device was calibrated to each participant based on their age, gender, height, and weight. The Fitbit

Charge models have demonstrated step count-based test-retest reliability (*ICC* = 0.92-0.96) and criterion-related validity in older adults in controlled lab settings (*ICC* = 0.90-0.95) (Burton et al., 2018). Some evidence suggests convergent validity of Fitbit Charge 2 step count, sedentary time, and MVPA measurements with symptom burden (*r* = .17-.52) (Low et al., 2017) and functional status (*r* = .63-.69), and predictive validity in relation to favorable cancer survival and reduced adverse events among cancer survivors (*OR* = 0.21-0.48) (Gresham et al., 2018). The Fitbit Charge models have demonstrated convergent validity with other commercial and research-grade PA monitors but tend to overestimate energy expenditure (Bai, Hibbing, Mantis, & Welk, 2018; Brooke et al., 2017; Feehan et al., 2018; Nazari, MacDermid, Sinden, Richardson, & Tang, 2019; Tedesco et al., 2019; Thomson et al., 2019).

***Self-reported physical activity*.** The Physical Activity Scale for the Elderly (PASE) (Washburn, McAuley, Katula, Mihalko, & Boileau, 1999; Washburn, Smith, Jette, & Janney, 1993) was used to compare total PA levels between the intervention and control groups. Confounding bias was suspected if the control group's PASE scores increased significantly from baseline to eight weeks and were equal or higher than the intervention group's scores at eight weeks.

The PASE is a 28-item self-report measure of total PA (leisure time, household, and occupational activities) performed over the past seven days. It contains six four-point Likert scale items that measure the frequency of (0, never; 3, often) and usual session duration spent (0, less than 1 hour; 3, more than 4 hours) performing various activities: occupational walking and standing, muscle strength exercises, leisure-time walking, and light to strenuous sports. Six items measure engagement (1, yes; 0, no) in household activities: house/lawn/yard care and repairs and care for another person. A single weighted PA sum score (*range* = 0-793) was calculated per the

scoring manual. Before summation, the raw item scores were multiplied by pre-determined weights that were originally obtained from the published principal components analysis (Physiopedia contributors, 2019; Washburn et al., 1999, 1993).

The PASE has demonstrated good content (*CVI* = 0.91) and face validity (Su, Lee, Yeh, Kao, & Lin, 2014), and adequate test-retest reliability (*ICC* = 0.67-0.90) (Dinger, Oman, Taylor, Vesely, & Able, 2004; Forsen et al., 2010; Washburn et al., 1993). Convergent validity has been supported by its associations with various performance status measures (r = .36-.59), the six-minute walk test (r = .40), and EORTC QLQ-C30-measured physical function and global QOL (r = .57) (Granger, Parry, & Denehy, 2015). Adequate criterion-related validity has been suggested by its correlations with the ActiGraph and pedometers (r = .50-.68) (Granger, Parry, & Denehy, 2015; Su, Lee, Yeh, Kao, & Lin, 2014). Finally, the PASE has shown capability of detecting decreases in PA throughout lung cancer treatment (*ES* = .23-.24; $p \leq .023$) (Granger et al., 2015).

***Motivational interviewing fidelity*.** The fidelity/integrity of the MET was assessed using the Motivational Interviewing Treatment Integrity Code (Moyers et al., 2016). An external MET expert used the tool to review and code three MET sessions at the beginning, middle, and end of the study (three to five months apart)..

***Oxaliplatin dose*.** The cumulative oxaliplatin dose (mg/m^2) was abstracted from the electronic medical record. Oxaliplatin dose was evaluated primarily as a continuous dose but also as a dichotomous variable (0, no dose reduction; 1, dose reduction).

***Demographic characteristic*s.** Participants self-reported their age, race, gender, and marital and employment status. They also verbally rated their confidence on a 0 to 10 scale in their ability to increase their aerobic exercise over the next eight weeks. Cancer type and stage, smoking and comorbidity history, ECOG status, and body mass index were gleaned from the

electronic medical record. The principal investigator obtained participants' lists of prescribed analgesic, anti-epileptic, and neuroprotectant medications from the electronic medical record and asked the participants in-person to confirm the dosages that they were regularly taking. Demographic characteristics that significantly differed between groups ($p < .05$) were explored as covariates in the analysis of the effects of the intervention on the outcomes.

Power Analysis

Reasonable parameter estimates for this power analysis were obtained from a secondary data analysis of the effects of a six-week home-based PA and strength training intervention on 0 to 10 numeric rating scale-measured numbness and tingling in individuals initiating platinum (oxaliplatin-like) treatment (Kleckner et al., 2018). The power analysis was conducted assuming that the observed magnitude of effect would be similar between the Kleckner et al. and present study, despite differing outcome measures. The present study was estimated to have an 85.9% power to detect significant differences in OIPN scores, assuming a one-tailed α of .05, *n* of 24 per group, linear increase in OIPN throughout oxaliplatin treatment (Pachman et al., 2015, 2016; Ventzel, Jensen, et al., 2016; Zimmerman et al., 2016), baseline numeric rating scale mean of 0.46, and projected inter-group difference in means of 1.86 at eight weeks and non-homogeneity of variance (*SD*s = 1.53 and 0.90).

Statistical Analysis

Statistical analyses were performed using the STATA version 15.0 statistical software (StataCorp, 2017). The normality of the standardized residuals for each outcome variable were assessed using spread-level residual and quantile-quantile plots, and histograms and centrality and dispersion statistics. Homoskedasticity was verified using the White and Breusch-Pagan tests (setting critical alpha to $p \geq .05$) (Breusch & Pagan, 1979; White, 1980). The Shapiro-Wilk test

was used to evaluate the normality of the distribution of residuals for each model. If the Shapiro-Wilk test was significant ($p \leq .05$), indicating possible violations to normality, the standardized residuals of each model were assessed. Outliers with a standardized residual ≥ 3 were considered overly influential and removed from analysis of the specified model, and model diagnostics were re-evaluated after removing them. Finally, lack of multicollinearity was determined based on variance inflation factors < 4.

Differences in the baseline sample characteristics and concomitant treatment changes between the intervention and control group were evaluated using two-sided independent t-tests and Fisher's exact and chi-square tests.Linear mixed model regression was conducted to evaluate changes in self-reported PA over time between groups.

Missing data. Table III.1 tabulates the patterns and amount of missing data for each variable. Qualitative researcher observations were also considered in assessing the reasons for each missing value. Imputation was only performed on the data assumed to be missing at random. All the outcome variables (e.g., OIPN and QOL) had complete data at baseline but missing data—all assumed to be missing at random—from 6 (11%) of participants at the eight-week timepoint. About 14% of the Fitbit data was missing, presumably "at random." Self-reported PA was missing for 11% of cases at baseline and 16% of cases at eight weeks but was not imputed due to the small sample size and limited imputation model variable capacity. The missing data pattern was mixed and/or arbitrary.

All dichotomous variables were coded 0 (no) and 1 (yes) and all factor variables were encoded into numeric variables. The missing Fitbit data for the control group participants were assigned a special missing code to indicate that they were not collected from and should not be

imputed for the control group participants. No calculated variables required passive imputation, because participants responded to all or none of the items in each subscale.

Table III.1

Missing Values

Variable	Missing at Eight Weeks	
	n	**%[a]**
Sensory OIPN	6	10.53
Motor OIPN	6	10.53
Oxaliplatin Dose	6	10.53
QOL	6	10.53
Physical Function	6	10.53
Emotional Function	6	10.53
Fitbit mean MVPA	4	13.79

Abbreviations. MVPA, moderate to vigorous physical activity; OIPN, oxaliplatin-induced peripheral neuropathy; QOL, quality of life

[a]Percent of subjects who did not provide a response for the listed item.

Multiple imputation. Multiple imputation and linear regression were used to address the aims by modified intent-to-treat analysis. Specifically, multivariate imputation by chained equations (MICE) with predictive mean matching was conducted based on group, age, gender, oxaliplatin dose, Fitbit-measured MVPA, and baseline and eight-week OIPN, global QOL, physical, role, and emotional function. The MICE-predictive mean matching method was chosen because multiple continuous variables with skewed residual distributions required semi-parametric imputation. Additionally, predictive mean matching was used due to the small sample size and potentially insufficient amount of observed data to restrict the imputations and avoid imputing data outside of a reasonable range. To maximize model convergence, 200 iterations of imputation were performed.

Several multiple imputation diagnostic methods were used before analyzing the aims to check the imputed data for unexpected values and obvious deviations from the original observed data. The distributions of the imputed versus observed values for each variable were visualized

using cumulative plots. Means and variances of each imputed variable were also calculated and compared to the observed data. Finally, the results of complete case analysis (with listwise deletion) on the observed data was compared to the study results obtained from regression on the imputed data. Reasonable similarity in the estimates obtained from the observed versus imputed data were verified prior to proceeding with analysis of the aims.

Analysis of the aims. Linear regression was used to address the aims. Robust regression—a very conservative alternative to linear regression—was used if the adequacy of the model fit, normality of residuals, and homogeneity of variances were questionable after evaluating the standardized residuals and removing outliers. Group assignment (the intervention) was the primary independent variable in each model. The first regression model evaluated eight-week sensory OIPN as the outcome and included baseline OIPN and oxaliplatin dose received by eight weeks as additional covariates. Mood and inter-group differing demographic covariates were added secondarily as exploratory covariates. The same covariates were used to model the eight-week motor OIPN outcome. Eight-week global QOL and physical and emotional function were each modeled separately; these models included baseline QOL/function and eight-week sensory OIPN severity as covariates.

Descriptive statistics of groups are presented as means with standard deviations ($\bar{X}\pm SD$) for continuously scaled and *n* (%) for categorical data. The *b* estimates for effects ($\bar{X}_{\Delta}$ for dichotomous variables), along with 95% confidence intervals (*CI*s) are used to evaluate and report effect magnitudes. Significance was determined by a two-tailed $\alpha \leq .05$ (a *CI* that did not contain zero) and pre-specified clinical significance cut-offs: a 30% difference in mean scores between groups was considered clinically significant (Dworkin et al., 2005; Farrar, Young, LaMoreaux, Werth, & Poole, 2001).

Results

Figure III.1 demonstrates the flow of participants through the study. Sixty (62%) of 97 screened individuals enrolled in the study. The individuals who enrolled reported significantly fewer comorbidities ($\bar{X}$ = 0.78; *SD* = 0.88; *range* = 0-3) than participants who declined participation ($\bar{X}$ = 1.12; *SD* = 0.48; *range* = 0-3), ($\bar{X}_1$-$\bar{X}_2$= 0.34; *95% CI* -0.67, -0.01; *p* = .01). The patients who enrolled versus declined were otherwise similar.

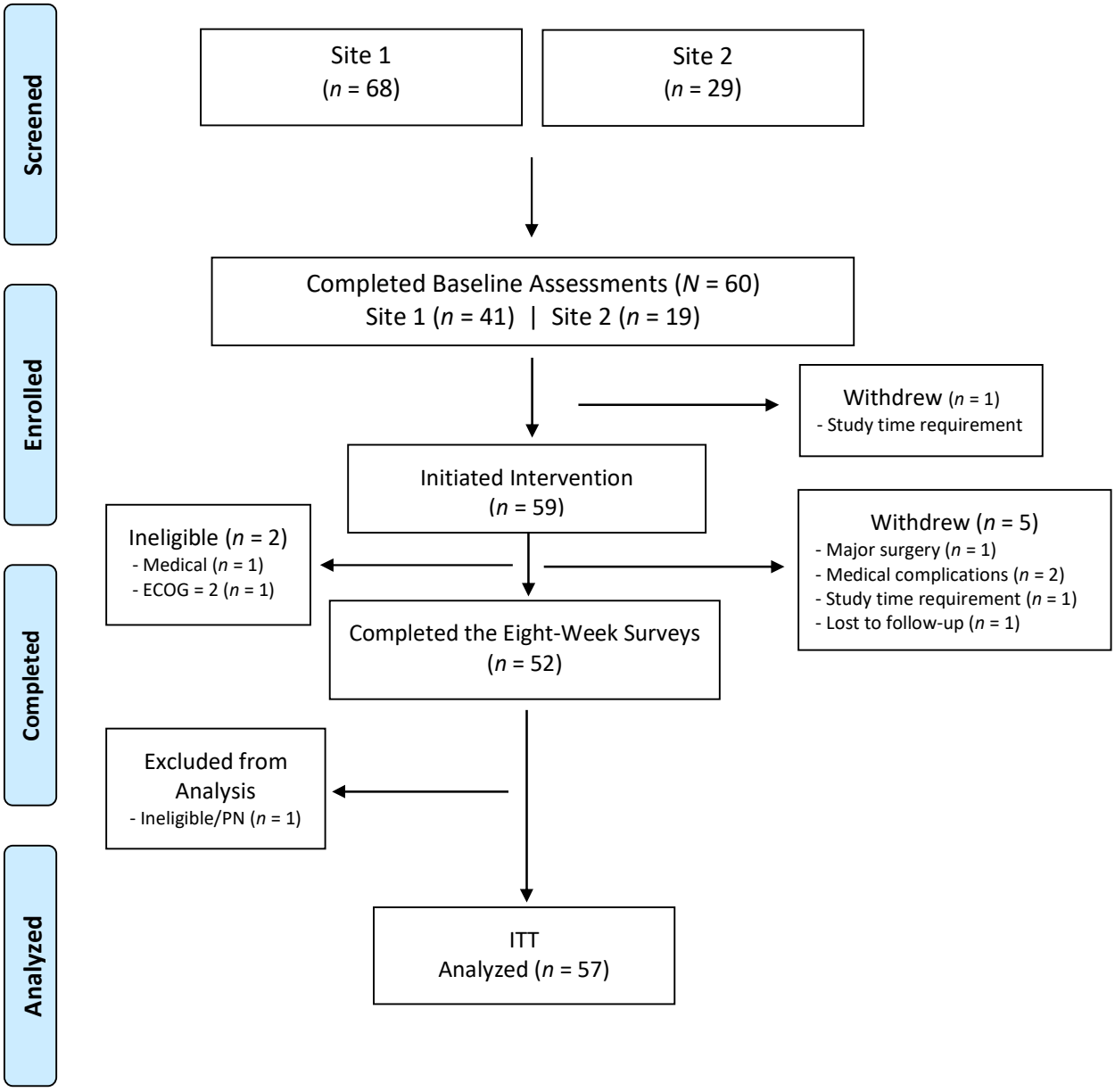
Of the 57 *eligible* enrolled participants, six individuals withdrew from the study (87% completion rate) due to major surgery (*n* = 1), medical complications (*n* = 2), perceived excessive study time requirement (*n* = 2), and lack of follow-up (*n* = 1). The participants who completed the study were significantly younger ($\bar{X}$ = 57.00; *SD* = 10.81; *range* = 19-75 years) than the participants who withdrew ($\bar{X}$ = 66.33; *SD* = 3.56; *range* = 61-72 years), ($\bar{X}_1$-$\bar{X}_2$= 9.33; *95% CI* -18.28, -0.39; *p* = .03).

Sample Characteristics

Table III.2 provides a summary of the baseline characterist ics of the participants. The sample included subjects with stage II-IV mainly colon and/or rectal (67%) or pancreatic cancers (31%). Most participants were male (63%), white (91%), and married (79%), and had the optimal ECOG functional status (77%). Nearly half the participants were former (42%) or current (7%) smokers. A higher proportion of males were randomized to the intervention than the control group (*p* = .01). All participants were receiving their first-ever oxaliplatin-based chemotherapy regimen; however, one participant (who reported no baseline peripheral neuropathy) had previously received paclitaxel for breast cancer. Twenty-three (41%) of the participants were taking at least one analgesic medication at baseline; 10 of these participants were taking an opioid analgesic.

Figure III.1

Recruitment Flowchart A



Abbreviations. ECOG, Eastern Cooperative Oncology Group functional status score; ITT, intention to treat analysis; PN, peripheral neuropathy.
Note. Missing data for all but the three ineligible participants were imputed for the ITT analysis.

Baseline peripheral neuropathy and QOL. Table III.2 also includes the baseline self-reported peripheral neuropathy scores, which were similar between the intervention and control group participants. At baseline, one participant gave a CIPN20 score (> 25) that indicated "a little" baseline motor peripheral neuropathy; and nine (16%) of patients had an autonomic peripheral neuropathy CIPN20 score > 25 at baseline. No between-group differences were found in QOL and the functional subscales at baseline.

Table III.2

Baseline Characteristics

Characteristic	**Combined**	**Intervention Group**	**Control Group**	**Inter-Group**	
	***N* = 57**	***n* = 29**	***n* = 28**		
		***n* (%)**		x^2	*p*
Male Gender	36 (63)	23 (79%)	13 (46)	6.62	.01*
Race				3.29	.18
White	52 (91)	28 (97)	24 (86)		
Black	2 (4)	1 (3)	1 (3)		
Other	3 (5)	0	3 (11)		
Marital Status				6.34	.20
Married	45 (79)	25 (87)	20 (71)		
Separated/Divorced	6 (11)	2 (7)	4 (14)		
Widowed	4 (7)	1 (3)	3 (11)		
Never Married	2 (3)	1 (3)	1 (4)		
Education Level				3.66	.89
High School or Less	10 (17)	5 (18)	5 (18)		
Some College	20 (36)	10 (34)	10 (36)		
Bachelors Degree	7 (12)	4 (14)	3 (10)		
Graduate Degree	20 (35)	10 (34)	10 (36)		
Employment Status				4.22	.69
Full-time	18 (32)	11 (38)	7 (25)		
Part-time	7 (12)	4 (14)	3 (11)		
Retired	16 (28)	7 (24)	9 (32)		
Not employed	3 (5)	1 (3)	2 (7)		
On disability/leave of absence	13 (23)	6 (21)	7 (25)		
Smoking History				0.02	>.99
Never smoked	29 (51)	15 (52)	14 (50)		
Former smoker	24 (42)	12 (41)	12 (43)		
Current smoker	4 (7)	2 (7)	2 (7)		
Cancer Type				1.23	.92
Colon	22 (39)	11 (38)	11 (39)		
Rectal/Colorectal	16 (28)	9 (31)	7 (25)		
Pancreatic	18 (31)	9 (31)	9 (32)		
Esophageal	1 (2)	0	1 (4)		

Cancer Stage				0.38	.94
II	12 (21)	6 (21)	6 (21)		
III	18 (32)	10 (34)	8 (29)		
IV	26 (46)	12 (41)	14 (50)		
Unknown	1 (1)	1 (4)	0		
ECOG				2.27	.21
0	44 (77)	20 (69)	24 (86)		
1	13 (23)	9 (31)	4 (14)		
Number of comorbidities				2.91	.37
0	27 (47)	16 (55)	11 (39)		
1	20 (35)	10 (35)	10 (36)		
2-3	10 (18)	3 (10)	7 (25)		
Number of pain medications				3.53	.39
0	33 (58)	16 (55)	17 (61)		
1	14 (25)	8 (28)	6 (21)		
2-3	9 (16)	5 (17)	4 (14)		
Unknown	1 (1)	0	1 (4)		

	$\bar{X}$ *(SD)*			$\bar{X}_1$-$\bar{X}_2$	*p*
Age	57.88 (10.68)	56.79 (11.72)	59.00 (9.58)	-2.21	.44
BMI	25.61 (3.96)	25.01 (3.73)	26.23 (4.16)	-1.23	.25
Oxaliplatin dose (mg/m^2)					
Baseline	85.17 (12.02)	83.38 (4.28)	87.02 (16.54)	-3.64	.26
8 weeks	376.29 (62.86)	373.22 (55.79)	379.46 (70.34)	-6.24	.71
Sensory PN	6.30 (6.93)	6.39 (6.33)	6.22 (7.61)	0.17	.93
Tingling F/H	16.96 (17.95)	17.24 (16.95)	16.67 (19.25)	0.57	.91
Tingling T/F	88.77 (16.09)	8.05 (14.52)	9.52 (17.82)	-1.48	.73
Numbness F/H	9.36 (15.11)	9.20 (15.16)	9.52 (15.33)	-0.33	.94
Numbness T/F	5.85 (12.79)	4.60 (11.70)	7.14 (13.93)	-2.55	.46
NP F/H	3.51 (10.32)	3.45 (10.33)	3.57 (10.50)	-0.12	.96
NP T/F	1.75 (7.51)	2.30 (8.60)	1.19 (6.30)	1.11	.58
Motor PN	3.62 (6.93)	3.61 (5.19)	3.64 (8.47)	-0.02	.99
Autonomic PN	10.72 (14.84)	10.73 (14.08)	10.71 (15.85)	0.01	>.99
QOL total score	69.30 (20.48)	72.41 (17.69)	66.07 (22.90)	6.34	.25
Physical function	92.16 (12.35)	92.64 (12.39)	91.67 (12.52)	0.98	.77
Mood / Emotional function	85.82 (12.09)	85.34 (12.13)	86.31 (12.26)	-0.96	.77
Self-reported PA (n= 51)	112.45 (91.79)	128.04 (120.14)	96.24 (44.50)	31.80	.22

Abbreviations. BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; F/H, fingers and hands; NP, neuropathic pain; PA, physical activity; PN, peripheral neuropathy; QOL, quality of life; SD, standard deviation; T/F, toes and feet

Physical Activity Trends

Per the Fitbit, the MI-Walk Intervention participants' (n = 25) minutes of MVPA per week increased significantly (b = 17.39; *95% CI* 1.38, 33.40; p = .03) and total PA per day increased significantly over the eight weeks (b = 7.80; *95% CI* 2.31, 13.29; p = .01). The increase in mean daily step count over time was not statistically significant (b = 157.98; *95% CI* -54.07, 370.03; p = .14).

Group comparison. The self-reported PA (PASE) scores were no different between the intervention and control groups at baseline (n = 51) and eight weeks (n = 48); the mean (SD) scores were 96.24 (44.50) in the control and 128.04 (120.14) in the intervention group at baseline and 144.17 (64.76) in the control and 156.67 (101.79) in the intervention group at eight weeks. A significant increase in self-reported PA from baseline to eight weeks was observed in the full sample (b = 44.85; 95% CI 12.57, 77.12; p = .01). On average, the intervention group's self-reported PA score was 33.07 points higher (95% CI -16.27, 82.41; p = .18) but their pre-posttest increase in PA was 24.02 points lower (95% CI -69.88, 21.83; p = .30) than those of the control group.

Motivational Interviewing Fidelity

Based on external expert review, the interventionist met basic motivational interviewing proficiency but missed key opportunities to strengthen participants' motivation for increasing their amount of aerobic exercise. The mean global Motivational Interviewing Treatment Integrity ratings were 3.67 (*range* = 3-4) for cultivating change talk, 3.67 (*range* = 3-5) for softening sustain talk, 4.33 (*range* = 4-5) for partnership, and 4.67 (*range* = 4-5) for expressing empathy.

OIPN Outcomes

OIPN severity between groups. Table III.3 shows the mean OIPN severities at the eight-week time point. Significant baseline to eight-week increases were found in the total sample's OIPN sensory ($\bar{X}_{\Delta}$ = 5.17; *95% CI* 2.44, 7.91; p < .01) and motor symptoms ($\bar{X}_{\Delta}$ = 3.41; *95% CI* 1.44, 6.26; p = .01). Specific sensory changes included an increase in tingling in the toes and feet ($\bar{X}_{\Delta}$ = 10.18; *95% CI* 3.01, 17.35; p < .01) and fingers and hands ($\bar{X}_{\Delta}$ = 20.95; *95% CI* 12.72, 29.18; p < .01). At eight weeks, the mean sensory OIPN scores were 13% lower (not significant) but motor OIPN scores were 28% higher in the intervention than the control group (not

significant). Overall, the mean severities of all the OIPN symptoms were below the CIPN20 cut-off score of 25 ("a little" OIPN, based on the 0-100 transformed scale; $\bar{X}$ = 11.76; *SD* = 10.57), except for the tingling in the fingers and hands at eight weeks ($\bar{X}$ = 37.91; *SD* = 24.96).

Table III.3

Mean OIPN Severities at the Eight-Week Time point (N = 57)

Eight-Week OIPN	Group		Intergroup		
	Intervention (*n* = 29)	Control (*n* = 28)	$\bar{X}_{\Delta}$	[95% *CI*	]
	$\bar{X}$ *(SD)*				
Sensory	10.70 (0.31)	12.28 (0.44)	1.59	-3.85	7.03
Motor	8.38 (0.32)	6.54 (0.35)	-1.84	-6.56	2.89
Tingling F/H	37.10 (0.88)	38.23 (0.97)	1.13	-12.04	14.29
Tingling T/F	17.33 (19.53)	20.51 (23.24)	3.18	-8.93	15.28
Numbness F/H	13.33 (16.67)	16.67 (27.08)	3.33	-9.38	16.05
Numbness T/F	8 (14.53)	12.82 (23.24)	4.82	-6.14	15.78
NP F/H	4.33 (12.47)	11.54 (20.96)	6.21	-3.55	15.96
NP T/F	2.67 (9.23)	2.56 (9.06)	-0.10	-5.25	5.04

Abbreviations. CI, confidence interval; F/H, fingers and hands; NP, neuropathic pain; OIPN, oxaliplatin-induced peripheral neuropathy; SD, standard deviation; T/F, toes and feet.

Statistical models. Table III.4 shows the OIPN outcome statistical models (*n* = 56-57; one outlier was removed from the motor OIPN models). The intervention had no significant effect on sensory OIPN at eight weeks ($\bar{X}_{\Delta}$ = -0.01; 95% *CI* -4.32, 4.31; $p > .99$), controlling for baseline peripheral neuropathy and oxaliplatin dose received. Mood and gender were added individually as exploratory factors. Poorer mood was significantly associated with more severe sensory OIPN at eight weeks (*b* = -0.15; 95% *CI* -0.27, -0.01; $p < .01$). Female gender was associated with an average 4.54 unit increase in eight-week sensory OIPN, adjusting for the other covariates in the model (95% *CI* -0.08, 9.17; $p = .05$). Altogether, the mood and gender covariate models each accounted for 33% and 31% of the variance in eight-week sensory OIPN, respectively ($p < .01$).

Regarding motor OIPN, the intervention did not significantly affect motor OIPN at eight weeks ($\bar{X}_{\Delta}$ = 2.39; 95% *CI* -1.04, 5.82; $p = .17$), controlling baseline motor neuropathy and oxaliplatin dose received (see Table III.4). However, adding gender to the model resulted in an

increased estimated effect ($\bar{X}_{\Delta}$) of the intervention on motor OIPN at eight weeks. The model including female gender as a covariate ($\bar{X}_{\Delta}$ = 2.38; *95% CI* –1.56, 6.32) accounted for 33% of the variance in eight-week motor OIPN (p = .01).

Concomitant medication dosage changes from baseline to eight weeks were minimal and did not differ between groups; participants' dosages decreased in 11 (21%), increased in eight (15%), and did not change in 33 (63%) participants by eight weeks.

Table III.4

Results of the OIPN Outcome ITT Analyses

Outcome	***b***	**[**	***95% CI***	**]**	**RVI**	**FMI**	**RE**	***R^2***	***p-value[a]***
Sensory OIPN (*n* = 57)									
Base model								.27	<.01*
Intervention	-0.01	-4.32	4.31		0.08	0.08	>0.99		
Baseline sensory OIPN	0.59*	0.23	0.94		0.30	0.24	>0.99		
Oxaliplatin dose	0.05*	0.01	0.09		0.14	0.13	>0.99		
Mood model								.33	< .01*
Intervention	0.27	-4.04	4.58		0.09	0.09	>0.99		
Baseline sensory OIPN	0.50*	0.13	0.87		0.29	0.24	>0.99		
Oxaliplatin dose	0.05*	0.01	0.09		0.13	0.12	>0.99		
Mood	-0.15*	-0.30	-0.00		0.11	0.11	>0.99		
Gender model								.31	<.01*
Intervention	1.29	-3.02	5.59		0.07	0.07	>0.99		
Baseline sensory OIPN	0.49*	0.15	0.83		0.35	0.27	>0.99		
Oxaliplatin dose	0.06*	0.02	0.09		0.14	0.12	>0.99		
Gender[b]	4.54	-0.08	9.17		5.27	0.11	>0.99		
Motor OIPN (*n* = 56)									
Base model								.30	.01*
Intervention	2.39	-1.04	5.82		0.13	0.12	>0.99		
Baseline motor OIPN	0.53*	0.12	0.93		0.95	0.51	>0.99		
Oxaliplatin dose	0.04*	0.01	0.06		0.10	0.10	>0.99		
Gender model								.33	.01*
Intervention	3.01	-0.62	6.64		0.17	0.16	>0.99		
Baseline motor OIPN	0.45*	0.02	0.89		1.32	0.59	>0.99		
Oxaliplatin dose	0.04*	0.01	0.07		0.13	0.12	>0.99		
Gender[b]	2.38	-1.56	6.32		0.20	0.18	>0.99		

Abbreviations. CI, confidence interval; FMI, fraction of missing information; ITT, intention to treat; OIPN, oxaliplatin-induced peripheral neuropathy; PA, physical activity; QOL, quality of life; RE, relative efficiency; RVI, relative variance increase.
[a]The *p-value* refers to the statistical significance of the full regression model.
[b]Males were coded as 0 and females were coded with a 1.
*, significant two-sided difference (p < .05).

QOL Outcomes

Table III.5 shows the QOL statistical models. The intervention did not significantly affect eight-week Global QOL and physical and emotional function outcomes. Baseline QOL/function were significant covariates in their respective models. Further, eight-week sensory OIPN was a statistically significant covariate in the emotional function outcome model (*b* = -0.36; *95% CI* -0.70, -0.03; *p* = .03). Exploratory analysis showed that improved mood was significantly associated with improved QOL (*b* = 0.51; *95% CI* 0.15, 0.87; *p* = .01). Exploring further, female gender was factored in the models and associated with an 11.00 unit decrease (*95% CI* -22.19, 0.20; *p* = .05) in QOL and an 8.21 unit decrease in physical function at eight weeks (*95% CI* -15.8, -0.57; *p* = .05), controlling for the intervention, baseline QOL/physical function, and eight-week sensory OIPN.

Table III.5

Results of the QOL Outcome ITT Analyses

Outcome	*b*	[*95% CI*]		RVI	FMI	RE	R^2	*p-value*[a]
QOL (*n* = 57)								
Base model							.38	< .01*
Intervention	-1.43	-11.21	8.35	0.10	0.09	>0.99		
Baseline QOL	0.61*	0.37	0.85	0.08	0.07	>0.99		
Eight-week sensory OIPN	-0.44	-0.91	0.03	0.09	0.08	>0.99		
Mood model							.48	<.01*
Intervention	0.25	-8.87	9.37	0.10	0.09	>0.99		
Baseline QOL	0.46*	0.21	0.70	0.12	0.11	>0.99		
Eight-week sensory OIPN	-0.15	-0.64	0.33	0.13	0.12	>0.99		
Mood	0.51*	0.15	0.87	0.22	0.18	>0.99		
Gender model							.43	<.01*
Intervention	-4.53	-14.53	5.47	0.12	0.10	>0.99		
Baseline QOL	0.56*	0.32	0.80	0.12	0.10	>0.99		
Eight-week sensory OIPN	-0.33	-0.80	0.14	0.09	0.08	>0.99		
Gender[b]	-11.00	-22.19	0.20	0.19	0.16	>0.99		
Physical Function (*n* = 57)								
Base model							.28	.06
Intervention	3.30	-2.34	8.95	0.24	0.20	>0.99		
Baseline physical function	0.28	-0.21	0.78	3.62	0.81	>0.99		
Eight-week sensory OIPN	-0.30*	-0.57	-0.03	0.17	0.15	>0.99		

Gender model							.33	.01*
Intervention	-0.11	-6.43	6.20	0.42	0.31	>0.99		
Baseline physical function	0.39	-0.01	0.79	2.64	0.75	>0.99		
Eight-week sensory OIPN	-0.20	-0.47	0.08	0.22	0.19	>0.99		
Gender[b]	-8.21*	-15.84	-0.57	0.85	0.48	>0.99		
Emotional Function (*n* = 56)								
Intervention	1.01	-5.79	7.82	0.12	0.11	>0.99	.32	<.01*
Baseline emotional function	0.54*	0.26	0.82	0.11	0.10	>0.99		
Eight-week sensory OIPN	-0.36*	-0.70	-0.03	0.13	0.11	>0.99		

Abbreviations. CI, confidence interval; FMI, fraction of missing information; ITT, intention to treat; OIPN, oxaliplatin-induced peripheral neuropathy; PA, physical activity; QOL, quality of life; RE, relative efficiency; RVI, relative variance increase.
[a]The *p-value* refers to the statistical significance of the full regression model.
[b]Males were coded as 0 and females were coded with a 1.
*, significant two-sided difference ($p < .05$).

Dose Reponse

Table III.6 provides the results just within the intervention group ($n = 29$) of the imputed mixed effects models that evaluate the effects of MVPA, total PA, and step count on the outcomes. Total PA minutes and step count per day had no effect on the outcomes. However, MVPA minutes per week had a small beneficial effect on the outcomes though not statistically significant.

MVPA and OIPN. Data trends showed that just within the intervention group, mean minutes of MVPA over the eight weeks could lead to less sensory OIPN ($b = -0.02$; 95% *CI* -0.03, 0.00; $p = .06$), controlling for baseline OIPN and eight-week oxaliplatin dose. The model accounted for 32% of the variance in sensory OIPN at eight weeks ($p = .04$). Trends also showed that mean minutes of MVPA over the eight weeks could lead to higher QOL ($b = 0.04$; 95% *CI* -0.00, 0.07; $p = .07$), controlling for baseline QOL and eight-week OIPN severity. The model accounted for 47% of the variance in QOL at eight weeks ($p < .01$). Mood and gender were not significant covariates in the models.

Table III.6

Effects of MVPA, Step Count, and Total PA on the Ouctomes (n = 29)

Outcome	*b*	[	*95% CI*	]	RVI	FMI	RE	R^2	*p-value*[a]
Sensory OIPN									
Model 1								.32	.04*
MVPA (min/week)	-0.02	-0.03	0.00[b]		0.14	0.13	>0.99		
Baseline sensory OIPN	0.66*	0.14	1.17		0.10	0.10	>0.99		
Oxaliplatin dose	0.04	-0.01	0.10		0.13	0.11	>0.99		
Model 2								.18	.21
Total PA (min/day)	-0.00	-0.06	0.06		0.13	0.12	>0.99		
Baseline sensory OIPN	0.52	-0.02	1.07		0.05	0.05	>0.99		
Oxaliplatin dose	0.04	-0.02	0.10		0.06	0.06	>0.99		
Model 3								.20	.16
Steps per day	-0.00	-0.00	0.00		0.10	0.09	>0.99		
Baseline sensory OIPN	0.55*	0.03	1.08		0.05	0.05	>0.99		
Oxaliplatin dose	0.04	-0.02	0.10		0.07	0.07	>0.99		
Motor OIPN									
Model 1								.24	.15
MVPA (min/week)	-0.01	-0.03	0.01		0.21	0.17	>0.99		
Baseline motor OIPN	0.51	-0.27	1.29		0.35	0.26	>0.99		
Oxaliplatin dose	0.05	-0.02	0.11		0.13	0.12	>0.99		
Model 2								.35	.06
Total PA (min/day)	0.02	-0.03	0.07		0.22	0.18	>0.99		
Baseline motor OIPN	0.69*	0.01	1.38		0.46	0.32	>0.99		
Oxaliplatin dose	0.07*	0.01	0.13		0.23	0.19	>0.99		
Model 3								.21	.24
Steps per day	-0.00	-0.00	0.00		0.30	0.23	>0.99		
Baseline motor OIPN	0.52	-0.27	1.32		0.34	0.26	>0.99		
Oxaliplatin dose	0.04	-0.02	0.11		0.17	0.15	>0.99		
QOL									
Model 1								.47	<.01*
MVPA (min/week)	0.04	-0.00	0.07		0.25	0.20	>0.99		
Baseline motor OIPN	0.56*	0.17	0.95		0.11	0.10	>0.99		
Oxaliplatin dose	-0.62	-1.52	0.28		0.25	0.20	>0.99		
Model 2								.20	.17
Total PA (min/day)	0.00	-0.14	0.14		0.15	0.13	>0.99		
Baseline QOL	0.53*	0.05	1.01		0.05	0.05	>0.99		
Eight-week sensory OIPN	-0.08	-0.24	0.08		0.13	0.12	>0.99		
Model 3								.27	.07
Steps per day	0.00	-0.00	0.00		0.16	0.14	>0.99		
Baseline QOL	0.44	-0.01	0.89		0.05	0.05	>0.99		
Eight-week sensory OIPN	-0.68	-1.66	0.31		0.12	0.11	>0.99		

Physical Function								
Model 1							.61	< .01*
MVPA (min/week)	0.02	-0.01	0.05	0.30	0.25	>0.99		
Baseline physical function	0.93*	0.49	1.38	0.13	0.13	>0.99		
Eight-week sensory OIPN	-0.29	-1.10	0.51	0.67	0.43	>0.99		
Model 2							.48	< .01*
Total PA (min/day)	0.00	-0.09	0.09	0.17	0.14	>0.99		
Baseline physical function	0.89*	0.45	1.33	0.04	0.04	>0.99		
Eight-week sensory OIPN	-0.03	-0.14	0.08	0.28	0.22	>0.99		
Model 3							.64	< .01*
Steps per day	0.00	-0.00	0.00	0.28	0.24	>0.99		
Baseline physical function	0.92*	0.48	1.35	0.10	0.10	>0.99		
Eight-week sensory OIPN	-0.53	-1.30	0.23	0.61	0.41	>0.99		
Emotional Function								
Model 1							.47	.01*
MVPA (min/week)	0.03	-0.01	0.06	0.37	0.27	>0.99		
Baseline emotional function	0.77*	0.23	1.31	0.20	0.17	>0.99		
Eight-week sensory OIPN	-0.71	-1.52	0.11	0.27	0.21	>0.99		
Model 2							.25	.13
Total PA (min/day)	0.03	-0.10	0.17	0.34	0.25	>0.99		
Baseline emotional function	0.82*	0.09	1.54	0.21	0.18	>0.99		
Eight-week sensory OIPN	-0.02	-0.17	0.13	0.25	0.20	>0.99		
Model 3							.40	.01*
Steps per day	0.00	-0.00	0.00	0.25	0.20	>0.99		
Baseline emotional function	0.71*	0.16	1.26	0.13	0.11	>0.99		
Eight-week sensory OIPN	-0.86*	-1.64	-0.07	0.16	0.14	>0.99		

Abbreviations. CI, confidence interval; FMI, fraction of missing information; MVPA, moderate to vigorous physical activity; OIPN, oxaliplatin-induced peripheral neuropathy; PA, physical activity; QOL, quality of life; RE, relative efficiency; RVI, relative variance increase.

*, Significant two-sided difference ($p < .05$).

[a]The *p-value* refers to the statistical significance of the full regression model.

[b]Estimate rounded to "0.00" from 0.0004; thus, the *b* coefficient was not marked with an *. Several "0.00" estimates had been rounded similarly.

Discussion

This pilot study revealed that the MI-Walk Intervention was no more or less effective than PA education alone in reducing OIPN severity and improving QOL and function by the eight-week study endpoint (10 weeks into oxaliplatin-based treatment) among GI cancer survivors. Sensory and motor OIPN symptoms significantly increased from baseline to eight-weeks but remained mild in severity at the eight-week time point. Tingling in the fingers and hands was most prevalent and demonstrated the greatest increase from baseline to the eight-week time point. Exploratory analysis showed that female gender and engagement in fewer minutes of MVPA per week may be additional factors associated with more severe eight-week sensory OIPN severity and worse QOL. Ultimately, self-reported PA level was similar between groups at and had significantly increased from baseline in the control group by eight weeks, suggesting potential bias and a lack of assay sensitivity..

No other studies to date have evaluated a comprehensive motivational enhancement therapy- and home-based eight-week aerobic walking intervention, compared to PA education alone, to reduce OIPN. However, several studies have tested home-based aerobic exercise interventions among individuals receiving neurotoxic chemotherapy treatment and provide insight on the effects of various interventions on MVPA levels, and CIPN and QOL outcomes. Confounding bias due to a lack of difference in PA levels between groups has been a prevalent problem in prior exercise trials among patients receiving cancer treatment (Furmaniak, Menig, & Markes, 2016). For example, some studies have shown equal increases in self-reported PA levels and/or fitness between control group participants who received weekly to every other week telephone follow-up alone and intervention participants who received a tailored MVPA prescription with telephone follow-up (Courneya et al., 2004; Griffith et al., 2009). Other studies

have shown efficacy of a simple exercise prescription from an oncologist in improving PA levels. Although increasing exercise in cancer survivors is theorized as a complex behavior that requires complex interventions like the MI-Walk Intervention, the current study suggests PA education with telephone follow-up every two weeks could be equally effective. Some evidence also suggests PA education and weekly to every two week-follow-up by a nurse, oncologist, or trained therapist may be sufficient to promote the optimal short-term increases in MVPA among patients receiving active cancer treatment (Cadmus et al., 2009; Griffith et al., 2009; Hawkes et al., 2013; L. W. Jones, Courneya, Fairey, & Mackey, 2004; Mock et al., 2005; Swenson, Nissen, & Henly, 2010).

The observed small increases in OIPN in the current study match the literature that suggests aerobic exercise may blunt but not completely prevent the development of acute CIPN. However, the mean sensory OIPN severities observed in both groups at eight weeks may have been less severe than the average sensory OIPN severities (CIPN20 sensory scores) that have previously been observed at the sixth cycle of oxaliplatin (M = 12-15) (Loprinzi et al., 2014; Pachman et al., 2015, 2016; Zimmerman et al., 2016). The observed mean motor OIPN severity in this study did not appear lower than the averages observed previously (Pachman et al., 2015, 2016). Reduction but not complete prevention of CIPN was also observed in other aerobic exercise-containing intervention trials among patients who were just starting active neurotoxic chemotherapy treatment and had no baseline peripheral neuropathy (Courneya et al., 2013, 2014; Henke et al., 2014; Kleckner et al., 2018; Streckmann et al., 2014). However, the studies were not designed to evaluate CIPN as the primary outcome and lacked optimal measurement and evaluation of the intervention effect on long term CIPN persistence. Specifically, the CIPN outcomes were heterogeneous and lacked specificity. For example, one study used a single item

on a general peripheral neuropathy on the EORTC QLQ-lung cancer 13 module to measure CIPN (Henke et al., 2014). Another study evaluated taxane- and platinum-based CIPN, using a zero to 10 numeric rating scale of numbness/tingling and hot/cold sensation that had not been previously tested for reliability and validity (Kleckner et al., 2018).

The finding that tingling in the fingers and hands was the most severe and bothersome mirrors the results of other studies that suggest tingling in the fingers, hands, toes, and feet are the earliest and most severe cumulative OIPN symptoms (Barton et al., 2011; Grothey et al., 2011; Loprinzi et al., 2014; Pachman et al., 2015, 2016; Ventzel, Jensen, et al., 2016; Zimmerman et al., 2016). Another recent study also showed tingling in the fingers and hands may interfere the most with daily activities (Drott et al., 2019). Thus, tingling in the fingers and hands should be a primary focus of subsequent studies in patients receiving oxaliplatin.

The optimal intensity of PA (i.e., step counts and light to vigorous PA versus MVPA) to target CIPN is unclear. The current study showed trends of associations between more Fitbit-measured minutes of MVPA and less severe OIPN and improved QOL and function at eight weeks. Other evidence also suggests that home-based aerobic exercise-containing interventions could lead to reduced CIPN (McCrary et al., 2019), and improved physical function and QOL (McCrary et al., 2019; Mizrahi et al., 2015). Specifically, one quasi-experiment found reductions in sensory CIPN signs and symptoms (per the CIPN20 and Total Neuropathy Score) and improved physical function and overall QOL after an eight-week home- and clinic-based aerobic, strength, and balance training intervention among individuals with baseline chronic CIPN (McCrary et al., 2019). Another RCT suggested the benefits of light-intensity PA for CIPN. Specifically, the study showed better sensory CIPN outcomes (per 0-10 numeric rating scale) among taxane- or platinum-based chemotherapy-receiving participants ($N = 355$) who received a

six-week home- and step count-based PA and elastic band strength training intervention compared to the no exercise control group (Kleckner et al., 2018).

The pathophysiology of OIPN and the potential mechanisms that could mediate the influence of aerobic exercise on OIPN is still under investigation. Some evidence suggests that aerobic exercise may decrease OIPN primarily by bolstering blood circulation and reducing oxidative stress and neuronal apoptosis (Azizbeigi et al., 2015; Chang et al., 2015; Di Cesare Mannelli et al., 2012; Gomez-Cabrera et al., 2015; L. W. Jones et al., 2014; Karimi & Roshan, 2013; Park et al., 2013; Schaun et al., 2011; Tofthagen et al., 2013; Zhou et al., 2016). Aerobic exercise may also reduce OIPN by decreasing inflammation (Chen, Tzeng, Lin, Hung, & Wang, 2014; S. B. Jones et al., 2013; Rogers et al., 2013; Schmidt et al., 2016; Yoon, Thakur, Isham, Fayad, & Chattopadhyay, 2015), and improving neuronal metabolism, homeostasis (Dobson, McMillan, & Li, 2014; Marcelino et al., 2013; Marques-Aleixo, Oliveira, Moreira, Magalhaes, & Ascensao, 2012), and coordination/regulation of firing and inhibition (Taube & Gollhofer, 2010; Taube, Gruber, et al., 2007; Taube, Kullmann, et al., 2007). The release of endogenous opioids (Kim, Byun, & Choi, 2015; Stagg et al., 2011), pain-inhibiting neurotransmitters (Bobinski et al., 2015; Kami, Taguchi Ms, Tajima, & Senba, 2016), and neurotrophic factors (Detloff, Smith, Quiros Molina, Ganzer, & Houle, 2014; Molteni, Zheng, Ying, Gomez-Pinilla, & Twiss, 2004; Seo et al., 2009; Zhou et al., 2016) are well-known effects of aerobic exercise that may moderate OIPN severity. Finally, aerobic exercise may help to reduce symptom and psychological distress that are known to cluster and interact with OIPN (e.g., fatigue, anxiety, and depression) (Cramp & Byron-Daniel, 2012; Furmaniak et al., 2016; Mishra, Scherer, Snyder, Geigle, & Gotay, 2015; Morielli et al., 2016; Van Vulpen et al., 2016; van Waart et al., 2015; Yang, Tsai, Huang, & Lin,

2011) and bolster coping, mood, and positive lifestyle behaviors (Courneya, 2014; Lynch, Cerin, Owen, Hawkes, & Aitken, 2008; Peddle, Au, & Courneya, 2008; Thraen-Borowski et al., 2013).

Exploratory findings of the current study noted that mood and female gender may independently be potential predictors of poorer OIPN and QOL outcomes in participants of an exercise intervention study. A prior study has demonstrated that higher baseline mood may predict better response to CIPN treatments, such as duloxetine—the only currently endorsed drug to treat established CIPN (Smith et al., 2017). Additionally, OIPN may cluster and interact with anxiety and depression; and influence QOL and function (Knoerl, Chornoby, & Smith, 2018, 2019; Mols et al., 2013; Skerman, Yates, & Battistutta, 2012). Mood may have also indirectly influenced the outcomes: aerobic exercise has frequently shown associations with improved mood and QOL (Ekkekakis, Parfitt, & Petruzzello, 2011; Hawkes et al., 2013; Henriksson, Arving, Johansson, Igelstrom, & Nordin, 2016; Mas et al., 2015) and potentially lower symptom burden (Low et al., 2017).

A similar home-based PA trial also showed that males responded and had better CIPN outcomes (Kleckner et al., 2018). The findings in the current study that gender effects only influenced physical but not emotional function suggest that several physiological differences are likely responsible for mediating or moderating the effects of aerobic exercise on OIPN. Gender-based differences in the cardiovascular, musculoskeletal, metabolic, immune, and neuroendocrine system adaptation to exercise training may alter and blunt the effects of aerobic exercise on OIPN. For example, prominent differences in the cardiovascular and pulmonary systems and their response to aerobic exercise include decreased lung capacity (Talaminos Barroso, Marquez Martin, Roa Romero, & Ortega Ruiz, 2018; Townsend, Miller, & Prakash, 2012), heart contractility and stroke volume, hemoglobin, and venous return in women compared

to men (Barnes & Fu, 2018; Kouvari, Yannakoulia, Souliotis, & Panagiotakos, 2018). Further, women may have increased pain sensitivity (Kowalczyk et al., 2010; Maurer, Lissounov, Knezevic, Candido, & Knezevic, 2016; Popescu, LeResche, Truelove, & Drangsholt, 2010), and greater activation of the amygdala, hypothalamus, and stress response to noxious stimuli than men (Jancke, 2018). Additional evidence is also emerging related to the effects of sex steroid hormones on gene expression, neurotransmitters, neurodegeneration, and inflammatory responses (Forger, Strahan, & Castillo-Ruiz, 2016; Kohman, Bhattacharya, Wojcik, & Rhodes, 2013; McCarthy, Nugent, & Lenz, 2017; McCarthy, Pickett, VanRyzin, & Kight, 2015; Popescu et al., 2010; Villa, Della Torre, & Maggi, 2019).

Limitations

The results of this study may only be applicable to younger, white, GI cancer survivors with few to no comorbidities. The small sample size may have limited the power to detect significant changes in the outcomes, and the convenience sampling method may have biased the results. Further, inadequate assay sensitivity—"the ability of a trial to distinguish an effective from an ineffective treatment" (Food and Drug Administration & HHS, 2001)—may have contributed to the current study's inability to detect significant results (Dworkin et al., 2012). Specifically, the timing of outcome measurement may have been premature in the study. Sensory and motor OIPN severities were still mild in severity at the eight-week time point (coinciding with the sixth infusion). Additionally, acute OIPN fluctuates; thus, recommendations suggest repeated pain measurements to obtain an adequately reliable response that could maximize the study's ability to detect significant differences (Heapy et al., 2014).

Additionally, total PA level could not be evaluated as a covariate in the analyses due to lack of reliable objective PA measurement. During the eight-week assessment visit, participants

received an ActiGraph GT9X Link and scripted instructions to wear it during the day even when napping or resting; yet, several participants did not wear the ActiGraph on days when they were physically inactive. Other participants lost their ActiGraphs while walking outside. Ultimately, over half of the ActiGraph data were missing, presumably not at random. The high risk of confounding bias due to the observed increase in self-reported PA among the control group participants inhibited the study's evaluation of whether the mild eight-week OIPN levels were due to the efficacy of the interventions/higher levels.

Additionally, the first author recruited participants, conducted the MI-Walk Intervention, and provided the PA education to the control group participants. The first author could have unintentionally provided motivational interviewing to both groups of participants during the intervention orientation and follow-up phone calls. Further, inadequate participant blinding could have led to compensatory rivalry bias and placebo effects, particularly because the PA education reviewed the broad health- and cancer treatment-related benefits of exercise.

Conclusions

The results of this study are inconclusive regarding the efficacy of home-based aerobic walking for OIPN due to limited assay sensitivity. The MI-Walk Intervention was no more effective than PA education alone at improving self-reported PA levels. Further consideration is needed regarding the most effective home-based aerobic exercise intervention components to maximize MVPA among individuals receiving neurotoxic chemotherapy and appropriate control conditions.

***Future directions*.** Further study of the effects of home-based aerobic exercise on OIPN is warranted. Future home-based aerobic walking studies should ensure that the participants

receive separate interventions. The control condition, if education-based, should focus on broad health or other education other than PA.

In future studies, the CIPN outcome measures should be specific to the type of neurotoxic chemotherapy. For example, this study found that tingling in the fingers and hands was the most severe symptom of OIPN; thus, investigators of OIPN outcomes may want to evaluate tingling of the fingers and hands as one of their primary measures. The utilization of both patient-reported measures and clinical assessment of OIPN would also strengthen the studies. Finally, future studies should evaluate mediators and moderators of the effects of aerobic exercise on OIPN development and QOL. For example, future studies could evaluate gender as a moderator of the effects of aerobic exercise on sensory OIPN, and studies could evaluate mood as a mediator of the effects of aerobic exercise on QOL and fatigue.

Ultimately, the goal is for future trials to contribute toward developing the most optimal exercise prescriptions for maximizing MVPA, QOL, and function, and reducing cancer treatment side effects, including OIPN. Currently, the focus must still be on establishing or refuting the efficacy of aerobic exercise for OIPN and understanding the intervention's mediating mechanism of actions. If shown effective, the science should aim to uncover the optimal type, dosage, and delivery of exercise for OIPN and other types of CIPN, as well as the most accessible, implementable, and cost-effective exercise interventions for chemotherapy-receiving cancer survivors.

References

Aaronson, N. K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N. J., … de Haes, J. C. (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute*, *85*(5), 365–376.

Alberti, P., Rossi, E., Cornblath, D. R., Merkies, I. S. J., Postma, T. J., Frigeni, B., … Cavaletti, G. (2014). Physician-assessed and patient-reported outcome measures in chemotherapy-induced sensory peripheral neurotoxicity: Two sides of the same coin. *Annals of Oncology*, *25*(1), 257–264. https://doi.org/10.1093/annonc/mdt409

American Cancer Society. (2014). Physical Activity and the Cancer Patient. Retrieved February 3, 2017, from https://www.cancer.org/treatment/survivorship-during-and-after-treatment/staying-active/physical-activity-and-the-cancer-patient.html%0D

Andre, T., Boni, C., Mounedji-Boudiaf, L., Navarro, M., Tabernero, J., Hickish, T., … de Gramont, A. (2004). Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *The New England Journal of Medicine*, *350*(23), 2343–2351. https://doi.org/10.1056/NEJMoa032709

Argyriou, A. A., Bruna, J., Marmiroli, P., & Cavaletti, G. (2012). Chemotherapy-induced peripheral neurotoxicity (CIPN): An update. *Critical Reviews in Oncology/Hematology*, *82*(1), 51–77. https://doi.org/10.1016/j.critrevonc.2011.04.012

Argyriou, A. A., Cavaletti, G., Briani, C., Velasco, R., Bruna, J., Campagnolo, M., … Kalofonos, H. P. (2013). Clinical pattern and associations of oxaliplatin acute neurotoxicity: A prospective study in 170 patients with colorectal cancer. *Cancer*, *119*(2), 438–444. Retrieved from http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L52110114

Azizbeigi, K., Azarbayjani, M. A., Atashak, S., & Stannard, S. R. (2015). Effect of moderate and high resistance training intensity on indices of inflammatory and oxidative stress. *Research in Sports Medicine (Print)*, *23*(1), 73–87. https://doi.org/10.1080/15438627.2014.975807

Bai, Y., Hibbing, P., Mantis, C., & Welk, G. J. (2018). Comparative evaluation of heart rate-based monitors: Apple Watch vs Fitbit Charge HR. *Journal of Sports Sciences*, *36*(15), 1734–1741. https://doi.org/10.1080/02640414.2017.1412235

Bao, T., Basal, C., Seluzicki, C., Li, S. Q., Seidman, A. D., & Mao, J. J. (2016). Long-term chemotherapy-induced peripheral neuropathy among breast cancer survivors: prevalence, risk factors, and fall risk. *Breast Cancer Research and Treatment*, *159*(2), 327–333. https://doi.org/10.1007/s10549-016-3939-0

Barnes, J. N., & Fu, Q. (2018). Sex-Specific Ventricular and Vascular Adaptations to Exercise BT - Sex-Specific Analysis of Cardiovascular Function. In P. L. M. Kerkhof & V. M. Miller (Eds.) (pp. 329–346). Cham: Springer International Publishing. https://doi.org/10.1007/978-3-319-77932-4_21

Barton, D. L., Wos, E. J., Qin, R., Mattar, B. I., Green, N. B., Lanier, K. S., … Loprinzi, C. L. (2011). A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. *Supportive Care in Cancer*, *19*(6), 833–841. https://doi.org/10.1007/s00520-010-0911-0

Beijers, A. J. M., Mols, F., Tjan-Heijnen, V. C. G., Faber, C. G., van de Poll-Franse, L. V, & Vreugdenhil, G. (2015). Peripheral neuropathy in colorectal cancer survivors: The influence of oxaliplatin administration. Results from the population-based PROFILES registry. *Acta Oncologica*, *54*(4), 463–469. https://doi.org/10.3109/0284186X.2014.980912

Berger, A. M. A. M. (2010). Fatigue and other variables during adjuvant chemotherapy for colon and rectal cancer. *Oncology Nursing Forum*, *37*(6), E359–E369. https://doi.org/10.1188/10.ONF.E359-E369

Binkley, J. M., Harris, S. R., Levangie, P. K., Pearl, M., Guglielmino, J., Kraus, V., & Rowden, D. (2012). Patient perspectives on breast cancer treatment side effects and the prospective surveillance model for physical rehabilitation for women with breast cancer. *Cancer*, *118*(8 Suppl), 2207–2216. https://doi.org/10.1002/cncr.27469

Bobinski, F., Ferreira, T. A. A., Cordova, M. M., Dombrowski, P. A., da Cunha, C., Santo, C. C. do E., … Santos, A. R. S. (2015). Role of brainstem serotonin in analgesia produced by low-intensity exercise on neuropathic pain after sciatic nerve injury in mice. *Pain*, *156*(12), 2595–2606. https://doi.org/10.1097/j.pain.0000000000000372

Borg, G. (1998). *Borg's perceived exertion and pain scales. Borg's perceived exertion and pain scales.* Champaign, IL, US: Human Kinetics.

Breusch, T., & Pagan, A. (1979). A simple test for heteroscedasticity and random coefficient variation. *Econometrica*, *47*, 1287–1294.

Brooke, S. M., An, H.-S., Kang, S.-K., Noble, J. M., Berg, K. E., & Lee, J.-M. (2017). Concurrent Validity of Wearable Activity Trackers Under Free-Living Conditions. *Journal of Strength and Conditioning Research*, *31*(4), 1097–1106. https://doi.org/10.1519/JSC.0000000000001571

Brydoy, M., Oldenburg, J., Klepp, O., Bremnes, R. M., Wist, E. A., Wentzel-Larsen, T., … Fossa, S. D. (2009). Observational study of prevalence of long-term Raynaud-like phenomena and neurological side effects in testicular cancer survivors. *Journal of the National Cancer Institute*, *101*(24), 1682–1695. https://doi.org/10.1093/jnci/djp413

Burton, E., Hill, K. D., Lautenschlager, N. T., Thogersen-Ntoumani, C., Lewin, G., Boyle, E., & Howie, E. (2018). Reliability and validity of two fitness tracker devices in the laboratory and home environment for older community-dwelling people. *BMC Geriatrics*, *18*(1), 103. https://doi.org/10.1186/s12877-018-0793-4

Cadmus, L. A., Salovey, P., Yu, H., Chung, G., Kasl, S., & Irwin, M. L. (2009). Exercise and quality of life during and after treatment for breast cancer: Results of two randomized controlled trials. *Psycho-Oncology*, *18*(4), 343–352. https://doi.org/10.1002/pon.1525

Cankurtaran, E. S., Ozalp, E., Soygur, H., Ozer, S., Akbiyik, D. I., & Bottomley, A. (2008). Understanding the reliability and validity of the EORTC QLQ-C30 in Turkish cancer patients. *European Journal of Cancer Care*, *17*(1), 98–104. https://doi.org/10.1111/j.1365-2354.2007.00827.x

Carozzi, V. A., Canta, A., & Chiorazzi, A. (2015). Chemotherapy-induced peripheral neuropathy: What do we know about mechanisms? *Neuroscience Letters*, *596*, 90–107. https://doi.org/10.1016/j.neulet.2014.10.014

Cavaletti, G., Cornblath, D. R., Merkies, I. S. J., Postma, T. J., Rossi, E., Frigeni, B., … Pessino, A. (2013). The chemotherapy-induced peripheral neuropathy outcome measures standardization study: From consensus to the first validity and reliability findings. *Annals of Oncology*, *24*(2), 454–462. https://doi.org/10.1093/annonc/mds329

Chang, C.-F., Chang, C.-C., Hwang, S.-L., & Chen, M.-Y. (2015). Effects of Buerger exercise combined health-promoting program on peripheral neurovasculopathy among community residents at high risk for diabetic foot ulceration. *Worldviews on Evidence-Based Nursing*, *12*(3), 145–153. https://doi.org/10.1111/wvn.12091

Chen, Y.-W., Tzeng, J.-I., Lin, M.-F., Hung, C.-H., & Wang, J.-J. (2014). Forced treadmill running suppresses postincisional pain and inhibits upregulation of substance P and cytokines in rat dorsal root ganglion. *The Journal of Pain*, *15*(8), 827–834. https://doi.org/10.1016/j.jpain.2014.04.010

Courneya, K. S. (2014). A multicenter randomized trial of the effects of exercise dose and type on psychosocial distress in breast cancer patients undergoing chemotherapy. *Cancer Epidemiology, Biomarkers & Prevention*, *23*(5), 857–864. https://doi.org/10.1158/1055-9965.EPI-13-1163

Courneya, K. S., Friedenreich, C. M., Quinney, H. A., Fields, A. L. A., Jones, L. W., & Fairey, A. S. (2004). Predictors of adherence and contamination in a randomized trial of exercise in colorectal cancer survivors. *Psycho-Oncology*, *13*(12), 857–866. https://doi.org/10.1002/pon.802

Courneya, K. S., McKenzie, D. C., Mackey, J. R., Gelmon, K., Friedenreich, C. M., Yasui, Y., … Segal, R. J. (2013). Effects of exercise dose and type during breast cancer chemotherapy: Multicenter randomized trial. *Journal of the National Cancer Institute*, *105*(23), 1821–1832. https://doi.org/10.1093/jnci/djt297

Courneya, K. S., McKenzie, D. C., Mackey, J. R., Gelmon, K., Friedenreich, C. M., Yasui, Y., … Segal, R. J. (2014). Subgroup effects in a randomised trial of different types and doses of exercise during breast cancer chemotherapy. *British Journal of Cancer*, *111*(9), 1718–1725. https://doi.org/10.1038/bjc.2014.466

Cox-Martin, E., Trahan, L. H., Cox, M. G., Dougherty, P. M., Lai, E. A., & Novy, D. M. (2017). Disease burden and pain in obese cancer patients with chemotherapy-induced peripheral neuropathy. *Supportive Care in Cancer*, *25*(6), 1873–1879. https://doi.org/10.1007/s00520-017-3571-5

Cramp, F., & Byron-Daniel, J. (2012). Exercise for the management of cancer-related fatigue in adults. *The Cochrane Database of Systematic Reviews*, *11*(2), CD006145. https://doi.org/10.1002/14651858.CD006145.pub3

de la Morena Barrio, P., Conesa, M. A. V., Gonzalez-Billalabeitia, E., Urrego, E., Garcia-Garre, E., Garcia-Martinez, E., … de la Pena, F. A. (2015). Delayed recovery and increased severity of Paclitaxel-induced peripheral neuropathy in patients with diabetes. *JNCCN*, *13*(4), 417–423.

Dermitzakis, E. V, Kimiskidis, V. K., Lazaridis, G., Alexopoulou, Z., Timotheadou, E., Papanikolaou, A., … Fountzilas, G. (2016). The impact of paclitaxel and carboplatin chemotherapy on the autonomous nervous system of patients with ovarian cancer. *BMC Neurology*, *16*(1), 190. https://doi.org/10.1186/s12883-016-0710-4

Detloff, M. R., Smith, E. J., Quiros Molina, D., Ganzer, P. D., & Houle, J. D. (2014). Acute exercise prevents the development of neuropathic pain and the sprouting of non-peptidergic (GDNF- and artemin-responsive) c-fibers after spinal cord injury. *Experimental Neurology*, *255*, 38–48. https://doi.org/10.1016/j.expneurol.2014.02.013

Dhawan, S., Andrews, R., Kumar, L., Wadhwa, S., & Shukla, G. (2019). 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*. https://doi.org/10.1097/NCC.0000000000000693

Di Cesare Mannelli, L., Zanardelli, M., Failli, P., & Ghelardini, C. (2012). Oxaliplatin-induced neuropathy: Oxidative stress as pathological mechanism. Protective effect of silibinin. *The Journal of Pain*, *13*(3), 276–284. https://doi.org/10.1016/j.jpain.2011.11.009

Dinger, M. K., Oman, R. F., Taylor, E. L., Vesely, S. K., & Able, J. (2004). Stability and convergent validity of the Physical Activity Scale for the Elderly (PASE). *The Journal of Sports Medicine and Physical Fitness*, *44*(2), 186–192.

Dobson, J. L., McMillan, J., & Li, L. (2014). Benefits of exercise intervention in reducing neuropathic pain. *Frontiers in Cellular Neuroscience*, *8*, 102. https://doi.org/10.3389/fncel.2014.00102

Drott, J., Fomichov, V., Starkhammar, H., Borjeson, S., Kjellgren, K., & Bertero, C. (2019). Oxaliplatin-induced neurotoxic side effects and their impact on daily activities: A longitudinal study among patients with colorectal cancer. *Cancer Nursing*, *42*(6), E40–E48. https://doi.org/10.1097/NCC.0000000000000674

Dworkin, R. H., Turk, D. C., Farrar, J. T., Haythornthwaite, J. A., Jensen, M. P., Katz, N. P., … Witter, J. (2005). Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*, *113*(1–2), 9–19. https://doi.org/10.1016/j.pain.2004.09.012

Dworkin, R. H., Turk, D. C., Peirce-Sandner, S., Burke, L. B., Farrar, J. T., Gilron, I., … Ziegler, D. (2012). Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations. *Pain*, *153*(6), 1148–1158. https://doi.org/10.1016/j.pain.2012.03.003

Ekkekakis, P., Parfitt, G., & Petruzzello, S. J. (2011). The pleasure and displeasure people feel when they exercise at different intensities: Decennial update and progress towards a tripartite rationale for exercise intensity prescription. *Sports Medicine*, *41*(8), 641–671. https://doi.org/10.2165/11590680-000000000-00000

El-Shami, K., Oeffinger, K. C., Erb, N. L., Willis, A., Bretsch, J. K., Pratt-Chapman, M. L., … Cowens-Alvarado, R. L. (2015). American Cancer Society colorectal cancer survivorship care guidelines. *CA Cancer Journal for Clinicians*, *65*(6), 427–455. https://doi.org/10.3322/caac.21286

Exposito Vizcaino, S., Casanova-Molla, J., Escoda, L., Galan, S., & Miro, J. (2018). Neuropathic pain in cancer patients treated with bortezomib. *Neurologia*, *33*(1), 28–34. https://doi.org/10.1016/j.nrl.2016.05.008

Farrar, J. T., Young, J. P. J., LaMoreaux, L., Werth, J. L., & Poole, R. M. (2001). Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*, *94*(2), 149–158.

Feehan, L. M., Geldman, J., Sayre, E. C., Park, C., Ezzat, A. M., Yoo, J. Y., … Li, L. C. (2018). Accuracy of Fitbit devices: Systematic review and narrative syntheses of quantitative data. *JMIR MHealth and UHealth*, *6*(8), e10527–e10527. https://doi.org/10.2196/10527

Fernandes, J., & Kumar, S. (2016). Effect of lower limb closed kinematic chain exercises on balance in patients with chemotherapy-induced peripheral neuropathy: A pilot study. *International Journal of Rehabilitation Research*. https://doi.org/10.1097/MRR.0000000000000196

Fitbit. (2019). What Are Active Minutes? Retrieved October 15, 2019, from https://help.fitbit.com/articles/en_US/Help_article/1379

Food and Drug Administration, & HHS. (2001). International Conference on Harmonisation. E10: Choice of control groups and related issues in clinical trials. *Federal Register*, *66*(93), 24390–24391. Retrieved from https://www.govinfo.gov/content/pkg/FR-2001-05-14/pdf/01-12026.pdf

Forger, N. G., Strahan, A. J., & Castillo-Ruiz, A. (2016). Cellular and molecular mechanisms of sexual differentiation in the mammalian nervous system. *Frontiers in Neuroendocrinology*, *40*, 67–86. https://doi.org/10.1016/j.yfrne.2016.01.001

Forsen, L., Loland, N. W., Vuillemin, A., Chinapaw, M. J. M., van Poppel, M. N. M., Mokkink, L. B., … Terwee, C. B. (2010). Self-administered physical activity questionnaires for the elderly: A systematic review of measurement properties. *Sports Medicine*, *40*(7), 601–623. https://doi.org/10.2165/11531350-000000000-00000

Furmaniak, A. C., Menig, M., & Markes, M. H. (2016). Exercise for women receiving adjuvant therapy for breast cancer. *Cochrane Database of Systematic Reviews*, *2016*(9). https://doi.org/10.1002/14651858.CD005001.pub3

Giannoccaro, M. P., Donadio, V., Gomis Perez, C., Borsini, W., Di Stasi, V., & Liguori, R. (2011, April). Somatic and autonomic small fiber neuropathy induced by bortezomib therapy: An immunofluorescence study. *Neurological Sciences*. Italy. https://doi.org/10.1007/s10072-010-0475-2

Gomez-Cabrera, M. C., Salvador-Pascual, A., Cabo, H., Ferrando, B., & Vina, J. (2015). Redox modulation of mitochondriogenesis in exercise. Does antioxidant supplementation blunt the benefits of exercise training? *Free Radical Biology & Medicine*, *86*, 37–46. https://doi.org/10.1016/j.freeradbiomed.2015.04.006

Granger, C. L., Parry, S. M., & Denehy, L. (2015). The self-reported Physical Activity Scale for the Elderly (PASE) is a valid and clinically applicable measure in lung cancer. *Supportive Care in Cancer*, *23*(11), 3211–3218. https://doi.org/10.1007/s00520-015-2707-8

Greenlee, H., Hershman, D. L., Shi, Z., Kwan, M. L., Ergas, I. J., Roh, J. M., & Kushi, L. H. (2017). BMI, lifestyle factors and taxane-induced neuropathy in breast cancer patients: The pathways study. *Journal of the National Cancer Institute*, *109*(2). https://doi.org/10.1093/jnci/djw206

Gresham, G., Hendifar, A. E., Spiegel, B., Neeman, E., Tuli, R., Rimel, B. J., … Shinde, A. M. (2018). Wearable activity monitors to assess performance status and predict clinical outcomes in advanced cancer patients. *Npj Digital Medicine*, *1*(1), 27.

Griffith, K., Wenzel, J., Shang, J., Thompson, C., Stewart, K., & Mock, V. (2009). Impact of a walking intervention on cardiorespiratory fitness, self-reported physical function, and pain in patients undergoing treatment for solid tumors. *Cancer*, *115*(20), 4874–4884. https://doi.org/10.1002/cncr.24551

Grothey, A., Nikcevich, D. A., Sloan, J. A., Kugler, J. W., Silberstein, P. T., Dentchev, T., … Loprinzi, C. L. (2011). Intravenous calcium and magnesium for oxaliplatin-induced sensory neurotoxicity in adjuvant colon cancer: NCCTG N04C7. *Journal of Clinical Oncology*, *29*(4), 421–427. https://doi.org/10.1200/JCO.2010.31.5911

Hawkes, A. L., Chambers, S. K., Pakenham, K. I., Patrao, T. A., Baade, P. D., Lynch, B. M., … Courneya, K. S. (2013). Effects of a telephone-delivered multiple health behavior change intervention (CanChange) on health and behavioral outcomes in survivors of colorectal cancer: A randomized controlled trial. *Journal of Clinical Oncology*, *31*(18), 2313–2321. https://doi.org/10.1200/JCO.2012.45.5873

Heapy, A., Dziura, J., Buta, E., Goulet, J., Kulas, J. F., & Kerns, R. D. (2014). Using multiple daily pain ratings to improve reliability and assay sensitivity: how many is enough? *The Journal of Pain : Official Journal of the American Pain Society*, *15*(12), 1360–1365. https://doi.org/10.1016/j.jpain.2014.09.012

Henke, C. C., Cabri, J., Fricke, L., Pankow, W., Kandilakis, G., Feyer, P. C., & de Wit, M. (2014). Strength and endurance training in the treatment of lung cancer patients in stages IIIA/IIIB/IV. *Supportive Care in Cancer*, *22*(1), 95–101. https://doi.org/10.1007/s00520-013-1925-1

Henriksson, A., Arving, C., Johansson, B., Igelstrom, H., & Nordin, K. (2016). Perceived barriers to and facilitators of being physically active during adjuvant cancer treatment. *Patient Education and Counseling*, *99*(7), 1220–1226. https://doi.org/10.1016/j.pec.2016.01.019

Hershman, D. L., Till, C., Wright, J. D., Awad, D., Ramsey, S. D., Barlow, W. E., … Unger, J. (2016). Comorbidities and risk of chemotherapy-induced peripheral neuropathy among participants 65 years or older in southwest oncology group clinical trials. *Journal of Clinical Oncology*, *34*(25), 3014–3022. https://doi.org/10.1200/JCO.2015.66.2346

Jancke, L. (2018). Sex/gender differences in cognition, neurophysiology, and neuroanatomy [version 1; peer review: 3 approved]. *F1000Research*, *7*(805). https://doi.org/10.12688/f1000research.13917.1

Jones, L. W., Courneya, K. S., Fairey, A. S., & Mackey, J. R. (2004). Effects of an oncologist's recommendation to exercise on self-reported exercise behavior in newly diagnosed breast cancer survivors: A single-blind, randomized controlled trial. *Annals of Behavioral Medicine*, *28*(2), 105–113. https://doi.org/10.1207/s15324796abm2802_5

Jones, L. W., Hornsby, W. E., Freedland, S. J., Lane, A., West, M. J., Moul, J. W., … Eves, N. D. (2014). Effects of nonlinear aerobic training on erectile dysfunction and cardiovascular function following radical prostatectomy for clinically localized prostate cancer. *European Urology*, *65*(5), 852–855. https://doi.org/10.1016/j.eururo.2013.11.009

Jones, S. B., Thomas, G. A., Hesselsweet, S. D., Alvarez-Reeves, M., Yu, H., & Irwin, M. L. (2013). Effect of exercise on markers of inflammation in breast cancer survivors: The Yale exercise and survivorship study. *Cancer Prevention Research*, *6*(2), 109–118. https://doi.org/10.1158/1940-6207.CAPR-12-0278

Kami, K., Taguchi Ms, S., Tajima, F., & Senba, E. (2016). Improvements in impaired GABA and GAD65/67 production in the spinal dorsal horn contribute to exercise-induced hypoalgesia in a mouse model of neuropathic pain. *Molecular Pain*, *12*. https://doi.org/10.1177/1744806916629059

Karimi, N., & Roshan, V. D. (2013). Change in adiponectin and oxidative stress after modifiable lifestyle interventions in breast cancer cases. *Asian Pacific Journal of Cancer Prevention*, *14*(5), 2845–2850.

Kawakami, K., Tunoda, T., Takiguchi, T., Shibata, K., Ohtani, T., Kizu, J., … Taguchi, K. (2012). Factors exacerbating peripheral neuropathy induced by paclitaxel plus carboplatin in non-small cell lung cancer. *Oncology Research*, *20*(4), 179–185.

Kerckhove, N., Collin, A., Conde, S., Chaleteix, C., Pezet, D., & Balayssac, D. (2017). Long-term effects, pathophysiological mechanisms, and risk factors of chemotherapy-induced peripheral neuropathies: A comprehensive literature review. *Frontiers in Pharmacology*, *8*, 86. https://doi.org/10.3389/fphar.2017.00086

Kim, Y.-J., Byun, J.-H., & Choi, I.-S. (2015). Effect of exercise on micro-opioid receptor expression in the rostral ventromedial medulla in neuropathic pain rat model. *Annals of Rehabilitation Medicine*, *39*(3), 331–339. https://doi.org/10.5535/arm.2015.39.3.331

Kleckner, I. R., Kamen, C., Gewandter, J. S., Mohile, N. A., Heckler, C. E., Culakova, E., … Musian, 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

Knoerl, R., Chornoby, Z., & Smith, E. M. L. (2018). Estimating the frequency, severity, and clustering of SPADE symptoms in chronic painful chemotherapy-induced peripheral neuropathy. *Pain Management Nursing*, *19*(4), 354–365. https://doi.org/10.1016/j.pmn.2018.01.001

Knoerl, R., Chornoby, Z., & Smith, E. M. L. (2019). Corrigendum to 'Estimating the frequency, severity, and clustering of SPADE symptoms in chronic painful chemotherapy-induced peripheral neuropathy' Pain Management Nursing 2018;19(4):354-365. *Pain Management Nursing*, *20*(1), 88. https://doi.org/10.1016/j.pmn.2018.12.010

Knoerl, R., Gray, E., Stricker, C., Mitchell, S. A., Kippe, K., Smith, G., … Lavoie Smith, E. M. (2017). Electronic versus paper-pencil methods for assessing chemotherapy-induced peripheral neuropathy. *Supportive Care in Cancer*. https://doi.org/10.1007/s00520-017-3764-y

Kohman, R. A., Bhattacharya, T. K., Wojcik, E., & Rhodes, J. S. (2013). Exercise reduces activation of microglia isolated from hippocampus and brain of aged mice. *Journal of Neuroinflammation*, *10*(1), 885. https://doi.org/10.1186/1742-2094-10-114

Kolb, N. A., Smith, A. G., Singleton, J. R., Beck, S. L., Stoddard, G. J., Brown, S., & Mooney, K. (2016). The association of chemotherapy-induced peripheral neuropathy symptoms and the risk of falling. *JAMA Neurology*, *73*(7), 860–866. https://doi.org/10.1001/jamaneurol.2016.0383

Kouvari, M., Yannakoulia, M., Souliotis, K., & Panagiotakos, D. B. (2018). Challenges in sex- and gender-centered prevention and management of cardiovascular disease: Implications of genetic, metabolic, and environmental paths. *Angiology*, *69*(10), 843–853. https://doi.org/10.1177/0003319718756732

Kowalczyk, W. J., Sullivan, M. A., Evans, S. M., Bisaga, A. M., Vosburg, S. K., & Comer, S. D. (2010). Sex differences and hormonal influences on response to mechanical pressure pain in humans. *The Journal of Pain*, *11*(4), 330–342.

Krishnan, A. V, & Park, S. B. (2014). Chemotherapy-induced peripheral neuropathy: The end of the beginning? *Journal of Neurology, Neurosurgery & Psychiatry*, *85*(4), 359. https://doi.org/10.1136/jnnp-2013-305600

Lavoie Smith, E. M., Barton, D. L., Qin, R., Steen, P. D., Aaronson, N. K., & Loprinzi, C. L. (2013). Assessing patient-reported peripheral neuropathy: The reliability and validity of the European Organization for Research and Treatment of Cancer QLQ-CIPN20 Questionnaire. *Quality of Life Research*, *22*(10), 2787–2799. https://doi.org/10.1007/s11136-013-0379-8

Lewis, M. A., Zhao, F., Jones, D., Loprinzi, C. L., Brell, J., Weiss, M., & Fisch, M. J. (2015). Neuropathic symptoms and their risk factors in medical oncology outpatients with colorectal vs. breast, lung, or prostate cancer: Results from a prospective multicenter study. *Journal of Pain and Symptom Management*, *49*(6), 1016–1024. https://doi.org/10.1016/j.jpainsymman.2014.11.300

Li, Q., Lin, Y., Qiu, Y., Gao, B., & Xu, Y. (2014). The assessment of health-related quality of life and related factors in Chinese elderly patients undergoing chemotherapy for advanced cancer: A cross-sectional study. *European Journal of Oncology Nursing*, *18*(4), 425–435. https://doi.org/10.1016/j.ejon.2014.03.005

Loprinzi, C. L., Qin, R., Dakhil, S. R., Fehrenbacher, L., Flynn, K. A., Atherton, P., … Grothey, A. (2014). Phase III randomized, placebo-controlled, double-blind study of intravenous calcium and magnesium to prevent oxaliplatin-induced sensory neurotoxicity (N08CB/Alliance). *Journal of Clinical Oncology*, *32*(10), 997–1005. https://doi.org/10.1200/JCO.2013.52.0536

Low, C. A., Dey, A. K., Ferreira, D., Kamarck, T., Sun, W., Bae, S., & Doryab, A. (2017). Estimation of symptom severity during chemotherapy from passively sensed data: Exploratory study. *J Med Internet Res*, *19*(12), e420. https://doi.org/10.2196/jmir.9046

Lynch, B. M., Cerin, E., Owen, N., Hawkes, A. L., & Aitken, J. F. (2008). Prospective relationships of physical activity with quality of life among colorectal cancer survivors.

Journal of Clinical Oncology, *26*(27), 4480–4487. https://doi.org/10.1200/JCO.2007.15.7917

Marcelino, T. B., Longoni, A., Kudo, K. Y., Stone, V., Rech, A., de Assis, A. M., … Matte, C. (2013). Evidences that maternal swimming exercise improves antioxidant defenses and induces mitochondrial biogenesis in the brain of young Wistar rats. *Neuroscience*, *246*, 28–39. https://doi.org/10.1016/j.neuroscience.2013.04.043

Marques-Aleixo, I., Oliveira, P. J., Moreira, P. I., Magalhaes, J., & Ascensao, A. (2012). Physical exercise as a possible strategy for brain protection: Evidence from mitochondrial-mediated mechanisms. *Progress in Neurobiology*, *99*(2), 149–162. https://doi.org/10.1016/j.pneurobio.2012.08.002

Mas, S., Quantin, X., & Ninot, G. (2015). Barriers to, and facilitators of physical activity in patients receiving chemotherapy for lung cancer: An exploratory study. *Journal of Palliative Care*, *31*(2), 89–96. Retrieved from https://www.scopus.com/inward/record.uri?eid=2-s2.0-84937859700&partnerID=40&md5=660e8d75227723bc158f1c91cb3aa42e

Maurer, A. J., Lissounov, A., Knezevic, I., Candido, K. D., & Knezevic, N. N. (2016). Pain and sex hormones: A review of current understanding. *Pain Management*, *6*(3), 285–296. https://doi.org/10.2217/pmt-2015-0002

McCarthy, M. M., Nugent, B. M., & Lenz, K. M. (2017). Neuroimmunology and neuroepigenetics in the establishment of sex differences in the brain. *Nature Reviews. Neuroscience*, *18*(8), 471–484. https://doi.org/10.1038/nrn.2017.61

McCarthy, M. M., Pickett, L. A., VanRyzin, J. W., & Kight, K. E. (2015). Surprising origins of sex differences in the brain. *Hormones and Behavior*, *76*, 3–10. https://doi.org/10.1016/j.yhbeh.2015.04.013

McCrary, J. M., Goldstein, D., Sandler, C. X., Barry, B. K., Marthick, M., Timmins, H. C., … Park, S. B. (2019). Exercise-based rehabilitation for cancer survivors with chemotherapy-induced peripheral neuropathy. *Supportive Care in Cancer*. https://doi.org/10.1007/s00520-019-04680-w

Miltenburg, N. C., & Boogerd, W. (2014). Chemotherapy-induced neuropathy: A comprehensive survey. *Cancer Treatment Reviews*, *40*(7), 872–882. https://doi.org/10.1016/j.ctrv.2014.04.004

Mishra, S. I., Scherer, R. W., Snyder, C., Geigle, P., & Gotay, C. (2015). The effectiveness of exercise interventions for improving health-related quality of life from diagnosis through active cancer treatment. *Oncology Nursing Forum*, *42*(1), E33–E53. https://doi.org/10.1188/15.ONF.E33-E53

Mizrahi, D., Broderick, C., Friedlander, M., Ryan, M., Harrison, M., Pumpa, K., & Naumann, F. (2015). An exercise intervention during chemotherapy for women with recurrent ovarian cancer: A feasibility study. *International Journal of Gynecological Cancer*, *25*(6), 985–992. https://doi.org/10.1097/IGC.0000000000000460

Mock, V., Frangakis, C., Davidson, N. E., Ropka, M. E., Pickett, M., Poniatowski, B., … McCorkle, R. (2005). Exercise manages fatigue during breast cancer treatment: A randomized controlled trial. *Psycho-Oncology*, *14*(6), 464–477. https://doi.org/10.1002/pon.863

Mols, F., Beijers, A. J. M., Vreugdenhil, G., Verhulst, A., Schep, G., & Husson, O. (2015). Chemotherapy-induced peripheral neuropathy, physical activity and health-related quality of life among colorectal cancer survivors from the PROFILES registry. *Journal of Cancer Survivorship*, *9*(3), 512–522. https://doi.org/10.1007/s11764-015-0427-1

Mols, F., Beijers, T., Lemmens, V., van den Hurk, C. J., Vreugdenhil, G., & van de Poll-Franse, L. V. (2013). Chemotherapy-induced neuropathy and its association with quality of life among 2- to 11-year colorectal cancer survivors: Results from the population-based PROFILES registry. *Journal of Clinical Oncology*, *31*(21), 2699–2707. https://doi.org/10.1200/JCO.2013.49.1514

Molteni, R., Zheng, J.-Q., Ying, Z., Gomez-Pinilla, F., & Twiss, J. L. (2004). Voluntary exercise increases axonal regeneration from sensory neurons. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(22), 8473–8478. https://doi.org/10.1073/pnas.0401443101

Monfort, S. M., Pan, X., Patrick, R., Singaravelu, J., Loprinzi, C. L., Lustberg, M. B., & Chaudhari, A. M. W. (2016). Natural history of postural instability in breast cancer patients treated with taxane-based chemotherapy: A pilot study. *Gait & Posture*, *48*, 237–242. https://doi.org/10.1016/j.gaitpost.2016.06.011

Morielli, A. R., Usmani, N., Boule, N. G., Tankel, K., Severin, D., Nijjar, T., … Courneya, K. S. (2016). A phase I study examining the feasibility and safety of an aerobic exercise

intervention in patients with rectal cancer during and after neoadjuvant chemoradiotherapy. *Oncology Nursing Forum*, *43*(3), 352–362. https://doi.org/10.1188/16.ONF.352-362

Nazari, G., MacDermid, J. C., Sinden, K. E., Richardson, J., & Tang, A. (2019). Inter-instrument reliability and agreement of Fitbit Charge measurements of heart rate and activity at rest, during the Modified Canadian Aerobic Fitness Test, and in recovery. *Physiotherapy Canada*, *71*(3), 197–206. https://doi.org/10.3138/ptc.2018-25

Nazir, H. F., AlFutaisi, A., Zacharia, M., Elshinawy, M., Mevada, S. T., Alrawas, A., … Wali, Y. (2017). Vincristine-induced neuropathy in pediatric patients with acute lymphoblastic leukemia in Oman: Frequent autonomic and more severe cranial nerve involvement. *Pediatric Blood & Cancer*, *64*(12), e26677. https://doi.org/10.1002/pbc.26677

Nicklasson, M., & Bergman, B. (2007). Validity, reliability and clinical relevance of EORTC QLQ-C30 and LC13 in patients with chest malignancies in a palliative setting. *Quality of Life Research*, *16*(6), 1019–1028. https://doi.org/10.1007/s11136-007-9210-8

Niezgoda, H. E., & Pater, J. L. (1993). A validation study of the domains of the core EORTC Quality of Life Questionnaire. *Quality of Life Research*, *2*(5), 319–325. Retrieved from http://www.jstor.org.proxy.lib.umich.edu/stable/4034756

Osoba, D., Zee, B., Pater, J., Warr, D., Kaizer, L., & Latreille, J. (1994). Psychometric properties and responsiveness of the EORTC quality of Life Questionnaire (QLQ-C30) in patients with breast, ovarian and lung cancer. *Quality of Life Research*, *3*(5), 353–364.

Pachman, D. R., Barton, D. L., Swetz, K. M., & Loprinzi, C. L. (2012). Troublesome symptoms in cancer survivors: Fatigue, insomnia, neuropathy, and pain. *Journal of Clinical Oncology*, *30*(30), 3687–3696. https://doi.org/10.1200/JCO.2012.41.7238

Pachman, D. R., Qin, R., Seisler, D. K., Smith, E. M. L., Beutler, A. S., Ta, L. E., … Loprinzi, C. L. (2015). Clinical course of oxaliplatin-induced neuropathy: Results from the randomized phase III trial N08CB (Alliance). *Journal of Clinical Oncology*, *33*(30), 3416–3422. https://doi.org/10.1200/JCO.2014.58.8533

Pachman, D. R., Qin, R., Seisler, D., Smith, E. M. L., Kaggal, S., Novotny, P., … Loprinzi, C. L. (2016). Comparison of oxaliplatin and paclitaxel-induced neuropathy (Alliance A151505). *Supportive Care in Cancer*, *24*(12), 5059–5068. https://doi.org/10.1007/s00520-016-3373-1

Park, J.-H., Miyashita, M., Takahashi, M., Kawanishi, N., Bae, S.-R., Kim, H.-S., … Nakamura, Y. (2013). Effects of low-volume walking programme and vitamin E supplementation on oxidative damage and health-related variables in healthy older adults. *Nutrition & Metabolism*, *10*(1), 38. https://doi.org/10.1186/1743-7075-10-38

Peddle, C. J., Au, H.-J., & Courneya, K. S. (2008). Associations between exercise, quality of life, and fatigue in colorectal cancer survivors. *Diseases of the Colon and Rectum*, *51*(8), 1242–1248. https://doi.org/10.1007/s10350-008-9324-2

Physiopedia contributors. (2019). Physical Activity Scale for the Elderly (PASE). Retrieved November 24, 2019, from https://www.physio-pedia.com/index.php?title=Physical_Activity_Scale_for_the_Elderly_(PASE)&oldid=225006

Popescu, A., LeResche, L., Truelove, E. L., & Drangsholt, M. T. (2010). Gender differences in pain modulation by diffuse noxious inhibitory controls: A systematic review. *Pain*, *150*(2), 309–318.

Postma, T. J., Aaronson, N. K., Heimans, J. J., Muller, M. J., Hildebrand, J. G., Delattre, J. Y., … Lucey, R. (2005). The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: the QLQ-CIPN20. *European Journal of Cancer (Oxford, England : 1990)*, *41*(8), 1135–1139. https://doi.org/10.1016/j.ejca.2005.02.012

Ringdal, G. I., & Ringdal, K. (1993). Testing the EORTC Quality of Life Questionnaire on cancer patients with heterogeneous diagnoses. *Quality of Life Research*, *2*(2), 129–140. Retrieved from http://www.jstor.org.proxy.lib.umich.edu/stable/4034394

Rodrigues, K. C., Toledo, R. A., Coutinho, F. L., Nunes, A. B., Maciel, R. M., Hoff, A. O., … Lourenço, D. M. J. (2017). Assessment of depression, anxiety, quality of life, and coping in long-standing multiple endocrine neoplasia type 2 patients. *Thyroid*, *27*(5), 693–706. https://doi.org/10.1089/thy.2016.0148

Rogers, L. Q., Fogleman, A., Trammell, R., Hopkins-Price, P., Vicari, S., Rao, K., … Hoelzer, K. (2013). Effects of a physical activity behavior change intervention on inflammation and related health outcomes in breast cancer survivors: Pilot randomized trial. *Integrative Cancer Therapies*, *12*(4), 323–335. https://doi.org/10.1177/1534735412449687

Saad, M., Tafani, C., Psimaras, D., & Ricard, D. (2014). Chemotherapy-induced peripheral neuropathy in the adult. *Current Opinion in Oncology*, *26*(6), 634–641. https://doi.org/10.1097/CCO.0000000000000139

Schaun, M. I., Dipp, T., Rossato, J. da S., Wilhelm, E. N., Pinto, R., Rech, A., … Reischak-Oliveira, A. (2011). The effects of periodized concurrent and aerobic training on oxidative stress parameters, endothelial function and immune response in sedentary male individuals of middle age. *Cell Biochemistry and Function*, *29*(7), 534–542. https://doi.org/10.1002/cbf.1781

Schmidt, M. E., Meynkohn, A., Habermann, N., Wiskemann, J., Oelmann, J., Hof, H., … Ulrich, C. M. (2016). Resistance exercise and inflammation in breast cancer patients undergoing adjuvant radiation therapy: Mediation analysis from a randomized, controlled intervention trial. *International Journal of Radiation Oncology, Biology, Physics*, *94*(2), 329–337. https://doi.org/10.1016/j.ijrobp.2015.10.058

Schmitz, K. H., Courneya, K. S., Matthews, C., Demark-Wahnefried, W., Galvao, D. A., Pinto, B. M., … Schwartz, A. L. (2010). American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Medicine and Science in Sports and Exercise*, *42*(7), 1409–1426. https://doi.org/10.1249/MSS.0b013e3181e0c112

Seo, T. B., Oh, M.-J., You, B.-G., Kwon, K.-B., Chang, I.-A., Yoon, J.-H., … Namgung, U. (2009). ERK1/2-mediated Schwann cell proliferation in the regenerating sciatic nerve by treadmill training. *Journal of Neurotrauma*, *26*(10), 1733–1744. https://doi.org/10.1089/neu.2008.0711

Seretny, M., Currie, G. L., Sena, E. S., Ramnarine, S., Grant, R., MacLeod, M. R., … 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

Shahriari-Ahmadi, A., Fahimi, A., Payandeh, M., & Sadeghi, M. (2015). Prevalence of oxaliplatin-induced chronic neuropathy and influencing factors in patients with colorectal cancer in Iran. *Asian Pacific Journal of Cancer Prevention*, *16*(17), 7603–7606.

Sherman, A. C., Simonton, S., Adams, D. C., Vural, E., Owens, B., & Hanna, E. (2000). Assessing quality of life in patients with head and neck cancer: cross-validation of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life

Head and Neck module (QLQ-H&N35). *Archives of Otolaryngology--Head & Neck Surgery*, *126*(4), 459–467.

Simon, N. B., Danso, M. A., Alberico, T. A., Basch, E., & Bennett, A. V. (2017). The prevalence and pattern of chemotherapy-induced peripheral neuropathy among women with breast cancer receiving care in a large community oncology practice. *Quality of Life Research*. https://doi.org/10.1007/s11136-017-1635-0

Skerman, H. M., Yates, P. M., & Battistutta, D. (2012). Cancer-related symptom clusters for symptom management in outpatients after commencing adjuvant chemotherapy, at 6 months, and 12 months. *Supportive Care in Cancer*, *20*(1), 95–105. https://doi.org/10.1007/s00520-010-1070-z

Smith, E. M. L., Haupt, R., Kelly IV, J. P., Lee, D., Kanzawa-Lee, G., Knoerl, R., … Donohoe, C. (2017). The content validity of a chemotherapy-induced peripheral neuropathy patient-reported outcome measure. *Oncology Nursing Forum*, *44*(5), 580–588. https://doi.org/10.1188/17.ONF.580-588

Smith, E. M. L., Knoerl, R., Yang, J. J., Kanzawa-Lee, G., Lee, D., & Bridges, C. (2018). In search of a gold standard patient-reported outcome measure for use in chemotherapy-induced peripheral neuropathy clinical trials. *Cancer Control*, *25*(1). https://doi.org/10.1177/1073274818756608

Smith, E. M. L., Pang, H., Ye, C., Cirrincione, C., Fleishman, S., Paskett, E. D. D., … Shapiro, C. L. L. (2017). Predictors of duloxetine response in patients with oxaliplatin-induced painful chemotherapy-induced peripheral neuropathy (CIPN): A secondary analysis of randomised controlled trial - CALGB/alliance 170601. *European Journal of Cancer Care*, *26*(2), e12421. https://doi.org/10.1111/ecc.12421

Snyder, C. F., Herman, J. M., White, S. M., Luber, B. S., Blackford, A. L., Carducci, M. A., & Wu, A. W. (2014). When Using Patient-Reported Outcomes in Clinical Practice, the Measure Matters: A Randomized Controlled Trial. *Journal of Oncology Practice*, *10*(5), e299–e306. https://doi.org/10.1200/JOP.2014.001413

Song, S. J., Min, J., Suh, S. Y., Jung, S. H., Hahn, H. J., Im, S.-A., & Lee, J.-Y. (2017). Incidence of taxane-induced peripheral neuropathy receiving treatment and prescription patterns in patients with breast cancer. *Supportive Care in Cancer*, *25*(7), 2241–2248. https://doi.org/10.1007/s00520-017-3631-x

Speck, R. M., DeMichele, A., Farrar, J. T., Hennessy, S., Mao, J. J., Stineman, M. G., & Barg, F. K. (2012). Scope of symptoms and self-management strategies for chemotherapy-induced peripheral neuropathy in breast cancer patients. *Supportive Care in Cancer*, *20*(10), 2433–2439. https://doi.org/10.1007/s00520-011-1365-8

Staff, N. P., & Windebank, A. J. (2014). Peripheral neuropathy due to vitamin deficiency, toxins, and medications. *Continuum: Lifelong Learning in Neurology*, *20*(5 Peripheral Nervous System Disorders), 1293–1306. https://doi.org/10.1212/01.CON.0000455880.06675.5a

Stagg, N. J., Mata, H. P., Ibrahim, M. M., Henriksen, E. J., Porreca, F., Vanderah, T. W., & Philip Malan, T. J. (2011). Regular exercise reverses sensory hypersensitivity in a rat neuropathic pain model: Role of endogenous opioids. *Anesthesiology*, *114*(4), 940–948. https://doi.org/10.1097/ALN.0b013e318210f880

StataCorp. (2017). Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.

Stratogianni, A., Tosch, M., Schlemmer, H., Weis, J., Katona, I., Isenmann, S., & Haensch, C. A. (2012). Bortezomib-induced severe autonomic neuropathy. *Clinical Autonomic Research*, *22*(4), 199–202. https://doi.org/10.1007/s10286-012-0164-8

Streckmann, F., Kneis, S., Leifert, J. A., Baumann, F. T., Kleber, M., Ihorst, G., … 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

Streckmann, F., Lehmann, H. C., Balke, M., Schenk, A., Oberste, M., Heller, A., … Baumann, F. T. (2018). Sensorimotor training and whole-body vibration training have the potential to reduce motor and sensory symptoms of chemotherapy-induced peripheral neuropathy-A randomized controlled pilot trial. *Supportive Care in Cancer*. https://doi.org/10.1007/s00520-018-4531-4

Su, C.-C., Lee, K.-D., Yeh, C.-H., Kao, C.-C., & Lin, C.-C. (2014). Measurement of physical activity in cancer survivors: A validity study. *Journal of Cancer Survivorship : Research and Practice*, *8*(2), 205–212. https://doi.org/10.1007/s11764-013-0325-3

Swenson, K. K., Nissen, M. J., & Henly, S. J. (2010). Physical activity in women receiving chemotherapy for breast cancer: Adherence to a walking intervention. *Oncology Nursing Forum*, *37*(3), 321–330. https://doi.org/10.1188/10.ONF.321-330

Talaminos Barroso, A., Marquez Martin, E., Roa Romero, L. M., & Ortega Ruiz, F. (2018). Factors affecting lung function: A review of the literature. *Archivos de Bronconeumologia*, *54*(6), 327–332. https://doi.org/10.1016/j.arbres.2018.01.030

Taube, W., & Gollhofer, A. (2010). Control and training of posture and balance. In *Neuromuscular Aspects of Sport Performance* (pp. 254–269). https://doi.org/10.1002/9781444324822.ch14

Taube, W., Gruber, M., Beck, S., Faist, M., Gollhofer, A., & Schubert, M. (2007). Cortical and spinal adaptations induced by balance training: Correlation between stance stability and corticospinal activation. *Acta Physiologica*, *189*(4), 347–358. https://doi.org/10.1111/j.1365-201X.2007.01665.x

Taube, W., Kullmann, N., Leukel, C., Kurz, O., Amtage, F., & Gollhofer, A. (2007). Differential reflex adaptations following sensorimotor and strength training in young elite athletes. *International Journal of Sports Medicine*, *28*(12), 999–1005. https://doi.org/10.1055/s-2007-964996

Tedesco, S., Sica, M., Ancillao, A., Timmons, S., Barton, J., & O'Flynn, B. (2019). Validity evaluation of the Fitbit Charge2 and the Garmin vivosmart HR+ in free-living environments in an older adult cohort. *JMIR MHealth and UHealth*, *7*(6), e13084–e13084. https://doi.org/10.2196/13084

Thomson, E. A., Nuss, K., Comstock, A., Reinwald, S., Blake, S., Pimentel, R. E., … Li, K. (2019). Heart rate measures from the Apple Watch, Fitbit Charge HR 2, and electrocardiogram across different exercise intensities. *Journal of Sports Sciences*, *37*(12), 1411–1419. https://doi.org/10.1080/02640414.2018.1560644

Thraen-Borowski, K. M., Trentham-Dietz, A., Edwards, D. F., Koltyn, K. F., & Colbert, L. H. (2013). Dose-response relationships between physical activity, social participation, and health-related quality of life in colorectal cancer survivors. *Journal of Cancer Survivorship: Research and Practice*, *7*(3), 369–378. https://doi.org/10.1007/s11764-013-0277-7

Tofthagen, C. S. (2010a). Patient perceptions associated with chemotherapy-induced peripheral neuropathy. *Clinical Journal of Oncology Nursing*, *14*(3), E22-8. https://doi.org/10.1188/10.CJON.E22-E28

Tofthagen, C. S. (2010b). Surviving chemotherapy for colon cancer and living with the consequences. *Journal of Palliative Medicine*, *13*(11), 1389–1391. https://doi.org/10.1089/jpm.2010.0124

Tofthagen, C. S., McAllister, R. D., & McMillan, S. C. (2011). Peripheral neuropathy in patients with colorectal cancer receiving oxaliplatin. *Clinical Journal of Oncology Nursing*, *15*(2), 182–188. https://doi.org/10.1188/11.CJON.182-188

Tofthagen, C. S., Visovsky, C. M., & Hopgood, R. (2013). Chemotherapy-induced peripheral neuropathy: An algorithm to guide nursing management. *Clinical Journal of Oncology Nursing*, *17*(2), 138–144. https://doi.org/10.1188/13.CJON.138-144

Townsend, E. A., Miller, V. M., & Prakash, Y. S. (2012). Sex differences and sex steroids in lung health and disease. *Endocrine Reviews*, *33*(1), 1–47. https://doi.org/10.1210/er.2010-0031

U.S. Department of Health and Human Services. (2018). *Physical Activity Guidelines for Americans, 2nd edition*. Washington, DC, US. Retrieved from https://health.gov/paguidelines/second-edition/pdf/Physical_Activity_Guidelines_2nd_edition.pdf

Van Vulpen, J. K., Velthuis, M. J., Steins Bisschop, C. N., Travier, N., Van Den Buijs, B. J. W., Backx, F. J. G., … May, A. M. (2016). Effects of an exercise program in colon cancer patients undergoing chemotherapy. *Medicine and Science in Sports and Exercise*, *48*(5), 767–775. https://doi.org/10.1249/MSS.0000000000000855

van Waart, H., Stuiver, M. M., van Harten, W. H., Geleijn, E., Kieffer, J. M., Buffart, L. M., … Aaronson, N. K. (2015). Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: Results of the PACES randomized clinical trial. *Journal of Clinical Oncology*, *33*(17), 1918–1927. https://doi.org/10.1200/JCO.2014.59.1081

Velasco, R., Bruna, J., Briani, C., Argyriou, A. A., Cavaletti, G., Alberti, P., … Kalofonos, H. P. (2014). Early predictors of oxaliplatin-induced cumulative neuropathy in colorectal cancer patients. *Journal of Neurology, Neurosurgery, and Psychiatry*, *85*(4), 392–398. https://doi.org/10.1136/jnnp-2013-305334

Velasco, R., Petit, J., Clapes, V., Verdu, E., Navarro, X., & Bruna, J. (2010). Neurological monitoring reduces the incidence of bortezomib-induced peripheral neuropathy in

multiple myeloma patients. *Journal of the Peripheral Nervous System*, *15*(1), 17–25. https://doi.org/10.1111/j.1529-8027.2010.00248.x

Ventzel, L., Jensen, A. B., Jensen, A. R., Jensen, T. S., & Finnerup, N. B. (2016). Chemotherapy-induced pain and neuropathy: A prospective study in patients treated with adjuvant oxaliplatin or docetaxel. *Pain*, *157*(3), 560–568. https://doi.org/10.1097/j.pain.0000000000000404

Ventzel, L., Madsen, C. S., Jensen, A. B., Jensen, A. R., Jensen, T. S., & Finnerup, N. B. (2016). Assessment of acute oxaliplatin-induced cold allodynia: A pilot study. *Acta Neurologica Scandinavica*, *133*(2), 152–155. https://doi.org/10.1111/ane.12443

Villa, A., Della Torre, S., & Maggi, A. (2019). Sexual differentiation of microglia. *Frontiers in Neuroendocrinology*, *52*, 156–164. https://doi.org/https://doi.org/10.1016/j.yfrne.2018.11.003

Washburn, R. A., McAuley, E., Katula, J., Mihalko, S. L., & Boileau, R. A. (1999). The Physical Activity Scale for the Elderly (PASE): Evidence for validity. *Journal of Clinical Epidemiology*, *52*(7), 643–651.

Washburn, R. A., Smith, K. W., Jette, A. M., & Janney, C. A. (1993). The Physical Activity Scale for the Elderly (PASE): Development and evaluation. *Journal of Clinical Epidemiology*, *46*(2), 153–162.

White, H. (1980). A heteroscedasticity consistent covariance matrix estimator and a direct test of heteroscedasticity. *Econometrica*, *48*, 817–818.

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

Wonders, K. Y. (2014). The effect of supervised exercise training on symptoms of chemotherapy-induced peripheral neuropathy. *Int J Phys Med Rehabil*, *2*(4), 1–5.

Yang, C., Tsai, J., Huang, Y., & Lin, C. (2011). Effects of a home-based walking program on perceived symptom and mood status in postoperative breast cancer women receiving adjuvant chemotherapy. *Journal of Advanced Nursing*, *67*(1), 158–168. https://doi.org/10.1111/j.1365-2648.2010.05492.x

Yoon, H., Thakur, V., Isham, D., Fayad, M., & Chattopadhyay, M. (2015). Moderate exercise training attenuates inflammatory mediators in DRG of Type 1 diabetic rats. *Experimental Neurology*, *267*, 107–114. https://doi.org/10.1016/j.expneurol.2015.03.006

Zanville, N. R., Nudelman, K. N. H., Smith, D. J., Von Ah, D., McDonald, B. C., Champion, V. L., & Saykin, A. J. (2016). Evaluating the impact of chemotherapy-induced peripheral neuropathy symptoms (CIPN-sx) on perceived ability to work in breast cancer survivors during the first year post-treatment. *Supportive Care in Cancer*, *24*(11), 4779–4789. https://doi.org/10.1007/s00520-016-3329-5

Zhou, W., Liu, G., Yang, S., Mi, B., & Ye, S. (2016). Low-intensity treadmill exercise promotes rat dorsal wound healing. *Journal of Huazhong University of Science and Technology*, *36*(1), 121–126. https://doi.org/10.1007/s11596-016-1553-3

Zimmer, P., Trebing, S., Timmers-Trebing, U., Schenk, A., Paust, R., Bloch, W., … 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

Zimmerman, C., Atherton, P. J., Pachman, D., Seisler, D., Wagner-Johnston, N., Dakhil, S., … Loprinzi, C. L. (2016). MC11C4: A pilot randomized, placebo-controlled, double-blind study of venlafaxine to prevent oxaliplatin-induced neuropathy. *Supportive Care in Cancer*, *24*(3), 1071–1078. https://doi.org/10.1007/s00520-015-2876-5

CHAPTER IV

Home-Based Aerobic Exercise Feasibility in Oxaliplatin-Receiving Cancer Survivors

Gastrointestinal (GI) cancer including colorectal, stomach, pancreatic, small bowel, and esophageal cancers are cumulatively the second most common type of cancer in the United States (American Cancer Society, 2019). Oxaliplatin-based chemotherapy regimens such as FOLFOX and FOLFIRINOX are mainstay treatments for invasive GI cancer. They have improved the length of survival for many patients but may cause significant long-term morbidity (André, Boni, & Navarro, 2009; Choi et al., 2019; Drott, Starkhammar, Kjellgren, & Bertero, 2016; Meyers, Cosby, Quereshy, & Jonker, 2017). People who have received FOLFOX/FOLFIRINOX commonly report distress from symptoms, such as oxaliplatin- (i.e., chemotherapy-) induced peripheral neuropathy (OIPN) (Andre et al., 2004; Mols et al., 2013; S. B. Park et al., 2013; Ventzel et al., 2015), fatigue, loss of appetite, insomnia, anxiety, and depression (Berger, 2010; Binkley et al., 2012; El-Shami et al., 2015; Mols et al., 2013; Pachman, Barton, Swetz, & Loprinzi, 2012; Skerman, Yates, & Battistutta, 2012; Yamagishi, Morita, Miyashita, & Kimura, 2009). Many of these symptoms cluster and affect long-term quality of life (QOL), including physical, emotional, social, and role function (Drott et al., 2016; Ezendam et al., 2014; Hershman et al., 2011; Kidwell et al., 2012; Mols et al., 2013; Pietrangeli, Leandri, Terzoli, Jandolo, & Garufi, 2006; Tofthagen, Donovan, Morgan, Shibata, & Yeh, 2013). For example, cancer treatment-related fatigue and OIPN may lead to weakness and difficulty

performing daily tasks such as climbing stairs and typing on a laptop (Bakitas, 2007; Drott et al., 2016; Monfort et al., 2016; Speck et al., 2012; Tofthagen, 2010b, 2010a). Impaired function may lead to sedentary behavior (Carels, Coit, Young, & Berger, 2007; Dunton, Atienza, Castro, & King, 2009; Hawkes et al., 2013; Henriksson, Arving, Johansson, Igelstrom, & Nordin, 2016; Liao, Chou, Huh, Leventhal, & Dunton, 2016; Liao, Shonkoff, & Dunton, 2015; Mata et al., 2012; Shang, Wenzel, Krumm, Griffith, & Stewart, 2012), worse balance and higher risk for falls (Bao et al., 2016; Kolb et al., 2016; Winters-Stone et al., 2017), and social isolation (Boehmke & Dickerson, 2005; Exposito Vizcaino, Casanova-Molla, Escoda, Galan, & Miro, 2018; Tofthagen, McAllister, & McMillan, 2011; Zanville et al., 2016). Thus, patients, families, and clinicians are faced with complex treatment decisions regarding the balance between preserving QOL and pursuing the most aggressive treatment to eradicate the cancer (Ko et al., 2019).

Aerobic exercise has been shown to globally benefit cancer survivors' length and quality of survival (American College of Sports Medicine, 2015; Baumann et al., 2015; Cadmus et al., 2009; Cramp & Byron-Daniel, 2012; Galvão & Newton, 2005; Knols, Aaronson, Uebelhart, Fransen, & Aufdemkampe, 2005; Lotfi-Jam et al., 2008; Mishra, Scherer, Snyder, Geigle, & Gotay, 2015; Mock et al., 2005; Morielli et al., 2016; Pachman et al., 2012; Stevinson et al., 2009; U.S. Department of Health and Human Services, 2018). Specifically, light-moderate-intensity home-based exercise has led to improved cancer treatment response (Baumann et al., 2015; Cadmus et al., 2009; Cramp & Byron-Daniel, 2012; Galvão & Newton, 2005; Knols et al., 2005; Lotfi-Jam et al., 2008; Mishra et al., 2015; Mock et al., 2005; Morielli et al., 2016; Pachman et al., 2012; Stevinson et al., 2009); and reduced fatigue (Cramp & Byron-Daniel, 2012; Mishra et al., 2015; Mock et al., 1994; Morielli et al., 2016; Schwartz, 2001; Van Vulpen et al., 2016; van Waart et al., 2015); OIPN (Kleckner et al., 2018), anxiety, depression, pain

(Irwin et al., 2015; Morielli et al., 2016), and sleep disturbance (Mishra et al., 2015; Speck, Courneya, Masse, Duval, & Schmitz, 2010).

However, many cancer survivors report not receiving education about the benefits of exercise during cancer treatment (Fernandez et al., 2015). Over 60% of individuals receiving cancer treatment are insufficiently active (Baumann et al., 2015; Cramp & Byron-Daniel, 2012; Dodd et al., 2010; Dreicer et al., 2014; Fernandez et al., 2015; Mishra et al., 2015; Morielli et al., 2016; Pachman et al., 2012). Individuals with colorectal cancer have previously demonstrated the lowest levels of physical activity (PA) and adherence in PA trials (48% to 76%) (Backman et al., 2014; Courneya et al., 2003; Griffith et al., 2009; Tofthagen, Visovsky, & Berry, 2012; van Waart et al., 2015) compared to other cancer populations such as individuals with breast cancer whose adherence rates were 72% to 77% (Blanchard, Courneya, & Stein, 2008; Courneya et al., 2003; Courneya, Katzmarzyk, & Bacon, 2008; Mock et al., 2005; Peddle, Au, & Courneya, 2008; Speed-Andrews et al., 2012; Tofthagen, Visovsky, Beckstead, Loy, & Eckelman, 2014; Yang, Tsai, Huang, & Lin, 2011).

Barriers to Exercise

Although cancer survivors generally view PA as important during cancer treatment (Chou, Lai, Lin, Liang, & Shun, 2017; Mikkelsen, Nielsen, Vinther, Lund, & Jarden, 2019), motivational supports may be needed to overcome barriers and maximize exercise adherence during cancer treatment. Common cross-culturally perceived exercise barriers in adults include lack of time (Mikkelsen et al., 2019), self-efficacy, motivation, energy, skill knowledge, sociocultural support/expectations (Mikkelsen et al., 2019), and safe and accessible exercise environments (Eyl et al., 2018; Horne & Tierney, 2012). Additionally, morbidities (Mikkelsen et al., 2019), age- or obesity-related deficits (Eyl et al., 2018; Fisher et al., 2016), suboptimal

weather, statuses of being employed and divorced (Eyl et al., 2018; van Putten et al., 2016), and negative exercise outcomes are common exercise barriers (Chou et al., 2017; Gho, Munro, Jones, & Steele, 2014; Horne & Tierney, 2012; Justine, Azizan, Hassan, Salleh, & Manaf, 2013; Leone & Ward, 2013; Tulloch et al., 2013). Further, individuals receiving cancer treatment may experience stronger barriers, due to chemotherapy treatment scheduling and side effects (e.g., fatigue, pain, diarrhea, depression (Chou et al., 2017; Fernandez et al., 2015; Kamath, 2012; Kang et al., 2014; Mikkelsen et al., 2019)), and fear of exercise injury (Kang et al., 2014; Mas, Quantin, & Ninot, 2015; Park et al., 2015; Rogers et al., 2005; Swenson, Nissen, & Henly, 2010; Zanville et al., 2016).

***Other factors that influence exercise intervention adherence*.** Various factors including acceptability of an intervention and interest in and confidence in one's ability to exercise have been theorized to influence exercise adherence (Chou et al., 2017; Sekhon, Cartwright, & Francis, 2017). The definition of acceptability and its relationship with the concepts of adherence, interest, and confidence are still under debate. Acceptability has been operationalized as evaluating intervention enrollment, dropout, uptake, and adverse outcomes. Additionally, cognitive/emotional aspects of acceptability include satisfaction with, understanding of, and perceived burden and usefulness of the intervention (Sekhon et al., 2017). It may be bi-directionally associated with intervention adherence (Chou et al., 2017). In a concept analysis of acceptability, confidence in one's ability to perform the intervention was conceptualized as a construct of acceptability; thus, confidence may also be bi-directionally associated with adherence (Sekhon et al., 2017). Interest (equated with intention to perform the intervention) was stated to be separate from but related to acceptability (Sekhon et al., 2017). However, evidence also suggests that interest is bi-directionally associated with adherence, but the relationship may

be negatively influenced by confidence (Gho et al., 2014; Mikkelsen et al., 2019). The following section focuses more on the role of other key theoretical constructs associated with exercise adherence.

Theoretical Approaches for Facilitating Exercise

The Social Cognitive Theory (SCT) and Self-Determination Theory (SDT) were used to guide the development of the intervention for this study. They have demonstrated strong predictive validity: the SCT has been shown to predict up to 89% (Phillips & McAuley, 2013), and the SDT has predicted up to 29% of the variance in PA behavior in cancer survivors (Edmunds, Ntoumanis, & Duda, 2006; Milne, Wallman, Guilfoyle, Gordon, & Corneya, 2008; Peddle, Plotnikoff, Wild, Au, & Courneya, 2008; Wilson, Blanchard, Nehl, & Baker, 2006).

Table IV.1 lists key constructs of the SCT and SDT, their definitions, and motivational techniques that have been used to support the defined constructs. Briefly, the SCT proposes that self-efficacy may directly and indirectly influence exercise behavior through the other SCT constructs: outcome expectations, perceived facilitators and impediments, and goals (Bandura, 1986, 2004). The SDT proposes three basic psychological needs—competence (akin to self-efficacy), autonomy, and relatedness—drive intrinsic (pleasure-driven) and extrinsic (external pressure or internal guilt-driven) motivation (Deci & Ryan, 1985; Ryan, 1995; Ryan & Deci, 2000). Autonomous motivation may be a combination of intrinsic and extrinsic motivation, and involves identification and integration of the behavior's importance with one's own beliefs and values (Ryan & Deci, 2000).

Table IV.1

Key Theoretical Constructs and Evidence-Based Motivational Techniques

Construct	Definition	Evidence-Based Motivational Techniques	MI-Walk Intervention
Self-Efficacy / Competence	One's perceived ability to perform a specific task and overcome barriers to performing the task. Sources of self-efficacy: -Mastery: prior personal task-specific success -Vicarious Experience: viewing the successes of other role models performing the task -Verbal Persuasion: affirmation and encouragement from a trusted source -Physiological and Affective States: interpretation of physiological and affective barriers and indicators of incapability	Mastery: -Heart rate monitors -Exercise logs -Progress summaries Vicarious Influences: -Idolized exercise partners or role models Verbal Persuasion: -Individual or group counseling -Encouragement from a health provider, family, or friends Physiological and Affective States: -Educational booklets	-Heart rate monitor -Exercise diaries -Progress summaries -Exercise testimonies from prior colorectal cancer survivors on oxaliplatin -In-person and telephone motivational interviewing. -Email group -Weekly walking groups -PA and Cancer treatment-specific educational pamphlets
Outcome Expectations	Perceived material or psychological gains from or negative effects of a behavior.	See Self-Efficacy	See Self-Efficacy
Perceived Facilitators and Impediments	Perceived physical, social, or situational facilitators or behaviors to performing a behavior.	If-then implementation statements	If-then implementation statements
Goals	Short or long-term goals	SMART goals	SMART goals
Autonomy -Autonomous Motivation	Perceived internal volitional control over one's behavior and outcomes. -Autonomous motivation stems from both a) inherent pleasure in the behavior or the pursuit of accomplishing the behavior, and b) integration of the behavior's importance with one's own values.	-Motivational interviewing	Motivational interviewing
Relatedness	Sense of social belongingness	-Partnered activities	-Weekly walking groups -Peer accountability phone calls

Note. Although many motivational techniques may target multiple constructs, the techniques are categorized under the construct that it may affect the most. The constructs and definitions are derived from the Social Cognitive Theory (Bandura 1986, 2004), and the Self-Determination Theory (Deci and Ryan 1985; Ryan 1995; Ryan and Deci 2000).
Abbreviations. PA, physical activity; SMART, specific, measurable, action-oriented, realistic, and time-based.

Ultimately, self-efficacy and autonomous motivation have consistently been identified as key and potentially synergistic behavioral predictors (Mosher et al., 2008; Pinto, Rabin, & Dunsiger, 2009; Rogers, 2008; Sweet, Fortier, Strachan, & Blanchard, 2017). Thus, the SCT and SDT provide a strong framework for developing interventions to promote exercise in adults, including those receiving cancer treatment.

Based on the theoretical framework, the MI-Walk Intervention was developed for and pilot tested in this study. The MI-Walk Intervention was an eight-week of home- and motivational enhancement therapy (MET)-based brisk walking intervention developed to reduce OIPN among oxaliplatin-receiving GI cancer survivors.

Purpose and Design

The purpose of this pilot study was to explore the feasibility of the MI-Walk Intervention compared to PA education alone among GI cancer survivors starting at the second FOLFOX or FOLFIRINOX treatment cycle. The specific aims of this dual-site, prospective, randomized, controlled, pilot study were to describe the rates of and explore the relationships between patient characteristics and 1) enrollment in and attrition from the study, 2) acceptability of the MI-Walk Intervention, and 3) intervention adherence. Overall PA levels were also explored.

Methods

A detailed description of the study methods are provided in another manuscript (Kanzawa-Lee et al., 2019, unpublished). Briefly, 60 adults, age 18 years or older, with stage II-IV GI cancers were recruited to the study between May 14, 2018 and April 22, 2019 from an NCI-designated comprehensive cancer center and neighboring community cancer center. The participants were also screened based on the following key eligibility criteria: 1) scheduled to receive at least 6 cycles of FOLFOX or FOLFIRINOX, 2) Eastern Cooperative Oncology Group

(ECOG) Status of zero to one, and 3) a prognosis greater than three months; and no 4) exercise- or mobility-limiting disease, 5) major surgery scheduled during the eight-week study time period, or 6) self-reported pre-existing peripheral neuropathy. Participants were also excluded if they were pregnant or unable to read or speak English.

The institutional review boards at both study sites reviewed and approved the study. All pre-screened eligible participants were offered the opportunity to participate; informed consent was obtained from the interested participants. Initially, participants were approached for recruitment at their new patient chemotherapy planning visit. To bolster recruitment, the study protocol was amended to change the timing of recruitment to the second FOLFOX or FOLFIRINOX infusion visit.

Control and Intervention Condition

Participants were randomly assigned to join the PA education control or eight-week MI-Walk Intervention group. The PA education was delivered by the interventionist (first author) at the patients' second FOLFOX/FOLFIRINOX infusion verbally and in written form based on the *Physical Activity and the Cancer Patient* pamphlet (American Cancer Society, 2014). Additionally, all participants received five-minute telephone follow-up calls to assess whether they were experiencing any adverse events. The follow-up phone calls for the control group participants occurred at the one-, two-, four-, and six-week timepoints.

The MI-Walk Intervention. The MI-Walk Intervention was an eight-week home-based aerobic walking program that supplemented the PA education and follow-up phone calls. The goal by the eight-week time point was for participants to reach or exceed the national aerobic PA guidelines: 150 minutes of moderate- to vigorous-intensity PA (MVPA) per week (American Cancer Society, 2014; Schmitz et al., 2010; U.S. Department of Health and Human Services,

2018). The weekly walking dosages were tailored based on the participants' baseline PA levels and preferences; the dosages ranged from 10 to 60 minutes, three to five days per week, at moderate intensity (a Borg rating of perceived exertion between 12 and 14).

In addition to PA education, participants assigned to the walking intervention received the following:

1. At orientation: semi-scripted motivational enhancement therapy (MET), supplemental cancer treatment and exercise education, and a tailored progressive walking plan, Fitbit Charge 2 device and app, exercise diary, and patient testimony about staying physically active during FOLFOX/FOLFIRINOX treatment.

2. At two and four weeks: an MET session by phone or in-person, progress summary, and an updated walking plan, SMART goals, and if-then statements.

3. Ongoing support through a private email group, weekly emailed scripted motivational messages and invitations to group walking events, and encouragement to engage in peer accountability phone calls. The walking sessions only occurred if participants expressed availability and interest by email.

The MET sessions included semi-scripted motivational interviewing and collaborative goal setting and planning. Motivational interviewing is a "collaborative conversation style for strengthening a person's own motivation and commitment to change" (Miller & Rollnick, 2013, p. 12). Motivational enhancement therapy is the combination of motivational interviewing with other self-efficacy-enhancing feedback techniques (e.g., progress summaries). Worksheets were provided to help the patients write specific measurable action-oriented realistic and time-bound (SMART) aerobic exercise goals, a progressive walking plan, and plans to address their exercise

barriers. The "if-then implementation intention" statement method was used to encourage participants to identify their major exercise barrier(s) and create a plan to address it/them. For example, if a participant's major barrier was forgetting to walk, their intention statement could be "if it is six PM on Saturday, then I will walk for 10 minutes."

Measurement

The participants completed the study surveys on a tablet at baseline and eight weeks. The baseline assessments coincided with the intervention orientation, which occurred during the participants' second FOLFOX/FOLFIRINOX treatment. The eight-week assessments occurred eight weeks after baseline, often at the sixth FOLFOX/FOLFIRINOX treatment. All study visits coincided with regularly scheduled clinic visits whenever possible. Adverse events were assessed via telephone at the one-, two-, four-, and six-week time points.

***Enrollment and attrition*.** The participants who were eligible for, enrolled in, and withdrew/were removed from the study were counted. Data were collected regarding the reasons for patient attrition.

***Adapted Acceptability E-Scale*.** After completing the intervention, participants rated the acceptability of the MI-Walk Intervention using the Adapted Acceptability E-Scale survey. This survey was derived from the original Acceptability E-Scale developed by Berry and colleagues (Mullen, Berry, & Zierler, 2004). Participants rated the MI-Walk Intervention based on individual domains of acceptability: satisfactoriness, difficulty, enjoyableness, helpfulness in managing OIPN symptoms, and acceptability of the time requirement of the intervention; and degree of clarity of the written intervention materials. Another survey question assessed participants' perceived likelihood that they would "continue the walking program (walking for exercise and using the materials and techniques given…during the program)." Additionally, the

survey measured the helpfulness of each intervention component. The scale for each item ranged from one (e.g., very unacceptable/unhelpful) to five (very acceptable/helpful), and the 14-item survey score ranged from 14 to 70. Prior literature has suggested 80% of the highest possible score is sufficient to categorize the intervention as acceptable; thus, a score of at least 59 overall (4 for individual items) will be used to indicate that the intervention may be acceptable (Tariman, Berry, Halpenny, Wolpin, & Schepp, 2011). The original survey—which measured acceptability of a computerized QOL and symptom-assessment system—demonstrated strong internal consistency reliability (Cronbach's $\alpha = 0.91$) in cancer populations (Mullen et al., 2004).

Intervention uptake. Uptake—also termed treatment receipt—is the degree of participant comprehension of, engagement in, and adherence to utilizing the provided skills and components of the intervention (Gearing et al., 2011). Uptake was examined based on participants' use of the exercise diaries and Fitbits. Additionally, the number of weekly walking sessions held, participant attendance, and duration of each group walking session was recorded. Throughout the study, the interventionist continuously observed and collected qualitative data about the participants' peer interactions, and acceptability and uptake of the intervention.

Exercise interest and confidence. Although interest is not considered a construct of acceptability, the results are reported together, because the same timing and format of measurement were used to assess exercise interest and confidence. During each MET session, the interventionist used scripted standard motivational interviewing questions to ask participants to rate on a 0 to 10 scale their 1) interest and 2) confidence in increasing their amount of aerobic exercise over the next eight weeks.

Adverse events. Intervention-related adverse events were assessed by the interventionist through brief semi-scripted interviews at one, two, four, six, and eight weeks. Participants were

provided with the principle investigator's contact information and encouraged to report their concerns anytime.

***Physical activity*.** The Fitbit Charge 2 was used to measure MVPA and total PA over the eight weeks of the MI-Walk Intervention. No baseline Fitbit data was collected, because the Fitbit was primarily intended as an intervention component and was provided when a participant initiated the MI-Walk Intervention. The cut-off for classifying minutes of MVPA was activity performed at or above 3 metabolic equivalent of tasks (METS) for at least 10 continuous minutes (American Cancer Society, 2014; Fitbit, 2019; U.S. Department of Health and Human Services, 2018). The Fitbit also recorded the number of steps per day. Finally, total PA was estimated based on the sum of "lightly active" (~1.1 to 2.9 METS), "fairly active" (3 to 5.9 METS), and "very active" (greater than 6 METS) minutes per day (Fitbit, 2019; U.S. Department of Health and Human Services, 2018).

Studies suggest convergent validity between research-grade activity monitor- and Fitbit Charge 2-measured minutes of MVPA (r = .658; *ICC* = .69) (Brewer, Swanson, & Ortiz, 2017; O'Driscoll et al., 2018; Reddy et al., 2018; Straiton et al., 2018; Tedesco et al., 2019) and step counts (r = .84-.86; *ICC* = .89-.95) in older adults in free-living conditions (Farina & Lowry, 2017; Reid et al., 2017; Straiton et al., 2018). No studies of Fitbit test-retest reliability have been found (Evenson, Goto, & Furberg, 2015).

***Secondary self-report PA measures*.** Self-reported PA was evaluated in both the intervention and control groups, using the PA Vital Sign (VS) tool (Greenwood, Joy, & Stanford, 2010) and Physical Activity Survey for the Elderly (PASE) (Washburn, McAuley, Katula, Mihalko, & Boileau, 1999; Washburn, Smith, Jette, & Janney, 1993). Both measures were

administered at baseline and eight weeks. Additionally, the PAVS was administered to the intervention group at two- and four-weeks.

The PAVS tool—a two-question interview—was used to collect participant self-reported average weekly minutes of MVPA (Greenwood et al., 2010). The two interview questions were "How many days during the past week have you performed PA where your heart beats faster and your breathing is harder than normal for 30 minutes or more? How many days in a typical week do you perform activity such as this?" (Greenwood et al., 2010). The PAVS has demonstrated convergent validity, based on its ability to predict body mass index (BMI) ($b = .91$; $p < .001$) (Greenwood et al., 2010) and comorbidity ($p < .05$) (Ball, Joy, Gren, Cunningham, & Shaw, 2016) and association with research-grade accelerometers ($r = .52$) (Ball et al., 2015) and PA surveys with strong validity ($r = .71$) (Ball, Joy, Gren, & Shaw, 2016; Golightly et al., 2017; Wald & Garber, 2018).

The 28-item PASE survey was used to measure self-reported total PA levels (Washburn et al., 1999, 1993). Six four-point Likert scale items measured the frequency (0, never; 3, often) and usual session duration (0, less than 1 hour; 3, more than 4 hours) of time spent leisure activities. Six items measured engagement (1, yes; 0, no) in household activities; and one question quantified the time spent on occupational activities. A single weighted PA score (*range* = 0-793 [Washburn et al., 1999, p. 2]) was calculated based on the PASE scoring instructions. The PASE has demonstrated test-retest reliability (*ICC* = 0.67-0.9) (Dinger, Oman, Taylor, Vesely, & Able, 2004; Forsen et al., 2010; Washburn et al., 1993) and validity per its associations with performance status ($r = .36$-$.59$), objectively-measured ($r = .4$) and self-reported physical function ($r = .57$) (Granger, Parry, & Denehy, 2015), and objectively-measured PA ($r = .16$-$.68$; $p < .005$) (Granger et al., 2015; Liu et al., 2011; Su, Lee, Yeh, Kao, & Lin,

2014). The PASE has also demonstrated responsiveness to decreasing PA levels during lung cancer treatment (ES = .23-.24; $p \leq .023$) (Granger et al., 2015).

***Participant characteristics*.** Clinical characteristics (e.g., cancer type, stage, and treatment, and analgesic drug use) were abstracted from the electronic medical record. Participants completed a battery of electronic surveys: a demographic survey of age, race, gender, and marital and employment status at baseline, and surveys of chemotherapy-induced neuropathy and QOL at baseline and eight weeks. The European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-Chemotherapy-Induced Peripheral Neuropathy 20-item supplement (CIPN20) (Postma et al., 2005) and Core 30-item (C30) surveys (Aaronson et al., 1993) were used to evaluate the degree of cancer treatment-related symptoms and QOL/function on a 0 ("not at all") to 100 ("very much") scale. Higher symptom item/subscale scores represented worse severity; higher QOL subscale scores equated to better QOL/function. A symptom score ≥ 25 ("a little") indicated mild presence of a symptom. Only the symptoms that were at least mild in severity at eight weeks (based on the scoring criteria) or that significantly worsened from baseline to eight weeks were evaluated in relation to MVPA and acceptability. The EORTC surveys have been used in numerous studies among multiple cancer populations globally and have demonstrated strong reliability and validity (Aaronson et al., 1993; Alberti et al., 2014; Cavaletti et al., 2013; Knoerl et al., 2017; Lavoie Smith et al., 2013; Li, Lin, Qiu, Gao, & Xu, 2014; Nicklasson & Bergman, 2007; Niezgoda & Pater, 1993; Osoba et al., 1994; Postma et al., 2005; Ringdal & Ringdal, 1993; Smith et al., 2018).

Statistical Analysis

Statistical analyses were performed using STATA version 15.0 statistical software (StataCorp, 2017). Given the exploratory nature of this pilot feasibility study, only *95% CIs* and effect sizes are presented in this paper. An $|r| \geq .50$ indicated a strong correlation and an $|r| \geq .30$ indicated moderate correlation, based on established conservative criteria (Cohen, 1988) and recent findings that demonstrated $|r| = .20\text{-}.40$ is a medium effect size in research on patient attitudes (Bosco, Aguinis, Singh, Field, & Pierce, 2015). Cohen's criteria were also used to interpret the results of ANOVA (η^2 of .14 was considered a medium to large effect size) (Cohen, 1988). The magnitude of significance of the t-tests and linear and logistic regression models were evaluated based on differences in means ($\Delta_{\bar{X}}$), *b* coefficients ($\bar{X}_{\Delta}$), and odds ratios (*OR*); and the 95% confidence intervals (*CI*s).

Descriptive statistics— *n* (%) and means with standard deviations ($\bar{X}\pm SD$)—were used to quantify study enrollment, attrition, participant characteristics, PA levels, intervention acceptability and fidelity, and exercise-related adverse events. The enrollment rate was calculated as the number of participants who enrolled in the study over the total number of contacted screened participants who had demonstrated preliminary eligibility via the medical record. The attrition rate was expressed as the percent of intervention group participants who did not complete the eight-week assessments out of the number of eligible participants randomized to the intervention. Logistic regression to obtain *OR*s and independent t-tests to identify inter-group $\Delta_{\bar{X}}$s were used to compare the characteristics of patients who enrolled versus declined participation and completed versus withdrew from the study. Additionally, Fisher's exact tests were used to analyze inter-group differences for categorical variables if the sample size was too small and unbalanced to conduct logistic regression. Paired t-tests were used to identify the

cancer treatment-related symptoms that significantly changed from baseline to eight weeks. The most severe symptoms at eight weeks and those that changed significantly over time were selected for evaluation in relation to acceptability of the intervention and Fitbit-measured weekly minutes of MVPA.

Two-sided independent t-tests, Analysis of Variance (ANOVA), linear regression, and bivariate Pearson correlations were used to assess the relationships between the various participant characteristics and intervention acceptability and average MVPA weekly minutes.

Line graphs were used to vizualize the patterns of Fitbit-measured minutes of MVPA and step counts over time. Independent t-tests, ANOVA with Tukey's honestly significant difference test, and Bonferroni-corrected Pearson bivariate correlations were used to explore the relationships between the participant characteristics and (a) Fitbit-measured MVPA averaged over the eight weeks among the intervention participants, and (b) self-reported MVPA and PA levels in the control group at eight weeks.

Results

Figure IV.1 is a flowchart of study screening and recruitment and the flow of participants through the study. Sixty individuals enrolled; 30 participants received PA education alone (the control) and 29 participants received the MI-Walk Intervention.

Enrollment

The overall enrollment rate was 62%, out of the 97 screened and eligible patients for the study. Due to low (38%) enrollment rate in the first three months of the study when patients were screened at a new patient visit, a protocol amendment was made to screen patients at the second FOLFOX/FOLFIRINOX infusion instead. A key additional component of the amendment was the elimination of the eligibility criteria that had been excluding a large proportion of patients

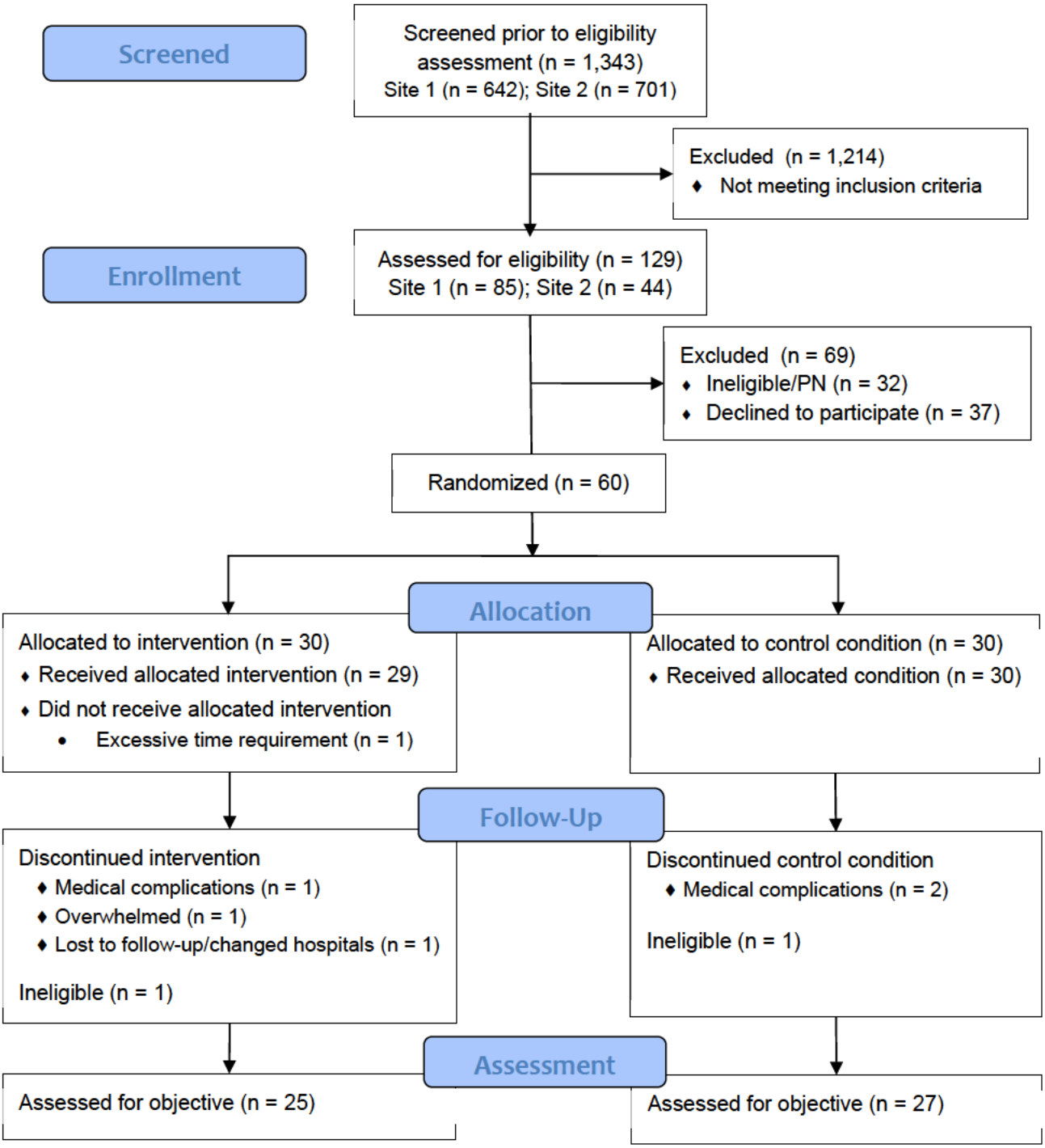
who already met the ACSM PA guidelines. After protocol amendment, the enrollment rate was 68%.

***Sample characteristics*.** Table IV.2 presents the differences in participant characteristics by enrollment. All but four participants resided in urban areas or clusters within the Bay, University, and Metro regions of Michigan. Most participants were male (60%), white (92%), married (78%), and full-time employed (32%) or retired (28%). The patients who enrolled—mean age 57.93 (*SD* = 10.67) years—had stage II-IV mostly colon and/or rectal (65%) or pancreatic cancers (32%). Participants had a range of zero (*n* = 27) to three (*n* = 1) comorbidities: mostly hypertension alone (*n* = 10).

Only the participants who enrolled completed the baseline surveys. Based on the surveys, the participants reported high physical ($\bar{X}$ = 91.00; *SD* = 14.25) and emotional function scores ($\bar{X}$ = 85.69; *SD* = 12.09) at baseline. The worst baseline cancer treatment symptom was fatigue ($\bar{X}$ = 27.59; *SD* = 18.47), followed by appetite loss ($\bar{X}$ = 23.89; *SD* = 26.10) and insomnia ($\bar{X}$ = 23.89; *SD* = 22.21). The baseline self-reported PA scores averaged 112.45 (*SD* = 91.79, *range* = 10-583) on a scale from zero to 793.

Figure IV.1

Recruitment Flowchart B



Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.

Abbreviations. PN, peripheral neuropathy (self-reported).

Characteristics associated with enrollment. Enrolled individuals reported significantly fewer comorbidities than patients who declined participation (*95% CI* -0.67, -0.01). As depicted in Table IV.2, no other differences were found between the individuals who enrolled and those who declined participation in the study.

Table IV.2

Characteristics of Patients by Enrollment

Characteristic	**Declined** $n = 32$	**Enrolled** $n = 60$	***OR***	**[*95% CI*]**	
	***n* (%)**				
Male Gender	16 (50)	36 (60)	1.5	0.63	3.56
Race					
White	27 (84)	55 (92)	Ref		
Black	4 (13)	2 (3)	4.07	0.70	23.65
Asian	1 (3)	2 (3)	1.02	0.09	11.74
Other	0	1 (2)	.	.	.
Cancer Type					
Colon	8 (25)	22 (37)	Ref		
Rectal/Colorectal	12 (38)	17 (28)	1.94	0.65	5.81
Pancreatic	5 (15.5)	19 (32)	0.72	0.20	2.59
Other GI	2 (6)	2 (3)	2.75	0.33	22.92
No response	5 (15.5)	0	.	.	.
Cancer Stage					
II	8 (25)	12 (20)	Ref		
III	13 (41)	20 (33)	0.98	0.31	3.03
IV	10 (31)	27 (45)	0.56	0.18	1.76
Unknown	1 (3)	1 (2)	.		.
	$\bar{X}$ ***(SD)***		**Inter-group** $\bar{X}_1$-$\bar{X}_2$	**[*95% CI*]**	
Age (years)	57.06 (15.35)	57.93 (10.67)	0.87	-4.56	6.30
BMI (kg/m^2)	25.82 (5.24)	25.78 (4.19)	-0.05	-2.04	1.95
Number of comorbidities	1.12 (0.48)	0.78 (0.88)	-0.34*	-0.67	-0.01

Abbreviations. BMI, body mass index; CI, confidence interval; GI, gastrointestinal; OR, odds ratio; SD, standard deviation.
*, medium to large effect

Attrition

Figure IV.1 includes participant attrition rates and reasons as described below. The overall attrition rate was 10% (14% in the MI-Walk Intervention group). Regarding solely the

MI-Walk Intervention group from here on (n = 30), one participant withdrew prior to initiating the MI-Walk Intervention due to perceived excessive time requirement of the intervention. After intervention initiation, one participant was removed from the study due to ineligibility (ECOG functional status = 2 prior to enrollment) and was not included in the attrition count. Three participants discontinued the intervention due to severe chemotherapy treatment side effects (n = 1), feeling overwhelmed with external life circumstances (n = 1), and changing hospitals (n = 1).

***Characteristics associated with attrition*.** Table IV.3 presents the differences in baseline characteristics between the MI-Walk Intervention participants who withdrew from (n = 4) and completed the study (n = 25). The participants who completed the study were younger than those who withdrew from the study ($\bar{X}_1$-$\bar{X}_2$ = -11.26; *95% CI* -23.67, 1.15). Further, participants whose oxaliplatin was already dose reduced by the second chemotherapy dose had a 24 times higher odds of withdrawing from the study than those who received the planned chemotherapy dose at cycle two (*95% CI* 1.46, 394.88). The oxaliplatin doses had been reduced due to provider discretion. Levels of MVPA/PA and neither exercise interest nor confidence were no different based on attrition.

***Eight-week clinical characteristics*.** Based on the participants who completed the study, the worst symptoms at eight weeks were fatigue ($\bar{X}$ = 37.78; *SD* = 23.57) and appetite loss ($\bar{X}$ = 34.67; *SD* = 36.62). Significant increases over the eight weeks were found in fatigue ($\bar{X}_\Delta$= 13.78; *95% CI* 6.26, 21.30), sensory OIPN ($\bar{X}_\Delta$= 5.04; *95% CI* 1.54, 8.54), and motor OIPN ($\bar{X}_\Delta$= 5.43; *95% CI* 1.89, 8.96). Participants had received 373.22 (*SD* = 55.79) mg/m^2 of oxaliplatin by eight weeks. In addition to general demographics and oxaliplatin dose, the eight-week severities of these symptoms were explored in relation to intervention attrition, acceptability, and Fitbit-measured minutes of MVPA.

Table IV.3

Baseline Characteristics of the MI-Walk Intervention Participants by Attrition

Characteristic	Withdrew *n* = 4	Completed *n* = 25
	***n* (%)**	
Cancer Type		
Colon	1 (25)	10 (40)
Rectal/Colorectal	0	9 (36)
Pancreatic	3 (75)	6 (24)
Cancer Stage		
II	1 (25)	5 (20)
III	3 (75)	7 (28)
IV	0	12 (48)
Marital Status		
Married	3 (75)	22 (88)
Separated/Divorced	0	2 (8)
Widowed	1 (25)	0
Never Married	0	1 (4)
Employment Status		
Employed	2 (50)	13 (52)
Not employed	2 (50)	12 (48)
Highest Education Degree		
≤ High school degree	1 (25)	4 (16)
Some college	1 (25)	9 (36)
≥ Bachelor degree	2 (50)	12 (48)
Smoking History		
Never smoked	3 (75)	12 (48)
Former smoker	1 (25)	11 (44)
Current smoker	0	2 (8)
Gender		
Male	3 (75)	20 (80)
Female	1 (25)	5 (20)
ECOG		
0	2 (50)	18 (72)
1	2 (50)	7 (28)
Oxaliplatin dose		
Given as planned	2 (50)	24 (96)
Reduced	2 (50)	1 (4)
	$\bar{X}$ ***(SD)***	
Age (years)	66.50 (4.51)	55.24 (11.81)
BMI (kg/m^2)	23.03 (3.07)	25.32 (3.78)
Number of comorbidities	0.75 (0.96)	0.52 (0.65)
Number of analgesics/neuroprotectants	0.75 (0.96)	0.60 (0.76)

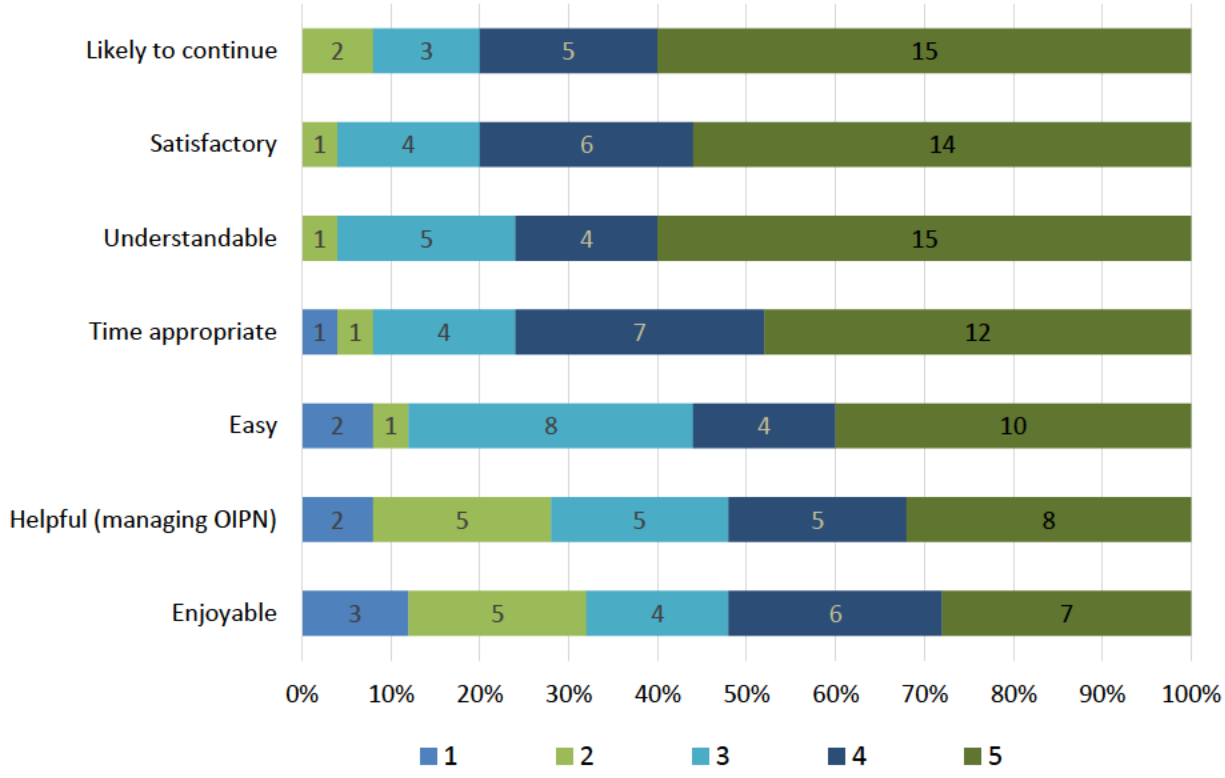
Note. Test of statistical significance comparing groups not conducted due to inadequate and uneven sample size.
Abbreviations. BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; SD, standard deviation.

Acceptability of the MI-Walk Intervention

Figure IV.2 is a 100% stacked bar chart that depicts the domains of acceptability and the *n* (%) of participants that rated the acceptability of each domain a "1" (e.g., very unacceptable), "2," "3," "4," or "5" (e.g., very acceptable). The overall acceptability score was 47.91 (*SD* = 11.45) on a scale from 14 to 70. Most (80%) of the participants said they were satisfied with the intervention and/or would likely continue the intervention (i.e., "walking for exercise and using the materials and techniques given to [them] during the program").

Figure IV.2

Acceptability of the MI-Walk Intervention



Abbreviation. OIPN, oxaliplatin-induced peripheral neuropathy
Note. A rating of one (far left) is very unacceptable/unhelpful/difficult/etc. Rating of five (far right) is very acceptable/helpful/easy/etc.

***Helpfulness and uptake of the intervention components*.** Figure IV.3 is a 100% stacked bar chart of the *n* (%) of participants that gave each rating between one (e.g., very unhelpful) and five (e.g., very helpful) for each MI-Walk Intervention component. Participants rated the Fitbit ($\bar{X}$ = 3.67; *SD* = 1.43) and MET sessions ($\bar{X}$ = 3.44; *SD* = 1.36) as most helpful. However, five participants were non-compliant with wearing the Fitbit (i.e., they forgot or refused to wear the Fitbit for more than two of the eight intervention weeks). The MET sessions ($\bar{X}$ duration = 40.88; *SD* = 18.05 minutes) were well-attended (98% completed) among the participants who completed the study;); the ratings of the PA education given at orientation was neutral ($\bar{X}$ = 2.96; *SD* = 1.14). Allowing for three attempts to reach each patient, 86% of the follow-up telephone assessments were completed. Anecdotally, many patients expressed a preference for communicating by text or email instead of by telephone call.

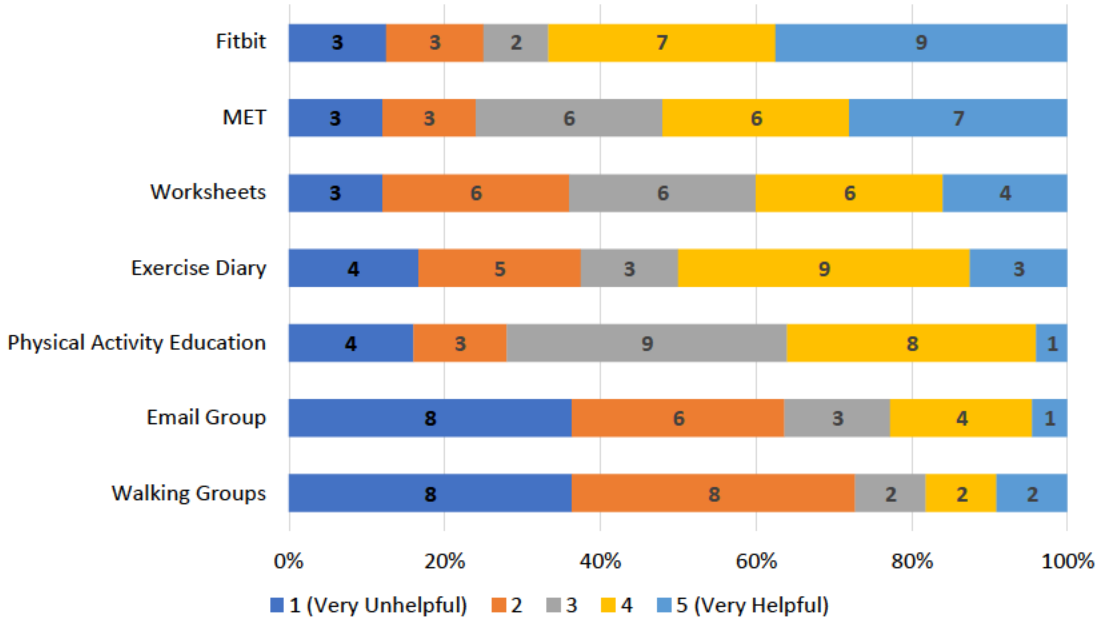
The participants were neutral regarding the helpfulness of the exercise diaries and worksheets ($\bar{X}$ = 3.08; *SDs* = 1.29 and 1.35). Fourteen (48%) of the intervention participants returned and were mostly compliant in completing the exercise diaries. Nine participants elected to keep their diary after turning in the required carbon copies of the pages they completed. Regarding the worksheets, most participants filled-out the SMART goals worksheet; however, no patients consistently utilized the if-then implementation (addressing exercise barriers) worksheet per interventionist observation. On the SMART goals worksheet, many participants also added strength training and/or step count-directed PA goals.

Finally, most (64%-73%) participants rated the email and walking groups as unhelpful. One participant had a Facebook account and joined the intervention Facebook group before it was terminated and replaced by an email group. No continuous conversations occurred through the email group, and one participant elected not to provide an email address to join the email group.

Five mall walking sessions (50 minutes – 1.5 hours in duration) occurred with one participant each between July 9, 2018 and June 17, 2019: one participant attended two late Saturday walking sessions and another participant attended three late Sunday morning walking sessions. No participants shared their phone number with a peer to engage in accountability phone calls.

Figure IV.3

Helpfulness of the MI-Walk Intervention Components



Abbreviation. MET, motivational enhancement therapy.

Exercise interest, confidence, and adverse outcomes. At baseline, the participants reported moderate interest in increasing ($\bar{X}$ = 6.38; *SD* = 3.14; *range* = 0-10) and moderate confidence in their ability to increase their amount of aerobic exercise over the next eight weeks ($\bar{X}$ = 7.88; *SD* = 2.03; *range* = 3-10). Many patients explained that they were giving a low score for their interest in increasing their aerobic exercise, because they preferred to focus on strength training to preserve muscle mass instead and/or just maintain their current level of PA, which already met the national PA guidelines. Additionally, some participants reported an inability and

low prioritization of/interest in trying to meet their PA goals, due to difficulty eating. Interest and confidence levels were unchanged at eight weeks. No study-related adverse events occurred.

Associations between acceptability and participant characteristics. Table IV.4 illustrates data regarding the acceptability of the intervention by MI-Walk Intervention participant characteristic. Part-time or un-employed participants rated the intervention higher in acceptability compared to participants who were retired ($\bar{X}_{\Delta}$ = 21.75; *95% CI* 2.97, 40.53). Further part-time or un-employed participants were the only group of individuals that rated the acceptability of the intervention above the 80% acceptability threshold. Retired individuals were the only group to rate the MET sessions as unhelpful (see Table IV.5; $\bar{X}$ = 2.50; *SD* = 1.52). Having a bachelor's degree or above predicted higher overall acceptability scores ($\bar{X}_{\Delta}$ = 13.92; *95% CI* = 0.25, 27.59). Additionally, baseline oxaliplatin dose was negatively correlated with acceptability (*r* = -.41) but eight-week oxaliplatin dose was positively correlated with ratings of acceptability (*r* = .36).

Table IV.4

Relationships between Intervention Acceptability Scores and Participant Characteristics

Characteristic	*n*	Acceptability	
		$\bar{X}$ (*SD*)[a]	η^2 [95% *CI*][b]
Employment Status			.34 [. , .52]**
Full-time employed	10	51.90 (13.76)	
Part time-/un-employed	4	62.25 (8.30)	
Retired	6	40.50 (5.54)	
On disability/leave of absence	5	49.40 (7.50)	
Cancer Type			.13 [. , .35]
Colon	10	50.00 (12.46)	
Rectal/Colorectal	9	46.00 (10.15)	
Pancreatic	6	57.33 (12.48)	
Highest Education Degree			.17 [. , .39]*
≤ High school degree	4	40.50 (6.86)	
Some college	9	49.22 (14.49)	
≥ Bachelor degree	12	54.42 (9.76)	
Smoking History			.07 [. , .26]
Never smoked	12	52.25 (10.73)	
Former smoker	11	50.00 (13.96)	
Current smoker	2	40.50 (3.54)	
			r [95% *CI*][c]
BMI (kg/m^2)	22		-.37 [-.69, .06]*
Oxaliplatin dose (mg/m^2)			
Baseline	22		-.41 [-.71, .01]*
Eight weeks	22		.36 [-.07, .68]*
Fitbit – weeks 1 to 4			
MVPA (min/week)	23		.01 [-.40, .42]
Total PA (min/day)	22		-.31 [-.64, .13]*
Baseline PA			
PAVS (min/week)	21		.33 [-.12, .67]*
Subjective PA (PASE)	19		.40 [-.07, .72]*
Eight Weeks			
Sensory OIPN	23		.34 [-.10, .66]*
Motor OIPN	23		.34 [-.09, .67]*

Abbreviations. BMI, body mass index; CI, confidence interval; MVPA, moderate to vigorous physical activity; OIPN, oxaliplatin-induced peripheral neuropathy; PA, physical activity; PASE, physical activity survey for the elderly; PAVS, physical activity vital sign; SD, standard deviation.

[a]Mean (SD) of the acceptability scores within each characterized patient group.

[b]Main effect of the characteristic (e.g., employment status) on acceptability scores.

[c]Correlation with eight-week overall acceptability scores.

*, medium effect size ($r \geq .3$; $\eta^2 \geq .14$)

**, large effect size ($r \geq .5$)

Table IV.5 explores the relationships between the participant characteristics and helpfulness ratings of the Fitbit and MET (the intervention components with the highest uptake and ratings of acceptability). The only factor strongly associated with helpfulness of the Fitbit

was BMI (r = -.50), which was also moderately associated with overall intervention acceptability (r = -.37). In contrast, helpfulness of the MET sessions, along with overall acceptability of the intervention, were associated with higher eight-week sensory (r = .34-.54) and motor OIPN severity (r = .34 -.37).

Regarding PA, Fitbit-measured PA over the first four weeks was negatively correlated with the overall acceptability (r = -.31) and Fitbit helpfulness scores (r = -.30); however, baseline self-reported MVPA and PA were positively correlated with overall acceptability (r = .33 to .40). Age, marital and ECOG status, gender, cancer stage, and exercise interest and confidence were not associated with acceptability and helpfulness scores. Fatigue, appetite loss, QOL, and physical function at eight weeks were also not associated with acceptability and helpfulness; however, further exploratory analyses showed that increase in physical function was positively correlated with acceptability (r = .34; *95% CI* -.10, .66).

Table IV.5

Helpfulness of the Fitbit and MET Sessions by MI-Walk Intervention Participant Characteristics

Characteristic	***n***	**Helpfulness**			
		Fitbit		**MET**	
		$\bar{X}$ **(*SD*)**[a]	η^2 **[95% *CI*]**	$\bar{X}$ **(*SD*)**[a]	η^2 **[95% *CI*]**
Employment Status			.16 [. , .35]*		.23 [. , .42]*
Full-time employed	10	3.40 (1.71)		3.50 (1.43)	
Not full-time employed	4	4.75 (0.50)		4.50 (0.58)	
Retired	6	3.17 (1.47)		2.50 (1.52)	
On disability/leave of absence	5	4.00 (0.82)		3.60 (0.89)	
			.23 [. , .45]*		.20 [. , .42]*
Cancer Type	10	3.30 (1.42)		3.10 (1.20)	
Colon	9	3.25 (1.58)		3.11 (1.54)	
Rectal/Colorectal	6	4.83 (0.41)		4.50 (0.84)	
Pancreatic					
Highest Education Degree			.10 [. , .31]		.07 [. , .27]
≤ High school degree	4	3.50 (1.29)		2.75 (1.71)	
Some college	9	3.13 (1.64)		3.33 (1.50)	
≥ Bachelor degree	12	4.08 (1.31)		3.75 (1.14)	
Smoking History			.07 [. , .27]		.17 [. , .39]*
Never smoked	12	3.91 (1.22)		3.92 (1.16)	
Former smoker	11	3.64 (1.57)		3.18 (1.40)	
Current smoker	2	2.50 (2.12)		2.00 (1.41)	
			r **[95% *CI*]**[c]		***r*** **[95% *CI*]**[c]
BMI (kg/m^2)	25		-.50 [-.75, -.13]**		-.07 [.45, .34]
Baseline oxaliplatin dose (mg/m^2)	25		-.29 [-.62, .13]		-.35 [-.65, .06]*
Fitbit – weeks 1 to 4					
MVPA (min/week)	23		-.29 [-.63, .15]		-.16 [-.54, .27]
Total PA (min/day)	22		-.30 [-.65, .15]*		-.19 [-.56, .26]
Eight weeks					
Sensory OIPN	25		.18 [-.24, .54]		.54 [.19, .77]**
Motor OIPN	25		.23 [-.19, .58]		.37 [-.04, .66]*

Abbreviations. BMI, body mass index; CI, confidence interval; MET, motivational enhancement therapy; MVPA, moderate to vigorous physical activity; OIPN, oxaliplatin-induced peripheral neuropathy; PA, physical activity; QOL, quality of life; SD, standard deviation.

[a]Mean (SD) of the helpfulness scores within each characterized patient group.

[b]Main effect of the characteristic (e.g., employment status) on helpfulness scores.

[c]Correlation with eight-week helpfulness scores

*, medium effect size ($r \geq .3$; $\eta^2 \geq .14$)

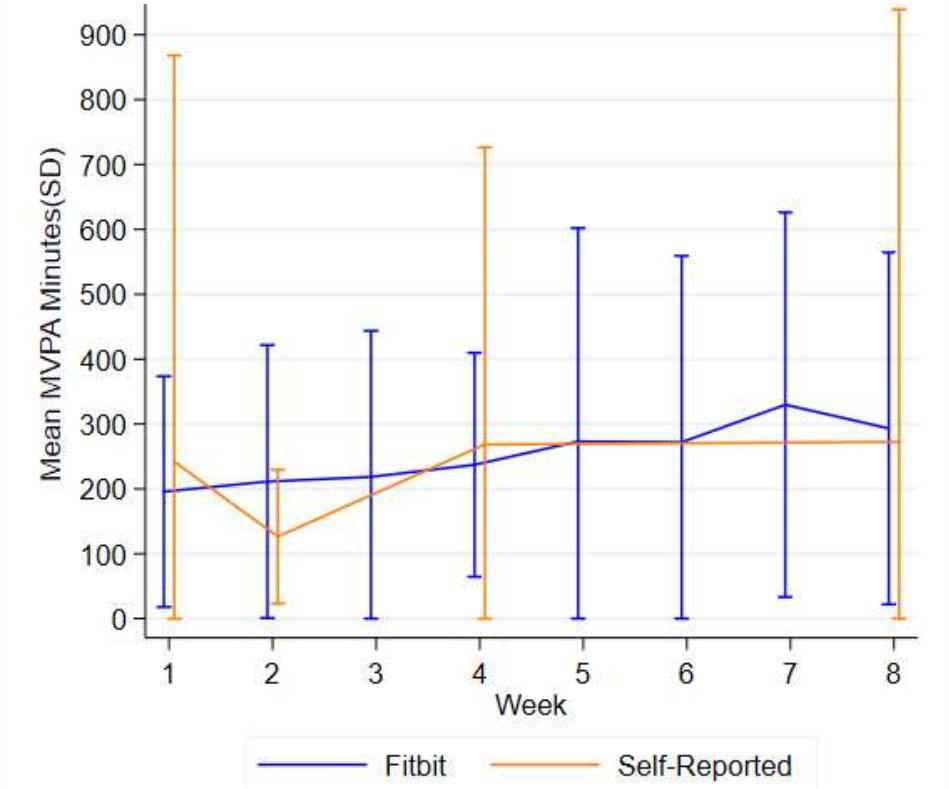
**, large effect size ($r \geq .5$)

Physical Activity Trends

Figure IV.4 plots the Fitbit-recorded and self-reported minutes of MVPA exhibited by participants over the eight weeks. Per the Fitbit (N = 25), the participants averaged 236.58 (SD = 197.60; *range* = 0-716.88) minutes of MVPA per week over the eight weeks: 205.91 (SD = 167.10) minutes per week over the first four and 273.80 (SD = 252.34) minutes per week over the last four weeks. Per self-report, the participants averaged 238.27 (SD = 525.61; *range* = 0-2,880).

Figure IV.4

Mean minutes of MVPA during the MI-Walk Intervention based on the Fitbit and self-report

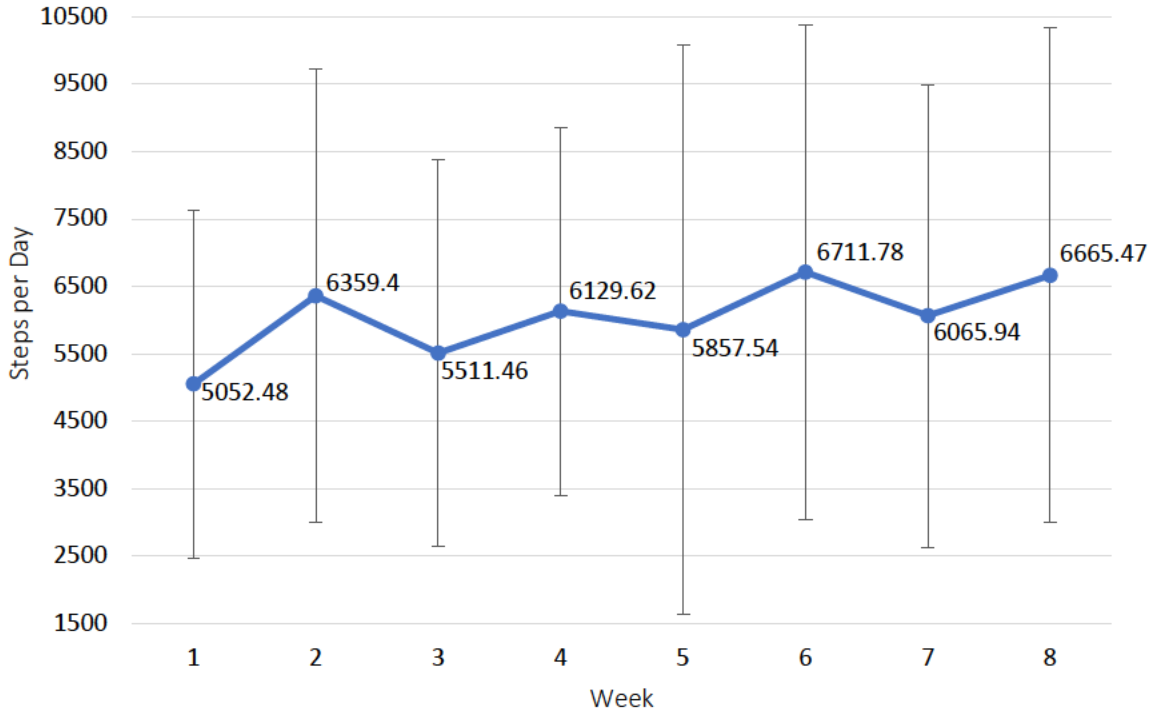


Abbreviations. MVPA, moderate to vigorous physical activity; SD, standard deviation

Figure IV.5 provides the Fitbit-recorded steps per day over the eight weeks. The participants (n = 25) averaged 5,918.82 (SD = 2,911.11) steps and 180.77 (SD = 65.54) minutes of total PA per day over the eight weeks: 7,922.91 (SD = 3,030.59) steps and 224.69 (SD = 72.14) minutes of total PA per day over the last four weeks of the intervention.

Figure IV.5

Fitbit-measured steps per day of the MI-Walk Intervention participants



Associations between MVPA and participant characteristics. Tables IV.6 and IV.7 describe the eight-week mean Fitbit-measured MVPA relationships with the participant demographics and correlations with other clinical characteristics. Males exhibited higher Fitbit-recorded minutes of MVPA per week than females ($\bar{X}_{\Delta}$= 207.1; *95% CI* 33.16, 381.03); however, 80% of the intervention group were males. Participants who were full-time employed engaged in significantly more MVPA than participants on disability/leave of absence ($\bar{X}_{\Delta}$ = 264.82; *95% CI*

4.47, 525.18). Fatigue at eight weeks was strongly associated with lower levels of Fitbit-recorded MVPA (r = -.62). As depicted in Table IV.6, several other clinical factors demonstrated small to moderate correlations with Fitbit-measured MVPA, such as baseline self-reported PA (r = .34), and eight-week confidence in the ability to increase one's amount of aerobic exercise (r = .34).

Table IV.6

Differences in Fitbit-Measured MVPA by Baseline Participant Characteristics among MI-Walk Intervention Participants (N = 25)

Characteristic	***n***	**MVPA (min/week)[a]**	
		$\bar{X}$ (*SD*)	**Inter-group $\bar{X}_1$-$\bar{X}_2$ [*95% CI*]**
Gender			207.1 [33.16, 381.03]**
Male	19	286.28 (199.5)	
Female	6	79.18 (70.82)	
ECOG			141.95 [-43.75, 327.65]*
0	19	270.65 (193.83)	
1	6	128.69 (183.81)	
Marital status			160.55 [-56.46, 377.56]*
Married	21	262.27 (194.54)	
Not married	4	101.71 (176.56)	
			η^2 [*95% CI*]
Highest Education Degree			.01 [. , .11]
≤ High school degree	4	197.06 (221.38)	
Some college	8	231.39 (231.37)	
≥ Bachelor's degree	13	251.93 (183.89)	
Smoking History			.18 [. , .40]*
Never smoked	13	254.46 (196.97)	
Former smoker	10	165.63 (143.87)	
Current smoker	2	475.13 (341.89)	
Cancer Stage			.03 [. , .18]
II	6	269.47 (219.98)	
III	7	275.27 (270.85)	
IV	11	210.08 (141.08)	
Employment Status			.35 [. , .53]**
Full-time employed	10	355.25 (119.9)	
Part time-/un-employed	4	97.79 (45.26)	
Retired	6	253.10 (291.79)	
On disability/leave of absence	5	90.43 (111.24)	
Cancer Type			.09 [. , .29]
Colon	11	283.49 (208.07)	
Rectal/Colorectal	9	256.11 (195.15)	
Pancreatic	10	147.24 (182.53)	

Abbreviations. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group functional status; MVPA, moderate-vigorous physical activity; SD, standard deviation.
[a]Fitbit-measured minutes of MVPA per week.
*, medium effect size (e.g., $\eta^2 \geq .14$)
**, large effect size

Anecdotally, some participants verbally reported that the cold weather (especially with the OIPN cold sensitivity) and cancer treatment side effects (especially fatigue) during the first three to six days were the main barriers to exercise.

Table IV.7

Exploration of MI-Walk Intervention Participant Characteristic Associations with Fitbit-Measured MVPA

Characteristic			**Association with MVPA[a]**		
	n	***$\bar{X}$ (SD)[b]***	***r***	***[95% CI]***	
Baseline					
Age (years)	25	55.8 (12.27)	.01	-.39	.40
BMI (kg/m^2)	25	25.33 (3.83)	.30*	-.11	.62
Self-reported PA					
PASE	25	121.32 (128.25)	.34*	-.06	.65
PAVS (min/week)	23	280.54 (686.47)	.22	-.21	.58
Exercise interest	23	6.39 (3.27)	.15	-.28	.53
Exercise confidence	23	7.91 (2.02)	.27	-.16	.61
Eight Weeks					
Oxaliplatin dose	23	379.63 (56.39)	.05	-.37	.46
Sensory OIPN	23	11.11 (8.65)	-.28	-.62	.15
Motor OIPN	23	8.10 (8.35)	-.32*	-.65	.11
Fatigue	23	36.71 (21.30)	-.62**	-.82	-.28
Mood	23	84.67 (18.89)	.31	-.12	.64
Exercise interest	22	6.55 (3.32)	-.02	-.43	.41
Exercise confidence	22	6.36 (2.72)	.34*	-.10	.67

Abbreviations. BMI, body mass index; CI, confidence interval; MVPA, moderate to vigorous physical activity; OIPN, oxaliplatin-induced peripheral neuropathy; PA, physical activity; PASE, physical activity survey for the elderly; PAVS, physical activity vital sign; SD, standard deviation.

[a] Fitbit minutes of MVPA per week averaged over eight weeks.

[b]Mean (SD) of the presented characteristic.

*Indicates a moderate correlation ($r \geq .3$)

**Indicates a strong correlation ($r \geq .5$)

Associations between MVPA and acceptability. Table IV.8 shows the correlations between MVPA level and acceptability scores. Participants' satisfaction with the intervention were strongly correlated with Fitbit-measured MVPA ($r = .55$). Understandability of the written intervention materials ($r = .49$) and likelihood of continuing to use the techniques and materials provided during the intervention ($r = .35$), were moderately correlated with MVPA. Greater perceived helpfulness of the group walking sessions and Fitbit were moderately correlated with lower minutes of MVPA ($r = -.32$).

Table IV.8

Correlations between Acceptability Scores and Fitbit-Measured MVPA

Acceptability	**Association with MVPA[a]**			
	n	***r***	**[**	***95% CI*** **]**
Overall acceptability	23	.04	-.38	.45
Easiness	23	-.22	-.58	.22
Understandability	23	.49*	.10	.75
Enjoyableness	23	.03	-.39	.44
Helpfulness in managing PN	23	-.11	-.50	.31
Time requirement acceptability	23	.18	-.25	.55
Satisfaction	23	.55**	.19	.79
Likelihood of continuing	23	.35*	-.08	.67
Helpfulness				
MET sessions	23	-.11	-.50	.32
Group walking sessions	20	-.32*	-.67	.14
Fitbit	22	-.32*	-.65	.12
Email group	20	-.03	-.47	.42
PA educational pamphlet	22	-.06	-.47	.37
Exercise diary	22	.11	-.33	.51
Worksheets	23	.07	-.35	.47

Abbreviations. CI, confidence interval; MET, motivational enhancement therapy; MVPA, moderate to vigorous physical activity; PA, physical activity; PN, peripheral neuropathy.

[a]Fitbit minutes of MVPA per week averaged over eight weeks.

*Indicates a moderate correlation ($r \geq .3$)

**Indicates a strong correlation ($r \geq .5$)

Discussion

Over 60% of patients screened at their second FOLFOX/FOLFIRINOX treatment enrolled in the trial and 83% of participants completed the MI-Walk Intervention. Most participants who enrolled in and completed the study were young (upper 50s), white, married, and with few comorbidities and high self-reported baseline PA levels. The overall acceptability of the intervention was low to moderate. Although participants reported high satisfaction with and likelihood of continuing the intervention, the mean helpfulness ratings of the intervention components were all below four out of five (80% the maximum score). The Fitbit and MET sessions were the sole intervention components that were rated “helpful” by most participants. Ultimately, 64% of participants adhered to the intervention prescription (i.e., averaged ≥ 127

minutes MVPA per week over the eight weeks); however, participants' MVPA varied from zero to 716.88 minutes per week.

The enrollment and attrition rates were in line with prior studies of home-based aerobic exercise interventions among patients receiving chemotherapy treatment. Prior similar studies have had an average enrollment rate of 53.16% (*range* = 33%-76.3%) out of the 233 (*range* = 48-728) mean patients approached for the studies; prior attrition rates ranged from 7% to 26% (Courneya et al., 2013; Courneya, McKenzie, et al., 2014; Dhawan, Andrews, Kumar, Wadhwa, & Shukla, 2019; Kleckner et al., 2018; McCrary et al., 2019; Mizrahi et al., 2015; Streckmann et al., 2014; Vollmers et al., 2018). After changing the timing of recruitment—recruiting patients during their second FOLFOX/FOLFIRINOX infusion instead of at their new patient (chemotherapy-planning) visit—the study's enrollment and completion rates exceeded those observed in prior trials. When approached during their new patient visit (prior to finalizing the chemotherapy treatment plan), most patients were overwhelmed and declined or asked to be approached at a later visit. Additionally, improved enrollment rates were observed after removing the eligibility criteria that had been excluding participants who were already meeting the national PA guidelines of 150 minutes per week of MVPA.

The participants who enrolled reported fewer comorbidities than those who declined. Health complications and comorobidities are a common barrier and/or patient-reported reason for deferring participation in an exercise clinical trial (Backman et al., 2014; Speed-Andrews et al., 2012).

The participants who completed the study were younger and had received higher doses (the planned dose) of oxaliplatin at the second cycle than participants who withdrew. In this study, the most common reason for oxaliplatin dose reduction at the second cycle was "MD

discretion." Clinically, the decision to reduce the oxaliplatin dose early in treatment is often based on the patient's age and baseline functional status. Exploratory analysis of the current data showed that patients whose baseline oxaliplatin dose had been reduced were significantly older than patients who received the standard 85 mg/m^2 dose ($p < .01$). A prior home-based aerobic exercise study has also shown a tendency for higher study completion rates among younger participants (Kleckner et al., 2018). Older age and age-related comorbidities have also been linked with lower engagement in MVPA (Speed-Andrews et al., 2012; van Putten et al., 2016).

Acceptability of the intervention and participants' baseline interest in increasing and confidence in their ability to increase their amount of aerobic exercise was wide-ranging and overall moderate. However, the overall acceptability ratings did not meet the arbitrary cut-off (80% of the maximum score) suggested in the literature to be considered *acceptable* (Tariman et al., 2011). The current study found that uptake and acceptance of the peer support components of the intervention (i.e., walking and email groups) were low. Although social support from a partner and family member is an empirical facilitator of exercise (Horne & Tierney, 2012; Mikkelsen et al., 2019; van Putten et al., 2016), prior evidence suggests that cancer survivors may prefer to receive exercise/lifestyle interventions individually during cancer treatment (Arthur et al., 2016).

Multiple demographic and clinical factors were associated with higher intervention acceptability, including lower BMI and higher education level and eight-week OIPN severity and oxaliplatin dose received. Several prior studies have suggested obesity may influence one's preferences in exercise type (Courneya, Segal, et al., 2014), and enjoyment of and purpose for exercising (Leone & Ward, 2013). Higher education level could be associated with a more comprehensive understanding and value of the health benefits of exercise during cancer

treatment. Prior studies have also shown links between higher education level and increased autonomously performed PA (Speed-Andrews et al., 2012). Most literature to date has focused on the (inverse) relationship between cancer treatment-related symptoms and adherence/MVPA levels but have not evaluated their relationship with intervention acceptability (Speed-Andrews et al., 2012). Part-time or un-employment (versus being retired) was also associated with higher acceptability ratings as well as MVPA and will be discussed further below.

Although acceptability scores were low to moderate, MVPA levels were exceptionally high over the eight weeks (mean of 236.58 minutes of MVPA per week). Prior studies reported that participants could adhere to 117 to 209 mean minutes of MVPA per week (Courneya et al., 2003; Djuric et al., 2011; Griffith et al., 2009; Mock et al., 2005; Shang, Wenzel, Krumm, Griffith, & Stewart, 2012). Both Fitbit-measured MVPA and self-reported PA levels were wide-ranging. For example, the participants averaged zero to 716.88 weekly minutes of MVPA per the Fitbit and zero to 2,880 weekly minutes of MVPA per self-report. On average, participants were already compliant with the PA guidelines at baseline and still exhibited increases in weekly minutes of MVPA during the study.

Fatigue exhibited the strongest associations with lower Fitbit-recorded minutes of MVPA but was not associated with intervention acceptability. Evidence suggests that fatigue is the most common and distressing cancer treatment-related symptom and is associated with sedentary behavior (Chou et al., 2017; Fernandez et al., 2015; Henriksson, Arving, Johansson, Igelstrom, & Nordin, 2016; Kamath, 2012; Kang et al., 2014; Mikkelsen et al., 2019).

Male gender and full-time employment (versus on disability or leave of absence) were also associated with higher Fitbit-recorded minutes of MVPA, which also has been suggested in

a prior population-based study of correlates with PA behavior in colorectal cancer survivors (Backman et al., 2014; Courneya et al., 2003; Djuric et al., 2011; Dodd et al., 2010; Speed-Andrews et al., 2012; Swenson et al., 2010; Trost, Owen, Bauman, Sallis, & Brown, 2002; Yang et al., 2011). However, 80% of the intervention participants were male. Employment was a key factor associated with both acceptability ratings and MVPA levels. Although full-time employed and retired participants rated the helpfulness of the intervention the lowest, they exhibited the highest MVPA levels. Exploratory post-hoc analysis also showed that full-time employed and retired individuals exhibited the highest Fitbit-measured levels of MVPA during the first four weeks of the intervention ($\bar{X}$ = 258.29-260.48, *SD* = 127.26-256.23). Fitbit-measured PA during the first four weeks of the intervention and MVPA over the eight weeks were also negatively correlated with the acceptability scores. These results may indicate that the intervention was less helpful to patients who were already physically active at baseline. Prior studies also suggest that history of PA is among the greatest predictors of future PA (Backman et al., 2014; Courneya et al., 2003; Djuric et al., 2011; Dodd et al., 2010; Swenson et al., 2010; Yang et al., 2011).

Other miscellaneous findings highlight the discrepancies and lack of clarity regarding the definition of and relationships among acceptability, interest, confidence, and objective and self-reported PA. In contrast to the above findings, self-reported baseline PA was consistently positively correlated with the acceptability scores; and strong correlations were observed between satisfaction with the intervention and minutes of objective MVPA. Anecdotally, participants often explained that their ratings of interest in increasing and confidence in their ability to increase their amount of aerobic exercise were tied to their current MVPA levels. The participants who self-reported weekly MVPA that exceeded the national guidelines at baseline reported low or neutral interest and varying levels of confidence. Further, some participants

explained that they rated their interest low, because they prioritized strength training over aerobic exercise due to their experience of appetite loss and concerns for losing weight and muscle mass. These findings hint at a stronger feedback association with baseline PA and eight-week mean MVPA minutes predicting intervention acceptability among GI cancer survivors receiving FOLFOX/FOLFIRINOX.

Limitations

The results of this study may only be applicable to younger, white, baseline physically active, and relatively financially stable GI cancer survivors with few to no comorbidities, and patients with strong, exercise- and health-promoting family social support. No data were collected on participants' specific home neighborhood conditions and walkability.

The absolute MVPA levels observed in this study may be questionable due to prior studies that have suggested a tendency for Fitbits to overestimate energy expenditure and time spent in MVPA (Bai, Hibbing, Mantis, & Welk, 2018; Brooke et al., 2017; Feehan et al., 2018; Nazari, MacDermid, Sinden, Richardson, & Tang, 2019; Tedesco et al., 2019; Thomson et al., 2019). Further, self-report bias likely influenced the measurements of total PA level, measured by the PASE. Self-reported minutes of MVPA (PAVS) may not have demonstrated increases over time correspondently with the Fitbit, because their self-report may have been inflated at baseline and were influenced by participation in the intervention (i.e., access to viewing their Fitbit stats).

Further, the reliability of the PAVS and measures of exercise importance and confidence among patients receiving neurotoxic chemotherapy may be decreased due to the variability in cancer treatment side effects and fatigue levels between each treatment. Participants frequently had difficulty responding to the PAVS, which originally asks participants to respond in

accordance to the prior week; however, the participants' PA the prior week differed grossly from the week before and fluctuated overall throughout treatment. Participants had difficulty responding about their interest and confidence without considering other factors, such as their current adequate MVPA levels (i.e., the participant just wanted to maintain their current level of exercise). For some participants, other cancer treatment-related concerns took precedence over increasing their aerobic PA (e.g., obtaining adequate nutritional intake and strength training to maintain muscle mass).

Finally, the interventionist (first author) was trained but amateur in providing motivational interviewing. Thus, a more impartial and skilled motivational interviewer may have improved the acceptability of the intervention. Future studies may be needed to evaluate the level of motivational interviewing and oncology clinical competency required to maximize the efficacy of interventions similar to the MI-Walk Intervention in the future.

Conclusions

This dual-site pilot randomized controlled trial showed safety and potential feasibility of an eight-week MET- and home-based aerobic walking intervention among adults with stage II-IV GI cancer who are receiving FOLFOX or FOLFIRINOX treatment. However, significant changes would be required to tailor the intervention based on key participant characteristics (e.g., age, employment status, and baseline PA levels) to improve the acceptability of the intervention.

With strategic timing of recruitment (ideally once participants have already experienced their first chemotherapy treatment), an eight-week home-based aerobic walking intervention study is feasible among adult GI cancer survivors during the first half of FOLFOX or FOLFIRINOX treatment. On average, patients receiving FOLFOX or FOLFIRINOX demonstrate the ability to adhere to the national PA recommendations to partake in 150 minutes

of MVPA per week. However, the levels of MVPA and acceptability may vary considerably based on various patient and clinical characteristics. Altogether, less comorbidity, younger age, and participants already engaging in high levels of MVPA may be most likely to succeed in a home-based aerobic walking intervention but may not need nor perceive a multi-component intervention to be helpful. Simplifying and tailoring the intervention may help to conserve resources and amplify the benefits for participants.

Future directions. Future studies are needed to identify the components of an aerobic exercise intervention that is most helpful for older adults, especially females, with functionally impairing disabilities, and higher levels of fatigue. Additionally, studies are needed to evaluate the intervention components that may be most helpful and satisfactory to individuals who are retired, overweight, and/or have varying levels of formal education and other physical barriers to exercise (e.g., fatigue, dyspnea from a history of smoking). Finally, exploratory studies are needed to evaluate the mediating factors between participant characteristics, such as employment status, and perceived helpfulness of various home-based aerobic walking intervention components. These studies may help to develop algorithms for tailoring future exercise interventions for GI cancer survivors who are receiving FOLFOX or FOLFIRINOX.

Finally, investigation of the concepts of and best ways to measure acceptability and participant interest and confidence in aerobic exercise is also warranted among FOLFOX/FOLFIRINOX-receiving patients. The clarity will help to build theory and understanding of the relationships among acceptability, interest, confidence, and ultimately, aerobic exercise adherence.

Practice implications. Eventually, the goal is to identify easily implementable, widely accessible, and effective exercise interventions for GI cancer survivors who are receiving

FOLFOX or FOLFIRINOX treatment. The current and prior studies have shown that home-based aerobic exercise is safe and can lead to significant increases in aerobic exercise among chemotherapy-receiving cancer survivors. Specific components of the MI-Walk Intervention—the Fitbits and MET—were helpful and should be studied to identify the types of participants that would benefit most from these and other exercise-promoting tools.

References

Aaronson, N. K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N. J., … de Haes, J. C. (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute*, *85*(5), 365–376.

Alberti, P., Rossi, E., Cornblath, D. R., Merkies, I. S. J., Postma, T. J., Frigeni, B., … Cavaletti, G. (2014). Physician-assessed and patient-reported outcome measures in chemotherapy-induced sensory peripheral neurotoxicity: Two sides of the same coin. *Annals of Oncology*, *25*(1), 257–264. https://doi.org/10.1093/annonc/mdt409

American Cancer Society. (2014). Physical Activity and the Cancer Patient. Retrieved February 3, 2017, from https://www.cancer.org/treatment/survivorship-during-and-after-treatment/staying-active/physical-activity-and-the-cancer-patient.html%0D

American Cancer Society. (2019). *Cancer facts & figures 2019*. Atlanta. Retrieved from https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf

American College of Sports Medicine. (2015). Your Prescription for Health. Exercise is Medicine. Fact Sheet. Retrieved September 23, 2017, from http://www.exerciseismedicine.org/assets/page_documents/eim-fact-sheet-2015.pdf

Andre, T., Boni, C., Mounedji-Boudiaf, L., Navarro, M., Tabernero, J., Hickish, T., … de Gramont, A. (2004). Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *The New England Journal of Medicine*, *350*(23), 2343–2351. https://doi.org/10.1056/NEJMoa032709

André, T., Boni, C., & Navarro, M. (2009). Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol*, *27*(19), 3109–3116. https://doi.org/10.1200/JCO.2008.20.6771

Arthur, A. E., Delk, A., Demark-Wahnefried, W., Christein, J. D., Contreras, C., Posey, J. A. 3rd, … Rogers, L. Q. (2016). Pancreatic cancer survivors' preferences, barriers, and facilitators related to physical activity and diet interventions. *Journal of Cancer Survivorship: Research and Practice*, *10*(6), 981–989. https://doi.org/10.1007/s11764-016-0544-5

Backman, M., Wengstrom, Y., Johansson, B., Skoldengen, I., Borjesson, S., Tarnbro, S., & Berglund, A. (2014). A randomized pilot study with daily walking during adjuvant chemotherapy for patients with breast and colorectal cancer. *Acta Oncologica*, *53*(4), 510–520. https://doi.org/10.3109/0284186X.2013.873820

Bai, Y., Hibbing, P., Mantis, C., & Welk, G. J. (2018). Comparative evaluation of heart rate-based monitors: Apple Watch vs Fitbit Charge HR. *Journal of Sports Sciences*, *36*(15), 1734–1741. https://doi.org/10.1080/02640414.2017.1412235

Ball, T. J., Joy, E. A., Goh, T. L., Hannon, J. C., Gren, L. H., & Shaw, J. M. (2015). Validity of two brief primary care physical activity questionnaires with accelerometry in clinic staff. *Primary Health Care Research & Development*, *16*(1), 100–108. https://doi.org/10.1017/S1463423613000479

Ball, T. J., Joy, E. A., Gren, L. H., Cunningham, R., & Shaw, J. M. (2016). Predictive validity of an adult physical activity "vital sign" recorded in electronic health records. *Journal of Physical Activity & Health*, *13*(4), 403–408. https://doi.org/10.1123/jpah.2015-0210

Ball, T. J., Joy, E. A., Gren, L. H., & Shaw, J. M. (2016). Concurrent validity of a self-reported physical activity "Vital Sign" questionnaire with adult primary care patients. *Preventing Chronic Disease*, *13*, E16. https://doi.org/10.5888/pcd13.150228

Bandura, A. (1986). *Social Foundations of Thought and Action: A Social Cognitive Theory.* Englewood Cliffs, NJ: Prentice Hall Inc.

Bandura, A. (2004). Health Promotion by Social Cognitive Means. *Health Education & Behavior*, *31*(2), 143–164. https://doi.org/10.1177/1090198104263660

Baumann, F. T., Hallek, M., Meyer, J., Galvão, D. A., Bloch, W., & Elter, T. (2015). Evidence and recommendations for oncologic clinical exercise - A personalized treatment concept for cancer patients . *Deutsche Medizinische Wochenschrift*, *140*(19), 1457–1461. https://doi.org/10.1055/s-0041-104465

Berger, A. M. A. M. (2010). Fatigue and other variables during adjuvant chemotherapy for colon and rectal cancer. *Oncology Nursing Forum*, *37*(6), E359–E369. https://doi.org/10.1188/10.ONF.E359-E369

Binkley, J. M., Harris, S. R., Levangie, P. K., Pearl, M., Guglielmino, J., Kraus, V., & Rowden, D. (2012). Patient perspectives on breast cancer treatment side effects and the prospective surveillance model for physical rehabilitation for women with breast cancer. *Cancer*, *118*(8 Suppl), 2207–2216. https://doi.org/10.1002/cncr.27469

Blanchard, C. M., Courneya, K. S., & Stein, K. (2008). Cancer survivors' adherence to lifestyle behavior recommendations and associations with health-related quality of life: Results from the American Cancer Society's SCS-II. *Journal of Clinical Oncology*, *26*(13), 2198–2204. https://doi.org/10.1200/JCO.2007.14.6217

Bosco, F. A., Aguinis, H., Singh, K., Field, J. G., & Pierce, C. A. (2015). Correlational effect size benchmarks. *The Journal of Applied Psychology*, *100*(2), 431–449.

https://doi.org/10.1037/a0038047

Brewer, W., Swanson, B. T., & Ortiz, A. (2017). Validity of Fitbit's active minutes as compared with a research-grade accelerometer and self-reported measures. *BMJ Open Sport & Exercise Medicine*, *3*(1), e000254–e000254. https://doi.org/10.1136/bmjsem-2017-000254

Brooke, S. M., An, H.-S., Kang, S.-K., Noble, J. M., Berg, K. E., & Lee, J.-M. (2017). Concurrent Validity of Wearable Activity Trackers Under Free-Living Conditions. *Journal of Strength and Conditioning Research*, *31*(4), 1097–1106. https://doi.org/10.1519/JSC.0000000000001571

Cadmus, L. A., Salovey, P., Yu, H., Chung, G., Kasl, S., & Irwin, M. L. (2009). Exercise and quality of life during and after treatment for breast cancer: Results of two randomized controlled trials. *Psycho-Oncology*, *18*(4), 343–352. https://doi.org/10.1002/pon.1525

Cavaletti, G., Cornblath, D. R., Merkies, I. S. J., Postma, T. J., Rossi, E., Frigeni, B., … Pessino, A. (2013). The chemotherapy-induced peripheral neuropathy outcome measures standardization study: From consensus to the first validity and reliability findings. *Annals of Oncology*, *24*(2), 454–462. https://doi.org/10.1093/annonc/mds329

Choi, J. G., Nipp, R. D., Tramontano, A., Ali, A., Zhan, T., Pandharipande, P., … Hur, C. (2019). Neoadjuvant FOLFIRINOX for patients with borderline resectable or locally advanced pancreatic cancer: Results of a decision analysis. *The Oncologist*, *24*(7), 945–954. https://doi.org/10.1634/theoncologist.2018-0114

Chou, Y.-J., Lai, Y.-H., Lin, B.-R., Liang, J.-T., & Shun, S.-C. (2017). Factors influencing amount of weekly exercise time in colorectal cancer survivors. *Cancer Nursing*, *40*(3), 201–208. https://doi.org/10.1097/NCC.0000000000000383

Cohen, J. (1988). Statistical power analysis for the behavioral sciences (2nd ed.). New York: Academic Press.

Courneya, K. S., Friedenreich, C. M., Quinney, H. A., Fields, A. L. A., Jones, L. W., & Fairey, A. S. (2003). A randomized trial of exercise and quality of life in colorectal cancer survivors. *European Journal of Cancer Care*, *12*(4), 347–357. https://doi.org/10.1046/j.1365-2354.2003.00437.x

Courneya, K. S., Katzmarzyk, P. T., & Bacon, E. (2008). Physical activity and obesity in Canadian cancer survivors: Population-based estimates from the 2005 Canadian Community Health Survey. *Cancer*, *112*(11), 2475–2482. https://doi.org/10.1002/cncr.23455

Courneya, K. S., McKenzie, D. C., Mackey, J. R., Gelmon, K., Friedenreich, C. M., Yasui, Y., … Segal, R. J. (2013). Effects of exercise dose and type during breast cancer chemotherapy:

Multicenter randomized trial. *Journal of the National Cancer Institute*, *105*(23), 1821–1832. https://doi.org/10.1093/jnci/djt297

Courneya, K. S., McKenzie, D. C., Mackey, J. R., Gelmon, K., Friedenreich, C. M., Yasui, Y., … Segal, R. J. (2014). Subgroup effects in a randomised trial of different types and doses of exercise during breast cancer chemotherapy. *British Journal of Cancer*, *111*(9), 1718–1725. https://doi.org/10.1038/bjc.2014.466

Courneya, K. S., Segal, R. J., Gelmon, K., Mackey, J. R., Friedenreich, C. M., Yasui, Y., … McKenzie, D. C. (2014). Predictors of adherence to different types and doses of supervised exercise during breast cancer chemotherapy. *The International Journal of Behavioral Nutrition and Physical Activity*, *11*, 85. https://doi.org/10.1186/s12966-014-0085-0

Cramp, F., & Byron-Daniel, J. (2012). Exercise for the management of cancer-related fatigue in adults. *The Cochrane Database of Systematic Reviews*, *11*(2), CD006145. https://doi.org/10.1002/14651858.CD006145.pub3

Deci, E. L., & Ryan, R. M. (1985). *Intrinsic Motivation and Self-Determination in Human Behavior* (1st ed.). New York: Plenum Press. https://doi.org/10.2307/2070638

Dhawan, S., Andrews, R., Kumar, L., Wadhwa, S., & Shukla, G. (2019). 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*. https://doi.org/10.1097/NCC.0000000000000693

Dinger, M. K., Oman, R. F., Taylor, E. L., Vesely, S. K., & Able, J. (2004). Stability and convergent validity of the Physical Activity Scale for the Elderly (PASE). *The Journal of Sports Medicine and Physical Fitness*, *44*(2), 186–192.

Djuric, Z., Ellsworth, J. S., Weldon, A. L., Ren, J., Richardson, C. R., Resnicow, K., … Sen, A. (2011). A diet and exercise intervention during chemotherapy for breast cancer. *The Open Obesity Journal*, *2*(3), 87–97. https://doi.org/10.2174/1876823701103010087

Dodd, M. J., Cho, M. H., Miaskowski, C., Painter, P. L., Paul, S. M., Cooper, B. A., … Bank, K. A. (2010). A randomized controlled trial of home-based exercise for cancer-related fatigue in women during and after chemotherapy with or without radiation therapy. *Cancer Nursing*, *33*(4), 245–257. https://doi.org/10.1097/NCC.0b013e3181ddc58c

Dreicer, R., MacLean, D., Suri, A., Stadler, W. M., Shevrin, D., Hart, L., … Agus, D. B. (2014). Phase I/II trial of orteronel (TAK-700)-an investigational 17,20-lyase inhibitor-in patients with metastatic castration-resistant prostate cancer. *Clinical Cancer Research*, *20*(5), 1335–1344. Retrieved from http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L372557599

Drott, J., Starkhammar, H., Kjellgren, K., & Bertero, C. (2016). The trajectory of neurotoxic side effects' impact on daily life: A qualitative study. *Supportive Care in Cancer*, *24*(8), 3455–3461. https://doi.org/10.1007/s00520-016-3179-1

Edmunds, J., Ntoumanis, N., & Duda, J. L. (2006). A test of self-determination theory in the exercise domain. *Journal of Applied Social Psychology*, *36*(9), 2240–2265.

El-Shami, K., Oeffinger, K. C., Erb, N. L., Willis, A., Bretsch, J. K., Pratt-Chapman, M. L., … Cowens-Alvarado, R. L. (2015). American Cancer Society colorectal cancer survivorship care guidelines. *CA Cancer Journal for Clinicians*, *65*(6), 427–455. https://doi.org/10.3322/caac.21286

Evenson, K. R., Goto, M. M., & Furberg, R. D. (2015). Systematic review of the validity and reliability of consumer-wearable activity trackers. *The International Journal of Behavioral Nutrition and Physical Activity*, *12*, 159. https://doi.org/10.1186/s12966-015-0314-1

Eyl, R. E., Koch-Gallenkamp, L., Jansen, L., Walter, V., Carr, P., Hoffmeister, M., … Arndt, V. (2018). Potential determinants of physical inactivity among long-term colorectal cancer survivors. *Journal of Cancer Survivorship: Research and Practice*, *12*(5), 679–690. https://doi.org/10.1007/s11764-018-0705-9

Ezendam, N. P. M., Pijlman, B., Bhugwandass, C., Pruijt, J. F. M., Mols, F., Vos, M. C., … van de Poll-Franse, L. V. (2014). Chemotherapy-induced peripheral neuropathy and its impact on health-related quality of life among ovarian cancer survivors: Results from the population-based PROFILES registry. *Gynecologic Oncology*, *135*(3), 510–517. https://doi.org/10.1016/j.ygyno.2014.09.016

Farina, N., & Lowry, R. G. (2017). The validity of consumer-level activity monitors in healthy older adults in free-living conditions. *Journal of Aging and Physical Activity*, 1–23. https://doi.org/10.1123/japa.2016-0344

Feehan, L. M., Geldman, J., Sayre, E. C., Park, C., Ezzat, A. M., Yoo, J. Y., … Li, L. C. (2018). Accuracy of Fitbit devices: Systematic review and narrative syntheses of quantitative data. *JMIR MHealth and UHealth*, *6*(8), e10527–e10527. https://doi.org/10.2196/10527

Fernandez, S., Franklin, J., Amlani, N., DeMilleVille, C., Lawson, D., & Smith, J. (2015). Physical activity and cancer: A cross-sectional study on the barriers and facilitators to exercise during cancer treatment. *Canadian Oncology Nursing Journal*, *25*(1), 37–48.

Fisher, A., Wardle, J., Beeken, R. J., Croker, H., Williams, K., & Grimmett, C. (2016). Perceived barriers and benefits to physical activity in colorectal cancer patients. *Supportive Care in Cancer*, *24*(2), 903–910. https://doi.org/10.1007/s00520-015-2860-0

Fitbit. (2019). What Are Active Minutes? Retrieved October 15, 2019, from

https://help.fitbit.com/articles/en_US/Help_article/1379

Forsen, L., Loland, N. W., Vuillemin, A., Chinapaw, M. J. M., van Poppel, M. N. M., Mokkink, L. B., … Terwee, C. B. (2010). Self-administered physical activity questionnaires for the elderly: A systematic review of measurement properties. *Sports Medicine*, *40*(7), 601–623. https://doi.org/10.2165/11531350-000000000-00000

Galvão, D. A., & Newton, R. U. (2005). Review of exercise intervention studies in cancer patients. *Journal of Clinical Oncology*, *23*(4), 899–909. https://doi.org/10.1200/JCO.2005.06.085

Gearing, R. E., El-Bassel, N., Ghesquiere, A., Baldwin, S., Gillies, J., & Ngeow, E. (2011). Major ingredients of fidelity: A review and scientific guide to improving quality of intervention research implementation. *Clinical Psychology Review*, *31*(1), 79–88. https://doi.org/10.1016/j.cpr.2010.09.007

Gho, S. A., Munro, B. J., Jones, S. C., & Steele, J. R. (2014). Perceived exercise barriers explain exercise participation in australian women treated for breast cancer better than perceived exercise benefits. *Physical Therapy*, *94*(12), 1765–1774. https://doi.org/10.2522/ptj.20130473

Golightly, Y. M., Allen, K. D., Ambrose, K. R., Stiller, J. L., Evenson, K. R., Voisin, C., … Callahan, L. F. (2017). Physical activity as a vital sign: A systematic review. *Preventing Chronic Disease*, *14*, E123. https://doi.org/10.5888/pcd14.170030

Granger, C. L., Parry, S. M., & Denehy, L. (2015). The self-reported Physical Activity Scale for the Elderly (PASE) is a valid and clinically applicable measure in lung cancer. *Supportive Care in Cancer*, *23*(11), 3211–3218. https://doi.org/10.1007/s00520-015-2707-8

Greenwood, J. L. J., Joy, E. A., & Stanford, J. B. (2010). The Physical Activity Vital Sign: A primary care tool to guide counseling for obesity. *Journal of Physical Activity & Health*, *7*(5), 571–576.

Griffith, K., Wenzel, J., Shang, J., Thompson, C., Stewart, K., & Mock, V. (2009). Impact of a walking intervention on cardiorespiratory fitness, self-reported physical function, and pain in patients undergoing treatment for solid tumors. *Cancer*, *115*(20), 4874–4884. https://doi.org/10.1002/cncr.24551

Henriksson, A., Arving, C., Johansson, B., Igelstrom, H., & Nordin, K. (2016). Perceived barriers to and facilitators of being physically active during adjuvant cancer treatment. *Patient Education and Counseling*, *99*(7), 1220–1226. https://doi.org/10.1016/j.pec.2016.01.019

Hershman, D. L., Weimer, L. H., Wang, A., Kranwinkel, G., Brafman, L., Fuentes, D., … Crew,

K. D. (2011). Association between patient reported outcomes and quantitative sensory tests for measuring long-term neurotoxicity in breast cancer survivors treated with adjuvant paclitaxel chemotherapy. *Breast Cancer Research and Treatment*, *125*(3), 767–774. https://doi.org/10.1007/s10549-010-1278-0

Horne, M., & Tierney, S. (2012). What are the barriers and facilitators to exercise and physical activity uptake and adherence among South Asian older adults: A systematic review of qualitative studies. *Preventive Medicine*, *55*(4), 276–284. https://doi.org/10.1016/j.ypmed.2012.07.016

Irwin, M. L., Cartmel, B., Gross, C. P., Ercolano, E., Li, F., Yao, X., … Ligibel, J. (2015). Randomized exercise trial of aromatase inhibitor-induced arthralgia in breast cancer survivors. *Journal of Clinical Oncology*, *33*(10), 1104–1111. https://doi.org/10.1200/JCO.2014.57.1547

Justine, M., Azizan, A., Hassan, V., Salleh, Z., & Manaf, H. (2013). Barriers to participation in physical activity and exercise among middle-aged and elderly individuals. *Singapore Medical Journal*, *54*(10), 581–586.

Kamath, J. (2012). Cancer-related fatigue, inflammation and thyrotropin-releasing hormone. *Current Aging Science*, *5*(3), 195–202.

Kang, D.-W., Chung, J. Y., Lee, M. K., Lee, J., Park, J.-H., Kim, D.-I., … Jeon, J. Y. (2014). Exercise barriers in Korean colorectal cancer patients. *Asian Pacific Journal of Cancer Prevention*, *15*(18), 7539–7545.

Kidwell, K. M., Yothers, G., Ganz, P. A., Land, S. R., Ko, C. Y., Cecchini, R. S., … Wolmark, N. (2012). Long-term neurotoxicity effects of oxaliplatin added to fluorouracil and leucovorin as adjuvant therapy for colon cancer: Results from National Surgical Adjuvant Breast and Bowel Project trials C-07 and LTS-01. *Cancer*, *118*(22), 5614–5622. https://doi.org/10.1002/cncr.27593

Kleckner, I. R., Kamen, C., Gewandter, J. S., Mohile, N. A., Heckler, C. E., Culakova, E., … Musian, 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

Knoerl, R., Gray, E., Stricker, C., Mitchell, S. A., Kippe, K., Smith, G., … Lavoie Smith, E. M. (2017). Electronic versus paper-pencil methods for assessing chemotherapy-induced peripheral neuropathy. *Supportive Care in Cancer*. https://doi.org/10.1007/s00520-017-3764-y

Knols, R., Aaronson, N. K., Uebelhart, D., Fransen, J., & Aufdemkampe, G. (2005). Physical exercise in cancer patients during and after medical treatment: A systematic review of

randomized and controlled clinical trials. *Journal of Clinical Oncology*, *23*(16), 3830–3842. https://doi.org/10.1200/JCO.2005.02.148

Ko, Y. J., Abdelsalam, M., Kavan, P., Lim, H., Tang, P. A., Vincent, M., … Gill, S. (2019). What is a clinically meaningful survival benefit in refractory metastatic colorectal cancer? *Current Oncology*, *26*(2), e255–e259. https://doi.org/10.3747/co.26.4753

Lavoie Smith, E. M., Barton, D. L., Qin, R., Steen, P. D., Aaronson, N. K., & Loprinzi, C. L. (2013). Assessing patient-reported peripheral neuropathy: The reliability and validity of the European Organization for Research and Treatment of Cancer QLQ-CIPN20 Questionnaire. *Quality of Life Research*, *22*(10), 2787–2799. https://doi.org/10.1007/s11136-013-0379-8

Leone, L. A., & Ward, D. S. (2013). A mixed methods comparison of perceived benefits and barriers to exercise between obese and nonobese women. *Journal of Physical Activity & Health*, *10*(4), 461–469.

Li, Q., Lin, Y., Qiu, Y., Gao, B., & Xu, Y. (2014). The assessment of health-related quality of life and related factors in Chinese elderly patients undergoing chemotherapy for advanced cancer: A cross-sectional study. *European Journal of Oncology Nursing*, *18*(4), 425–435. https://doi.org/10.1016/j.ejon.2014.03.005

Liu, R. D. K., Buffart, L. M., Kersten, M. J., Spiering, M., Brug, J., van Mechelen, W., & Chinapaw, M. J. M. (2011). Psychometric properties of two physical activity questionnaires, the AQuAA and the PASE, in cancer patients. *BMC Medical Research Methodology*, *11*, 30. https://doi.org/10.1186/1471-2288-11-30

Lotfi-Jam, K., Carey, M., Jefford, M., Schofield, P., Charleson, C., & Aranda, S. (2008). Nonpharmacologic strategies for managing common chemotherapy adverse effects: A systematic review. *Journal of Clinical Oncology*, *26*(34), 5618–5629. https://doi.org/10.1200/JCO.2007.15.9053

Mas, S., Quantin, X., & Ninot, G. (2015). Barriers to, and facilitators of physical activity in patients receiving chemotherapy for lung cancer: An exploratory study. *Journal of Palliative Care*, *31*(2), 89–96. Retrieved from https://www.scopus.com/inward/record.uri?eid=2-s2.0-84937859700&partnerID=40&md5=660e8d75227723bc158f1c91cb3aa42e

McCrary, J. M., Goldstein, D., Sandler, C. X., Barry, B. K., Marthick, M., Timmins, H. C., … Park, S. B. (2019). Exercise-based rehabilitation for cancer survivors with chemotherapy-induced peripheral neuropathy. *Supportive Care in Cancer*. https://doi.org/10.1007/s00520-019-04680-w

Meyers, B. M., Cosby, R., Quereshy, F., & Jonker, D. (2017). Adjuvant chemotherapy for stage II and III colon cancer following complete resection: A cancer care ontario systematic

review. *Clinical Oncology*, *29*(7), 459–465. https://doi.org/10.1016/j.clon.2017.03.001

Mikkelsen, M. K., Nielsen, D. L., Vinther, A., Lund, C. M., & Jarden, M. (2019). Attitudes towards physical activity and exercise in older patients with advanced cancer during oncological treatment - A qualitative interview study. *European Oncology Nursing*, *41*, 16–23. https://doi.org/10.1016/j.ejon.2019.04.005

Milne, H. M., Wallman, K. E., Guilfoyle, A., Gordon, S., & Corneya, K. S. (2008). Self-determination theory and physical activity among breast cancer survivors. *Journal of Sport & Exercise Psychology*, *30*(1), 23–38.

Mishra, S. I., Scherer, R. W., Snyder, C., Geigle, P., & Gotay, C. (2015). The effectiveness of exercise interventions for improving health-related quality of life from diagnosis through active cancer treatment. *Oncology Nursing Forum*, *42*(1), E33–E53. https://doi.org/10.1188/15.ONF.E33-E53

Mizrahi, D., Broderick, C., Friedlander, M., Ryan, M., Harrison, M., Pumpa, K., & Naumann, F. (2015). An exercise intervention during chemotherapy for women with recurrent ovarian cancer: A feasibility study. *International Journal of Gynecological Cancer*, *25*(6), 985–992. https://doi.org/10.1097/IGC.0000000000000460

Mock, V., Burke, M., Sheehan, P., Creaton, E., Winningham, M., McKenney-Tedder, S., … Liebman, M. (1994). A Nursing Rehabilitation Program for Women with Breast Cancer Receiving Adjuvant Chemotherapy. *Research and Commentary*, *21*(5), 899–907.

Mock, V., Frangakis, C., Davidson, N. E., Ropka, M. E., Pickett, M., Poniatowski, B., … McCorkle, R. (2005). Exercise manages fatigue during breast cancer treatment: A randomized controlled trial. *Psycho-Oncology*, *14*(6), 464–477. https://doi.org/10.1002/pon.863

Mols, F., Beijers, T., Lemmens, V., van den Hurk, C. J., Vreugdenhil, G., & van de Poll-Franse, L. V. (2013). Chemotherapy-induced neuropathy and its association with quality of life among 2- to 11-year colorectal cancer survivors: Results from the population-based PROFILES registry. *Journal of Clinical Oncology*, *31*(21), 2699–2707. https://doi.org/10.1200/JCO.2013.49.1514

Morielli, A. R., Usmani, N., Boule, N. G., Tankel, K., Severin, D., Nijjar, T., … Courneya, K. S. (2016). A phase I study examining the feasibility and safety of an aerobic exercise intervention in patients with rectal cancer during and after neoadjuvant chemoradiotherapy. *Oncology Nursing Forum*, *43*(3), 352–362. https://doi.org/10.1188/16.ONF.352-362

Mosher, C. E., Fuemmeler, B. F., Sloane, R., Kraus, W. E., Lobach, D. F., Snyder, D. C., & Demark-Wahnefried, W. (2008). Change in self-efficacy partially mediates the effects of the FRESH START intervention on cancer survivors' dietary outcomes. *Psycho-Oncology*,

17(10), 1014–1023. https://doi.org/10.1002/pon.1327

Mullen, K. H., Berry, D. L., & Zierler, B. K. (2004). Computerized symptom and quality-of-life assessment for patients with cancer part II: acceptability and usability. *Oncology Nursing Forum*, *31*(5), E84-9. https://doi.org/10.1188/04.ONF.E84-E89

Nazari, G., MacDermid, J. C., Sinden, K. E., Richardson, J., & Tang, A. (2019). Inter-instrument reliability and agreement of Fitbit Charge measurements of heart rate and activity at rest, during the Modified Canadian Aerobic Fitness Test, and in recovery. *Physiotherapy Canada*, *71*(3), 197–206. https://doi.org/10.3138/ptc.2018-25

Nicklasson, M., & Bergman, B. (2007). Validity, reliability and clinical relevance of EORTC QLQ-C30 and LC13 in patients with chest malignancies in a palliative setting. *Quality of Life Research*, *16*(6), 1019–1028. https://doi.org/10.1007/s11136-007-9210-8

Niezgoda, H. E., & Pater, J. L. (1993). A validation study of the domains of the core EORTC Quality of Life Questionnaire. *Quality of Life Research*, *2*(5), 319–325. Retrieved from http://www.jstor.org.proxy.lib.umich.edu/stable/4034756

O'Driscoll, R., Turicchi, J., Beaulieu, K., Scott, S., Matu, J., Deighton, K., … Stubbs, J. (2018). How well do activity monitors estimate energy expenditure? A systematic review and meta-analysis of the validity of current technologies. *British Journal of Sports Medicine*. https://doi.org/10.1136/bjsports-2018-099643

Osoba, D., Zee, B., Pater, J., Warr, D., Kaizer, L., & Latreille, J. (1994). Psychometric properties and responsiveness of the EORTC quality of Life Questionnaire (QLQ-C30) in patients with breast, ovarian and lung cancer. *Quality of Life Research*, *3*(5), 353–364.

Pachman, D. R., Barton, D. L., Swetz, K. M., & Loprinzi, C. L. (2012). Troublesome symptoms in cancer survivors: Fatigue, insomnia, neuropathy, and pain. *Journal of Clinical Oncology*, *30*(30), 3687–3696. https://doi.org/10.1200/JCO.2012.41.7238

Park, J.-H., Lee, J., Oh, M., Park, H., Chae, J., Kim, D.-I., … Jeon, J. Y. (2015). The effect of oncologists' exercise recommendations on the level of exercise and quality of life in survivors of breast and colorectal cancer: A randomized controlled trial. *Cancer*, *121*(16), 2740–2748. https://doi.org/10.1002/cncr.29400

Park, S. B., Goldstein, D., Krishnan, A. V, Lin, C. S.-Y., Friedlander, M. L., Cassidy, J., … Kiernan, M. C. (2013). Chemotherapy-induced peripheral neurotoxicity: A critical analysis. *Cancer Journal for Clinicians*, *63*(6), 419–437. https://doi.org/10.3322/caac.21204

Peddle, C. J., Au, H.-J., & Courneya, K. S. (2008). Associations between exercise, quality of life, and fatigue in colorectal cancer survivors. *Diseases of the Colon and Rectum*, *51*(8), 1242–1248. https://doi.org/10.1007/s10350-008-9324-2

Peddle, C. J., Plotnikoff, R. C., Wild, T. C., Au, H.-J., & Courneya, K. S. (2008). Medical, demographic, and psychosocial correlates of exercise in colorectal cancer survivors: An application of self-determination theory. *Supportive Care in Cancer*, *16*(1), 9–17. https://doi.org/10.1007/s00520-007-0272-5

Phillips, S. M., & McAuley, E. (2013). Social cognitive influences on physical activity participation in long-term breast cancer survivors. *Psycho-Oncology*, *22*(4), 783–791. https://doi.org/10.1002/pon.3074

Pietrangeli, A., Leandri, M., Terzoli, E., Jandolo, B., & Garufi, C. (2006). Persistence of high-dose oxaliplatin-induced neuropathy at long-term follow-up. *European Neurology*, *56*(1), 13–16. https://doi.org/10.1159/000094376

Pinto, B. M., Rabin, C., & Dunsiger, S. (2009). Home-based exercise among cancer survivors: Adherence and its predictors. *Psycho-Oncology*, *18*. https://doi.org/10.1002/pon.1465

Postma, T. J., Aaronson, N. K., Heimans, J. J., Muller, M. J., Hildebrand, J. G., Delattre, J. Y., … Lucey, R. (2005). The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: the QLQ-CIPN20. *European Journal of Cancer (Oxford, England : 1990)*, *41*(8), 1135–1139. https://doi.org/10.1016/j.ejca.2005.02.012

Reddy, R. K., Pooni, R., Zaharieva, D. P., Senf, B., El Youssef, J., Dassau, E., … Jacobs, P. G. (2018). Accuracy of wrist-worn activity monitors during common daily physical activities and types of structured exercise: Evaluation study. *JMIR MHealth and UHealth*, *6*(12), e10338. https://doi.org/10.2196/10338

Reid, R. E. R., Insogna, J. A., Carver, T. E., Comptour, A. M., Bewski, N. A., Sciortino, C., & Andersen, R. E. (2017). Validity and reliability of Fitbit activity monitors compared to ActiGraph GT3X+ with female adults in a free-living environment. *Journal of Science and Medicine in Sport*, *20*(6), 578–582. https://doi.org/10.1016/j.jsams.2016.10.015

Ringdal, G. I., & Ringdal, K. (1993). Testing the EORTC Quality of Life Questionnaire on cancer patients with heterogeneous diagnoses. *Quality of Life Research*, *2*(2), 129–140. Retrieved from http://www.jstor.org.proxy.lib.umich.edu/stable/4034394

Rogers, L. Q. (2008). Correlates of physical activity self-efficacy among breast cancer survivors. *Am J Health Behav*, *32*. https://doi.org/10.5993/AJHB.32.6.4

Rogers, L. Q., Shah, P., Dunnington, G., Greive, A., Shanmugham, A., Dawson, B., & Courneya, K. S. (2005). Social cognitive theory and physical activity during breast cancer treatment. *Oncology Nursing Forum*, *32*(4), 807–815. https://doi.org/10.1188/05.ONF.807-815

Ryan, R. M. (1995). Psychological needs and the facilitation of integrative processes. *Journal of*

Personality, *63*(3), 397–427.

Ryan, R. M., & Deci, E. L. (2000). Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. *The American Psychologist*, *55*(1), 68–78.

Schmitz, K. H., Courneya, K. S., Matthews, C., Demark-Wahnefried, W., Galvao, D. A., Pinto, B. M., … Schwartz, A. L. (2010). American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Medicine and Science in Sports and Exercise*, *42*(7), 1409–1426. https://doi.org/10.1249/MSS.0b013e3181e0c112

Schwartz, A. L. A. L. (2001). Exercise reduces daily fatigue in women with breast cancer receiving chemotherapy. *Medicine and Science in Sports and Exercise*, *33*(5), 718–723.

Sekhon, M., Cartwright, M., & Francis, J. J. (2017). Acceptability of healthcare interventions: An overview of reviews and development of a theoretical framework. *BMC Health Services Research*, *17*(1), 88. https://doi.org/10.1186/s12913-017-2031-8

Shang, J., Wenzel, J., Krumm, S., Griffith, K., & Stewart, K. (2012). Who will drop out and who will drop in: Exercise adherence in a randomized clinical trial among patients receiving active cancer treatment. *Cancer Nursing*, *35*(4), 312–322. https://doi.org/10.1097/NCC.0b013e318236a3b3

Skerman, H. M., Yates, P. M., & Battistutta, D. (2012). Cancer-related symptom clusters for symptom management in outpatients after commencing adjuvant chemotherapy, at 6 months, and 12 months. *Supportive Care in Cancer*, *20*(1), 95–105. https://doi.org/10.1007/s00520-010-1070-z

Smith, E. M. L., Knoerl, R., Yang, J. J., Kanzawa-Lee, G., Lee, D., & Bridges, C. (2018). In search of a gold standard patient-reported outcome measure for use in chemotherapy-induced peripheral neuropathy clinical trials. *Cancer Control*, *25*(1). https://doi.org/10.1177/1073274818756608

Speck, R. M., Courneya, K. S., Masse, L. C., Duval, S., & Schmitz, K. H. (2010). An update of controlled physical activity trials in cancer survivors: A systematic review and meta-analysis. *Journal of Cancer Survivorship*, *4*(2), 87–100. https://doi.org/10.1007/s11764-009-0110-5

Speed-Andrews, A. E., Rhodes, R. E., Blanchard, C. M., Culos-Reed, S. N., Friedenreich, C. M., Belanger, L. J., & Courneya, K. S. (2012). Medical, demographic and social cognitive correlates of physical activity in a population-based sample of colorectal cancer survivors. *European Journal of Cancer Care*, *21*(2), 187–196. https://doi.org/10.1111/j.1365-2354.2011.01290.x

StataCorp. (2017). Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.

Stevinson, C., Steed, H., Faught, W., Tonkin, K., Vallance, J. K., Ladha, A. B., … Courneya, K. S. (2009). Physical activity in ovarian cancer survivors: Associations with fatigue, sleep, and psychosocial functioning. *International Journal of Gynecological Cancer*, *19*(1), 73–78. https://doi.org/10.1111/IGC.0b013e31819902ec

Straiton, N., Alharbi, M., Bauman, A., Neubeck, L., Gullick, J., Bhindi, R., & Gallagher, R. (2018). The validity and reliability of consumer-grade activity trackers in older, community-dwelling adults: A systematic review. *Maturitas*, *112*, 85–93. https://doi.org/10.1016/j.maturitas.2018.03.016

Streckmann, F., Kneis, S., Leifert, J. A., Baumann, F. T., Kleber, M., Ihorst, G., … 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

Su, C.-C., Lee, K.-D., Yeh, C.-H., Kao, C.-C., & Lin, C.-C. (2014). Measurement of physical activity in cancer survivors: A validity study. *Journal of Cancer Survivorship : Research and Practice*, *8*(2), 205–212. https://doi.org/10.1007/s11764-013-0325-3

Sweet, S. N., Fortier, M. S., Strachan, S. M., & Blanchard, C. M. (2017). Testing and integrating self-determination theory and self-efficacy theory in a physical activity context. *Canadian Psychology*, *53*(4), 319–327.

Swenson, K. K., Nissen, M. J., & Henly, S. J. (2010). Physical activity in women receiving chemotherapy for breast cancer: Adherence to a walking intervention. *Oncology Nursing Forum*, *37*(3), 321–330. https://doi.org/10.1188/10.ONF.321-330

Tariman, J. D., Berry, D. L., Halpenny, B., Wolpin, S., & Schepp, K. (2011). Validation and testing of the Acceptability E-scale for Web-based patient-reported outcomes in cancer care. *Applied Nursing Research : ANR*, *24*(1), 53–58. https://doi.org/10.1016/j.apnr.2009.04.003

Tedesco, S., Sica, M., Ancillao, A., Timmons, S., Barton, J., & O'Flynn, B. (2019). Validity evaluation of the Fitbit Charge2 and the Garmin vivosmart HR+ in free-living environments in an older adult cohort. *JMIR MHealth and UHealth*, *7*(6), e13084–e13084. https://doi.org/10.2196/13084

Thomson, E. A., Nuss, K., Comstock, A., Reinwald, S., Blake, S., Pimentel, R. E., … Li, K. (2019). Heart rate measures from the Apple Watch, Fitbit Charge HR 2, and electrocardiogram across different exercise intensities. *Journal of Sports Sciences*, *37*(12), 1411–1419. https://doi.org/10.1080/02640414.2018.1560644

Tofthagen, C. S., Donovan, K. A., Morgan, M. A., Shibata, D., & Yeh, Y. (2013). Oxaliplatin-induced peripheral neuropathy's effects on health-related quality of life of colorectal cancer survivors. *Supportive Care in Cancer*, *21*(12), 3307–3313. https://doi.org/10.1007/s00520-

013-1905-5

Tofthagen, C. S., Visovsky, C., Beckstead, J., Loy, I., & Eckelman, E. (2014). Results of a strength and balance training pilot study for colorectal cancer survivors with peripheral neuropathy caused by oxaliplatin. *Rehabilitation Oncology*, *32*(4), 38-44 7p. Retrieved from http://proxy.lib.umich.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=ccm&AN=103906075&site=ehost-live&scope=site

Tofthagen, C. S., Visovsky, C., & Berry, D. L. (2012). Strength and balance training for adults with peripheral neuropathy and high risk of fall: Current evidence and implications for future research. *Oncology Nursing Forum*, *39*(5), E416-24. https://doi.org/10.1188/12.ONF.E416-E424

Trost, S. G., Owen, N., Bauman, A. E., Sallis, J. F., & Brown, W. (2002). Correlates of adults' participation in physical activity: review and update. *Medicine and Science in Sports and Exercise*, *34*(12), 1996–2001. https://doi.org/10.1249/01.MSS.0000038974.76900.92

Tulloch, H., Sweet, S. N., Fortier, M., Capstick, G., Kenny, G. P., & Sigal, R. J. (2013). Exercise facilitators and barriers from adoption to maintenance in the diabetes aerobic and resistance exercise trial. *Canadian Journal of Diabetes*, *37*(6), 367–374. https://doi.org/10.1016/j.jcjd.2013.09.002

U.S. Department of Health and Human Services. (2018). *Physical Activity Guidelines for Americans, 2nd edition*. Washington, DC, US. Retrieved from https://health.gov/paguidelines/second-edition/pdf/Physical_Activity_Guidelines_2nd_edition.pdf

van Putten, M., Husson, O., Mols, F., Luyer, M. D. P., van de Poll-Franse, L. V, & Ezendam, N. P. M. (2016). Correlates of physical activity among colorectal cancer survivors: Results from the longitudinal population-based profiles registry. *Supportive Care in Cancer*, *24*(2), 573–583. https://doi.org/10.1007/s00520-015-2816-4

Van Vulpen, J. K., Velthuis, M. J., Steins Bisschop, C. N., Travier, N., Van Den Buijs, B. J. W., Backx, F. J. G., … May, A. M. (2016). Effects of an exercise program in colon cancer patients undergoing chemotherapy. *Medicine and Science in Sports and Exercise*, *48*(5), 767–775. https://doi.org/10.1249/MSS.0000000000000855

van Waart, H., Stuiver, M. M., van Harten, W. H., Geleijn, E., Kieffer, J. M., Buffart, L. M., … Aaronson, N. K. (2015). Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: Results of the PACES randomized clinical trial. *Journal of Clinical Oncology*, *33*(17), 1918–1927. https://doi.org/10.1200/JCO.2014.59.1081

Ventzel, L., Madsen, C. S., Jensen, A. B., Jensen, A. R., Jensen, T. S., & Finnerup, N. B. (2015).

Assessment of acute oxaliplatin-induced cold allodynia: a pilot study. *Acta Neurologica Scandinavica*. https://doi.org/10.1111/ane.12443

Vollmers, P. L., Mundhenke, C., Maass, N., Bauerschlag, D., Kratzenstein, S., Rocken, 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

Wald, A., & Garber, C. E. (2018). A review of current literature on vital sign assessment of physical activity in primary care. *Journal of Nursing Scholarship*, *50*(1), 65–73. https://doi.org/10.1111/jnu.12351

Washburn, R. A., McAuley, E., Katula, J., Mihalko, S. L., & Boileau, R. A. (1999). The Physical Activity Scale for the Elderly (PASE): Evidence for validity. *Journal of Clinical Epidemiology*, *52*(7), 643–651.

Washburn, R. A., Smith, K. W., Jette, A. M., & Janney, C. A. (1993). The Physical Activity Scale for the Elderly (PASE): Development and evaluation. *Journal of Clinical Epidemiology*, *46*(2), 153–162.

Wilson, P. M., Blanchard, C. M., Nehl, E., & Baker, F. (2006). Predicting physical activity and outcome expectations in cancer survivors: An application of Self-Determination Theory. *Psycho-Oncology*, *15*(7), 567–578. https://doi.org/10.1002/pon.990

Yamagishi, A., Morita, T., Miyashita, M., & Kimura, F. (2009). Symptom prevalence and longitudinal follow-up in cancer outpatients receiving chemotherapy. *Journal of Pain and Symptom Management*, *37*(5), 823–830. https://doi.org/10.1016/j.jpainsymman.2008.04.015

Yang, C., Tsai, J., Huang, Y., & Lin, C. (2011). Effects of a home-based walking program on perceived symptom and mood status in postoperative breast cancer women receiving adjuvant chemotherapy. *Journal of Advanced Nursing*, *67*(1), 158–168. https://doi.org/10.1111/j.1365-2648.2010.05492.x

Zanville, N. R., Nudelman, K. N. H., Smith, D. J., Von Ah, D., McDonald, B. C., Champion, V. L., & Saykin, A. J. (2016). Evaluating the impact of chemotherapy-induced peripheral neuropathy symptoms (CIPN-sx) on perceived ability to work in breast cancer survivors during the first year post-treatment. *Supportive Care in Cancer*, *24*(11), 4779–4789. https://doi.org/10.1007/s00520-016-3329-5

CHAPTER V

Conclusion

This dissertation presented the premises for and results of a dual-site pilot randomized controlled trial of an eight-week home-based aerobic walking intervention—the MI-Walk Intervention—to reduce oxaliplatin-induced peripheral neuropathy (OIPN). The sample was composed of gastrointestinal (GI) cancer survivors who had just begun FOLFOX or FOLFIRINOX (oxaliplatin-based chemotherapy) treatment. The control condition was physical activity education alone. The objectives of the study were exploratory: intended to observe trends in the effects of the MI-Walk Intervention on OIPN and quality of life (QOL). Additionally, exploratory analyses were conducted to observe patterns among participant characteristics and indicators of study feasibility (e.g., intervention acceptability and adherence).

Efficacy Study Results

The Chapter III provides the results of the first two study aims: to explore the effects of the MI-Walk Intervention, on 1) OIPN severity and 2) QOL at eight weeks, compared to physical activity (PA) education alone in oxaliplatin-receiving GI cancer survivors. The hypothesis was that the MI-Walk Intervention would lead to significantly reduced sensory OIPN severity at eight weeks in the intervention participants than patients who received PA education alone.

The study revealed that the MI-Walk Intervention was no more or less effective than PA education alone at reducing sensory and motor OIPN and bolstering QOL. However, supplementary exploratory analysis showed that fewer minutes of moderate to vigorous PA

(MVPA), mood, and female gender may be associated with more severe eight-week sensory OIPN severity and worse QOL. Ultimately, the increase in PA in the control group per self-report was suspected to confound the results. Although the intervention group participants exhibited increases in Fitbit-measured minutes of MVPA, the PA education alone group also self-reported significant increases in PA. Insufficient data was collected from the research-grade activity monitors (ActiGraph GT9X Link) at the eight-week time point often due to lost ActiGraphs during walks, insufficient wear time, device errors, and participants refusing to wear the ActiGraph when they were engaging in less PA than usual. The lack of objective PA measurement limited the study findings, because the confounding effects of total PA could not be controlled for in the analysis of the outcomes nor compared between groups. Altogether, the results of the study emphasized the importance of evaluating the feasibility of the MI-Walk Intervention and best modes of PA measurement among GI cancer survivors receiving FOLFOX or FOLFIRINOX treatment.

Feasibility Study Results

The Chapter IV presented the results of the third study aim: to describe the rates of and explore the relationships between patient characteristics and 1) enrollment in and attrition from the study, 2) acceptability of the MI-Walk Intervention, and 3) intervention adherence. Chapter IV also further describes participants overall PA levels.

The 60% enrollment and 14% intervention attrition rates were excellent compared to the average 50% enrollment (Courneya et al., 2013, 2014; Dhawan, Andrews, Kumar, Wadhwa, & Shukla, 2019; Kleckner et al., 2018; McCrary et al., 2019; Mizrahi et al., 2015; Streckmann et al., 2014; Vollmers et al., 2018) and 1%-30% attrition rates reported in the literature (Courneya et al., 2013, 2014; Mizrahi et al., 2015). Less comorbidity was associated with enrollment, and

younger age and receiving the planned oxaliplatin dose by the second FOLFOX/FOLFIRNOX treatment was associated with intervention completion.

The acceptability of some components of the multifaceted intervention were low, primarily attributed to the poor uptake of and perceived unhelpfulness of the walking and email groups. However, participants reported satisfaction with and likelihood of continuing the intervention. The Fitbit and motivational enhancement therapy (MET) sessions were the most helpful. Several demographic and clinical characteristics, consistent with the literature (e.g., part-time or un-employment and lower body mass index) (Courneya et al., 2014; Leone & Ward, 2013; Speed-Andrews et al., 2012), were associated with higher intervention acceptability ratings.

Fitbit-measured minutes of MVPA and self-reported PA levels were exceptionally high but variable. The participants in the current study averaged 236.58 (*SD* = 197.60) minutes of MVPA per week. Fitbit-measured MVPA increased over the eight weeks despite the participants' high baseline MVPA levels per self-report and Fitbit measurement during the first four weeks of the intervention. Fatigue, female gender, and employment status of "on disability/leave of absence" were associated with lower adherence. In general, higher Fitbit-measured PA levels were associated with a lower perceived helpfulness of most of the intervention components; however, higher satisfaction with the intervention was associated with higher MVPA levels. Participants anecdotally had difficulty responding to the confidence rulers asking their interest in increasing and confidence in their ability to increase their amount of aerobic exercise; neither interest nor confidence were notably associated with acceptability and MVPA levels.

Gaps and Limitations

No treatments have been found that prevent or cure OIPN (Hershman et al., 2014; Majithia et al., 2016). A primary contributing factor toward the lack of progress in developing treatments may be due to the current lack of understanding about the pathophysiologic mechanisms of OIPN. This study was developed, based on the understanding that oxaliplatin accumulates around the collections of peripheral nerve cell bodies (i.e., the dorsal root ganglia) and induces oxidative stress and nerve cell death. Thus, the MI-Walk Intervention was designed with a focus on aerobic walking to promote blood circulation and the sweeping of oxaliplatin away from the dorsal root ganglia to reduce OIPN.

Based on the integrative review conducted in Chapter II, three studies have demonstrated potentially clinically significant benefits of light to moderate-intensity aerobic exercise in reducing OIPN and other types of chemotherapy-induced peripheral neuropathy among patients receiving neurotoxic chemotherapy (Henke et al., 2014; Kleckner et al., 2018; Zimmer et al., 2018). However, the prior studies all had a moderate to high risk of bias, mainly due to lack of strong OIPN measurement, control for OIPN-influencing (i.e., confounding) factors, and intervention design. Further, no studies have focused on testing home-based aerobic exercise to reduce OIPN among individuals actively receiving oxaliplatin treatment.

Due to the unclear and/or lack of efficacy of the MI-Walk Intervention in increasing MVPA, the current study could not adequately evaluate the effects of home-based aerobic walking on sensory OIPN severity compared to PA education alone. The primary study limitation was insufficient assay sensitivity. Specifically, increases in self-reported PA from baseline to eight weeks were observed among the control but not intervention group participants. Reliable objective PA measurement was not available to control for overall PA in the models evaluating

the effects of the intervention on OIPN and QOL. Finally, timing of outcome measurement may have been premature in the study. Sensory and motor OIPN severity was still mild in severity at the eight-week time point (coinciding with the sixth infusion).

The current study highlighted several gaps in the knowledge regarding the feasibility of home-based aerobic exercise among FOLFOX/FOLFIRINOX-receiving GI cancer survivors. First, no studies have specifically evaluated the helpfulness of individual aerobic exercise intervention components for GI cancer survivors who are receiving FOLFOX/FOLFIRINOX and generally show the lowest rates of adherence (e.g., females or people who are on disability or leave of absence). Additionally, there remains a lack of clarity regarding the definitions of and relationships among acceptability, adherence and interest and confidence. Only one recent review has attempted to empirically define acceptability and factors associated with acceptability (Sekhon, Cartwright, & Francis, 2017).

Future Directions

Given the study results and the current state of the science, future studies are still needed to evaluate the (a) effects of home-based aerobic exercise on OIPN and (b) most helpful components of a home-based aerobic exercise intervention among GI cancer survivors who are receiving FOLFOX or FOLFIRINOX. The current data can be used to evaluate trends in results from the intervention group participants and further explore the associations between Fitbit-measured minutes of MVPA and tingling in the fingers and hands (the most severe acute OIPN symptom), as well as other sensory and motor OIPN symptoms. Additionally, future exploratory studies could evaluate other factors (e.g., mood) that may be associated with aerobic exercise adherence, self-reported PA levels, and OIPN outcomes. Finally, the current study data may be used to explore whether OIPN severity mediates the relationship between Fitbit-measured

minutes of MVPA and QOL outcomes. This data may be used to direct future prospective trials of aerobic exercise for OIPN.

Future prospective trials of aerobic exercise for OIPN among FOLFOX/FOLFIRINOX-receiving GI cancer survivors should focus on improving assay sensitivity by using a strong measurement approach; delaying the outcome measurement time point (e.g., at the eighth infusion or later) to maximize the ability to detect clinically significant differences; focusing on the most bothersome symptom at the given outcome time point (e.g., tingling in the fingers and hands if evaluating acute OIPN); and ensuring the control condition receives no PA education or intervention. A strong measurement approach may include using both clinical assessment of pre-clinical OIPN signs (especially important for preventative trials) and repeated measurements of self-reported OIPN at each timepoint.

Further investigation is also needed of 1) OIPN mechanisms and 2) potential biological mediators (e.g., vascular function) of the effects of aerobic exercise on OIPN. A better understanding of the mechanisms of OIPN will allow for stronger future studies that evaluate whether and how aerobic exercise can biologically combat OIPN. If home-based aerobic walking demonstrates potential efficacy and biological mechanisms involved in reducing OIPN, future studies will be needed to identify optimal exercise prescriptions and behavioral interventions to promote adherence.

Feasibility studies are needed to help identify the most helpful components of an aerobic exercise intervention for individuals with GI cancer who are receiving FOLFOX/FOLFIRINOX. The participants in the current study showed a preference toward engaging in independent exercise or exercise with their own family member. Studies are needed to evaluate the types of participants (e.g., unemployed versus employed; males versus females; obese versus healthy

weight) who benefit most from a group versus individual home-based intervention. Further research is also needed to evaluate technological supports that may be used to assist participants, given that most patients in the current study found the Fitbit tool to be helpful. Additionally, research is needed to identify the types of participants that would benefit from motivational interviewing/MET; as well as the training requirements of the therapist and motivational interviewing dosage required for efficacy.

Evaluation of adherence and control for PA as a confounding factor in future studies will depend on the successful acquisition of PA data from FOLFOX or FOLFIRINOX-receiving cancer survivors. Yet, obtaining good data can be challenging. Participants exhibited fluctuating PA levels between oxaliplatin infusions due to the chemotherapy side effects. Thus, the optimal timing (in relation to chemotherapy) and duration of PA measurement must be studied. New activity count cut-offs to quantify PA time and identify valid wear time may need to be established that are specific to individuals receiving neurotoxic chemotherapy every other week. Thus, future studies are needed to evaluate the validity and reliability of ActiGraph data and other PA trackers among oxaliplatin-receiving survivors, based on the timing of ActiGraph measurement (the week before and/or after oxaliplatin treatment), required hours per day and days per week of wear, and location of wear (wrist versus hip). Defining ActiGraph validity based on the number of week and weekend days of measurement required may be inappropriate for oxaliplatin-receiving survivors. The variation in treatment side effects between the first and second weeks after oxaliplatin infusion may be a larger influencer of PA levels in this population. The number of days required for valid ActiGraph measurement may best be defined in relation to the oxaliplatin infusion (e.g., at least one day of measurement within days one to four, one day within days five to eight, and one day within days nine through 13 after the infusion).

Implications for Practice

Patients with GI cancer who are receiving FOLFOX or FOLFIRINOX are at a high risk of developing OIPN. Transient acute OIPN often causes discomfort and difficulty with daily tasks such as grabbing a cold item out of the refrigerator or typing on a laptop. Acute OIPN may also evolve into long-lasting sensory and motor deficits that interfere with QOL and increase patients' risks for adverse outcomes, including falls and social isolation and depression. Due to the lack of proven interventions to prevent or cure OIPN, patient education should be a priority to maintain safety and optimize patient outcomes.

Although the efficacy of aerobic walking to reduce OIPN is unknown, the general health benefits and safety of home-based aerobic exercise is well established for GI cancer survivors with no other contraindicators to PA. Further, this study demonstrated that GI cancer survivors are capable of surpassing the national physical activity recommendations of participating in at least 150 minutes of MVPA per week during FOLFOX/FOLFIRINOX treatment; however, the levels of MVPA may be wide-ranging. Some participants with the lowest levels of MVPA may benefit from MET. Participants in the current study found that the time requirement of MET was highly acceptable, potentially because the MET sessions were delivered while the participants were receiving their several hour-long oxaliplatin infusion. Thus, employing a therapist to visit the most-in-need patients during their infusions may be an excellent way to promote home-based aerobic exercise and other healthy behaviors.

Various patient and clinical characteristics may influence a patients' receptiveness to and acceptability of an exercise intervention. Thus, clinicians should tailor the exercise intervention to the participant to optimize aerobic exercise adherence and optimize physical and mental health outcomes. For some patients, a simple intervention, including distribution of a Fitbit with or

without motivational interviewing may be most beneficial and feasible. Ultimately, further studies are needed to help identify the most helpful interventions based on patient characteristics.

References

Courneya, K. S., McKenzie, D. C., Mackey, J. R., Gelmon, K., Friedenreich, C. M., Yasui, Y., … Segal, R. J. (2013). Effects of exercise dose and type during breast cancer chemotherapy: Multicenter randomized trial. *Journal of the National Cancer Institute*, *105*(23), 1821–1832. https://doi.org/10.1093/jnci/djt297

Courneya, K. S., McKenzie, D. C., Mackey, J. R., Gelmon, K., Friedenreich, C. M., Yasui, Y., … Segal, R. J. (2014). Subgroup effects in a randomised trial of different types and doses of exercise during breast cancer chemotherapy. *British Journal of Cancer*, *111*(9), 1718–1725. https://doi.org/10.1038/bjc.2014.466

Courneya, K. S., Segal, R. J., Gelmon, K., Mackey, J. R., Friedenreich, C. M., Yasui, Y., … McKenzie, D. C. (2014). Predictors of adherence to different types and doses of supervised exercise during breast cancer chemotherapy. *The International Journal of Behavioral Nutrition and Physical Activity*, *11*, 85. https://doi.org/10.1186/s12966-014-0085-0

Dhawan, S., Andrews, R., Kumar, L., Wadhwa, S., & Shukla, G. (2019). 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*. https://doi.org/10.1097/NCC.0000000000000693

Henke, C. C., Cabri, J., Fricke, L., Pankow, W., Kandilakis, G., Feyer, P. C., & de Wit, M. (2014). Strength and endurance training in the treatment of lung cancer patients in stages IIIA/IIIB/IV. *Supportive Care in Cancer*, *22*(1), 95–101. https://doi.org/10.1007/s00520-013-1925-1

Hershman, D. L., Lacchetti, C., Dworkin, R. H., Lavoie Smith, E. M., Bleeker, J., Cavaletti, G., … Loprinzi, C. L. (2014). Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *Journal of Clinical Oncology*, *32*(18), 1941–1967. https://doi.org/10.1200/JCO.2013.54.0914

Kleckner, I. R., Kamen, C., Gewandter, J. S., Mohile, N. A., Heckler, C. E., Culakova, E., … Musian, 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

Leone, L. A., & Ward, D. S. (2013). A mixed methods comparison of perceived benefits and barriers to exercise between obese and nonobese women. *Journal of Physical Activity & Health*, *10*(4), 461–469.

Majithia, N., Temkin, S. M., Ruddy, K. J., Beutler, A. S., Hershman, D. L., & Loprinzi, C. L.

(2016). National Cancer Institute-supported chemotherapy-induced peripheral neuropathy trials: Outcomes and lessons. *Supportive Care in Cancer*, *24*(3), 1439–1447. https://doi.org/10.1007/s00520-015-3063-4

McCrary, J. M., Goldstein, D., Sandler, C. X., Barry, B. K., Marthick, M., Timmins, H. C., … Park, S. B. (2019). Exercise-based rehabilitation for cancer survivors with chemotherapy-induced peripheral neuropathy. *Supportive Care in Cancer*. https://doi.org/10.1007/s00520-019-04680-w

Mizrahi, D., Broderick, C., Friedlander, M., Ryan, M., Harrison, M., Pumpa, K., & Naumann, F. (2015). An exercise intervention during chemotherapy for women with recurrent ovarian cancer: A feasibility study. *International Journal of Gynecological Cancer*, *25*(6), 985–992. https://doi.org/10.1097/IGC.0000000000000460

Sekhon, M., Cartwright, M., & Francis, J. J. (2017). Acceptability of healthcare interventions: An overview of reviews and development of a theoretical framework. *BMC Health Services Research*, *17*(1), 88. https://doi.org/10.1186/s12913-017-2031-8

Speed-Andrews, A. E., Rhodes, R. E., Blanchard, C. M., Culos-Reed, S. N., Friedenreich, C. M., Belanger, L. J., & Courneya, K. S. (2012). Medical, demographic and social cognitive correlates of physical activity in a population-based sample of colorectal cancer survivors. *European Journal of Cancer Care*, *21*(2), 187–196. https://doi.org/10.1111/j.1365-2354.2011.01290.x

Streckmann, F., Kneis, S., Leifert, J. A., Baumann, F. T., Kleber, M., Ihorst, G., … 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

Vollmers, P. L., Mundhenke, C., Maass, N., Bauerschlag, D., Kratzenstein, S., Rocken, 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

Zimmer, P., Trebing, S., Timmers-Trebing, U., Schenk, A., Paust, R., Bloch, W., … 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