EXERCISE INFLUENCE ON TAXANE SIDE EFFECTS IN WOMEN WITH BREAST CANCER

by

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Abstract

Taxane-based chemotherapy is frequently administered to treat breast cancer. However, side effects of taxanes include chemotherapy-induced peripheral neuropathy (CIPN) and cardiovascular complications, which negatively impact patient quality of life and long-term health. Exercise can significantly reduce cancer treatment side effects. However, information on exercise's influence on taxane-specific side effects is limited. The primary aim of this dissertation was to evaluate the effect of exercise on taxane side effects, including CIPN and cardiovascular outcomes, in women with breast cancer. **METHODS:** Women with early-stage breast cancer were randomized to thrice-weekly exercise (EX) or usual care (UC) during taxane chemotherapy (4 cycles, 2-3 weeks apart). Patient-reported CIPN symptoms and quality of life (EORTC QLQ-C30 + CIPN20 subscale), clinical CIPN tests (vibration sensation and pinprick), patient-reported pain (Brief Pain Inventory) and cardiovascular outcomes, including heart rate and blood pressure at rest, and during and after submaximal exercise testing, were evaluated at baseline (pre-taxane chemotherapy) and end of chemotherapy. CIPN symptoms and quality of life were also evaluated at 0-3 days pre-chemotherapy cycle 4. **RESULTS:** Twenty-four women enrolled (EX: n=11, UC: n=13). Patient-reported CIPN symptoms were significantly worse by the end of chemotherapy in both groups for sensory ($p<0.01$) and motor symptoms ($p=0.04$), with a trend towards reduced sensory symptom progression among exercisers ($p=0.08$). Significantly more participants in the usual care group had impaired vibration sensation at 0-3 days pre-chemotherapy cycle 4 at the left interphalangeal joint (UC: 80%, EX: 10%, $p<0.01$), with a similar trend for the right interphalangeal joint (UC: 60%, EX: 10% $p=0.06$). Resting heart rate was significantly

lower by the end of chemotherapy in the exercise group (EX: 71±2, UC: 77±2 bpm, $p<0.05$). The exercise group also had significantly lower heart rates during submaximal exercise testing ($p<0.01$) and significantly faster heart rate recovery ($p=0.02$) by the end of chemotherapy. Lastly, a non-significant trend towards higher blood pressure during submaximal exercise testing was observed among the usual care group by the end of chemotherapy. **CONCLUSION:** This study provides preliminary evidence supporting the positive influence of exercise on CIPN and cardiovascular outcomes in early-stage breast cancer patients undergoing taxane chemotherapy.

Lay Summary

Peripheral neuropathy is often experienced as numbness, tingling and pain in the hands and feet and is a known side effect of anti-cancer drugs, including taxane chemotherapy. Chemotherapy also negatively impacts cardiovascular health and can increase cardiovascular disease risk in cancer survivors. Exercising during chemotherapy is safe and a potential strategy to reduce numerous treatment side effects; yet little research specific to taxane chemotherapy exists. This study investigated exercise's effect on peripheral neuropathy and cardiovascular health in breast cancer patients undergoing taxane chemotherapy. Women who engaged in structured exercise training had reduced peripheral neuropathy symptoms, relative to a non-exercise control group. However, this difference was not statistically significant. Further, exercise significantly improved measures of cardiovascular health, including heart rate at rest and during and after exercise. Altogether, exercise may improve taxane chemotherapy side effects. More research is needed to definitively determine exercise's impact on chemotherapy-induced peripheral neuropathy.

Preface

This thesis contains the work of a research study conducted by the candidate, Kelcey A. Bland, under the supervision of Dr. Kristin L. Campbell, with guidance from Drs. Donald C. McKenzie and Margot K. Davis. Dr. Amy A. Kirkham assisted in early aspects of the study design and protocol development. Study data collection, analysis and writing of the manuscript were primarily the work of the candidate.

Sections of this thesis will be submitted for publication as a manuscript in a peer-reviewed journal.

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List of Abbreviations

ANOVA = analysis of variance

ANS = autonomic nervous system

BCCA = British Columbia Cancer Agency

BDNF = brain-derived neurotrophic factor

BMI = body mass index

BPI = Brief Pain Inventory

bpm = beats per minute

CVD = cardiovascular disease

CIPN = chemotherapy-induced peripheral neuropathy

mmHG = millimeter of mercury

NCI CTCAE = National Cancer Institute Common Terminology Criteria Adverse Event

CI = confidence interval

EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire

FACT-G = Functional Assessment of Cancer Therapy-General Questionnaire

FACT-NTx = Functional Assessment of Cancer Therapy-Taxane Questionnaire

GDNF = glial-derived neurotrophic factor

GLM = generalized linear model

HR = hazard ratio

IGF = insulin-like growth factor

OR = odds ratio

PN = peripheral neuropathy

PNS = parasympathetic nervous system

QOL = quality of life

QST = quantitative sensory testing

RM = repetition-maximum

RPE = rating of perceived exertion

RPM = revolutions per minute

SNS = sympathetic nervous system

TNS = total neuropathy score

VO_{2peak} = peak oxygen consumption

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Chapter 1: Introduction

Worldwide, breast cancer remains the most commonly diagnosed cancer in women, accounting for 26% of newly diagnosed cancers and 14% of deaths due to cancer each year.[1] Due to early-detection and treatment advancements for breast cancer, the five-year survival rate has improved dramatically, and in Canada is approximately 88%.[2] Thus, much of research is now directed towards addressing short and long-term treatment side effects and competing risks for morbidity and mortality among women who have had a breast cancer diagnosis.

Treatment for breast cancer is multi-modal and often includes all or a combination of the following: surgery, chemotherapy, radiotherapy, targeted therapies, and endocrine therapy. In British Columbia, polychemotherapy treatment protocols for early and locally advanced breast cancer typically contain cyclophosphamide and a taxane agent, with or without anthracyclines. At the Vancouver Centre of the British Columbia Cancer Agency (BCCA) the two most commonly administered treatment protocols for breast cancer include doxorubicin combined with cyclophosphamide followed by paclitaxel, or docetaxel combined with cyclophosphamide.

Docetaxel and paclitaxel are taxane-based chemotherapeutic agents and are currently some of the most effective agents used in the treatment of breast cancer today.[3,4] While anthracyclines have been considered standard chemotherapy agents in both adjuvant and metastatic breast cancer settings since the 1980's, taxanes have been used in breast cancer treatment protocols since the mid-1990's to reduce risk of cancer recurrence and death.[3,4] In a meta-analysis comparing long-term outcomes in women with

early breast cancer, data from 44, 000 women in 33 randomized trials found anthracycline-taxane combinations significantly improved response rates and progression-free survival in first-line treatment, when compared with anthracycline treatment without taxanes.[5] Further, docetaxel is the first drug shown to have a superior effect compared to anthracyclines alone, and is also highly active in anthracycline-resistant breast cancer patients.[6]

While the safety and efficacy of taxanes is well established, taxanes are known to cause significant unique side effects that pose a major challenge for clinical oncological practice. As with all antineoplastic agents, the efficacy of the treatment needs to be balanced against both short and long-term toxicities, as well as the impact of such toxicities on patient quality of life (QOL) and survival.[4] Taxanes share many of the common side effects of other chemotherapy agents, such as fatigue,[7,8] arthralgia and myalgia,[9–11] and nausea.[7,8] In addition, a specific side effect of taxanes is chemotherapy-induced peripheral neuropathy (CIPN).[12–15] CIPN in particular, can not only negatively impact patient QOL,[14] but may also impact disease outcome and survival, as symptoms can require chemotherapy dose-reductions, delays and cancellations.[7,16] Further, while early breast cancer therapies are extending the life expectancy of survivors, these therapies can result in competing causes for morbidity and mortality. In particular, antineoplastic agents, including taxanes, are associated with acute and long-term cardiac complications, including heart failure, arrhythmias and myocardial ischemia.[17] Cardiovascular disease (CVD) is now the leading cause of death in older breast cancer survivors,[18] and this is in part due to the direct and indirect effects of breast cancer therapies, including cardio-toxic chemotherapeutics, such as taxanes.[17] While the

mechanisms underpinning the association between chemotherapy and CVD risk have not been fully elucidated, one theory is that antineoplastic agents impact autonomic nervous system (ANS) function.[19–22] The ANS is a key regulator of the cardiovascular system and ANS dysfunction has been shown to predict CVD and CVD-related death in non-cancer populations.[23]

Exercise during chemotherapy for breast cancer has been shown to play an important role in improving physical and psychological function, and reducing common treatment side effects, including fatigue and nausea.[24–27] However, whether the beneficial effects of exercise shown for other chemotherapy protocols extend to taxane-specific toxicities has been underexplored. There is biological plausibility and preliminary evidence in non-cancer clinical populations that formal exercise training may be effective in counteracting peripheral neuropathy (PN) symptoms[28–31] and reducing CVD risk.[32] Thus, the theme of this dissertation was to investigate the efficacy of exercise as an intervention to address taxane-treatment side effects in women with early-stage breast cancer. The primary aim was to determine the influence of exercise on patient-reported CIPN symptoms and QOL. The secondary aim was to explore the impact of exercise on responses to clinical tests of CIPN and patient-reported pain. The third aim was to evaluate exercise's influence on cardiovascular outcomes, including indices of cardiac autonomic control.

Chapter 2: Background

2.1 Taxane chemotherapy cytotoxic mechanisms

The two primary taxane agents used in chemotherapy regimens are paclitaxel and docetaxel. Both drugs have similar preclinical activity, mechanism of action and spectrum of clinical activity.[33] Taxanes exert their antineoplastic effect by binding to the β-tubulin of microtubules.[34] Microtubules are dynamically instable heterodimers, comprised of α and β tubulin, that continually assemble and disassemble in order to carry out a variety of cellular processes, including cell transport and forming mitotic spindles during the M-phase of cell division.[35] By binding to the β-tubulin, taxanes inhibit the natural disassembly of microtubules.[34] This hyper-stabilization disrupts microtubule dynamics, causing cell-cycle arrest and ultimately apoptosis.[33,34] This unique mechanism of action contrasts other microtubule-targeting chemotherapy agents, such as vinca alkaloids, colchicine, and cryptophycines, which prevent tubulin assembly.[36] In addition to targeting tubulin, paclitaxel has also been found to target the mitochondria and inhibit the function of B-cell Leukemia 2, an apoptosis inhibitor protein.[37]

2.2 Chemotherapy-induced peripheral neuropathy

2.2.1 Characteristics

CIPN is damage to the peripheral nerves caused by exposure to neurotoxic chemotherapeutic agents including taxanes, platinum agents, and vinca alkaloids.[13,14] CIPN symptoms are primarily sensory in nature and typically reflect either a gain in sensory neuronal function, a loss of function, or a combination of both.[38] Symptoms include diminished reflexes, numbness, loss of proprioception sense, tingling, pins and

needles sensation, and hyperalgesia or allodynia, in the hands and feet in a "stocking and glove" distribution.[13,38] In rare cases, there may be damage to the motor fibres, resulting in motor neuropathy.[13] However, whether motor neuropathy is simply a severe variant of the same process, or caused by an alternate mechanism, remains unclear.[38] It is also unknown why some patients experience primarily symptoms of loss of function versus symptoms of enhanced excitability, or whether this distinction matters when considering preventative and treatment therapies.[38]

Taxanes are perhaps the most important class of agents with the potential for serious and long-lasting CIPN.[39] CIPN with taxane-based treatments can occur after the first taxane infusion,[40] and tends to progressively worsen with each treatment cycle.[41,42] Taxane CIPN is most often sensory neuropathy described as paresthesia, numbness or pain in the hands and feet, and thick myelinated nerve fibres conducting vibration sensation and sense of position are primarily affected.[13,43] Loss of balance has also been reported in >50% of patients treated with docetaxel and paclitaxel,[10] and motor deficits in the distal regions of the somatic nervous system have been also known to occur.[44] As graded by the National Cancer Institute Common Terminology Criteria Adverse Event (NCI CTCAE) system, CIPN caused by taxanes can interfere with function (grade 2 neuropathy, e.g. difficulty buttoning a shirt), activities of daily living (grade 3 neuropathy, e.g. brushing teeth or bathing), and potentially result in permanent and disabling symptoms (grade 4 neuropathy, e.g. paralysis).[45] In addition to interfering with daily activities[10] and negatively impacting patient QOL,[14] CIPN can influence disease outcome and survival, as symptoms may become so intolerable that oncologists are forced to prescribe dose-reductions, treatment delays or cancel the therapy altogether.[15,16] Thus, a

patient's inability to tolerate the full dose and duration of the prescribed taxane treatment is a primary oncological concern, especially for those at high risk for cancer recurrence.

2.2.2 Mechanisms

The neurotoxic effects of chemotherapy agents on the peripheral nervous system are wide-ranging, targeting many components of the peripheral nervous system, such as the axons and cell bodies of dorsal root ganglion neurons.[12] Although all neurons are non-dividing cells, peripheral nerves may be more vulnerable to neurotoxic damage due to their extended axonal length and permeability of the blood nerve barrier.[46] Biopsies of nerves treated with paclitaxel have shown axonal degeneration, secondary demyelination and in severe instances, complete nerve fibre loss.[47]

Several mechanisms have been proposed to illustrate how taxanes induce neurotoxicity. These mechanisms include impaired mitochondrial function, disrupted calcium signaling, changes in sodium ion channel function leading to increased paraesthesia, and altered transient receptor potential, resulting in hyper-responsiveness of nociceptors predisposing pain and CIPN.[48] Specifically, vascular and mitochondrial dysfunction[48] may result in sensory loss, decreased muscular strength, and impaired energy production in taxane-treated patients.[10] Animal studies have found abnormal amounts of swollen and vacuolated mitochondria in peripheral nerve sensory axons and in the lumbar dorsal root ganglion in rats treated with paclitaxel.[49,50] This mitochondrial injury results in energy deficits, which may lead to spontaneous nerve impulses and neuronal degeneration, which typically first appears in the terminal receptor arbor, or intraepidermal fibre.[51] Evidence also suggests that taxanes may alter peripheral vascularization, which attenuates nerve blood supply primarily through a reduction in

vaso nervorum, the small arteries supplying peripheral nerves.[52] Altogether, mitochondrial dysfunction reduces energy production within the body, while vascular impairment deprives cells of oxygen and nutrients, further impairing neuronal cell function. Finally, there is growing evidence suggesting that various inflammation phenomena such as an increase in Langerhans cells, up-regulation of pro-inflammatory cytokines, macrophage accumulation and microglia activation may be associated with the development of pain with taxane treatment.[48] Overall, there is a current lack of understanding of the precise mechanism of CIPN and further research is needed to fully elucidate how CIPN in taxane-treated patients develops.

2.2.3 Risk factors

Important risk factors for the development of CIPN with taxane agents include drug type, dose level, treatment schedule, and pre-existing medical conditions, including diabetes.[14] Additionally, paclitaxel appears to be more neurotoxic than docetaxel.[39,40,53] One of the most prominent triggers of CIPN is the accumulation of doses over the course of chemotherapy, with a neurotoxic threshold of 1,000 mg/m^2 for paclitaxel, and 400 mg/m^2 for docetaxel.[54] For example, in the Cancer and Leukemia Group B 9840 study, there was a dose response effect of neuropathy symptoms and paclitaxel therapy administered every three weeks. [55] The 250 mg/m^2 dose of paclitaxel produced the highest rate of grade 3/4 sensory and motor neuropathy (33 and 14%, respectively), followed by the 210 mg/m^2 dose (19 and 11%, respectively) and the 175 mg/m^2 dose (7 and 5%, respectively). Age may also be an important risk factor for neurotoxicity during taxane treatment. In the same CALGB study, older patients had a significantly higher incidence of sensory ($p<0.01$) and motor symptoms ($p<0.01$).[55] In addition, recent

evidence suggests body weight and lifestyle factors including levels of physical activity may influence the development of CIPN. In a 2017 observational study of women (n=1237) receiving taxane treatment for breast cancer, a 10% increase in CIPN symptoms, evaluated via self-report using the Functional Assessment of Cancer Therapy-Taxane (FACT-NTx scale), was more likely to occur in overweight and obese patients (BMI >25 kg/m^2) (OR=2.37, 95% CI=1.19 to 4.88) and less likely to occur in patients with higher moderate-vigorous physical activity levels (OR=0.43, 95% CI=0.21 to 0.87), when symptoms were evaluated 24 months after initiating chemotherapy.[56]

2.2.4 Evaluation

CIPN can be measured using subjective and objective methodologies. CIPN is often clinically assessed and then graded using the NCI-CTCAE system.[13,45] The NCI CTCAE is a uniform system of nomenclature, originally designed to classify adverse events and their associated severity in cancer clinical trials.[57] However, it is currently frequently used in routine oncological care to guide treatment decisions, including drug dosing and supportive care interventions.[57] CIPN grading using the NCI-CTCAE is determined via the evaluation of symptom severity, including weakness, loss of tendon reflexes and sensory alterations, and their degree of impact on physical function and activities of daily living. However, toxicity grading systems like the NCI-CTCAE rely on the judgment of clinicians and/or nurses and disagreement among examiners is frequent.[58] Further, while these scales are useful in determining treatment dosage, they overlook potential variations in CIPN types and manifestations and therefore, do not uncover potential CIPN mechansims.[13,59] The Total Neuropathy Score (TNS) is another commonly used composite scale designed to evaluate PN. The TNS was first designed

and validated for diabetic neuropathy and includes both subjective, namely grading PN symptoms by a clinician, and objective ratings, obtained from nerve conduction studies and quantitative sensory testing (QST), to quantify neuropathy.[60] The TNS and its modified version, which eliminates the nerve conduction study element of the score, have been shown to correlate with the NCI-CTCAE scoring of CIPN ($r=0.75$ and $r=0.88$, $p<0.01$) and are more sensitive to CIPN changes.[61] Nerve conduction studies are considered the gold standard for evaluating CIPN due to their ability to precisely evaluate nerve pathophysiology, severity of nerve involvement and overall neurologic deficit.[62] However, nerve conduction studies are limited to the evaluation of large myelinated nerve fibres and therefore cannot detect impairment or dysfunction of small or unmyelinated nerve fibres, including the fibres responsible for transmitting pain and light touch sensation.[62] Further, nerve conduction studies are rarely used in the clinical oncology setting due to the need for specialized equipment, trained personnel and discomfort to patients.[13] Alternatively, QST is a noninvasive way of assessing and quantifying nerve function, and has been defined as techniques used to measure the intensity of stimuli needed to produce specific sensory perceptions.[63] This can be assessed through vibration threshold detection, thermal detection, light touch sensation and sharpness detection.[39,64,65] QST is considered an important addition to the assessment of CIPN because it can reliably assess large and small sensory nerve fibre function.[63] However, QST relies on subjects being alert, cooperative, and able to follow instructions, and lacks the objectivity of nerve conduction studies.[63]

Due to the subjective nature of CIPN symptoms, it has also been proposed that the assessment of CIPN be at least in part, based on patient reported outcomes.[66] Patient-

reported outcome measures, including the FACT-NTx/Gynecologic Oncology Group-neurotoxicity (GOG) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) CIPN20 subscale are now frequently incorporated as a primary study end-point.[59] Patient-reported outcomes are useful for identifying the significance and impact of neuropathic symptoms on daily life, and can be used to correlate a clinician rating or objective findings to the patient's experience.[67] In particular, the EORTC QLQ-CIPN20 subscale includes sensory, motor and autonomic scales to capture both the experience and functional limitations of CIPN. The EORTC QLQ-CIPN20 has been shown to be highly reproducible with no statistically significant differences in a test–retest analysis of most of the functional and symptom scales.[68] Furthermore, evidence suggests there may also be a strong association between patient-reported outcomes, for example, FACT-NTx scale neurotoxicity score, and QST, including hand vibration ($p=0.02$) and foot vibration ($p<0.01$) sensation.[39]

2.2.5 Impact on patient quality of life

Health-related QOL can decline during chemotherapy for breast cancer, and it is possible CIPN may contribute to this decline.[69] QOL among cancer survivors has become an increasingly used outcome measure in randomized control trials within the past two decades.[70] Several measures of patient-reported outcomes have been developed to assess QOL, with the EORTC QLQ and the FACT-General (G) being the two most popular. In a meta-review comparing these two widely used questionnaires, eight systematic reviews were identified where QOL had been recorded (n=101 trials).[71] Results of the meta-review demonstrated that the FACT-G and EORTC QLQ version 3 (C30) were administered in 20.8% and 77.2% of the trials, respectively.[71] Overall, comparison of the

two questionnaires showed strong agreement, except for two psychometric properties, cultural validity and baseline compliance, in which the reported EORTC QLQ-C30 data was more complete.[71]

The direct impact of CIPN on QOL evaluated using patient-reported outcomes remains somewhat unclear. In a 2014 systematic review by Mols et al. 25 studies were reviewed and most pointed towards an association between increased CIPN symptoms and lower QOL.[72] Eleven of the studies directly assessed the relationship between QOL and CIPN, three of which did not find a correlation. The remaining 14 studies described the two constructs separately, but did not directly assess their association. QOL was commonly evaluated using the EORC QLQ-C30 and FACT-G questionnaire and assessment of CIPN was quite diverse including the NCI-CTCAE, EORTC QLQ-CIPN20 subscale, TNS, QST and self-designed interviews. Study samples were also fairly diverse, including mixed-cancer populations and several chemotherapy protocols, further hindering the ability to draw concrete conclusions. Only two studies have evaluated QOL and CIPN in breast cancer patients receiving taxane-containing chemotherapy.[39,73] One of these was a high-quality study by Hershman et al., which included both cross-sectional (6–24 months after chemotherapy) and prospective data (before chemotherapy, and up to 12 months after chemotherapy), and described that patients with more severe CIPN were more likely to have lower scores on the physical well-being scale of the FACT-G; however, data were not shown.[39] Overall, findings suggest CIPN may negatively impact QOL among cancer patients. However, more research on this topic, with validated QOL and CIPN questionnaires, is needed.

2.2.6 Incidence

Both the incidence and severity of CIPN caused by taxanes are clinically under- and misreported, and this may be a result of the significant inter-observer variability using common toxicity scales, such as the NCI-CTCAE system.[14] Large adjuvant trials report that the rates of grade 2-4 CIPN with taxane treatment can range from 15 to 23%, as graded by the CTCAE system.[39] However, higher incidence rates have been reported elsewhere, and therefore may depend on the method of symptom evaluation. For example, in a longitudinal prospective study of 21 adult cancer patients treated with paclitaxel and carboplatin, 14 patients (66.6%) experienced sensory neuropathy symptoms as measured using clinical (including QST) and electrophysiological (nerve conduction) examinations.[53] Further, in the prospective and cross-sectional study by Hershman et al. previously mentioned, cross-sectional results demonstrated that 80% of breast cancer patients (n=50) treated with paclitaxel reported numbness or discomfort in the hands or feet measured using QST (vibration threshold) and the FACT-NTx questionnaire.[39] In the same Hershman et al. study, the prospective cohort results demonstrated 67% of breast cancer patients (n=50) reported persistent numbness 12 months post-treatment, including 27% who had severe symptoms similar to what was observed in the cross-sectional group.[39] Lastly, in a large prospective longitudinal trial, 597 women (34%) reported grades 2-4 neuropathy symptoms during docetaxel treatment for breast cancer, as measured by the NCI-CTCAE version 2.0.[40] Altogether, more data produced from reliable and validated methods of subjective and objective symptom evaluation is needed to definitively determine the incidence of CIPN in taxane-treated patients.

2.2.7 Pharmacological treatment and prevention

Effective treatment is still an unmet clinical need for CIPN. There is limited evidence demonstrating the positive impact of pharmacological agents for standard use in clinical practice on CIPN symptoms.[42] Agents used to treat diabetic PN have been tested and deemed less effective in improving CIPN symptoms, likely due to differences in pathology.[13] The only treatment with moderately conclusive evidence for symptom management is duloxetine.[70] A 2013 clinical trial by Smith et al. reported 59% of patients treated with duloxetine experienced a significant reduction in pain compared to 38% of placebo-treated patients ($p=0.003$).[70] However, in an exploratory subgroup analysis, the benefit was less clear among those treated with taxanes compared to oxaliplatin, a chemotherapy drug commonly used to treat colon cancer. Thus, current management of CIPN in those undergoing taxane-based treatments includes dose reduction, use of alternate chemotherapy agents, or temporary cessation of chemotherapy.[15,42] Due to few available treatment options for symptom prevention and management, CIPN with taxane treatment represents a major challenge within current oncological care.

2.2.8 Exercise

The benefits of exercise during breast cancer therapy are well-established and include increased physical fitness, reduced cancer treatment side effects, and improved patient-reported QOL.[24,27] Despite the frequency of taxane use in anti-cancer regimes and high prevalence of dose-limiting side effects, information regarding exercise's influence on taxane-specific side effects, especially CIPN, is limited. A 2014 systematic review of 18 exercise studies in individuals with PN from varied causes, including diabetic PN, liver-transplanted familial amyloid polyneuropathy, hereditary sensorimotor neuropathy,

chronic acquired PN as well as CIPN, reported exercise as feasible, safe and beneficial for patients experiencing PN.[28] The best evidence, revealing the largest number of randomized trials (n=11) and therefore the highest quality data, supported the use of exercise in the treatment and management of diabetic PN.[28] Overall, endurance training among diabetic patients was found to prevent the onset and reduce the progression of PN symptoms. Conclusions about other types of PN could not be determined due to the small number of studies representing certain populations, as well as small sample sizes and heterogeneous patient groups within existing trials.

A limited number of studies have explored exercise's role in managing CIPN symptoms in humans. One randomized control trial reported that a supervised aerobic, resistance and balance training program (twice weekly for 36 weeks) diminished CIPN sensitivity, evaluated using a vibrating tuning fork, and improved balance in lymphoma patients receiving chemotherapy (n=31) compared to usual care (n=30).[74] However, participant chemotherapy protocols were not explicitly reported and may have included agents other than taxanes. In another randomized control trial, 19 women with breast cancer undergoing paclitaxel chemotherapy were randomized to either a 12-week home-based aerobic and strength exercise training group or educational information group.[75] A reduction in CIPN symptoms measured using the FACT-NTx was observed in the exercise group. However, due to a limited sample size, a definitive statistical difference between groups could not be demonstrated. More recently, a randomized control trial in a mice model showed daily vigorous aerobic exercise was found to prevent the development of paclitaxel-induced PN.[76] Mice were given three doses of 25 mg/kg of paclitaxel via tail vein injections every other day to induce PN, and mice randomized to

exercise performed 50 minutes of aerobic exercise on the treadmill seven days/week for four weeks. Evaluation of intraepidermal nerve fiber density in the hind paw showed that exercise prevented the reduction in unmyelinated axon numbers caused by paclitaxel. Overall, this preliminary evidence suggests exercise may play an important role in the prevention of CIPN onset and progression.

The mechanisms behind the potential positive impact of exercise on CIPN are unknown. Exercise may exert a neuro-protective effect through the enhancement of vasculature and metabolic activity at the level of the peripheral nerves.[31] Exercise in healthy and clinical populations can greatly improve mitochondrial function in skeletal muscle,[77] and there is some evidence suggesting exercise may positively influence mitochondria in nerve cells.[78] Furthermore, some human and animal studies have demonstrated that exercise stimulates endothelium-dependent vasodilation and vascular endothelial growth factor expression, increasing endoneurial blood flow and energy generating capacity through mitochondrial protein synthesis and glycolysis.[79,80] Along with enhanced mitochondrial and vascular function exercise may also reduce the risk of CIPN through the up-regulation of protective neurotrophic factors, including glial-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF) and insulin-like growth factor (IGF). This group of biomolecules promotes the growth, survival and differentiation of both mature and developing neurons. BDNF in particular, can be produced in the central nervous system, along with tissues in the periphery, and has been implicated in neural development and functioning, including neurogenesis, dendritic growth and the long-term potentiation of neurons.[81] A single exercise bout has been shown to moderately increase BDNF in humans, while regular exercise intensifies

the effect of a single session on BDNF levels and can modestly improve resting levels of BDNF.[82–84] Further, in a randomized mice model study, daily exercise versus control, following median nerve transection and repair resulted in improved recovery of compound motor action potentials, increased number of axons in the median nerve, and larger myofiber size in target muscles.[85] These improvements correlated with higher levels of GDNF, BDNF and IGF-1 in the serum, nerve and muscle, suggesting an increase in muscle derived neurotrophic factors could be an underlying mechanism for improved regeneration. Lastly, in a 2016 systematic review and meta-analysis of 80 studies (n=478) exercise training was shown to improve serum concentrations of pro-inflammatory mediators, including IL6 with a weighted mean difference of -0.55 pg/mL (95% CI=-1.02 to -0.09) in women with breast cancer.[86] This evidence suggests exercise may help manage chronic inflammation with chemotherapy and its potential associated side effects, including pain with CIPN. Together with the knowledge that exercise is safe, feasible and beneficial in both cancer and other PN populations, there exists a strong rationale for further investigating the role of exercise in managing CIPN.

2.3 Cardiovascular health

2.3.1 Cardiovascular disease and breast cancer

Relative to women who have not had breast cancer, breast cancer survivors are at an increased risk for developing CVD in their lifetime. Several factors potentially predispose breast cancer survivors to increased CVD risk including pre-existing comorbidities, as most women diagnosed with breast cancer are over the age of 55 and have a least one comorbidity.[87] In addition, lifestyle alterations, including reductions in physical activity and weight gain, can occur during and following treatment for breast

cancer,[88,89] and may independently predict the presence of CVD and risk of future CVD-related events.[90] Chemotherapy also induces menopause in approximately 30-60% of women.[91] The onset of menopause is a known determinant of CVD risk,[92] and in breast cancer survivors, early menopause may increase this risk independently of breast cancer treatment. Finally, breast cancer treatment, namely chemotherapy agents such as anthracyclines (doxorubicin and epirubicin) and taxane drugs, radiotherapy (especially left-sided), and targeted therapies, including Trastuzumab, may directly cause cardiovascular injury in women with breast cancer.[17] Thus, predicting CVD risk and identifying CVD prevention and management strategies within this population is both a clinical and research priority.

2.3.2 Indices of cardiovascular health

Given the increased risk of CVD facing breast cancer survivors, it is recommended that treatable cardiac risk factors, including hypertension, hyperlipidemia and diabetes, be monitored and managed, especially among those receiving treatments known to cause cardiovascular injury.[93] Hypertension is an important modifiable risk factor for cardiovascular-related morbidity and mortality.[94] Hypertension is more than twice as prevalent in breast cancer survivors 55 years of age and older, relative to the normal population,[95] and may be linked to treatment with chemotherapy.[96] In a large observational study (n=6673) evaluating comorbidities among older cancer survivors, hypertension was the most common comorbidity among women with breast cancer (>50%, n=1709) and was much more prevalent as a "current management problem" rather than a "pre-existing condition."[95] In a large epidemiology study of 8491 participants from the Framingham cohorts, 10-year absolute risk for CVD events,

including coronary heart disease and heart failure, or mortality was significantly predicted by variations in systolic blood pressure.[97] Specifically, systolic resting blood pressure values of approximately >150 mmHG in women with treated hypertension, and >160 mmHg in women with untreated hypertension, significantly predicted high-risk (≥20%) for CVD-events and mortality.[97] Thus, the importance of monitoring and treating hypertension cannot be understated. Further, treatment with chemotherapy for breast cancer is also associated with elevated triglyceride levels,[98] and prior to chemotherapy, women diagnosed with breast cancer may have poor lipid profiles, including higher total cholesterol, triglyceride and low-density lipoprotein levels, and lower high-density lipoprotein levels relative to healthy controls.[99,100] For example, in an observational study, serum cholesterol and low density lipoproteins were found to be significantly higher in untreated breast cancer patients (n=100) compared to normal controls (n=50).[99] Breast cancer survivors are also at an elevated risk of diabetes approximately 2-10 years after initial diagnosis, potentially as a result of weight gain and estrogen suppression with treatment.[101] Risk for diabetes is also the highest in the first two years among women who undergo adjuvant breast cancer treatment suggesting cancer and its therapy may have a long-term metabolic effect.[101] In women with early-stage breast cancer, high blood insulin levels, indicating insulin resistance, significantly correlate with obesity, poor lipid profiles,[102] and predict distant recurrence and death.[103] Among the general population, poor blood lipid profiles, including total cholesterol and high-density lipoproteins, and the presence of diabetes mellitus, strongly predict 10-year CVD risk.[97] While more data regarding the exact CVD risk profile of breast cancer survivors is needed, evidence implies CVD risk is a known concern within this population.

2.3.3 Autonomic nervous system function

Compelling evidence suggests certain measures of ANS function in the setting of CVD are linked with a poor prognosis. The ANS is both an efferent and afferent system responsible for relaying information to and from the central nervous system in order to regulate numerous bodily systems. The ANS influences the control of heart rate and force of heart rate contraction, constriction and dilation of blood vessels, contraction and relaxation of smooth muscle in various organs, and glandular secretion. Healthy autonomic regulation includes a balanced transmission of appropriate stimulatory and inhibitory signals via the two main divisions of the ANS: the parasympathetic and sympathetic nervous systems (PNS and SNS, respectively). These two components of the ANS system play a key role in regulating the cardiovascular system.

The PNS and SNS operate simultaneously but have distinct structural pathways and transmitter systems in order to carry out regulation of the cardiovascular system. Sympathetic innervation originates mainly in the right and left stellate ganglia. These fibers travel along the epicardial vascular structures of the heart into the underlying myocardium and end as sympathetic nerve terminals reaching the endocardium.[104] The sympathetic cardio-accelerator nerves release the catecholamines, epinephrine and norepinephrine, which increase sino-atrial depolarization to increase heart rate (chronotropic effect). Further, catecholamines also stimulate myocardial contractility (inotropic effect) to regulate the amount of blood the heart pumps with each beat. Parasympathetic effects are carried by the right and left vagus nerves, originating in the medulla. The vagus nerve further divides into the superior and inferior cardiac nerves, finally merging with the postganglionic sympathetic neurons to form a plexus of nerves at the base of the heart, known as the cardiac plexus.[104] PNS neurons release the neuro-

hormone acetylcholine, which acts to lower heart rate. The vagus nerves carry 80% of all PNS fibres, and vagal stimulation has no effect on myocardial contractility.[104]

The ANS plays a critical role in modulating the cardiovascular system during exercise.[105] In healthy individuals, the combined response of reduced vagus nerve activity, increased cardiac sympathetic nerve activity, and stimulation of epinephrine release from the adrenal medulla during exercise increases heart rate, ventricular contractility, stroke volume and ultimately cardiac output.[106] During low-moderate intensity exercise, or in the initial phases of vigorous exercise, heart rate increases primarily as a result of PNS withdrawal.[107] At higher levels of intensity, activation of the SNS cardio-accelerator nerves further increases heart rate. The magnitude of heart rate acceleration is directly related to exercise intensity and duration.[108] Globally, the release of norepinephrine results in vasoconstriction, with the exception of the coronary vessels. However, at the level of the active skeletal muscles, vasoconstriction is overridden by metabolically and mechanically-induced vasodilation.[105] Thus, the net effect is a diversion of blood flow from the skin and splanchnic muscles, and enhanced blood flow to the skeletal muscle, in order to meet the energy demands required for exercise.[105] At the immediate cessation of exercise, the initial recovery of heart rate is often abrupt and then followed by a more gradual reduction occurring over minutes.[105] This immediate heart rate recovery following exercise has been attributed to the rapid restoration of cardiac PNS activity.[109] Overall, several autonomic adjustments are made in response to exercise and work interactively to orchestrate an appropriate cardiovascular response to exercise in an intensity-dependent manner.[105]

2.3.4 Autonomic nervous system dysfunction

ANS dysfunction is often characterized by SNS overdrive and reduced PNS activity.[21] In particular, both increased SNS input and decreased PNS activity are associated with an increased risk of sudden death and susceptibility to ventricular arrhythmias.[23] This can directly impact the cardiovascular system leading to unfavorable changes in resting heart rate, electrical conduction, left ventricular contractility, vascular tone, and blood pressure.[110] Recent reviews have highlighted the association between breast cancer and its therapy and ANS dysfunction.[19,21] A 2015 review by Lakoski et al. proposes that both antineoplastic therapy and secondary exposures, such as psychological distress, disrupted sleep, and weight gain may lead to ANS changes in this population.[21] The authors suggest that changes in ANS regulation may be associated with increased oxidative stress, reduced vasodilation, increased inflammation and atherosclerosis progression.

Resting heart rate, measured in beats per minute (bpm), is one of the simplest measures of cardiac autonomic control and is a valued index of SNS and PNS input on the sinus node.[23] Among those with ANS dysfunction, a chronically elevated resting heart rate may be present.[21] In a cross sectional study by Jones et al., average resting heart rate measured among breast cancer survivors at different stages of treatment (including pre, during and post-adjuvant therapy, n=248) was 89±16 bpm, with 27% of the participants displaying resting tachycardia (defined as a resting heart rate of ≥100 bpm).[111] Further, women undergoing adjuvant chemotherapy (n=46) had significantly higher resting heart rate (91±17 bpm) relative to those who had completed therapy (89±16 bpm).[111] Resting heart rate has been shown to be a powerful predictor of future CVD events and survival.

One large prospective study (n=7746) demonstrated that resting heart rate >75 bpm in patients without any evidence of coronary disease had almost a 4-fold increased risk for sudden cardiac death, relative to those who had a resting heart rate of <60 bpm.[112] In addition, a population-based study by Cooney et al. among 10, 519 men and 11, 334 women reported that a 15-beat increase in resting heart rate was associated with a 24% and 32% increase in future CVD-related death among men and women, respectively.[113] Importantly, while resting heart rate is a useful, noninvasive assessment of cardiovascular autonomic tone, resting heart rate only provides a static index of the net effects of autonomic input.[23] For example, resting tachycardia demonstrates a net predominance of sympathetic innervation. However, SNS stimulation, PNS withdrawal, or other combinations of input from both systems, may contribute to this resting heart rate.[23]

2.3.5 Cardiovascular response to exercise

Cardiorespiratory exercise testing provides valuable information regarding cardiovascular health and ANS regulation.[107] In particular, exercise testing is being increasingly used in clinical settings as resting cardiac function testing cannot reliably predict exercise performance and functional capacity.[114] Peak oxygen consumption (VO_{2peak}) evaluated during a maximal exercise test is the gold standard of cardiorespiratory fitness.[114] VO_2 is determined by cellular oxygen demand up to a level that equates to maximal rate of oxygen transport, which then determines VO_2 at its maximum. As VO_2 increases with increasing external work, VO_2 becomes limited by one or more factors including stroke volume, heart rate, or oxygen extraction capability at the tissue level, which may cause VO_2 to plateau despite increasing work rate.[114] This plateau in VO_2 has traditionally been used as the best evidence of VO_{2max}.[114] However, among

clinical populations exhaustion or muscle fatigue may occur prior to a true VO_{2max} value, and thus the term VO_{2peak} is often used instead. Cancer patients have been found to have marked reductions in cardiorespiratory fitness.[115] Among women with breast cancer, VO_{2peak} has been shown to be significantly lower than healthy sedentary controls (ranging from 17-34%, with greater differences among younger women), with a VO_{2peak} <15.0 mL/kg/min significantly predicting all-cause mortality.[111] Overall, exercise intolerance in cancer survivors, including breast cancer, is likely largely influenced by the toxic effects of modern cancer treatments, including chemotherapy.[116]

The heart rate and blood pressure response to an incremental exercise test and recovery rate are also important clinical indicators. Exercise produces a physical stress that leads to inclines in blood pressure and heart rate, which in turn increase cardiac output to meet the metabolic demands of the involved organs, especially the musculature.[105] In the setting of heart disease and autonomic dysfunction, abnormal heart rate and blood pressure responses to exercise may be observed, including failure to appropriately increase heart rate during exercise, defined as chronotropic incompetence, exaggerated or blunted blood pressure responses to exercise, or impaired heart rate recovery following exercise.[107,117] Chronotropic incompetence may reflect either a loss of normal cardiac autonomic control, or failure of the heart to respond to normal autonomic signaling,[107] and is a significant predictor of mortality.[118] A decrease in blood pressure below resting pressure during exercise is a sign of insufficient increase in cardiac output to accommodate exercise-induced systemic vasodilation[114] and has been identified in patients with hypertrophic cardiomyopathy and other cardiac cases.[119] Alternatively, an exaggerated blood pressure response to exercise has been shown to predict future resting

hypertension and cardiac events.[120] Unlike resting blood pressure, elevated exercise-related blood pressure is not well defined. However, a systolic peak blood pressure of >210 mmHg for men and >190 mmHg for women during a maximal exercise test has been defined as a hypertensive test result.[121] In a 2017 systematic review by Keller and colleagues, exaggerated blood pressure responses during exercise testing significantly predicted future hypertension in normotensive patients (18 studies, n=35, 151) and cardiovascular events (11 studies, n=43, 012).[120] Lastly, normal post-exercise recovery is accompanied by changes in autonomic tone, primarily reactivation of the PNS, to gradually return heart rate to resting level.[23] Faster heart rate recovery is typically associated with a better prognosis.[112,122,123] One population-based cohort study by Cole et al. found that heart rate recovery after exercise testing was a strong predictor of all-cause mortality after multivariable adjustment (HR=2.0; 95% CI=15 to 2.7).[123] Another large prospective study conducted by Jouven et al. reported that a heart rate recovery <25 bpm after the first minute of recovery was associated with a relative risk of 2.2 for sudden cardiac death compared with the highest-percentile heart rate recovery group (>40 bpm).[112] Delayed heart rate recovery has also been correlated with exaggerated blood pressure responses.[124] The prognostic significance of exercise-related cardiovascular outcomes in breast cancer patients has been underexplored. However, one prospective cohort of Hodgkin lymphoma patients (n=263) treated with thoracic irradiation demonstrated that abnormal heart rate recovery at one minute (≤12 bpm during active cool down, or ≤18 bpm if passive recovery) significantly correlated with exercise capacity and three-year all-cause mortality,[125] suggesting this relationship exists in cancer survivors as well.

2.3.6 Exercise

Numerous studies have examined the relationship between physical activity, exercise and cardiovascular health. As a result, sedentary lifestyle has been deemed one of five major risk factors for CVD, along with hypertension, abnormal blood lipid values, smoking and obesity.[32] Regular exercise is able to mediate CVD risk through numerous pathways, such as reducing body weight, blood pressure and low density lipoproteins, and increasing exercise tolerance, high density lipoproteins and insulin sensitivity.[32] Exercise training is also a promising non-pharmacological strategy for mitigating ANS dysfunction by altering the neuro-regulatory control of the heart.[107] Endurance trained athletes commonly have lower resting heart rates and more rapid heart rate recovery following exercise relative to sedentary controls.[109,126] Although the exact physiological mechanism has not been confirmed, aerobic exercise is hypothesized to offset autonomic dysfunction by reducing SNS outflow and increasing cardiac PNS (vagal) tone.[21] Human studies that have used autonomic blockade to investigate the effect of endurance training on autonomic balance have consistently found decreased sympathetic control of heart rate with aerobic training.[127,128] In particular, studies that have reported a large increase in VO_{2peak} (>12 mL/kg/min) after endurance training report an increase in parasympathetic control of heart rate.[127,128] Altogether, evidence supports the use of exercise and physical activity as a strategy to improve cardiovascular health and autonomic function.

Several studies have evaluated the effects of exercise on CVD risk including indices of autonomic function, such as resting heart rate and heart rate recovery, in women with breast cancer during and after treatment.[129–136] However, to-date no studies have specifically tested the influence of exercise on these outcomes in women

undergoing taxane-based treatments. In one study of 113 women with breast cancer who completed six months of exercise training 2-3 days/week (n=96 completed treatment, n=17 undergoing chemotherapy or radiation), a significant reduction in resting heart rate occurred in the group of women who had completed breast cancer treatment (from 84±11 to 80±12 bpm, $p<0.05$). Furthermore, in one randomized control trial, breast cancer survivors (n=51) who were randomized to exercise (n=25, three aerobic sessions/week for three months, followed by one session/week until one-year follow-up) experienced significant improvements in heart rate recovery (from 17.6±6.4 to 23.0±8.3 bpm, $p<0.01$) compared to controls (n=26).[134] These improvements directly correlated with improvements in VO_{2peak} ($r=0.58$, $p<0.01$). Several other studies have also demonstrated the positive impact of exercise on blood pressure at rest and during exercise in women with breast cancer, [129,132,137,138] however, most of the evidence supports this effect post-breast cancer treatment. In a randomized control trial evaluating the effect of moderate intensity aerobic exercise performed three days/week for eight weeks in women undergoing breast cancer treatment (n=41), exercise resulted in a significant reduction in resting systolic blood pressure (-5.36±11.49 mmHg, $p=0.04$) and maximal systolic blood pressure during exercise (-11.05±20.9 mmHg, $p=0.02$).[132] However, participants in this trial were undergoing heterogeneous treatment modalities (chemotherapy, radiation or a combination of both). Overall, more evidence outlining the potential cardio-protective effect of exercise concurrent to breast cancer treatment, especially chemotherapy, is warranted.

2.4 Conclusion

In conclusion, exercise training has been shown to be safe, feasible and beneficial

for breast cancer survivors both during and following adjuvant therapy.[24,27] However, there is limited evidence demonstrating the influence of exercise on taxane-specific side effects among women with breast cancer. Of the few studies available, only one small study[75] has exclusively enrolled breast cancer patients receiving taxane-containing chemotherapy. Overall, the rationale that exercise may help mitigate CIPN, one of the most debilitating taxane side effects, justifies further investigation into the potential role of exercise in improving QOL among breast cancer survivors actively undergoing taxane treatment.

2.5 Study objectives and hypotheses

Primary Aim: To compare patient reported CIPN and overall QOL, among early-stage breast cancer patients enrolled in a structured exercise program during taxane chemotherapy relative to usual care, using the using the EORTC QLQ-C30 and CIPN20 subscale.

Secondary Aim: To compare responses to clinical tests of CIPN and self-reported pain in early-stage breast cancer patients enrolled in a structured exercise program during taxane chemotherapy relative to usual care, using vibration sensation and summation of multiple pinprick tests, as well as the Brief Pain Inventory.

Tertiary Aim: To compare cardiovascular outcomes, including blood pressure and heart rate at rest, and during and following submaximal aerobic exercise testing, among women with early-stage breast cancer enrolled in a structured exercise program during taxane chemotherapy relative to usual care.

Relative to usual care, the hypothesis is that structured exercise training during taxane-containing chemotherapy for breast cancer will mitigate patient-reported CIPN symptoms and improve overall QOL (primary aim), prevent onset of new pain and improve responses to clinical tests of CIPN (secondary aim), and maintain or improve cardiovascular outcomes (tertiary aim).

Chapter 3: Methods

3.1 Study participants

Participants were recruited through BCCA oncologist referral, posters and word-of-mouth. All eligible participants received approval from their treating medical oncologist to enroll in the trial. To be included in this trial women had to be >19 years of age, diagnosed with stage I-III breast cancer, scheduled to receive taxane-containing chemotherapy and able to read and write in English. Exclusion criteria included receipt of taxane chemotherapy in a weekly format, diagnosis of stage IV cancer, acute or uncontrolled health conditions including heart disease and respiratory disease, diabetes, a history of neurological disorder, mobility issues that require the use of a mobility aid, body mass index >40 kg/m^2, or previous receipt of chemotherapy or radiation to the chest for a past cancer diagnosis.

3.2 Study design and randomization

This study was a randomized control trial. Randomization was stratified by chemotherapy type to ensure an equal distribution of docetaxel and paclitaxel protocols within each group. Participants were randomized after their baseline assessment to: 1) exercise (EX) or 2) usual care (UC).

The length of the exercise intervention matched the length of the participants' taxane treatment protocol (8-12 weeks, depending on the regimen prescribed). The exercise intervention could begin up to one week prior to the first taxane treatment and ended 2-3 weeks after their last cycle. The exercise prescription included supervised aerobic, resistance and balance exercise training three days per week, as well as home-

based aerobic exercise. For the duration of their taxane treatment, participants randomized to usual care were asked to continue with their usual habits, but were not specifically told to refrain from exercise. Upon chemotherapy completion, the usual care group was offered the same 8-12 week exercise intervention, based on the length of their taxane treatment protocol.

3.3 Exercise training intervention

The exercise prescription was based on previously completed clinical trials by our group (START,[139] CARE,[140] and NExT[141]). These exercise protocols are proven to be efficacious and safe for breast cancer survivors receiving adjuvant chemotherapy and are based on current exercise recommendations for cancer survivors from the American College of Sports Medicine.[142] While shown to be beneficial, these exercise prescriptions, along with the majority of those reported within the exercise-oncology literature, prescribe exercise that linearly increases in intensity and duration. However, chemotherapy received multiple times in 2-3 week cycles can result in fluctuations and accumulations in side effects, such as fatigue. Therefore, linear exercise prescriptions may fail to account for patient-reported and physiological changes during chemotherapy, which may reduce exercise adherence. Therefore, for this study a "chemotherapy-periodized" exercise approach was developed. Periodized exercise training has been shown to be feasible among inactive individuals and is potentially superior to non-periodized training.[143] This exercise training approach was modified for a breast cancer population undergoing chemotherapy (Figure 1). Aerobic and resistance exercise progressed in exercise volume throughout the intervention. However, for the week following chemotherapy, a lower volume (for e.g. aerobic exercise intensity) was

prescribed. This approach aimed to account for anticipated increases in treatment side effects experienced the first week after each chemotherapy cycle.

The aerobic and resistance exercise prescription is outlined in Table 1. Each supervised exercise session began with five minutes of quiet seated rest to allow for the measurement of resting heart rate. Resting heart rate was then used to calculate participants' target aerobic exercise intensities using the heart rate reserve method calculated via: target heart rate = ((age-predicted max heart rate − resting heart rate) × (% intensity) + resting heart rate). The aerobic intervention progressed from 50–75% of heart rate reserve by the eighth week (30-40 minutes in duration per supervised session). The aerobic exercise intensity progression only occurred during non-chemotherapy treatment weeks. In the week following receipt of a chemotherapy treatment, target aerobic exercise intensities were decreased to 50-55% of heart rate reserve (duration was increased to maintain load) to make the exercise prescription more tolerable, as this was when treatment side effects were expected to peak. This pre-emptive decrease in intensity following each treatment was also implemented to encourage participants to attend the supervised exercise sessions despite the possibility of not feeling well.

Participants had the option of using the treadmill, cycle ergometer or elliptical trainer and wore heart rate monitors during all supervised aerobic sessions (Polar Electro Inc., Lake Success, NY) to ensure they reached their target heart rate. A five-minute warm-up and cool down were also enforced. The average heart rate, duration and type of activity were recorded after every session. Following week three, home-based aerobic exercise was also prescribed (up to two days/week) to work toward achieving 150 minutes/week of aerobic exercise by the end of the intervention. Home-based exercise

sessions progressed from 15-30 minutes in duration at a prescribed intensity of 13 using the Borg Rating of Perceived Exertion (RPE) scale (6=no exertion, 20=maximal exertion). Supervised resistance exercise included leg press, seated row, forward reach, triceps extensions and calf raises, using machines, free weights or resistance bands, to target the primary upper and lower body muscle groups. Participants began with one set of 10 repetitions at 50% of their estimated one-repetition maximum (1-RM) and progressed towards two sets of 10-12 repetitions of 65% of 1-RM. The resistance exercise prescription was also periodized according to chemotherapy treatment cycles. During the week of chemotherapy, participants' resistance prescription was reduced to one set of each exercise (Table 1).

Lastly, participants completed two single-legged standing balance exercises. Balance exercises progressed from being performed on a stable surface with support (one hand lightly touching the wall) to being performed on an unstable surface (next to a wall for safety). In addition, targeted hand and foot exercises were performed to increase strength, and potentially blood flood to these areas most at risk of neurotoxic damage and CIPN symptoms. Participants also completed two mat exercises to improve abdominal strength. Participant balance, core and hand and foot exercises are described in detail in Appendices A and B.

3.4 Outcome measures

Unless otherwise noted, all outcome measures were completed at two main time points: 1) Baseline, up to one week prior to the first taxane treatment and 2) End of chemotherapy, 2-3 weeks after the last taxane treatment.

3.4.1 Primary outcome measures: Patient-reported CIPN and QOL

Patient-reported CIPN symptoms:

The EORTC QLQ-CIPN20 subscale was the primary outcome for this study. This subscale was designed to specifically investigate patient-reported CIPN symptoms. The EORTC QLQ-CIPN20 contains 20 items assessing sensory (nine items), motor (eight items) and autonomic symptoms (three items). However, one of the autonomic items only applies to men as it is a question regarding erectile dysfunction, and was therefore not included in this trial. Using a Likert scale participants indicate the level at which they are experiencing sensory, motor and autonomic symptoms within the past week (1="not at all", 2="a little", 3="quite a bit" and 4 ="very much"). All scale scores were linearly converted to a 0-100 scale, with higher scores indicating greater symptom burden.

Overall patient-reported health-related QOL:

In addition to the CIPN20 subscale, the EORTC QLQ-C30 core questionnaire was administered. This questionnaire has been widely used to measure patient-reported health-related QOL among cancer patients.[144] This questionnaire contains an overall global health status/QOL scale, five functional subscales, including physical, role, emotional, social and cognitive functioning, three symptom subscales for pain, nausea and vomiting, and fatigue, and six single items evaluating dyspnea, insomnia, loss of appetite, constipation, diarrhea and financial impact. However, financial impact was not included as an outcome, as this study was primarily interested in evaluating the influence of exercise on physical symptoms. Each item was scored by participants on a scale from 1="not at all" to 4="very much", except for overall global health status/QOL scale, which is scored from 1="very poor" to 7="excellent." All scores were linearly converted to a 0-100 scale. Higher scores for the functional scales and overall QOL indicate better

functioning and QOL, while higher scores for symptom scales indicate greater symptom burden. In addition to the main time points, the EORTC QLQ-C30 and CIPN-20 were administered 0-3 days pre-chemotherapy cycle 4 to assess whether exercise delays the onset of CIPN symptoms.

3.4.2 Secondary outcome measures: Clinical tests of peripheral neuropathy

Current evidence suggests that patient-reported CIPN symptoms in cancer patients are primarily sensory in nature.[12,14] The inclusion of clinical tests of CIPN (i.e. QST) allows for the assessment of changes in sensory-loss and stimulus-evoked symptoms.[145] A short sensory examination of vibration sense and neuropathic pain were performed based on preliminary evidence demonstrating exercise training's ability to potentially prevent changes or improve these senses.[31,74] Examination of vibration sense and temporal summation of pain was performed at the main time points, and 0-3 days pre-chemotherapy cycle 4, to capture changes in CIPN symptom onset and progression.

Vibration sensation:

A standard C 128 Hz tuning fork was used to test vibration sense at three different lower limb landmarks. The vibrating tuning fork was first placed on top of the participant's proximal interphalangeal joint of the toe with the examiner's index finger underneath the joint. The examiner was previously tested to ensure intact vibration sense. With their eyes closed, participants were asked to indicate when they no longer felt the vibration. The examiner then recorded whether the participant reported feeling the vibration stop at the same time as the examiner ('normal'), before the examiner ('impaired'), or if she does not sense the vibration at all ('lacking'). The vibrating tuning fork was also applied to the medial malleolus and inferior pole of the patella. For these

tests, the participant was asked to indicate whether they sensed the vibration and the examiner recorded the response as ‘present’ or ‘absent.’

Pain:

An Owen Mumford Neuropen, Peripheral Neuropathy Screening Device was utilized to standardize a pinprick applied to the end of the big toe 10 times at one-second intervals. The participant was then asked to report whether the sensation of the prick stayed the same, increased, or decreased from the first to the last pinprick. This test is intended to identify temporal summation, referred to as ‘wind-up’, as modestly sharp stimuli may evoke an abnormal painful sensation, referred to as static mechanical hyperalgesia.[145] Alternatively, loss of nociceptors from neuropathy may also cause sensation of sharpness to be diminished in symptomatic areas.[145] These differences may reflect both peripheral and central sensitization.

In addition, the Brief Pain Inventory (BPI), a 14-item questionnaire, was administered to evaluate pain intensity, the level of interference of pain in patient life including, walking, mood, and sleep, pain relief, pain quality and patient perception of cause of pain.

3.4.3 Tertiary outcome measures: Cardiovascular outcomes

Resting heart rate and blood pressure, the heart rate and blood pressure response to submaximal aerobic exercise testing, and heart rate and blood pressure recovery following exercise were evaluated. To measure the cardiovascular response to exercise, participants performed a submaximal incremental exercise test on a cycle ergometer (Upright bike, UBK 835, Precor, Woodinville, WA) to 70% of age-predicted maximal heart rate calculated via: ((207-0.7*age)-resting heart rate)*0.7 + resting heart rate). The

test started at 40 watts (stage one), and increased by 20 watts every three minutes until the target heart rate was reached. Participants were instructed to keep a minimum pedaling speed of 70 revolutions per minute (RPM) throughout the test. The Borg RPE was collected at the end of each stage. The stage in which the target heart rate was reached was then completed before the test was ended. Following the test, participants were asked to rest while seated on the bike for five minutes. Tests were ended prematurely if RPE>17 or symptom limitation occurred (e.g. shortness of breath or leg cramps). Continuous blood pressure and heart rate were measured for two minutes of seated rest on the cycle ergometer prior to exercise testing to calculate resting measures, during the exercise test to calculate the response to exercise, and during a passive recovery period to evaluate recovery using the Finometer Pro (Finapres Medical Systems, Amsterdam, NL).

The Finometer Pro uses an inflatable finger cuff with built-in infrared plethysmography to detect changes in arterial volume. The device contains a small box, which attaches to the wrist and encloses a fast servo-led pressurizing system for the continuous adjustment of cuff pressure according to changes in the plethysmographic output. Using built-in algorithms, the Finometer can measure brachial pressure, correcting for finger pressure, and the hydrostatic height of the finger with respect to the level of the heart. The device has been validated against the mercury sphygomomanometer[146] and is a reliable alternative to invasive intra-arterial readings.[147] To evaluate resting measures and the cardiovascular response to exercise, Finometer data, including systolic and diastolic blood pressure and heart rate, from the last minute of the rest period and at the end of each minute (30-second average) of the exercise test was

evaluated. Due to the small sample size, and varying number of stages completed by participants for each incremental exercise test, data was only evaluated for the first six minutes (i.e., stage one and stage two) of the exercise test. To evaluate heart rate and blood pressure recovery following exercise, heart rate and blood pressure values 60 seconds into the recovery period were examined. Heart rate recovery and blood pressure recovery at 60 seconds was defined as the difference between peak values achieved during exercise testing and values collected after 60 seconds of passive recovery (change in bpm or mmHg). Both peak values and values at 60 seconds into the recovery were calculated based on a five beat average. A five beat average was selected to avoid both selecting an erroneous single value or over-averaging the data and missing the true heart rate and blood pressure values of interest.

3.4.4 Descriptive measures

The following measures were also performed for descriptive purposes.

Body Mass Index: Body weight was measured at each assessment with a digital scale, and height was measured at baseline only using a measuring tape, to calculate body mass index (BMI).

Cancer-related fatigue: The Piper Fatigue scaled was administered to evaluate fatigue. The Piper Fatigue scale contains 22 items with four subscales: behavioral/severity, sensory, cognitive, and affective meaning of subjective fatigue measured on a scale of 0 to 10 (none to extreme fatigue).

Cardiorespiratory fitness: During the incremental exercise test, a portable metabolic cart (Fitmate Pro, Cosmed, Italy) was used to measure VO_2 via indirect calorimetry during the exercise test. The VO_2 measured in the last stage of the submaximal test was then

extrapolated to the participants age-predicted maximal heart rate to gain an estimate of VO_{2peak}.[148]

Handgrip strength: A handgrip dynamometer was used to measure maximum isometric strength of the hand and forearm muscles. Participants were seated with their shoulders adducted, elbows flexed to 90◦, with their forearms in a neutral position. They were then asked to squeeze the dynamometer maximally, alternating between their left and right hands for a total of three times per side. The highest value of the three attempts was selected for participants' surgical and non-surgical sides. If participants had not undergone surgery, their values were categorized based on dominant and non-dominant arms instead.

Lower limb strength: Leg press 1-RM was estimated using a submaximal leg press strength test.[149] The goal of this protocol was to find the weight that can be lifted for 7-10 repetitions, and an established equation was used to estimate the 1-RM based on the weight lifted and number of repetitions achieved.

3.5 Ethics and informed consent

This study received ethical approval through the University of British Columbia Clinical Research Ethics Board. All study participants signed an informed consent form prior to beginning the study. Participants were not remunerated for their participation or reimbursed for expenses related to study participation. Upon study completion, all participants were offered exercise guidelines and an individualized prescription.

3.6 Statistical analysis

Descriptive statistics were used to characterize study participants at baseline for age, demographics, menopausal status, cancer diagnosis and treatment, and comorbid

conditions. Supervised exercise program adherence was defined as adherence to the prescribed session frequency, aerobic exercise intensity and duration, and resistance exercise prescription. Frequency was termed attendance and calculated as the percentage of sessions attended out of the total offered. Adherence to the exercise prescription was calculated as the total percentage of exercise sessions where the target prescription was met out of the total sessions completed. Home-based aerobic exercise adherence was calculated as adherence to the prescribed session frequency, duration and intensity (RPE). All exercise adherence data is reported as mean±SD.

For the assessment of differences between groups and time points for patient-reported symptoms and physiological data, including cardiovascular outcomes and cardiorespiratory fitness, repeated measure analysis of variance (ANOVA) was not an ideal option for this small data set as it excludes any cases with a missing data point. Repeated-measures ANOVA is also not ideal for data that does not follow a normal distribution or have equal variance, which is common with patient-reported data. Therefore, a generalized linear mixed model (GLM) was selected using SPSS version 23.0 (IBM, Corporation, Armonk, New York) to evaluate the change in QOL and patient-reported CIPN symptoms between baseline, pre-chemotherapy cycle 4 and end of chemotherapy (primary aim). A GLM uses a "link function" to define the relationship between the systematic component of the data and the dependent variable such that normality and equal variances are not required.[150] For these analyses, an "identity" link function, that does not transform the data, was selected. To evaluate physiological data, including cardiovascular outcomes (tertiary outcome) as well as estimated VO_{2peak} (descriptive outcome) that passed testing for normality, a linear mixed methods model

was selected. For all of the above outcomes, time point was selected as a repeated measure and the model included group and time as main effects as well as a group by time interaction. Because the group by time interaction was hypothesized, the main effects were only interpreted if the interaction was not significant. In case of an interaction effect, pairwise differences were investigated using contrasts for hypothesized differences only. However, it is recommended that non-significant interaction actions should not preclude comparisons between treatment and control groups, especially when there is biological relevance for the potential difference.[151] Therefore, in order to minimize multiple comparisons but not miss potential real effects, pairwise comparisons were performed for non-significant interactions, but only for variables potentially explanatory for other significant effects detected. For all interaction effects, main effects and pairwise contrasts, the result was considered significant if $p<0.05$.

In addition, statistically significant differences in QOL scores may not translate into clinically meaningful differences. Therefore, minimally clinically meaningful differences between groups can be established relative to a standard deviation or to the questionnaire scale range. Specifically, a change of 5-10% of the scale range has been claimed as perceptible to patients as a meaningful difference.[152] Therefore, changes in the EORTC QLQ-C30 core questionnaire overall QOL, functional and symptom subscales were also evaluated between time points based on this established definition. Mean changes in scores were calculated between baseline, 0-3 days pre-chemotherapy cycle 4 and end of chemotherapy. A mean change of $\geq$5% was considered a small clinically meaningful change and $\geq$10% was considered a moderate change.[152]

The Fischer's exact test was used to detect differences in responses to the clinical tests of CIPN between groups at each time point. This test was selected as it is used to detect a relationship between two categorical variables. Due to the small sample size, the Fischer's exact test was selected over a chi-squared test for independence as it corrects for cells that have an expected count of less than five. For this study this included group assignment and responses to vibration sensation or pinprick summation testing. Responses for vibration threshold were collapsed into two levels for the interphalangeal joint including, "normal" or "impaired." Impaired responses included responses where participants stopped feeling the vibration sensation before the examiner, or could not feel the vibration sensation at all (absent). Responses for vibration sensation at the medial malleolus and patella were recorded as "normal" or "absent." Responses for the pinprick summation test were also collapsed into two levels, including "normal" or "altered." Altered responses for the pinprick summation tests included responses where participants reported either increased or diminished sensations. SPSS version 23.0 (IBM, Corporation, Armonk, New York) was used to perform the analysis and statistically significant outcomes were defined as $p<0.05$.

For all other measures including patient-reported pain (tertiary outcome) and descriptive outcomes including muscular strength (leg press and hang grip strength) and patient-reported fatigue, repeated measures ANCOVA was used to evaluate the difference in mean scores between baseline and end of chemotherapy between groups. Repeated measures ANCOVA was selected over repeated measures ANOVA to allow for baseline values to be used as a covariate. SPSS version 23.0 (IBM, Corporation, Armonk,

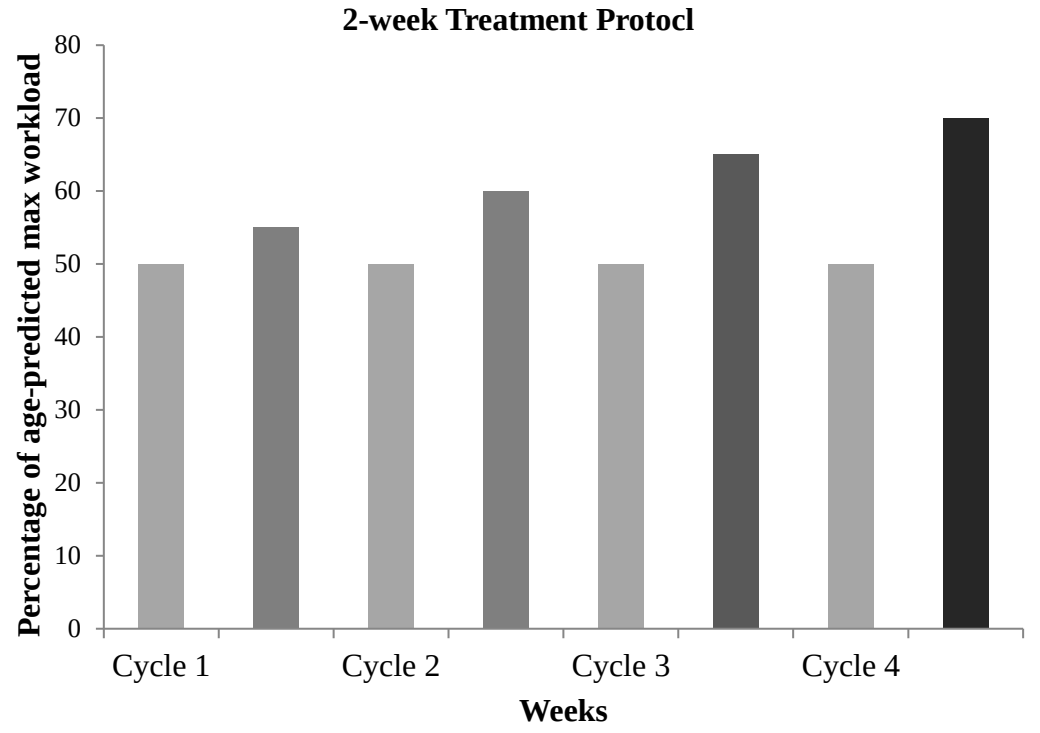
New York) was used to perform the analysis and statistically significant outcomes were defined as $p<0.05$.

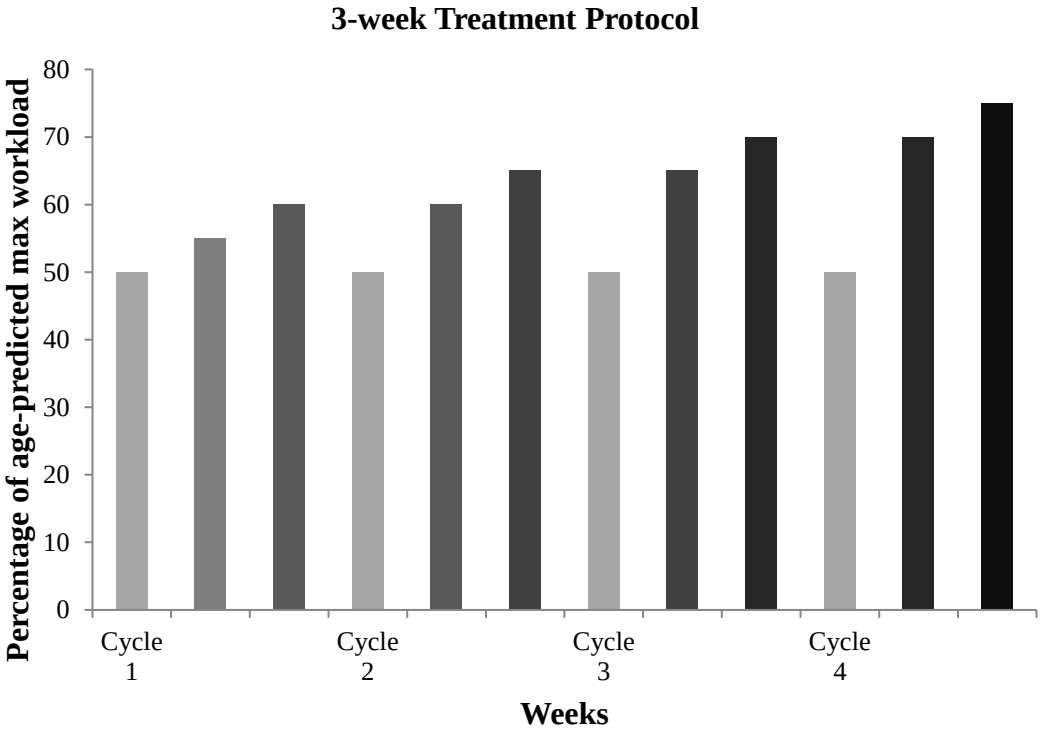
Table 1: Supervised aerobic and resistance exercise prescription

		Aerobic Prescription			Resistance Prescription			
2-week Protocol	**Week**	**Intensity (%HRR)**	**Time (min)**	**Load**	**Intensity (%1-RM)**	**Sets**	**Reps**	**Load**
	0	50%	25	12.5	50%	1	10	5.0
Cycle 1	1	50%	25	12.5	50%	1	10	5.0
	2	55%	30	16.5	50%	2	10	10.0
Cycle 2	3	50%	40	20.0	55%	1	10	5.5
	4	60%	35	21.0	55%	2	10	11.0
Cycle 3	5	50%	40	20.0	60%	1	10	6.0
	6	65%	35	22.8	60%	2	10	12.0
Cycle 4	7	50%	40	20.0	65%	1	10	6.5
	8	70%	35	24.5	65%	2	10	13.0
3-week Protocol	**Week**	**Intensity (%HRR)**	**Time (min)**	**Load**	**Intensity (%1-RM)**	**Sets**	**Reps**	**Load**
	0	50%	25	12.5	50%	1	10	5.0
Cycle 1	1	50%	25	12.5	50%	1	10	5.0
	2	55%	30	16.5	50%	2	10	10.0
	3	60%	30	18.0	55%	2	10	11.0
Cycle 2	4	50%	40	20.0	55%	1	10	5.5
	5	60%	35	21.0	55%	2	10	11.0
	6	65%	35	22.8	60%	2	10	12.0
Cycle 3	7	50%	40	20.0	60%	1	10	6.0
	8	65%	35	22.8	60%	2	10	12.0
	9	70%	35	24.5	65%	2	10	13.0
Cycle 4	10	50%	40	20.0	65%	1	10	6.5
	11	70%	35	24.5	65%	2	10	13.0
	12	75%	35	26.3	70%	2	10	14.0

%HRR: percentage of age-predicted heart rate reserve %1-RM: percentage of estimated 1-repetition maximum

Figure 1: "Chemotherapy-periodized" aerobic exercise prescription





Chapter 4: Results

4.1 Participants

Fifty-six patients were referred to the study (Figure 2). Of these, 13 were ineligible, two did not respond regarding study enrollment, and 13 declined to participate. In total, 28 women were baseline tested and randomized. Following enrollment, one participant requested withdrawal due to personal reasons and three participants became ineligible. Of those who became ineligible, one participant developed metastatic disease and two participants had their chemotherapy treatment protocols changed to either anthracycline chemotherapy or weekly paclitaxel after their first taxane cycle, due to severe treatment side effects. Participants who became ineligible during the study were still offered an immediate or delayed supervised exercise program; however, their results were excluded from the final analysis. Altogether, 24 women completed the study, with 11 women randomized to EX and 13 women randomized to UC.

Baseline demographic characteristics are described in Table 2. Mean age for participants was 49.5±10.2 years and the majority of participants were Caucasian, married or in a common-law partnership, and had postsecondary education. Participant cancer and medical characteristics are described in Table 3. The majority of participants were pre-menopausal (n=12, 50%), had stage II breast cancer (n=11, 46%) and received adjuvant chemotherapy (n=16, 67%). Four cycles of 60 mg/m^2 of doxorubicin and 600 mg/m^2 of cyclophosphamide followed by four cycles of 175 mg/m^2 of paclitaxel (+/- trastuzumab) was the most common treatment protocol (n=18, 75%). Four cycles of 600 mg/m^2 of cyclophosphamide and 75 mg/m^2 of docetaxel (+/- trastuzumab) was received by n=5 participants (21%) and four cycles of 60 mg/m^2 of doxorubicin and 600 mg/m^2 of

cyclophosphamide followed by four cycles of 100 mg/m^2 of docetaxel (+/- trastuzumab) was received by n=1 participant (4%). The most commonly reported comorbidities in both groups were arthritis (n=6, 25%) and asthma (n=4, 17%).

4.2 Exercise program adherence

Exercise intervention adherence is summarized in Table 4. Mean exercise program length, based on the length of each participant's taxane chemotherapy protocol, was 10.8±2.1 weeks. In total, 348 supervised exercise sessions were offered. Supervised attendance as a mean of each participant's attendance was 77±24%. Adherence to the supervised aerobic exercise prescription for intensity and duration was 74±31% and 85±20%, respectively. Adherence to the resistance exercise prescription was 71±36%. Adherence to the prescribed home-based aerobic exercise session frequency was 80±35%. The majority of participants exceeded the prescribed home-based aerobic exercise duration, with a mean adherence of 111±35%. Adherence to prescribed home-based exercise intensity based on a target RPE was 76±19% (mean RPE: 12.0±0.8). Out of a total 11 participants, eight participants (73%) achieved >70% supervised exercise attendance and nine participants (82%) achieved >70% adherence to home-based exercise session frequency. No serious adverse events occurred during any of the supervised or home-based exercise sessions. Altogether, the exercise intervention was delivered safely and effectively. Adherence was also higher than a previous recent study that delivered exercise programming during chemotherapy to women with a breast cancer diagnosis in Vancouver.[141]

4.3 Patient-reported CIPN symptoms

Change in patient-reported CIPN symptoms using the CIPN20 subscale are depicted in Figure 3. No significant interaction between group and time was detected for any of the CIPN20 subscales. For the sensory symptom subscale, there was a significant main effect of time ($p<0.01$). A significant increase in mean sensory symptoms in both groups between baseline (5.2±1.4) and 0-3 days pre-chemotherapy cycle 4 (20.0±4.9, $p<0.01$), and baseline and end of chemotherapy (28.0±4.9, $p<0.01$) was observed. There was also a significant main effect of group on sensory symptoms ($p=0.04$). Mean sensory symptoms were significantly lower among exercisers relative to the usual care group (EX: 13.4±3.0, UC: 22.1±2.8, $p=0.04$). Pairwise contrasts revealed a borderline significant difference between groups at 0-3 days pre-chemotherapy cycle 4 (EX: 13.5±5.4, UC: 26.5±4.9, $p=0.08$), however, this between group difference was less apparent by the end of chemotherapy (EX: 23.6±7.1, UC: 32.8±6.8, $p=0.4$). For the motor symptom subscale, a significant main effect of time was detected ($p=0.04$). Mean motor symptoms were significantly higher by the end of chemotherapy relative to baseline in both groups (from 6.3±2.2 to 16.5±3.2, $p=0.01$), with no significant differences between groups at any time point. No significant main effects were detected for group or time for the autonomic symptom subscale. Overall, sensory and motor symptoms worsened over time in both groups, with symptoms peaking at the end of chemotherapy. A modest trend in fewer sensory symptoms was observed among those randomized to exercise.

4.4 Patient-reported QOL

There was no significant interaction between group and time for any of the EORTC QLQ-C30 QOL, functional or symptom scales evaluated for health-related QOL

(Table 5). There was a significant main effect of group on social functioning ($p=0.02$), with pairwise contrasts revealing significantly higher social functioning in the exercise group compared to the usual care group by the end of chemotherapy (EX: 77.3±7.7, UC: 55.6±7.4, $p<0.05$). There was also a significant main effect of time on nausea and vomiting ($p=0.02$) with pairwise contrasts revealing a significant reduction in symptoms from baseline (17.93±3.7) to 0-3 days pre-chemotherapy cycle 4 in both groups (6.0±1.8, $p<0.01$). A significant main effect of group was found for appetite symptoms ($p<0.02$), where mean values for the usual care group were significantly higher, indicating worse symptoms, at baseline (UC: 30.6±4.9, EX: 12.1±5.1, $p=0.01$). There was also a significant main effect of group for constipation ($p<0.01$), but no significant differences between groups were detected following pairwise contrasts. No other significant main effects for group or time were detected for any other outcomes.

Clinically meaningful changes in overall patient reported QOL and subscales using the EORTC QLQ-C30 are depicted in Figure 4 and Figure 5. A small clinically meaningful improvement in overall QOL was seen among exercisers (+5%) by the end of chemotherapy, while those randomized to usual care had a modest clinically meaningful reduction in overall QOL (-9%). Small to moderate clinically meaningful decreases were also observed in three of the functional subscales by the end of chemotherapy in both groups including physical functioning (EX: -6%, UC: -12%), role functioning (EX: -17%, UC: -8%) and cognitive functioning (EX: -14%, UC: -17%). For the social functioning subscale, a moderate clinically meaningful decrease was observed in the usual care group only (EX: +3%, UC: -10%). For the symptom subscales, clinically meaningful changes were observed in both groups by the end of chemotherapy for nausea and vomiting (EX: -

6%, UC: -10%), dyspnea (EX: +15%, UC: -6%) and insomnia (EX: +18%, UC: +11%). In the usual care group only, there was a clinically meaningful increase in pain (EX: 0%, UC: +19%) and fatigue (EX: +3%, UC: +9%), and decrease in appetite symptoms (EX: 0%, UC: -14%) by the end of chemotherapy. In the exercise group only, a small clinically meaningful increase in diarrhea symptoms was observed (EX: +6%, UC: 0%).

4.5 Responses to clinical neuropathy tests and patient-reported pain

Two participants did not complete the summation of multiple pinprick testing for any of the time points as they felt the test was too painful. In addition, four participants are missing data for the 0-3 days pre-chemotherapy cycle 4 time point. Two of these individuals had their fourth taxane treatment cycle cancelled and thus, end of chemotherapy testing was performed instead. One individual refused to come in for testing due to increased treatment side effects and the other could not attend due to personal reasons.

No significant differences between groups existed at baseline for any of the clinical neuropathy test outcomes. At the pre-chemotherapy cycle 4 time point, there was a significantly higher proportion of participants in the usual care group who reported an impaired response to vibration threshold testing for the left interphalangeal joint (EX: 10%, UC: 80%, $p<0.01$). This relationship was on the border of significance for the right interphalangeal joint at the same time point (EX: 10%, UC: 60%, $p=0.06$). By the end of chemotherapy, there was no significant difference between groups for impaired vibration threshold responses for the left interphalangeal joint (EX: 46% UC: 69%, $p=0.4$) or right interphalangeal joint (EX: 36%, UC: 46%, $p=0.7$). No significant differences were found between groups for vibration testing at the medial malleolus and patella. Only one usual

care group participant had a positive response for vibration sensation for the left malleolus at the pre-chemotherapy cycle 4 time point. For the summation of multiple pinprick testing, no significant differences were detected between groups for any of the time points (Figure 7). In addition, there were no significant differences between groups in self-reported pain (Table 6).

4.6 Resting heart rate and blood pressure

Resting heart rate and blood pressure values are reported in Table 7. There were no group differences in resting diastolic or systolic blood pressure. There was a significant group by time interaction for resting heart rate ($p<0.01$). By the end of chemotherapy, resting heart rate had decreased in the exercise group (from 81±3 to 71±2 bpm) and was significantly lower than the usual care group (-6±3 bpm, $p<0.05$).

4.7 Heart rate and blood pressure response to exercise

Incremental exercise test data was evaluated for all participants except for two participants at baseline and three participants at the end of chemotherapy. One participant was unable to maintain the 70 RPM requirement during the incremental exercise test and was therefore excluded for both time points. Three other tests had data deemed unusable due to excessive noise in the Finometer Pro heart rate and blood pressure output.

The blood pressure response to exercise is depicted in Figure 8. No significant differences in blood pressure during exercise testing existed between groups at baseline. There was a significant main effect for time for systolic blood pressure at minute 4 ($p<0.01$) and minute 5 ($p=0.02$) of the exercise test. By the end of chemotherapy, the usual care group had higher systolic blood pressure at minute 4 (EX: 141±7 mmHg, UC:

155±6 mmHg, p=0.2) and minute 5 (EX: 142±7 mmHg, UC: 156±6 mmHg, p=0.1), although this difference did not reach statistical significance. There was a significant group by time interaction for diastolic blood pressure for minutes 2-5 of the exercise test (all $p<0.05$). Pairwise contrasts revealed a trend towards higher diastolic blood pressure at the end of chemotherapy in the usual care group at minute 4 (EX: 80±3 mmHg, UC: 87±3 mmHg, p=0.1) and minute 5 (EX: 80±3 mmHg, UC: 87±3 mmHg, p=0.1). Altogether, while no significant pairwise differences existed for hypothesized outcomes, a trend towards an increased blood pressure response was observed in the usual care group during submaximal exercise testing by the end of chemotherapy. This increased blood pressure response appeared to be attenuated by exercise training.

The heart rate response to exercise is depicted in Figure 9. There were no significant differences in heart rate during exercise at baseline. There was a significant interaction effect for heart rate at minute 3 of the exercise test ($p<0.05$) and a significant main effect of time for all other minutes of the exercise test (all $p<0.05$). Mean heart rate was significantly lower in the exercise group relative to the usual care group by the end of chemotherapy for all minutes examined during the exercise test: minute 1 (EX: 95±3 bpm, UC: 106±3 bpm, $p<0.01$), minute 2 (EX: 98±3 bpm, UC: 113±3 bpm, $p<0.01$), minute 3 (EX: 98±3 bpm, UC: 113±3 bpm, $p<0.01$), minute 4 (EX: 104±4 bpm, UC: 120±3 bpm, $p<0.01$), minute 5 (EX: 108±5 bpm, UC: 124±3 bpm $p<0.01$) and minute 6 (EX: 110±5 bpm, UC: 128±4 bpm, $p<0.01$). Overall, exercise training resulted in a significantly lower heart rate response during submaximal exercise testing relative to usual care.

4.8 Heart rate and blood pressure recovery after exercise

Heart rate and blood pressure recovery are depicted in Figure 10. There were no significant differences between groups for systolic and diastolic blood pressure recovery at 60 seconds following submaximal exercise testing. However, there was a significant main effect of time ($p=0.02$) and a borderline significant interaction between group and time ($p=0.06$) for heart rate recovery. Heart rate recovery was significantly greater in the exercise group compared to the usual care group by the end of chemotherapy (EX: 53±4 bpm, UC: 40±3 bpm, $p=0.02$). Overall, exercise training appeared to result in faster heart rate recovery at 60 seconds following submaximal exercise testing.

4.9 Physical fitness

Changes in BMI and physical fitness are reported in Table 8. There were no significant differences in estimated $VO_{2peak,}$ estimated leg press strength, maximal handgrip strength or BMI.

4.10 Patient-reported fatigue

There were no significant differences in patient-reported fatigue (Table 9).

4.10 Tables and Figures

Table 2: Participant demographics

	Total n=24	**Exercise n=11**	**Usual Care n=13**
Age (years) (mean±SD)	49.5±10.2	51.1±8.5	48.1±11.6
Marital Status (n (%))			
Married	17 (71%)	8 (73%)	9 (69%)
Living as Common-law	6 (25%)	2 (18%)	4 (31%)
Single	1 (4%)	1 (9%)	0 (0%)
Ethnicity (n (%))			
White	16 (67%)	8 (73%)	8 (62%)
Asian	7 (29%)	3 (27%)	4 (31%)
Other	1 (4%)	0 (0%)	1 (8%)
Education (n (%))			
High School Diploma/Some University	5 (21%)	3 (27%)	2 (15%)
Technical/Community College	5 (21%)	2 (18%)	3 (23%)
Bachelor's Degree	9 (38%)	4 (36%)	5 (38%)
>Bachelor's Degree	4 (17%)	2 (18%)	2 (15%)
Prefer not to answer	1 (4%)	0 (0%)	1 (8%)
Pre-diagnosis working status (n (%))			
Full-time	12 (50%)	6 (55%)	6 (46%)
Part-time	5 (21%)	1 (9%)	4 (31%)
Maternity Leave	1 (4%)	1 (9%)	0 (0%)
Homemaker/Retired	2 (8%)	0 (0%)	2 (15%)
Short-term/Long-term Disability	2 (8%)	2 (18%)	0 (0%)
Not working/Unemployed	2 (8%)	1 (9%)	1 (8%)
Income (n (%))			
$20,000-$39,999	2 (8%)	1 (9%)	1 (8%)
$40,000-$59,999	2 (8%)	0 (0%)	2 (15%)
$60,000-$79,999	1 (4%)	1 (9%)	0 (0%)
$80,000-99,999	3 (13%)	2 (18%)	1 (8%)
>$100,000	12 (50%)	5 (46%)	7 (54%)
Prefer not to answer	4 (17%)	2 (18%)	2 (15%)

Table 3: Participant cancer and medical characteristics

	Total n=24	Exercise n=11	Usual Care n=13
Comorbidities (n (%))			
Heart disease	3 (13%)	1 (9%)	2 (15%)
Stroke	2 (8%)	1 (9%)	1 (8%)
Diabetes	2 (8%)	1 (9%)	1 (8%)
Asthma/lung disease	4 (17%)	2 (18%)	2 (15%)
Arthritis	6 (25%)	3 (27%)	3 (23%)
Fibromyalgia	3 (13%)	2 (18%)	1 (8%)
Hip or joint replacement	4 (17%)	2 (18%)	2 (15%)
Osteoporosis	1 (4%)	1 (9%)	0 (0%)
Hypertension	3 (13%)	1 (9%)	2 (15%)
Menopausal Status (n (%))			
Pre-menopausal	12 (50%)	5 (45%)	7 (54%)
Peri-menopausal	2 (8%)	0 (0%)	2 (15%)
Post-menopausal	10 (42%)	6 (55%)	4 (31%)
Cancer Stage (n (%))			
I	5 (21%)	1 (9%)	4 (31%)
II	11 (46%)	4 (36%)	7 (54%)
III	6 (25%)	4 (36%)	2 (15%)
Unknown	2 (8%)	2 (18%)	0 (0%)
Chemotherapy timing (n (%))			
Adjuvant	16 (67%)	8 (73%)	8 (62%)
Neoadjuvant	8 (33%)	3 (27%)	5 (38%)
Cancer side (n (%))			
Right	13 (54%)	6 (55%)	7 (54%)
Left	11 (46%)	5 (45%)	6 (46%)
Primary Surgery (n (%))			
Partial Mastectomy	10 (63%)	3 (38%)	7 (88%)
Total Mastectomy	5 (31%)	4 (50%)	1 (13%)
Bilateral Mastectomy	1 (6%)	1 (13%)	0 (0%)
Chemotherapy protocol (n (%))			
Docetaxel and cyclophosphamide	5 (21%)	2 (18%)	3 (23%)
Doxorubicin, cyclophosphamide followed by paclitaxel	18 (75%)	8 (73%)	10 (77%)
Doxorubicin, cyclophosphamide followed by docetaxel	1 (4%)	1 (9%)	0 (0%)

Table 4: Exercise intervention adherence

Supervised Exercise (n=11)	**(mean±SD)**
Session Frequency (Attendance)	77±24%
Aerobic Exercise Intensity	74±31%
Aerobic Exercise Duration	85±20%
Resistance Exercise Prescription	71±36%
Home Exercise (n=11)	
Session Frequency (Attendance)	80±35%
Aerobic Exercise Duration	111±35%
Aerobic Exercise Intensity	76±19%
Average Rating of Perceived Exertion	12.0±0.8

Table 5: EORTC QLQ-C30 QOL, functional and symptom scales

Outcome	Group	Baseline	Pre-chemo Cycle 4	End of Chemo	Time p-value	Group p-value	Group*Time p-value
Total Quality of Life	Exercise	55.3±5.3	57.1±5.7	60.6±5.0	p=0.7	p=0.3	p=0.3
	Usual Care	59.7±5.1	49.3±5.1	50.7±4.8			
Physical	Exercise	86.7±5.0	85.3±4.5	81.21±5.0	p=0.2	p=0.2	p=0.5
Functioning	Usual Care	87.8±4.7	76.1±4.1	75.6±4.8			
Role Functioning	Exercise	75.8±8.5	56.7±8.8	59.1±8.3	p=0.2	p=0.1	p=0.7
	Usual Care	56.9±8.1	52.8±8.1	48.6±8.0			
Emotional	Exercise	72.0±6.1	74.2±5.3	70.5±5.2	p=0.9	p=0.3	p=0.7
Functioning	Usual Care	70.8±5.9	64.6±4.9	67.4±4.9			
Social Functioning	Exercise	74.2±6.2	68.3±6.4	77.3±7.7‡	p=0.7	p=0.02*	p=0.5
	Usual Care	65.3±5.9	61.1±5.9	55.6±7.4‡			
Cognitive	Exercise	75.8±6.2	66.7±5.6	62.1±6.9	p=0.06	p=0.4	p=0.1
Functioning	Usual Care	73.6±5.9	62.5±5.1	56.9±6.6			
Fatigue	Exercise	41.4±7.0	46.7±6.0	44.4±7.2	p=0.7	p=0.2	p=0.6
	Usual Care	48.1±6.7	46.3±5.4	57.4±6.8			
Nausea/Vomiting	Exercise	13.6±5.4	5.0±2.6‡	7.6±5.0	p=0.02*	p=0.2	p=0.7
	Usual Care	22.2±5.2	6.9±2.4‡	12.5±4.8			
Pain	Exercise	20.8±8.7	35.7±9.4	20.4±7.6	p=0.4	p=0.8	p=0.2
	Usual Care	19.7±7.4	24.1±8.3	38.3±7.2			
Dyspnea	Exercise	6.1±5.5	23.3±7.0	21.2±6.0	p=0.4	p=0.5	p=0.2
	Usual Care	22.2±5.3	22.2±6.4	16.7±5.8			
Insomnia	Exercise	36.4±8.1	36.7±8.8	54.5±8.6	p=0.2	p=0.2	p=0.7
	Usual Care	44.4±7.7	52.8±8.0	55.6±8.2			
Appetite	Exercise	12.1±5.1‡	10.0±5.3	12.1±5.2	p=0.2	p=0.02*	p=0.3
	Usual Care	30.6±4.9‡	16.7±4.9	16.7±4.9			
Constipation	Exercise	9.1±8.2	6.7±6.0	12.1±6.3	p=0.5	p=0.01*	p=0.9
	Usual Care	27.8±7.8	19.4±5.5	27.8±6.0			
Diarrhea	Exercise	6.1±5.6	6.7±4.6	12.1±6.0	p=0.4	p=0.2	p=0.7
	Usual Care	16.7±5.4	8.3±4.2	16.7±5.8			

Data are mean±SE. ‡Significantly different between groups ($p<0.05$). ‡Significantly different from baseline ($p<0.01$).

Table 6: Patient-reported pain

	Group	Baseline	End of Chemotherapy	p-value
Worst Pain	Exercise	1.5±1.7[c]	2.6±2.1[c]	p=0.3
	Usual Care	3.8±3.5[b]	4.5±1.9[c]	
Average	Exercise	1.0±1.2[a]	1.8±1.9	p=0.4
	Usual Care	2.4±1.9[b]	3.2±2.5	

Results are from the Brief Pain Inventory. Data displayed as mean±SD. [a]n=9, [b]n=12 [c]n=10

Table 7: Resting heart rate and blood pressure

	Group	Baseline	End of Chemotherapy	Mean Change	Group*Time p-value
Systolic Blood Pressure (mmHg)	Exercise	130±5	122±7	-8	p=0.6
	Usual Care	120±4	115±6	-5	
Diastolic Blood Pressure (mmHg)	Exercise	72±2	70±3	-2	p=0.4
	Usual Care	66±2	68±3	2	
Heart Rate (bpm)	Exercise	81±3	71±2[‡]	-10	p<0.01*
	Usual Care	78±3	77±2[‡]	-1	

Data displayed as mean±SE.*Significant group by time interaction. [‡]Significantly different between groups (p<0.05)

Table 8: Physical fitness

	Group	Baseline	End of Chemotherapy	Change	Group*Time p-value
BMI (kg/m^2)	Exercise	26.7±1.6	27.0±1.6	0.3	p=0.9
	Usual Care	24.0±1.5	24.5±1.4	0.5	
VO_{2peak} (mL/kg/min)	Exercise	26.0±2.0	28.8±1.6	2.8	p=0.6
	Usual Care	25.4±1.9	26.8±1.5	1.4	
Leg Press 1-RM (lbs)	Exercise	228±28	233±22	5	p=0.8
	Usual Care	214±26	208±21	-6	
Handgrip Strength (lbs)					
Surgical/Non-dominant	Exercise	21.1±1.2	20.6±1.3	-0.5	p=0.8
	Usual Care	22.5±1.5	21.2±1.2	-1.3	
Non-surgical/Dominant	Exercise	23.1±1.5	22.2±1.3	-0.9	p=0.9
	Usual Care	23.2±1.4	22.8±1.2	-0.4	

Data displayed as mean±SE.

Table 9: Patient-reported fatigue

	Group	Baseline	End of chemotherapy	p-value
Behavioural/Severity	Exercise	2.4±2.3	3.4±2.6	p=0.53
	Usual Care	3.4±2.1[a]	4.6±2.1[a]	
Affective Meaning	Exercise	3.0±2.4	3.6±2.6	p=0.20
	Usual Care	3.8±2.9[b]	5.4±2.5[b]	
Sensory	Exercise	4.1±2.6	5.1±2.5	p=0.72
	Usual Care	3.4±2.1[c]	4.5±1.5[b]	
Cognitive	Exercise	3.2±2.1	4.6±2.3	p=0.83
	Usual Care	3.2±1.9[b]	4.2±1.9[b]	
Total Fatigue	Exercise	3.1±2.1	4.1±2.3	p=0.44
	Usual Care	3.1±1.8[b]	4.6±1.8	

Results are from the Piper Fatigue Scale. Data displayed as mean±SD. [a]n=9, [b]n=11, [c]n=12

Figure 2: Flow through study

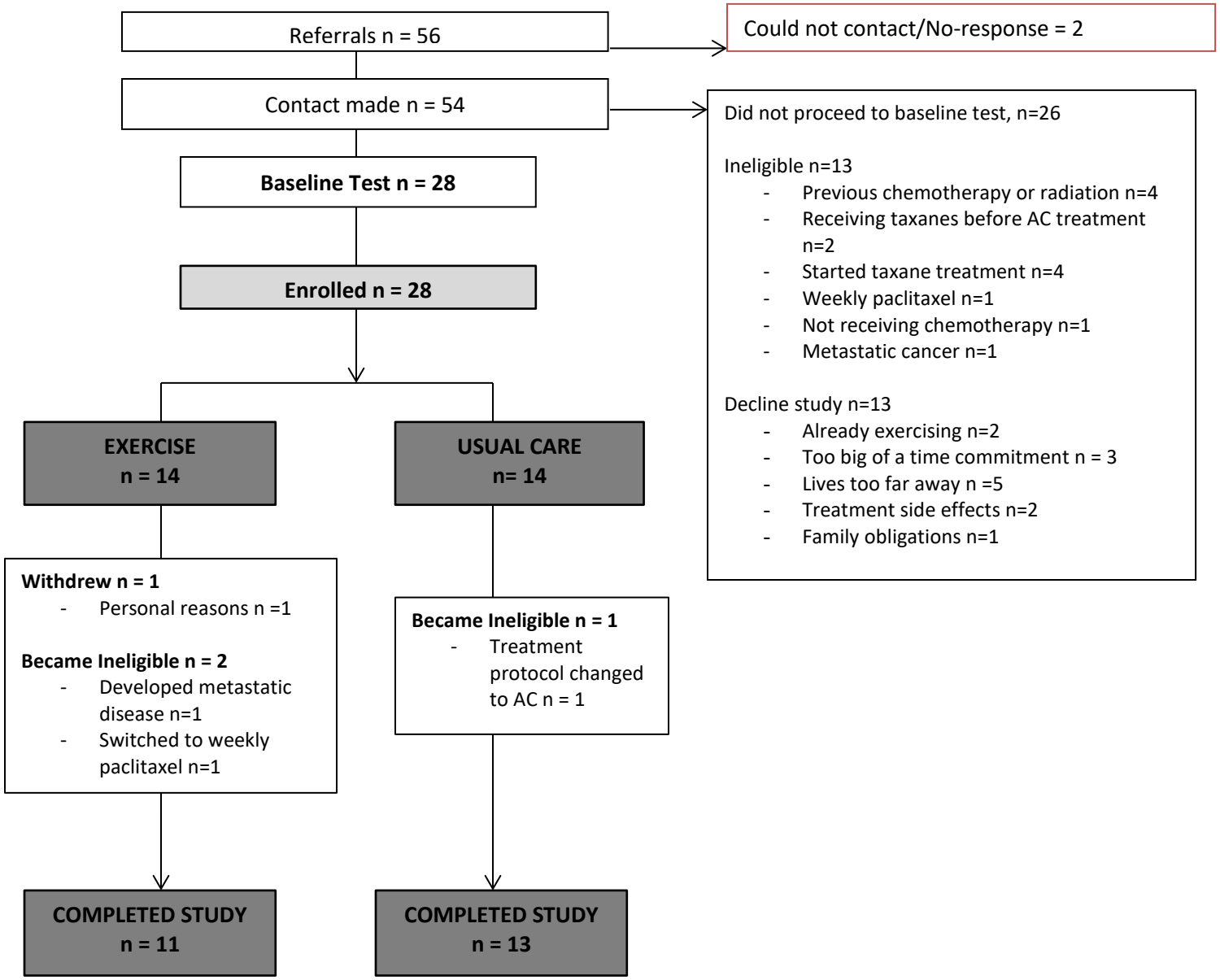
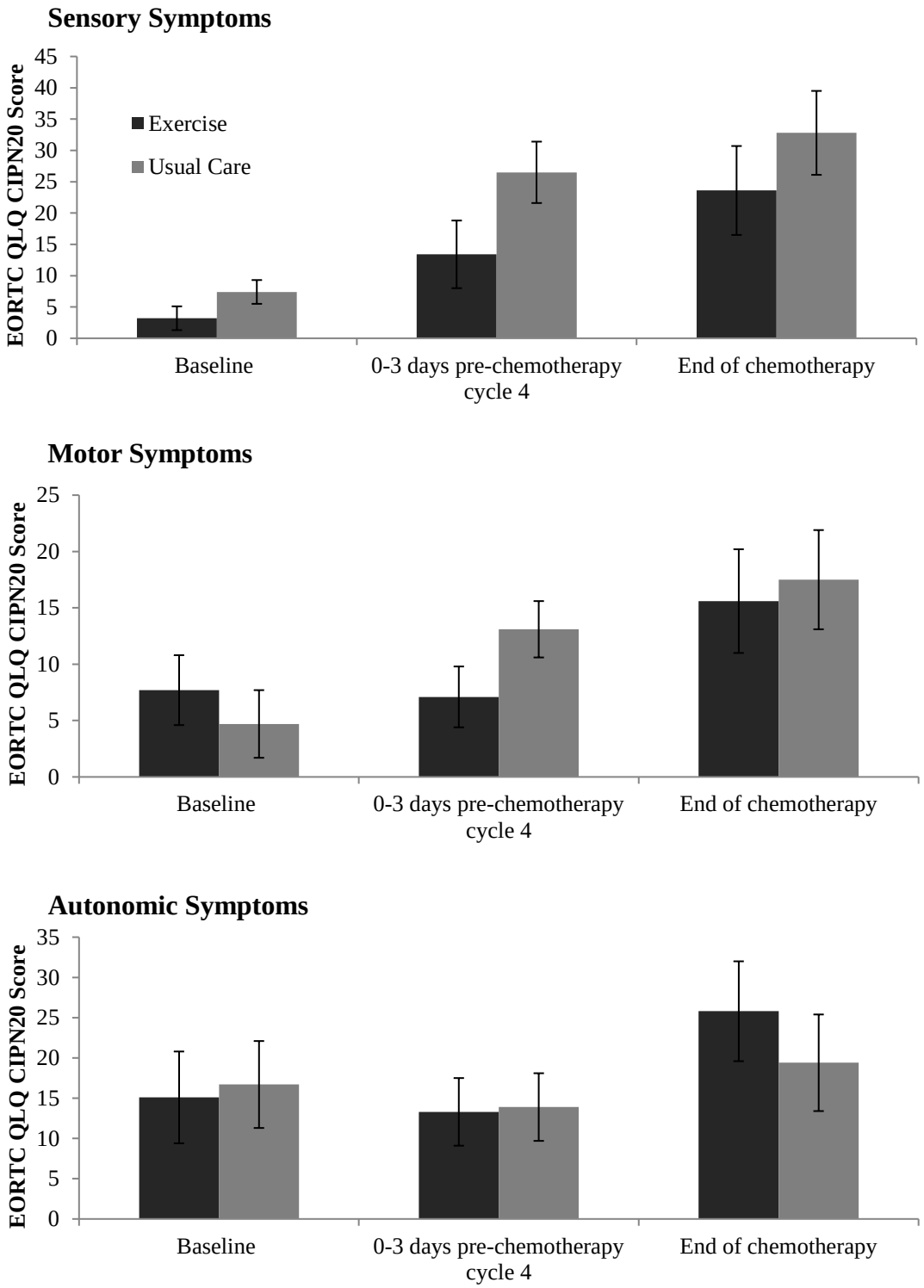
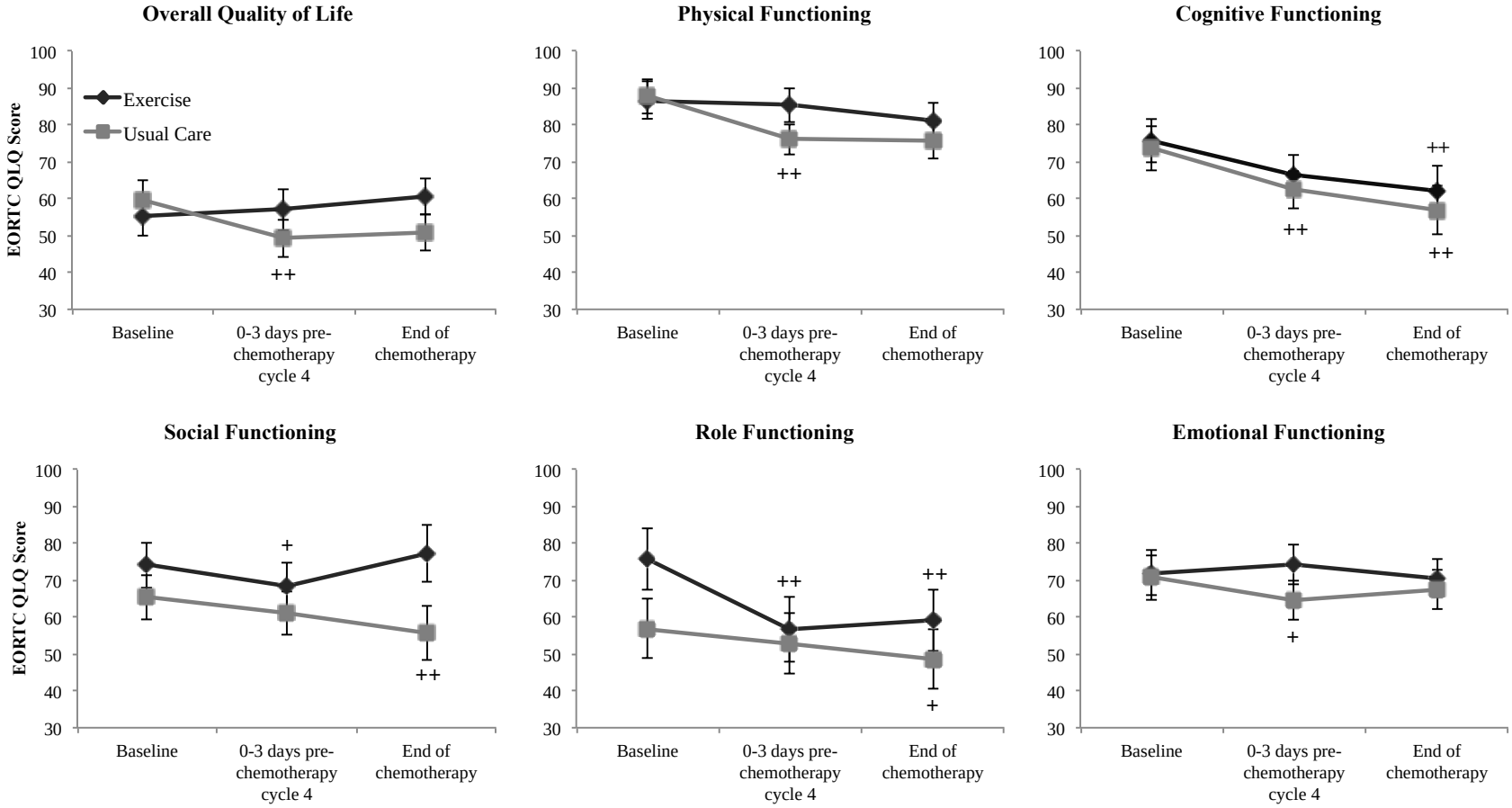


Figure 3: Patient-reported CIPN symptoms



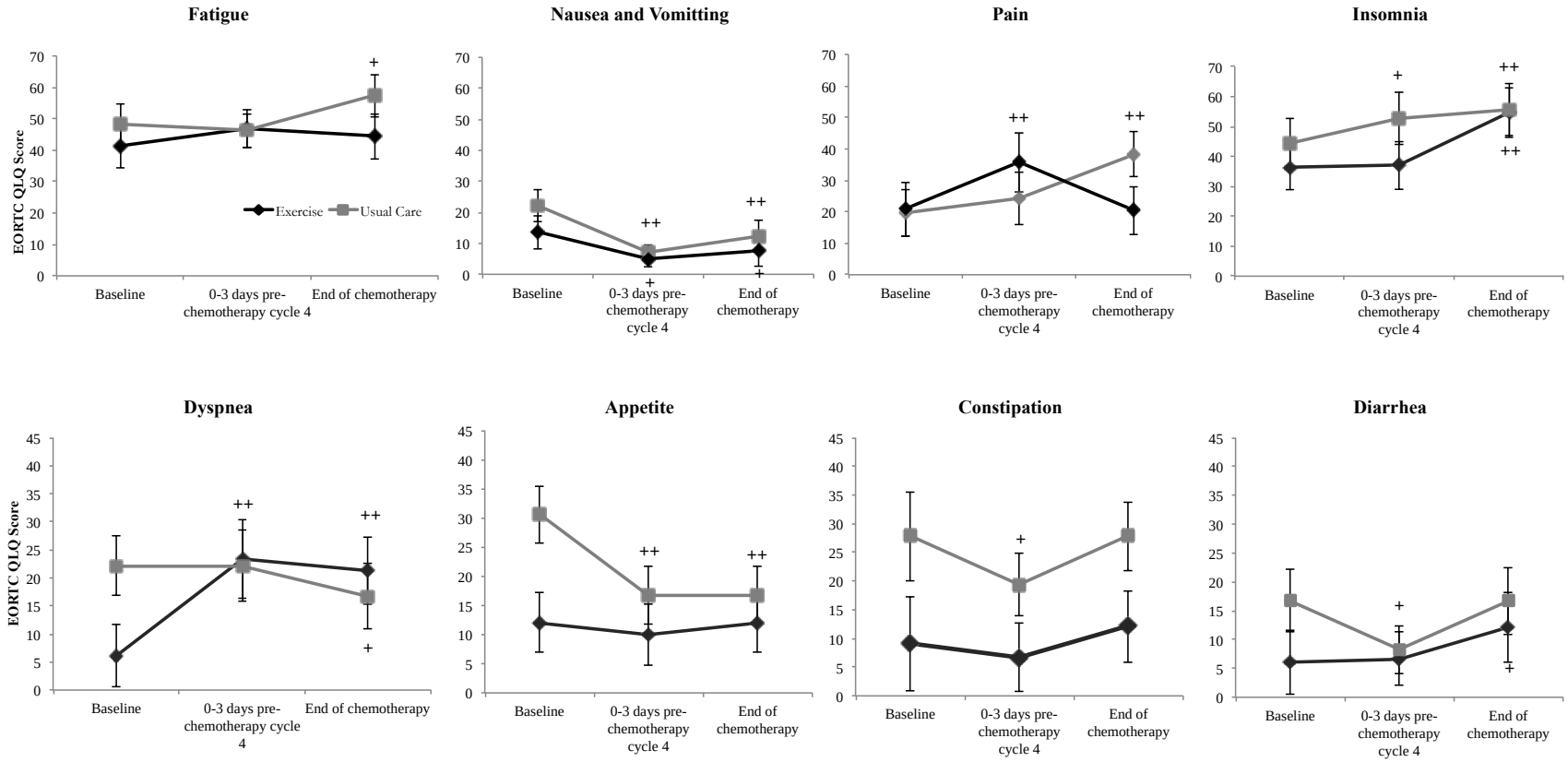
Mean scores (mean±SE) for the EORTC QLQ-CIPN20 subscales for each time point. Significant main effect of time for sensory symptoms ($p<0.01$) and motor symptoms ($p=0.04$). No statistically significant differences between groups for any of the subscales.

Figure 4: Clinically meaningful changes in EORTC QLQ-C30 overall QOL and functional scales



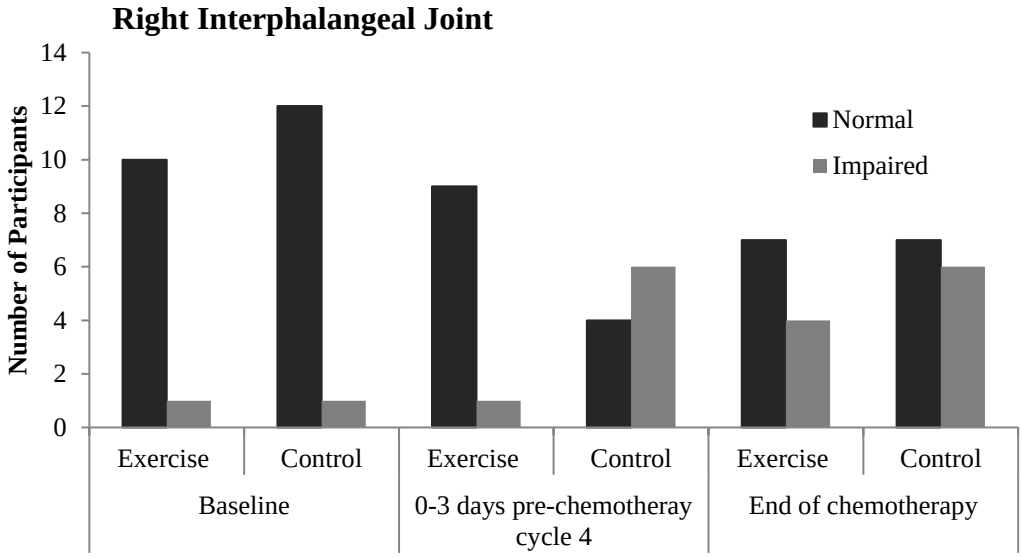
Mean scores (mean±SE) for the EORTC QLQ-C30 overall QOL and functional subscales. Higher scores indicate higher overall QOL or functioning. Clinically meaningful changes from baseline for ≥ 5% and 10% are indicated by + and ++, respectively.

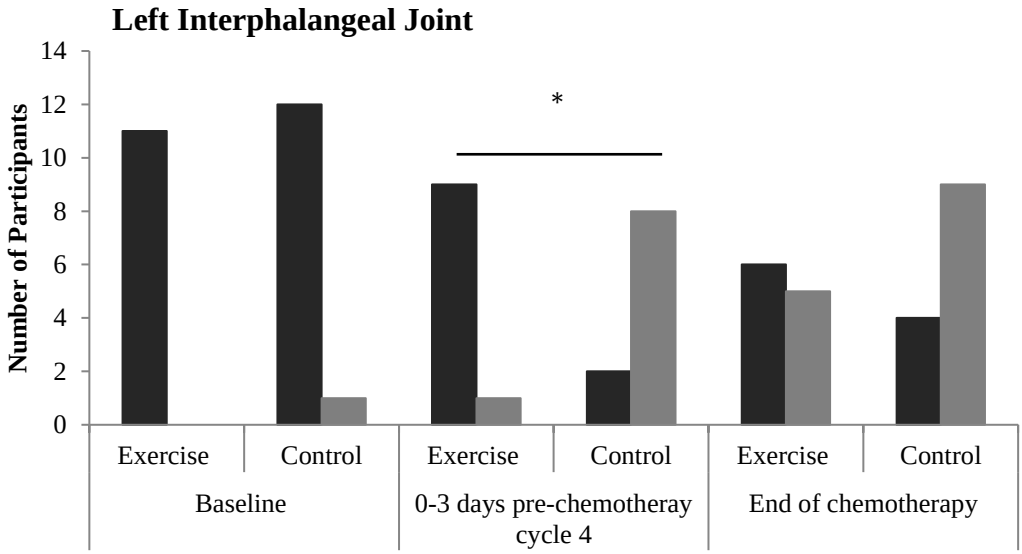
Figure 5: Clinically meaningful changes in EORTC QLQ-C30 symptom scales



Mean scores (mean±SE) for the EORTC QLQ-C30 symptom subscales. Higher scores indicate greater symptom burden. Clinically meaningful changes from baseline for ≥ 5% and 10% are indicated by + and ++, respectively.

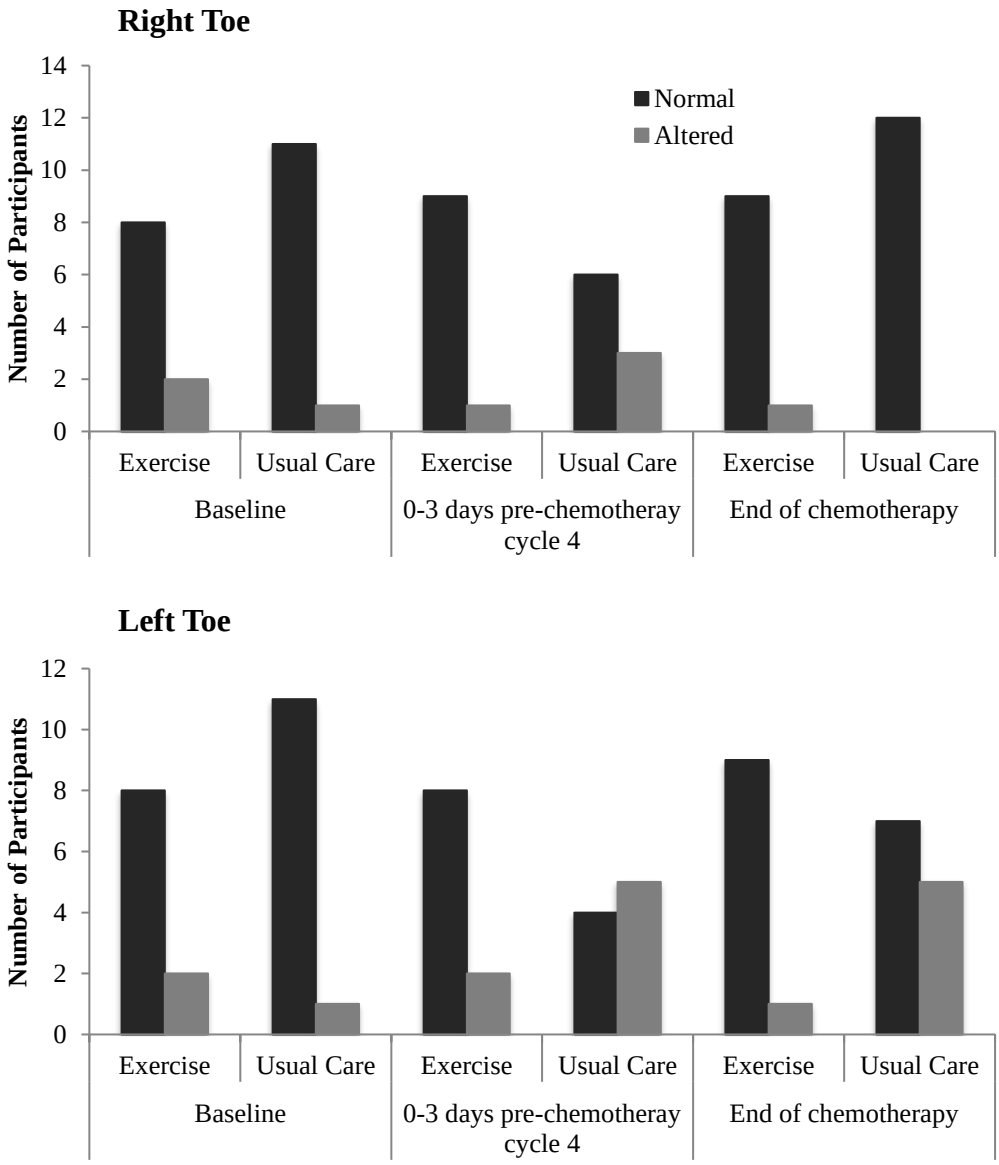
Figure 6: Responses to vibration timing test





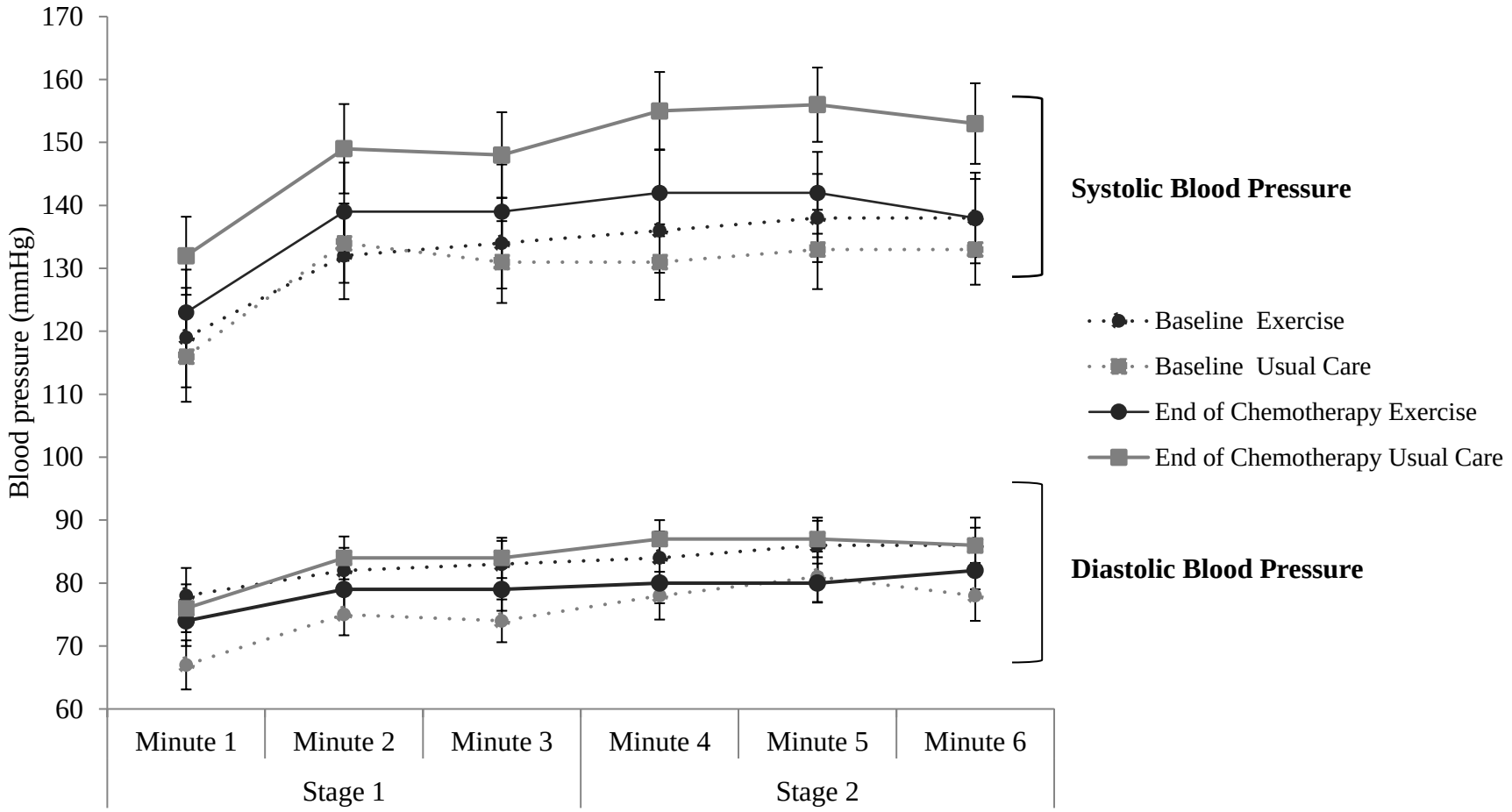
No statistically significant differences between groups at any of the time points for the right interphalangeal joint. *Significant difference between groups at 0-3 days pre-chemotherapy cycle 4 ($p<0.01$) for the left interphalangeal joint. Borderline significant difference for the right interphalangeal joint at 0-3 days pre-chemotherapy cycle 4 ($p<0.06$).

Figure 7: Responses to summation of pinprick testing



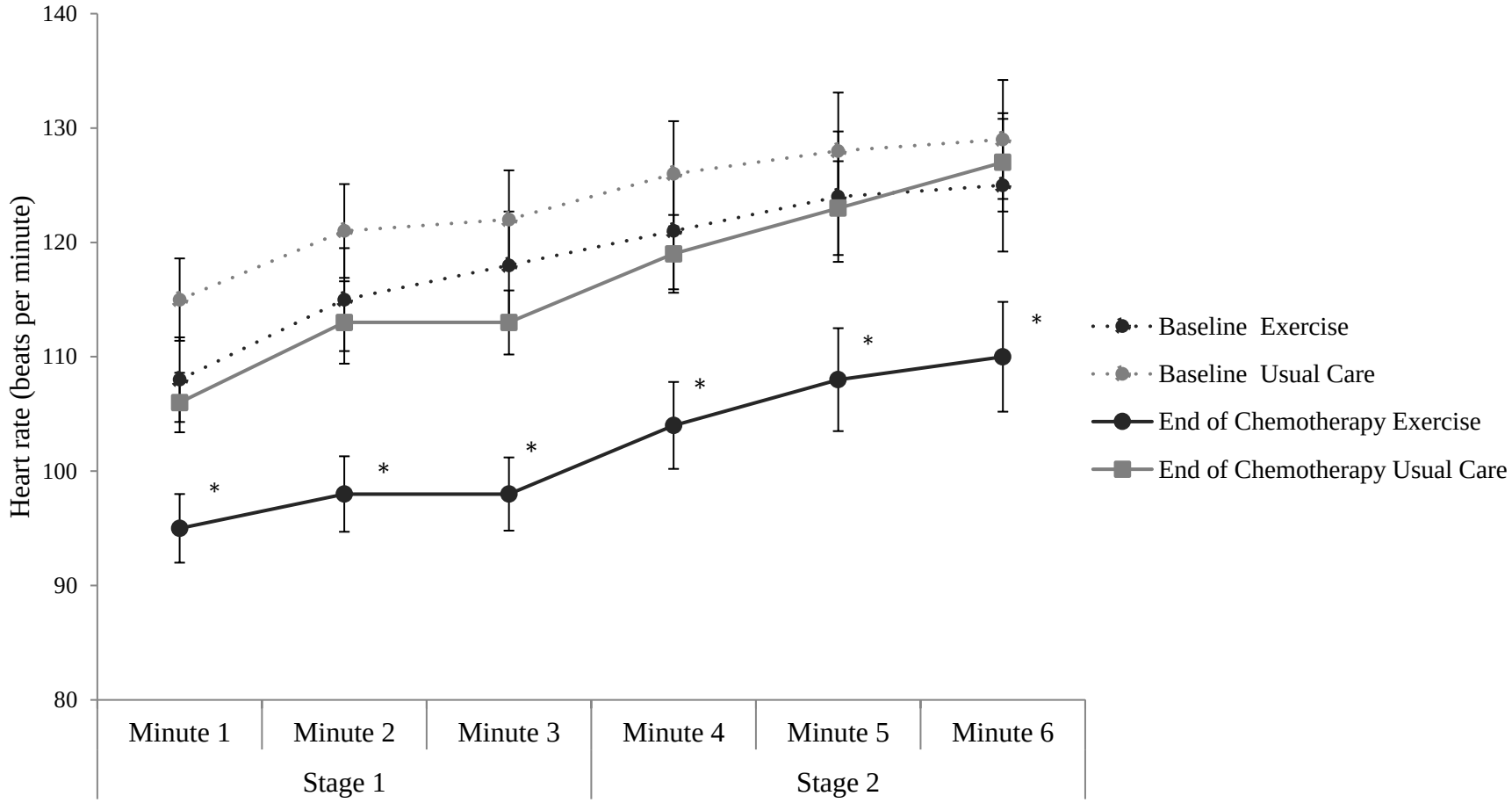
No statistically significant differences between groups at any of the time points.

Figure 8: Blood pressure response to incremental exercise test



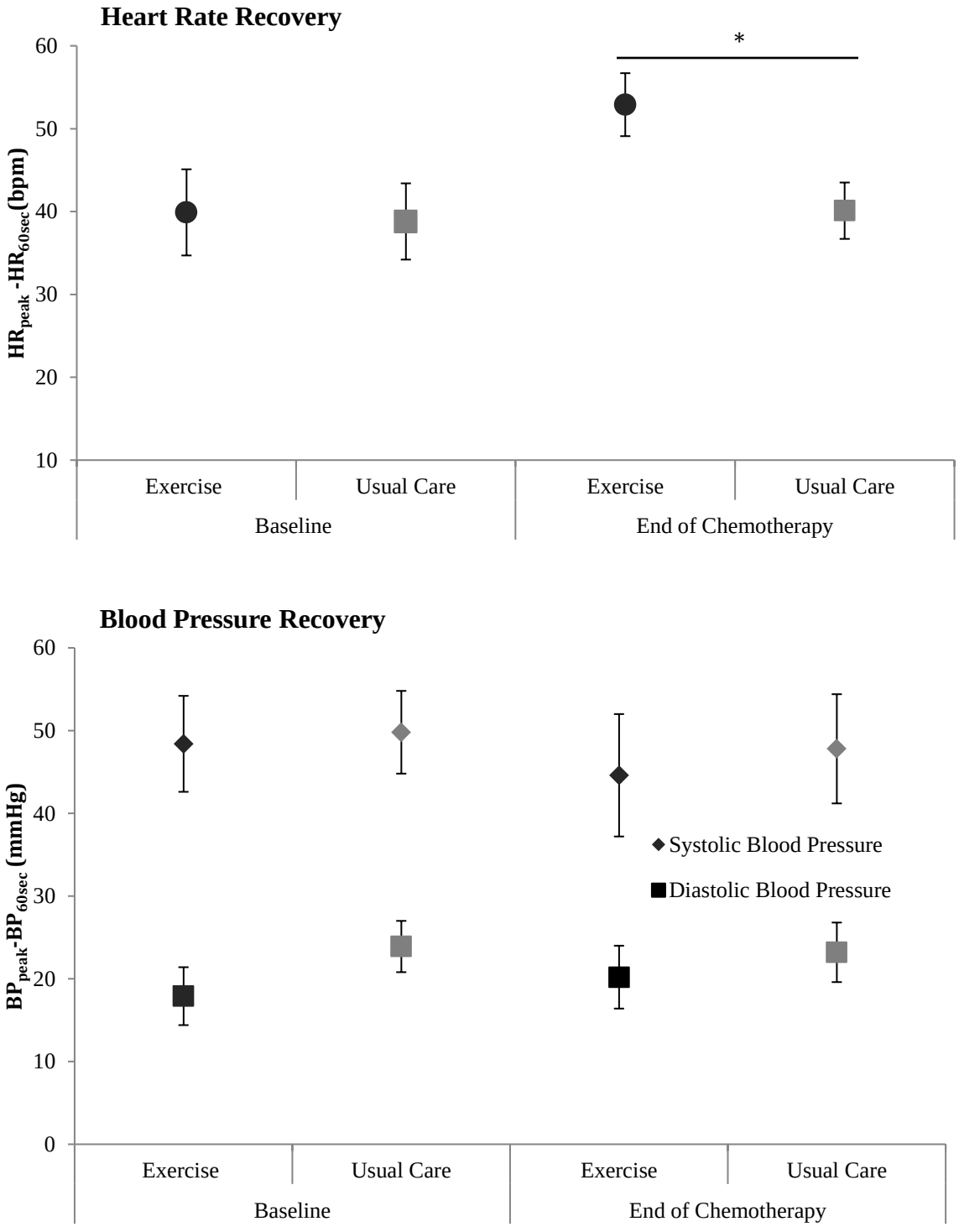
Data displayed as mean±SE for systolic and diastolic blood pressure response to an incremental submaximal exercise test. No statistically significant differences between groups.

Figure 9: Heart rate response to incremental exercise test



Data displayed as mean±SE for heart rate response to an incremental submaximal exercise test. *Significant difference in heart rate between groups at end of chemotherapy ($p<0.01$).

Figure 10: Heart rate and blood pressure recovery at 60 seconds following exercise



Data displayed as mean±SE for heart rate (HR) and blood pressure (BP) recovery at 60 seconds following an incremental exercise test. *Significant difference between groups at end of chemotherapy (p=0.02).

Chapter 5: Discussion

This is the first study to investigate the role of supervised exercise *specifically* on taxane side effects in women with early-stage breast cancer. The primary aim of this study was to evaluate the influence of exercise on the progression and severity of CIPN symptoms. This study also evaluated the influence of exercise on cardiovascular outcomes, including indices of cardiac ANS control at rest and during and after exercise. Overall, adherence to the study's exercise intervention was good, with 77% attendance for supervised exercise and 80% attendance for home-based exercise. Exercise concurrent to taxane-based chemotherapy was hypothesized to attenuate or slow the development of CIPN, primarily patient-reported and clinically evaluated symptoms, as well as improve cardiovascular outcomes. While no statistically significant differences in CIPN symptoms were detected at the end of chemotherapy, a trend towards reduced CIPN symptom progression, specifically impaired vibration sensation, was observed among exercisers. Further, exercise training appeared to significantly lower heart rate at rest and during submaximal exercise testing, as well as improve heart rate recovery in women undergoing taxane treatment for breast cancer. Taken together, the current study's findings suggest exercise during taxane-based chemotherapy for breast cancer may be beneficial.

5.1 CIPN symptoms

Overall, there was a progressive increase in patient-reported and clinically measured CIPN symptoms in both groups. This is in line with the literature that suggests the accumulation of doses over the course of chemotherapy is one of the most prominent causes of CIPN, suggesting a dose-response relationship between neurotoxic agents and neuropathy development.[54] Relative to baseline, participants self-reported significantly worse sensory symptoms at 0-3 days prior to their fourth taxane treatment ($\Delta 14.8$, $p<0.01$) and in sensory and motor symptoms by the end of

their chemotherapy (Sensory: Δ22.8, p<0.01, Motor: Δ10.2, p=0.04). However, there appeared to be higher mean sensory symptom scores, representing worse CIPN, in the usual care group relative to the exercise group, although this difference did not reach statistical significance. In addition, results for the clinical sensory CIPN tests, namely the vibration threshold test at the interphalangeal joint, mirrored the trend observed in self-reported CIPN symptoms. Importantly, at 0-3 days prior to the fourth taxane treatment, a significantly higher proportion of usual care group participants had impaired vibration sensation at the left interphalangeal joint (EX: 10%, UC: 80%, p<0.01) and this difference was on the border of significance for the right interphalangeal joint (EX: 10%, UC: 60%, p<0.06).

The toxic elements of taxane agents are known to primarily produce distal sensory impairments, caused by sensory nerve dysfunction, which can result in paresthesia and numbness, and potentially pain, in both the hands and feet.[13,43] In addition, altered vibratory perception threshold in the distal extremities is often one of the first signs of sensory neuropathy.[54] Out of all the QSTs, vibration threshold (specifically, near the big toes) has been shown to be the most sensitive assessment of CIPN.[54] In a prospective cohort study by Hershman et al. vibration sensation at the hand and foot significantly worsened in 50 women with breast cancer treated with paclitaxel and this correlated with patient-reported numbness and pain, while no significant changes in tactile sensation using von Frey's filaments were detected.[39] Another prospective cohort study by Forsyth et al. found that vibration sensation was also more sensitive than thermal testing in 37 women with metastatic breast cancer treated with paclitaxel.[153] While vibration sensation and patient-reported symptoms increased over time in the current study, no changes were found for the test of temporal summation of pain, using the summation of multiple pinprick test, or patient-reported pain. Thus, the summation of multiple pinprick test is potentially a less

sensitive QST for the evaluation of CIPN development and severity in taxane-treated patients. Further research establishing the most salient clinical neuropathy tests for patients undergoing taxane-based treatments is warranted.

While no differences in CIPN symptoms existed between groups at the end of chemotherapy, our data provides preliminary evidence that women who engage in supervised exercise training during taxane chemotherapy for breast cancer may have delayed onset or less severe CIPN symptoms. In particular, our data supports the notion that exercise may play a role in preventing the progression of impaired vibration sensation, which is one of the most prevalent side effects of taxane-based treatments.[39,153] To date, no studies have tested the effect of a supervised exercise intervention *specifically* during taxane-containing chemotherapy on CIPN symptoms in women with breast cancer. In fact, only one study has examined the effect of supervised exercise on CIPN. Streckmann et al. reported that 36-weeks of supervised exercise during chemotherapy (heterogeneous treatment protocols) for lymphoma significantly reduced CIPN-related vibration sensation evaluated using a vibrating tuning fork among those randomized to exercise (n=30) versus usual care (n=31).[74] A significant difference in overall QOL (EORTC QLQ-C30) was also observed between groups at 12-weeks, but not at 36-weeks, and self-reported CIPN symptoms were not measured. Key differences exist between the current study and the study by Streckmann and colleagues, which may explain the current study's lack of statistically significant findings at the end chemotherapy. First, the current study had a relatively short intervention, as the duration of taxane treatment is typically four cycles 2-3 weeks apart for a total intervention length of 8-12 weeks. Secondly, the current exercise prescription may not have been sufficient, as the optimal type, frequency, intensity and duration of exercise needed to prevent and treat most cancer treatment side effects, including CIPN, is unknown. Thirdly, the total taxane treatment dosage

received by participants in the exercise and usual care groups in the current study varied, as two participants in the control group had their fourth taxane treatment cycles cancelled. In the study by Streckmann et al., patients who had received a reduction in their planned treatment dosage while enrolled in the study were excluded from the vibration sensation analysis. Due to the current study's small sample size, this was not done and thus, there may have been an unanticipated reduction in the prevalence and severity of CIPN symptoms in the usual care group at the end of chemotherapy. Finally, this analysis may be hampered in its ability to detect change due to the small sample size. Despite these limitations, this study's positive preliminary findings, in conjunction with the current literature, compliment a larger body of evidence supporting the beneficial impact of exercise in the treatment of PN in other patient populations. While the biological underpinning of the proposed benefits of exercise on CIPN remains unknown, improved vascular function and metabolic activity at the level of the peripheral nerves,[31] the upregulation of protective neurotrophic factors, including BDNF,[84] and reduced inflammation,[86] are possible explanations.

5.2 Quality of life

Exercise is recommended for patients with cancer, including breast cancer, as a part of standard care to help manage side effects of cancer and its treatment as well as improve overall QOL.[25] Systematic review evidence supports the beneficial impact of exercise on QOL in cancer populations.[154,155] In a meta-analysis of 34 randomized control trials (n=4519) exercise significantly improved QOL (β=0.15, 95% CI: 0.10 to 0.20) and physical functioning (β=0.18, 95% CI: 0.12 to 0.23) in individuals with cancer, and the effect of exercise was significantly greater in supervised versus home-based interventions (QOL: $\beta_{difference}$=0.13, 95% CI: 0.03 to 0.22, physical function: $\beta_{difference}$=0.10, 95% CI: 0.01 to 0.20).[155] This evidence suggests that

exercise can positively impact QOL; however effect sizes appear to be relatively small. In the current study, no statistically significant differences in overall QOL between women who exercised versus received usual care during taxane chemotherapy were observed. Non-significant or small effects might exist for several reasons. First, exercise interventions delivered during cancer treatment often focus on managing treatment side effects and maintaining physical fitness, and may not address all dimensions of QOL (e.g. emotional, social and mental function/well-being).[156] Further, QOL is a self-evaluated outcome and is susceptible to response shift, defined as a change in the meaning of one's self-evaluation of QOL as a result of a change in health status.[157] Thus, to fully capture the true impact of an intervention on QOL in individuals with an illness, it may be necessary to measure patients at multiple time points and incorporate standardized assessments of selected experiences, mechanisms and perceived QOL, as well as an additional measure of response shift.[157]

In the current study, overall QOL was also examined using a benchmark for clinically meaningful differences reported for the EORTC QLQ-C30 instrument. This methodological approach has been rarely reported in the majority of published studies of exercise for cancer survivors. However, clinically meaningful differences in patient-reported outcomes provides valuable insight on changes in QOL and treatment symptoms that are perceptible to patients.[152] While no statistically significant differences in overall QOL were detected in the present study, a clinically meaningful improvement in global health status/overall QOL was observed among exercisers (+5%) versus a clinically meaningful reduction among the usual care group (-9%) by the end of chemotherapy. To put this in context, in a population-based study in Sweden (n=1086) women who had been treated with breast cancer within the past year had clinically meaningfully reduced overall QOL (-10.7, 95% CI=-12.1 to -9.2), social functioning (-15.1, 95% CI=-16.8 to -

13.4) and higher levels of fatigue (+14.1, 95% CI=12.5 to 15.7) compared to women who had not been diagnosed with breast cancer evaluated using the EORTC QLQ. While results from the current study should be interpreted with caution due to the lack of statistically significant differences, the data points towards the potential role of exercise in improving or offsetting clinically meaningful declines in dimensions of QOL.

5.3 Cardiovascular outcomes

The tertiary aim of this study was to evaluate the influence of exercise on cardiovascular outcomes, including indices of cardiac autonomic control. Resting heart was significantly lower in the exercise group compared to the usual care group by the end of chemotherapy (-6±3 bpm, $p<0.05$). Further, the exercise group had a significantly lower heart rate during the first six minutes of a submaximal exercise test and significantly faster heart rate recovery relative to the usual care group by the end of chemotherapy. These findings suggest exercise training resulted in significantly enhanced vagal tone and are consistent with previous exercise trials in women with breast cancer, which have shown that exercise training can reduce resting heart rate and improve heart rate recovery.[129–133,135,136] Interestingly, the magnitude of resting heart rate change from baseline to end of chemotherapy among exercisers in the current study (mean reduction of 10 bpm) is larger than what has been previously reported for women undergoing breast cancer treatment. For example, in a study of women undergoing a combination of adjuvant treatment protocols (chemotherapy, radiation or both), those who were randomized to a thrice-weekly moderate intensity aerobic exercise intervention for eight weeks (n=22) versus standard of care control (n=19) experienced significant decreases in resting heart rate of -5±10 bpm (p=0.03), while no change occurred in the control group.[132] A possible explanation for this discrepancy is that different treatment types may have different impacts on heart rate. In the case of the current

study, the effect of taxane-based chemotherapy may differ from other chemotherapy agents or radiation, as exercise intervention adherence and prescribed aerobic exercise intensity was similar to what has been previously reported. Anthracycline chemotherapy, in particular, is known to be significantly more cardio-toxic than taxane-based chemotherapy, and is associated with dose-dependent, cumulative, progressive cardiac dysfunction.[158] Therefore, the impact of exercise on cardiovascular outcomes concurrent to different types of antineoplastic therapies could be markedly different. A randomized control trial by Hornsby et al. reported that in women who were exclusively undergoing anthracycline chemotherapy, resting heart rate did not improve among those randomized to a 12-week aerobic exercise intervention (75±13 to 82±12 bpm, p=0.2) despite a significant increase in cardiorespiratory fitness (19.5±7.6 to 22.1±7.0 mL/kg/min, p=0.04).[159] In the current study, the majority of women had undergone four cycles of doxorubicin, an anthracycline chemotherapy agent, and cyclophosphamide prior to enrolling in the trial. Thus, our exercise training intervention might have facilitated the participants' physiological recovery from this cardio-toxic treatment, resulting in greater improvements in resting heart rate. Altogether, more research is needed to unpack these differences in breast cancer treatment effects on cardiovascular outcomes, including indices of cardiac autonomic control, and the mediating effect of exercise.

Another finding in the current study was the effect of exercise training on the blood pressure response to exercise. While no differences in resting blood pressure were observed, mean systolic blood pressure during a submaximal exercise test was higher by the end of chemotherapy in both groups. Interestingly, the extent of this increase was much larger in the usual care group, although this difference should be interpreted with caution, as it did not reach statistical significance. A handful of randomized control trials have demonstrated the positive

impact of exercise performed both during and after treatment on resting blood pressure and blood pressure during exercise testing in women with breast cancer.[129,132,137] In the current study, exercise training appeared to prevent the large rise in systolic blood pressure during submaximal exercise testing observed in the usual care group. Other studies have reported significant reductions in peak systolic blood pressure during maximal exercise testing among women with breast cancer who engaged in exercise during treatment[132] and post-treatment.[137] While data in the general population supports that a systolic blood pressure response >190 mmHG during maximal exercise testing in women is considered abnormal and associated with a poor prognosis, more research is needed to clarify submaximal exercise testing blood pressure thresholds.[160] However, in a systematic review and meta-analysis summarizing 12 longitudinal studies (n=46, 314), the authors reported that each 10 mmHg increase in blood pressure during submaximal exercise was accompanied by a 4% increase in cardiovascular events and mortality.[161] Thus, in the current study, the difference in blood pressure responses detected between groups at the end of chemotherapy (e.g. 14±7 mmHg at minute six of the exercise test) holds clinical relevance. Another important consideration is that the majority of exercise oncology trials to-date have evaluated blood pressure manually, while in the current trial, a Finometer Pro was used to record beat-to-beat blood pressure that was then averaged to provide blood pressure readings that are potentially more sensitive to acute changes.[160] In addition, ausculatory blood pressure readings at maximal levels of exertion are prone to artifact and measurement error, while blood pressure readings at lower levels of exercise intensity are generally more accurate.[162] Altogether, exercise-induced modulation of autonomic function and CVD risk in women with breast cancer is plausible during chemotherapy. In particular, mechanisms of change in heart rate and blood pressure may be due to neuro-hormonal adaptations as well as structural adaptations.[105]

Importantly, the timing of the exercise intervention, namely during versus after treatment, may impact the degree of improvement in blood pressure responses during submaximal and maximal exercise testing, depending on the specific acute and long-term side effects associated with different treatment modalities. Overall, more extensive research on the influence of exercise training at different time points along the breast cancer continuum, namely pre, during and post-treatment, on CVD risk factors, including indices of autonomic control, is needed.

5.4 Strengths, limitations and considerations

To the author's knowledge, this is the first randomized control trial to test the influence of supervised exercise *specifically* on taxane side effects, including CIPN, in women with early-stage breast cancer. This is also the first study to evaluate the influence of exercise on cardiovascular outcomes, including indices of autonomic function, during taxane chemotherapy for breast cancer. Additional study strengths include the randomized control trial design with a relatively homogenous sample with respect to treatment type, disease stage, and medical history. Furthermore, attendance and adherence to the exercise prescription in this trial was good and higher than what has been previously reported for women undergoing adjuvant treatment for breast cancer.[141] This study is the first to use a "chemotherapy-periodized" supervised exercise program that meets the current recommended exercise guidelines for cancer patients,[25] while attempting to account for anticipated fluctuations in treatment side effects. This novel exercise prescription attempted to optimize exercise training during chemotherapy by pre-emptively reducing exercise intensity for one week following each participant's chemotherapy treatment. However, a direct comparison between a linear and "chemotherapy-periodized" exercise prescription approach is needed to determine the true impact of this prescription on physiological outcomes and exercise adherence.

A limitation of this study is the small sample size. While several trends emerged, the lack of significant differences for several measures may be due to low statistical power. Future studies with larger sample sizes are needed to definitively determine the influence of exercise on taxane-specific side effects, especially CIPN, in women with breast cancer. Another limitation is the exclusion of women who received weekly paclitaxel, as this treatment protocol would require an altered periodized exercise prescription approach. While it is certainly possible to design a "chemotherapy-periodized" exercise prescription for weekly treatment protocols, the current study was restricted to chemotherapy received in two or three-week cycles to test the feasibility of delivering this exercise prescription. Furthermore, a submaximal exercise test was used to estimate VO_{2peak} to evaluate change in aerobic fitness, versus maximal exercise testing, which is considered the gold standard measurement to determine cardiorespiratory fitness. The majority of women included in this trial had also received non-taxane chemotherapy, specifically anthracycline chemotherapy, before enrolling in the study. Thus, baseline values were not true "pre-chemotherapy" values and given that anthracyclines can significantly impact cardiovascular health and have a host of additional treatment side effects, such as nausea, it is reasonable to expect some improvement from these side effects upon anthracycline treatment completion. This could explain a few of our non-significant findings, including measures of physical fitness as well as self-reported treatment side effects. Finally, this study was at risk of contamination of the usual care group. All participants who enrolled in the study were interested in engaging in exercise during treatment and may have been more motivated to exercise on their own regardless of randomization, potentially limiting our ability to detect differences between groups.

Overall, optimizing the benefits of exercise during cancer treatment requires a better understanding of important participant and intervention-specific characteristics, such as the

exercise intervention setting, use of principles of exercise training, including exercise session frequency, intensity, timing and type (FITT principles), and participant willingness and response to exercise. More research evaluating the most salient aspects of exercise for specific outcomes of interest in patients with cancer is warranted. Further, for any given intervention, attendance and adherence to the exercise prescription are important considerations. Namely, the importance of "showing up" to exercise sessions cannot be understated. Thus, strategies to promote exercise adherence, for e.g. flexible workout schedules, motivational coaching and exercise-related feedback, and individualized exercise prescriptions, should be implemented when possible. While adherence in the current study was good, this intervention was delivered in a private research facility in a large urban setting and thus, results may not be generalizable to exercise delivered in home-based, one-on-one, community-based, or fee-for-services settings. Finally, patients who decline to participate in an exercise study may be less motivated to exercise, or have lower exercise levels at baseline. These individuals may therefore benefit the most from an exercise intervention. Furthermore, participants in the current study also had a younger mean age than the general breast cancer population in Canada. Accordingly, findings from the current study and other exercise oncology studies to-date may not be generalizable to all cancer patients.

Chapter 6: Conclusion

Taxane-containing chemotherapy agents are some of the most effective agents used to treat breast cancer and are currently administered as first and second-line breast cancer treatment protocols to reduce the risk of cancer recurrence and death. While safe and effective in treating breast cancer, taxanes often result in a wide-range of short and long-term treatment toxicities. In particular, CIPN is a prevalent and potentially devastating side effect of taxane-containing chemotherapy, and there are few available treatment options to prevent and manage CIPN symptoms. Further, cardiac complications, and potentially the loss of healthy cardiac ANS regulation, have been linked to several breast cancer therapies, including taxanes. Cardiac injury caused by chemotherapeutic agents may independently increase the risk of future CVD and mortality in women who have been diagnosed with breast cancer. Thus, as with all antineoplastic agents, the efficacy of taxanes needs to be balanced against treatment toxicities, and the impact of these toxicities on patient QOL and long-term health and survival.

The benefits of exercise during chemotherapy for breast cancer are extensive and include the management of common treatment side effects, such as fatigue and nausea, as well as improvements in physical fitness and overall QOL. However, there is a lack of evidence on the impact of exercise on taxane-specific treatment toxicities in women with early-stage breast cancer. Current research supports the use of exercise as an intervention to manage PN in non-cancer populations[28] and preliminary evidence suggests exercise has the potential to offset the development of CIPN in cancer patients.[31,74,75] Thus, the primary objectives of this study were to investigate the effect of a supervised exercise training program relative to usual care on patient-reported CIPN symptoms, as well as overall QOL, using the EORTC QLQ-C30 questionnaire and CIPN20 subscale, in women with breast cancer undergoing taxane chemotherapy. The

second objective was to evaluate exercise's influence on a clinical test of sensory CIPN, including a vibration sensation test and summation of multiple pinprick test, as well as patient-reported pain using the Brief Pain Inventory. It was hypothesized that exercise training would prevent or reduce the severity of both patient-reported and clinically measured CIPN. In both groups, there was a significant increase in patient-reported sensory and motor CIPN symptoms by the end of chemotherapy relative to baseline. However, the progression in patient-reported sensory symptoms was trending towards being attenuated by exercise. Further, while no statistically significant difference in patient-reported QOL was found, a clinically meaningful improvement in overall QOL was observed in the exercise group, relative to a clinically meaningful reduction in the usual care group. In the QST of sensory CIPN symptoms, significantly fewer participants in the exercise group had impaired sensory responses to the vibration timing testing compared to the usual care group at 0-3 days pre-chemotherapy cycle 4. However, this difference disappeared by the end of chemotherapy. While these findings may be hampered by the study's small sample size, they point to the potential of exercise concurrent to taxane treatment to attenuate sensory CIPN symptoms. Randomized controlled trials with appropriate statistical power should seek to examine this cause and effect in the future. There were no significant differences between groups for the other clinical tests of CIPN or patient-reported pain.

Exercise is also an effective strategy to reduce CVD risk and mortality. Thus, the third objective of this study was to evaluate the effect of exercise training on cardiovascular outcomes, including indices of cardiac autonomic control at rest, and during and after exercise testing. There was a significant difference in resting heart rate between groups by the end of chemotherapy ($p<0.05$). The exercise group also had a significantly lower heart rate during

submaximal exercise testing ($p<0.01$), and significantly faster heart rate recovery following submaximal exercise testing by the end of chemotherapy ($p=0.02$). No significant differences between groups or changes over time were observed in resting blood pressure, blood pressure during exercise, or blood pressure recovery. However, there was a borderline significantly greater increase in systolic blood pressure during exercise in the usual care group relative to the exercise group by the end of chemotherapy. Overall, this data suggests exercise training during chemotherapy for breast cancer may play an important role in managing cardiovascular outcomes. In particular, interesting differences in heart rate and blood pressure responses to a submaximal exercise test were identified. For example, while no differences in resting blood pressure were identified, notable changes in the blood pressure response to submaximal exercise testing were observed. Thus, exercise testing is a useful tool to evaluate cardiovascular health and may be more sensitive to blood pressure and heart rate changes compared to measures at rest.

The main findings from this study further support the use of exercise training to improve the health of breast cancer patients undergoing chemotherapy. While breast cancer treatment side effects are diverse in nature, exercise training is a promising integrative therapy for side effect management. In particular, this study has demonstrated the effect of exercise on side effects associated specifically with taxane-based treatments. Future prospective studies should assess this effect with a larger sample size and seek to evaluate factors that may contribute to this potential benefit, including physiological factors supporting mechanisms of action. Overall, findings from the current study, along with the vast majority of exercise-oncology research to-date, suggest exercise training should be prescribed as a part of standard care for breast cancer.

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Appendices

Appendix A: Description of balance and core exercises

A.1 Balance Exercises

1. Helicopter (week 1 to week 4-6)

- Start standing with feet hip width apart. Reach the leg farthest from the wall forward and lift it a few inches off the ground, keeping your knee straight.
- Bring leg back to centre, and then move to the side. Bring leg back to centre and then move it to the back.
- Repeat 6-8 times. Switch legs and repeat.
- Begin by performing while lightly touching wall. Progress to light touching the wall or not touching the wall (week 3-4).

2. Flamingo (week 1 to week 8-12)

- Start with feet together facing wall.
- Lift one foot off the ground to ankle height. Hold for 2-3 seconds. Then, lift foot to knee height and hold for 2-3 seconds. Try to keep hips level. Slowly lower foot to ground.
- Repeat 6-8 times. Switch to other leg and repeat.
- Begin by performing while lightly touching wall. Progress to light touching the wall or not touching the wall (week 3-4). Progress to performing while standing on a gym mat (unstable surface; week 6-8).

3. Balancing Rainbow (week 4-6 to week 8-12)

- Start facing the mirror, holding onto a free weight
- Lift one foot off the floor, with knee bent. Hold onto to weight with both hands.
- Start with weight vertical, in front of one hip. Lift weight forward to shoulder height.
- Bring weight down to opposite hip. Repeat 4-5 times.
- Repeat another 4-5 times in the opposite direction.
- Begin (week 4-6) with a 5lb free weight. Progress to holding an 8lb free weight (week 6-8).

A.2 Core Exercises

1. Hip Escalator (week 1 to weeks 4-6)

- Start lying supine with knees bent. Place feet flat on the mat, hip width apart.
- Use pelvic floor, hamstrings and buttocks to lift pelvis and lower back off the mat.
- Hold for 2-5 seconds and slowly lower pelvis down. Repeat 6-8 times.

2. Butterfly Legs (week 1 to weeks 4-6)

- Start lying supine with knees bent. Place feet flat on the mat, hip width apart. Place hands on hips.
- Slowly open one leg to the side, while keeping the pelvis level on the mat.
- Alternate sides. Repeat 6-8 times each side.

3. Bird Dog (weeks 4-6 to weeks 8-12)

- Start on hands and knees with knees hip width apart.
- Slowly extend and lift right leg and left arm. Keep pelvis and shoulders level.
- Slowly lower leg and arm.
- Repeat on opposite side. Repeat 6-8 times on each side.

4. Ball Supine (weeks 4-6 to weeks 8-12)

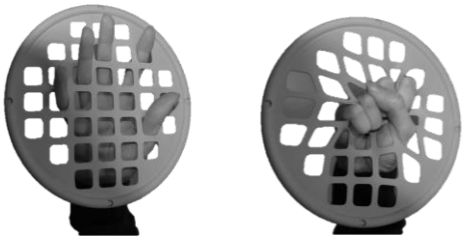
- Start lying supine with legs lifted and bent at 90 degrees. Place ball on top of knees and hold with hands.
- Slowly extend one leg and opposite arm as far as you can without lifting ribs or lower back off the mat. Slowly bring arm and leg back to the starting position.
- Repeat on opposite side. Repeat 6-8 times on each side.

Appendix B: Description of hand and foot exercises

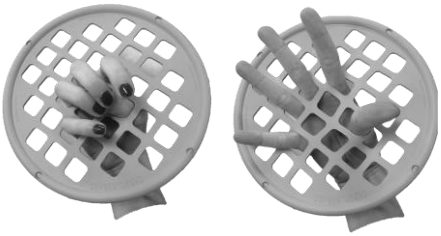
B.1 Hand exercises

B.1.1 Hand web (week 1 to week 8-12)

- Version 1: Start with fingers wide apart. Squeeze web by making a fist and hold for 2-3 seconds. Release. Repeat 6-8 times.

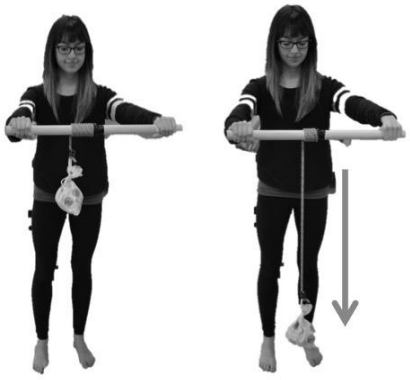


- Version 2: Start with fingers close together. Expand web by spreading fingers and hold for 2-3 seconds. Repeat 6-8 times.



B.1.2 Bean bag stick (week 1 to week 8-12)

- Stand with feet hip width apart and hold stick with hands forward, just below shoulder height. Keep elbows straight.
- Keep stick level as you slowly unroll the bean back to the floor and roll it back up.
- Repeat twice.

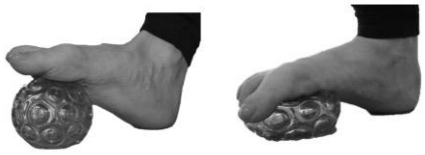


B.2 Foot exercises

B.2.1 Ball Rolling (week 1 to week 8-12)

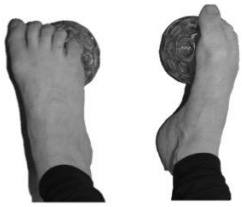
1. Squish ball with ball of foot

- Start with ball of foot on ball. Keep heel on floor. Keep toes relaxed.
- Bend knee and press ball of foot on ball and release. Repeat 4-6 times.



2. Roll ball side to side on ball of foot

- Keep ball of foot on ball and roll ball side-to-side. Alternate between reaching big toe to the ground and pinky toe to the ground. Repeat 4-6 times.

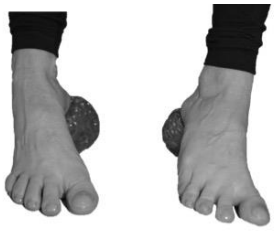


3. Squish ball with heel

- Start with heel on the ball. Keep ball of your foot on the floor.
- Bend knee and press heel on ball and release. Repeat 4-6 times.

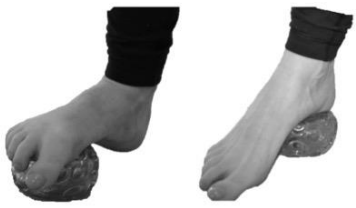
d) Roll ball side to side on heel

- Keep the heel on the ball and roll heel side to side on ball (think of opening one side of your ankle and then the other). The movement should be fairly small. Repeat 4-6 times.



4. Roll ball back and forth

- Roll ball back and forth from toes to heel. Goal is to massage the bottom of the whole foot. Repeat 4-6 times.



5. Balance on arch

- Lift back leg off the floor and balance on the ball.
- Place foot back on floor and repeat 4-6 times.

B.2.2 Calf Stretch (week 1 to week 8-12)

- Place heel at the end of the wedge and rock heel towards the floor. Keep toes and ankles relaxed.
- Try to keep leg straight to increase stretch. Keep foot in line with leg.
- Hold for 20-30 seconds.

Appendix C: Baseline demographics questionnaire

It is important for to be able to describe the demographic information of subjects who participated in the research study. This date is combined for all participants and presented as averages or percentages. Your participation is voluntary and your answers will be kept strictly confidential. This questionnaire is **not** related to your medical treatment.

1. What is your current age: _____

2. Presently are you are:

   □ Married □ Living as Married or in a Common-law partnership □ Divorced

   □ Single □ Widowed □ Separated but still legally married

3. What ethnic or cultural group do you consider yourself to belong to? (select all that apply)

   - □ White
   - □ Aboriginal
   - □ Pacific Islander
   - □ Asian
   - □ Other: _____
   - □ South Asian
   - □ Black or African
   - □ Prefer not to answer

4. What is the highest level of formal education that you have completed?(select all that apply)

   - □ Elementary school
   - □ Some high school
   - □ High school diploma
   - □ Technical/Community College
   - □ Some University
   - □ Bachelor's Degree at University
   - □ University degree above a Bachelor's Degree

5. Which of the following described your work situation(s) just prior to your cancer diagnosis?

		Check all that apply
a.	Working a full-time (>35 hours /week) paying job?	☐
b.	Working a part-time (1-34 hours/week) paying job?	☐
c.	Full-time student?	☐
d.	Part-time student?	☐
e.	Homemaker?	☐
f.	Not working and on Employment Insurance?	☐
g.	Not working without Employment Insurance?	☐
h.	Maternity leave?	☐
i.	Unemployed	☐
j.	Short-term disability? *(indicate source)*	☐ CPP/federal ☐ Provincial ☐ Employer ☐ Don't Know
k.	Long term disability? *(indicate source)*	☐ CPP/federal ☐ Provincial ☐ Employer ☐ Don't Know
l.	Disability for another reason?	Specify:
m.	Retired	☐

6. What was your total <u>household</u> income from before taxes in the last calendar year? (includes wages, salaries and self-employment earnings)

- ☐ < $19,999
- ☐ $20,000-$39,999
- ☐ $40,000-$59,999
- ☐ $60,000-$79,999
- ☐ $80,000-$99,999
- ☐ > $100,000

7. Do you now have or have you ever had any of the following medical conditions? Please answer for each condition. If unsure, check "unknown".

		No	**Yes**	**Unknown**
7.1	Heart disease	☐1	☐2	☐3
7.2	Stroke	☐1	☐2	☐3
7.3	Diabetes	☐1	☐2	☐3
7.4	Asthma / Lung Disease	☐1	☐2	☐3
7.5	Arthritis	☐1	☐2	☐3
7.6	Fibromyalgia	☐1	☐2	☐3
7.7	Hip or joint replacement	☐1	☐2	☐3
7.8	Osteoporosis / Osteopenia	☐1	☐2	☐3
7.9	Hypertension (high blood pressure)	☐1	☐2	☐3

Appendix D: EORTC QLQ-C30 questionnaire

We are interested in some things about you and your health. Please answer all the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The Information that you provide will remain strictly confidential.

	Not At All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the Past Week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing you hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4

During the past week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
9. Did you have pain?	1	2	3	4

10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4

During the past week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

Appendix E: EORTC QLQ-CIPN20 questionnaire

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

	During the past week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
1.	Did you have tingling fingers or hands?	1	2	3	4
2.	Did you have tingling toes or feet?	1	2	3	4
3.	Did you have numbness in your fingers or hand?	1	2	3	4
4.	Did you have numbness in your toes or feet?	1	2	3	4
5.	Did you have shooting or burning pain in your fingers or hands?	1	2	3	4
6.	Did you have shooting or burning pain in your toes or feet?	1	2	3	4
7.	Did you have cramps in your hands?	1	2	3	4
8.	Did you have cramps in your feet?	1	2	3	4
9.	Did you have problems standing or waking because of difficulty feeling the ground under your feet?	1	2	3	4
10.	Did you have difficulty distinguishing between hot and cold water?	1	2	3	4

11. Did you have problem holding a pen, which made writing difficult?	1	2	3	4
12. Did you have difficulty manipulating small objects with your fingers (for example, fastening small buttons)?	1	2	3	4

During the Past Week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
13. Did you have difficulty opening a jar or bottle because of weakness in your hands?	1	2	3	4
14. Did you have difficulty walking because your feet dropped downwards?	1	2	3	4
15. Did you have difficulty climbing stairs or getting up out of a chair because of weakness in your legs?	1	2	3	4
16. Were you dizzy when standing up from a sitting or lying position?	1	2	3	4
17. Did you have blurred vision?	1	2	3	4
18. Did you have difficulty hearing?	1	2	3	4

Please answer the following question only if you have a car

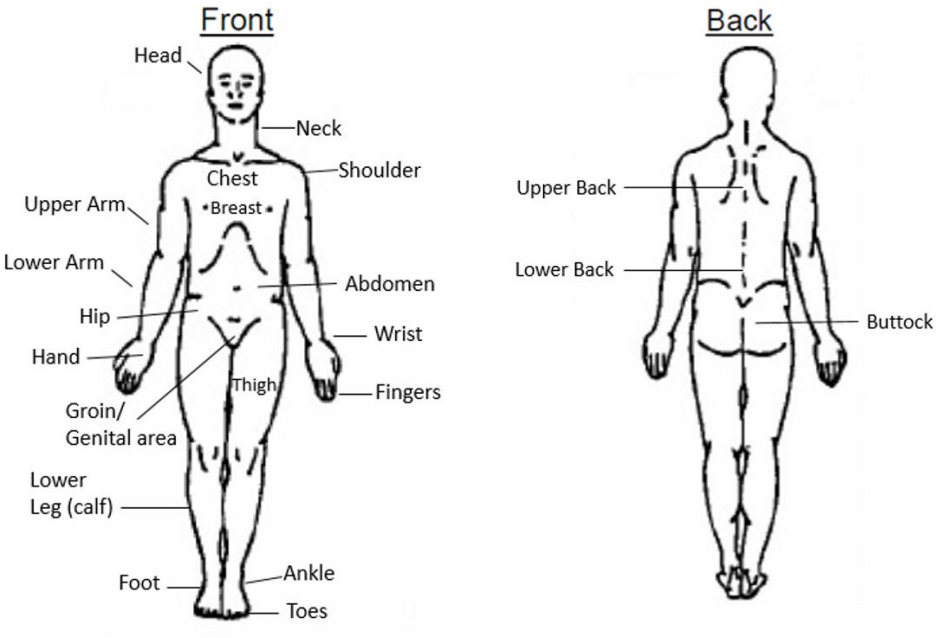
19. Did you have difficulty using the pedals?	1	2	3	4

Appendix F: Brief Pain Inventory

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had any pain other than these everyday kinds of pain today?

   ☐ Yes ☐ No

2. a) On the diagrams below, **CIRCLE ALL** the areas where you feel pain. Put an X or star on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its **worst** in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain at **least** in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No pain — Pain As Bad As You Can Imagine

7. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No pain — Pain As Bad As You Can Imagine

9. Please rate your pain by marking the box beside the number tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No pain — Pain As Bad As You Can Imagine

11. What treatments or medications are you receiving for your pain?

_____

_____

12. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

☐ 0% ☐ 10% ☐ 20% ☐ 30% ☐ 40% ☐ 50% ☐ 60% ☐ 70% ☐ 80% ☐ 90% ☐ 100%

No relief — Complete Relief

13. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Does not Interfere — Completely Interferes

B. Mood

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Does not Interfere — Completely Interferes

C. Walking Ability

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Does not Interfere — Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Does not Interfere — Completely Interferes

E. Relations with other people

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

F. Sleep

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Does not Interfere — Completely Interferes

G. Enjoyment of life

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Does not Interfere — Completely Interferes

Appendix G: Piper Fatigue Scale

Directions: Many individuals can experience a sense of unusual or excessive tiredness whenever they become ill, receive treatment, or recover from their illness/treatment. This unusual sense of tiredness is not usually relieved by either a good night's sleep or by rest. Some call this symptom "fatigue" to distinguish it from the usual sense of tiredness.

For each of the following questions, please fill in the space provided for that response that best describes the fatigue you are experiencing now or for today. Please make every effort to answer each question to the best of your ability. If you are not experiencing fatigue now or for today, fill in the circle indicating "0" for your response. Thank you very much.

1. How long have you been feeling fatigue? (Check one response only).

   ☐ 1. Not feeling fatigue
   ☐ 2. Minutes
   ☐ 3. Hours
   ☐ 4. Days
   ☐ 5. Weeks
   ☐ 6. Months
   ☐ 7. Other (Please describe)_____

2. To what degree is the fatigue you are feeling now causing you distress?

   ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

   No Distress A Great Deal of Distress

3. To what degree is the fatigue you are feeling now interfering with your ability to complete your work or school activities?

   ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

   None A Great Deal

4. To what degree is the fatigue you are feeling now interfering with your ability to socialize with your friends?

   ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

   None A Great Deal

5. To what degree is the fatigue you are feeling now interfering with your ability to engage in sexual activity?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

None A Great Deal

6. Overall how much is the fatigue, which you are experiencing now, interfering with your ability to engage in the kind of activities you enjoy doing?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

None A Great Deal

7. How would you describe the degree of intensity of the fatigue which you are experiencing now?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Mild Severe

8. To what degree would you describe the fatigue which you are experiencing now as being?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Pleasant Unpleasant

9. To what degree would you describe the fatigue which you are experiencing now as being?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Agreeable Disagreeable

10. To what degree would you describe the fatigue which you are experiencing now as being?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Protective Destructive

11. To what degree would you describe the fatigue which you are experiencing now as being?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Positive Negative

12. To what degree would you describe the fatigue which you are experiencing now as being:

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Normal Abnormal

13. To what degree are you now feeling:

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Strong Weak

14. To what degree are you now feeling:

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Awake Sleepy

15. To what degree are you now feeling:

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Lively Listless

16. To what degree are you now feeling:

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Refreshed Tired

17. To what degree are you now feeling:

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Energetic Unenergetic

18. To what degree are you now feeling:

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Patient Impatient

19. To what degree are you now feeling:

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Relaxed Tense

20. To what degree are you now feeling:

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Exhilarated Depressed

21. To what degree are you now feeling:

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Able to Concentrate Unable to Concentrate

22. To what degree are you now feeling:

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Able to Remember Unable to Remember

23. To what degree are you now feeling:

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Able to Think Clearly Unable to Think Clearly

24. Overall, what do you believe is ***most*** directly contributing to or causing your fatigue?

_____

_____

25. Overall, the ***best*** thing you have found to relieve your fatigue is:

26. Is there anything you would like to add that you describe your fatigue better to us?

27. Are you experiencing any other symptoms right now? If yes please describe.

Appendix H: Clinical neuropathy tests data collection sheet

Date: _____ Time: _____

Initials:	Study ID: Age:	Med hx/medications:

Vibration timing: holding tuning fork in left hand strike maximally, hold to top of proximal interphalangeal joint of big toe, with right index finger underneath joint. Ask the participant to indicate when they stop feeling the vibration.

Right:	☐NORMAL (same timing)	☐IMPAIRED (stops feeling vibration early)	☐LACKING (no feeling)
Left:	☐NORMAL	☐IMPAIRED	☐LACKING

Ankle vibration sense: strike tuning fork and touch to middle of medial malleolus.

Right: ☐PRESENT ☐ABSENT Left: ☐PRESENT ☐ABSENT

Patella vibration sense: strike tuning fork and touch to middle of patella.

Right: ☐PRESENT ☐ABSENT Left: ☐PRESENT ☐ABSENT

Pin prick test: use Neuropen to poke end of big toe 10 times in a row, one second apart.

Right:

☐SAME SENSATION ☐INCREASED OVER TIME ☐DECREASED OVER TIME

Left:
☐SAME SENSATION ☐INCREASED OVER TIME ☐DECREASED OVER TIME

Appendix I: Exercise test data collection sheet

Date: _____ Time: _____

Initials:	Study ID: Age:	Med hx/medications:

INCREMENTAL BIKE TEST:

1) Calculate APMHR: 207 – 0.7*age _____bpm
2) Calculate test termination HR target: (APMHR – Resting HR)*0.7 + Resting HR_____bpm
3) Explain incremental test, and attach finometer, ECG, and facemask while next to Precor upright bike.
4) Ask participant to sit on bike with hands forward onto horizontal bar.
5) Press 'OK' to start calibration, verify that HR and VO2 seem normal, then press 'OK' and verbalize for Team V to start measurement.
6) Using time on Fitmate, at 1:50, inform participant "in 10 seconds I'm going to ask you to start pedaling" then count down from 5 so that Team V can place marker on Beat Scope.
7) Press **'quick start'** on bike at the same time they start cycling, **increase level to '2'** and press bottom right button once to display RPM.
8) Instruct participant "*During the exercise test please try to stay seated with your hands in this position without gripping the handlebars. Please keep your revolutions per minute, which you can read here [point to screen] above 70*."
9) Using bike computer time, at 15 seconds remaining in each three-minute stage (i.e. 2:45, 5:45, 8:45, 11:45, 14:45, 17:45) ask participant for their current RPE and record below.
10) Continue with the test until the target heart rate is reached, note the bike time, and immediately ask for a RPE. Record the RPE and the test time below.
11) Continue the test until the end of the current three-minute stage (e.g. if HR is reached at 9:45, then continue the test until 12:00).
12) With 15 seconds remaining in that stage, ask for one final RPE, then inform the participant "*in a few seconds I will ask you to stop pedaling and sit as quietly as possible on the bike for five minutes*" and count them down from 5 seconds and press '1' for 'recovery' on the Fitmate Pro.
13) Ensure they sit in the same position with their hands forward on handlebars.
14) After 5 minutes, press 'OK' to end the test.
15) Press 'OK' when asked whether to calculate the anaerobic threshold.
16) Press 'OK' to confirm.
17) Remove the facemask by unclipping two clips on the side closest you.
18) End test prematurely if RPE>17 is reported or any of the following signs or symptoms shortness of breath, wheezing, leg cramps, light-headedness, confusion, ataxia, pallor, cyanosis, nausea, cold, clammy skin or severe fatigue. If possible try to do the 5-minute test measurements at the end.

Stage	Time (Min)	Level	RPE
0	Fitmate: 0-2	Rest*	
1	Bike: 1:00	2	
	Bike: 2:00	2	
	Bike: 3:00	2	
2	Bike: 4:00	4	
	Bike: 5:00	4	
	Bike: 6:00	4	
3	Bike: 7:00	6	
	Bike: 8:00	6	
	Bike: 9:00	6	
4	Bike: 10:00	8	
	Bike: 11:00	8	
	Bike: 12:00	8	
5	Bike: 13:00	10	
	Bike: 14:00	10	
	Bike: 15:00	10	
6	Bike: 16:00	12	
	Bike: 17:00	12	
	Bike: 18:00	12	
7	Bike: 19:00	14	
	Bike: 20:00	14	
	Bike: 21:00	14	
8	Bike: 22:00	16	
	Bike: 23:00	16	
	Bike: 24:00	16	
If participant has not yet reached HR target, continue to level 18 for 3 min, then level 20 for 3			
Target HR:_____bpm **Time to HR target: _____min _____s RPE @ HR target _____**			
Post ex	Fitmate: test length + 5	Rest*	

STRENGTH TESTS:

20) Record dominant side (hand used to lift, throw etc.): ☐right ☐left

21) Hand grip strength: Sit on bench with shoulders adducted, elbows flexed to 90◦, and forearms in neutral position. Hold the dynamometer with dial facing away. Record measurement achieved before resetting dial and testing opposite side.

Right trial 1:_____kg	Left trial 1: _____kg
Right trial 2:_____kg	Left trial 2: _____kg
Right trial 3:_____kg	Left trial 3: _____kg

22) Leg press estimated 1 RM: The goal is to find a weight that the participant can lift for 7 to 10 repetitions. Time 60 seconds of rest in between attempts. Adjust seat to allow 90 degree angle at hips.

Seat height: _____ Leg press weight (lb.): _____ Reps: _____