HIGH-INTENSITY EXERCISE AND SAFETY CONCERNS IN BREAST CANCER SURVIVORS

by

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Abstract

Prescribing exercise as an adjuvant therapy for cancer survivors is becoming an acknowledged rehabilitative tool to offset the numerous biological toxicities that can develop with cancer treatments. Exercise interventions for breast cancer survivors typically prescribe low-to- moderate intensities to counteract the treatment-induced dysfunctions. These prescriptions have elicited inconsistent results. Interval training is currently being explored in many clinical populations with positive outcomes; however, the use of higher intensity exercise in the cancer population is not yet encouraged.

Through four different studies, this doctoral dissertation investigated the safety of implementing higher intensity exercise protocols into breast cancer survivor rehabilitative programs during chemotherapy (N=60) and post-primary therapy (N=33). The influence of intensity on safety, aerobic capacity and anaerobic capacity was explored. Supervised exercise programs and maximal aerobic stress tests were administered on a treadmill as it was demonstrated to be the preferred mode of exercise; in spite of this, the measure of anaerobic capacity was determined to be the most reliable on a cycle ergometer. Safety issues concerning neutropenia, altered chemotherapy dose, and biomarkers associated with poor outcome, were investigated.

During chemotherapy (FEC-D), 30 early-stage breast cancer patients exercised at intensities between 70- 90% $V0_{2peak,}$ thrice weekly, for the duration of their treatment (18.5 weeks). Women were able to safely incorporate bouts of higher intensity exercise

without increased hospitalization, immunosuppression, or negatively impacting their chemotherapy dose (achieved RDI was 92%, achieved RDI in the matched, usual care group was 90%).

Post-primary therapy, 33 postmenopausal breast cancer survivors were randomized into 3 groups (supervised high-intensity interval training (HIT), supervised continuous moderate-intensity exercise training (CMT) and an unsupervised control group). For 6 weeks, women in the HIT group exercised at intensities between 70 to 100% $V0_{2peak}$, while the CMT group exercised between 60-70% $V0_{2peak}$. HIT and CMT led to significant improvements in health-associated outcomes, however the mechanisms that led to these benefits may have differed between the groups.

No adverse events occurred due to high-intensity exercise in either supervised intervention. This dissertation provides evidence that breast cancer survivors can incorporate bouts of higher intensity exercise into their supervised rehabilitation programs during, or post-primary therapy.

Preface

All experimental procedures used to collect the data included in this dissertation, (Chapters 2-5), were approved by the University of British Columbia's Clinical Research Ethics Board, (Certificate H07-02498, H08-00968, H10-00060).

This dissertation contains work conducted by Lianne Dolan, under the supervision of Dr. Donald McKenzie, with guidance from Dr. K. Campbell, and Dr. W. Sheel. The study designs, subject recruitment, data collection, analysis and writing of the manuscript were primarily the work of the Lianne Dolan.

A version of Chapter 2 has been published as: Dolan LB, Lane K, and McKenzie, DC (2012) Optimal Mode for Maximal Aerobic Exercise Testing in Breast Cancer Survivors. *Integr Cancer Ther*. *E*-Pub Feb 2012. Volume 11, Issue 4, December 2012, pp. 321 - 326. Our group identified the research question, and Lianne Dolan was responsible for experimental design, data collection, data analysis, manuscript preparation and publication. Dr. K Lane assisted with data collection. All coauthors provided editorial feedback on the manuscript.

In addition, Dr. Karen Gelmon and Diana Jespersen assisted with the study design and subject recruitment in Chapter 3. Diana Jespersen played an integral role in the exercise supervision. In Chapter 5, Dr. Holmes assisted with measurement of the blood biomarkers.

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Abbreviations

%	Percent
<	Less than
>	Greater than
1-RM	One-repetition maximum (estimated)
6MWT	Six-minute walk test
ACTT	Adriamaycin (doxorubicin), Cyclophosphamide, Trastuzumab (Herceptin), Paclitaxel
AMPK	AMP- activated protein kinase regulates cellular energy metabolism
ANOVA	Analysis of variance
ATP	Adenosine triphosphate
BCRL	Breast cancer related lymphedema
BMI	Body mass index (kg/m2)
BP	Blood pressure (systolic - S, Diastolic - D)
bpm	Beats per minute
BSA	Body surface area
Ca^{2+}	Calcium ion
cm	Centimeters
CMT	Continuous moderate- intensity exercise training
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise test
CRP	C-reactive protein
FEC-D	Fluorouracil, Epirubicin, Cyclophosphamide, Docetaxel – drugs used in the FEC-D chemotherapy protocol
g	Grams
G-CSF	Granulocyte colony-stimulating factor -drug to stimulate bone marrow to increase white blood cell development
GLUT 4	Glucose transporter type 4 (insulin-regulated glucose uptake)
H^+	Hydrogen ion
Hb	Hemoglobin, also notes as [Hb] for hemoglobin concentration
HIT	High-intensity interval training
HOMA	Homeostatic model assessment (method to quantify insulin resistance and beta cell function
HR	Heart rate
HR_{rest}	Heart rate at rest
HR_{submax}	Submaximal heart rate
$HR_{max\ predicted}$	Maximal heart rate from age-predicted equation, or predictive test
HR_{rec}	Heart rate recovery

HRR	Heart rate reserve (maximum heart rate – resting heart rate)
ht	Height
IGF- (#)	Insulin like growth factor (e.g., IGF-1, IGF-2)
IL-10	Interleukin-10 (anti-inflammatory cytokine)
IL-6	Interleukin-6 (pro and anti-inflammatory cytokine)
kg	Kilogram
L	Liter
LA	Lactate
LVEF	Left ventricular ejection fraction
MCT1	Monocarboxylate transporter 1
MCT4	Monocarboxylate transporter 4
METS	Metabolic equivalent of task (3.5 ml 0_2/kg/min)
mg	Milligram
min	Minute
ml	Milliliters
mmol	Millimoles
mph	Miles per hour
0_2	Oxygen
pH	Measure depicting hydrogen ion concentration
pmol	Picomoles
QOL	Quality of life
RDI	Relative dose intensity
ROM	Range of motion
ROS	Reactive oxygen Species
RPE	Rating of perceived exertion (based on the Borg scale, 1-10, or 6-20)
rpm	Revolutions per minute
SR	Sarcoplasmic reticulum
SRT	Steep ramp test
T(#)N(#)	Tumour () nodes ( ) used to classify tumour stage based on characteristics. (#)Numbers in brackets associated with level of abnormalities
TNF-alpha	Tumour necrosis factor - alpha, cytokine associated with inflammation
TRAM	Transverse rectus abdominis myocutaneious flap surgery - used in breast reconstruction surgery
$V_{threshold}$	Ventilatory threshold
$V0_{2max}$	Maximal oxygen consumption
$V0_{2peak}$	Peak oxygen consumption
$Ve/VC0_2$	Ventilatory equivalent
VEGF	Vascular endothelial growth factor
W	Watts
wt	Weight
yrs	Years

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1 Introduction

Physical activity is a non-pharmaceutical intervention that provides recognized health benefits to healthy and clinical populations. Prescribing exercise as an adjuvant therapy for cancer survivors[i] is being recommended as a rehabilitative tool to offset the numerous biological toxicities that develop during cancer treatments.[155, 324, 337, 385] Treatment to combat tumour growth produces diverse, short and long-term side effects due to cancer's complicated biology. Cancer is a generic term used to describe a group of diseases in which the cells have the capability to undergo accelerated, abnormal growth and can invade adjoining tissues.[412] A mutation could cause any cell to rapidly grow and divide, thus complicating the term 'cancer' as it encompasses not just one, but many tissues. With numerous hypotheses surrounding the trigger of cancer development, it is recognized that cancer is a multi-factorial disease; accordingly, each individual cancer diagnosis has different treatment combinations that may elicit a vast array of side effects.

Breast cancer is the most common cancer in Canadian women over the age of 20, with approximately 22 700 women diagnosed in 2012.[48] Currently, treatment for non-metastatic breast cancer involves multiple procedures, such as surgical removal of the tumor, adjuvant chemotherapy, radiation, targeted therapies and/or hormonal therapy. The type of therapy and the combination of treatments are individualized for each patient according to the characteristics of their tumor (e.g., size, grade, receptor status). With earlier diagnoses, coupled with advances in treatment and technology (i.e., screening,

[i] This dissertation will use the term survivor in the context defined by the National Cancer Institute. "An individual is considered a survivor from the time of diagnosis through the balance of their life."

improvements in surgery, radiation techniques, new chemotherapeutic agents or combinations, and advances in hormone and biologic therapies) the 5-year survival rate for breast cancer survivors has improved to approximately 88%.[48] As breast cancer is such a diverse disease, the treatment and side effects are equally mixed. Treatment will not only target the tumour cells, but it can alter the cardiopulmonary, musculoskeletal, immune, endocrine, nervous and cognitive systems resulting in a growing, heterogeneous, clinical population of survivors.

In addition to the normal aging process, the maturing cells of post-menopausal breast cancer survivors must cope with the additive, lingering toxic effects of treatment. Understanding the functional dynamics between the biological systems pre- and post-therapy can pave a path for improved outcomes. The measurement of cardiorespiratory fitness, through a maximal aerobic capacity (or cardiopulmonary exercise) test, provides a means to investigate the functional outcome of a metabolic abnormality that may occur due to treatments. Poor cardiorespiratory fitness, or aerobic capacity, is a powerful predictor of mortality, with research in women demonstrating a small increase (i.e., 3.5ml/kg/min) can lead to a 17- 25% decrease in risk of all- cause mortality.[211, 326, 396] It is documented that breast cancer survivors have below- average aerobic capacity values compared to age-matched controls.[190] The mechanisms that hinder the cardiorespiratory dynamics remain unknown and are complicated to decipher due to the uniqueness of the patients' biology coupled with personalized cancer therapy. To understand this integrated framework, a brief explanation of possible treatment-sensitive mechanisms that contribute to cardiorespiratory fitness will be outlined prior to discussing the general

long-term side effects. Previous exercise interventions, and the key role that exercise intensity may play in survivorship will be summarized (see Table A1.1 to reference intensities). The synopsis will be limited to breast cancer as the adverse affects of the numerous different cancer treatments is beyond the scope of this dissertation.

Pathophysiology and treatment side-effects

There are multiple metabolic pathways that are intricately linked to maintain optimal functional capacity. At different points along this integrated network, disease or human interference can modify one, or multiple steps, initiating a deficiency in the biological machinery that hinders normal performance. To maintain homeostasis, physiological compensation of an adjacent system may occur, but total metabolic function will eventually be affected leading to a decline in health or chronic disease. Primarily, this section will discuss potential sensitive points in postmenopausal breast cancer patients by focusing on 2 major metabolic pathways: anaerobic metabolism (also referred to as substrate phosphorylation) and aerobic metabolism (i.e., oxidative phosphorylation).

Anaerobic capacity

Anaerobic pathways can supply energy quickly, in large amounts, and aid in restoring energy balance post-exercise. Glycolysis and the degradation of phosphocreatine are two major pathways in skeletal muscle that rely on substrate delivery; accordingly, both replenish energy stores quickly, but optimal anaerobic function is limited by enzymatic activity and substrate availability.[150] It remains unknown to what extent cancer therapy influences these pathways, as few have investigated anaerobic capacity during treatment. Previous research has investigated various glycolytic enzymes throughout treatment and demonstrated relationships between altered enzyme concentrations, tumour growth and

outcome.[164, 362] There has been no research detailing the change in dynamics of whole body anaerobic function with treatment.

Chemotherapy is designed to alter the cellular environment within the tumour tissue, but it also damages healthy tissues as treatment elicits high levels of reactive oxygen species.[4, 26, 67, 279] Increases in free radical production will damage DNA[7] and negatively affect enzymatic activity.[187] Defective enzyme function will limit the breakdown of substrates, which will lead to a reduction in anaerobic energy supply. Declines in an energy source will lead to a global dysfunction within the integrative metabolic pathways impeding optimal human health and performance.

Aerobic capacity

The aerobic pathway relies on the ability of oxygen to be efficiently transported from the environment to the metabolically active cell. Oxygen moves through the body via diffusion and convection. Upon reaching the target organ it is extracted and utilized within the mitochondria to replenish energy.[171, 172] This respiratory, or oxygen cascade,[171, 172] is commonly discussed in the literature and the efficiency of this pathway, (quantified by a maximal cardiorespiratory exercise test), can be used to investigate and understand health, disease and mortality. Treatment for breast cancer could alter one or more mechanisms along the oxygen cascade,[191, 216] influencing risk of recurrence, accelerating the aging process, developing co-morbidities or increasing risk of death.

Chemotherapy, targeted therapy, and site-specific radiation are treatments that can hinder gas exchange by inducing pulmonary toxicity that prevents efficient oxygen diffusion.[2,

[316, 376] Further, treatments can exacerbate this faulty point along the oxygen cascade with alterations in respiratory muscle function[103] coupled with declines in hemoglobin concentration.[240] Notably, 40% of breast cancer patients (Stage II-III) will suffer from chemotherapy-induced anemia.[206] This means almost half of patients who undergo chemotherapy will suffer from limited oxygen transport during treatment.

A wide range of cancer therapies are associated with cardiac toxicity[208, 287] generating altered cardiomyocyte cellular energetics.[68] The metabolic change can negatively affect contractile function, induce bradyarrhythmias, initiate hypertension and cause declines in left ventricular ejection fraction (LVEF).[416] This weakened 'pump' will impede efficient oxygen transport to the metabolically active sites in the periphery causing a decline in aerobic energy supply. In addition to the central pump abnormalities, vascular health within the periphery diminishes with cancer therapies. Oxygen delivery could be further hindered due to barriers created by treatment-associated abnormalities in the red blood cell, [420] inhibition of vascular relaxation, increased arterial stiffness, and endothelial dysfunction.[107, 245]

In the periphery, diffusion of oxygen from the red blood cell to the site-in-demand requires efficient extraction, but will be limited by changes in diffusion distance due to increased cellular membrane toxicities, dysfunctions within the cell, or abnormal enlargement of cells. These aforementioned modifications commonly arise due to acute increases in reactive oxygen species (ROS) and depletion in estrogen levels,[356] both of these side-effects occur with cancer therapy. Previous research has demonstrated that

exposure to high levels of reactive oxidative species, initiates disfiguration of the mitochondrial membrane inhibiting function.[27, 102, 351] Antineoplastic agents are known to cause a rise in oxidative stress[394] and early-stage breast cancer patients are typically prescribed antineoplastic agents that can elicit the highest level of oxidative stress (doxorubicin and/or epirubicin).[67] These agents target susceptible areas along mitochondrial pathways, which can reduce function within the electron transport chain, thus limit ATP production.[68, 288] Further, stress to the endoplasmic reticulum or the sarcoplasmic reticulum (SR) in skeletal muscle will lead to downstream metabolic dysfunction that encourages the development of various diseases.[205, 229] SR dysfunction triggers abnormal insulin and glucose metabolism, alters Ca^{2+} dynamics and decreases myofibril sensitivity, which will suppress the energy capacity of the muscle; consequently, leading to peripheral fatigue and diminishing contractile ability.[8, 90, 398, 399] Impairment in the mitochondria membrane and skeletal muscle machinery translates to inefficient cellular respiration. Depending on volume of affected cells, the dysfunction can result in a decline in aerobic capacity.

Aging and estrogen

The toxicities from cancer therapy not only accelerate the menopausal status of some women and loss of estrogen function in others, but can hasten the premature expression of the usual age-related changes.[136, 243] In general, aging is not only associated with cancer development,[121] but is associated with a decline in aerobic capacity due to decreases in strength, muscle fiber loss, weight gain, decreases in bone density, alterations in blood flow, poor vascular reactivity, mitochondria dysfunction, delays in neuromuscular function and a rise in co-morbidities.[151, 390] Estrogen, which decreases

with age, plays a key role in preserving optimal function within the skeletal muscle, the cardiovascular system and the brain.[382] Oophorectomies, chemotherapy and endocrine therapy can trigger abrupt depletions in estrogen levels, causing an acute, senescent stress on the metabolic pathways. Anti-estrogen receptor treatments may alter estrogen receptor-alpha expression, which will diminish mitochondrial biogenesis.[49] This treatment-induced systemic depletion aids in preventing recurrence in estrogen positive patients;[105] however, the impact of a decline in estrogen function in healthy women is associated with increases in systemic inflammation[367], visceral adiposity, insulin resistance, hepatic dysfunction, cardiac dysfunction, skeletal muscle dysfunction, disruption in the mitochondrial membrane, cell size abnormalities, dysfunctional cell metabolism, declines in glycerol oxidation and alterations in membrane transporters.[356,387] Many of these estrogen-linked, age-related changes influence the oxygen cascade but the rate of decline can be attenuated with exercise. These changes could be points of interest for cancer rehabilitative programs. The mechanisms behind delaying the aging process and reducing treatment effects are most likely to differ, but it is important to note that understanding these sensitive areas could provide insight into potential locations (targets) for the reversal process to occur.

General side-effects and rehabilitative targets

Cancer treatment not only targets tumour cells, but it can impact nearly all other biological systems. With breast cancer treatment, many women experience short-term and long-term side effects such as weight gain, decline in aerobic capacity, fatigue, pain, depression, vasomotor symptoms, loss of fertility, early onset of menopause, fear of recurrence, decreased bone mineral density, decreased physical functioning and decreased overall quality of life.[70, 299] These treatment-induced side effects have associations with disease development and early mortality; consequently, treatments can prevent acute death from cancer, but in-turn they predispose survivors to increased risk for developing co-morbidities.[91, 130] A clinical trial following a large cohort of breast cancer patients past their 5-year survival mark, found that 60% of women were more likely to die from non-breast cancer-related causes than from breast cancer-related causes.[50] Survivors are also experiencing excess levels of cardiovascular disease related events, relative to their age-matched (cancer free) controls.[169, 300] Discovering the reversible mechanisms behind the shift to increased mortality, due to potential treatment induced co-morbidities, is necessary to improve survivorship.

Weight gain

Treatments can predispose breast cancer survivors to weight-gain,[183, 325] a problem that is associated with a range of co-morbid conditions such as metabolic syndrome, cardiovascular disease and type 2 diabetes.[183, 203] The increase in adiposity may be a direct affect of the treatment due to alterations along the metabolic pathways,[203] or a secondary outcome due to an accelerated reduction in estrogen levels, which is associated with decreased exercise motivation and heightened visceral adiposity.[356] Irwin and

colleagues noted that weight gain occurs within the first year following diagnosis, with few individuals returning to their pre-diagnosis weight[183]. Whether treatment directly or indirectly causes weight gain may be too multi-factorial to pinpoint; nonetheless, weight gain during treatment is associated with increased risk for recurrence and death compared to those who are able to sustain a normal weight. [42, 44, 82, 215] Adipose tissue is metabolically active and produces inflammatory cytokines, which in excess, will cause dysfunctional effects downstream along the growth signaling cascade that is associated with cancer progression.[93] Managing weight gain post-treatment needs to be a priority to improve overall health, prevent recurrence, and enhance survivorship. It has yet to be demonstrated in post-menopausal breast cancer survivors, but guidelines, based on results from the general population, promote a 5% to 10% reduction in body weight, over a 6-to-12 month period, to decrease factors (i.e., elevated plasma lipids and fasting insulin levels) that are related to the development of chronic disease (i.e., metabolic syndrome and type 2 diabetes).[99]

Insulin

Insulin, a hormone released from the pancreas, stimulates the growth of breast cancer cells; consequently, high levels are associated with poor prognostic outcome.[140] After following 512 non-diabetic breast cancer survivors, Goodwin et al discovered that individuals with higher levels of insulin had a 2-3 fold risk of recurrence and death; however, the concept of a minimum level/threshold (e.g., 50 pmol/L) associated with recurrence risk is under debate.[140] With these results, finding a means to reduce a rise in insulin levels has become a major topic in treatment such that diabetic pharmaceutical treatments (e.g., metformin) that reduce hepatic gluconeogenesis and peripheral insulin

sensitivity[318] are being given to breast cancer survivors as a possible way to improve survivorship.[138, 141, 159] However, the mechanisms behind metformin's potential success is still elusive as one of the hypotheses investigated led to increased angiogenesis triggering tumour progression.[306] The second theory hypothesizes that there is an enhanced peripheral cellular sensitivity, but it is also controversial, for enhanced sensitivity could increase tumour cell sensitivity to insulin, thus stimulate cancer growth.[159] In 2006, Pollack's lab uncovered that metformin limited growth and division through activating the AMPK pathway, (i.e. having the antagonistic affect to insulin).[417] Methods that can enhance the AMPK pathway (key in maintaining ATP levels) without triggering an angiogenic response from the tumour is an ongoing battle for researchers.

Skeletal muscle

Sarcopenia, which is associated with decreases in strength and power, is also a side effect of cancer treatments that parallels the aging process.[389] Whether it is a direct effect of treatment myotoxicity or a secondary effect due to reduced estrogen and inactivity remains to be clarified. The treatment related mechanisms behind the long term side-effect of cancer-related fatigue remains debated.[414] It is unknown if chemotherapy or radiation lead to long-term damage within the architecture of the muscle; hence, more mechanistic research is required, as peripheral and central fatigue can both be related to metabolic and peripheral disturbances. In estrogen-positive breast cancer survivors, estrogen depletion could exacerbate the myotoxic environment, increase systemic inflammation, and hinder the maintenance of skeletal membrane integrity; consequently, this lack of stability would influence normal metabolic function.[374] The muscle fiber type that is the most sensitive to treatment has not been elucidated nor has the impact on

contractile function been clarified; however, possible discoveries in the aging and other clinical populations with similar side effects could reveal mechanisms of interest behind cancer-related fatigue and weakness. Exercise training is hypothesized to remove damaged mitochondria, (which if left alone can lead to insulin resistance)[197, 320] and modulate dysfunctional sarcoplasmic reticulum[90], (allowing for improved release and re-uptake of calcium); consequently enhancing the quality of muscle contraction and decreasing mechanisms related to muscle fatigue and insulin resistance.

It is important to note that the mechanisms behind treatment-induced alterations within the metabolic pathways of skeletal muscle (mitochondria and vascular function) are hypothesized based on animal studies, *in vitro* studies or in other clinical populations that have similar tissue environmental changes, as muscle biopsies in breast cancer patients are difficult to obtain.

Inflammation

Reactive oxygen species (ROS) formation is associated with an inflammatory response, and is key for many cell functions, adaptations and repair mechanisms; however in surplus, oxidative stress will ensue, triggering a damaging inflammatory reaction and hinder many cellular functions.[187, 383] Cancer treatments produce circulating free radicals that aid in initiating tumour necrosis, but high levels will negate some of the benefits of adjuvant therapy [67, 288] In addition, excessive levels of systemic inflammation in survivors are associated with cancer-related cognitive dysfunction, cancer-related fatigue[4] and trigger the development of co-morbidities.

C- reactive protein (CRP) is a serum protein that is primarily made in the liver in response to inflammation, (i.e., IL-6 and other metabolic irritants). It is a key marker that indicates a source of inflammation in the body and is associated as an indicator of future cardiovascular disease, cardiovascular events and other co-morbididities.[109, 249, 313, 322] The concept that cancer therapy encourages a treatment-induced, unfavorable cardiovascular risk profile is a major concern for survivors,[194] as cardiovascular disease is currently the world-wide leading cause of death in females.[400] New research is uncovering different biological active isoforms of CRP revealing that it may not just be an indicator of disease, but it could also be a participant in disease development.[388] Information involving inflammation is evolving, demonstrating associations with side-effects,[408] recurrence, survivorship,[63] cancer development[75] and poor cancer prognosis.[9, 310] These connections are worrisome, for breast cancer survivors appear to have increased chronic levels of CRP compared to the general population.[309]

Therefore, to survive cancer, patients are not only battling their primary cancer, the side effects of the primary treatment, but also the treatment induced co-morbidities that can increase their risk of disease-specific and all-cause mortality. To improve overall survival, it is critically important for cancer survivors to find a means to reverse the treatment-induced metabolic dysfunctions that may have developed. For many of the aforementioned dysfunctions, physical activity has reversed, suppressed, or prevented the co-morbidity in other at-risk populations.[30]

Exercise interventions

Many cancer survivors may suffer from one, or many of the previously mentioned side-effects; however, due to their treatment-induced metabolic dysfunctions, this clinical population is at increased risk for developing type 2 diabetes, cardiovascular disease and metabolic syndrome, making this a major public concern. Fortunately, many of the aforementioned side effects and diseases can be influenced with increased physical activity.[13, 29, 225, 256, 307] Exercise can preserve bone mineral density,[144] decrease oxidative stress and inflammation,[38, 186, 305, 411] improve cardiovascular function, and positively modify the endocrine system, which in turn reduces the risk of cardiovascular disease as well as diabetes;[30, 225, 256] accordingly, it is hypothesized that these benefits will extend to breast cancer survivors.[168]

Regular exercise may have the ability to trigger rehabilitative stresses eliciting an adaptive response along the damaged metabolic pathways, restoring the cancer survivor back toward their optimal health. Exercise-sensitive mechanisms that may prevent cancer development or recurrence, have been hypothesized in a variety of reviews;[36, 93, 126, 178, 257, 258, 284] however, this section will focus on the results of exercise interventions, which were founded on those well-reviewed mechanisms (e.g., estrogen exposure, energy balance, dysregulated growth signaling, abnormal cellular energetics (insulin derivatives, systemic inflammation, AMPK, adinopectin), immune dysfunction, angiogenesis modulators).

In breast cancer survivors, exercise is associated with improved fitness, reduced fatigue[21], decreases in body weight, decreases in body fat,[256] improved quality of life,[52, 54, 73, 81, 162,

[263, 402] superior body composition, improved lipid profile,[260] greater functional capacity and decreased insulin levels.[228] In addition, interventions have demonstrated that exercise does not exacerbate breast-cancer-related-lymphedema[5, 219, 254, 336]. Due to these adaptations, physical activity is now becoming an accepted, cost-effective, non-pharmacological method to ameliorate the psychological and physiological side effects in breast cancer patients. In addition, evidence is growing demonstrating that women who engage in physical activity after breast cancer diagnosis (compared to those who are sedentary), have significantly lower rates of recurrence,[168] as well as declines in disease-specific and overall mortality rates.[166, 168, 185] Further, four large, observational studies also support the notion that exercise improves disease specific or all-cause mortality compared to inactive lifestyles. [53, 168, 184, 364] The total volume of exercise remains debated and exercise intensity is difficult to determine as these studies based their findings on self-reported measures. It is hypothesized that in breast cancer survivors specifically, the association between physical activity levels and disease-specific mortality may be explained by the positive influence of exercise on circulating levels of sex hormones, insulin, inflammatory markers and obesity.[258]

Exercise interventions during primary therapy

Exercise prescriptions during and post-primary therapy for breast cancer survivors have been reviewed and are typically conservative, involving low-to- moderate intensities, for less than an hour a day, 2-5 days a week, over a range of durations from weeks to a year (see Table A1.2).[45, 71, 72, 177, 180, 204, 209, 238, 246, 255, 338, 339, 357] For logistical reasons, mortality is not a measured outcome during interventions; however, outcomes associated with mortality, recurrence and general health are frequently analyzed. During adjuvant

treatment, low-to-moderate exercise is commonly prescribed due to the fear associated with exacerbating fatigue and exercise-induced immunosuppression (for this population, moderate-to-vigorous exercise tends to be bundled together as approximately 40% $HR_{reserve}$).[357] These general guidelines have elicited positive, but inconsistent results concerning changes in surrogate markers of recurrence and future co-morbidities (e.g., aerobic capacity, fitness, body composition, weight gain, fatigue, depression, nausea, and quality of life).[74, 80, 81, 212, 244, 246, 265, 266, 278, 308, 341, 343, 405] This general exercise prescription has been assigned to treat not just one side effect, but to treat a complex, multi-dimensional problem, consequently producing in inconsistent results.

Exercise interventions post-primary therapy

Post-primary therapy, many prescriptions follow aerobic exercise protocols but few studies measure the direct change in aerobic capacity. Studies typically use a variety of predictive methods to assess changes in health and changes associated with the oxygen cascade. These mild-to- moderate intensity aerobic exercise prescriptions produce inconsistent results regarding body mass and biomarkers. Three exercise interventions reported no change in aerobic capacity[20, 120, 157]. A 12-week walking program (3-5 days /week) demonstrated no change in body composition compared to usual care.[251] Another 12-week program used a walking protocol to demonstrate improved physical activity behavior and increased muscle strength, but there was no change in body fat, bone mineral density or body mass index (BMI).[327] A thrice weekly, 15-week moderate aerobic exercise intervention found improvements in aerobic capacity and insulin-like growth factors, but not in body weight or insulin levels.[117] An association between improved aerobic capacity and quality of life in post-menopausal survivors was reported,

but there was no change in body mass after 15 weeks.[73] Further, this study analyzed a variety of cardiovascular variables (e.g., CRP levels, resting heart rate, blood lipids and blood pressure) and reported trends signifying a potential for exercise to lower the risk of cardiovascular and all-cause mortality in this clinical population.[116] Increasing duration to 6-months, a randomized control trial (YES trial) prescribed moderate-intensity exercise, (15-30 minutes at 50-80% $HR_{max\ predicted}$) 3-5 days a week, and reported no influence of exercise on body weight, BMI, hip or waist circumferences when compared to the control group.[181] However, the aerobic prescription prevented declines in bone mineral density, decreased body fat and improved lean mass, compared to the non-exercising controls (it is important to note that resistance exercise and yoga were performed but were not tracked).[181] Further, this trial revealed positive findings concerning insulin-like growth factors but did not find changes in insulin levels.[179]

Resistance exercise has a range of beneficial effects in cancer survivors, summarized in a recent review by De Baker and colleagues, highlighting positive effects for cardiopulmonary and muscle function, but only slight changes in body composition, endocrine function, immune function, and hematological variables.[86] Against popular guidelines, two groups of scientists have used high-intensity resistance training in mixed-group cancer survivors with positive benefits in a variety of physiological and psychological health markers (e.g., $V0_{2max}$, strength, QOL).[3, 88] De Backer et al acknowledged that the previous guidelines promoted gentle workouts as the patients were suspected to be undergoing high amounts of physiological and psychological stress. Nonetheless, the group felt those guidelines could not elicit the required training effect

and the published results demonstrated that high-intensity resistance exercise was safe, as no adverse events occurred, and a rehabilitative effect was demonstrated.[88]

Moderate-intensity aerobic programs combined with resistance exercise have produced an assortment of results. Following treatment, a 6-month moderate training program for breast cancer survivors demonstrated improvements in cardiopulmonary function, resting heart rate, blood pressure and fatigue levels, but no information was provided concerning change in body weight.[340] Ligibel et al published results from a 16-week intervention that led to a decrease in insulin levels within the exercise group, but the within-group change did not result in significance when compared to the change within the control group.[228] Further, this study revealed a slight trend for an improvement in the homeostatic model assessment (HOMA) but there was no change in fasting glucose levels, body mass, body composition and adipocytokine levels.[227, 228] In a 6 and 12-month combined program of moderate aerobic and resistance exercise, improvements were discovered in IGF-II, lean mass and fat mass, but no change occurred in insulin, glucose, HOMA score, IGF-1, body weight and waist circumference.[335]

In summary, these exercise interventions for breast cancer survivors all prescribed moderate-intensity aerobic exercise with or without resistance training, and the programs elicited at least one beneficial health change but lacked consistency between trial outcomes. It is acknowledged that measurements vary due to logistics, which makes direct comparisons between exercise volume (modality, intensity, duration etc…) and health outcomes extremely difficult. In accordance with a recent review on exercise

interventions in breast cancer survivors,[45] we also speculate that the poorly applied principles of training[165] (i.e., the lack of a specific exercise program based on a specific goal that will treat the side effect), coupled with the initial low-intensity baseline prescriptions, may prevent the rehabilitative capability of exercise to target the wide range of dysfunctional cellular mechanisms within the anaerobic and aerobic pathways.

High-intensity interval training

To optimize overall athletic performance the concept of high-intensity interval training (HIT) has been practiced in sport programs for years.[222] The term "interval training" covers a wide range of intensities and durations, and the prescription usually depends on the overall goal, and capability of the individual. In general, it involves short, intermittent periods of fast muscle contraction performed at close to maximal effort.[152] Previously, endurance-training protocols were the main staple for programs that needed to enhance performance; however, interval training has also proven to be successful at altering mechanisms linked to directly enhancing the oxygen cascade. Unlike continuous, moderate-intensity exercise, high-intensity interval training elicits a wide range of intensities that engages a greater volume of different muscle fiber types.[380] This is likely to stress a wider spectrum of tissues along the different metabolic pathways causing a greater global change. HIT interventions have been reviewed[222] with consistent results showing improvements in skeletal muscle metabolism, such as: increased oxidative capacity in type IIa fibers (via enzyme activity of succinate dehydrogenase and cytochrome oxidase);[24] enhanced mitochondrial fatty acid oxidation rates in rats;[56] (hypothesized to be a reason for improved fat oxidation observed in humans);[112] increased activity in gylcolytic enzymes;[167] improved ability to buffer H^+ ions (enhanced

skeletal muscle buffering capacity);[232] greater enzyme activity within the sarcoplasmic reticulum; adaptations of the central nervous system (reduced sympathetic outflow); increased myoglobin; greater capillary density and improved fiber type characteristics.[222] If one type of exercise prescription, such as HIT, could effectively influence a larger range of metabolic pathways it could translate into a more efficient stress to prescribe in the diverse, cancer rehabilitative environment.

These improvements do not only occur in highly-trained athletes but also in untrained individuals.[222] A significant barrier to participating in a regular endurance-based exercise program is the amount of dedicated time required to attain the desired results.[29, 363, 397] One of the benefits that is commonly cited for interval training is the minimal time required to generate a metabolic change.[134] Previous research has shown improvements in aerobic capacity with as little as six interval training sessions that each consisted of 2-3 minutes of high-intensity training.[40, 133] In women, two weeks of high-intensity training stimulated marked increases in whole body and skeletal muscle capacity for fatty acid oxidation,[372] it also improved aerobic capacity, post-lactate levels and time to exhaustion[319] In both sexes, mitochondrial biogenesis,[40, 41] arterial distensibility,[317] aerobic capacity, anaerobic power, and time to exhaustion have all improved with short bouts of interval training; consequently, all had a significant decrease in total exercise time/volume compared to the endurance training groups.[40, 41, 133, 142, 217, 317, 370] Further, matched-work designs that compare HIT with moderate-intensity training have reported a greater change in $V0_{2max}$ with HIT.[59, 143, 160, 285, 329, 375, 406, 407] Yet, there are matched designs that have published similar improvements regardless of training modality in

aerobic capacity,[84, 106] blood pressure,[58, 145, 375] enzyme activity[143] and skeletal muscle adaptations.[393] The results led the authors to speculate that the mechanisms behind the similar improvements between training modalities, differed. After analyzing the additional measures, the HIT-induced adaptations appeared to provide a greater range of health benefits (e.g., improvements in arterial stiffness,[145] neuro-hormonal levels,[58] muscle oxidative capacity[84] and insulin signaling[58]).

Conversely, even with this accumulating amount of evidence, the concept of implementing higher intensity interval exercise prescriptions to ameliorate health conditions is just being adopted in clinical populations (see Table A1.3). As the fuel source is dominantly lipids during lower intensity exercise, it was hypothesized that HIT would not be beneficial in obese clinical populations.[154] Yet research has demonstrated that training at higher intensities triggers mitochondrial biogenesis[236, 237] and encourages the fuel source to be from fats for a longer duration, prior to switching over to carbohydrate sources.[150] Further, health improvements such as changes in aerobic capacity, fatty oxidation, insulin sensitivity, and cardiac function have been demonstrated in a wide range of clinical populations: obese individuals,[334] individuals with metabolic syndrome,[375] heart failure patients,[406] elderly heart failure patients,[407] individuals with type 2 diabetes,[37] those with abnormal glucose tolerance,[293] and in COPD patients.[69, 314] In older men and women, walking intervals were also investigated, and generated positive results in physical functioning and cardiovascular variables.[270] The intensity prescribed influenced the duration of the high-intensity bout, but the general findings

demonstrate that greater improvements are seen in the higher-intensity, low duration protocols.

Many researchers promote the use of HIT to improve aerobic capacity in populations suffering from cardiovascular and heart-related diseases.[198, 268, 273, 369, 406, 407] The success of HIT in cardiac and other clinical populations may be the result of the incorporated rest breaks. The rest bouts decrease the feeling of dyspnea and prevent accumulation of ROS in the myocardium, preventing further cardiac damage.[261, 262] The breaks delay fatigue, while the intense exercise bouts provide adequate stimuli to the endothelium. The pulsatile shear stress that is produced with intervals can enhance mechanisms responsible for vascular relaxation and contraction. Enhanced distensibility (decrease in arterial stiffness) seen with HIT,[60, 145, 317] could improve local blood flow distribution in aging women, thus contribute to greater oxygen availability, improving oxygen kinetics at the periphery.

It is speculated that two weeks of HIT improved fatty acid oxidation in women through improved transport of glycerol and mitochondrial capacity.[40, 372] Consistent bouts of physical activity can increase the number of healthy organelles, improve the mitochondria efficiency thru eliminating dysfunctional organelles and consequently enhance the dynamics of the mitochondrial network.[413] Perry et al, demonstrated that after only seven HIT sessions the biological machinery responsible for maintaining optimal mitochondrial dynamics improved, enhancing metabolic capacity.[304] Exercise during cancer therapy may not be able to overcome all the suppressive effects of

treatment but some aspects may be altered, which could decrease recovery time, post-primary therapy. This highlights the importance of discovering which mechanisms can change during or post-primary therapy, depending on the type of treatment, in regards to the specific goal of the exercise program.

Only two exercise programs have prescribed interval protocols to improve functional capacity in breast cancer survivors, but neither used high-intensity protocols. In 1989, MacVigar and colleagues used unidentified durations at 65-80% of heart rate reserve and elicited a 40% improvement in functional capacity.[244] The second study occurred post-initial therapy (30 second bouts at 65% maximal work load followed by 30-60 seconds at 30% over an 8 minute period);[87] however, the program was a combined program so the impact of the intervals on the outcomes cannot be defined. Fear of negatively impacting immune function, in a population that can suffer from long term immune dysfunction,[196] may be a key reason to why so few have challenged the low-to- moderate-intensity guidelines.[338] Two studies observed a positive benefit from moderate-intensity exercise training on immune function[115, 175] and one study in healthy individuals has addressed the concern associated with high-intensity exercise bouts and immune dysfunction.[122] Fischer and colleagues noted that after a week of high-intensity interval training, there was an expected rise in oxidative stress, but the immune parameters demonstrated greater resistance to inflammation coupled with an upregulation in antioxidant enzyme activity.[122] The authors concluded that interval training could be an ideal stress to improve health with minimal immunosuppression.

Population specifics and exericse design

Few exercise-training studies have the resources to separate their subjects by cancer therapy, leading to vast differences in subject characteristics, creating limited, almost non-existent, homogenous sample populations. An intervention study from the Rocky Mountain Cancer Rehabilitation Institute, observed that exercise elicited improvements, independent of treatment;[173] nonetheless, an observational cohort study found that physical activity post-treatment lowered the risk of death, but the strongest benefit occurred in women treated for estrogen positive tumors.[168] It remains unknown if cancer treatment creates a different physiological response to exercise stimuli compared to the adaptation response seen in healthy, age-matched women. The thesis by Drum, SN attempted to tackle this question with an eight-week, low-to-moderate intensity intervention, but there was high variability within the groups and limited measures.[101] Overall, the published literature has provided general evidence linking exercise with positive health-related outcomes (i.e., factors influencing quality of life);[54, 255] yet, the research is inconclusive concerning the response to exercise depending on type of treatment, as well as specific exercise prescriptions that will influence surrogate markers of recurrence and mortality risk.

Ideally to achieve an effective outcome, the design of an exercise program should take into consideration the physiology that has the potential to change with an exercise stimulus, to ensure attainment of the program goal. Cancer survivors are reported to suffer from poor aerobic capacity when compared to age-matched controls;[190, 377] hence, their exercise design needs to uncover, and focus on which biological mechanisms are presently weak and are disproportionally contributing to O_2 flux.[188] Thus, the goal needs

to revolve around rehabilitating these limiting factors that have the potential to change with exercise, resulting in improved efficiency within the oxygen cascade.

Accordingly, decreased estrogen levels may suppress adaptations within the heart, while adaptations in the periphery may still be sensitive to change. Rehabilitative interventions in older women reveal a lack in central adaption with exercise training. [156, 274, 359, 360] Previous studies in cardiopulmonary disease-free individuals observed that older women (unlike men) tend to show increases in aerobic capacity, not to due increases in cardiac performance (ie. left ventricular systolic performance)[361] but due to peripheral adaptations (muscle oxidative capacity and larger arterio-venous oxygen content) meanwhile improvements in younger women coincide with central adaptations (stroke volume and cardiac output).[274, 360] Previous research in animal models hypothesized that peripheral adaptations only contribute to 25% of one's maximal aerobic capacity;[95] however, when Murias and colleagues investigated this concept by separating their results by age and gender, the results revealed that older women attributed 65% of the post-training improvement in aerobic capacity to peripheral adaptations.[274] Similarly, using evidence from a cross-sectional study design, Lee et al discovered that the drop in aerobic capacity post-primary therapy occurs from treatment-induced metabolic changes in the periphery, as cardiac function (% LVEF) was similar to age-matched controls.[190] Based on these studies, the peripheral vasculature and mechanisms in skeletal muscle in estrogen deficient women may be more sensitive (than cardiac adaptations) to exercise stimuli. This specific effect should influence the exercise design, as targeting peripheral

mechanisms may be key in improving the health of post-menopausal breast cancer survivors.

Enrolling individuals at baseline based on age and fitness backgrounds, is a common method used by many exercise intervention studies to create homogenous groups; however, with this assumption, it is acknowledged that there is significant variability among individuals in vascular architecture, muscle fiber type and enzyme activities. Further, there is a genetic component associated with the adaptive response to exercise.[32] This individuality is then confounded in the unhealthy population with such diverse treatment options and the personalized pharmacokinetic response to cancer therapy. This provides an explanation for the wide range of results within, and between clinical interventions. The breast cancer survivor population will have high biological variability, as treatment differs with each diagnosis and each treatment may cause differing metabolic responses unique to each patient. Motor units and thus specific fiber type recruitment (and thus accompanying metabolic enzymes),[312, 371] will vary according to exercise intensity.[104]As the limiting mechanisms behind the biological alterations from cancer treatments remain elusive, a program that has the potential to target a wider range of peripheral physiology should be explored in the breast cancer population.

Statement of the problem

Breast Cancer survivors face a multitude of health issues post-diagnosis. Exercise interventions have been implemented to ameliorate these side effects, but with varying results. The array in published outcomes could be related to the range in metabolic dysfunction due to the heterogeneity within this population. Implementing high-intensity interval training as a rehabilitative tool could target a wider range of metabolisms, providing improved results. In spite of this, few studies have investigated interval training using high-intensity levels in the breast cancer survivor population.

Purpose and hypotheses

The purpose of this series of studies is to examine a new method of exercise prescription in breast cancer survivors, to investigate whether it is safe during treatment, and to determine its effect, post-primary therapy, on the general health of breast cancer survivors. High-intensity exercise will be considered unsafe if it elicits any adverse events that could harm the present or future health of a cancer survivor. Specifically, the aim and hypotheses of this dissertation are:

1. To determine which mode of exercise is the most effective to quantify aerobic capacity in breast cancer survivors.

   H1: The use of the treadmill protocol compared to the use of a protocol on a cycle ergometer will be the preferred mode to elicit $V0_{2peak}$ in breast cancer survivors.

2. To investigate the safety of higher intensity exercise on chemotherapy delivery (i.e., relative dose intensity (RDI)) and immune parameters during a specific chemotherapy protocol (FEC-D) in early-stage breast cancer survivors.

   H2: Higher intensity interval exercise will not negatively influence RDI or immune parameters in women undergoing FEC-D chemotherapy for early-stage breast cancer.

3. To explore the possibility of determining a safe method to quantify anaerobic capacity in breast cancer survivors by comparing a treadmill speed test to a steep ramp protocol on a cycle ergometer.

   H3: A treadmill speed test will provide reproducible and reliable results to quantify anaerobic capacity in post-menopausal breast cancer survivors.

4. To evaluate the safety and the effects of different exercise intensities on anaerobic and aerobic capacity in post-menopausal breast cancer survivors over a six-week period. A progressive, high-intensity interval training group will be compared to a continuous, moderate-intensity exercise group and a control group.

   H4: High-intensity interval training will be a safe protocol to implement into rehabilitative programs for post-menopausal breast cancer survivors, and will be

the most effective exercise prescription to improve both aerobic and anaerobic capacity.

It is important to note that breast cancer is a multifactorial disease, thus it is acknowledged that the variables to be evaluated are merely associations to recurrence or mortality. The variables of interest that were selected for analysis have strong correlations to the future health of breast cancer survivors and are: relative dose intensity, aerobic capacity, cardiovascular variables, lower body strength, waist circumference, hip circumference, inflammatory markers and fasting glucose and insulin levels.

2 Aerobic Capacity in Breast Cancer Survivors [ii]

Introduction

Exercise capacity in breast cancer survivors is a growing concern with recent studies highlighting the importance of physical activity and overall mortality in survivors.[166, 168] Many treatments can plague survivors with a variety of long term side effects,[70, 299] which in turn, can decrease their quality of life, predispose them to future disease and promote early mortality.[91, 130] To combat these negative effects, researchers have implemented a variety of exercise interventions during treatment, immediately post-treatment and years after primary treatment.[72, 177, 357, 358]

Exercise therapy as a rehabilitative tool is growing in popularity due to its potential to alter various biomarkers (e.g., estrogen,[258] adinopectin,[283] and insulin[178]) associated with cancer development, and due to the positive correlation found between improvements in aerobic capacity and improved quality of life in cancer survivors.[54, 73, 77] In addition, physical activity can decrease the risk for cardiovascular disease, obesity, diabetes, and potentially diminish the chance of recurrence and increase overall survival.[185, 384] Accordingly, aerobic stress testing in breast cancer survivors is becoming more common with recent guidelines demonstrating its safety;[192] yet, there is a lack of information concerning which mode of exercise this patient population should use to elicit a maximal cardiopulmonary response.

[ii] A version of this chapter has been published as:
Dolan LB, Lane K, and McKenzie, DC (2012) Optimal Mode for Maximal Aerobic Exercise Testing in Breast Cancer Survivors. *Integr Cancer Ther*. Online Feb 2012. Volume 11 Issue 4 December 2012 pp. 321 - 326.

Past research has noted that as a general exercise preference, the survivor population prefers to walk,[71, 189, 328] meanwhile researchers use a variety of modes and methods to administer stress tests and prescribe exercise to breast cancer survivors. This may be a reason behind the poor adherence and retention rates documented in this population. We speculate that the effectiveness of a personalized exercise prescription may decrease if the testing mode does not correspond to the preferred training mode. Even if the individual is capable of walking, the use of a cycle ergometer seems to be a preferred choice due to ease for the researcher, and the ability to use additional sensitive equipment such as an electrocardiogram or pulse oximeter. The preference of mode for maximal cardiopulmonary exercise testing, within the survivor population, has yet to be evaluated.

Statement of the problem

Personalized exercise prescriptions are developed using a variety of variables produced from a maximal exercise test, such as: heart rate, ventilatory threshold, power and oxygen consumption. Previous research concerning the influence of exercise mode (between the cycle ergometer and the treadmill) on the outcomes of maximal stress testing has demonstrated similarities and/ or discrepancies in these variables. The aforementioned variables used in exercise prescriptions have been shown to be similar, or significantly different between modes depending on the gender being tested,[85] the fitness level,[17] age, [161] and the clinical population chosen.[250, 296, 323] Many complications, which may influence the variables that are derived from a maximal test, can arise with breast cancer treatments: lung function may be altered, muscle strength can decrease, peripheral limitations can develop and accelerated aging may occur. Consequently, it remains

unknown if female breast cancer survivors elicit similar cardiopulmonary responses between these different modes of exercise and if these modes are interchangeable. Therefore, the purpose of this study was to determine which mode of exercise breast cancer survivors prefer for the assessment of peak aerobic capacity, and to evaluate this response to graded exercise testing.

Methods

Study particpants and procedure

Sixteen females, who were currently disease-free after completing treatment (surgery and/or chemotherapy and/or radiation) for early-stage breast cancer, were recruited through the *Abreast-in-a-Boat* e-newsletter to undergo two different maximal aerobic stress tests on two, non-consecutive days, completed within ten days of each other. Women were included if they were peri- or postmenopausal, greater than one year post-diagnosis and had no contra-indications to undergo a maximal exercise test. Current activity level was not used as exclusion criteria. Informed consent was obtained from each subject prior to testing. In a medical clinic, the women underwent a 15 $W \cdot min^{-1}$ ramp protocol on an electronically braked cycle ergometer (Lode Excalibur, Netherlands) and an incremental step protocol on a treadmill that kept a constant, personalized speed (3.5 ±0.5 mph) while the grade increased by 2% every 2 minutes until volitional fatigue. The test began only when the women felt comfortable walking without holding onto the handlebars. Test order was randomized. Using a mask, pulmonary ventilation and expired gas concentrations were collected with a TrueOne 2400 metabolic cart (Parvo Medics Inc, Sandy, UT) for the determination of peak aerobic capacity ($V0_{2peak}$), ventilatory efficiency ($Ve/VC0_{2\ slope}$), and ventilatory threshold (Vthresh, (V-Slope method)). Peak

oxygen consumption was determined by taking the highest value over a 15 second period. Relative and absolute $V0_{2peak}$ were compared. Heart rate (Polar T31 heart rate monitor, Polar Electro Inc, Lake Success NY) and rating of perceived exertion, using a modified Borg scale (RPE; from 0 – no effort, until 10- maximal effort),[31] were recorded throughout each test and final power output was also noted at the end of the bike protocol. Treadmill power output was estimated by standard conversion of vertical work, body weight and speed.[64, 110] After completing both tests, women were asked which mode of exercise they preferred.

Statistical anaylsis

A one-way multivariate analysis of variance (MANOVA, Hotelling's Trace) was conducted using PASW Statistics, version 18.0 to determine if there was an overall exercise mode effect on the key dependent variables used in exercise prescriptions ($V0_2$, heart rate, ventilatory threshold). Univariate analyses of variance (ANOVAs for each dependent variable were conducted as follow-up tests to the MANOVA, using Bonferroni method for controlling for Type 1 error rates for multiple comparisons, each ANOVA was tested at 0.017 level. Other variables of interest were compared with paired t-tests with Bonferroni adjustment. Data is reported as mean (standard deviation).

Table 2. 1 Subject treatment characteristics

Characteristics	Subjects (N=12)
Stage	
I (T1N0)	5
IIa (T1N1, T2N0)	6
IIb (T2N1, T3, N0)	0
IIIa (T1N2 T2N2, T3N0)	1
Surgery	100%
Masectomy	8
Lumpectomy	2
Masectomy + Tram	2
Chemotherapy	83%
ACTT	2
ACT	2
AC	3
FEC	2
Cisplatin + AT	1
Radiation	75%
Yes	9
Hormone Therapy	
Aromatase Inhibitor	58%
Tamoxifen	
Yes	7

Data are presented as the number of subjects unless stated as the overall frequency (percentage) for categorical variables.
Participant side effects: arthralgias (n=6), coordination problems (n=1), chemotherapy-induced ventricular dysfunction (n=2)
4 individuals were diagnosed and underwent treatment for breast cancer twice.

Results

Twelve female, breast cancer survivors (age = 55(6) yrs; ht = 163.7(6.6) cm; wt = 70 (12.8) kg, BMI= 26.3(6.0)) completed both maximal tests with no adverse advents. Descriptives concerning treatment are described in Table 2.1. Exercise mode had a significant affect on the response to graded exercise in this population, $P = 0.003$. As depicted in Figure 1.1, the VO_{2peak} elicited using the treadmill was significantly greater than the VO_{2peak} elicited when using the cycle ergometer (1.97(0.2) $L \cdot min^{-1}$ vs. 1.64 (0.28) $L \cdot min^{-1}$ respectively, $P = 0.003$), while maximal ventilation was equivalent between modes ($P = 0.731$). During the treadmill protocol, ventilatory threshold occurred at 1.3(0.2) $L \cdot min^{-1}$, while the cycling protocol elicited an earlier response at 1.0(0.3) $L \cdot min^{-1}$ ($P = 0.008$). As presented in Table 2.2, the use of the stationary bike resulted in a significantly shorter time to completion ($P = 0.006$), while $Ve/VC0_2$ slope indicated possible mode dependency, ($P = 0.018$). Maximal heart rate was significantly higher by 11 bpm when obtained using the treadmill compared to using the cycle ergometer (p= 0.004), with a similar trend for the heart rate at ventilatory threshold (132(19) vs. 116 (16) bpm, respectively, $P = 0.02$). RPE scores at the end of the treadmill protocol exhibited a higher trend than with the bike protocol ($P = 0.07$). A large effect size (cohen's $d = 0.971$) was calculated, noting the correlation between variables. Ten of the twelve women preferred completing the maximal aerobic stress test on the treadmill than on the cycle ergometer. Two women, who were casual, seasonal, commuter cyclists, were indifferent to the mode.

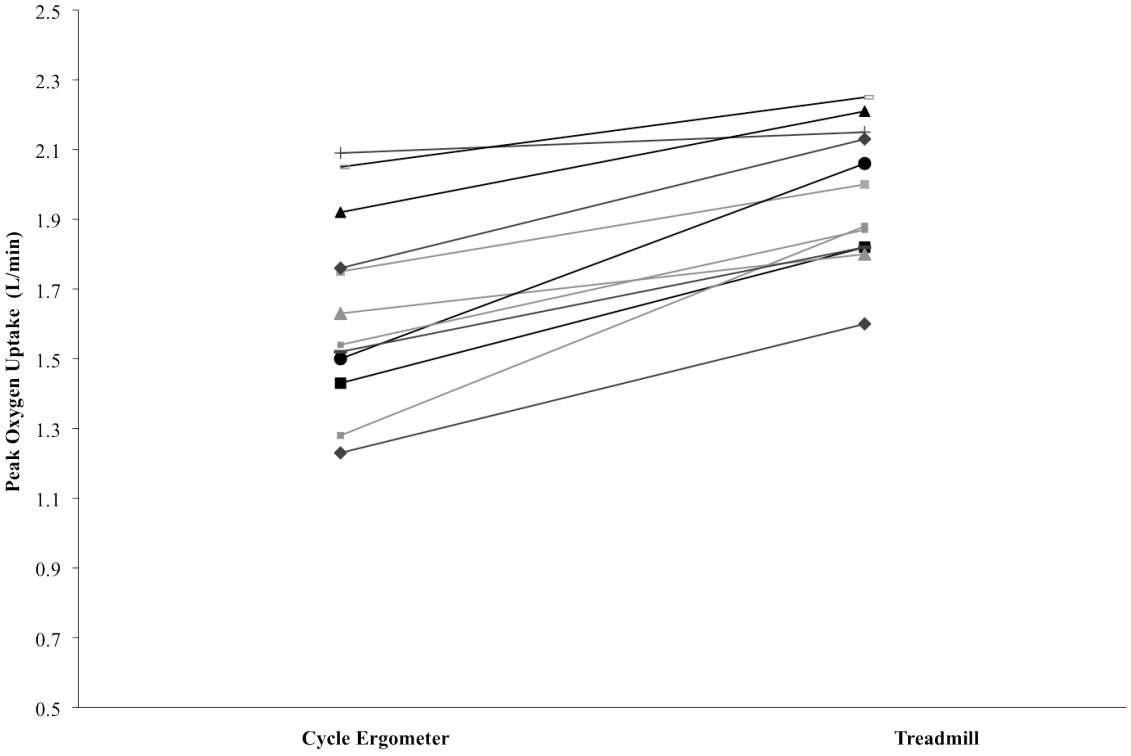

Figure 2. 1 Peak oxygen uptake values obtained in all subjects using the treadmill and the cycle ergometer, (n=12).

Table 2. 2 Subject results between the cycle ergometer and treadmill tests

	$V0_{2\ peak}$ A ($L \cdot min^{-1}$)	$V0_{2peak}$ R (ml/kg/min)	HR_{max} (bpm)	TTC (s)	Ve (L/min)	V_{thresh} (L/min)	V_{thresh} (%HR_{max})	Ve/ $VC0_{2slope}$	Watts
CE (n=12)	1.64(0.28)*	23.9(4.7)*	161.8(11)*	556(122)*	59.2(8.9)	1.3(0.2)*	72.3(0.1)	33.6(2.4)	145 (34)*
T (n=12)	1.97 (0.20)	28.7 (4.7)	172.3 (11)	727 (151)	57.9(9.4)	1.0 (0.3)	76.6(0.1)	30.9(3.2)	127 (23)

Values are presented as means (SD) for the cycle ergometer test (CE) as well as the treadmill test (T). Absolute (A) and relative (R) peak aerobic capacity ($V0_{2peak}$), maximal heart rate (HR_{max}), time to completion (TTC), ventilation (Ve), ventilatory threshold in L/min ($V_{thresh,}$), ventilatory threshold as a percent of the respective HR_{max} (V_{thresh}, %HR_{max}), ventilatory efficiency(Ve/$VC0_2$ slope) and peak watts (Watts) are compared between the bicycle and treadmill maximal protocols.

* Significant difference, adjustment for multiple comparisons: Bonferroni, when compared to the maximal aerobic stress test on the treadmill.

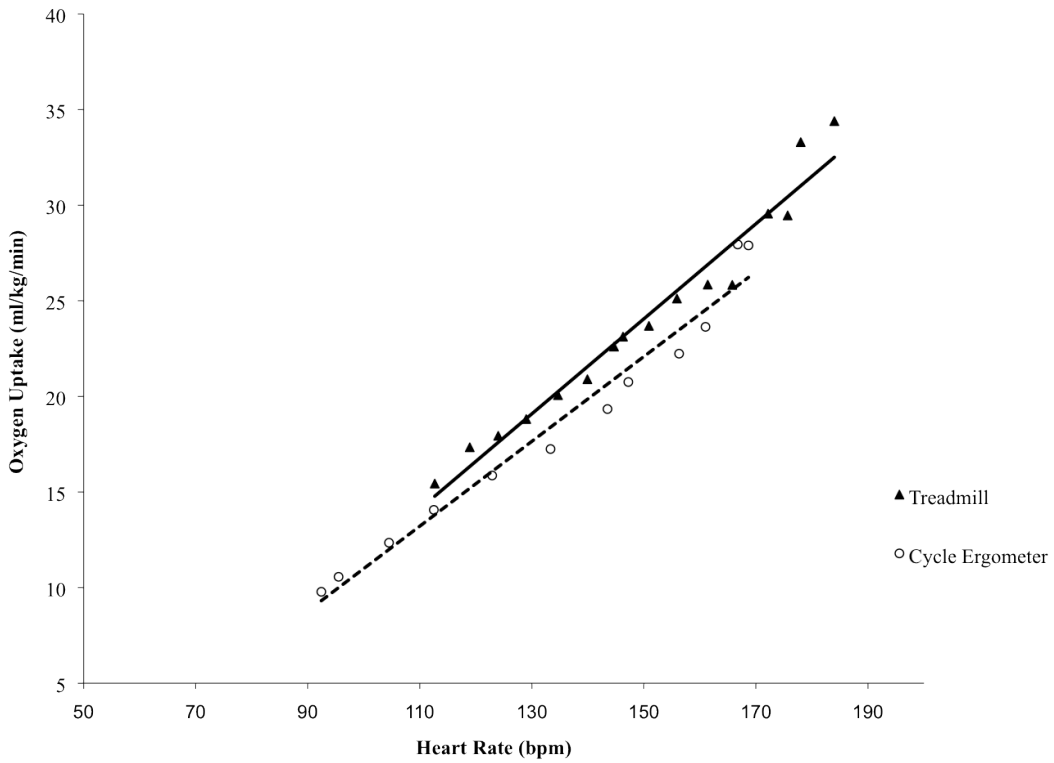

Figure 2. 2 Average oxygen consumption versus heart rate obtained at each minute of exercise during two maximal aerobic stress tests using the treadmill (-) and the stationary bike (- -).

Discussion

The major findings of this study were: 1) women achieved their highest $V0_{2peak}$ using a graded treadmill protocol; 2) women preferred the treadmill to the cycle ergometer when undergoing a maximal aerobic stress test; and 3) Twenty-four maximal stress tests were completed in the survivor population with no adverse events.

Breast cancer survivors face many obstacles post-treatment. They suffer from cancer-related fatigue, changes in body composition, decreased cardiovascular and respiratory function, which can lead to decreased physical functioning and an overall decline in

quality of life. With growing evidence encouraging the use of physical activity to maintain a healthy body weight,[224, 307] coupled with the strong association between healthy body weight and the ability to fend off recurrence or future disease,[114] health specialists are increasingly prescribing exercise interventions to combat these long-term side effects.

Common guidelines to improve overall health and fitness encourage the survivor population to engage in physical activity,[155, 337] yet researchers are producing mixed results from their exercise interventions. Only small to moderate effects are being seen in aerobic fitness, overall quality of life, IGF-1, fatigue and other symptoms and side effects.[357] The varying outcomes may be due to an average adherence of only 70%[365] (up to 90%[358]) but even high adherence programs avoid commenting on compliance to the exercise prescription.[358] It is unknown if researchers are tracking compliance rates or neglecting to publish these results.[46] If individuals are exercising below their prescribed intensity (low compliance rates), they may lack the ability to generate significant health changes. Intensity thresholds have been discussed in other populations, implying that individuals must exercise above a specific threshold to cause enough stress on biological mechanisms to improve cardiorespiratory fitness.[368] This study, which evolved from observations within our lab throughout the years of testing breast cancer patients, has confirmed previous thoughts that the survivor population prefers to walk during a maximal test, and when engaging in physical activity on a bicycle, the intensity decreases as well as motivation. Achieving the proper intensity and staying motivated are critical to

adhering to a lifestyle change. The lower intensity and longer duration required to attain the desired results on a cycle ergometer may affect adherence and compliance rates.

As described in Table 2.2, the difference in aerobic capacity, as well as the differences in ventilatory threshold, heart rate, and time to completion reveals the inconsistency between two different maximal aerobic stress tests in the survivorship population. Cycling requires a different skill set than walking, and cycling is less relevant to the daily life of the general population.[297] This lack of skill could influence the results if using a $V0_{2max}$ test for a clinical diagnosis, for future clinical reference values, or for an exercise intervention. These variable results demonstrate how experience and local muscular fatigue may have been limiting factors during the cycling protocol and not central fatigue of the cardiorespiratory system, accordingly inaccurately portraying the patient's level of aerobic fitness. Thus, an individualized exercise prescription that is based on a maximal aerobic stress test using a cycle ergometer, may not prescribe a high enough intensity. This lower intensity level might be below the necessary threshold to induce the physiological changes required to produce the desired health benefits, such as weight loss, peripheral adaptations or cardiac improvements.

Aerobic capacity is influenced by the recruitment of lean body mass, such that the treadmill can elicit greater oxygen consumption than on a cycle ergometer.[264, 296] However, this ten percent difference is not always seen in the athletic population,[342] nor in the COPD population.[250] This study supports the notion that maximal aerobic stress testing in the breast cancer population is influenced by mode of exercise.

Ideally maximal heart rate is equivalent between both modes of exercise tests, but can vary depending on the age range and experience.[161] As illustrated in Figure 2.2, this study demonstrates that breast cancer survivors within a similar age range did not achieve equivalent heart rates when comparing different modes of maximal stress tests. The significant lower value in heart rate during the cycle ergometer test depicts that the women ended the test too early, possibly due to lower leg discomfort. This peripheral limitation was the main reason reported for ending the cycle ergometer test, while the treadmill test elicited the two responses associated with central limitations: total body fatigue and/ or dyspnea. If heart rate is to be a main variable in an exercise prescription, the large difference in peak heart rates encourages the use of the treadmill for exercise testing.

Ventilatory efficiency is not a common tool used to assess the health of breast cancer patients, even though increased ventilation-perfusion mismatching can occur due to the toxicity of cancer treatments. This relationship has not been evaluated in the breast cancer population. Researchers in other clinical populations are being encouraged to look at ventilatory efficiency and not just aerobic capacity, due to its ability to provide independent and complementary information in clinical settings as well as with interventions.[12, 100] Future analysis of this relationship in the obese survivor population is encouraged. Age, sex,[281] and mode dependency have been previously demonstrated in healthy women.[85] Further testing in breast cancer survivors with a larger sample size would be beneficial.

Eleven of the twelve subjects had little or no experience using a treadmill or a cycle ergometer – a common occurrence in this age range. The women in this group had varied fitness backgrounds (low-to-moderate) and a multitude of long-term side effects (cardiomyopathies, minor neuropathies and arthralgias), yet all completed both maximal tests safely and preferred the treadmill test. It was noted that extra precaution, post-test, had to be taken when dismounting from the cycle ergometer (than with the treadmill). Women felt unsafe, even with assistance, when trying to dismount from the bike. An unexpected observation occurred during testing, which could affect future study adherence rates (thus results) in the field of exercise oncology: subjects revealed that they would return to complete the treadmill test, but would be less likely to return to repeat the test on the cycle ergometer. This remark correlated with our 4 drop-outs. All drop-outs completed the test on the cycle ergometer first, and did not return for the treadmill test.

The results from this study provide an argument that mode selection for aerobic stress testing is important for developing an appropriate exercise prescription required for this population. The survivorship population must feel comfortable with the stress test administered, thus accurate values can be attained and not underestimated. Basic safety awareness of the patient is always a priority when determining which testing modality to use[192]. The use of a treadmill elicits higher levels of oxygen consumption in survivors (see Figure A2.1), and this elevated value will allow for accurate clinical assessments and more efficient intensities to be prescribed during exercise intervention programs. This improvement in design could help detect and produce greater changes in

cardiorespiratory fitness, weight loss and overall health. The results from a walking intervention in middle age and elderly women support the importance of selecting appropriate measures. No beneficial change in $V0_{2peak}$ was detected when using a cycle ergometer test; whereas, the $V0_{2peak}$ elicited from the treadmill test demonstrated a 7% increase, supporting the benefits of a walking program.[285] These findings have implications for potential epidemiological studies, which may use aerobic capacity to develop reference values within the breast cancer population, for the design and interpretation of exercise interventions, and it highlights the importance to define exercise testing within special populations.

We recognize that this is a small sample size that limits us from generalizing this conclusion to all breast cancer survivors. In addition, baseline activity levels varied among the individuals (low to moderate). Further, this study was designed for individuals who were medically cleared to begin an exercise intervention. All women were capable of walking and did not suffer from metastatic disease or severe neuropathies.

This study demonstrates that a group of breast cancer survivors were able to undergo two maximal stress tests with no adverse outcomes. The results provide evidence suggesting the treadmill test is more suited for exercise testing for intervention prescriptions that place importance on accurate exercise intensity values. This paper supports the notion that exercise mode can influence the outcome of maximal aerobic exercise tests in the breast cancer survivor population.

3 Exercise Intensity and Safety in Patients

Introduction

The clinical benefits of adjuvant chemotherapy in patients with early-stage breast cancer may be compromised by a reduction in relative dose intensity (RDI).[10, 28, 105, 241, 353] Dose reductions usually result from abnormal hematological counts, severe treatment related toxicities or the patients' inability to cope with treatment-related toxicities.[271, 403] Common chemotherapy-induced toxicities that influence scheduled RDIs are neutropenia, anemia, neurotoxicity, nausea and vomiting.[419] Neutropenia alone has been related to dose modifications in approximately 28% of patients,[231] while febrile neutropenia has been associated with increased mortality in cancer patients.[242] Further efforts to understand and minimize conditions that lead to abnormal hematological counts as well as reductions in RDIs are warranted.

Exercise therapy during chemotherapy has been investigated with positive results concerning quality of life,[3] nausea,[404] and fatigue[76, 340]. As well, exercise during adjuvant therapy can prevent or reduce a decline in aerobic capacity[74]. However, the effect of exercise on relative dose intensity and hematological counts has been poorly documented. One study described an improved chemo-completion rate in early-stage breast cancer patients undergoing a personalized, moderate-intensity resistance training program compared to usual care controls,[74] but the reasoning behind this outcome remains unknown. Our group recently analyzed the effect of adjuvant exercise on hemoglobin concentration in early-stage breast cancer patients.[97] We concluded that moderate-

intensity exercise did not influence the myelosuppressive effect of chemotherapy; however, unlike usual care group, the exercise group prevented a decline in aerobic capacity. The relationship between the safety of exercise intensity and neutrophil counts in breast cancer patients has not been investigated.

In the field of exercise immunology, researchers have highlighted both positive and negative effects of exercise on immune function.[33, 34, 315] Athletes who train for prolonged durations at high intensities, may develop short-term immunosuppression.[34, 137, 290, 347] These reports have led to a fear of encouraging the wrong type of exercise in the cancer population, who may have some immune compromise inherent in their disease as well as compounded by their treatment. As this type of immune response depends on fitness levels, as well as duration and intensity,[269] deconditioned individuals may not have the stamina required to induce this extended level of exercise stress. Studies have demonstrated that short periods of high-intensity exercise under 30 minutes have no immunosuppressive effects.[94, 122] Interval training is a technique used in a variety of deconditioned clinical populations because the short burst of high-intensity exercise can be completed with the addition of recovery phases between bouts, thus avoiding premature fatigue. Interval training programs have been used in individuals with metabolic syndrome,[375] heart failure patients,[406] elderly heart failure patients,[407] diabetics,[37] COPD patients,[69, 314] and in one of the first exercise studies involving cancer patients[244].

Statement of the problem

Exercise-induced febrile neutropenia has not been reported in the cancer population, yet exercise guidelines suggest that deconditioned cancer patients only perform easy bouts of

exercise, with extreme caution against anything above moderate-intensity due to the potential effect of exercise-induced immunosuppression.[71] Since the release of these guidelines, the results of exercise interventions during therapy have been published and are summarized in the findings by Schmitz and Speck.[339] The review noted that the inverted J hypothesis[410, 411] concerning exercise dose and immune dysfunction was commonly used by authors, and in guidelines, to dissuade the use of high intensity exercise in survivors.[339] In addition, the current guidelines recommend no physical activity in individuals with, ataxia, anemia and extreme fatigue.[337] The purpose of this study is to investigate the effect of higher intensity exercise during a supervised exercise program on achieved RDI and hematological counts in women undergoing chemotherapy for early-stage breast cancer.

Hypothesis: Bouts of high-intensity exercise administered concurrently with chemotherapy will not endanger the safety of the patient through negatively influencing achieved RDI or hematological values.

Methods

Study population

Sixty women, who were prescribed a specific chemotherapy protocol (FEC-D) for early-stage breast cancer between 2008 -2010, were monitored for the duration of their treatment. All women were prescribed a planned regime of three cycles of 500 mg/m^2 of Fluorouracil, 500mg/m^2 of Cyclophosphamide and 100 mg/m^2 of Epirubicin every three weeks, followed by three cycles of 100 mg/m^2 docetaxel every three weeks. The total regimen is delivered in eighteen weeks.

Thirty women who selected to participate in a supervised, personalized exercise program were matched for age, time of treatment, and planned dose intensity (via height, weight and body surface (BSA)) with thirty women who selected not to participate in a concurrent exercise program (usual care group).

Clinical measures

Hematological data were collected within three days of chemotherapy delivery or if hospitalization occurred. The percent decline in hemoglobin concentration ([Hb]) was determined by the difference in concentration from baseline to the lowest value of Hb that occurred during treatment. Episodes of when neutrophil counts dropped between 1-1.5 g/L and <1.0g/L were noted. Each episode required 4 days of normal values prior to be considered another decline. Hospitalization days were recorded. Incidence of chemotherapy dose delay was defined as ≥ 1 week. Achieved RDI was defined as (dose received/dose planned) where dose was calculated by (total dose received mg)/(BSA)(total time)[239] over six cycles of treatment. It is considered to be suboptimal if the achieved RDI falls below 0.85 (RDI < 85%).[28]

Granulocyte colony-stimulating factor has been shown to reduce the complications associated with chemotherapy, thus contributes to increased full dose delivery;[355] consequently secondary use of G-CSF prophylaxis was tracked to verify similar usage between groups.

Exercise program

Women provided informed consent prior to starting the exercise program, and prior to the start of chemotherapy they underwent a maximal cardiopulmonary exercise test on a

treadmill to volitional fatigue. Expired gases were collected and analyzed using a TrueOne 2400 metabolic cart (Parvo Medics Inc, Sandy UT) to calculate peak aerobic capacity ($V0_{2peak}$). All patients wore a heart rate monitor throughout the test (Polar Electro Inc, Lake Success NY). Peak oxygen consumption was determined by recording the highest values during a 15-second period and was used to develop a personalized exercise program for each women based on heart rate and $V0_{2peak}$.

Women were prescribed a gradual, progressive, thrice weekly program for the duration of their chemotherapy treatment. All exercise sessions were supervised. The initial exercise intensity started at 55% $V0_{2peak}$ and progressed to 75% $V0_{2peak}$ of continuous exercise for 30 -60 minutes. The fitness levels of the patient, therapy side effects and fatigue levels were used to determine safety prior to progression. The immediate week following chemotherapy, the intensity prescribed was between 50-75% $V0_{2peak}$ depending on the subjective energy levels of the patient. During the second and third week post-chemotherapy, women participated in a progressive interval training program, which involved exercising for 2-7 continuous minutes at 80-90% $V0_{2peak}$, followed by 3-6 minutes at 55-70% $V0_{2peak}$ and repeated until the total prescribed time was completed. Prescribed time was based on a predetermined amount of calories (170-330 kcals/session). Resting heart rate was monitored prior to each exercise session and was taken into account prior to prescribing heart rate goals.

Statistical analysis

Potential group differences for subject characteristics were verified using independent t-tests. Chi-Square tests were used to determine differences between categorical variables.

Group comparisons for achieved RDI and percent decline in [Hb] were compared using independent t-tests. Repeated measures ANOVA was used to detect differences between groups in prescribed RDI over the six cycles. All tests were 2-tailed. Bonferroni corrections were used due to multiple comparisons. Data analysis was performed using PASW Statistics, version 18.

Results

The present study is based on a retrospective analysis of 60 women who underwent FEC-D chemotherapy treatment for early-stage breast cancer between 2008 and 2010. Eighty-three women were followed post-surgery and 23 were excluded from analysis. Women in the usual care group who discussed exercising with their oncologist were excluded because exercise intensity could not be monitored. If the treating oncologist did not note physical activity behaviors in the patients' medical records, it was assumed the patient was inactive during chemotherapy treatment. Women in both arms were also excluded if their chemotherapy regime changed. Patient and treatment characteristics are described in Table 3.1.

Table 3. 1 Patient and treatment characteristics

Characteristic	Exercise (n=30)	Usual Care (n=30)
Age (years)		
Mean (Standard Deviation)	49.1 (8.4)	49.0 (8.6)
BSA (m^2)		
Mean (Standard Deviation)	1.75 (0.27)	1.75 (0.25)
BMI (m/kg^2)		
Mean (Standard Deviation)	25.95 (6.9)	25.85 (6.7)
Tumor Stage (n, %)		
I	1 (3%)	0 (0%)
IIa	14 (47%)	7 (23%)
IIb	8 (27%)	12 (40%)
III	7 (23%)	11 (37%)
Surgery (n)		
lumpectomy and axillary node excision	11 (37%)	21 (70%)
Modified radical mastectomy, full or partial mastectomy	19 (63%)	9 (30%)

All groups were balanced for mean length of treatment of 18.5 (0.7) weeks, (*P*= 0.67). Women who exercised at high intensities during their treatment were prescribed similar planned dose intensities as those in usual care, (*P*= 0.925), the effect size was insignificant, r= 0.104. Both groups completed their regime with an achieved RDI of 91.0 (8.7)%, (*P*= 0.420) as described in Table 3.2. The distribution of achieved RDIs between groups is illustrated in Figure 3.1. There was no significant difference in dose received between groups per chemotherapy cycle, (*P= 0.765*). The decline in dose intensity per cycle between groups is illustrated in Figure 3.2.

Table 3. 2 Patient results

	Exercise (n=30)		Usual Care (n=30)		*P* value
Measure	Mean	CI	Mean	CI	
Achieved RDI (%)	91.91	88.7-95.1	90.07	86.7-93.4	0.420
[Hb] decline (%)	20.2	18.0-22.3	18.4	15.8-21	0.285

Adherence rate for gym attendance was 90.3%. Compliance for successfully attaining their prescribed exercise goal was 94.7%. Both groups had an equivalent decrease in [Hb] of approximately 19%, (*P*= 0.285). There was no significant association between groups in the number of hospitalization visits or in the number of neutrophil events defined by a decline in counts between 1-1.5 g/L or less than 1.0g/L, ($\chi^2 < 1$, *P*= 0.670, 0.290, 0.530 respectively).

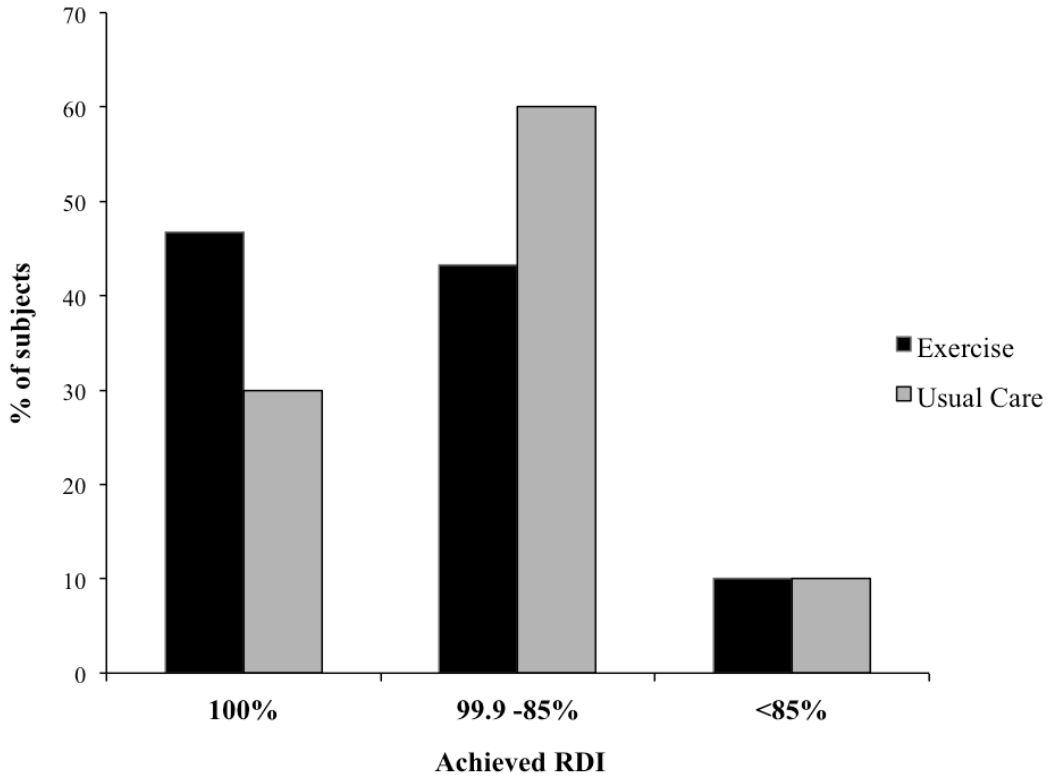

Figure 3. 1 Distribution of achieved relative dose intensity (as a percent of planned relative does) for early-stage breast cancer patients undergoing chemotherapy (FEC-D) in the exercise and usual care groups. $P = 0.388$

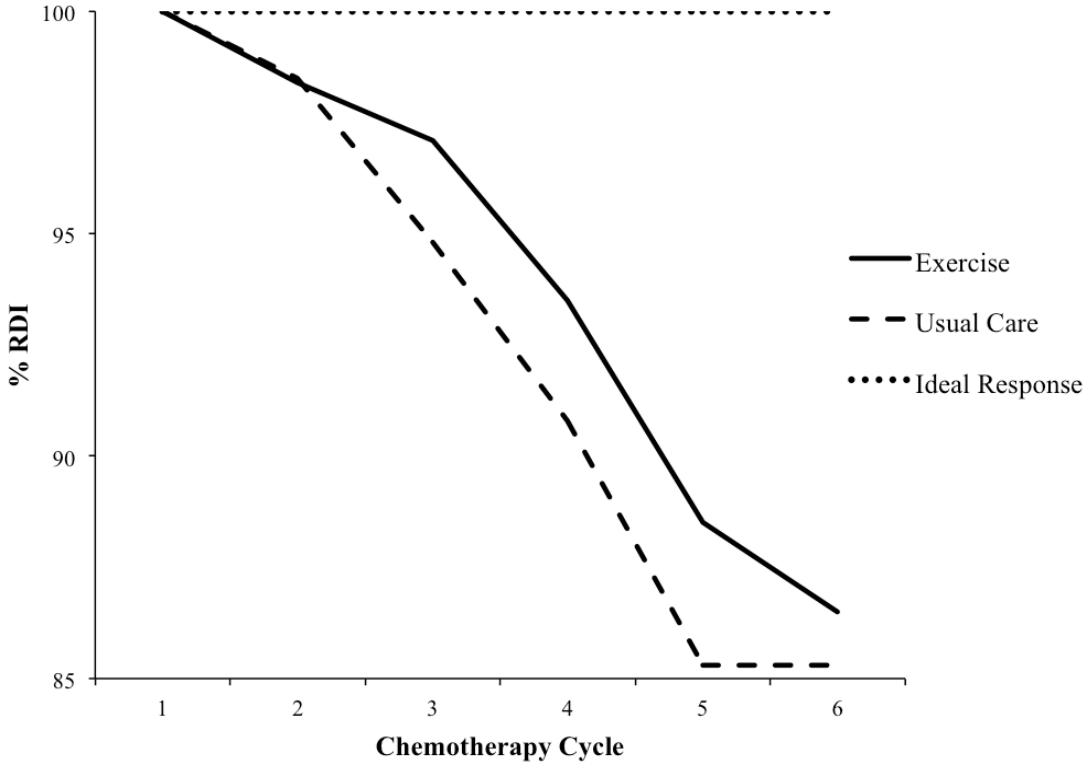

Figure 3. 2 Relative dose intensity received per cycle of chemotherapy between groups. FEC was administered cycles 1-3, while D was administered cycles 4-6. $P = 0.756$

Discussion

Contrary to common belief, exercising for short bouts at intensities above 75% $V0_{2peak}$ did not escalate the myelosuppressive effect of adjuvant chemotherapy in women undergoing treatment for early-stage breast cancer. Patients, who opted to exercise at relative high intensities for short periods of time, did not experience greater delays or reductions in their chemotherapy dose, nor did they have greater declines in their neutrophil counts. There were no dropouts in the exercise group due to over-exertion.

A moderate amount of treatment related myelosuppression has been associated with trends toward improved clinical benefit and survival.[43, 65, 253, 332] To our knowledge this is the first study to demonstrate that short exercise bouts of moderate-to-high intensity, does not prevent or exacerbate the myelosuppressive effect of chemotherapy.

Moderate-intensity exercise in early-stage breast cancer patients was reported to have no influence on the myelosupressive effect of chemotherapy on [Hb]. The treatment led to a 14% decline in [Hb] in the exercise and in the usual care (inactive) group. The usual care group experienced an 8% decline in aerobic capacity, while the exercise group maintained their baseline $V0_{2peak}$.[97] With the use of increased intensity associated with interval training, in lieu of mild-to-moderate intensity, there is a greater possibility to cause physiological changes related to improved health as seen in other populations.[198] During chemotherapy, the implementation of short bouts of higher intensity exercise during the two weeks prior to the next treatment could translate to greater changes in aerobic capacity, improved cardiac function, possible cardioprotection, prevention of excessive weight gain, and improved lean mass and strength. The goal of this study was to investigate the safety of exercise intensity in relation to achieved RDI; consequently, a limitation of this study is that physical characteristics, such as aerobic capacity or body composition were not measured in the usual care group. However our group has previously demonstrated that a decline in physical functioning does occur in patients who do not participate in a supervised exercise program during adjuvant chemotherapy.[74] This treatment-induced decline has been confirmed by other trials.[246, 337]

Although the sample size is small, this study provides encouraging evidence as the groups are matched for age, treatment type, time of treatment and prescribed dose intensity. Women undergoing FEC-D therapy for early stage breast cancer were able to exercise three days a week, for 25 to 45 minutes. Each session consisted of small bouts of high-intensity exercise similar to running, or fast, uphill walking that did not hinder their scheduled treatment. This study demonstrates that exercise therapy is a safe stimulus to use to improve physical functioning through potentially attenuating the treatment related impairments. We acknowledge the limitation of our study design as it was a retrospective study, not a randomized control trial; however, with the current published evidence, it would be unethical to randomize patients, who are interested in exercising during chemotherapy, to a usual care group.

Patients that were in the exercise program were not forced to exercise at higher intensities when feeling fatigued. Patients that suffered from fatigue were given a continuous, exercise prescription that prescribed a mild-to-moderate walking pace (55-75% $V0_{2peak}$) for up to 60 minutes. Patients were given low-to-moderate intensity exercise prescriptions the week post-chemotherapy when fatigue and neurotoxicity were most common. The two weeks prior to the scheduled chemotherapy treatments, women were given interval programs that varied in intensity depending on their energy and fitness levels. Women frequently expressed their enjoyment due to the variety and the challenge of the interval programs.

Fischer et al published results highlighting an immunosuppressive effect with endurance training, but the effect was not demonstrated with high-intensity interval training.[122] The authors concluded that interval training may be the recommended mode to improve health over endurance training programs. Our study supports this recommendation with further evidence demonstrating that progressive high-intensity interval protocols can be safely implemented into exercise interventions in immunosuppressed populations. Further, this study reveals that the immediate effect of exercise therapy coinciding with adjuvant chemotherapy for early-stage breast cancer does not negatively influence chemotherapy delivery. Exercise during the treatment phase can prevent treatment related side-effects such as loss in bone density, declines in cardiovascular health and excessive weight gain; however, the long-term outcome of women who exercise during chemotherapy at moderate or higher intensities is unknown.

This study provides evidence that women undergoing FEC-D treatment for early-stage breast cancer can incorporate bouts of higher intensity exercise without fear of negatively impacting their treatment. No adverse events were associated with bouts of high-intensity exercise, and the results support the implementation of higher intensity prescriptions into future rehabilitative interventions to explore potential differences between exercise intensity and clinical outcomes.

4 Anaerobic Capacity in Breast Cancer Survivors

Introduction

The body of information concerning aerobic capacity in breast cancer survivors has been accumulating over the last decade. The importance of understanding the mechanisms behind the decline in aerobic capacity, and how to prevent the decline due to possible treatment side effects is becoming commonly cited in the literature.[190, 216] However, as the human body relies on a variety of physiological pathways to perform day-to-day functions, investigating more than just one energy pathway may contribute to improving the quality of life and survivorship in cancer patients.

To keep up with the constant energy demand of day-to-day life, there are multiple, integrated metabolic pathways that are continually active providing energy. Aerobic metabolism is the major source that aids in replenishing adenosine triphosphate (ATP) energy stores; consequently, if the demand increases too quickly, anerobic metabolism will quickly supply the additional, required energy.[150] There are two main pathways which provide energy via anaerobic metabolism, 1) through a reaction of the degradation of phosphocreatine; or 2) through gylcogenolysis and glycolysis.[35] These pathways are key in providing energy when aerobic metabolism cannot match the workload demand. These pathways work in harmony to maintain energy levels, thus allowing the maintenance of ideal physical function to meet the demands of any stress. Surprisingly, few exercise physiologists have explored the relationship between these synergistic pathways and cancer treatments in the breast cancer patient.

Anaerobic capacity is complicated to measure as it involves examining the closely linked relationship between the coordinated energy systems. Quantifying anaerobic capacity is controversial[131] but some common methods are: the peak power from a Wingate test[14] (a supramaximal test on a cycle ergometer that requires an individual to pedal 'all out' for a set duration against a fixed resistance dictated by a fraction of their body mass); the time achieved in the Cunningham Faulkner Speed Test[78] (individuals run on a treadmill at 8.0 mph at a 20% incline till fatigue) and the maximal accumulated oxygen deficit that occurs during 2- 3 minutes of exhaustive exercise[259] (an individual completes multiple bouts of treadmill running requiring constant collection and analysis of expired air). Due to pathophysiology- induced limits to individual exercise tolerance, measuring anaerobic capacity in clinical populations using the aforementioned tests may be a challenge. Nonetheless, measuring and thus learning how to improve the energy pathways that aid in the regeneration of ATP could influence functional capacity and accordingly, quality of life. A steep ramp test on a stationary bike was created and designed to challenge the muscles maximally prior to being limited by the cardiorespiratory system, consequently minimizing the influence of a clinical dysfunction. The steep ramp test was first implemented as a test for patients with heart failure;[261] consequently, it was then used in patients with COPD[314] and then in cancer survivors (54% breast cancer)[87]. These groups found it to be a useful tool to determine anaerobic capacity, peak power and for adjusting exercise intensities. To determine the type of energy utilization, the steep ramp test was validated as a tool to reflect the power of the anaerobic system from a study that compared it to a standard aerobic, cardiopulmonary exercise test (CPET) and an anaerobic test (modified Wingate test).[57]

Statement of the problem

An efficient use of anaerobic metabolism may influence the body's ability to respond to the energy demands of daily life tasks, but little is known about how cancer treatment affects the metabolic physiology within the muscle. The confirmation of a validated anaerobic stress test for the breast cancer population will provide a path towards a greater understanding of the dynamics that occur within the muscle under stress. Our previous findings encourage the development of a treadmill test, to enhance adherence and patient motivation[98]. The purpose of this study is to compare two different exercise protocols (one on a cycle ergometer, and one on a treadmill) to determine anaerobic capacity in cancer survivors.

Hypothesis: A variation of the Cunningham Faulkner speed test[78] will be a safe and valid test to determine anaerobic capacity in post-menopausal breast cancer survivors.

Methods

Study participants

Breast cancer survivors were recruited through the *Abreast-in-a-Boat* e-newsletter. Eleven women volunteered to undergo multiple exercise tests to determine if a variation to Cunningham and Faulkner speed test,[78] defined as the modified speed test, could become a valid measure of anaerobic capacity in the breast cancer survivor population.

Inclusion criteria: postmenopausal women were included if it had been a minimum of one year from completion of initial treatment (surgery/ chemotherapy/ radiation) for stage

I-IIIA breast cancer. Targeted, or hormonal therapy may have been taken or be in current use.

Exclusion criteria: women were excluded if they were not postmenopausal, had metastatic disease, uncontrolled hypertension, history of cardiac disease or pulmonary disease, a BMI > 40, participation in a carbohydrate-free diet, or any other contraindications to exercise were also be excluded.

Design and procedure

A randomized, cross-over design was used to investigate the physiological response to multiple, brief, high-intensity exercise tests. Within ten days, all participants underwent a time limited walking test, the steep ramp test and two trials of the new, modified speed test. The modified speed test required two trials to establish reliability of the measures. Testing was conducted at the same time of day for all subjects.

Women arrived at the medical clinic and gave consent prior to undergoing initial assessment. Anthropometric measures were determined while demographic and medical data were reported. All women were informed that they were required to eat 1-3 hours prior to undergoing any of the exercise tests.

Participants completed a six-minute walk test (6MWT)[1] over a 30 meter course, which occurred on the straight portion of an outdoor track. To avoid errors associated with familiarization, women were given time to practice the walk test prior to starting the

documented test. The outcome measure was the distance travelled within six minutes and was used to describe group fitness level based on previous published norms[111].

Modified speed test: The women completed a warm-up that consisted of brisk walking and a familiarization phase. During this phase, the treadmill was set to a slow speed allowing the subject to become familiar with the sharp incline. The test began when the subject began walking on the treadmill to a set, standardized maximal incline of 13%. Depending on individual gait, the walking speed was set at 3.0 or 4.0 mph. Pilot data previously determined that this incline and speed range were the safest, most challenging level for this population. The test ended when the subject fatigued and grabbed onto the handle bar. The primary outcome variable for the modified speed test is time achieved. Final heart rate and ratings of perceived exertion (RPE) using the Borg scale[31] were recorded and compared. After the completion of the test, the subject moved to a chair. After three minutes of sitting, blood lactate was measured with a Lactate Pro Analyzer (Arkray Inc, Japan).

The contribution of work from aerobic energy sources exceeds anaerobic capacity between two and three minutes of exercise; thus, a time criteria of a maximum of 120 seconds was established in advance to optimize the measure of the subject's maximal use of their anaerobic capacity.[35] To separate familiarization and a training effect, a maximum difference of 20 seconds between trials was allowed.

Steep ramp test: Women underwent a similar warm-up then followed the steep ramp test protocol that was previously validated in cancer survivors.[87] The test begins with 30 seconds of cycling at 25 watts on an electronically braked cycle ergometer (Lode Excalibur, Netherlands). After the initial 30 seconds, the load increased by 25 watts every 10 seconds until exhaustion. Throughout the test, the subject is instructed to cycle with a pedal frequency between 70 and 80 rpm. The test is considered over when the pedal frequency drops below 60. The primary outcome variable is maximal wattage achieved. Final heart rate and RPE were recorded. Immediately following the test, the women moved to a chair. After three minutes of sitting, blood lactate was measured using the Lactate Pro Analyzer (Arkray Inc., Japan).

Statistical analysis

Results were first analyzed for violation of the pre-determined time criteria to ensure that the tests reflected the measurement of anaerobic capacity. The time criteria for validating the modified treadmill test were not met; consequently, no statistical analysis occurred.

Results

Eleven breast cancer survivors underwent a 6MWT and three high-intensity stress tests without any adverse events. Subject characteristics are presented in Table 4.1.

Table 4. 1 Characteristics of study participants

Characteristic (N=11)	Mean (sd)
Age (years)	59.1 (7)
Weight (kg)	67.2 (6.2)
BMI (kg/m^2)	24.3 (2.4)
Years from menopause*	9.8 (6.3)
Time from diagnosis (years)	10.0 (6.2)
Treatment (%)	
Surgery	100%
Chemotherapy	81.8%
Radiation	72.7%
Hormonal	63.6%
6MWT (m)	640.62 (57.96)
Activity level (%)**	
Low (< 3 days/ week, RPE <9)	27%
Moderate (3-6 days/ week RPE 10-13)	73%
High (> 3 days/ week, RPE >14)	0%

* Natural or treatment induced.
Hormonal therapy included tamoxifen and aromatase inhibitors
** Activity level self reported (d = days, wk = week) RPE based on the Borg 6-20 scale

The modified treadmill test did not meet the pre-determined criteria for assessing anaerobic capacity in the breast cancer survivor population. The average times for both tests were greater than 150 seconds, and the time difference between both trials surpassed 20 seconds. The results from the three tests are presented in Table 4.2.

Table 4. 2 Results from 3 exercise tests investigating anaerobic capacity

	Bike – SRT°	Treadmill 1	Treadmill 2
HR_{max} (bpm)	147 (10)	160 (14)	164 (10)
Time (s) *	95. 5 (15)	153 (94)	182 (107)
Blood Lactate **(mmol)	6.8 (2)	6.1 (3)	6.4 (3)
RPE (Borg°°)	17.7	17.9	17.8
$Watts_{max}$	268 (41)		

Values presented as: mean (standard deviation), n= 11

* As wattage, not time, was the main outcome, time values noted above are after the initial 30s free spin at 25 watts

** Lactate values assessed at 3minutes post-exercise with a pin prick (Lactate Pro analyzer)

° SRT = steep ramp test

°° RPE determined using the 6-20 Borg scale

Discussion

The modified treadmill test was the preferred test among the eleven cancer survivors (and researchers, as it mimicked the preferred mode of exercise training); in spite of this, it did not meet the time criteria to have it validated as a measure of anaerobic capacity. Four women took more than 150 seconds to complete the first treadmill trial while five women took over 200 seconds to complete the second treadmill trial. After approximately two minutes of intense exercise, energy contribution from anaerobic metabolism declines, while aerobic metabolism becomes the stronger source behind energy regeneration.[35] Final heart rates and RPE scores were alike in both treadmill tests, but the total exercise time differed. The second treadmill test took longer to complete, yet the post-lactate levels are similar. With the longer duration and similar quantified effort levels, the plateau in lactate concentration demonstrates a switch to aerobic metabolism. This confirms that by using a test that lasts over three minutes, the results no longer highlight the capacity of the anaerobic system, but begin to describe the relative contribution from aerobic metabolism.

In pilot trials it was determined by our lab that for this population, the 13% grade was the safest, highest incline to elicit a maximal response, though it appears that the walking speed or the incline would need to be increased to prevent the test from going past 120 seconds. Due to the wide range in gaits and the common lack of confidence on the treadmill (whether it's due to age, neurotoxicity or inexperience), using a greater incline or speed would be dangerous and not ethically plausible.

The results from the 6MWT allowed us to categorize our participants into the higher-end range of the published healthy norms for adults (400-700m[111]). Our results (approximately 268 W_{max} with a HR_{max} of 147 bpm) compare to the baseline steep ramp test values demonstrated in De Backer et al's training study in cancer patients.[87] Their results included a mix sample of men and women, but 54% of the participants were breast cancer survivors, and 73% of the total sample were women. The maximal wattage achieved in their baseline steep ramp test was 270 (75) watts with a maximal heart of 154(18) bmp. After 18 weeks of training, the wattage achieved improved by 13% with a 5% increase in maximal heart rate.

Overall, this study demonstrated that the treadmill test could not elicit an accurate measure of anaerobic capacity. For safety reasons, increasing the incline or speed to attain more accurate measures could only occur in a restricted number of individuals within this population, preventing it from being a useful generic test for breast cancer survivors. Further, we acknowledge that the sample size is small, and the individuals

were moderately active so it limits the generalization of our findings. However, the steep ramp test has elicited similar responses to a multi-modal, survivorship exercise intervention, which encourages its validity. In addition, we recommend shortening the initial duration of 30 seconds to 5 seconds at 25 watts. This minimal wattage did not cause any level of exertion in the women, except instigate a thirty-second flurry of complaints concerning the discomfort of sitting on a bike.

Understanding the dynamics of the altered physiology of cancer survivors is an important area to explore to improve survivorship; as such, designing exercise tests that investigate the potential dynamic changes need to be determined. Tests and protocols for analyzing aerobic capacity in the breast cancer population are well described;[98, 192, 193, 337] however, little is known about the importance of changes that may occur in the glycolytic pathway. Anaerobic energy sources are quickly engaged with short bursts of exercise, typical of day-to-day activities that some cancer survivors find fatiguing. If there are treatment-induced faults within this pathway, or with the lactate dynamics, perhaps using exercise prescriptions that can challenge anaerobic metabolism could lead to improvement in enzymatic activity, substrate utilization and greater skeletal muscle adaptations. Understanding ways of improving the recovery process when efficient energy regeneration is required, could translate into prescriptions that may lead to a decrease in fatigue, greater consistency in energy levels and improved quality of life.

The steep ramp test is a short test that eases the breast cancer population into a difficult stress test. In conclusion, the present study has demonstrated the safety of the steep ramp

test and the results have provided additional support for its validity to investigate anaerobic capacity in breast cancer survivors.

5 High-Intensity Interval Training in Breast Cancer Survivors

Introduction

Early-stage breast cancer treatment is an individualized therapy, which encompasses a combination of surgery, chemotherapy, radiation, hormonal therapies and/or targeted therapies. As previously discussed, these treatments may alter different metabolic pathways in the musculoskeletal, endocrine, and cardiopulmonary systems, which could result in detrimental side effects associated with poor health.[216, 415] Physical activity, as a means to improve quality of life via increasing functional capacity in breast cancer survivors,[92, 182] is supported by major organizations around the world.[18, 155] Rehabilitative exercise guidelines for cancer survivors have been published;[155, 337, 385] yet, to our knowledge, few have investigated exercise prescriptions using higher intensities above 80% $V0_{2max}$. High-intensity exercise is a key training tool in sport programs to enhance and optimize athlete physiology.[222] In spite of this, increased exercise intensity has only recently become of interest for use in the clinical population, as short bouts of increased intensity may be more powerful to induce beneficial psychological, as well as acute and chronic physiological changes than the previously recommended guidelines.[132, 198] Nonetheless, individuals are cautious to adopt new methods, as patient safety is a priority; consequently, researchers have been slow to investigate this area.

High intensity interval training (HIT) is appealing as it permits individuals to train at greater intensities (70-110% $V0_{2max}$) potentially eliciting a more effective adaptation.[142, 368] These physically demanding interval bouts are short, lasting anywhere between 10

seconds to 6 minutes and are followed by brief, low-intensity recovery periods. The recovery periods allow for multiple repeats of the high intensity exercise, (potentially accelerating the adaptation process), which would not be achieved if individuals were to maintain a steady-state intensity.[25] The scheduled recovery breaks also permit the relief from symptoms such as leg fatigue or dyspnea, thus creating interest for physiologists to apply the HIT concept within the exercise rehabilitation setting for clinical populations. HIT programs were successfully tolerated in patients with COPD,[69] type 2 diabetes,[235] metabolic syndrome,[375] heart failure,[406] and in obesity[401] (see Table A1.3). Meyer's et al discovered that HIT was successful in improving functional capacity in heart failure patients, but most importantly it was also safe, as lower levels of cardiac stress were produced by the HIT group when compared to the continuous moderate-intensity exercise group.[262] Even with the demonstrated gains in aerobic capacity, strength, weight loss and cardiometabolic improvements,[176, 202] few individuals have used interval training in cancer patients, perhaps due to fear of exacerbating fatigue, immunosuppression or potential causing metabolic changes related to an environment favoring recurrence.

Unlike moderate-intensity aerobic exercise, vigorous exercise elicits an altered metabolic response to maintain energy levels; hence, altering the steady-state response of specific metabolites that are associated with poor survivorship (e.g., insulin[140], glucose[277] and inflammation[109, 310]). Inflammatory cytokines,[295] as well as insulin and glucose,[248] fluctuate dramatically as intensity increases (and during the post recovery phase). As exercise intensity surpasses 80% $V0_{2max}$, the surge in catecholamine response causes a suppressed response in insulin secretion, allowing for a rise in blood glucose levels

during exercise;[247] consequently, following the cessation of exercise, a surge in insulin occurs[349] followed by a brief pro-inflammatory response.[381] Acute bouts of high-intensity exercise may cause large fluctuations and potentially increase acute exposure to glucose, insulin, and inflammatory cytokines; nonetheless, long-term exercise training may minimize the total exposure.

Depending on the treatment for breast cancer, survivors may not have a normal metabolic response during exercise or during the recovery phase;[113, 174, 379] thus, there is a heightened concern within this population regarding any potential increase in exposure to insulin and glucose. The acute affect of exercise on increasing circulating insulin and blood glucose has been investigated in other populations. Heath et al, compared the trained athlete's acute response to exercise, post-training and post-detraining, and discovered training elicited a blunted insulin response to acute exercise.[158] The lower levels of circulating blood glucose and insulin in trained individuals have also been demonstrated after an exercise intervention in healthy, non-athletes.[223] Furthermore, total exposure to glucose (using a 24-hour continued glucose monitoring technique) improved following two weeks of HIT in type 2 diabetics.[235] The danger of an abnormal metabolic response after one, acute bout of high-intensity in type 2 diabetics was investigated.[135] The published results demonstrated that even with the high spike in glucose post-exercise, the total exposure to glucose over 24-hours was significantly less following an acute bout of HIT when compared to the non-exercising, control measure.[135] Monitoring the acute glucose response to HIT over 24-hours has yet to occur in breast cancer patients but the present study will provide information on the metabolic response to HIT.

Statement of the problem

High-intensity interval training protocols have yet to be implemented into rehabilitative programs for breast cancer survivors. The objective of this study is to investigate the safety and the benefits of HIT by comparing the results from a six-week progressive exercise intervention between three groups of breast cancer survivors: a control (CON) group, a moderate-intensity, continuous training (CMT) group and a high-intensity interval training (HIT) group.

Hypothesis: A progressive six-week HIT program will cause improvements in the primary outcome (aerobic capacity) and secondary outcomes (anaerobic capacity, anthropometric characteristics, heart rate recovery, HOMA, resting heart rate, strength) without an abnormal change (rise) in fasting glucose, insulin or inflammation, compared to women in the CMT or CON group.

Methods

Study participants

Thirty-three post-menopausal women, who completed different combinations of surgery, chemotherapy, radiation and hormonal therapy for early-stage breast cancer, were recruited to participate in a six-week exercise intervention.

Inclusion criteria: Women were included if it was greater than six months post surgery/chemotherapy/radiation for stage I-IIIA breast cancer, and up to twelve years from diagnosis. Post-menopausal status had to be confirmed by their oncologist or GP due to the influence of treatment on accelerating menopause. Women may or may not be taking targeted therapy or hormonal therapy.

Exclusion criteria: Women were not included if they were diagnosed with metastatic disease, uncontrolled hypertension, history of cardiac disease or pulmonary disease, or did not have approval from their oncologist, surgeon or general practitioner. Individuals who were above the age of 75, who had a BMI greater than 40, could not commit to eighteen exercise sessions, or had any other contraindications to exercise were also excluded.

Design and procedure

This study was a randomized controlled trial with the subjects recruited through local general practitioners, participating oncologists, public advertisements, and by word of mouth. Participants were stratified by their baseline $V0_{2peak}$ (25 ml/kg/min), and then randomized, using a random number table, to either the high-intensity interval training group (HIT), the continuous moderate-intensity training group (CMT) or the control group (CON). The design compared the magnitude of change (pre-post value gain) in the dependent variables between the three groups.

Interested participants were required to seek medical approval prior to enrolling in the exercise program. After informed consent was received, eligible women underwent multiple days of baseline testing within two weeks of program initiation. To potentially enhance adherence, the exercise intervention was designed to be performed on a treadmill due to observations from our lab that were previously discussed,[98] and from recommendations that brisk walking is the preferred exercise choice among post-menopausal women.[185, 189, 328] Women were asked, and were reminded throughout the six weeks, to maintain their normal dietary habits and current daily activities for the duration of the intervention.

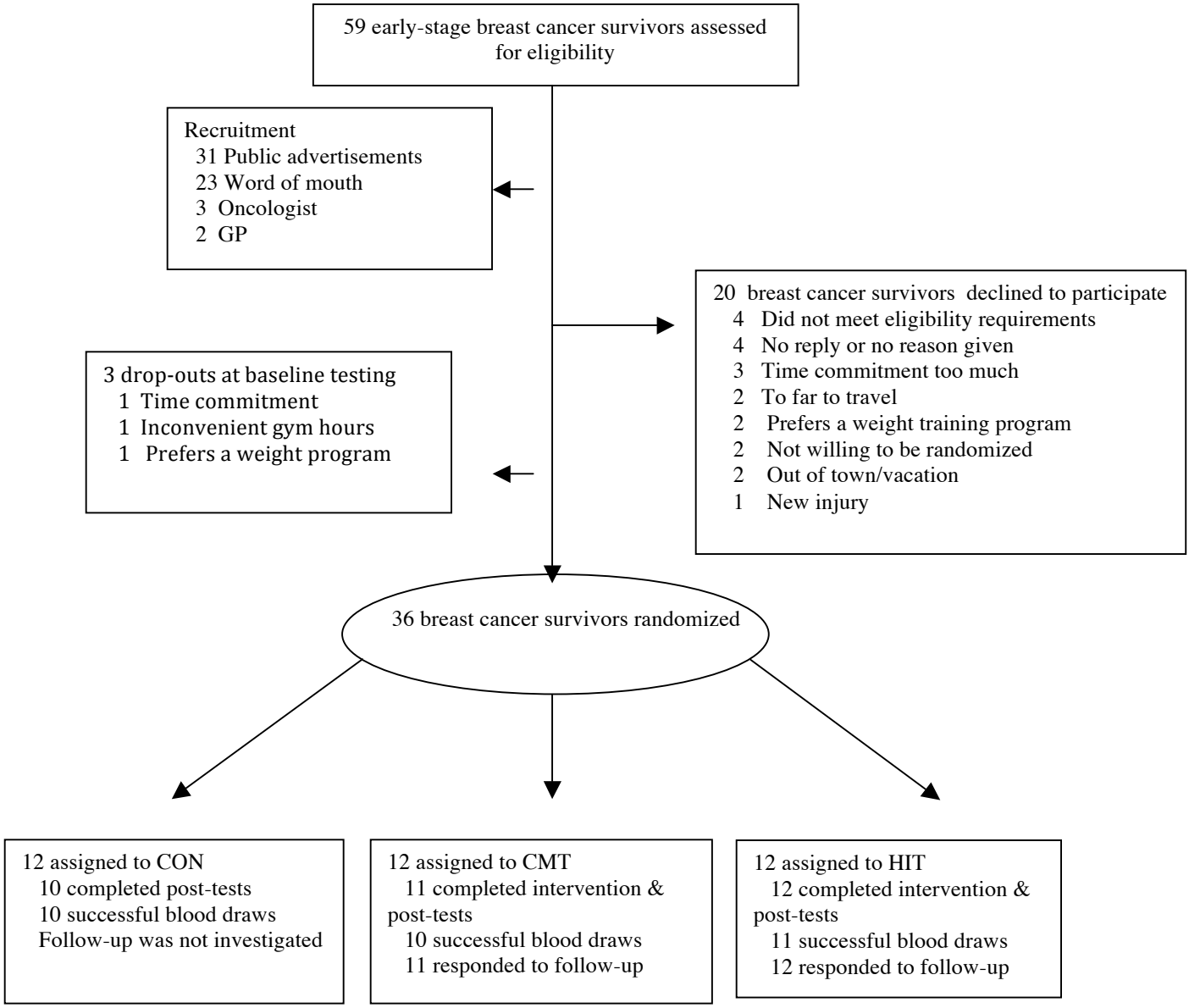

Figure 5. 1 Flow of participants through the trial

Assessment of primary and secondary outcome measures

Objectively measured outcomes were assessed at baseline and after the six-week intervention. The exercise program started within two weeks of completing baseline measures while identical post-measures occurred within 48-72 hours of the final exercise session.

Demographic and medical data were self-reported at baseline (presented in Table 5.1). The primary outcome was change in aerobic capacity, and secondary outcomes were changes in anaerobic capacity, anthropometric characteristics, lower body strength, fasting glucose, fasting insulin and the inflammatory response (*hs*-CRP).

Primary outcome: Aerobic capacity ($V0_{2peak}$) was determined using a maximal, incremental cardiopulmonary exercise protocol on a treadmill, that maintained a set speed with the grade increasing every two minutes to volitional fatigue.[98] Expired gases were analyzed using the TrueOne 2400 metabolic cart (Parvo Medics Inc, Sandy, UT)). Peak oxygen consumption was defined by the average top three consecutive 15-second values in the last two minutes of exercise.

Secondary Outcomes: Resting heart rate, height, weight, and trunk circumferences were assessed prior to the maximal cardiopulmonary exercise test. Resting heart rate was noted after five minutes of seated silence. Circumference measurements were taken at the waist (at the umbilicus)[213, 331] and the hips (at the widest part of the buttocks). Heart rate

Table 5. 1 Participant profiles as self-reported at baseline

Characteristics			Total N= 33	CON n= 10	CMT n= 11	HIT n= 12
Age (years)			57.2	59.4	56.3	56.2
Weight (kg)			67.6	66	67	69.5
BMI (kg/m^2)			24.9	24.8	23.9	25.8
Years from menopause (years)			8	11	7	7
Ethnicity (n)						
	Caucasian (British/Irish/German)		23	7	8	8
	Caucasian (Iraqi)		2	1	0	1
	Asian (Japanese)		2	0	0	2
	Asian (Chinese)		6	2	3	1
Years since diagnosis			6	7	4	6
Stage at diagnosis		Stage 0	2	1	1	0
		Stage I	9	4	2	3
		Stage II	9	2	2	5
		Stage III	11	3	5	3
		Other	2	0	1	1
Treatment						
Surgery		Lumpect/Ax dis	15	5	4	7
		Masectomy	15	5	7	5
		Tram	4	0	3	1
Adjuvant Chemotherapy			18	4	6	8
Neoadjuvant Chemotherapy			4	2	1	1
Radiation (yes)			21	7	7	7
Targeted (Herceptin)			8	2	3	3
Hormone modulating therapy						
		Tamoxifen	13	4	4	5
		Aromatase Inhibitors	8	3	2	3
Side effects		Decreased ROM	3	0	0	3
		Neurotoxicity	4	1	1	2
		Myalgia	5	3	1	1
		Balance	5	1	2	2
		BCRL	7	3	3	1
		Arthritis	4	2	0	2
		Other (knee pain, tendonopathy, depression, GERD, headaches)	12	5	5	2
Previous level of activity						
Frequency		<1 day/week	7	2	4	1
		2-4 days	18	5	5	8
		> 5days	8	3	1	4
Intensity		low	12	3	6	3
		moderate	20	6	5	9
		high	1	1	0	0
Time (min per session)		< 30	11	3	7	1
		30-60	16	4	4	8
		>60	5	3	0	2
No treadmill experience			16	4	9	3
Walking -primary choice of activity			25	7	9	9

recovery, as a means to assess autonomic function[62, 233, 272, 348] was determined at the 2-minute mark during an active recovery. Ventilatory threshold, expressed as percent of $V0_{2peak}$ was determined by graphing ventilation versus time and manually applying a line of best-fit to determined the point when ventilation departed from linearity.

The steep ramp test was used to assess potential changes in anaerobic capacity (via maximal wattage attained).[87] After completion of the test, to investigate lactate dynamics during passive recovery, individuals sat for approximately ten minutes, and blood lactate was assessed at three and ten minutes using a Lactate Pro Analyzer (Arkray Inc, Japan). The change between the three-minute value and the recovery value at ten minutes was calculated. This change was then calculated as a percent change between pre and post-intervention values to allow for between group comparisons. On a separate day, muscular strength was assessed on the leg press. The maximum weight and number of repetitions were used to estimate the one-repetition maximum.[218] As a follow-up, women in the two exercise groups had the choice of responding to a three month follow-up email concerning their post-intervention exercise activity level.

Blood Collection: Participants were instructed not to exercise for at least 48 hours prior to blood collection. The time frame for the blood draw was specified to occur 48-72 hours post-intervention to determine if potential changes occurred due to the cumulative effect of exercise training and not due to just an acute bout of exercise. Individuals documented their meals over a 24-hour period prior to baseline blood collection and were asked to mimic those meals prior to endpoint blood collection. After a 10-hour water only fast, blood was collected in a seated position between 7 and 11am. Blood was drawn via

venipuncture and serum was centrifuged, aliquoted and stored at -20° C until analysis. To investigate the dynamics between hepatic glucose output and insulin secretion in the basal state, the homeostasis model assessment (HOMA1-IR), an estimate of insulin sensitivity, was used.[252] A single blood sample was used, which can increase the intra-subject coefficients of variation to 10.3%.[391]

Laboratory Analyses: Fasting insulin, fasting glucose, and C-reactive protein (*hs*- CRP) were analyzed by standardized automated analyses used for clinical samples at St. Paul's Hospital (Vancouver, BC, Canada). *hs*-CRP levels were measured using Siemens BNII (Siemens Healthcare Diagnostics, Newark, DE, USA) with a within-run CV of 2.1- 4.6%. Glucose was measured with Siemens ADIVA 1800 with a within-run CV of 1.1% and Insulin with Siemens Immulite 2500 with a within-run CV of 2.5- 2.8%.

Exercise intervention

Participants were randomized into either an unsupervised control group, a supervised moderate-intensity exercise group, or a supervised high-intensity interval training group. The control group was not provided with any information concerning existing exercise guidelines, but all participants were asked to maintain their current lifestyle habits, which included continuing with any exercise or diet instructions they were currently following from other sources. To verify that intensity was the variable of interest, exercise volume (total work) was made equivalent between the two exercise groups. Exercise volume refers to the sum of work performed during a training period; hence, it can encompass the duration of the activity, the distance covered, and the number of times an exercise session was completed within a training period.[153] Both groups had to walk an equivalent distance (progression from 2 miles to 2.5 miles) at a relative-intensity that would average

out to be equal between groups. Duration was expected to differ. If an individual could not complete their distance within the defined interval number, they were instructed to walk at a pace that would elicit < 30% of $V0_{2reserve}$, or at an intensity below their first ventilatory threshold as these training intensities are not expected to cause significant metabolic changes within the muscle or cardiovascular system.[280 125]

During the exercise intervention, women were required to participate in their program three days a week, for six weeks, for a total of eighteen sessions. Both programs followed a progressive protocol to prevent cardiovascular or musculoskeletal complications. As this population has greater health concerns, all participants followed a mandatory warm-up and light cool-down.[15] The CMT group followed an exercise prescription that involved continuous moderate-intensity (progression from 55-70% of their $V0_{2peak}$) aerobic exercise, on a treadmill. The experimental HIT group was prescribed an interval program that involved two weeks of 3-4 minute introductory intervals at a maximal intensity of 80% $V0_{2peak}$, followed by four weeks of higher intensity interval bouts eventually requiring 2 minute efforts that would elicit > 90% $V0_{2peak}$. Table 5.2 presents an example of the HIT training protocol. Individuals wore programmable individualized heart rate monitors (Polar Electro Inc, Lake Success NY) to verify time spent in the desired interval range and average heart rate for each exercise session. RPE was also used to verify intensity, based on Wisloff's protocol and results when implementing interval training in clinical populations (RPE of 17 then 12).[375, 406]

Table 5. 2 Exercise prescription for a HIT participant for 6 weeks

Session	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
1	3 min @ 50% 4min @ 65%	2min @ 55% 4min @ 75%	2min @ 55% 3min @ 80%	2min @ 55% 3min @ 80%	2min @ <60% 2min @ 90%	2min @ <60% 2min @ 95%
2	3 min @ 50% 4min @ 70%	2min @ 55% 4min @ 75%	2min @ 55% 3min @ 80%	2min @ < 60% 3min @ 85%	2min @ <60% 2min @ 90%	2min @ <60% 2min @ 95%
3	2 min @ 50% 4min @ 75%	1min @ 55% 3min @ 75%	2min @ 55% 3min @ 80%	2min @ < 60% 3min @ 85%	2min @ <60% 2min @ 90%	2min @ <60% 2min @ 95%

4-6 interval repetitions calculated for a % of VO_{2peak}

Statistical analysis

Data is presented as an average percent change, or the mean values (standard deviation). Due to the expected, high variability between the personalized cancer treatments, normal distribution was verified by combining the Kolmogorov-Smirnov test, verification of skewness and kurtosis (z-score: 1.96) and if it was still questionable, visual analysis using a Q-Q plot. Baseline characteristics of each group, that could potentially influence data analysis, were initially compared (one-way ANOVA) to verify no covariates were needed with analysis. With this three group, pre-post design, the magnitude of change (gain) between groups (HIT, CMT and CON) was compared using a one-way ANOVA.[96] Due to slight difference in sample sizes, Gabriel's post-hoc test was selected for analysis due to its greater power when significance was found. Data that was not normally distributed were analyzed using independent samples Kruskal-Wallis non-parametric tests with the H-value being presented. As recommended, the baseline HOMA1-IR data was log-transformed due to common lack of normality, and compared for initial differences; furthermore, results were then compared using relative percent change.[392] If a CRP value was abnormally high (> 15mg/L)[322] the individual's value was altered to the mean plus two standard deviations[119] (n_{HIT}= 1). Controlling for Type 1 error rates for multiple comparisons, a Bonferroni correction was made based on the four major categories of

interest (results from CPET, results from SRT, results from blood analysis and changes in anthropometrics). A two-sided *P* -value <0.0125 was considered statistically significant. A *P*-value of 0.05 was considered a trend towards significant difference. Statistical analyses were carried out on IBM SPSS Statistics version 20.

Results

The flow of the trial is presented in Figure 1. Thirty-three women completed the six-week intervention with no adverse events. At baseline, age, weight, BMI, $V0_{2peak}$ and HOMA1-IR scores were equivalent between groups (see Table 5.3).

Table 5. 3 Participant characteristics at baseline

	HIT (n=12)	CMT (n=11)	CON (n=10)	Total N=(33)	*P* value
Age (years)	56.2 (9)	56.3 (9)	59.4 (9)	57.18 (9)	0.647
BMI (kg/m^2)	25.8 (5.8)	23.9 (3.7)	24.8 (4.4)	24.87 (4.7)	0.623
Wt (kg)	69.5 (14.7)	67 (10.5)	67.6 (11.8)	67.6 (12.2)	0.797
$V0_{2peak}$(ml/kg/min)	26.6 (6.7)	23.9 (4.3)	25.3 (5.1)	25.32 (5.4)	0.503
HR_{rest} (bpm)	71 (6)	73 (7)	66 (11)	70 (8)	0.168
Strength (lbs)	176.4 (48.7)	162.8 (33.6)	145.3 (27)	164.2 (39.9)	0.265
HOMA*	0.16 (.38)	0.20 (.23)	0.14 (.29)	0.17 (0.30)	0.898

Values presented as mean (sd)
* HOMA1-IR values are log transformed (HIT n=11, CMT n=10, CON n=10)
HR – heart rate taken after 5 minutes of silent, seated rest; VO_{2peak} –peak aerobic capacity elicited from a maximal exercise test on a treadmill; Strength – lower body, estimated 1-repetition maximum on a leg press

Over six weeks, eleven women completed 17.75 moderate-continuous exercise sessions that took an average of 40 minutes to complete and covered a total distance of 40.6 miles. Twelve women completed 17.76 high-intensity interval sessions with an average time of 36 minutes and covered a total distance of 40.3 miles.

Table 5.4 presents the results as a percent change in physical outcomes, raw values are presented in Table 5.5. HIT and CMT both increased their aerobic capacity by 11.48% and 12.95% respectively, whereas a 6% decline occurred in the CON group (P <0.001). There was no significant change in aerobic capacity between the exercise groups. Individual data is presented in Figure A2.2- 4. The effect size (η^2) for aerobic capacity was calculated; noting 45.4% of variance was likely caused by the exercise treatment. Post hoc analysis using G*Power software[118] produces a calculated power of 0.996.

A moderate 13.3% improvement in lower body strength occurred in the HIT group (P_{trend}= 0.026); however, after six weeks, the results from the steep ramp test demonstrated no significant difference in the change in W_{max} or Watts/Kg between groups, (H= 0.913, 0.641 respectively). Nonetheless, after repeating the steep ramp test with no gain in peak wattage after six weeks, the lactate measures demonstrated a trend towards improvement from baseline (P= 0.042) as the HIT group improved by 9.05%, whereas the control group continued to accumulate lactate ten minutes post-exercise (-4.22%).

There were no significant changes in fasting glucose, insulin or *hs*-CRP between the three groups (H= 0.509, 0.615, 0.232 respectively).

Only the HIT group showed a trend towards a decrease in body weight (P =0.04) while the hip and waist circumferences of both exercising groups declined significantly (P = 0.002, 0.004 respectively) compared to the control group.

Resting heart rate significantly declined by approximately 10% in the exercising groups while the control group experienced a slight 3.5% rise. Heart rate recovery at two minutes demonstrated a trend towards improvement in the exercise groups, meanwhile the control group demonstrated no change after six weeks (H = 0.04).

Table 5. 4 Results from a six-week exercise intervention in post-menopausal breast cancer survivors comparing average percent change from baseline values

	HIT (n=12)	CMT (n=11)	CON (n=10)	*P* value
Weight	-0.67 (1.91)	-0.41 (2.08)	1.44 (1.62)˚˚	0.031
Circumference				
Waist	-2.16 (2.9)	-2.51 (2.5)	1.95 (2.98)*	0.002
Hip	-1.81 (2.21)	-2.17 (2.26)	0.77 (1.24)*	0.004
HR_{rest}	-9.6 (10.4)	-9.2 (7.5)	4.9 (12.6)*	0.004
Strength 1RM	13.28 (7.9)	10.26 (10)	0.34 (11.1)˚˚	0.026
CPET				
$V0_{2peak}$	11.48 (10.5)	12.95 (10.4)	-5.97 (7.2)*	<0.001
Vt as $\%V0_{2peak}$	4.20 (8.3)	6.60(4)	-5.10 (8.6)*	0.003
HR_{rec} ˆ	19.78 (9)	17.83 (5)	0.33 (6) ˚*	0.041
SRT				
La change	9.05 (3.82)	3.65 (2.44)	-4.22 (4.1)˚˚	0.042
Wmax ˆ	7.93 (6.2)	8.65 (5.9)	4.95 (14.2)	0.913
W/Kg SRT ˆ	8.7 (7.1)	9.13 (6.2)	3.6 (15)	0.641
Blood (fasting)** ˆ				
Insulin	11.99 (6.2)	4.49 (12.0)	6.66 (11.9)	0.615
Glucose	2.68 (3.8)	0.89 (2.7)	-1.18 (2.2)	0.509
hs-CRP	-5.54 (12.4)	-11.02 (19.4)	228.9 (192.6)	0.232
HOMA1-IR	14.44 (21.4)	6.48 (43)	7.07 (44.5)	0.384

Total Sessions (18 max)	17.76	17.75
Total Distance (40.5 Miles)	40.3	40.6
Total Time (min)	640	712
Total Time (min) > 80% $V0_{2peak}$	198	0
Average Intensity ($\%V0_{2peak}$)	72%	68%
3 month follow-up (% physically active)	92%	42%

Values presented as mean percent change (standard deviation) unless otherwise noted
CPET– maximal cardiopulmonary exercise test on the treadmill; HR_{rest} – heart rate after 5 minutes of seated rest; HR_{rec} – heart rate recovery at 2minutes; SRT – Steep Ramp Test; $V0_{2peak}$ – peak aerobic capacity; Vt – ventilatory threshold; Wmax – peak wattage attained on the SRT; % physically active- minutes/ week based on current guidelines
P-Value reported for between group differences; ˆ reported H value for Kruskal-Wallis test
* significant difference or ˚* trend between control and exercise groups; ˚ significant difference or ˚˚ trend between control and HIT ** blood draws occurred in HIT n=11; CMT n=10; CON n=10,

Table 5. 5 Average pre-post data describing results from a six-week exercise intervention in postmenopausal breast cancer survivors

	HIT		CMT		CON	
	Pre	Post	Pre	Post	Pre	Post
Weight (kg)	69.48 (14.7)	68.95 (14.2)	66.99 (10.5)	66.78 (11.0)	66.01 (11.8)	66.9 (11.6)
Waist (cm)	93.59 (18.6)	91.37 (17.1)	92 (13.1)	89.68 (12.0)	90.04 (12.3)	91.79 (13)
Hip (cm)	106.96 (13.6)	104.85 (11.9)	103.95 (7.4)	101.72 (8.1)	103.43 (10.1)	104.16 (9.5)
$V0_{2peak}$ (ml/kg/min)	26.61 (6.7)	29.25 (5.8)	23.89 (4.3)	26.78 (4.3)	25.34 (5.1)	23.78 (4.8)
HR_{rest} (bpm)	71 (6)	64 (7)	73 (7)	66 (6)	66 (11)	68 (7)
HR_{rec} 2min (beats)	38 (9.5)	43 (13.5)	38 (9.3)	44 (11.5)	37 (9.5)	37 (7.1)
Strength 1RM (lbs)	176.41 (48.7)	197.97 (48.7)	162.79 (33.6)	179.85 (41.4)	145.85 (27)	144.85 (24.2)
W_{max} SRT	229.2 (42.2)	245.8 (46.7)	209.1 (48.7)	227.3 (46.3)	192.5 (31.3)	200 (28.9)
W/Kg SRT	3.4 (0.88)	3.67 (0.88)	3.14 (0.56)	3.43 (0.57)	3.02 (0.75)	3.06 (0.58)
La @ 3 min (mmol)	7.2 (1.9)	7.4 (1.6)	6 (1.4)	6.9 (1.5)	5.6 (1.3)	5.8 (2.1)
La @10 min (mmol)	6.3 (2.3)	5.7 (1.2)	4.8 (1.3)	5.4 (1.3)	4.2 (0.8)	4.7 (1.5)
Insulin (pmol/L)	61.82 (53.6)	67.91 (59.9)	52.6 (24.7)	49.7 (21)	51.9 (42.7)	54 (45)
Glucose (mmol/L)	5.05 (0.39)	5.15 (0.46)	5.26 (0.38)	5.3 (0.5)	5.11 (0.4)	5.04 (0.41)
CRP (mg/L)	1.58 (2.3)	1.4 (2)	1.35 (0.8)	1.21 (1.1)	1.51 (2.2)	2.21 (2.3)
HOMA-IR	2.06 (0.38)	2.28 (2.1)	1.8 (0.23)	1.68 (0.74)	1.74 (0.29)	1.77 (1.5)

Data is presented as the mean (standard deviation)

N = 33, n for each group: HIT= 12 (fasting blood draw n=11), CMT = 11 (fasting blood draw n=10), CON = 10

HR_{rest} – heart rate after 5 minutes of seated rest; HR_{rec} – heart rate recovery at 2minutes; La – lactate; SRT- Steep Ramp Test; W – maximal watts achieved; W/Kg – maximal watts achieved per kg of body weight; 1RM - predictive maximal strength test for lower body on a leg press

Table 5. 6 Percent of participants per group stratified into health risk categories

	*CRP (> 3 mg/L)		*HOMA (>2)		*Insulin (>95 pmol)		*glucose (>5.5 mmol/L)		*Waist > 88 cm		*BMI > 25 kg/m^2		**HR rest (10 bpm)		^ Mets (> 1 Met)	
	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	drop	rise	rise	drop
%																
CMT	10	20	50	20	10	10	20	30	73	55	36	36	18	0	27	0
HIT	18	18	45	36	18	18	18	18	58	42	42	42	42	0	33	0
CON	10	20	30	40	10	10	20	20	50	60	50	50	10	20	0	30

* Measures which have been associated with future co-morbidities and/or breast cancer recurrence

** Resting Heart Rate: 10 beat change linked to mortality risk from the Copenhagen City Heart Study, 2011

^ 1 MET change related to a 17% risk reduction in mortality from the St. James Women's Take Heart Project, 2003

Discussion

The present study provides support for implementing higher-intensity exercise protocols into rehabilitation programs for breast cancer survivors. This evidence endorses its safety; consequently, it provides an alternate exercise prescription that may potentially enhance exercise adherence in the breast cancer population. In addition, the results highlight that a lack of direction in the exercise prescription will negatively impact aerobic capacity in breast cancer survivors.

Similar improvements in aerobic capacity were elicited from the HIT and the CMT stimuli, but the total exercise time requirement was less in the HIT group. Time has been investigated as a major barrier to adherence to adopting a healthy lifestyle,[29, 363, 397] and this study contributes information concerning how to potentially improve future program designs when long-term change and adherence are key goals. The similar percent improvement in aerobic capacity may be due to the accelerated progressive program that the CMT group followed. Current guidelines and previous studies (see Tables A1.1 and A1.2) initially prescribe low intensities and progress at a slow rate. This slow transition period means that women may not train at an intensity of 70% $V0_{2peak}$ until the twelfth week. The lack of intensity stimulus may attenuate the development of physiological changes, preventing the women from noticing improvements. Without immediate feedback, participants may feel less motivated to continue exercising. Within two weeks of the program, in both exercise groups, women expressed excitement concerning noticeable changes in their daily lives (e.g., sleeping, climbing stairs, increased energy levels), which may explain the high compliance rate. On the basis of these results, exercise physiologists, who are working with survivors who are medically cleared to

exercise, need to reconsider the guidelines and tailor the prescription based on the individual's clinical and functional status, prior to prescribing baseline, universal intensities between 45- 55% $V0_{2peak}$ and the corresponding time for progression.

Further, the physiology of older women seems to differ when considering the training adaptation time course.[274-276] Older women develop a minor central adaptation within three weeks of exercise stimuli, but from weeks three to nine, peripheral adaptations occur which contribute up to 65% of the improvement in aerobic capacity.[274] The authors hypothesized that training adaptations in older women, (unlike the adaptations in men and younger women), may have a ceiling effect due to their natural decline in vascular conductance and blood flow. Long-term training interventions (> 6 months)[47, 123, 127, 179, 352] for postmenopausal women (breast-cancer, and cancer-free) as well as short-term interventions (8-15 weeks)[52, 73, 162, 418] have demonstrated similar 12% improvement in $V0_{2peak}$ (8-15%). The lack of large improvements with time, supports the notion of an early ceiling effect concerning $V0_{2peak}$. Direct measures that could differentiate if there were disparities in the type of adaptation, and the time it evolved due to HIT or CMT were not investigated in our 6-week trial. Accelerated adaptations may have occurred with HIT due to its unique ability to cause recurring disturbances to cellular homeostasis. This distinctive stress can enhance the efficiency of mitochondrial function within the active muscle,[413] enhance vasodilatory response, and improve peripheral arterial distensibility;[317] thus, leading to greater blood flow distribution and an increase in oxygen availability at the periphery. In addition to stimulating faster adaptations that improve VO_{2peak}, HIT may target different mechanisms that once enhanced, are less susceptible to

being altered with aging and inactivity. A long-term follow-up study post-cardiac rehabilitation eludes to potential benefits of HIT compared to CMT as individuals in the HIT group reported an attenuated decline in aerobic capacity (compared to CMT) over thirty months.[267] Long-term follow-up to investigate changes in $V0_{2peak}$ did not occur in our study.

Fasting glucose,[277] fasting insulin,[159 139-141] HOMA-IR,[294] *hs*-CRP,[310] and inflammation[310] have been related to potential recurrence, or poor outcome in breast cancer survivors depending on the diagnosis.[294] As exercise intensity can influence these markers, the results from this study demonstrate that it is unlikely that breast cancer survivors have an abnormal, long-term, metabolic reactions to higher intensity exercise, as there was no chronic rise in these biomarkers after six weeks. We did not expect to see a decline in values (improvement) based on our study design. Higher intensity exercise was safe and efficient, as it required less time to cause improvements in risk factors related to potential co-morbidities (Table 5.6). The acute change in this populations' metabolism after one episode of HIT, in a trained or untrained state, remains unknown. The effect of adding HIT into long-term rehabilitative interventions to improve the levels of surrogate markers associated with recurrence remains to be investigated.

Autonomic function can influence mechanisms that can modify insulin resistance,[230] glucose regulation[298] and inflammation[195]. Cancer therapy is continually evolving; still, it has been demonstrated that certain chemotherapy drugs can negatively influence autonomic function in cancer patients.[22, 108, 245] This study noted a modest improvement in

autonomic function in the HIT group via an accelerated heart rate recovery. Changes in heart rate recovery, over 2 minutes, due to four weeks of training has been previously noted in coronary artery patients.[226] The 20% improvement in the CMT and HIT groups demonstrates possible enhanced cardiovagal activity eluding to potential improvements between the intricate dynamics of sympathetic withdrawal and parasympathetic reactivation.[330] The decline in resting heart rate in both exercise groups may be attributed to improved peripheral vasculature, vagal tone,[201] improved cardiomyocte contractility and enhanced diastolic and systolic cellular mechanisms (intracellular Ca^{2+} handling, synchrony, t-tubule density).[366] [199, 366] It could be speculated that in addition to neural adaptations, high-intensity exercise may enhance alternate mechanisms that endurance protocols do not stress, and thus be able to overcome the barrier of decreased estrogen and its corresponding suppressive affect on preventing cardiac improvements.

The follow-up occurred approximately three months from the last exercise session, and 92% of women in the HIT group reported to still be exercising a minimum of 150 minutes of moderate exercise or 75 minutes of vigorous exercise per week, whereas only 42% of the CMT group were following the recommended exercise dose according to recent guidelines.[337] Self- efficacy was not measured in this study, but women in the HIT group commented on feeling empowered with their new knowledge concerning their ability to exercise safely at high intensities; consequently, they expressed a feeling of accomplishment. This empowerment through applying their new knowledge concerning effective workouts may have improved the long-term adherence rates.[234] The lack of boredom, due to the cognitive challenge that occurs with high-intensity and alternating

interval bouts, is another possibility for the high adherence numbers.[11] These findings are consistent with other studies, which have investigated exercise preference and adherence when associated to exercise intensity.[16, 83, 146, 375]

Six weeks of unsupervised activity levels, caused a 6% decline in aerobic capacity (½ MET) whereas individuals who followed a supervised, individualized exercise program, demonstrated a marked increase in aerobic capacity of approximately 12% (0.8 METS). In a similar population, Herrero and colleagues reported an 8% rise in aerobic capacity after 8 weeks of a combined training program, followed by a decline of 1.8 METS after 8 weeks of low physical activity levels (ie. less than 120 minutes per week of walking).[163] Studies are just beginning to look at the relationship between declines or improvements in aerobic capacity with morbidity and mortality in breast cancer survivors. [147, 190, 194] Our only guide to date on the importance of increasing aerobic capacity in females, is from two studies: 1) the St. James Women's Take Heart Project, which linked a 1 MET improvement in exercise capacity to a 17% risk reduction in mortality;[147] and 2) Rogers et al followed a cohort of females in the 1980s to discover that a 1 MET change reduced risk of all-cause mortality by 25%.[326]

With reference to anaerobic activity, there was a trend towards an increase in lower body strength with HIT, but the maximal wattage or W/Kg did not change with the six-week training program. In addition, there was a corresponding trend towards improved change in lactate dynamics. It is speculated that strength improvements in the HIT group were secondary to the increased stress imposed by more frequent skeletal muscle contractions,

compared to the CMT group. The more frequent contractions coupled with the greater demand for heightened enzymatic activity created an environment where accelerated neuromuscular training occurred, allowing for earlier onset of metabolic changes which induced a physiologic change in muscle fibers, enhanced recruitment strategy or improved the quality of muscle fiber. Maintaining and improving functional capacity of the sarcoplamsic reticulum and muscle fiber quality (e.g., muscle architecture, protein synthesis, neuromuscular function) is hypothesized to be key in preventing the decline in strength and power associated with aging, functional limitations, and disease. [90, 321]

The lack of change in the steep ramp test can be attributed, in part, to the participants discomfort on the cycle ergometer. The women did not use the bikes during training, implying either the testing tool lacks specificity or the test ended pre-maturely as the women were unfamiliar to the leg discomfort elicited by the bike. The measurement of lactate dynamics was limited by our measurement tool, as we did not use a lactate tracer, but measured peripheral blood lactate at two time points. Nevertheless, it does provide information concerning potential change in the recovery dynamics in breast cancer survivors. The ability to recover post-exercise is an area of interest for exercise physiologists, as improving metabolic dynamics is a way to delay fatigue and enhance performance in athletes. Recovery dynamics could translate into improving daily functioning and quality of life in survivors. Recovery post-exercise is influenced by the body's ability to replenish energy supplies (adenosine triphosphate and creatine phosphate), to re-establish the balance of ions that are key in the breakdown of glycogen during heavy exercise (Ca^{2+} and H^{+}), and to restore balance to the catecholamine levels.[19]

Exercise training, (endurance or HIT), can improve many of these variables by enhancing transport via the cardiovascular system through increases in the metabolic enzymes, the number mitochondria, more efficient transporter proteins, capillary density, and an improved ability to vasodilate.[40, 51, 61, 170, 378] The percent change from the amount of lactate circulating at three minutes to the drop in the amount at ten minutes may be attributed to the enhanced ability of the HIT group to utilize lactate during recovery via training-induced improvements in the aforementioned physiology.

During the intervention, women were asked to maintain their normal extracurricular habits; however, two women in the HIT group, who were exercising more than six hours a week, stopped their outside programs during the first week of the intervention. Both of these women were able to maintain their aerobic capacity even with the dramatic drop in their physical activity minutes from over 120 minutes to 60-75 minutes/week (see individual results in Figure A2.2-4). If these women are not included in analysis, the HIT group demonstrates an approximate 15% improvement in $V0_{2peak}$. The lack of control over the nutritional habits prevents any discussion concerning metabolic outcomes relating to changes in weight and body circumferences.

The blood sampling also had its limitations as 1 -2 participants per group admitted to exercising within 48 hours of their post-blood draw as well as only partially following the food diary (i.e., participants selected to eat unhealthy, high fat, high sugar foods). It is also important to note that the HOMA1-IR measure provides information on hepatic insulin sensitivity, not whole-body insulin sensitivity, and the speed to which HIT or

CMT can alter hepatic metabolism in post-menopausal women remains unknown. We acknowledge that the use of a dynamic measure of glucose and insulin metabolism, such as an oral glucose tolerance test, would be preferred when investigating the short-term results of training studies in women, especially who have undergone metabolic disturbances (menopause, cancer treatment and the addition of any type of hormonal treatment). The measurement in the basal state prevents any definitive statement relating potential improvements in peripheral glucose dynamics with the increase in aerobic capacity or lower body strength.

Further limitations concern the goal of equalizing volume between the exercise groups. Distance was selected, as it was a goal that could easily translates into day-to-day life. Two women in the HIT group had short stride lengths; consequently, to cover the prescribed distance, without increasing the number of intervals, an additional 15 minutes of walking at a light intensity were added to their workout. If we exclude their times, women in the HIT group averaged 34 minutes per workout session (total of 605 minutes compared to 712 minutes in the CMT group). The duration differences and similar increase in aerobic capacity is comparable to previously published data (see Table A1.3). In addition, the average intensity was equivalent between groups, but the CMT group started at a higher intensity and progressed quickly compared to common guidelines. It is important to acknowledge this difference in CMT prescription compared to other HIT studies and other breast cancer interventions. If we had used a similar progression CMT model as previous interventions, we speculate that the duration of the CMT group would have greatly differed. As well, the design for interval progression decreased the recovery

time between repeated bouts, which allows the contribution of the majority energy yield to be from aerobic metabolism.[129] Perhaps this design did not impose enough stress on the anaerobic system to induce greater changes compared to CMT.

These breast cancer survivors have undergone a vast array of treatments, thus we acknowledge that comparing their different metabolic responses may have its limits. Differences demonstrated can be attributed to the individual response to the exercise stimuli. Designing interventions with matched groups based on treatments (as in Chapter 3) would address this concern, however this is unlikely to occur due to the common difficulty with recruitment. We also acknowledge that multiple statistical tests were conducted in analysis, such that it is important that follow-up studies occur to confirm these results.

This study supports the implementation of progressive, high-intensity interval training protocols into supervised rehabilitation programs for breast cancer survivors. HIT and CMT prescriptions are safe methods to counter the treatment-induced decline in physical functioning. Both exercise programs followed protocols that involved higher than previously prescribed intensity goals, and both demonstrated the ability to safely attenuate risk factors related to future co-morbidities and early mortality.

6 Conclusion

Four studies were safely completed providing evidence to support the implementation of higher intensity exercise prescriptions into rehabilitative programs for breast cancer survivors.

Initially, the most effective mode for assessing aerobic capacity was investigated. We hypothesized that a maximal aerobic protocol on a treadmill would be the preferred choice of exercise mode and thus, elicit the most effective values. The results demonstrated that the use of a treadmill protocol was safe, effective, and due to preference choice could impact adherence rates of future intervention studies. These results provided reasoning to incorporate treadmill programs into the subsequent studies.

The second study sought to determine if implementing HIT during chemotherapy was a safe exercise prescription. In accordance with our second hypothesis, the data provided evidence suggesting that increased exercise intensity does not impact chemotherapy delivery (i.e., the prescribed RDI), nor does it cause change in immune function as reflected in the neutrophil counts. This was the first exercise and cancer-related study with treatment-matched controls (i.e., matched by BSA/treatment dose, age, and timing of therapy). The results support HIT to be a safe exercise option to add to current rehabilitative programs, as it was well tolerated by the patients during chemotherapy.

The third aim was to establish an exercise testing protocol to measure anaerobic capacity in postmenopausal breast cancer survivors. Contrary to the third hypothesis, the results from the study revealed support for using the steep ramp test[262] instead of the proposed treadmill speed test.

The final study was designed to determine if HIT, (when compared to CMT and CON), is a safe and an effective exercise prescription that can enhance aerobic and anaerobic capacity in post-menopausal breast cancer survivors post-primary therapy. The results from this exercise intervention highlight that a progressive HIT protocol, as well as a more aggressive CMT protocol, are both efficient prescriptions to quickly improve aerobic capacity in this clinical population.

There are four key points that summarize the findings of implementing short, intermittent bouts of high-intensity exercise into breast cancer survivor rehabilitative programs:

1) It is safe to implement HIT into exercise programs for breast cancer survivors
    a. When administered as adjuvant therapy, progressive HIT protocols did not negatively affect the immune system in immunosuppressed individuals.
    b. When administered post-initial therapy, a progressive HIT program did not cause a rise in biomarkers (e.g., *hs*-CRP, insulin, glucose) that are related to recurrence or other co-morbidities.
    c. No serious adverse advents occurred during testing or during the interventions

2) Many of the participants expressed altered perceptions with symptoms commonly associated with exercise (i.e., fear of sweating, dyspnea or increases in heart rate). Prescribing short intense bouts of exercise safely exposes the participants to the symptoms associated with close to maximal effort, without any negative repercussions. The implementation of rest breaks between bouts may dissipate the feelings of boredom, fatigue and dyspnea for the exerciser, motivating long-term exercise adherence.

3) During treatment, HIT provides a means to introduce higher intensities. Future research may decipher if the stimulus is strong enough to overcome some of the suppressive effects of treatment that are associated with long-term dysfunction.

4) HIT may cause more efficient peripheral metabolic adaptations among anaerobic and aerobic pathways, resulting in a greater range of adaptations. This may be key in trying to offset the wide range of biological dysfunction that occurs with treatment, and in preventing the increased risk of developing future co-morbidities.

Improvements in the treatment-altered anaerobic and aerobic pathways have been discussed in the last five chapters leading to a conclusion that the addition of increased intensity may cause adaptations in a greater range of skeletal muscle fibers addressing a wider heterogeneous population. With HIT's capability to target more metabolic pathways, a greater reduction in the risk factors associated with developing future co-

morbidities is hypothesized to occur. Not all mechanisms within the pathways were measured in the final study; however, different adaptations were seen in HIT compared to CMT. This chapter will summarize key points concerning the adaptations associated with aerobic capacity and morbidity prevention. General benefits and limitations of the design will be discussed. These speculations will provide foundations for future research to improve survivorship.

Cancer treatment and training specificity in post-menopausal women

Cardiovascular variables

Implementing HIT into rehabilitative programs can be a cost effective technique, as HIT benefits can occur at an accelerated rate.[40] This provides more efficient timelines within exercise programs, and as we have demonstrated, can translate into longer lasting adherence rates. In six weeks, variables associated with cardiovascular health (e.g., HR_{rest}, $HR_{recovery}$, $V0_{2peak,}$ waist and hip circumferences) in post-menopausal breast cancer survivors improved with both the CMT and HIT prescriptions, but significant weight loss and improved strength only occurred in the HIT group.

Within our study, CMT and HIT both elicited adaptations that caused increases in aerobic capacity; however, the location and type of modification may differ. Previous studies using matched-work designs have published comparable findings (see Table A1.3).[84, 106, 148] If there is a ceiling effect in older women, (as discussed in Chapter 5), implementing a HIT workout two-to-four times a month may facilitate long-term adherence such that aerobic capacity will be maintained. In addition, HIT can provide enough stimuli to

improve mechanisms, other than what we measured with a CPET, related to functional capacity and quality of life.

Dr. Laukkanen recently released new, unpublished data from the Kuopio Ischemic Heart Disease Risk Factor Study (Finland) at the American Heart Association Conference, November 2012, warning that a 15% decline in aerobic capacity over a ten year period doubled the risk of experiencing an acute myocardial infarction and death (i.e., the chance of dying of any other cause doubled).[220] Our results demonstrated that it took only six weeks of uneducated, unsupervised training to experience a 6% (½ MET) decline in aerobic capacity. The Finnish study followed male subjects; nonetheless, the results are distressing in regards to women's health and fosters the public health concern for finding a program that inspires long-term adherence to an efficient exercise program. The results from our control group support Dr. Laukkanen's findings, which encourages the measurement of cardiorespiratory fitness as a clinical practice. In summary, the follow-up observed that the Finnish participants overestimated their health/fitness levels, which led to a rise in developing co-morbidities and in early mortality. Accordingly, the rapid 6% decline in aerobic capacity observed in our control group, (who were physically active at low-to-moderate levels), emphasizes that post-menopausal survivors are at high risk for developing cardiovascular disease.

Anaerobic capacity and lactate dynamics

High-intensity exercise training may enhance the dynamics within the skeletal muscle to either protect the non-cancerous cells during treatment, or rehabilitate the cells post-treatment. Recently, fatigued and non-fatigued breast cancer survivors were compared

with published results summarizing that both groups suffered from neuromuscular fatigue when compared to previous published control values; however, due to limitations involving the measures, the researchers felt that lactate threshold was the greater contributor to fatigue symptoms.[282] In Chapter 5, the more aggressive CMT protocol, as well as the HIT protocol, caused improvements in the ventilatory threshold; however, the enhanced recovery lactate values were only observed in the HIT group. Alternating intensities could stress a wider spectrum of mechanisms (e.g., MCT1, MCT4) among the different muscle fiber types,[39] which could influence the lactate threshold, and elicit a greater global change.

It was not officially measured in our study, but verbal and written feedback indicated that the physiological changes that were measured, translated into improved energy levels during activities of daily living. Challenging these pathways within different fiber types with increased intensity could improve recovery dynamics, providing an explanation to why women felt less exhausted during their day-to-day tasks. Training at higher intensities may delay peripheral fatigue by stressing the systems that buffer, or transport the by-products of anaerobic metabolism. This stress over numerous bouts may ameliorate the body's ability to protect itself from chemotherapy cellular disruption, or initiate the needed adaptation post-therapy.

To verify this, further research would be required to first separate the different responses to muscle metabolism with cancer treatment (i.e., do slow twitch fibers suffer the greatest insult with treatment) and then secondly, to decipher if the altered skeletal muscle

metabolism responds differently to exercise intensity. Direct measures of lactate threshold or the lactate dynamics during exercise were not taken in any of our studies. We speculate that HIT may be more beneficial to cancer survivors as their altered physiology may require higher intensity stimuli to cause the necessary physiological changes to counteract the suppressive effects of treatment.

Insulin

Postmenopausal breast cancer survivors did not demonstrate an abnormal insulin response to higher intensity exercise training as reflected in the fasting insulin and glucose levels. Implementing HIT into the monthly calendar could be an excellent mean to decrease total exposure to insulin and glucose, potentially influencing survivorship. In type 2 diabetics, total glucose exposure over 24 hours declined after only one bout of HIT, compared to a matched, control day.[135] In addition, it was observed that a six-week HIT intervention upregulated GLUT4 (a protein that is an insulin-regulated glucose transporter within the cell) within the skeletal muscle, but surprisingly, after six weeks of detraining, GLUT4 remained elevated above baseline levels.[39] If breast cancer survivors respond with similar metabolic adaptations, this unique, time-efficient response associated with HIT could translate into a major health benefit (i.e., prevent the onset of diabetes or metabolic syndrome).

The mechanism behind the role of insulin in cancer recurrence is under investigation; however, as it remains elusive, the connection between physical activity, insulin and recurrence is difficult to pinpoint. Whether it is insulin exposure or if it's the insulin pathway itself is unknown. Current knowledge in the literature suggests that in diabetics,

a physically active lifestyle was more effective in reducing circulating glucose (58% decline) than supplementing with the drug metformin, (31% decline).[210] Both metformin and exercise can activate AMP-activated protein kinase (AMPK),[6, 55, 346] a protein that maintains homeostasis by maintaining adequate ATP sources through it's ability to switch off the ATP-consuming energy pathways and activate energy pathways that will replenish ATP.[149, 200] Alteration of AMPK with metformin is hypothesized to be a mechanism behind cancer recurrence prevention;[159, 417] nonetheless, these two methods that influence insulin metabolism may not act on the same metabolic pathway (in hepatic or peripheral muscle cells). The confusion of deciphering which AMPK isoform, thus the metabolic pathway associated with recurrence risk, that can be activated by exercise continues, as 1) there is no additive affect when combining exercise and metformin, eluding to different mechanisms or isoforms of activation;[346] and 2) new evidence reveals that different exercise intensity levels can influence which AMPK isoform is upregulated.[128] Further, metformin's influence on survivorship is based on mechanistic hypotheses from diabetic studies involving hepatic tissue. It is unknown how metformin influences breast cell lines. Exercise training has the ability to modulate mechanisms within the hepatic cells that could influence recurrence; still, the type of exercise that can improve this elusive area of hepatic function is unknown. As exercise intensity increases, hepatic blood flow decreases.[289] The question remains if blood flow stress is important to elicit modifications within the liver. Exercise intensity, the duration to prompt an hepatic change, and the biological pathway to be targeted by exercise, remain unknown.

Inflammation

Exercise training elicits an enhanced antioxidant response[302, 305] and has the potential to minimize the unnecessary levels of ROS released from treatments that may be damaging the pathways required for chemotherapy invasion. Accumulated bouts of physical activity are hypothesized to enhance the anti-oxidant dynamics by causing a faster release of specific myokines (e.g., IL-6 and IL-10), which decreases the inflammation caused by exercise stress.[302] These myokines may be able to scavenge, not just cytokines released with exercise, but also excessive levels of ROS accrued with chemotherapy.[409] Implementing chronic bouts of physical activity during or post-primary therapy may upregulate the natural anti-oxidant defense protecting the body from an excessive surge in ROS and pro-inflammatory cytokines. As some oxidative stress is required for a successful outcome, it is unlikely exercise could completely inhibit the treatment-induced rise in inflammation. This is speculation, as we did not measure the inflammatory response between exercise and non-exercising patients during chemotherapy. Our post-primary intervention verified that there was no rise in chronic inflammation; however, the survivors' acute antioxidant response via myokines to exercise remains to be determined. Exercise intensity is hypothesized to influence the release of the myokine IL-6, [291] as such, HIT may be an effective protocol for postmenopausal women to attain the minimal intensity that can elicit the beneficial anti-inflammatory response. Further research is required to determine which suppressive effects of cancer treatments, other than the decline in aerobic capacity, could be sensitive enough to be rehabilitated through a HIT program.

Abnormalities within skeletal muscle, the endocrine and the cardiovascular systems that lead to co-morbidities, are associated with excessive ROS production.[303, 373, 395] Tumor necrosis factor alpha (TNF-alpha) is a major inflammatory cytokine that can influence a key metabolic pathway related to cancer recurrence, and its release is also associated with exercise. A surplus of TNF-alpha is associated with insulin resistance, disease, aging and exercise-induced muscle damage.[23, 207] Exercise protocols that elicit muscle damage stimulate excessive release of TNF-alpha that will inhibit the downstream signal to GLUT4, impairing the insulin-mediated glucose uptake, causing acute insulin resistance for up to three days.[89] The HIT interventions prescribed a gradual progressive exercise model, without any emphasis on eccentric exercise based on recommendations to prevent an excessive release of TNF-alpha.[207] During therapy, the immune system's response is more influential to outcome, so neutrophil count was measured, not inflammation. To ensure there was no chronic, stressful effect with higher intensities post-primary therapy, chronic inflammation (CRP), fasting glucose and fasting insulin were monitored to ensure the exercise stimulus did not endanger these women to future co-morbidities, including recurrence. No chronic rise in the biomarkers of concern occurred with the HIT protocol.

Erythrocytes

During treatment, the patients were exercising with lower than normal hemoglobin levels (up to a 20% decline in [Hb]). Even with this inefficiency in oxygen transport, women maintained a high adherence rate (>90%) and did not succumb to an inactive lifestyle. The short bouts allow the patient to tolerate the exercise symptoms that coincide with treatment-induced anemia. Chemotherapy can cause erythrocytes to deform, and this

membrane modification may prevent the removal of senescent erythrocytes from circulation (via macrophages or splenic clearance).[420] With abnormal amounts of deformed red blood cells, blood flow is hindered, leading to alterations in microcirculation and oxygen delivery.[350] Regular physical activity provides a greater population of younger erythrocytes, which are more resistant to oxidative stress and more efficient with oxygen delivery.[345, 354] During treatment, higher exercise intensities did not prevent a decline in [Hb]. This inability of exercise to counteract the myelosuppressive effect of chemotherapy was previously demonstrated in a moderate-intensity intervention.[97] Implementing a HIT program post-chemotherapy could enhance removal of senescent erythrocytes by providing adequate stress to ensure destruction of dysfunctional red blood cells. The rest breaks and the short duration exercise bouts could prevent erythrocyte deformity and dysfunction seen with exhaustive exercise.[286, 386] Red blood cell deformability and function (i.e., the ability to release ATP and carry 0_2), in response to exercise interventions have yet to be explored in clinical populations. Erythrocyte deformability and its relationship to aerobic capacity or fatigue during or post-adjuvant therapy could provide insightful information concerning functional capacity.

Exercise design and limitations

Pulmonary, cardiovascular and skeletal muscle function synergistically influence oxygen transport, to influence aerobic capacity and day-to-day function. It was previously discussed how cancer treatments may influence anyone of these steps during oxygen transport, and deficiencies could vary between each individual depending on their personalized treatment combined with their biological make-up. The goal of an exercise

program is to recruit and enhance multiple metabolic pathways to elicit a beneficial synergistic response between the energy systems. We acknowledge with our sample size and measures that it is difficult to define the differences of the tightly linked physiology between exercise protocols; furthermore, it is unlikely one protocol will benefit all individuals. Individuals have a varying genetic response to exercise stimuli[32], accordingly, understanding the specific goal that the patient must achieve to improve their quality of life, and to know which exercise prescription will elicit the greatest change in that specific biological make-up, is an important part of the research and exercise design.

This dissertation has provided results encouraging the use of either a more intensive CMT program or a progressive HIT program to improve aerobic capacity in postmenopausal breast cancer survivors. However the biological mechanism that was most sensitive to the exercise stimuli, which led to the key increase in aerobic capacity, remains elusive. The mechanisms that adapted to the HIT stimuli are likely to differ from the mechanisms that developed with CMT. For example, previous research has demonstrated that HIT and CMT both improve blood pressure in hypertensive patients; however, the additional measurement of arterial stiffness differentiated the importance of the protocols.[145] Further analysis discovered that HIT, not CMT, improved arterial stiffness (a well established marker associated with mortality[221]). The findings from another CMT versus HIT study revealed that HIT was required to enhance insulin sensitivity in women with greater metabolic abnormalities, whereas moderate-intensity proved to be an adequate stimuli in healthy women.[58] Cognitive function improvements

have been observed with HIT but not with long duration (moderate or low-intensity) exercise. It is hypothesized that the variation in protocol intensities coupled with the change in program duration creates ideal stimulation to enhance cognition.[11] This relationship encourages further investigation of HIT into programs helping survivors who suffer from post-chemotherapy cognitive impairment (i.e., chemo brain). In Chapter 5 improvements in aerobic capacity occurred in both exercise groups; however, the selected measures prevented the ability to differentiate the health benefits that were more sensitive to a HIT stimuli.

Designing an effective exercise program for post-menopausal breast cancer survivors faces some immeasurable barriers that are worth mentioning. Primarily, this population is typically unfamiliar with the exercise equipment and it may take between six and nine sessions to dissuade the participants' anxiety of falling off a treadmill. Secondly, other than inexperience, women can suffer from neurotoxicities that can influence their gait, or hinder their stride on treadmills or cross-trainers. Lack of balance and foot tingling were the most common discomforts that were noted throughout these studies; however, with some basic, personalized modifications, symptoms were minimized. Thirdly, educating women about exercise and explaining the basic symptoms associated with intense exercise[176] (e.g., familiarization with dyspnea, heart rate monitoring, understanding the reasoning behind sweat, exercise progression and importance of consistency), can reduce the fear associated with the aforementioned symptoms, thus influence long-term adherence and potentially be a major factor in overcoming program barriers.

Women who were undergoing, or who had completed, primary treatment for early-stage breast cancer used HIT to help ameliorate side-effects associated with treatment. It remains unknown if this translates to other cancer populations. We did not measure angiogenic biomarkers and cannot comment on the response to high-intensity exercise; however previous training studies have noted that the VEGF response post exercise does not differ with training status and returns to baseline levels within two hours.[214] Consequently, the use of high-intensity exercise in patients with metastases requires further examination, as there may be local metabolic concerns, thus potential safety issues.

Concluding statement

The physiology behind exercise as a tool to rehabilitate treatment-induced biological limitations has been presented in this dissertation. Supervised exercise delivered in short, high-intensity bouts has been discussed and the evidence presented supports its safe use as adjuvant therapy.

It is recognized that CMT is safe to administer to breast cancer survivors, and those that adhere to the present guidelines[155, 337] can elicit positive health changes. The implementation of short bouts of high-intensity exercise are effective when executed using interval programs; however, prescribing high-intensity was worrisome for fear it could negatively influence long-term side effects or treatment delivery by either exacerbating fatigue or causing additional immunosuppression. The studies presented in this dissertation were designed to investigate if this population could safely undergo a HIT program. Further, the design determined if there were abnormal responses that might

occur with increased intensity due to potential treatment-induced metabolic differences. The results from these studies provide support for implementing supervised, progressive HIT programs into rehabilitation programs as higher intensity exercise bouts did not produce any detrimental effects on chemotherapy delivery, the immune system, fasting insulin levels, fasting glucose levels, inflammation or adherence rates. HIT can elicit, safe and effective adaptations in breast cancer survivors.

Future studies are required to decipher the influence of exercise intensity on treatment-specific alterations within the musculoskeletal, endocrine, nervous, immune and cognitive systems. To investigate whether HIT elicits different responses than CMT within the cardiorespiratory system, or within key tissues that influence metabolism in survivors, such as the liver, or adipose tissue, remains to be investigated. The results from the presented studies are a stepping-stone to encourage other exercise oncology researchers to investigate the potential behind HIT, and to clarify if there are greater physiological and psychosocial benefits.

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Appendices

Appendix 1- Tables

Table A1. 1 Intensity guidelines

American College of Sports Medicine (ACSM)[337] BCS Guidelines: 150 min/week of moderate exercise or 75 minutes /week of vigorous exercise as per the PAGA[66]
In addition to previous ACSM guidelines concerning cardiovascular and pulmonary contraindications to exercise BCS contraindications are: ataxia, adequate time to heal post-surgery, anemia, and extreme fatigue

	ACSM 2006 Guidelines				ACSM 2009 Guidelines and PAG for Americans			
	% $V0_{2max}$	% HR_{max}	RPE	MET		%$V0_2R$ & %HRR	% HR_{max}	RPE
Very Light	<30	<35	<10	<3	Very Light	< 20	<50	<10
Light	30-49	35-59	10-11	3-4	Light	20-39	50-63	10-11
Moderate	50-74	60-79	12-13	5-6	Moderate	40-59	64-76	12-13
Strenuous	75-84	80-89	14-16	7-8	Hard (vigorous)	60-84	77-93	14-16
Very Strenuous	>85	>90	>16	>8	Very Hard	>85	>96	17-19

HR_{max} – maximal heart rate; HRR- heart rate reserve; MET - 3.5 ml 0_2/kg/min; RPE -based on the 6- 20 Rating of Perceived Exertion Borg Scale: 6 represents 'no exertion at all', 13 represents 'somewhat hard' and 20 represents 'maximal' exertion; $V0_2$ – maximal oxygen consumption; $V0_2R$ - $V0_2$ reserve

Note: Many Breast Cancer Survivors (BCS) have an average $V0_{2max}$ of 6-8 METS. The physical activity recommendations for an individual with a $V0_{2peak}$ of 8 METS translates to 150 min of exercise at 3.8- 5.1 METS or 75 minutes at 5.2 -6.9 METS (as per Table D1 from Physical Activity Guidelines for Americans, (PAGA)[64])

Table A1. 2 Exercise interventions in post-menopausal or peri-menopausal breast cancer survivors

Study	N	Age	CON group	Length (weeks)	Intensity	Duration (min per session)	Frequency (days per week)	Wts	Key Physiological Outcomes		Other Outcomes of Interest	
									↑$V0_{2peak}$ (direct)	Body Mass	Improved	Improvement not found
Exercise interventions in post-menopausal or peri-menopausal breast cancer survivors post-primary therapy												
Berglund et al, 1993	60	54	Y	7	"light triaining"	120	1 (total -4)	N	N/A	N/A	Strength, tiredness, physical training	QOL, anxiety, depression, pain
Cheema et al, 2006	27	58	N	8	65-85% HR_{max}	15-30	3	Y	↑	→	QOL, WC, HC, strength	N/A
Courneya et al, 2003	53	59	Y	15	70-75% $V0_{2peak}$	15 -35 (35min: week 12-15)	3	N	↑	→	QOL improved	See Fairey et al, 2003, 2005
Fairey et al, 2003, 2005	Same data set from Courneya et al, 2003										IGF -1, IGFBP-3, natural killer cell activity	Insulin, glucose, IGF-II, CRP, IL-6, TNF-alpha, IL-10, IL -4, neutrophil function, BP, $HR_{rest,}$ cholesterol
Daley et al, 2007*	108	51	Y	8	65-85% $HR_{max\ pred}$	50	3	N	N/A	N/A	QOL, FACT-G, fitness, depression	BMI, body fat, fatigue (note: exercise placebo group similar to exercise group)
Haykowsky et al, 2009	17	53	N	16	60-90% $V0_{2peak}$	30-60	3	N	→	NR	N/A	↓ Ejection fraction
Herrero et al, 2006	16	50	Y	8	70-80% HR_{max}	20 -30	3	Y	↑	→	QOL, muscle mass, lower body strength	Fat mass, upper body strength

Table A1. 2 Exercise interventions in post-menopausal or peri-menopausal breast cancer survivors

Study	N	Age	CON group	Length (weeks)	Intensity	Duration (min per session)	Frequency (days per week)	Wts	Key Physiological Outcomes		Other Outcomes of Interest	
									↑$V0_{2peak}$ (direct)	Body Mass	Improved	Improvement not found
Irwin et al, 2009, 2009	75	56	Y	24	50-80% $HR_{max\ pred}$	15-30	5	Y, NR	N/A	→	Lean mass, %body fat, IGF-1, IGFBP-3	Insulin, WC, HC
				52				Y, NR	N/A	→	Body fat	Lean mass
Ligibel et al, 2008, 2009	82	52	Y	16	55-85% HR_{max}	Not defined	90 min/ week	Y	N/A	→	HC, insulin, strength	WC, BMI, body fat, adinopectin, leptin
Mathews et al, 2007	22	51	Y	12	11-13 RPE	20-40	3-5	N	N/A	→	Activity levels	Body fat, fat mass, lean mass
Milne et al, 2008	58	55	Y	12	NR	20	3	Y	N/A	NR	QOL, strength, physical fitness (submax test)	None reported
Nieman et al, 1995[292]	12	60	Y	8	75% HR_{max}	30	3	Y	N/A	N/A	6min walk test	Natural killer cell function
Payne et al, 2008[301]	20	65	Y	12- 14	Light - Mod	20	4	N	N/A	N/A	Sleep, sleep quality, serotonin levels	Fatigue, sleep efficiency, IL-6, cortisol
Pinto et al, 2005[311]	86	53	Y	12	55-65% $HR_{max\ pred}$	10 -30	2-5	N	N/A	N/A	1-mile walk time	BMI, %body fat
Schnieder et al, 2007	96	57	N	24	40-75% HRR	40	2-3	Y	N/A	NR	Fatigue, HR_{rest}, $V0_{2\ predicted}$, BP	NR
Segar et al, 1998[344]	24	49	Cross over	10	60% HRR	30-40	4	N	N/A	N/A	Depression, anxiety	NR

Table A1. 2 Exercise interventions in post-menopausal or peri-menopausal breast cancer survivors

Study	N	Age	CON group	Length (weeks)	Intensity	Duration (min per session)	Frequency (days per week)	Wts	Key Physiological Outcomes		Other Outcomes of Interest	
									↑$V0_{2peak}$ (direct)	Body Mass	Improved	Improvement not found
Interventions during primary therapy for early-stage breast cancer												
Courneya et al, 2007	194	49	Y	17	60-80 %$V0_{2max}$	15-45	3	(°)	→	→	Self-esteem	QOL, RDI, strength, lean mass
Kolden et al, 2002	40	55	N	16	40-70% $V0_{2max\ pred}$	20	3	Y	N/A	→	Estimated $V0_{2max}$, strength, SBP, QOL measures	HR_{rest}, body fat, QOL measures
MacVigar et al, 1989	45	44	Y	10	60-85 % HRR	20-30	3	N	↑	NR	Workload	NR
Mock et al, 1994	14	44	Y	until chemo ended	Moderate	30	3-5	N	N/A	NR	Fatigue, nausea, depression, fitness	NR
Mock et al, 2001	108	52	Y	6-24	Brisk 50-70% $HR_{max\ pred}$	15- 30	5- 6	N	N/A	NR	Activity behavior, fitness, fatigue	NR
Mutrie et al, 2007	174	52	Y	12	50-75% $HR_{max\ pred}$	20	3	N	N/A	N	Fitness, mobility FACT-B	FACT –G, -GS, -GP, –F, -ES
Pickett et al, 2002	48	48	Y	6- until chemo ended	60-80% $HR_{max\ pred}$	10-30	5	N	N/A	NR	NR	Physical activity did not impact side effects

Table A1. 2 Exercise interventions in post-menopausal or peri-menopausal breast cancer survivors

Study	N	Age	CON group	Length (weeks)	Intensity	Duration (min per session)	Frequency (days per week)	Wts	Key Physiological Outcomes		Other Outcomes of Interest	
									↑$V0_{2peak}$ (direct)	Body Mass	Improved	Improvement not found
Schnieder et al, 2007	17	55	N	NR	40-75% HRR	40	2-3	Y	N/A	NR	Treadmill time, SBP, fatigue	$V0_{2predicted}$, HR_{rest}, cognitive fatigue
Schwartz et al, 2001	61	47	Y	8	Moderate	15-30	3-4	N	N/A	N/A	Fitness, fatigue	NR
Segal et al, 2001	99	51	Y	26	50-60% $V0_{2max}$	NR (walking program)	3-5	N	N/A	→	SF-36	$V0_{2predicted}$ and Weight changed with exercise but not when compared with controls
Winningham et al, 1989	24	45	Y	10-12	60-85% HRR	20-30	3	N	N/A	↑	Muscle mass	NR

Post-primary therapy exercise studies are presented if the majority of participants were postmenopausal. Post-primary interventions presented are post-chemotherapy and/or radiation. Women may or may not have been taking hormonal therapy, or biological therapies.
Primary therapy interventions that occurred solely during radiation were not recorded.
Majority of trials did not adjust for multiple statistical comparisons. Trends are not reported as improvements in this table.
* Depression, self-worth and physical fitness improved in the exercise and the placebo exercise group to usual care. No comment on difference between exercise and placebo. Fatigue improved in the exercise-placebo group only. (°) Results from resistance exercise group are not included in this table
Number of participants analyzed (N), weight program included (Wts?), Yes (Y), No (No), no change: →, decrease:↓, increase:↑
NR – data measured but not reported, or data not presented
N/A – not applicable as measures were not taken at baseline or at follow-up.
Values based on age adjusted calculations or from a predictive maximal test ($HR_{max\ pred}$), body mass index (BMI), blood pressure (BP), waist circumference (WC), hip circumference (HC)
HRR – heart rate reserve – see Table A1.3 for relative % similarities between intensities based on ACSM's guidelines in 2006 and 2009

Table A1. 3 Exercise interventions comparing high-intensity interval training (HIT) to continuous moderate exercise training (CMT)

Study	Subjects N	Age	Sex M:F	Equal Work	Group	Length	HIT #sets/time hard:rest %:%intensity	CMT time % intensity	Results		
									HIT > CMT	Improved (CMT & HIT)	No Change
Clinical populations											
Ciolac et al, 2010	Risk HT 44	25	F	Y	CMT HIT CON CON	3d/w for 16w	40min 1:2min 80-90: 50-60%$V0_{2max}$	40min 60-70% $V0_{2max}$	$V0_{2max}$, HR_{rec}, DBP, PWV endothelial function	HIT & CMT =insulin & HOMA, $V0_2$, BP (24hrs)	Wt, BMI, WC, triglycerides, cholesterol
Guimaraes et al, 2012	HT 43	47	13: 30	Y	CMT HIT CON	2d/w for 16w	40min 1:2min 80:50% HRR	40min 60% HRR	PWV	HIT & CMT = for reducing 24 hour BP (ABPM)	x
Lamina, S 2011	HT 357	58	M	No comment	CMT HIT CON	3d/w for 8w	45 -60min 6:6min 60-79% HRR: rest	40-60min 60-79% HR_{max}	x	$V0_2$, BP	x
Moholdt et al, 2009	CABG 59	61	48: 11	Iso-K	CMT HIT	4d/w for 5w	4 sets 4: 3min 90: 70% HR_{max}	46 min 70% HR_{max}	$V0_{2peak}$ @6 month follow-up	$V0_{2peak}$, $HR_{recovery}$, resting heart rate, QOL	body mass, triglycerides, glucose, cholesterol

Table A1. 3 Exercise interventions comparing high-intensity interval training (HIT) to continuous moderate exercise training (CMT)

Study	Subjects N	Age	Sex M:F	Equal Work	Group	Length	HIT #sets/time hard:rest %:%intensity	CMT time % intensity	Results		
									HIT > CMT	Improved (CMT & HIT)	No Change
Rognmo et al, 2004	CAD 17	69	14:3	Iso-K by group	CMT HIT	3d/w for 10w	4 sets/ 33min 4:3min 80-90:50-60%HR_{max}	41 min 50-60% $V0_{2peak}$	$V0_{2peak}$	$V0_{2peak}$	body mass, BP, HR_{rest}
Tjonna et al, 2008	MetS 28	52	13:15	Iso-K by group	CMT HIT CON	3d/w for 16w	4 sets/40min 4:3min 90:70% HR_{max}	47min 70% HR_{max}	PGC-1∝, glucose, NO insulin, CA^{2+} reuptake	$V0_2$, BMI, WC, BP, FMD, adinopectin	triglycerides, insulin, C-peptide, Hb, cholesterol
Wisloff et al, 2007	HF 27	76	20:7	Iso-K by group	CMT HIT CON	3d/w for 12w	4 sets 4:3min 90-95: 50-70% HR_{peak}	47 min 70-75% HR_{peak}	PGC-1∝, $V0_{2peak}$, CA^{2+} re-uptake, ↓pro-BNP	QOL, Anaerobic threshold	HR_{rest} CMT: SV, Q, %EF
Non clinical populations											
Burgomaster et al, 2008	Untrained 20	23	10:10	N	CMT, HIT	3d/w for 6w	4-6 bouts 30s: 4.5 min WinG: 30W	40-60mim 65%$V0_{2peak}$	↓Dedicated training time	Mitochondrial markers, lipid oxidation	Body mass

Table A1. 3 Exercise interventions comparing high-intensity interval training (HIT) to continuous moderate exercise training (CMT)

Study	Subjects N	Age	Sex M:F	Equal Work	Group	Length	HIT #sets/time hard:rest %:%intensity	CMT time % intensity	Results		
									HIT > CMT	Improved (CMT & HIT)	No Change
Cunningham et al, 1979[79]	In-active 15	18-25	F	Y	CMT HIT CON	4d/w for 12w	7-8 sets 2:1min >90% $V0_{2max}$:rest	20 min 70-80% VO_{2max}	x	HR_{submax}, D(A-$V0_2$), SV (first 4 weeks of HIT)	SV – CMT & HIT w4-12, Q
Daussin et al, 2008	In-active 11	45	6:5	Y	CMT HIT	3d/w for 8w	20-35min 1:4min 90%W_{max}: $V_{threshold}$	Time till mechanical work =HIT 61% W_{max}	Q_{max}, muscle mitochondrial function	$V0_{2max}$ (CMT > muscle capillary density)	x
Eddy et al, 1977	Untrained 14	21	6:8	Y	CMT HIT	4d/w for 7w	8-19 sets 1:1min 100%$V0_{2max}$: rest	12-30min 70%$V0_{2max}$	x	$V0_{2max}$, $Lactate_{submax}$, $_{max}$ anaerobic power	x
Fournier et al, 1982[124]	Untrained 12	17	M	Y (time)	CMT HIT	4d/w for 12w	20-60min of 50-250m sprints	2x10min to 2x30min 60-90% $V0_{2max}$	PFK activity	HR_{submax}, CMT only: slow twitch fast twitch A, C & SDH activity	Muscle fiber distribution, fast twitch B
Gibala et al, 2006	Untrained 16	21	M	N	CMT HIT	3d/w for 2w	4-6 sets 30s: 4.5min WinG: 30W	90-120min 65%$V0_{2peak}$	↓Dedicated training time	Performance time, muscle buffering & oxidative capacity	COX II, IV mRNAs

Table A1. 3 Exercise interventions comparing high-intensity interval training (HIT) to continuous moderate exercise training (CMT)

Study	Subjects N	Age	Sex M:F	Equal Work	Group	Length	HIT #sets/time hard:rest %:%intensity	CMT time % intensity	Results		
									HIT > CMT	Improved (CMT & HIT)	No Change
Helgerud et al, 2007	Untrained 40	25	M	Y	CMT CMT HIT HIT	3d/w for 8w	47 sets 15s:15s or 4 sets 4:3min 90-95% HR_{max}: rest	45min 70% HR_{max} or 24.25min 85% HR_{max}	$V0_{2max}$, SV	running economy, velocity at lactate threshold	hematological response, body mass, lactate threshold
Nemoto et al, 2007	Middle-age Elderly 139	63	28: 111	Iso-K	CMT HIT CON	4^{+}d/w for 20w	5^{+} sets 3:2-3min 70-85: 40%$V0_{2peak}$	8000 steps/day 50%$V0_{2peak}$	$V0_2$, SBP, thigh muscle strength	women - BMI, body mass	compared to controls: HR_{rest}, $V0_{2peak}$ on bike
Rakobowchuk et al, 2008	Untrained 20	23	10:10	N	CMT HIT	3d/w_{HIT} or 5d/w_{CMT} for 6w	4-6 sets 30s: 4.5 min WinGate: 30W	40-60min 65%$V0_{2peak}$	↓Dedicated training time	$V0_{2peak}$, HR_{submax}, vascular function	HR_{rest}, BP, central arterial distensibility
Saltin et al, 1976[333]	Untrained 13	22	M	Y	CMT HIT	4d/w for 4w	20-30 sets 40-50:90s max effort :rest	35-45min 75%$V0_{2max}$	x	$V0_{2max}$, HR_{submax} - local response in trained leg, lactate response	x

Table A1. 3 Exercise interventions comparing high-intensity interval training (HIT) to continuous moderate exercise training (CMT)

Study	Subjects N	Age	Sex M:F	Equal Work	Group	Length	HIT #sets/time hard:rest %:%intensity	CMT time % intensity	Results		
									HIT > CMT	Improved (CMT & HIT)	No Change
Tabata et al, 1996	Untrained 14	23	M	Iso-K	CMT HIT	5d/w for 6w	7-9 sets 20s:10s 170%$V0_{2max}$: rest	60 min 70%$V0_{2max}$	Anaerobic capacity (oxygen deficit)	$V0_{2peak}$	x

Subjects: description of population: CABG – coronary artery bypass grafting, HT – hypertension, HF- heart failure, MetS – metabolic syndrome, Untrained – may be active but not training competitively, In-active – sedentary or is active less than once a week;
Groups: HIT – high intensity interval training, CMT – continuous moderate exercise, CON – control group, did not participate in a supervised exercise program;
M –male, F- female; N: total number of subjects analyzed;
Equal Work – interventions used a matched work design (wattage, kpm, intensity, or Iso-K (isoenergetic/caloric)), Y- yes, N- no
Length: duration of intervention, d- days, w- weeks
Variables: $V0_{2max}$ or $_{peak}$ – maximal oxygen consumption, peak commonly used in clinical populations, HRR – hear rate recovery, $HR_{rest,}$ or $_{submax}$- resting heart rate, or submaximal heart rate at a set load, QOL – quality of life, HOMA – insulin sensitivity index, NO – nitric oxide availability, SV – stroke volume, Q – cardiac output, BMI – body mass index, WC – waist circumference, PWV – pulse wave velocity & FMD – flow mediated dilatation (used for an index of arterial stiffness and endothelial function), BP – blood pressure (S or D – systolic/ diastolic), CA^{2+} SR $uptake_{max}$ – calcium reuptake within the sarcoplamic reticulum, pro-BNP- cardiac marker, PGC-1∝ - marker for mitochondria biogenesis
x – not noted or no differences found; Intensity – please see Appendix for comparison of intensities (HR_{max}, HRR, Vo_{2max}, RPE)
Note- some HIT studies required individuals to exercise for 10min @ 70% $V0_{2max}$ in interval group

Appendix 2- Figures

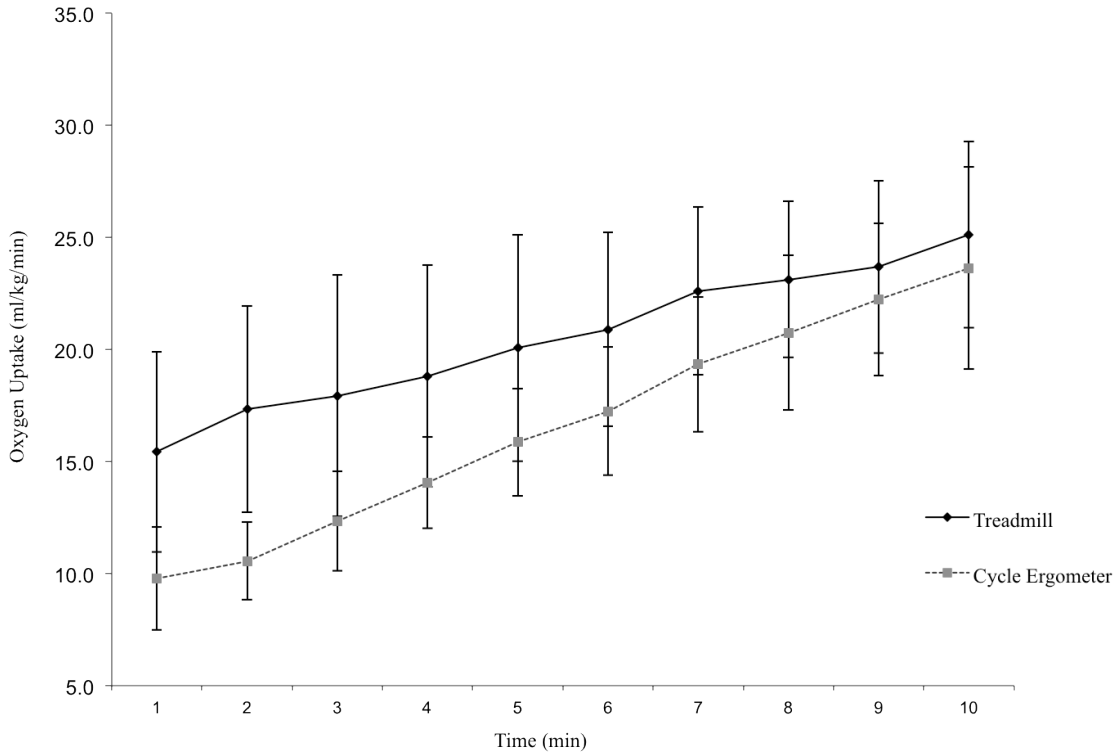

Figure A2. 1 Oxygen uptake differences per minute between the cycle ergometer (--) and treadmill (-) maximal aerobic stress tests (n=12).

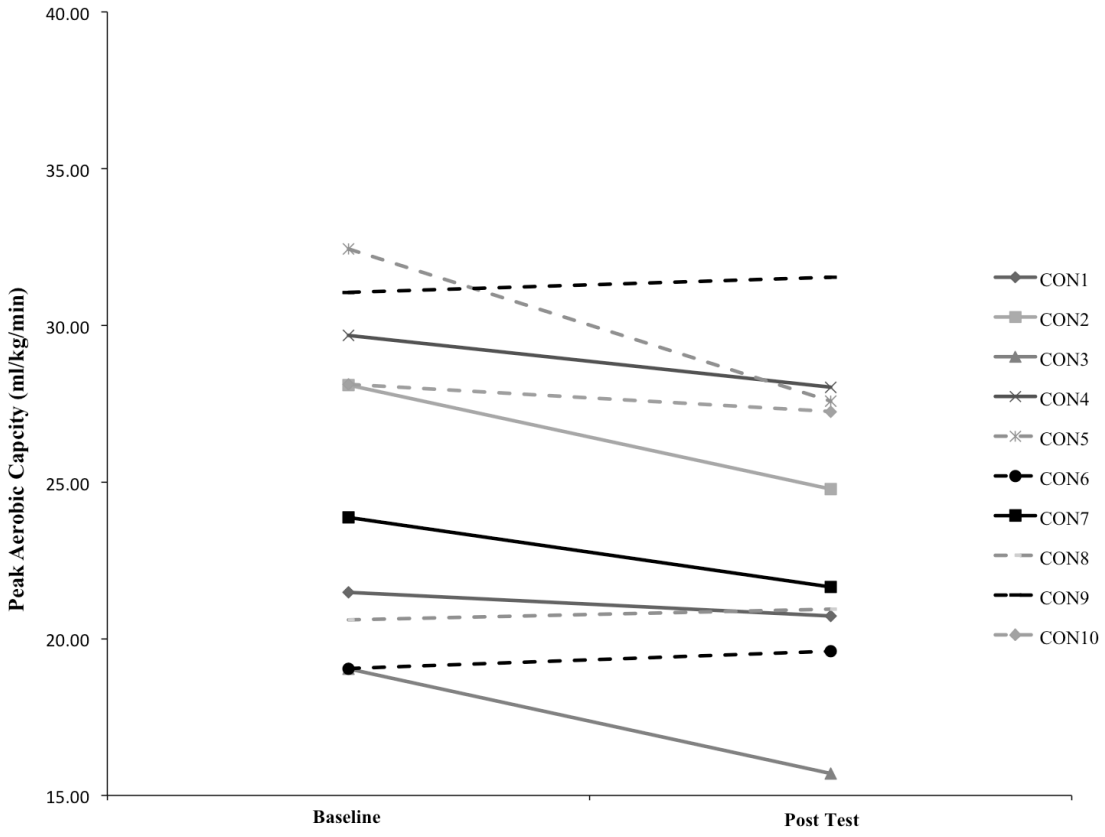

Figure A2. 2 Individual peak aerobic capacity pre-post values for the control group. Individuals who followed an unsupervised exercise program for a minimum of 3 days per week (--).

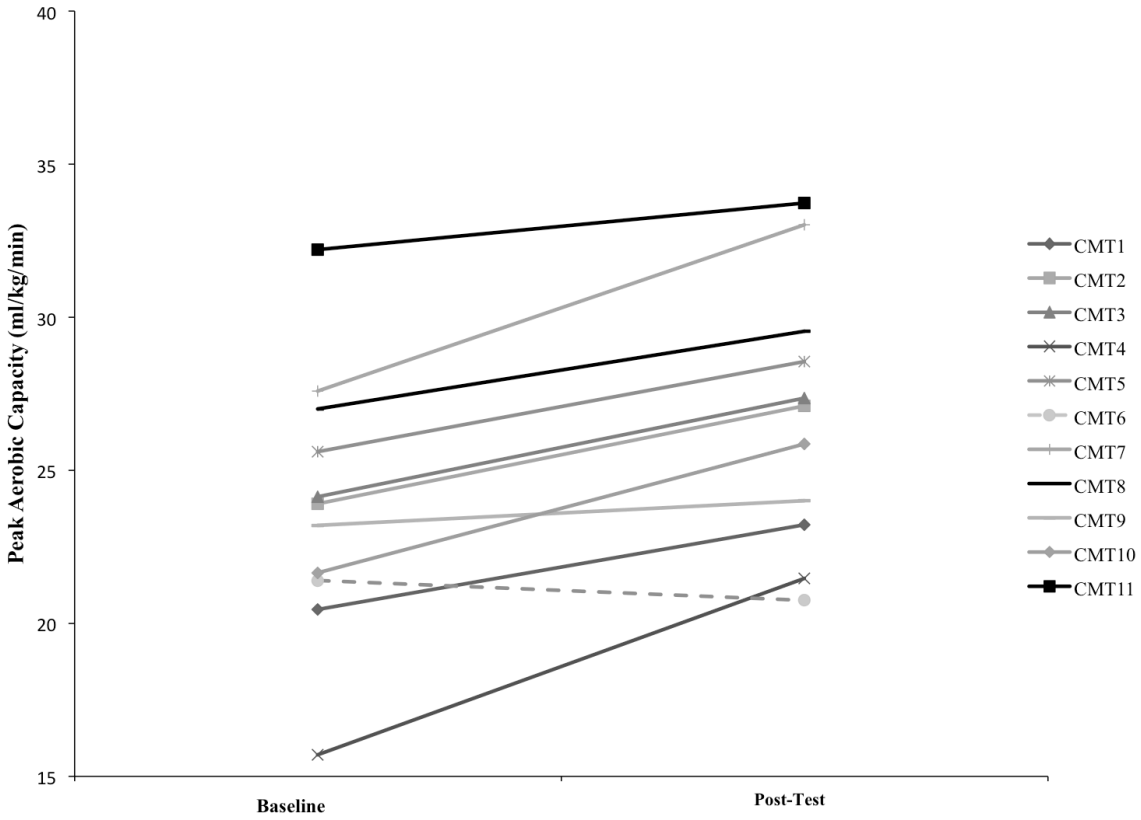

Figure A2. 3 Individual peak aerobic capacity pre-post values for the moderate-intensity group. Individual was diagnosed with dysfunctional thyroid week 4 and began medication week 5 (---).

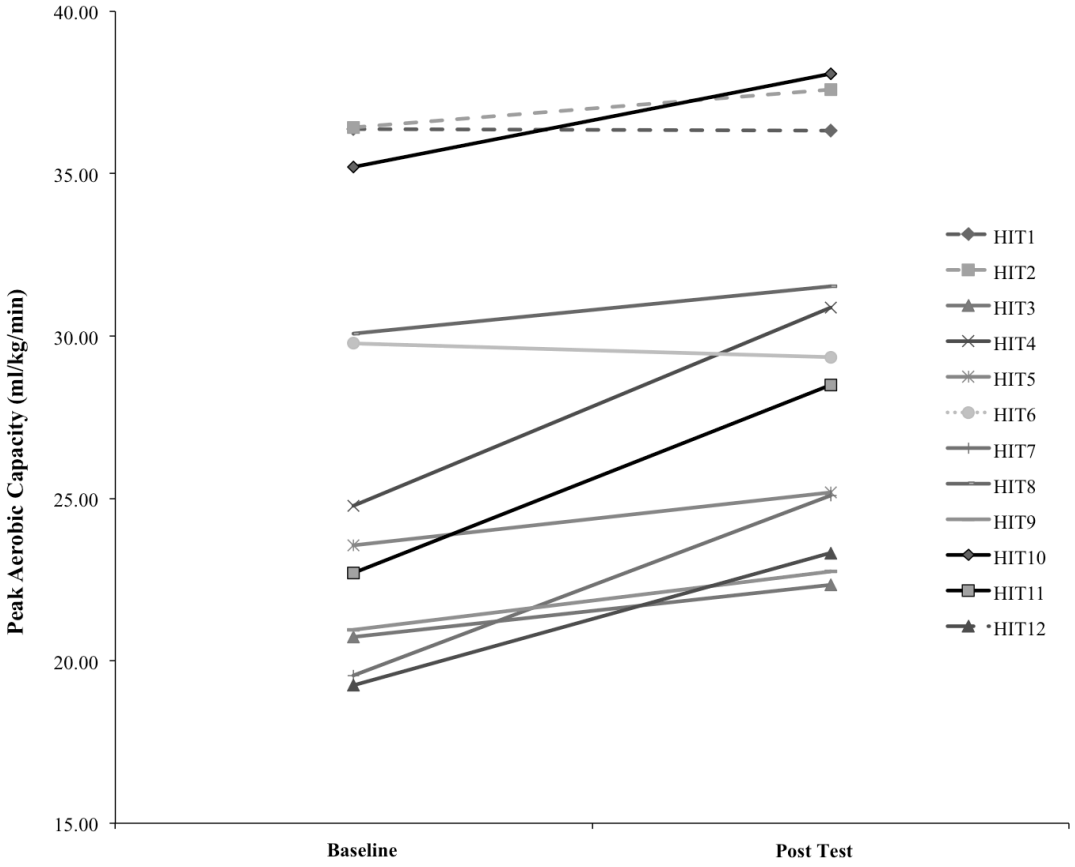

Figure A2. 4 Individual peak aerobic capacity pre-post values for the high-intensity group. Individuals who stopped participating in their outside exercise programs upon starting the HIT intervention (---).