Abstract
Fatigue is one of the most commonly reported side effects during treatment for breast cancer, and for some individuals can continue for an extended period following treatment completion. Cancer-related fatigue is multi-factorial in nature, and one hypothesized mechanism of both development and persistence of cancer-related fatigue following treatment is cardiorespiratory and muscular deconditioning. The purpose of this study is to compare lactate threshold, VO$_2$ peak and central vs. peripheral causes of muscular fatigue in breast cancer survivors with persistent cancer-related fatigue (FG) and the control group (CG), breast cancer survivors without persistent cancer-related fatigue following treatment for breast cancer. METHODS: During the first testing visit, power output at lactate threshold, lactate threshold as a percentage of peak power output, and absolute and relative VO$_2$ peak were determined using a graded incremental maximal exercise test on a cycle ergometer. During the second testing visit central and peripheral muscle fatigue following a sustained contraction of the right quadriceps were assessed using the twitch interpolation technique and measurement of voluntary activation, control twitch, maximum voluntary contraction and endurance time. RESULTS: There were no significant differences in age, body weight, or time since completion of treatment between groups. There were no significant differences between groups in power output at lactate threshold (FG 60.7±17.0 vs. CG 73.3±22.2 W, p=0.14), lactate threshold as a percentage of peak power output (FG 46.8±8.6 vs. CG 55.0±14.7%, p=0.11), peak power output (FG132.12±38.2 vs. CG 140.6±5.9 W, p=0.66), absolute VO$_2$ peak (FG 1.51±0.39 vs. CG 1.74±0.38 L/min, p=0.19), or relative VO$_2$ peak (FG 22.4±4.9 vs. CG 23.6±7.1 ml/kg/min, p=0.62). Results did approach significance for power output at lactate threshold (p=0.10) and absolute VO$_2$ peak (p=0.08) when adjusted for age. Central fatigue was responsible for muscular fatigue in the
control group, while muscular fatigue in the cancer-related fatigue group was more due to peripheral mechanisms. CONCLUSION: While no statistically significant differences were found between groups, results suggest that deconditioning may play a role in cancer-related fatigue. Future research into the use of exercise training as a tool to improve deconditioning and thereby reduce this proposed aspect of cancer-related fatigue is warranted.
Preface

This thesis contains the work of a two-part research study conducted by the candidate, Sarah E. Neil, under the supervision of Dr. Kristin L Campbell with guidance from Drs. Donald C McKenzie, S. Jayne Garland and Riggs J. Klika. The study design, data collection and analysis, and writing of the manuscript were primarily the work of the candidate.

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

Ethical approval for this research study was provided by the UBC Clinical Research Ethics Board (H10-01288).
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List of Abbreviations

ATP Adenosine Triphosphate
BDI Beck Depression Inventory
BMI Body Mass Index
CT Control Twitch
CG Control Group
ET Endurance Time
FACT-B Functional Assessment of Cancer Therapy - Breast
FACT-F Functional Assessment of Cancer Therapy - Fatigue
FG Cancer-related Fatigue Group
Hb Hemoglobin
ICD-10-CM International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Clinical Modification
IT Interpolated Twitch
MAF Multidimensional Assessment of Fatigue
MET Metabolic Equivalent
MVC Maximum Voluntary Contraction
RPE Rating of Perceived Exertion
RER Respiratory Exchange Ratio
RPM Revolutions Per Minute
SEE Standard Error of Estimate
VA Voluntary Activation
VO$_2$ max Maximum Volume of Oxygen Consumed
VO$_2$ peak Peak Volume of Oxygen Consumed
W Watts
Acknowledgements

I would first and foremost like to acknowledge and thank my supervisor, Dr. Kristin Campbell, for her guidance, encouragement, and support over the last two years and most importantly for allowing me countless opportunities and experiences that have developed my interest and passion for research in the field of exercise and cancer. To my co-supervisor, Dr. Don McKenzie, thank you for your expert advice and support throughout my degree, as well as your time in drawing blood during data collection. To committee member Dr. Jayne Garland thank you for your input and guidance on this project as well as allowing me to use your lab space for data collection. To Dr. Riggs Klika, thank you for your assistance with both developing the protocol for the study and cleaning and interpreting the exercise testing data.

To Tanya Ivanova and Diana Jespersen, thank you for your time, expertise and assistance in obtaining equipment and developing the testing protocols. I would also like to thank Courtney Pollock and Vicki Gray for your help with the Biodex, and for allowing me to intrude on your workspace during data collection. To my fellow graduate students and lab mates, Amy Kirkham, Lianne Dolan, and Sherry Hunt, thank you for your input and help with developing the protocols and recruiting participants for the study, and for listening and offering advice when things weren’t going the way I had hoped.

Finally, I would like to acknowledge those at the British Columbia Cancer Agency, Inspire Heath, and Burnaby Hospital who assisted with recruitment, as well as the participants themselves who volunteered their time to participate in this study.
1 Chapter: Literature Review

1.1 Introduction

Today there are over one million cancer survivors living in Canada, including over 223,000 female breast cancer survivors\(^1\). An estimated 23,200 women in Canada will be diagnosed with breast cancer each year, making it the most common cancer among Canadian women\(^2\). Due to improvements in screening and early detection, as well as advancements in adjuvant treatment (chemotherapy and radiation therapy) and hormonal therapy, the 5-year relative survival rate for female breast cancer is currently 87%\(^2\). Although survival rates are high, these women are faced with a number of late and long lasting side effects, which have a great impact on their future health and quality of life\(^3,4\).

Following diagnosis, the most common treatment pathway for breast cancer is surgical resection of the tumour followed by adjuvant treatment, namely chemotherapy and/or radiation\(^5\). The type of adjuvant treatment used is based on tumor stage and characteristics. If chemotherapy is used, it is commonly administered first, and is administered in cycles with treatment every 2-3 weeks for 4-8 cycles. Chemotherapy is then followed by radiation for 3-6 weeks. Therefore, the duration of time from diagnosis to the completion of adjuvant treatment is approximately nine months. For women with hormone sensitive tumors, hormonal therapy is initiated following adjuvant treatment using selective estrogen receptor modulators (SERM), such as tamoxifen, or the newer aromatase inhibitors, which limit estrogen exposure in the body by blocking binding of estrogen to receptors or production of estrogen. Breast surgery and radiation can cause shoulder and upper-limb pain, decreased range of motion and lymphedema, an accumulation of lymph in the arm, shoulder or chest area\(^6-9\). Adjuvant treatment and hormonal therapy commonly prescribed following primary breast cancer can also result in premature
menopause\textsuperscript{10-12}, weight gain\textsuperscript{13,14}, cognitive impairment\textsuperscript{15,16}, cardiotoxicity\textsuperscript{17,18}, decreased bone mineral density\textsuperscript{19}, fatigue\textsuperscript{20,21}, and psychological problems including anxiety, depression, and sleep disturbance\textsuperscript{22,23}. The focus of this project is on the fatigue experienced by breast cancer survivors.

1.2 Cancer-Related Fatigue

Cancer-related fatigue is quite distinguishable from a general feeling of tiredness. The National Comprehensive Cancer Network defines this fatigue as “a distressing persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning”\textsuperscript{24}. Cancer-related fatigue is present regardless of activity level and is not relieved by sleep or rest.

The prevalence of cancer-related fatigue varies based on the measurement scale used, but it has been reported to be as high as 70-100\%\textsuperscript{25,26} in individuals undergoing or recently completed adjuvant treatment for cancer. Although fatigue as a symptom is reported to be highest among patients during adjuvant treatment\textsuperscript{27,28}, it can continue for months or years after treatment has finished\textsuperscript{29,30}. The percentage of breast cancer survivors who report persistent cancer-related fatigue (which continues long after treatment has been completed) is approximately 30\%\textsuperscript{31-34}. A longitudinal study of 763 disease-free breast cancer survivors who had completed adjuvant treatment reported that 35\% of women reported significant fatigue in the first 1-5 years post-treatment. During the 5-10 year follow-up period, 64\% of the women who had originally reported fatigue continued to experience significant fatigue\textsuperscript{32}. Although
individuals with no history of cancer can also experience fatigue, especially related to aging, when a cohort of breast cancer survivors 5-15 years post-diagnosis were compared to a group of women with no cancer history, scores on a fatigue inventory were higher in the breast cancer group (5.88±16.48 vs. −3.89±9.72, p<0.001)\(^3\).

Fatigue is reported by those diagnosed with breast cancer as one of the most common and debilitating side effects following the diagnosis and treatment of a variety of cancer types\(^{25,36-39}\). Unlike other side effects such as nausea, fatigue cannot be well managed by medication, and therefore can interfere with completion of adjuvant treatment on schedule\(^{25}\) and with activities of daily living\(^{25,40,41}\). With the huge number of survivors potentially living with cancer-related fatigue, the need to determine both the cause and an effective intervention to reduce cancer-related fatigue becomes of great importance for increasing the quality of life in these individuals.

### 1.2.1 Causes of Cancer-Related Fatigue

The exact etiology of cancer-related fatigue is currently unknown. Many factors have been suggested to contribute to fatigue in cancer survivors including an increase in inflammatory cytokines, dysregulation of the hypothalamic-pituitary-adrenal axis, anemia, psychological conditions, and deconditioning.\(^{25}\)

#### 1.2.1.1 Inflammatory Cytokines and Fatigue

Circulating levels of inflammatory cytokines such as interleukin-6, interleukin-8 and tumor-necrosis factor-alpha, are known to increase during cancer treatment due to production of these cytokines by the tumor itself, chemotherapeutic agents and radiation treatment\(^{42,43}\). These
cytokines are associated with a decrease in muscle mass and strength and increased fatigue in other populations, such as fibromyalgia and multiple sclerosis. Research into a correlation between increases in inflammatory cytokines and cancer-related fatigue has yielded mixed results. While some studies have found an association between levels of fatigue in disease-free cancer survivors and presence of inflammatory biomarkers in blood samples, others have failed to find this relationship.

1.2.1.2 Hypothalamic-Pituitary-Adrenal Axis Dysfunction and Fatigue

The hypothalamic-pituitary-adrenal axis is responsible for maintaining homeostasis and is the body’s system for dealing with a stimulus that causes stress. At rest, when the body encounters a stressor the hypothalamic-pituitary-adrenal axis is activated and cortisol is released, resulting in heightened arousal, improved motor reflexes, improved attention and cognitive function and decreased appetite. It has been found that breast cancer survivors with persistent cancer-related fatigue have a blunted cortisol response to a stressor compared to breast cancer survivors who do not report cancer-related fatigue. Bower et al. conducted a study in which breast cancer survivors with and without cancer-related fatigue were asked to perform the stressful task of public speaking. While free salivary cortisol was similar at baseline, those who reported cancer-related fatigue had lower levels during and after the task was completed, indicating dysfunction in the hypothalamic-pituitary-adrenal axis. Diurnal cortisol levels measured over the course of 24-hours have also been shown to be different between fatigued and non-fatigued breast cancer survivors, with the fatigued survivors having a flatter cortisol slope. Cortisol suppresses the release of inflammatory cytokines, therefore a decrease in cortisol release...
allows for an increase in the release of inflammatory cytokines, which have also been linked to fatigue\textsuperscript{54,55}.

\subsection*{1.2.1.3 Anemia and Fatigue}

The World Health Organization defines anemia in women as a hemoglobin (Hb) level below 12.0 g/dL. In individuals without cancer, anemia can be caused by dietary deficiency in iron, vitamin B12 or the B-vitamin folate, renal insufficiency, or chronic inflammation. One of the major side effects of anemia is fatigue\textsuperscript{56}. Anemia is a common side effect of breast cancer treatment, in particular chemotherapy. Chemotherapy, which is commonly myelosuppressive, impairs erythropoiesis (red blood cell production). This effect may also be cumulative over repeated cycles of chemotherapy treatment\textsuperscript{57}. Findings from a large cohort study of 2890 breast cancer patients found that 62\% became anemic at some point during treatment, and incidence increased with the number of chemotherapy cycles\textsuperscript{56}. Anemia can be treated by red blood cell transfusion, or erythropoiesis stimulating agents (i.e., epoetinalfa and darbepoetin alfa), however treatment is often not initialized until hemoglobin levels fall below 9g/dL or there are other comorbid conditions present\textsuperscript{58}. Red blood cell transfusion carries the risk of transfusion reactions, as well as viral or bacterial infections\textsuperscript{59}. Treatment with erythropoiesis stimulating agents has been shown to increase the risk of venous thromboembolism and decrease survival in meta-analyses\textsuperscript{59}. Anemia often resolves after chemotherapy treatment is complete\textsuperscript{56}.

\subsection*{1.2.1.4 Psychological Factors and Fatigue}

The multi-factorial nature of fatigue involves not only physiological and biological mechanisms, but also psychological factors. Clinical depression and anxiety are common after a
diagnosis of and/or during treatment for breast cancer, and the prevalence is estimated at approximately 50% in the year following treatment. A feeling of fatigue or lethargy is a common symptom of depression. Several cross-sectional and longitudinal studies have demonstrated a correlation between psychological distress (such as depression, anxiety and fear of recurrence) and high levels of fatigue. As with anemia, when attempting to manage or treat cancer-related fatigue, it is important to rule out clinical depression as a cause of fatigue.

In addition to clinical diagnoses, individual differences in coping style may have an effect on the development and persistence of fatigue in breast cancer survivors. Several cross-sectional studies have determined that those with persistent cancer-related fatigue have a higher use of catastrophizing and cognitive avoidance coping styles. One randomized controlled trial has shown the benefit of a cognitive behavioural therapy intervention focused on psychological factors, such as coping style and fear of recurrence, at improving fatigue in individuals with persistent cancer-related fatigue after treatment.

1.2.1.5 Deconditioning and Fatigue

Deconditioning is a decrease in functional capacity due to lack of activity. The cause of deconditioning in cancer survivors is multi-factorial. Physical activity levels have been reported to decrease from pre-diagnosis levels during treatment for breast cancer and to remain below pre-diagnosis levels following treatment, despite evidence that shows those who are physically active have increased quality of life and may decrease all-cause mortality. These lower levels of physical activity, combined with the potential toxic effects of chemotherapy and radiation therapy (including cardiac toxicity, pulmonary fibrosis, and muscle atrophy) on the
cardiorespiratory and muscular systems result in decreased functional capacity, making everyday tasks more difficult\textsuperscript{71}. As ordinary tasks such as housework, and climbing stairs become more fatiguing, individuals are less likely to become active or participate in purposeful exercise, and the cycle of fatigue is perpetuated\textsuperscript{72} (See Figure 1). Deconditioning has been suggested as a contributing factor to fatigue in other clinical populations, such as chronic fatigue syndrome, stroke\textsuperscript{73}, multiple sclerosis\textsuperscript{74} and chronic obstructive pulmonary disease\textsuperscript{75}. Overall deconditioning leading to fatigue can be a product of deconditioning of the cardiorespiratory system, the skeletal muscle system, or a combination of both.

**Figure 1: Cycle of Deconditioning and Fatigue**

1.2.2 Assessment of Fatigue and Deconditioning

1.2.2.1 Assessment of Fatigue

A Visual Analog Scale\textsuperscript{76} of 0-10 is often used as a quick and simple tool to quantify the level of fatigue in a range of populations. A variety of questionnaires and tools are commonly
used to capture levels of fatigue in the cancer population, such as the Functional Assessment of Cancer Therapy – Fatigue scale (FACT-F)\textsuperscript{76,77}, the Brief Fatigue Inventory (BFI)\textsuperscript{78}, the Piper Fatigue Scale (PFS)\textsuperscript{79,80} and the Multidimensional Assessment of Fatigue (MAF)\textsuperscript{81}. The World Health Organization has also developed a list of criteria as part of the International Statistical Classification of Disease and Related Health Problems, Tenth Revision, Clinical Modification International Classification of Diseases (ICD-10-CM) for the diagnosis of cancer-related fatigue. The ICD-10-CM is a list meant for use as a diagnostic tool, and does not provide a value for severity of fatigue\textsuperscript{82} (See Appendix A).

1.2.2.2 Assessment of Cardiorespiratory Deconditioning

The gold standard for assessment of cardiorespiratory fitness or aerobic capacity is to measure maximal oxygen uptake (VO\textsubscript{2} max). This is defined as the body’s maximal ability to uptake and utilize oxygen to produce energy for work. VO\textsubscript{2} max is the product of maximal cardiac output (L/min) and arterio-venous oxygen difference (mL of O\textsubscript{2} per L of blood). VO\textsubscript{2} max is assessed using a maximal graded exercise test, most commonly using a motorized treadmill or cycle ergometer. Open-circuit spirometry is used, during which participants breathe through a mouthpiece or facemask while pulmonary ventilation and expired levels of oxygen and carbon dioxide are measured using a metabolic cart. To accurately measure VO\textsubscript{2} max, participants must push themselves to their absolute maximum, which requires significant effort and motivation. This may be difficult in a non-athletic population, therefore maximum oxygen consumption values are often reported as VO\textsubscript{2} peak in clinical studies\textsuperscript{83}. 

8
Lactate threshold can also be used as an assessment of cardiorespiratory fitness or functional capacity. Adenosine triphosphate (ATP) is the main source of energy for muscle contraction, but limited quantities are stored in muscle cells. Therefore, ATP must be produced in the cell to supply energy to the muscle during exercise. Lactate is produced in the cytosol of muscle cells during exercise as an end product of the glycolytic pathway. Glycolysis involves the breakdown of a glucose or glycogen molecule to form pyruvate or lactic acid, while producing a net 2 ATP. Glycolysis is anaerobic, meaning it does not require oxygen. Many cells such as liver and neurons metabolize lactate, through the conversion by lactate dehydrogenase to pyruvate which can then enter Krebs cycle for oxidative phosphorylation. Oxidative phosphorylation is aerobic (requires oxygen) and is the most effective method of ATP production. At workloads below an individual’s lactate threshold, lactate is produced and metabolized at equal rates, and the blood lactate concentration is relatively stable. As exercise intensity increases, blood lactate concentration increases due to an increase in lactate production by muscles and greater reliance on anaerobic energy production. As well, lactate removal by liver and other tissues may decrease with exercise intensity as blood flow is directed away from non-working muscles, kidney, liver gastrointestinal tract.

A blood lactate curve is used to show levels of blood lactate during a graded incremental exercise test (Figure 2). The point at which lactate values begin to rise exponentially is termed the lactate threshold. Different criteria have been utilized for defining this point. A recent review identified 25 different lactate threshold definitions utilized in the literature that can be generally categorized as 1) fixed blood lactate value (i.e., 4mmol/L), 2) first rise in blood lactate above baseline levels or 3) the point at which a rapid/distinct change in the slope of the blood lactate
curve was identified, also known as the anaerobic threshold\textsuperscript{87}. For the purposes of this study, the third definition will be used. The exercise intensity at lactate or anaerobic threshold is regarded as the upper border of exercise that can be sustained for any extended period of time, as the energy that can be generated using the anaerobic system is limited\textsuperscript{83}. Exercise above this level is associated with excretion of stress hormones and quickly leads to fatigue\textsuperscript{87-89}.

**Figure 2: Blood Lactate Curve During a Graded Incremental Exercise Test**

Previous studies in cancer survivors have failed to show a strong correlation between fatigue and physical performance using a measure of VO\textsubscript{2} max. Dimeo et al\textsuperscript{90} measured VO\textsubscript{2} max using a graded incremental exercise test as well as mental state, using the Profile of Mood States and the Symptom Check List-90-R, in cancer patients with solid tumors or hematological malignancies. Somatization, anxiety and depression were strongly correlated to fatigue, while VO\textsubscript{2} max was only weakly correlated\textsuperscript{90}. It has been shown in healthy populations that a leftward shift of the blood lactate curve can be interpreted as a decrease in functional capacity independent of a decrease in VO\textsubscript{2} max\textsuperscript{84}. The concept of lactate threshold has been studied as a
contributor to fatigue during exercise in healthy populations\textsuperscript{91}, and other clinical populations such as chronic fatigue syndrome\textsuperscript{92,93} but not in cancer survivors.

1.2.2.3 Assessment of Muscle Deconditioning

Muscle fatigue has been defined as “a loss in the capacity for developing force and/or velocity of a muscle, resulting from muscle activity under load, which is reversible, by rest”\textsuperscript{94}. The causes of muscular fatigue in the healthy population are multi-factorial but can generally be classified as centrally or peripherally mediated\textsuperscript{95}. Central fatigue is the result of a loss of voluntary muscle activation due to mechanisms proximal to the neuromuscular junction, such as reduced neural drive, reduced motor unit recruitment or reduced motor unit firing rates, while peripheral causes of fatigue include failure of excitation-contraction coupling or metabolic changes within the muscle tissue itself\textsuperscript{96,97}.

The twitch interpolation technique has been used in healthy and clinical populations, such as chronic fatigue syndrome\textsuperscript{98} and Guillain–Barre´ syndrome\textsuperscript{99}, to determine whether central or peripheral mechanisms are limiting performance. When imposing supra-maximal electrical stimulation during a maximal voluntary contraction (MVC), an increase in force seen with the addition of the electrical pulse indicates the voluntary activation of the muscle is not complete, suggesting that drive from the central nervous system is insufficient\textsuperscript{95}. Likewise, if electrical stimulation fails to increase force generated, it is assumed that voluntary activation is complete, and therefore the mechanism underlying fatigue is peripheral, or within the muscle itself. There has been some debate in the literature as to whether or not the average individual is fully able to achieve 100% voluntary activation\textsuperscript{100}. This may be muscle and/or task dependent, however the
technique is viewed as useful for comparing voluntary activation between two groups. By including a control twitch in resting muscle before and after a bout of exercise, we can measure level of peripheral fatigue. A decrease in the force produced by a supramaximal electrical stimulation applied to a muscle at rest indicates fatigue within the muscle itself.

Yavuzsen et al compared cancer patients entering palliative care to healthy age, gender and body mass index-matched controls on central and peripheral causes of muscular fatigue using the twitch interpolation technique. Findings indicated greater central fatigue and impaired neuromuscular junction conduction in the cancer patient group compared to the control group. The ratio of twitch force to voluntary force was significantly greater in the cancer patient group indicating a failure in the ability to voluntarily recruit skeletal muscle to maintain the contraction. In addition, the cancer group had only a 15% decline in twitch force after the sustained contraction, while the control group experienced a 37% decline, indicating the cause of fatigue in the control group was due to peripheral factors. However, it is unknown whether the differences found are related to cancer-related fatigue specifically or if they are side effects of cancer or therapy that would be found in fatigued and non-fatigued survivors. As well, patients entering palliative care may be different from cancer survivors who are attempting to overcome fatigue and return to their previous lifestyle.

1.2.3 Interventions to Improve Fatigue

Previous studies have demonstrated a decrease in cancer-related fatigue following a period of aerobic and/or resistance training both during and after treatment, however the exact mechanism behind these changes remains elusive. Jacobsen et al conducted a
systematic review and meta-analysis of non-pharmacological interventions (physical activity and psychological based) aimed at reducing fatigue in the adults who had been diagnosed with cancer. While 41 papers were reviewed, only 30 were included in the meta-analysis (18 psychological and 12 activity-based interventions). Across all interventions, there was a small effect size of 0.09 favoring the intervention, but when studies were analyzed as psychological versus activity based, the only statistically significant effect was for psychological interventions. Recently, Speck et al\textsuperscript{109} conducted a meta-analysis of all randomized-controlled trials of exercise in the cancer population. The meta-analysis divided studies based on timing of the exercise intervention, either during adjuvant treatment or following completion of adjuvant treatment. Although 80\% of studies found a significant positive effect of exercise on fatigue, pooled data analysis determined that the overall effect was not statistically significant for exercise interventions undertaken during adjuvant treatment. In studies of individuals who had completed cancer treatment, the pooled-data analysis did indicate a significant positive effect for exercise in reducing fatigue. Despite the positive effect demonstrated, both reviews identified key methodological flaws in studies of physical activity or exercise related to assessing the effect on reducing cancer-related fatigue. Firstly, the tools used to assess fatigue vary widely across the studies, making it difficult to pool data. Secondly, although these interventions report fatigue as an outcome, few randomized controlled trials have specifically recruited patients who are suffering from persistent cancer-related fatigue\textsuperscript{108,109}. 

\textsuperscript{108}
2 Chapter: Research Study

2.1 Introduction

Breast cancer is one of the most commonly diagnosed cancers in women in Canada. As treatment for breast cancer improves, and the number of breast cancer survivors increases both in Canada and around the world, the importance of addressing long-term and late effects of breast cancer and its treatment become of even greater importance to the health and quality of life of these individuals. During adjuvant treatment for breast cancer, fatigue is one of the most commonly reported side effects. Fatigue often diminishes following the completion of adjuvant treatment, but in a subgroup of breast cancer survivors, fatigue can persist for months or years after treatment is complete. This type of fatigue, termed cancer-related fatigue due to its relation to cancer and/or its treatment, is defined as “a distressing persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.” The etiology of cancer-related fatigue is unknown. It is most likely multifactorial in nature, and the result of a combination of both physiological and psychological factors.

One factor thought to contribute to cancer-related fatigue is physical deconditioning. Deconditioning is defined as a loss of functional capacity due to lack of activity. Physical activity levels tend to decline during treatment for breast cancer, and despite recommendations, remain lower after treatment is complete. These sedentary behaviors, combined with the toxic effects of adjuvant treatment on many of the bodies systems, lead to a decrease in functional capacity, making not only exercise or structured physical activity more difficult, but also simply completing everyday tasks. Overall functional capacity is a product of both cardiorespiratory fitness as well as muscular strength. The gold standard of for the assessment of cardiorespiratory
capacity is VO\(_2\) max, using measurement of expired gas exchange during a maximal graded incremental exercise test. A second component of cardiorespiratory fitness is lactate threshold, which is also determined during a graded incremental exercise test. The most common assessment of muscular strength is through a maximum voluntary contraction, with force measured by dynamometry. The twitch interpolation technique, using supramaximal electrical stimulation, can be used to determine the force generating capability of a muscle, and whether central or peripheral factors are limiting muscle performance.

### 2.2 Purpose

The purpose of this present study was to compare measures of cardiorespiratory and muscular deconditioning between a group of breast cancer survivors who are experiencing persistent cancer-related fatigue after treatment and a control group who had also undergone treatment for breast cancer that was not experiencing cancer-related fatigue. With our findings we hoped to gain new knowledge about the causes and contributors to cancer-related fatigue in order to provide a basis for the future development of an exercise intervention specifically designed to decrease fatigue in this population.

### 2.3 Objectives and Hypotheses

1. To compare power output at lactate threshold as a percentage of maximal power output in breast cancer survivors with fatigue to a control group of breast cancer survivors who do not complain of fatigue.

   *We hypothesize that the fatigued group will have a significantly lower power output at lactate threshold as a percentage of maximal power output than non-fatigued survivors.*
2. To compare differences in cardiorespiratory fitness, measured as VO$_2$ peak on a cycle ergometer test between fatigued and non-fatigued survivors.

   We hypothesize that the cancer-related fatigue group will have a lower VO$_2$ peak than the control group.

3. To compare voluntary activation before and after muscle fatiguing exercise as an indicator of central fatigue in fatigued and non-fatigued breast cancer survivors through the use of an objective neuromuscular test and the use of the twitch interpolation technique.

   We hypothesize that breast cancer survivors experiencing cancer-related fatigue will have a lower percentage of voluntary activation both before and after muscle-fatiguing exercise than the control group, and a greater decline in voluntary activation indicating greater central fatigue.

2.4 Methods

2.4.1 Participants

2.4.1.1 Population

   Women previously diagnosed with stage I-IIIa breast cancer, but who had completed adjuvant treatment of radiation, with or without chemotherapy were recruited into one of two groups. The fatigue group (FG) included women who complained of persistent fatigue following
completion of breast cancer treatment. The second group, the control group (CG), included women who had also completed breast cancer treatment, but did not experience fatigue. Inclusion and exclusion criteria are listed in Figure 3. Females were chosen as less than 1% of breast cancers in Canada occur in men\textsuperscript{2}. Post-menopausal status and stage I-IIIa diagnosis was chosen in order to obtain a study sample with a more homogeneous breast cancer prognosis and treatment protocol. Treatment by radiation with or without chemotherapy was an inclusion criterion as the symptom of fatigue is one of the most common acute side effects of radiation therapy\textsuperscript{30}. Participants were required to be able to read and understand English to ensure completion of questionnaires and to understand instructions during exercise and neuromuscular testing. Interested participants completed eligibility screening over the phone, and were provided with verbal information about the first study visit. The phone screen had a series of standard questions to assess eligibility (see Appendix C). Participants were not eligible if they self-reported a diagnosis of clinical depression in the telephone screening questionnaire, however mild depression is commonly associated with fatigue in the cancer population\textsuperscript{111} and individuals reporting mild depression that was stable and did not impact daily function were eligible for participation.
Inclusion Criteria

**All Subjects:**
- Female, post-menopausal
- Diagnosis of stage I-IIIa breast cancer
- Have undergone radiation therapy with or without chemotherapy; Treatment completed within the last 3 months to 5 years
- Obtained consent from oncologist or family doctor for participation in exercise testing
- Ability to read and understand English

**Fatigue Group:**
- Potential participants were screened by phone for fatigue using criteria for cancer-related fatigue adopted from the ICD-10-CM\textsuperscript{82} (See Appendix A)

Exclusion Criteria

**All subjects:**
- Diagnosis of and/or receiving treatment for other co-morbid conditions that may contribute to fatigue including anemia (using the World Health Organization’s definition of hemoglobin <12.0g/dL)\textsuperscript{112}, clinical depression or uncontrolled thyroid disorder
- Diagnosis of and/or receiving treatment for co-morbid conditions that may prevent completion of exercise testing including cardiovascular or pulmonary disease, musculoskeletal injuries, peripheral neuropathy or previous stroke
- Currently following a low-carbohydrate diet due to possible interference with measurement of accurate blood lactate levels
- Cancer recurrence or metastases

2.4.1.2 Recruitment

Participants were recruited through oncologist referral, word of mouth, postings at the British Columbia Cancer Agency – Vancouver site, Inspire Health (Vancouver, BC), Complimentary Medicine Education and Outcomes Program (Vancouver, BC), and Burnaby
Hospital, and through breast cancer survivor groups in the Greater Vancouver area. Separate advertising posters were used to target fatigued and non-fatigued survivors (See Appendix B).

2.4.1.3 Sample Size

The number of participants required was based on an estimate using a sample size calculator for an independent t-test. Using an alpha level of 5%, statistical power of 80% and assuming a between group difference in power output at lactate threshold of 20 watts (corresponding to one stage on the cycle ergometer test) with a standard deviation of 15.0, a sample size of n=9 per group is needed. For this observational study that involved only two testing visits, no participant drop out was expected.

2.4.2 Procedures

An overview of the components of the study is presented in Figure 4.
2.4.2.1 Demographic Data

Participants’ date of birth, date of breast cancer diagnosis, type of treatment received (chemotherapy, radiation therapy, and/or surgery), date of treatment completion and current medications were collected by participant self-report during eligibility screening by telephone (See Appendix C).

2.4.2.2 Visit One

2.4.2.2.1 Screen for Anemia

During the first testing visit, a physician at the Allan McGavin Sports Medicine Clinic (Vancouver, BC) drew approximately 1.0mL of venous blood to screen for anemia. Blood
samples were analyzed for hemoglobin levels using the I-Stat system (Abbott Laboratories, Abbott Park, IL, USA). The I-Stat is a handheld blood analysis system that has been shown to have minimal error when compared to traditional laboratory testing, while delivering results in only a few minutes\textsuperscript{113}. Participants were excluded if they met the World Health Organization’s definition of anemia as a hemoglobin level of less than 12.0\textit{dg}/L\textsuperscript{112}.

2.4.2.2.2 Questionnaires

Participants were asked to complete several questionnaires during their first study visit, or at home, returning the questionnaires during the second visit. The \textit{Functional Assessment of Cancer Therapy – Breast} (FACT-B) questionnaire was used to assess quality of life (see Appendix D). This 37-item questionnaire has been widely used and validated in breast cancer survivors, and gives a score for quality of life ranging from 0-144, with a higher score indicating a better quality of life\textsuperscript{114}. The \textit{Functional Assessment of Cancer Therapy – Fatigue} (FACT-F) questionnaire was used to assess level of fatigue (See Appendix E). This 13-item questionnaire is an addition to the FACT-F, and has been used to assess levels of fatigue in breast cancer survivors. When combined with subscales of the FACT-B, the FACT-F gives a fatigue trial outcomes index score ranging from 0-108 with a higher score indicating less fatigue\textsuperscript{77}. A clinically significant difference on the FACT-F subscale has been found to be five points\textsuperscript{115}. The \textit{Multidimensional Assessment of Fatigue} (MAF) was used to quantify the impact fatigue has on activities of daily living\textsuperscript{81} (See Appendix F). This 16-item questionnaire has been shown to be a reliable and valid test in breast cancer survivors and also to be sensitive to change in fatigue levels with adjuvant cancer treatment\textsuperscript{81}. The \textit{Beck Depression Inventory} (BDI) was used to assess level of depression (See Appendix G). The BDI has been used widely in a variety of
clinical populations, including breast cancer, and has been deemed to be reliable and valid\textsuperscript{116}.

Participants were administered a modified version of the \textit{Minnesota Leisure Time Physical Activity Questionnaire}\textsuperscript{117} adapted from McTiernan\textsuperscript{118} to quantify average metabolic equivalents (MET) hours per week as well as minutes of moderate-vigorous physical activity per week (See Appendix H). Finally, participants were asked about their current medication use, in particular anti-hormonal medications (i.e., tamoxifen, letrozole).

\subsection*{2.4.2.2.3 Resting Measurements}

Participants’ height (m) and weight (kg) were measured twice and an average of the two measures was recorded. Participants were then asked to sit quietly for five minutes to measure resting heart rate using a Polar FS3c heart rate monitor (Polar Electro, Lake Success, NY, USA), and resting blood pressure using an aneroid sphygmomanometer. Resting blood lactate was measured via a prick of the distal tip of the third finger and analyzed by the Lactate Pro analyzer (Arkay, KDK Corporation, Kyoto, Japan) which has been shown to have good reliability and validity in comparison to other handheld lactate analysis systems\textsuperscript{119}. The finger was cleaned using an alcohol wipe; pricked using the Arkay Multi-Lancet II (KDK Corporation, Kyoto, Japan) and then the first drop was swabbed away with a clean gauze pad to remove any remaining alcohol on the skin before the drop of blood was collected for analysis.

\subsection*{2.4.2.2.4 Cycle Ergometer Test}

A maximal incremental exercise test was performed using a cycle ergometer with a continuous protocol adapted from one that had been previously used in the breast cancer
population by Klika et al\textsuperscript{120}. Participants were set up on the bike, and were asked to perform a warm-up at 0 watts, with a cadence of 60-70 rpm for 5 minutes. After the warm-up, heart rate was allowed to return to resting level before the test began. During the warm-up participants were asked how hard they felt they were working, as well as their previous cycling experience to determine the appropriate rate of increase in watts (W) during the test. The majority of participants (n=11) followed the planned protocol of an increase of 20 W per stage, however several were deemed to be less fit, and better suited to an increase of 15 W (n=4), or more fit and better suited to an increase of 25 W per stage (n=8), to reduce test time as recommended by the American College of Sports Medicine\textsuperscript{121}.

The cycle test consisted of two parts; the goal of part one was to reach lactate threshold, and part two was to reach VO\textsubscript{2} max. During part one of the test, each stage was three minutes long to allow lactate accumulation in order to obtain an accurate measure of blood lactate. Heart rate was recorded every 30s, and blood lactate and Rating of Perceived Exertion (RPE) (See Appendix I) were recorded during the last minute of each stage. For the purpose of the test, participants were determined to have reached lactate threshold after an increase in blood lactate greater than 1.0 mmol/L followed by a subsequent increase of greater than 1.0 mmol/L. After this criterion had been met, part two of the test began. During part two, stages were one minute in duration in order to decrease the amount of time spent at the most difficult stages of the test and obtain a VO\textsubscript{2} peak as close to maximum as possible. Heart rate was recorded every 30s, RPE was recorded during the final 30s of each stage, and blood lactate was recorded during the last 30s of every other stage. The test was terminated at volitional exhaustion or when participants met two out of three criteria for VO\textsubscript{2} peak: 1) a plateau in VO\textsubscript{2} with increased workload; 2) a
respiratory exchange ratio (RER) greater than 1.15; 3) a maximal heart rate within 5 beats per minute of age-predicted maximal heart rate \[206.9-(0.67)\times \text{age}\]^{122}.

\[\text{VO}_2\] peak was recorded as the average \[\text{VO}_2\] during the last 30s of the test. Lactate threshold was determined in two steps as described by Klika et al^{120}. Firstly, blood lactate versus power output was plotted using Excel software (Microsoft Corporation, Redmond, WA). Two investigators who were blinded to group allocation independently cleaned the data by removing erroneous/oulier data points and identified lactate threshold by visual inspection. Secondly, for each individual participant’s data, blood lactate and power output were plotted and the linear regression line and corresponding standard error of estimate (SEE) were calculated for the first two data points (stage 1 and stage 2). Step-by-step each individual data point was entered (i.e., add in data point from stage 3, followed by stage 4, etc.), and linear regression and SEE were calculated. For workloads below the lactate threshold, the trend should remain linear and the SEEs stay stable or decreases slightly. The point at which the slope of the line changes and causes an increase in SEE indicates the stage, and therefore power output at which lactate threshold was reached.

2.4.2.3 Visit Two

During the second visit, central and peripheral fatigue were assessed using the twitch interpolation technique on the right quadriceps muscle. Each participant sat on an adjustable chair in an upright position with her back against a rigid backrest in front of a Biodex dynamometer (Shirley, NY, USA). The leg was placed in approximately 85° of hip flexion and 90° of knee flexion with the axis of the dynamometer aligned with the lateral epicondyle of the
femur, and the force transducer pad positioned against the anterior tibia. The subject’s upper body and pelvis were secured with padded straps and arms folded across the chest. Electrical stimulation was applied through lead stimulating electrodes (10 cm x 5 cm) covered with gauze and soaked in saline solution. The electrodes were positioned over the quadriceps muscle, and were placed over the motor points of the proximal rectus femoris and the distal portion of the vastus medialis muscles. Stimulation was produced by a constant current stimulator (Digitimer DS7AH, Welwyn Garden City, Hertfordshire, UK) externally triggered to produce a doublet with frequency of 100 Hz. Each pulse in the doublet was a rectangular pulse with 50µs duration.

The intensity of electrical stimulation to be used was determined for each individual participant before the experiment began. A series of doublets with progressively greater current were applied at rest until a maximal twitch was obtained. The stimulus intensity to be used throughout the experiment was set at 10% higher to ensure supramaximal stimulation. Force was digitized at 500 Hz and recorded using Spike2 data acquisition and analysis system (1401 Plus, Cambridge Electronic Design, Ltd., Cambridge, UK). Visual feedback was given on a screen placed in front of the participant.

After a familiarization with the protocol and two submaximal learning trials, participants were asked to perform an isometric maximum voluntary contraction (MVC) of the quadriceps muscle. Next, muscle force generating capability was assessed using the twitch interpolation technique. A doublet was applied during a second maximal voluntary contraction (interpolated twitch [IT_{pre}]) and in resting muscle (control twitch [CT_{pre}]). Voluntary activation (VA) was calculated using the equation described by Gandevia\(^95\)\[VA = 100(1-IT/CT)\]. Participants were then asked to perform a muscle fatiguing protocol, which consisted of a sustained isometric
quadriceps contraction at 30% of MVC until volitional exhaustion. The target force level was displayed on the screen and verbal encouragement was provided to maintain the contraction as long as possible. Endurance time (ET) was recorded from the initiation of the submaximal contraction until voluntary exhaustion or failure to maintain the force at the target level for more than 5 seconds. Immediately following the termination of the sustained contraction, MVC$_{\text{Post}}$, IT$_{\text{Post}}$ and CT$_{\text{Post}}$ were measured and recorded and VA$_{\text{Post}}$ was calculated. Percent change before and after the muscle fatiguing exercise was determined for each variable (X$_{\text{change}}$) using the equation \[\frac{(X_{\text{post}} - X_{\text{pre}})}{X_{\text{pre}}} \times 100\%\].

2.4.3 Statistical Analysis

Data were analyzed using statistical software package SPSS (IBM, Chicago, IL), and the accepted level of significance was set at \(p<0.05\). An independent samples t-test was performed to assess differences between groups on participant characteristics including age, height, weight, BMI, time since treatment and physical activity levels (MET hours per week and minutes of moderate-vigorous exercise per week), as well as scores from the FACT-B, FACT-F, MAF and BDI questionnaires. Fisher’s exact test was performed and used to determine between group differences in treatment type (chemotherapy + radiation or radiation alone) and current use of anti-hormonal medication.

An independent samples t-test was performed to assess differences between groups on power output at lactate threshold, lactate threshold as a percentage of peak power output, absolute and relative VO$_2$ peak and peak power output. Power output at lactate threshold, lactate threshold as a percentage of peak power output, VO$_2$ peak and peak power output were plotted.
against potential covariates (age and body weight) to determine whether a relationship existed. If a relationship was evident, covariates were entered into an ANCOVA.

An independent t-test was performed to determine differences in $CT_{\text{pre}}$, $CT_{\text{post}}$, $CT_{\text{change}}$, $VA_{\text{pre}}$, $VA_{\text{post}}$, $VA_{\text{change}}$, $MVC_{\text{pre}}$, $MVC_{\text{post}}$, $MVC_{\text{change}}$, and ET between FG and CG. Paired t-tests were performed to determine within-group differences in CT, VA and MVC before and after muscle fatiguing exercise for the FG and CG.

2.5 Results

2.5.1 Participants

The flow of participants recruited and entered into the study is reported in Figure 5. Contact was made regarding study participation with 45 individuals. Thirty-nine women were screened for eligibility. Of those women, thirteen were ineligible and three declined participation (all due to lack of time). Twenty-three participants were enrolled in the study, fourteen in the fatigue group and nine in the control group. No participants were excluded from study participation following screening for anemia during visit 1. Three participants did not complete day two testing. One participant from the fatigue group and one from the control group did not attend the second visit, stating they did not have time to participate. A second participant from the control group came for the testing visit but did not complete the post-exercise interpolated twitch portion of the visit due to discomfort.
Demographic data are presented as mean and standard deviation for the FG and CG in Table 1. No statistically significant differences were found between groups in age, height, weight, BMI, or time since treatment. Participants were on average 52-58 years of age (FG 52.4±8.4 vs. CG 58.1±10.6 years, p=0.16) with normal to overweight BMI (FG 24.5±4.6 vs. CG 27.1±4.1 kg/m², p=0.17) and had completed treatment just under two years prior (FG 23.1±18.2 vs. CG 21.4±20.5 months, p=0.84). There were no significant differences between groups on current use of anti-hormonal medication (FG 57.1% vs. CG 33.3%, p=0.66) or treatment by
chemotherapy plus radiation vs. radiation alone (chemotherapy plus radiation: FG 85.7% vs. CG 66.7%, p=0.34).

The groups differed significantly in all self-report measures. The FG self-reported less physical activity (FG 22.5±17.6 MET hours per week vs. CG 35.1±5.5 MET hours per week, p<0.05) and fewer minutes of moderate to vigorous exercise (FG 133.6±123.4 minutes vs. CG 298.3±96.5 minutes, p<0.01) than the CG. Groups also differed in psychosocial measures, with the FG reporting a lower quality of life (FG 87.3±18.2 vs. CG 114±17.0, p<0.01), and scores indicating higher levels of depression (FG 12.5±8.1 vs. CG 7.4±4.5, p<0.001) and fatigue (FACT-F: FG 58.5±13.7 vs. CG 92.9±9.3, p<0.001; MAF: FG 32.5±9.0 vs. CG 10.3±8.0, p<0.001). Scores between both measures of fatigue (FACT-F and MAF) were highly correlated (r=0.80). Across both groups, scores on the FACT-F had a moderate correlation with depression (r=-0.69) and high correlation with quality of life (r=0.95), and scores on the MAF were also correlated with depression (r=0.53 and quality of life (r=-0.75).
## Table 1: Participant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Fatigue Group</th>
<th>Control Group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=14</td>
<td>N=9</td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>52.4 (8.4)</td>
<td>58.1 (10.6)</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Height (m)</strong></td>
<td>1.67 (0.1)</td>
<td>1.67 (0.1)</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>68.5 (15.1)</td>
<td>76.1 (14.6)</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>24.5 (4.6)</td>
<td>27.1 (4.1)</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Time Since Treatment Completed (months)</strong></td>
<td>23.1 (18.2)</td>
<td>21.4 (20.5)</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Physical Activity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MET hours per week</td>
<td>22.5 (17.6)</td>
<td>35.1 (5.5)</td>
<td>0.05*</td>
</tr>
<tr>
<td>Minutes of moderate-vigorous exercise/week</td>
<td>133.6 (123.4)</td>
<td>298.3 (96.5)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td><strong>FACT-B</strong></td>
<td>87.3 (18.2)</td>
<td>114.0 (11.7)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td><strong>FACT-F</strong></td>
<td>58.5 (13.7)</td>
<td>92.9 (9.3)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>MAF</strong></td>
<td>32.5 (9.0)</td>
<td>10.3 (8.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>BDI</strong></td>
<td>12.5 (8.1)</td>
<td>7.4 (4.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Anti-hormonal Medication Use</strong></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (57.1)</td>
<td>3 (33.3)</td>
<td>0.66</td>
</tr>
<tr>
<td>No</td>
<td>6 (42.9)</td>
<td>5 (55.6)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0)</td>
<td>1 (11.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Adjuvant Treatment Type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy plus Radiation</td>
<td>12 (85.7)</td>
<td>6 (66.7)</td>
<td>0.34</td>
</tr>
<tr>
<td>Radiation Alone</td>
<td>2 (14.3)</td>
<td>3 (33.3)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI = Body Mass Index, MET = Metabolic Equivalents, FACT-B = Functional Assessment of Cancer Therapy – Breast; FACT-F = Functional Assessment of Cancer Therapy – Fatigue; MAF = Multidimensional Assessment of Fatigue; BDI = Beck Depression Inventory

*p <0.05
2.5.2 Cardiorespiratory Data

No significant differences were found between groups in power output at lactate threshold (FG 60.7±17.0 vs. CG 73.3±22.2 W, p=0.14), lactate threshold as a percentage of peak power output (FG 46.8±8.6 vs. CG 55.0±14.7%, p=0.11) peak power output (FG132.12±38.2 vs. CG 140.6±5.9 W, p=0.66), absolute VO$_2$ peak (FG 1.51±0.39 vs. CG 1.74±0.38 L/min, p=0.19), or relative VO$_2$ peak (FG 22.4±4.9 vs. CG 23.6 ± 7.1 ml/kg/min, p=0.62) (Table 2). Six participants had one missing value for blood lactate. One value of LO was recorded and five values appeared outside of physiological limits. Two researchers independently reviewed the plots of power output versus blood lactate and determined the lactate threshold as the point at which the line broke from linearity as previously described by Klika et al$^{120}$. The two researchers had 100% agreement on determination of lactate threshold.

Although there were no significant differences between groups on participant characteristics (Table 1), a difference in age and body weight approached significance. A secondary analysis was performed to determine if these differences had any effect on the cardiorespiratory variables measured. Participant age and body weight were examined as potential covariates in the relationship between groups on measures of lactate threshold, absolute VO$_2$ peak, and peak power output. No relationship was found between body weight and power output at lactate threshold, lactate threshold as a percentage of peak power output, peak power output or absolute VO$_2$ peak. Because relative VO$_2$ peak is based on body weight, body weight is not independent from relative VO$_2$ peak and therefore cannot be entered into an ANCOVA as a covariate. Older age was associated with a lower power output at lactate threshold (r=-0.35) and lower absolute VO$_2$ peak (r=-0.31). When age was adjusted for in an ANCOVA between the FG
and CG, the difference between groups approached significance for power output at lactate threshold (FG 59.9 ± 5.2 vs. CG 74.6 ± 6.6 W, p=0.10) and absolute VO₂ peak (FG 1.48 ± 0.10 vs. CG 1.79 ± 0.13 L/min, p=0.08). Age was not associated with lactate threshold as a percentage of peak power output or relative VO₂ peak, therefore age could not be entered into the ANCOVA as covariates for these variables.
Table 2: Measures of Cardiorespiratory Fitness

<table>
<thead>
<tr>
<th></th>
<th>Fatigue Group N=14 Mean (SD)</th>
<th>Control Group N=9 Mean (SD)</th>
<th>Between-Group Difference Mean (SD)</th>
<th>p</th>
<th>Age-adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fatigue Group N=14 Mean (SD)</td>
</tr>
<tr>
<td>Power Output at Lactate Threshold (Watts)</td>
<td>60.7 (17.0)</td>
<td>73.3 (22.2)</td>
<td>12.6 (8.2)</td>
<td>0.14</td>
<td>59.9 (5.2)</td>
</tr>
<tr>
<td>Lactate Threshold (% of Peak Power Output)</td>
<td>46.8 (8.6)</td>
<td>55.0 (14.7)</td>
<td>8.2 (4.9)</td>
<td>0.11</td>
<td>-</td>
</tr>
<tr>
<td>Peak Power Output (Watts)</td>
<td>132.1 (38.2)</td>
<td>140.6 (5.9)</td>
<td>8.4 (19.0)</td>
<td>0.66</td>
<td>-</td>
</tr>
<tr>
<td>VO₂ Peak</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute (L/min)</td>
<td>1.51 (0.39)</td>
<td>1.74 (0.38)</td>
<td>0.23 (0.17)</td>
<td>0.19</td>
<td>1.48 (0.10)</td>
</tr>
<tr>
<td>Relative (mL/kg/min)</td>
<td>22.4 (4.9)</td>
<td>23.6 (7.1)</td>
<td>1.3 (2.5)</td>
<td>0.62</td>
<td>-</td>
</tr>
</tbody>
</table>

Legend: † Age entered as a covariate into an ANCOVA, age set at 54.61 years
2.5.3 Neuromuscular Testing Data

There were no significant differences between groups in CT or MVC before the muscle fatiguing exercise (Table 3). There were also no significant differences between pre- and post-exercise measures within either group in VA or CT. There was a significant decrease in MVC following exercise for the FG (MVC\textsubscript{pre} 106.9 ± 31.5 Nm vs. MVC\textsubscript{post} 78.2 ± 28.9 Nm, p<0.001) and the CG (MVC\textsubscript{pre} 94.5 ± 23.9 Nm vs. MVC\textsubscript{post} 74.4 ± 19.1 Nm, p<0.001). There was a significant difference both before (FG 86.2±14.8% vs. CG 75.7±6.9%, p=0.03) and after exercise in VA (FG 81.5 ±14.5% vs. CG 65.7 ± 14.7%, p=0.03). There were no significant between group differences in % change in VA, CT or MVC. ET was also similar between groups (FG 177.3 ± 71.5% vs. CG 198.6 ± 95.5%, p=0.57).

When boxplots were constructed, a number of outliers were identified in the data for VA (Figure 6), CT (Figure 7) and MVC (Figure 8). An outlier was defined as a data point greater than two standard deviations from the mean. The means and standard deviations of the data with outliers removed are listed in Table 4. No outliers were found for measures of ET, therefore data for this variable is only presented in Table 3. Significant differences between groups were found in VA\textsubscript{pre} (FG 93.3 ±5.0% vs. CG 77.1 ± 6.3%, p<0.001) and VA\textsubscript{post} (FG 89.6 ± 5.3% vs. CG 66.7 ± 15.9%, p=0.02) and CT\textsubscript{pre} (FG 45.8 ± 8.0 Nm vs. CG 037.9 ± 2.7 Nm, p=0.04), however no significant differences were found in VA\textsubscript{change} (FG -3.6 ± 9.6% vs. CG -13.4 ± 18.9%, p=0.22), a measure of central fatigue or CT\textsubscript{change} (FG -6.3±15.9 Nm vs. CG -1.2 ±7.7 Nm, p=0.49), a measure of peripheral fatigue (Figure 9-11).
<table>
<thead>
<tr>
<th></th>
<th>Fatigue Group</th>
<th>Within-Group difference</th>
<th>Control Group</th>
<th>Within-Group difference</th>
<th>Between-Group Difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=13 Mean (SD)</td>
<td></td>
<td>N=8 Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA &lt;sub&gt;pre&lt;/sub&gt; (%)</td>
<td>86.2 (14.8)</td>
<td>-4.7 (10.6)</td>
<td>75.7 (6.9)</td>
<td>-10.0 (13.6)</td>
<td>10.8 (4.7)</td>
<td>0.14</td>
</tr>
<tr>
<td>VA &lt;sub&gt;post&lt;/sub&gt; (%)</td>
<td>81.5 (14.5)</td>
<td></td>
<td>65.7 (14.7)</td>
<td></td>
<td>15.7 (6.8)</td>
<td>0.03*</td>
</tr>
<tr>
<td>VA change (%)</td>
<td>-4.7 (12.3)</td>
<td></td>
<td>-13.2 (17.3)</td>
<td></td>
<td>8.4 (6.6)</td>
<td>0.22</td>
</tr>
<tr>
<td>CT &lt;sub&gt;pre&lt;/sub&gt; (Nm)</td>
<td>44.8 (11.1)</td>
<td>-4.9 (12.1)</td>
<td>36.7 (4.1)</td>
<td>0.3 (3.6)</td>
<td>8.1 (4.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>CT &lt;sub&gt;post&lt;/sub&gt; (Nm)</td>
<td>39.9 (10.9)</td>
<td></td>
<td>37.0 (2.0)</td>
<td></td>
<td>2.9 (3.1)</td>
<td>0.37</td>
</tr>
<tr>
<td>CT change (%)</td>
<td>-8.9 (19.8)</td>
<td></td>
<td>1.6 (10.3)</td>
<td></td>
<td>10.5 (8.1)</td>
<td>0.21</td>
</tr>
<tr>
<td>MVC &lt;sub&gt;pre&lt;/sub&gt; (Nm)</td>
<td>106.9 (31.5)</td>
<td>-28.7 (16.0)</td>
<td>94.5 (23.9)</td>
<td>-20.1 (7.3)</td>
<td>12.5 (13.7)</td>
<td>0.37</td>
</tr>
<tr>
<td>MVC &lt;sub&gt;post&lt;/sub&gt; (Nm)</td>
<td>78.2 (28.9)</td>
<td></td>
<td>74.4 (19.1)</td>
<td></td>
<td>3.8 (12.2)</td>
<td>0.76</td>
</tr>
<tr>
<td>MVC change (%)</td>
<td>-27.3 (11.6)</td>
<td></td>
<td>-21.1 (5.5)</td>
<td></td>
<td>6.2 (4.7)</td>
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</tr>
<tr>
<td>ET (seconds)</td>
<td>177.3 (71.5)</td>
<td></td>
<td>198.6 (95.5)</td>
<td></td>
<td>21.3 (36.5)</td>
<td>0.57</td>
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</table>

**Abbreviations:** VA = Voluntary Activation; CT = Control Twitch force; MVC = Maximum Voluntary Contraction; ET = Endurance Time; Nm = newton metres

**Legend:** † Comparison of pre – post value by group; ‡ Comparison of FG to CG; * p<0.05.
Figure 6: Boxplot of Voluntary Activation (%) Before and After Sustained Contraction

Figure 7: Boxplot of Control Twitch (Nm) Before and After a Sustained Contraction
Figure 8: Boxplot of Maximum Voluntary Contraction (Nm) Before and After a Sustained Contraction
<table>
<thead>
<tr>
<th></th>
<th>Fatigue Group</th>
<th></th>
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<th>Control Group</th>
<th></th>
<th></th>
<th>Between-Group Difference</th>
<th>p</th>
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<tr>
<td></td>
<td>N=8 Mean (SD)</td>
<td>Within-Group difference Mean (SD)</td>
<td>p</td>
<td>N= 6 Mean (SD)</td>
<td>Within-Group difference Mean (SD)</td>
<td>p</td>
<td></td>
<td></td>
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<tr>
<td>VA pre (%)</td>
<td>93.3 (5.0)</td>
<td>-3.7 (9.0)</td>
<td>0.28</td>
<td>77.1 (6.3)</td>
<td>-10.4 (14.8)</td>
<td>0.15</td>
<td>16.2 (3.0)</td>
<td>&lt;0.001*</td>
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<td>VA post (%)</td>
<td>89.6 (5.3)</td>
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<td></td>
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<td></td>
<td>22.9 (6.7)</td>
<td>0.02*</td>
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<tr>
<td>VA change (%)</td>
<td>-3.6 (9.6)</td>
<td>-13.4 (18.9)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>9.9 (7.7)</td>
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<tr>
<td>CT pre (Nm)</td>
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<td>0.34</td>
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<td>CT post (Nm)</td>
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<td>CT change (%)</td>
<td>-6.3 (15.9)</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>MVC pre (Nm)</td>
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<td>&lt;0.01*</td>
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<td>MVC post (Nm)</td>
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<td>12.1 (11.6)</td>
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<tr>
<td>MVC change (%)</td>
<td>-23.6 (10.2)</td>
<td>-21.4 (5.9)</td>
<td></td>
<td>2.2 (4.7)</td>
<td></td>
<td></td>
<td></td>
<td>0.65</td>
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</tbody>
</table>

Abbreviations: VA = Voluntary Activation; CT = Control Twitch force; MVC = Maximum Voluntary Contraction; Nm = newton metres
Legend: † Comparison of pre – post value by group; ‡ Comparison of FG to CG; * p<0.05.
NOTE: No outliers were found for ET, therefore data are listed in Table 3 only
Figure 9: Boxplot of Voluntary Activation (%) Before and After Sustained Contraction with Outliers Removed

Figure 10: Boxplot of Control Twitch (Nm) Before and After a Sustained Contraction with Outliers Removed
Figure 11: Boxplot of Maximum Voluntary Contraction (Nm) Before and After Sustained Contraction with Outliers Removed
2.6 Discussion

2.6.1 Participant Characteristics

The purpose of the study was to compare measures of cardiorespiratory and muscular fitness between a group of breast cancer survivors experiencing persistent cancer-related fatigue after treatment and a group of breast cancer survivors who did not experience fatigue. Eligibility criteria were developed to identify two groups of women who were closely matched in age, body weight/BMI and time since treatment, as these factors could potentially affect measures of cardiorespiratory fitness. Although there were no statistically significant differences between groups on these parameters, there was a small difference that approached significance for age (FG 52.4±8.4 vs. CG 58.1±10.6 years, p=0.16) and body weight (FG 68.5±15.1 vs. CG 76.1±14.6 years, p=0.24).

While there were no statistical differences, there are apparent differences in both use of anti-hormonal medications and adjuvant or hormonal treatment received between groups. Fisher’s exact test was chosen as it is designed for use when sample sizes are small. A yes/no classification was used for use of anti-hormonal medication. However, types of anti-hormonal medications (i.e., aromatase inhibitors such as letrozole or anastrazole or selective estrogen receptor modulators such as tamoxifen) may differentially affect levels of fatigue. In order to look specifically at the effects of medication on fatigue, a much greater sample would be needed. Similarly, a wide variety of adjuvant therapy protocols exist for the treatment of breast cancer. A yes/no classification was used for adjuvant treatment type, but it is acknowledged that within the chemotherapy plus radiation or radiation-only groups there is some heterogeneity of treatments type and duration of adjuvant cancer treatment.
Self-reported physical activity was significantly different between groups. The FG fell just short of the current physical activity guidelines for cancer survivors released by the American College of Sports Medicine of 150 minutes a week of moderate to vigorous physical activity\textsuperscript{121}, while the control group greatly exceeded these recommendations. This finding may be a cause and/or effect of both deconditioning and cancer-related fatigue. Those who participate in regular moderate-vigorous exercise may be more fit, or have higher energy levels, and therefore not experience cancer-related fatigue because of the exercise they complete, and may therefore be less deconditioned. Alternatively, those who experience cancer-related fatigue may be less likely to exercise, thus perpetuating the cycle of fatigue, and may be even more deconditioned (as discussed in Chapter 1).

Self-report questionnaires confirm differences in the experience of fatigue between the groups. The FG reported lower scores on the FACT-F, indicating greater fatigue, and the differences were both statistically significant (p<0.001) and exceeded the clinically important difference described by Cella et al.\textsuperscript{115} of five points. Although a clinically important difference has not been determined for the MAF, the FG scored significantly higher than the CG, and scores on the FACT-F and MAF were highly correlated (r=0.80). The FG also reported significantly lower quality of life and higher levels of depression. Fatigue scores on the FACT-F were moderately correlated with scores on the BDI (r=-0.69), with lower scores on the FACT-F (indicating greater fatigue) correlated with higher levels of depression. FACT-F scores were also highly correlated with FACT-B scores (r=0.95), with lower scores on the FACT-F (indicating
greater fatigue) correlated with lower scores for quality of life. Fatigue scores using the MAF were also correlated with depression ($r=0.53$) and quality of life ($r=-0.75$).

### 2.6.2 Measures of Cardiorespiratory Fitness

No statistically significant differences were found between the FG and the CG in any measures of cardiorespiratory fitness including power output at lactate threshold, lactate threshold as a percentage of peak power output, peak power output or VO$_2$ peak. However, differences between groups in power output at lactate threshold, and lactate threshold as a percentage of peak power output both approach approached significance ($p=0.14$ and $p=0.11$ respectively), especially when age was entered as a covariate for difference in power output at lactate threshold ($p=0.10$). Because no previous studies had reported lactate threshold in this population, sample size calculations were based on an estimated mean and standard deviation. When the actual mean and standard deviation of the two groups was entered into a sample size calculator, it is determined that future studies would need to recruit 16 participants per group to have enough power to reach statistical significance, if a true difference exists.

Aside from statistical significance, it is important to consider whether the differences seen between the two groups are meaningful, and whether a difference in power output at lactate threshold of 13 watts would have an effect on completion of daily activities. This study was based on the hypothesis that individuals with persistent cancer-related fatigue would reach lactate threshold at a lower power output, and therefore were potentially reaching or exceeding lactate threshold while completing regular physical activity and perhaps even during normal activities of daily living, thus exacerbating feels of fatigue. It is difficult to compare wattage on a
cycle ergometer to the intensity that a given individual reaches while completing her own activities of daily living. A rough estimate can be given using ACSM’s equation for energy expenditure during cycle ergometry and the Compendium of Physical Activities. Using the age-adjusted results for power output at lactate threshold for the FG and CG and average body weight of all participants (72.3kg), the FG would reach lactate threshold during activities of approximately 4.6 METs, while the CG would reach lactate threshold at activities of approximately 5.2 METs. Most daily household activities are given a MET score of 2.0-4.0, i.e., sweeping floors (3.3 METS), multiple household tasks, moderate-vigorous effort (4.0 METs), washing dishes – standing (2.5 METS), food shopping (2.3 METS), ironing (2.3 METS) and cooking or food preparation (2.0 METS). Examples of physical activity in the range of 4.0-5.0 METs include walking briskly and carrying objects less than 25 pounds (4.5 METS), lawn mowing using a power mower (4.5 METS), and playing with children (5.0 METS). Based on these estimates, it may be possible that individuals in the FG exceed their lactate threshold during activities of daily living. However, it is important to note that actual energy expenditure depends on body mass, adiposity, age, sex, environmental conditions as well as personal effort, and therefore individual differences in the actual energy cost of an activity can be large. In order to determine whether or not individuals with cancer-related fatigue were actually working at or above lactate threshold during their daily activities, that intensity must be measured directly via portable indirect calorimetry.

VO₂ peak is reported in both absolute values (L/min) and relative to participants’ body weight (ml/kg/min). Both groups demonstrated very low levels of aerobic fitness, placing them between the 10th and 20th percentile for women age 50-59 according to ACSM’s normative data.
for cardiorespiratory fitness. When age was entered as a covariate into the ANCOVA calculation, a difference of 0.31 L/min that approached significance (p=0.08) was found between groups, suggesting that there may be a difference between the two groups, and that the relationship between cancer-related fatigue and VO\textsubscript{2} peak is also affected by age. Using an ANCOVA increases statistical power by removing the variance that is accounted for by the covariates. It is known that VO\textsubscript{2} peak tends to decrease with age. Because the control group was slightly older, they may have a lower VO\textsubscript{2} peak due to older age, which may eliminate any potential difference from the FG. Using an ANCOVA removes the variation in VO\textsubscript{2} peak due to age, allowing us to see differences that may exist between the groups due to fatigue.

Of note is the low VO\textsubscript{2} peak in both groups, despite the high self-reported physical activity, especially in the control group. There are several possible explanations for this finding. As discussed in Chapter 1, treatment for breast cancer has a long list of potential negative side effects, and decline in cardiorespiratory fitness and usual levels of physical activity before and after cancer treatment have been well documented. While randomized controlled trials of exercise in breast cancer survivors have shown an increase in VO\textsubscript{2} peak following both supervised and home-based exercise programs, the volume and/or intensity of exercise completed by women enrolled in structured exercise trials may not reflect the exercise undertaken by women in the community. The volume and intensity of exercise completed by participants in the current study may not have been enough to increase VO\textsubscript{2} peak to an appropriate age-predicted value. Secondly, while the self-report questionnaire that was used does take into account the intensity of exercise, it is subjective and participants may have overinflated the intensity of exercise they complete. Also, the retrospective nature of the self-report measure
of physical activity used in this study has the potential to be influenced by both recall bias and social desirability bias\textsuperscript{124}. All participants were aware that the purpose of the study was to investigate variables related to physical activity, and many may also have been aware of the benefits of exercise following breast cancer treatment, and therefore may have reported a higher volume and/or intensity of physical activity.

### 2.6.3 Neuromuscular Testing

The twitch interpolation technique was used to determine whether central or peripheral mechanisms are primarily responsible for muscle fatigue during a sustained contraction. As defined in Chapter 1, for the purposes of this study muscle fatigue was defined as “a loss in the capacity for developing force and/or velocity of a muscle, resulting from muscle activity under load, which is reversible, by rest”\textsuperscript{94}. Contrary to previous findings by Yavuzsen et al\textsuperscript{102}, muscle fatigue following a sustained contraction was not found to be more centrally mediated in the cancer-related fatigue group. Although results did not reach statistical significance, VA declined by more than 13% in the CG, but only 4.7% (3.6% with outliers excluded) in the FG after the sustained contraction. VA is used to assess muscle fatigue that is centrally mediated. This indicates that the muscle fatigue, or failure to maintain the force during the sustained contraction, was due to factors proximal to the neuromuscular junction, such as reduced neural drive, reduced motor unit recruitment or reduced motor unit firing rates. However, there has been some contention in the literature as to the appropriateness of the use of the twitch interpolation technique in assessment of voluntary activation and muscle fatigue. It is generally agreed upon that while twitch interpolation may not be a valid method for determining absolute maximal force-generating capability of the muscle, it can be a useful tool for determining voluntary
activation before and after an intervention (i.e., a muscle-fatiguing protocol) or between patient
groups to help determine underlying pathology.\textsuperscript{125,126}

Although we hypothesized that muscle fatigue following sustained contraction would be
more centrally mediated in the cancer-related fatigue group based on prior work by Yavuzsen et
al\textsuperscript{102} our results contradicted our hypothesis. However, this is not surprising based on the
differences in eligibility criteria between the two studies. In this study we compared breast
cancer survivors who had completed adjuvant therapy but who were experiencing persistent
cancer-related fatigue to a group of breast cancer survivors who had undergone similar treatment
regimens but did not experience persistent cancer-related fatigue. The patient group in the study
by Yavuzsen et al.\textsuperscript{102} was a group of patients with various cancer types, who were undergoing
treatment for palliative cancer and the control group was healthy individuals who had never
undergone cancer treatment. By using a control group who had also undergone treatment for
breast cancer, we attempted to control for any differences that were related to diagnosis and/or
treatment for breast cancer that were unrelated to cancer-related fatigue.

One major methodological issue with measurement of voluntary activation using twitch
interpolation is the importance of participant motivation in achieving a maximum voluntary
muscle contraction. Previous research has shown that healthy older adults (greater than age 65)
are able to achieve a mean VA of 94\% before a muscle fatiguing exercise, which is similar to the
VA in the FG of 93\% demonstrated in the present study.\textsuperscript{127} It is surprising that the CG did not
achieve a similar voluntary activation. Before the muscle fatiguing exercise, the CG had
significantly lower voluntary activation than the FG. While there may have been inherent
differences between groups in ability maximally activate quadriceps muscle, participant motivation may have had a large contribution to the observed differences. The FG was recruited to participate in a study to help determine potential underlying causes or contributors to cancer-related fatigue after breast cancer treatment. Because these participants were experiencing a symptom that has a significant impact on their lives and for which there is little available treatment or guidance for management, they may have been more motivated during testing. MVC at baseline was 18% greater in the FG, although the difference was not statistically significant (p=0.37). While the FG may have been inherently stronger than the CG, a higher MVC may also be the result of increased effort/motivation.

During testing visits all participants were given the same instructions, to contract their muscles and push against the dynamometer as hard and as fast as possible. Submaximal learning trials were given for familiarization, and visual feedback was available on the computer screen in front of the Biodex. Some participants were apprehensive about the interpolated twitch, and as a result may not have maximally contracted in anticipation of the twitch. In future studies, a second baseline measurement may be beneficial for further familiarization and to ensure actual maximal contraction during the interpolated twitch.

A control twitch in resting muscle was used as a measure of peripheral muscle fatigue. At baseline there was a small difference between the FG and CG that reached significance when outliers were excluded (p=0.04). The percent changed before and after the sustained contraction was not statistically significant between groups, indicating that the level of peripheral muscle fatigue was similar in both the FG and the CG.
The ET was also similar between groups, meaning it took a similar time to reach voluntary exhaustion or failure to maintain the target force for both groups. ET is also affected, to a certain degree, by motivation. While all participants were verbally encouraged to maintain the target force for as long as possible, different individuals may perceive a task as more or less difficult and therefore may reach volitional exhaustion before the muscles are actually fatigued. In future studies it may be helpful to record and look at differences between participants who reached volitional exhaustion and said they did not wish to continue and compare to those where the test was terminated because the individual had fallen below the target force for more than 5 seconds, but had still attempted to continue. In addition, the target force during the sustained contraction was set at 30% of the force achieved during the pre-exercise MVC. If a participant did not reach achieve a maximal contraction, the target force would be lower which could influence the endurance time.

2.6.4 Study Strengths and Limitations

One of the strengths of the study was the clear definition of both the group of interest (those experiencing persistent cancer-related fatigue) and the control group (breast cancer survivors who had experienced similar treatment). Separate recruitment materials to identify those who are experiencing cancer-related fatigue, as well as use of the ICD-10 CM criteria ensured that the correct patient group was targeted. While there are many potential causes of fatigue in breast cancer survivors, by excluding those who were anemic (through hemoglobin testing) and those who had had been diagnosed with clinical depression, as well as any other co-morbidities unrelated to cancer diagnosis or treatment that could be related to fatigue (i.e.,
thyroid disorder) we attempted to identify a more homogeneous group for testing. Treatment to
address fatigue related to both anemia and depression are well documented, and the purpose of
this research study was to examine potential causes of fatigue that was not related to another co-
morbid condition. However, due to the small sample size, it was not possible to control for the
exact chemotherapy and/or radiation regime. The groups were matched well on time since
treatment, and would be expected to be at similar stages of recovery from both the effects of
breast cancer itself and the adjuvant treatment.

Another strength of this study was the assessment of both cardiorespiratory and muscular
aspects of deconditioning, using gold standard techniques. The majority of studies to date have
assessed only cardiorespiratory fitness, often with submaximal estimates of VO\textsubscript{2} max. However,
the interpretation of the results of this study is limited by the multi-factorial nature of cancer-
related fatigue. While many attempts were made to exclude participants based on other co-
morbidities related to fatigue, cancer-related fatigue itself has several underlying mechanisms (as
discussed in Chapter 1). While deconditioning related to fatigue may be a primary cause for
some individuals, psychological variables, presence of inflammatory cytokines, or other
unknown factors may also play a role, and their contribution to fatigue may be more or less
depending on the individual. Participants in the FG scored higher on measures of depression and
lower on quality of life, despite the attempt at excluding individuals were had been diagnosed
with clinical depression. This indicates that there may be a psychological component to the
equation, either as a cause or a consequence of the symptom of fatigue.
Blood lactate testing using the Lactate Pro has been shown to be reliable and valid in measuring blood lactate. However, correct readings are contingent on a calibrated analyzer, use of recently manufactured lactate strips that are not past their expiry date, and good sampling technique. On occasion during testing the blood lactate analyzer would give either a reading of “LO” (lower than limit of detection) or a value that was not physiological (either extremely high or extremely low) given the intensity of exercise and previous values. A quickly repeated sample to confirm values was not possible during the graded exercise protocol as the lactate measures was taken during the last minute at each workload, and the analyzer takes 60 seconds to give a reading. By the time an erroneous value was detected, the next stage of the exercise test had commenced and that data point was lost. Given the small number of data points for each participant, missing a data point can make interpretation of the blood lactate threshold difficult. Six participants in this study had one missing value. Another potential drawback of blood lactate testing in this population is that assumptions of lactate threshold and physiological implications for activity at or above that threshold are based on healthy individuals. It is unknown whether breast cancer and/or its treatment have any effect on the physiological processes related to blood lactate during exercise as described in Chapter 1.

As discussed previously, participant motivation has a bearing on the data obtained during neuromuscular testing. Because of this, data was examined for outliers, and a number of participants were removed from second analysis. This further decreased the sample size, and limited the power of the study to detect true difference. A familiarization visit with neuromuscular testing, and twitch interpolation may have yielded more reliable results, although this approach would also increase the burden of participating in the study and may make
recruitment more difficult. In addition, many participants found the twitch interpolation technique unpleasant, and may not have been willing to participate in a second day of testing.

One of the biggest limitations to the interpretation of the results of this study was the small sample size. While several of the hypotheses approached statistical significance, the sample size did not allow sufficient power to make clear distinctions between groups. While a great deal of effort was put towards recruitment, a greater focus was put towards recruiting participants with fatigue, and less attention towards those without fatigue. In addition, based on the small time commitment to study participation of only two visits, no drop out was anticipated. However two participants (one from the FG and one from the CG) did decline participation in the second study visit, stating travel distance and lack of time as reasons for not participating. A larger sample size would have given greater statistical power, and more confidence either accept or reject the null hypothesis, and to state that there were or were not true differences between the experimental groups.

2.6.5 Study Implications

While many of the findings from the study failed to reach statistical significance, it does lay a basis for future investigation into the role of deconditioning following treatment for breast cancer survivors. The promising beneficial effects of exercise interventions in the research literature in reducing fatigue in cancer survivors lend support to the hypothesis that deconditioning may play an important role. However in order to maximize the potential therapeutic benefits of exercise in reducing fatigue, the underlying mechanisms relating to both
the cause of fatigue and how exercise can help to eliminate cancer-related fatigue must be closely examined.

2.7 Conclusion

While a small sample size limits the conclusions we can draw from this study, it does appear that breast cancer survivors who are experiencing persistent cancer-related fatigue after completion of adjuvant treatment are more deconditioned than breast cancer survivors who do not experience fatigue. Although no hypotheses reached statistical significance, the FG seemed to reach lactate threshold at a lower power output and a lower percentage of their maximal power output and also had a lower aerobic capacity than the fatigued group. In addition, following a muscle-fatiguing exercise, the muscle fatigue in the FG seemed to be more peripherally mediated than muscle fatigue in the control group. Participant motivation may have played a role in these findings, despite identical encouragement and instruction given to both groups. This study lends support for future studies further investigating the effects of deconditioning in the causation and continuation of cancer-related fatigue after treatment for breast cancer.
3 Chapter: Conclusion

Current research in the field supports the use of exercise as an intervention to reduce cancer-related fatigue in survivors of breast and other types of cancer. Therefore, it can be assumed that one or more of the factors that either cause cancer-related fatigue to develop, or contribute to the perpetuation of persistent cancer-related fatigue are affected by exercise. The benefits of exercise are wide reaching. In addition to improvements in cardiorespiratory fitness and muscular strength and endurance as measured in this research study, other factors that are hypothesized to contribute to cancer-related fatigue are also affected by exercise. Exercise has been shown to have a beneficial effect on inflammatory biomarkers\textsuperscript{128-130} and improve hypothalamic-pituitary-adrenal axis function\textsuperscript{131}, and has been an effective treatment for depression and anxiety disorders\textsuperscript{132,133}.

The purpose of this study was to examine factors related to cardiorespiratory and muscular deconditioning between breast cancer survivors with cancer-related fatigue and breast cancer survivors without cancer-related fatigue. Deconditioning has been implicated as a cause or contributing factor to fatigue during and after cancer treatment. Individuals who are have higher cardiorespiratory fitness and muscular strength and endurance are able to more efficiently carry out their activities of daily living, and may be less likely to be fatigued by general day-to-day tasks.

The first objective was to compare power output at lactate threshold between groups. The hypothesis was that individuals with cancer-related fatigue would reach lactate threshold at a lower power output than breast cancer survivors who did not experience fatigue. Although results did not reach the accepted significance level of $p=0.05$, they did approach significance,
suggesting that there may be a small difference between the groups on both power output at lactate threshold (p=0.14) and lactate threshold as a percentage of peak power output (p=0.11).

As discussed in Chapter 1, activities above the lactate threshold are difficult to maintain, and are associated with excretion of stress hormones, and quick development of fatigue. If an individual was to reach or exceed their lactate threshold during their activities of daily living, this could lead to a feeling of persistent fatigue, as has been suggested for individuals with chronic fatigue syndrome. While results from this study suggest that women with cancer-related fatigue following treatment for breast cancer do exhibit a left-ward shift of the blood lactate curve when compared to breast cancer survivors without fatigue, it is important to consider whether the magnitude of the shift is large enough that these women are reaching or exceeding their lactate threshold during their activities of daily living. Self-reported physical activity questionnaires, and approximations of intensities of various activities using metabolic equivalents suggest that these women may reach their lactate threshold during activities of daily living (as discussed above). However these approximations do not take into account individual differences, and in order to determine whether or not lactate threshold has an impact on the development of cancer-related fatigue, future studies should attempt to objectively measure intensity of daily activities in these women. In addition, future exercise interventions should consider incorporating an assessment of lactate threshold, and/or prescribe exercise intensity based on this threshold in order to ensure participants are working at an exercise intensity that will not worsen their fatigue, but will result in an improvement in lactate threshold and aerobic capacity.
The second objective was to determine whether cardiorespiratory fitness, as measured by VO$_2$ peak was different between women with cancer-related fatigue following breast cancer treatment, and a control group of breast cancer survivors without persistent cancer-related fatigue. We hypothesized that the cancer-related fatigue group would have a lower VO$_2$ peak than the control group. A lower VO$_2$ peak is a sign of cardiorespiratory deconditioning, and individuals who are more deconditioned may experience more physical difficulty with daily tasks, which may contribute to fatigue. Therefore, an improvement in fatigue with reported exercise interventions in the literature may be due to improvements in cardiorespiratory fitness. Although our results did not reach statistical significance, they do suggest that there may be a difference that exists between groups for absolute VO$_2$ peak. While many studies have reported an improvement in fatigue following an exercise intervention$^{108}$, few randomized controlled trials of exercise have been conducted to specifically target individuals who are experiencing cancer-related fatigue. While an improvement in VO$_2$ peak has been hypothesized as a mechanism for improvement in fatigue in these studies, many studies have used estimates of aerobic capacity from submaximal exercise testing$^{62,134}$. Further support for the role of deconditioning in cancer-related fatigue comes from a study which reported that exercise during treatment for breast cancer may prevent the development of fatigue. Drouin et al$^{135}$ conducted a randomized controlled trial of aerobic exercise in women undergoing radiation for breast cancer, and found that improvement in VO$_2$ peak (measured using a maximal graded incremental treadmill test) over the course of the exercise intervention was negatively correlated with levels of fatigue. Future studies should use objective measurements of VO$_2$ peak to determine whether an improvement in aerobic capacity is related to an improvement in levels of fatigue in breast cancer survivors with significant cancer-related fatigue after treatment.
The third objective was to determine causes of muscular fatigue during a sustained contraction in women with cancer-related fatigue following breast cancer treatment and a control group of breast cancer survivors without fatigue. Based on previous findings by Yavuszen et al\textsuperscript{102}, we hypothesized that central mechanisms would be responsible for the development of muscle fatigue in the cancer-related fatigue group. Our hypotheses were incorrect, and central mechanisms were found to contribute to muscle fatigue to a greater extent in the control group, and results suggest that peripheral mechanisms (as assessed by a control twitch in resting muscle) contributed to muscular fatigue to a greater extent in the cancer-related fatigue group.

While the majority of exercise interventions aimed at improving fatigue in cancer survivors have focused on aerobic exercise, two small studies have used a combination of aerobic and resistance training to improve fatigue in this population\textsuperscript{136,137}. Dimeo et al\textsuperscript{136} demonstrated an improvement in power output at anaerobic threshold that corresponded with a decrease in levels of fatigue in patients with a many types of cancer who complained of fatigue at various time points during treatment following three weeks of aerobic and resistance training. Heim et al\textsuperscript{137} reported improvements in fatigue scores as well as an improvement in muscular strength in a group who performed a physical activity program of muscle strength and aerobic exercise, but not in a control group who received standard rehabilitation during radiation treatment. Results from the present study support the further investigation into the use of resistance training to improve cancer-related fatigue after treatment. Similar to the way in which an increase in aerobic capacity can make everyday tasks seem less difficult, an improvement in muscular strength and endurance may allow individuals with cancer-related fatigue complete their daily tasks with less effort, therefore reducing fatigue.
As discussed previously, cancer-related fatigue is multi-factorial in nature, and the most significant factors that cause or perpetuate cancer-related fatigue may vary amongst individuals. Future prospective studies should assess several factors that may contribute to fatigue simultaneously, including psychological factors, inflammatory biomarkers, sleep behaviors, as well as cardiorespiratory and muscular fitness, to further understand how each interact, while future exercise intervention studies focused on improving cancer-related fatigue should recruit individuals who are experiencing cancer-related fatigue. The main findings from this study lends further support to the use of targeted exercise interventions including both aerobic and resistance training to reduce fatigue in individuals who experience persistent cancer-related fatigue after treatment for breast cancer.
References


## Appendices

### Appendix A - ICD-10 Criteria for Cancer-Related Fatigue

The following symptoms have been present every day or nearly every day during the same 2-week period in the past month:

<table>
<thead>
<tr>
<th>A. Significant fatigue, diminished energy or increased need to rest, disproportionate to any recent change in activity level, plus five or more of the following</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Complaints of generalized weakness, limb heaviness</td>
</tr>
<tr>
<td>• Diminished concentration or attention</td>
</tr>
<tr>
<td>• Decreased motivation or interest in engaging in usually activities</td>
</tr>
<tr>
<td>• Insomnia or hypersomnia</td>
</tr>
<tr>
<td>• Experience of sleep as un-refreshing or non-restorative</td>
</tr>
<tr>
<td>• Perceived need to struggle to overcome inactivity</td>
</tr>
<tr>
<td>• Marked emotional reactivity (e.g. sadness, frustration, or irritability) to feeling fatigued.</td>
</tr>
<tr>
<td>• Difficulty completing daily tasks attributed to feeling fatigued</td>
</tr>
<tr>
<td>• Perceived problems with short-term memory</td>
</tr>
<tr>
<td>• Post-exertional fatigue lasting several hours</td>
</tr>
</tbody>
</table>

| B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning |

| C. There is evidence from the history, physical examination, or laboratory findings that the symptoms are a consequence of cancer or cancer therapy |

| D. The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatisation disorder, somatoform disorder or delirium |
Appendix B - Recruitment Posters

Recruitment Poster for Fatigue Group

Are You a Breast Cancer Survivor Suffering from Fatigue?

“Measuring physiological differences between fatigued and non-fatigued breast cancer survivors”

We are conducting a study to measure differences between breast cancer survivors who are suffering from fatigue and those who do not experience fatigue after treatment.

To be eligible you must:

- Have completed radiation therapy for at least 3 months
- Experience significant fatigue which has an impact on your daily activities
- Be able to come to the University of British Columbia for two testing visits

You will receive an evaluation of your current level of aerobic fitness

If interested, please contact:

Sarah Neil, BA, M Sc Candidate

Phone: 

E-mail: 

Principal Investigator: Kristin Campbell, BSc PT, PhD, Assistant Professor, Department of Physical Therapy
Phone: 
Fax:
Are You a Breast Cancer Survivor?

"Measuring physiological differences between fatigued and non-fatigued breast cancer survivors"

We are conducting a study to measure differences between breast cancer survivors who are suffering from fatigue and those who do not experience fatigue after treatment.

We are looking for those experiencing fatigue and healthy breast cancer survivors to act as a control group.

To be eligible you must:

- Have completed radiation therapy for at least 3 months
- Be able to come to the University of British Columbia for testing

You will receive an evaluation of your current level of aerobic fitness

If interested, please contact:
Sarah Neil, BA, M Sc Candidate
Phone: 604 382 7319
E-mail: sneil2@interchange.ubc.ca

Principal Investigator: Kristin Campbell, BSc PT, PhD, Assistant Professor, Department of Physical Therapy
Phone: 604 827 4704
Fax: 604 822 1870

Fatigue in BC survivors
Fatigue in BC survivors
Fatigue in BC survivors
Fatigue in BC survivors
Fatigue in BC survivors
Fatigue in BC survivors
Fatigue in BC survivors
Fatigue in BC survivors
Fatigue in BC survivors
Measuring Physiological Differences in Fatigued and Non-Fatigued Breast Cancer Survivors

Name: ___________________ Phone Number: ________________

Address: ____________________________________________________

E-mail: ___________________

First of all, how did you hear about the study?

☐ 1 Flyer  ☐ 3 Support Group  ☐ 5 Other

☐ 2 Oncologist  ☐ 4 Newsletter

Our study has some eligibility criteria based on the research question.

1. What stage was your breast cancer? (if Stage IV, person ineligible)

☐ □ Stage I-IIIA  ☐ In situ  ☐ Stage 4  ☐ Don’t know  ______________

2. What type of treatment did you receive and when was it completed?

☐ ☐ Surgery  ____________________________ (if <6 months, ineligible)

☐ ☐ Radiation  ____________________________ (if no or <6 months, ineligible)

☐ ☐ Chemotherapy  ____________________________ (if <6 months, ineligible)

4. Are you currently experiencing fatigue on a regular basis that interferes with functioning? (If yes, complete ICD-10 Checklist for CRF, if no continue as control group)

☐ Yes  ☐ No

If person is still eligible: Let me tell you a bit more about what we’re doing. We are testing differences between breast cancer survivors who are suffering from fatigue and those who are not experiencing fatigue in hopes to help determine causes of or factors that may contribute to fatigue. All testing will take place at the University of British Columbia campus.

Prior to testing, we will send you several questionnaires to fill out that will help us to determine the level of fatigue you may be experiencing, general quality of life, as well as level of depression. You will bring completed questionnaires with you to your first day of testing.

The first day will consist of a blood draw by a physician at the sports medicine clinic to screen for anemia, which is a decreased red blood cell count. If your hemoglobin levels are high enough, you will be included in the study. If your hemoglobin levels are low, we will provide you with this information but at that point we cannot enroll you in the study. Following the blood draw you will perform an exercise test on a stationary bicycle. The test will start of easy and get progressively harder until you cannot continue. Before, during and after the test we will be monitoring your heart rate, using a polar heart rate strap and watch, blood pressure, using a stethoscope and BP cuff, and blood lactate.
which is measured via a finger prick and a blood lactate analyzing machine. You will be asked to breath through a mouthpiece during the test so we can measure your inspired and expired gases. The exercise test is expected to take less than 15 minutes.

The second day of testing is at the Garland lab in the Department of Physical Therapy. We will have you sit on a chair in front a machine called a Biodex that measures the amount of force your muscles can produce. We will ask you to perform several quadriceps contractions on the machine. Does this sound interesting to you?

If you are interested in participating, the first step is to complete a telephone screening interview. I’ll ask you some questions about your health & medical history. We have certain guidelines on eligibility that will help us reach our research goals and these questions will help us determine if this study is right for you. This can take about 20 minutes. Complete or schedule interview.

1. Would you be willing and able to come to the University of British Columbia on two separate days scheduled 1-3 weeks apart for testing? (If no, ineligible)
   - [ ] No
   - [ ] Yes

2. Are you currently or have you in the past taken part in any other research studies that involve taking some type of medication or changing diet or exercise pattern in any way?
   - [ ] No
   - [ ] Yes (If yes, specify and give dates: ________________________)
   (If <6 months, may be ineligible if potential to contribute to fatigue)

3. Are you currently following a low carbohydrate diet? (if yes, ineligible)
   - [ ] No
   - [ ] Yes

4. Are you willing to discuss your participation in this study with your oncologist and family practitioner and obtain their consent? (If no, ineligible)
   - [ ] No
   - [ ] Yes

5. We understand that some degree of depression can be common with a cancer diagnosis and that it can also contribute to fatigue. We would like to ask you some questions about it to determine eligibility. If you do not feel comfortable answering a question I ask, please say “pass”.
   Are you currently being treated for depression?
   - [ ] No (go to 5b)
   - [ ] Yes (go to 5a)

   a) Are you taking medications? ________________________ (If yes, ineligible, if no go to 5b)

   b) Are you currently feeling sad or hopeless?
   - [ ] No
   - [ ] Yes

   c) Do you feel this way:
   - [ ] Every day, [ ] Once a week, [ ] Once a month, [ ] < Once a month

   d) Is this impacting your ability to do daily activities?
   - [ ] Yes
   - [ ] No

   If yes, do you feel this way:
   - [ ] Every day, [ ] Once a week, [ ] Once a month, [ ] < Once a month

   If yes to treatment, but frequency/impact on daily activities is once a month or less, still eligible.

Eligible:
   - [ ] No
   - [ ] Yes
If ineligible at this point:
“Thank you for your time today. For this study, we are trying to better understand one of the proposed causes of cancer-related fatigue by looking specifically at how muscles respond to exercise. We know that CRF is a complex issue and that other factors, such as depression, play a major role. However, in order to look at the specific research question in muscle, we must limit recruitment to those who are not experiencing depression. Do you have any questions about this?”

6. In the past year, have you exercised at a gym (or “Curves”) or outside doing activities such as jogging, aerobics, or fast walking that increase your heart rate and cause you to sweat?
   □ No  □ Yes

   If yes, are you now regularly exercising 3+ times per week for greater than 30 minutes?
   □ No  □ Yes (If yes, ineligible)

In order to make sure the study will be safe for you, we would like to ask you about your current health and how this may impact your activities.

7. Do you have any health problems that significantly limit your ability to exercise (such as severe arthritis or bursitis, or asthma that worsens with exercise)? (If yes, ineligible)
   □ No  □ Yes (If yes, please specify: ____________________________)

8. When you exercise, walk, or walk up stairs, do you have any problems with your breathing (shortness of breath/wheezing)? (If yes, may be ineligible, physician consent)
   □ No  □ Yes

9. When you exercise, walk or walk up stairs, do you have any chest pain or discomfort in your chest, arms or neck? (If yes, may be ineligible, physician consent)
   □ No  □ Yes

10. Has a doctor ever told you that you should not exercise? (If yes, may be ineligible if reason still current)
    □ No  □ Yes (If yes, what was the reason? ____________________________)

11. During the past 6 months, have you had any serious medical problems or hospitalizations? (If yes, may be ineligible)
    □ No  □ Yes (If yes, specify ________________)

12. Have you seen a cardiologist for any reason in the past 2 years?
    □ No  □ Yes (If yes, complete section below)

Contact information of cardiologist (name, address, telephone #)
________________________________________________________
________________________________________________________
________________________________________________________

If person is eligible after completion of interview – a letter should be sent to the above cardiologist for passive consent. Allow 2 weeks from date of letter mailed before scheduling the cycle test.

□ Letter sent _____/_____/_____  Letter sent by _____ Staff ID#

Version 2  Page 3 of 5  06/30/2010
Do you now have or have you ever had any of the following medical problems?

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Eligibility</th>
<th>No</th>
<th>Yes</th>
<th>?</th>
<th>Date</th>
<th>Review/Initial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>Ineligible if yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart attack. When was your last heart attack? ___ no ___ yr</td>
<td>If yes, should be reviewed by physician – possibly ineligible if within the past 6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart disease, angina or chest pain</td>
<td>If yes, should be reviewed by physician – possibly ineligible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart catheterization or heart surgery</td>
<td>This should be reviewed by clinic staff – possibly ineligible</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Stroke?</td>
<td>If yes, ineligible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA (transient ischemic attack or “mini stroke”)</td>
<td>If yes, should be reviewed by physician – possibly ineligible if within the past 6 months</td>
<td></td>
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</tr>
<tr>
<td>Abnormal Electrocardiogram (ECG or heart tracing)</td>
<td>If yes, should be reviewed by physician – possibly ineligible if within the past 6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Diabetes</td>
<td>If yes, is it well controlled? – may be ineligible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emphysema</td>
<td>Ineligible if yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma / Lung Disease</td>
<td>If yes, should be reviewed by physician – possibly ineligible if within the past 6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>If yes, specify type, ask if capable of performing moderate &amp; vigorous exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>If yes, ask if capable of performing moderate to vigorous exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>If yes, should be reviewed by physician – possibly ineligible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip fracture</td>
<td>If yes, do you have any activity restrictions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip or joint replacement</td>
<td>If yes, do you have any activity restrictions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any other chronic health problem? Please specify:</td>
<td>If yes, should be reviewed by physician – possibly ineligible if within the past 6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Ineligible if yes
* Possibly ineligible if yes
* Ineligible if no
* Possibly ineligible if no

Date: 06/30/2010
(If answered yes to Question 4)
Finally, we would like to ask you some specific questions related to cancer fatigue.

ICD-10 Criteria for Cancer-Related Fatigue

I will now ask you about a series of symptoms that you may be experiencing in relation to the fatigue you identified earlier. To answer “Yes” the symptoms must have been present every day or nearly every day during the same 2-week period in the past month.

- Significant fatigue, diminished energy or increased need to rest, disproportionate to any recent change in activity level *(If no, ineligible)*
  - Y N Generalized weakness or limb heaviness
  - Y N Diminished concentration or attention
  - Y N Decreased motivation or interest engaging in usual activities
  - Y N Insomnia or hypersomnia
  - Y N Experience of sleep as un-refreshing or non-restorative
  - Y N Emotional reactivity (ex. Sadness, frustration, or irritability) to feeling fatigued
  - Y N Difficulty completing daily tasks because of fatigue
  - Y N Problems with short term memory
  - Y N Post-exertion fatigue lasting several hours

**Total: Yes** ☐ **Total: No** ☐ *(If not at least 5, ineligible)*

- Y N Do the symptoms cause significant distress or impairment in social settings, occupation or other important areas of functioning? *(If no, ineligible)*
- Y N Are the symptoms a consequence of cancer or cancer therapy, and were not present prior? *(If no, ineligible)*
- Y N The symptoms are not primarily associated with other co-morbid disorder such as clinical depression, somatisation disorder, delirium *(If no, ineligible)*

Cancer Related Fatigue: ☐ No ☐ Yes *(If no, ineligible)*
**Functional Assessment of Cancer Therapy – Breast**

**FACT-B (Version 4)**

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

### PHYSICAL WELL-BEING

<table>
<thead>
<tr>
<th>Statement</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP1: I have a lack of energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP2: I have nausea</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP3: Because of my physical condition, I have trouble meeting the needs of my family</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP4: I have pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP5: I am bothered by side effects of treatment</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP6: I feel ill</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP7: I am forced to spend time in bed</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### SOCIAL/FAMILY WELL-BEING

<table>
<thead>
<tr>
<th>Statement</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS1: I feel close to my friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS2: I get emotional support from my family</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS3: I get support from my friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS4: My family has accepted my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS5: I am satisfied with family communication about my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS6: I feel close to my partner (or the person who is my main support)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS7: I am satisfied with my sex life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.
FACT-B (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

### EMOTIONAL WELL-BEING

<table>
<thead>
<tr>
<th>Item</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Some-what</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I feel sad</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am satisfied with how I am coping with my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am losing hope in the fight against my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel nervous</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I worry about dying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I worry that my condition will get worse</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### FUNCTIONAL WELL-BEING

<table>
<thead>
<tr>
<th>Item</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Some-what</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am able to work (include work at home)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>My work (include work at home) is fulfilling</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am able to enjoy life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have accepted my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am sleeping well</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am enjoying the things I usually do for fun</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am content with the quality of my life right now</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
FACT-B (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<table>
<thead>
<tr>
<th>ADDITIONAL CONCERNS</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Some-what</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1 I have been short of breath</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>B2 I am self-conscious about the way I dress</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>B3 One or both of my arms are swollen or tender</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>B4 I feel sexually attractive</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>B5 I am bothered by hair loss</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>B6 I worry that other members of my family might someday get the same illness I have</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>B7 I worry about the effect of stress on my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>B8 I am bothered by a change in weight</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>B9 I am able to feel like a woman</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>P2 I have certain parts of my body where I experience pain.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Appendix E: Functional Assessment of Cancer Therapy – Fatigue

FACT-B (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<table>
<thead>
<tr>
<th>Item</th>
<th>Statement</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>HI7</td>
<td>I feel fatigued</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>HI12</td>
<td>I feel weak all over</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>An1</td>
<td>I feel listless (“washed out”)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>An2</td>
<td>I feel tired</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>An3</td>
<td>I have trouble starting things because I am tired</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>An4</td>
<td>I have trouble finishing things because I am tired</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>An5</td>
<td>I have energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>An6</td>
<td>I am able to do my usual activities</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>An8</td>
<td>I need to sleep during the day</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>An12</td>
<td>I am too tired to eat</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>An14</td>
<td>I need help doing my usual activities</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>An15</td>
<td>I am frustrated by being too tired to do the things I want to do</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>An16</td>
<td>I have to limit my social activity because I am tired</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Appendix F: Multidimensional Assessment of Fatigue

MULTIDIMENSIONAL ASSESSMENT OF FATIGUE (MAF) SCALE

Instructions: These questions are about fatigue and the effect of fatigue on your activities.

For each of the following questions, circle the number that most closely indicates how you have been feeling during the past week.

For example, suppose you really like to sleep late in the mornings. You would probably circle the number closer to the “a great deal” end of the line. This is where I put it:

Example: To what degree do you usually like to sleep late in the mornings?

Not at all A great deal

Now please complete the following items based on the past week.

1. To what degree have you experienced fatigue?

Not at all A great deal

If no fatigue, stop here.

2. How severe is the fatigue which you have been experiencing?

Mild Severe

3. To what degree has fatigue caused you distress?

No distress A great deal of distress

Circle the number that most closely indicates to what degree fatigue has interfered with your ability to do the following activities in the past week. For activities you don't do, for reasons other than fatigue (e.g. you don't work because you are retired), check the box.

In the past week, to what degree has fatigue interfered with your ability to:

(Note: Check box to the left of each number if you don't do activity)

☐ 4. Do household chores

Not at all A great deal

☐ 5. Cook

Not at all A great deal
6. Bathe or wash

Not at all  
A great deal

7. Dress

Not at all  
A great deal

8. Work

Not at all  
A great deal

9. Visit or socialize with friends or family

Not at all  
A great deal

10. Engage in sexual activity

Not at all  
A great deal

11. Engage in leisure and recreational activities

Not at all  
A great deal

12. Shop and do errands

Not at all  
A great deal

13. Walk

Not at all  
A great deal

14. Exercise, other than walking

Not at all  
A great deal

15. Over the past week, how often have you been fatigued?

Every day  
Most, but not all days  
Occasionally, but not most days  
Hardly any days

16. To what degree has your fatigue changed during the past week?

Increased  
Fatigue has gone up and down  
Stayed the same  
Decreased
Appendix G: Beck Depression Inventory

Beck Depression Inventory-II

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully and then pick out the one statement in each group that best describes the way you have been feeling during the past two weeks, including today. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleep Pattern) or Item 18 (Changes in Appetite).

1. Sadness
   ◦ I do not feel sad
   ◦ I feel sad much of the time
   ◦ I am sad all of the time
   ◦ I am so sad or unhappy that I can’t stand it

2. Pessimism
   ◦ I am not discouraged about my future
   ◦ I feel more discouraged about my future than I used to be
   ◦ I do not expect things to work out for me
   ◦ I feel my future is hopeless and will only get worse

3. Past Failure
   ◦ I do not feel like a failure
   ◦ I have failed more than I should have
   ◦ As I look back, I see a lot of failures
   ◦ I feel I am a total failure as a person

4. Loss of Pleasure
   ◦ I get as much pleasure as I ever did from the things I enjoy
   ◦ I don’t enjoy things as much as I used to
   ◦ I get very little pleasure from the things I used to enjoy
   ◦ I can’t get any pleasure from the things I used to enjoy

5. Guilty Feelings
   ◦ I don’t feel particularly guilty
   ◦ I feel guilty over many things I have done or should have done
   ◦ I feel quite guilty most of the time
   ◦ I feel guilty all of the time

6. Punishment Feelings
   ◦ I don’t feel I am being punished
   ◦ I feel I may be punished
   ◦ I expect to be punished
   ◦ I feel I am being punished

7. Self-Dislike
   ◦ I feel the same about myself as ever
   ◦ I have lost confidence in myself
   ◦ I am disappointed in myself
   ◦ I dislike myself

8. Self-Criticalness
   ◦ I don’t criticize or blame myself more than usual
   ◦ I am more critical of myself than I used to be
   ◦ I criticize myself for all of my faults
   ◦ I blame myself for everything bad that happens

9. Suicidal Thoughts or Wishes
   ◦ I don’t have any thoughts of killing myself
   ◦ I have thoughts of killing myself, but I would not carry them out
   ◦ I would like to kill myself
   ◦ I would kill myself if I had the chance

10. Crying
    ◦ I don’t cry anymore than I used to
    ◦ I cry more than I used to
    ◦ I feel like crying, but I can’t

11. Agitation
    ◦ I am no more restless or wound up than usual
    ◦ I feel more restless or wound up than usual
    ◦ I am so restless or agitated that its hard to stay still
    ◦ I am so restless or agitated that I have to keep moving or doing something

12. Loss of Interest
    ◦ I have not lost interest in other people or activities
    ◦ I am less interested in other people or things than before
    ◦ I have lost most of my interest in other people or things
    ◦ Its hard to get interested in anything
13. Indecisiveness
   - I make decisions about as well as ever
   - I find it more difficult to make decisions
   - I have much greater difficulty in making decisions than I used to
   - I have trouble making any decisions

14. Worthlessness
   - I do not feel I am worthless
   - I don’t consider myself as worthwhile and useful as I used to
   - I feel more worthless as compared to other people
   - I feel utterly worthless

15. Loss of Energy
   - I have as much energy as ever
   - I have less energy than I used to have
   - I don’t have enough energy to do very much
   - I don’t have enough energy to do anything

16. Changes in Sleeping Pattern
   - I have not experienced change in my sleep
   - I sleep somewhat more than usual
   - I sleep somewhat less than usual
   - I sleep a lot more than usual
   - I sleep a lot less than usual
   - I sleep most of the day
   - I wake up 1-2 hours early and can’t get back to sleep

17. Irritability
   - I am not more irritable than usual
   - I am more irritable than usual
   - I am much more irritable than usual
   - I am irritable all the time

18. Changes in Appetite
   - I have not experienced any change in my appetite
   - My appetite is somewhat less than usual
   - My appetite is somewhat more than usual
   - My appetite is much less than before
   - I have no appetite at all
   - I crave food all the time

19. Concentration Difficulty
   - I can concentrate as well as ever
   - I cant concentrate as well as usual
   - Its hard to keep my mind on anything for very long
   - I find I cant concentrate on anything

20. Tiredness or Fatigue
   - I am not more tired or fatigued than usual
   - I get more tired or fatigued more easily than usual
   - I am too tired or fatigued to do a lot of the things I used to do
   - I am too tired or fatigued to do most of the things I used to do

21. Loss of Interest in Sex
   - I have not noticed any recent change in my interest in sex
   - I am less interested in sex than I used to be
   - I am much less interested in sex now
   - I have lost interest in sex completely
Appendix H - Physical Activity Interview

Leisure Time Activity Chart

<table>
<thead>
<tr>
<th>1. Activity Name</th>
<th>2. # Months / Year</th>
<th>3. Average # Times / Month</th>
<th>4. Average # Mins / Time</th>
<th>Interviewer Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>J A N</td>
<td>F E B</td>
<td>M A R</td>
<td>A P R</td>
</tr>
<tr>
<td>1. Jogging / Running (outdoor or treadmill)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Walking for exercise (outdoor or treadmill)</td>
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</tr>
<tr>
<td>3. Other walking (e.g., walking your dog)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>4. Bicycling (outdoor or stationary)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Swimming laps</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>6. Aerobics</td>
<td></td>
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<tr>
<td>36. Elliptical trainer (EFX)</td>
<td></td>
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<tr>
<td>7. Stairmaster</td>
<td></td>
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<tr>
<td>8. Nordic Track</td>
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<tr>
<td>9. Rowing machine</td>
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<tr>
<td>10. Weight lifting (free or Nautilus)</td>
<td></td>
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<tr>
<td>11. Lt. calisthenics / Water aerobics</td>
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<tr>
<td>12. Martial arts (karate, judo)</td>
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<tr>
<td>13. Fast dancing</td>
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<tr>
<td>14. Kayaking</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>15. Canoeing</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>16. Rowing</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Probe for amount of HR increase, any SOB, level of perspiration (intensity), average duration
<table>
<thead>
<tr>
<th>1. Activity Name</th>
<th>2. # Months / Year</th>
<th>3. Average # Times / Month</th>
<th>4. Average # Mins / Time</th>
<th>Interviewer Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Tennis</td>
<td></td>
<td></td>
<td></td>
<td>Probe for amount of HR increase, any SOB, level of perspiration (intensity), average duration</td>
</tr>
<tr>
<td>18. Racquetball / Squash</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>19. Golfing with a cart</td>
<td></td>
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<tr>
<td>20. Golfing without a cart</td>
<td></td>
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<tr>
<td>21. Skiing – downhill</td>
<td></td>
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<tr>
<td>22. Skiing – cross country</td>
<td></td>
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</tr>
<tr>
<td>23. Snow shoeing</td>
<td></td>
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<tr>
<td>24. Skating (roller, ice, blading)</td>
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<tr>
<td>25. Horseback riding</td>
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<tr>
<td>26. Hiking</td>
<td></td>
<td></td>
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<tr>
<td>27. Climbing mountains</td>
<td></td>
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<tr>
<td>28. Rock climbing</td>
<td></td>
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<tr>
<td>29. Softball / Baseball</td>
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</tr>
<tr>
<td>30. Basketball</td>
<td></td>
<td></td>
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<tr>
<td>31. Volleyball</td>
<td></td>
<td></td>
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<tr>
<td>32. Soccer</td>
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<td></td>
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</tr>
<tr>
<td>33. Football</td>
<td></td>
<td></td>
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<tr>
<td>34. Other</td>
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</tr>
<tr>
<td>35. Other</td>
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</tr>
<tr>
<td>37. Yoga</td>
<td></td>
<td></td>
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<tr>
<td>38. Pilates</td>
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</tbody>
</table>
Appendix I - Rating of Perceived Exertion (RPE) Scale

<table>
<thead>
<tr>
<th>Borg’s RPE Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>No exertion at all</td>
</tr>
<tr>
<td>7</td>
<td>Extremely light</td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Very light</td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Light</td>
</tr>
<tr>
<td>12</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Somewhat hard</td>
</tr>
<tr>
<td>14</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Hard (Heavy)</td>
</tr>
<tr>
<td>16</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Very hard</td>
</tr>
<tr>
<td>18</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Extremely hard</td>
</tr>
<tr>
<td>20</td>
<td>Maximal exertion</td>
</tr>
</tbody>
</table>

Borg RPE scale
Appendix J - Exercise Testing Data Collection Form

Exercise Testing Form

Demographic Information

<table>
<thead>
<tr>
<th>Initials:</th>
<th>Study ID:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age:</td>
<td>Date of Birth:</td>
</tr>
</tbody>
</table>

Medical History/Exercise Contraindications/Medications

Pre-Test Assessments

Resting HR (bpm): _______________  Weight (kg): _______________

Resting BP (mmHg): _______________  Height (cm): _______________

Resting BLact: _______________  BMI (kg/m²) _______________

Cart Specifications

Pre Test Cal 0₂: _______________  Pre Test Cal C0₂: _______________

Post Test Cal 0₂: _______________  Post Test Cal C0₂: _______________

Correction Needed? Yes  No
Temp (°C): _______________  Hum (%): _______________  P₀ (mmHg): _______________

Bike Baseline Wattage: ___________  Increments: _______________
### Graded Exercise Bicycle Test

<table>
<thead>
<tr>
<th>Stage</th>
<th>Time (Min)</th>
<th>Wattage</th>
<th>Heart Rate</th>
<th>BP</th>
<th>Blood Lactate</th>
<th>RPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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Post-Test Assessments

2 min recovery HR: ______________  2 min recovery BP: ______________

5 min recovery HR: ______________  5 min recovery BP: ______________

Reason for Test Termination

Dyspnea                  Leg Fatigue       Both

Other:

Comments:

Supervised By: ______________

Testers: ____________________  ____________________
Appendix K - Neuromuscular Testing Data Collection Form

Date:

Neuromuscular Testing Form

Demographic Information

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<th>Study ID:</th>
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<td>CCI ID:</td>
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<tr>
<td>Height:</td>
<td>Weight:</td>
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Settings

50µs x 10 mA

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<th>Voltage</th>
<th>Maximal Stimulation</th>
<th>Supra-maximal</th>
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<td>TF Rest</td>
</tr>
<tr>
<td>30% MVC</td>
</tr>
<tr>
<td>Time to failure</td>
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<td>MVC Fatigue</td>
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<tr>
<td>TF Fatigue</td>
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Comments: