A Comparison Between Estimated and Direct Measurements Of Oxygen Uptake In Breast Cancer Survivors

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ABSTRACT

DUSTIN BUTTARS: A Comparison Between Estimated and Direct Measurements Of Oxygen Uptake In Breast Cancer Survivors
(Under the direction of Dr. Claudio Battaglini)

Purpose: This study compared maximal oxygen uptake (VO_{2max}) between estimated and directly measured VO_{2max} values obtained during a maximal cycle ergometer test in breast cancer survivors. Methods: Nine women (50 ± 6 years) diagnosed with early stage breast cancer (BCS) who had completed all primary cancer treatments within the past 3 to 6 months and nine age, weight, and fitness level matched women (59 ± 5), with no history of cancer participated in the study. All subjects performed a VO_{2max} test on an electronically-braked cycle ergometer. Using results of the test, an estimated VO_{2max} was calculated, then compared to the directly measured VO_{2max} obtained during the test using a dependent samples t-test. Results: Significant difference ($p=0.01$) was observed between directly measured (18.1± 2.7ml/kg/min) and estimated (16.3 ± 3.6ml/kg/min) VO_{2max} values in BCS. Conclusion: Estimated VO_{2max} calculated from a submaximal cycle ergometer test underestimates VO_{2max} when compared to directly measured VO_{2max}.

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Chapter I

Introduction

Breast cancer is the second most common form of diagnosed cancer and second leading cause of cancer death among women [American Cancer Society (ACS), 2013]. An estimated 234,580 new cases in the U.S. are expected in 2013 of which 40,030 are expected to die from the disease (ACS, 2013). Five-year survival rate for female breast cancer has increased from 63% in the 1960's to 90% today (ACS, 2013). Survival however has come with a price. Treatments such as chemotherapy, hormone therapy, radiation and surgery each cause different side effects for cancer patients. Many of these side effects are treated with pharmacological interventions, however, the efficacy of pharmaceuticals may only provide temporary relief and long term effects of treatment may persist for years post completion of treatment.

Recently, the medical community has given a great deal of attention to complementary non-pharmacological interventions that have proven to off-set or even reverse many of the side-effects commonly experienced by cancer patients during and after completion of cancer treatments. Among the different complementary interventions such as psychotherapy, dietary manipulations, stress management, and exercise; exercise is an intervention that has shown in cancer patients to positively affect many treatment-related side effects (Battaglini et al., 2007, 2008; Burnham et al., 2002; Courneya et al., 2003; Daley et al., 2007; Jones et al., 2008).

Current exercise guidelines for the breast cancer population recommend moderate to vigorous intensity activity, three to five days per week which mimic the age-appropriate physical activity guidelines for Americans (Courneya et al., 2011; Irwin, 2012; Schmitz et al., 2010; Thompson et al., 2010). Due to the beneficial effects exercise can have on treatment related side effects, it is imperative that exercise-testing guidelines be implemented to increase safety as well as to provide the most accurate information which is critical for the development of more precise exercise prescriptions.

The integrative ability of the cardiopulmonary and skeletal muscle system, allows for the transport and utilization of oxygen by tissues for the production of energy. This is necessary for proper physiological function as well as to endure changes in energy expenditure necessary for the performance of activities of daily living as well as maintenance of health. Furthermore, cardiorespiratory fitness (CRF), commonly expressed as maximal oxygen uptake (VO_{2max}) is considered the best cardiovascular fitness indicator (Brooks et al., 2005) and has been inversely associated with all-cause mortality as well as cardiovascular disease deaths in a wide range of adult populations (Kavanagh et al., 2002, 2003). In breast cancer survivors, CRF is reduced by an average of 30% throughout the treatment process (Jones et al., 2011). The necessity of improving CRF in cancer patients cannot be overstated since higher CRF is associated with a significant reduction in breast cancer mortality (Holmes et al., 2005; Peel et al., 2009) and increases in overall quality of life (Burnham et al., 2003; Courneya et al., 2003; Daley et al., 2007; Herrero et al., 2006).

Research in the area of exercise testing and training for breast cancer patients is still young and underdeveloped. Jones et al., (2008) conducted a systematic review of the literature evaluating several methodological issues including (but not limited to) exercise testing paradigms and subject (patient) characteristics. It was concluded that the current literature is so broad in scope and methodology that methodological testing and prescription of exercise standardization among researchers is essential for the interpretation of the results of the studies examining the effects of exercise in cancer survivors.

In cancer survivors, exercise testing most often involves the administration of submaximal cardiopulmonary protocols that estimate maximal oxygen uptake as well as maximal cardiopulmonary exercise tests (CPET) using treadmills and cycle ergometers (Jones et al., 2008). The result of CPET is not only used to evaluate the effects of exercise training on CRF, but is also used to establish training thresholds in the development of aerobic exercise prescriptions. Among the scientific community studying the effects of exercise in the cardiopulmonary system of cancer survivors, direct measures of CRF are considered the most accurate method of CRF evaluation. The results of maximal tests are usually reported as peak oxygen uptake (VO_{2peak}) due to the inability of cancer patients to reach the pre-defined criteria for a maximal test. Furthermore, treadmill exercise testing offers its own set of limitations in the cancer survivor population due to many physical side effects derived from cancer treatments such as balance problems recently reported in the literature (Wampler et al., 2007; Winters-Stone et al., 2011). The negative impact of the treatment-related side effects, which often leads to reduction in physical activity and consequently decreases in overall functionality, reduces cancer survivors exercise tolerability making it more difficult to perform maximal cardiopulmonary exercise tests. Also, the effects of cancer and treatment on pathophysiology may increase the risk of an adverse exercise-test related event (Jones et al., 2008). Not only do these safety hazards and physical limitations disallow the use of maximal exercise testing outside clinical settings due to the need of physician supervision, but also the accuracy of such tests administered in cancer survivors may be questionable. Often these tests are terminated prematurely due to muscle strength limitations and/or discomfort from equipment harnesses (mouth pieces or masks) used to collect gas exchange; factors not related to the true cardiopulmonary ability and the ability of the skeletal muscle system to uptake and use oxygen for energy production. In addition to these potential issues associated with the accuracy of maximal oxygen uptake testing protocols in cancer survivors, the results of the effects of exercise on CRF in cancer survivors even though promising, in regards to improvements that have been reported in the literature, have not been of similar magnitude to improvements seen in apparently healthy populations when matched by age, gender, and similar fitness condition. The smaller increases in VO_{2peak} evaluated from direct measures raises the following questions; 1) Are the aerobic exercise prescriptions commonly administered, which include 3 times per week for approximately 30 minutes of moderate intensity (Jones et al., 2012), to cancer survivors not promoting the expected changes in CRF because they are not intense enough? 2) Are there cardiovascular or metabolic alterations due to cancer treatments that are not allowing for patients to experience the desirable changes in oxygen uptake with exercise training? 3) Or is it simply, the fact that exercise prescriptions devised from direct measures of VO_{2peak} are not precise enough to elicit the desirable changes in oxygen uptake efficiency due to the fact that these measurements may be underestimating the determination of training thresholds? In order for these questions to be answered, an initial evaluation on the potential differences in testing procedures needs to be addressed; for example comparing estimated, versus direct, measurements of VO_{2max} in cancer survivors and the evaluation of the results to determine training thresholds for the prescription of the exercise training for cancer survivors is necessary. These evaluations are paramount in the quest to answering the interesting question regarding the small improvement in VO_{2ma} seen in the exercise oncology literature.

Statement of Purpose

The purpose of this study was to compare the results of maximal oxygen uptake (VO_{2max}) between estimated and directly measured VO_{2max} values obtained during maximal cycle ergometer testing in breast cancer survivors. A secondary purpose was to compare training thresholds devised from estimated and direct measurements of VO_{2max}, measured in watts, at 40%, 60%, 70%, and 80% of maximal oxygen uptake.

Research Question

RQ1: Will the estimated and direct measurements ofVO_{2max} elicit similar maximal oxygen uptake values in breast cancer survivors?

RQ2: Will training thresholds devised from estimated and direct measurement of maximal oxygen uptake in watts at 40%, 60%, 70%, and 80% of maximal oxygen uptake elicit similar values?

Hypothesis

H1: There will be a significantly higher maximal oxygen uptake (VO_{2max}) estimated from a submaximal oxygen uptake exercise evaluation when compared with the directly measured maximal oxygen uptake test in a group of breast cancer survivors.

H2: There will be a significant difference in watts at 40%, 60%, 70%, and 80% of VO_{2max} devised from the estimated and directly measured maximal oxygen uptake testing evaluations, with higher wattage resulting at all percentages of VO_{2max} from the estimated maximal oxygen uptake evaluation versus directly measured maximal oxygen uptake values.

Definitions of Terms

<u>Breast Cancer Survivors:</u> Early stage breast cancer patients who have completed major cancer treatment such as chemotherapy, radiation, surgery or a combination of these within the past 12 months. They may or may not be currently on hormonal therapy.

<u>Maximal Oxygen Consumption (VO_{2max})</u>: The maximum amount of oxygen consumed by an individual during an exercise test. Certain criteria must be decided upon before the test begins and must be met upon completion of the test to be considered a max. These criteria are: 1) A respiratory exchange ratio (RER) of >1.10, 2) A rating of perceived exertion (RPE) of $\geq$18, 3) Heart rate (HR) within 10 beats of age-predicted maximum, 4) A 150ml/min or less rise in VO_2 with an increase in workload, or 5) An increase of 8 mmol in lactate**.** Criteria are selected based on the design of the study and is usually determined by at least three of the criteria mentioned above being met to determine

whether the test was maximal. Should less than three criteria be met, the test is termed a peak test (VO_{2peak}). A maximal test is considered the best measure of cardiovascular fitness (Brooks et al., 2005).

<u>Metabolic Equivalent (MET):</u> A common expression of energy expenditure. One metabolic equivalent is equal to approximately 3.5 ml/kg/min of air consumed by an individual at rest (Brooks et al., 2005).

<u>Respiratory Exchange Ratio (RER)</u>: The ratio of oxygen consumed and carbon dioxide produced. An RER of 1.00 suggests 100% utilization of carbohydrates as the primary energy substrate, whereas an RER of 0.70 suggests predominant reliance on fats as the energy substrate. RER is not to be used solely as an indicator of substrate utilization due to the fact that metabolic conditions can artificially inflate the carbon dioxide (CO_2) values (Brooks et al., 2005).

<u>Rating of Perceived Exertion (RPE)</u>: Currently, two RPE scales are widely used: the original or category scale, which rates exercise intensity on a scale of 6 to 20, and the category-ratio scale of 0 to 10. The RPE can be used as an indication of impending fatigue. Most apparently healthy subjects reach their subjective limit of fatigue at and RPE of 18 to 19 (very, very hard) on the category Borg scale or 9 to 10 (very, very strong) on the category-ratio scale; therefore, RPE can be used to monitor progress toward maximal exertion during exercise testing (Thompson et al., 2010).

Assumptions

1. All of the subjects followed the pre-test guidelines.

2. All of the subjects were honest in answering questions related to medical history, cancer history, and lifestyle evaluation.
3. Every subject gave 100% effort on the maximal cardiopulmonary exercise test.

Limitations

1. The sample consists of only female breast cancer survivors therefore outcomes are not generalizable to other cancer types or male breast cancer survivors.
2. A relatively small sample size.
3. Despite all subjects being post-treated, it is possible those most recently finished with treatment (i.e.: within two weeks), may be experiencing more severe side effects thus potentially compromising their ability to perform the maximal cardiopulmonary exercise test.
4. Previous testing experience may influence the performance of the breast cancer survivors on the maximal exercise test.
5. Previous exercise history may skew the results.

Delimitations

1. The sample contained only female, breast cancer survivors.
2. Only post-treated, early stages (I-III), breast cancer survivors were eligible.
3. All subjects had undergone both chemotherapy and radiation as part of their major treatment plan.
4. All subjects were no longer than 1 year post-treatment.

Significance of the Study

Cardiorespiratory fitness is commonly assessed using maximal exercise testing protocols (i.e., Cardiopulmonary Exercise Testing (CPET)). Measuring objectively cardiorespiratory fitness has gained significant attention in oncology patients due to the association between maximal oxygen uptake, cancer recurrence and mortality in patients with certain types of cancers. Furthermore, the result of a CPET is often used in exercise prescriptions for the determination of training thresholds for this patient population. A large number of cancer patients have difficulty performing even basic activities of daily living due to the deconditioned state they present during and after completion of cancer treatments; which is believed to be a result of the effects of cancer treatments themselves that lead to reduced physical activity and increased sedentary living. Therefore assuming cancer survivors would respond similarly to a maximal cardiopulmonary exercise test when compared to healthy counterparts, may produce different responses therefore compromising the ability of a precise interpretation of testing results commonly used for the evaluation of the efficacy of exercise training programs as well as for the determination of exercise prescriptions. A first step in improving the way aerobic exercise is currently prescribed to cancer patients is to identify tests that are more suitable for this population of cancer survivors. The fact that most survivors may not be able to perform well during a maximal cardiopulmonary test due to physical limitations that arise from cancer treatment or the discomfort of giving a maximal physical effort when experiencing severe fatigue, may influence the results of a maximal test thus raising the question whether a submaximal test can produce more meaningful results in the cancer survivor population. Also, due to the fact that most studies examining the effects of cardiorespiratory function in cancer survivors have shown modest to low improvements in cardiorespiratory function after participating in an exercise training protocol, raises the question regarding the validity of using the results of a maximal test to devise training threshold in the cancer survivor population. Therefore, the first step in the quest of answering the question regarding the modest improvement in cardiopulmonary function in cancer survivors is to compare different testing protocols and then, if different results from these tests are in fact observed, implement exercise prescriptions using training thresholds devised from these tests so training responses can be compared. This study was designed to answer the first part of the question regarding potential differences in testing protocols and their influence in devising aerobic training thresholds in breast cancer survivors. The results of this initial study has the potential to serve as a starting point for future experiments that will be designed to improve current exercise training guidelines for breast cancer survivors.

Chapter II

Literature Review

This review is divided into five sections. Current breast cancer statistics are reviewed in section 1. The different breast cancer treatments commonly administered is discussed in section 2. Section 3 provides an overview of the physiologic impact cancer treatments cause to different physiological systems of survivors. Section 4 provides a summary of the exercise oncology literature. In section 5, the influence of cardiorespiratory fitness on cardiovascular and all-cause mortality is reviewed as well as the importance of cardiorespiratory fitness for cancer survivors. Lastly, section 6 discusses the current literature on exercise testing in cancer patients.

Section 1: Breast Cancer Statistics in the United States

Among women, breast cancer is the second most common form of diagnosed cancer and second leading cause of cancer death [American Cancer Society, (ACS) 2013]. Over 200,000 new cases in the U.S. are expected in 2013 of which nearly 40,000 are expected to die from the disease (ACS, 2013). From 2005 to 2008 the incidence of breast cancer was 124 per 100,000 women and mortality for the same period was 23 per 100,000 women (National Cancer Institute, 2013). New and more effective treatments and the decreased use of menopausal hormone therapy (MHT), or hormone replacement therapy, are partially to thank for reductions in death rate from the disease. However, with these new and improved treatments comes a multitude of side effects which cause acute or chronic alterations in physiological functioning of the patient. Insults to the myocardium and skeletal muscular system, weight gain and fatigue are very impactful side effects that occur from the various cancer treatments.

Section 2: Breast Cancer Treatments

Chemotherapy

Chemotherapy is a very common treatment used in breast cancer. Patients with all different stages of disease may need to undergo some form of chemotherapy. Many of these cause unwanted and debilitating side effects associated with reduced quality of life and physical function (ACS, 2013). Suppressed immune function, peripheral sensory neuropathy, nausea, decreased spatial awareness and balance, loss of muscle mass and function, loss of appetite, and psychological alterations such as fatigue, quality of life and motivation to perform daily activities are common side effects, but certainly not the full range (ACS, 2013; Shapiro et al., 1997). Chemotherapy is a broad class of treatment but is systemic in nature. Either intravenous or oral mode of treatment is used to target cancer cells throughout the body. Neoadjuvant chemotherapy is commonly used before surgery to shrink a solid tumor. Adjuvant therapy is often performed after surgery or radiation as insurance of killing any cancer cells that may have broken away from the original tumor site. Chemotherapy is usually given as a cocktail of numerous drugs each with different physiological killing specificity. It is given in cycles lasting weeks to months and the longer a treatment lasts, the more severe side effects can become.

Radiation

Radiation poses its own set of challenges after treatment. Radiation is a targeted treatment in which the size of the tumor is reduced. Radiation can be implemented as either external beam or brachytherapy. External beam is the most common and uses high energy beams from a machine to directly target the tumor. Depending on the type and severity of the breast cancer, different lengths of treatment may be used. Longer radiation courses have stronger associations with causing cancer induced fatigue. Approximately 70% of patients report experiencing some level of fatigue ranging from mild to debilitating (Courneya et al., 2003; Shapiro et al., 1997). Along with fatigue, radiation can cause pulmonary and cardiovascular injury in the form of fibrosis to the lung or pericarditis of the heart (Shapiro et al., 1997). Skin breakdown and possible loss of range of motion are quite common among patients treated with radiation. Lymphedema is another common side effect for breast cancer patients who receive surgery and then radiation. Lymphedema is evidenced by swelling of the limb associated with the side of treatment and in some cases can cause total incapacitation of the limb until the fluid is drained. The cause of lymphedema is unknown and can manifest at any point during or after treatment. Radiation is a difficult treatment to undergo and the combination of chemotherapy and radiation can cause increased fatigue and exacerbation of side effects which ultimately has negative impacts on physical function and CRF of the patient (Irwin, 2012).

Surgery

Surgery is a typical treatment used for early stage breast cancers to fully remove the tumor. In breast cancer patients, surgery can incidentally cause inflammation at the surgery site, chording of the axilla, and increased risk of lymphedema dependent upon the number of lymph nodes removed. Infection is another risk associated with surgery and can set the patient back even further. Surgery combined with radiation can increase the risk of lymphedema greatly, cause loss of range of motion around the affected limb and reduce muscular function. Psychologically, the patient may be apprehensive to use the affected limb, for fear of injuring it further, which has an effect on quality of life and overall physical function.

Hormonal Therapy

Hormonal therapy is a typically adjuvant treatment used in breast cancer to block the active hormones that breast cancer often targets, estrogen and progesterone. Cancers that are estrogen receptor positive are called ER positive breast cancers, where progesterone receptor positive cancers are PR positive. A few of the common hormone agents used are Tamoxifen, Femara and Aromasin. Each of these drugs works in slightly different ways but ultimately they reduce estrogen production in the body. These drugs reduce risk of cancer recurrence by about 40%, however many patients report side effects such as weight gain and hot flashes.

Another hormone therapy drug used is Herceptin. Herceptin works by reducing the expression of Human Epidermal Growth Factor Receptor 2 (HER2/neu), a protein associated with more aggressive breast disease. A major side effect of this agent is cardiotoxicity, and thus cardiac function should be monitored (Irwin, 2012). Any exercise specialist working with patients taking Herceptin must understand the cardiac risks. Herceptin interferes with normal heart function by reducing the ejection fraction, similar to anthracycline treatment.

Section 3: Physiologic Impact of Treatment

The five year survival rate for breast cancer in women has increased from 63% in the 1960's to 90% in 2012 (ACS, 2013). This improvement however, comes with a price. Treatments such as chemotherapy, hormone therapy, radiation and surgery each produce different side effects for these survivors. An incomplete list of treatment related side effects is listed in Table 1.

Cancer Treatment Related Side Effects
Myelosuppression
Nausea
Weight Gain
Cardiac Toxicity
Fatigue
Decreased Strength
Reduced Quality of Life
Cognitive Dysfunction
Reduced Cardiorespiratory Fitness
Lymphedema
Muscular Atrophy
Hair Loss
Peripheral Neuropathy

Table 1: List adapted from Burnham et al., 2002; Shapiro et al., 2001.

Many of these side effects have a compounding effect where the end result can be loss of skeletal muscle or atrophy from disuse along with even greater declines in cardiorespiratory fitness (CRF). These two issues are part of the proposed mechanisms behind cancer related fatigue. Fatigue is a very common side effect of cancer treatment and has been reported to affect approximately 70% of all patients' currently on or post treatment (Lucia et al., 2003; Shapiro et al., 2001). As fatigue grows more severe or starts to negatively impact the overall physical activity of the patient, physical inactivity begins to take hold. Skeletal muscle atrophy, reduced CRF, physical inactivity and age related physiologic declines all exacerbate the decline in quality of life and physical function of cancer patients. These, along with the impact each form of cancer treatment has directly on physical and physiological functioning, leads to an even greater functional decline in this population. Jones et al. (2010) observed that VO_2 peak in cancer patients consistently is 30% lower than matched sedentary individuals with no history of cancer. The exact cause of the poor VO_2 peak is unclear but likely the result of normal age related physical decline, direct insult from treatment and indirect causes resulting from treatment such as reduced physical activity levels (Courneya et al., 2003; DeBacker et al., 2007; Jones et al., 2010). Reduced physical activity in even healthy adults leads to muscle atrophy and a loss of CRF, both of which have direct influences on the oxygen cascade.

The oxygen cascade refers to the volume of oxygen (VO_2) consumed through respiration from environmental air, its transport through the systemic vasculature and subsequent uptake at skeletal muscle that contributes to overall cardiorespiratory fitness. As either consumption or uptake declines from direct impact of treatment or deconditioning, the individuals VO_2 decreases, elevating the risk of mortality. Certain chemotherapy agents, such as anthracyclines, can cause direct loss of compliance of cardiac tissue reducing left ventricular ejection fraction (LVEF) (Shapiro et al., 2001; Wonders et al., 2008). Reduced LVEF subsequently lowers the ability to supply adequate blood volume to skeletal muscle thereby reducing oxygen delivery. Heart rate and respiration therefore need to increase to keep up with oxygen demand causing the individuals cardiorespiratory system to become overworked quite possibly leading to increased fatigue (Dimeo 2001). Thus the oxygen cascade is further reduced in a vicious cycle.

Section 4: Summary of Exercise Oncology Literature

The field of exercise oncology is growing at an exponential pace. This may be due to the growing number of cancer survivor's worldwide, increased survival rates due to better treatments and earlier diagnosis, and possibly a general shift in the attitude of oncologists to avoid inactivity during cancer. The past decade has seen a large number of exercise oncology studies compared to the previous two decades.

A systematic review conducted by Jones, Pituskin and Battaglini (2012) identified 56 exercise oncology studies from 1980 forward, in which efficacy outcomes for cardiorespiratory fitness were measured objectively and that did not include assessment of exercise in combination with other interventions. The researchers found that after the year 2000 to date, 51 studies fit the inclusion criteria, compared with only 5 between 1980 and 2000. 91% of the qualified studies had been performed after the year 2000. The review also showed that 41% of the qualified studies examined the breast cancer population only and that 96% of the studies involved patients with curative disease compared to only 4% palliative. Furthermore, the review found that approximately 73% of the interventions were conducted in non-clinical settings, and nearly half of those did not include supervision. The outcome of this review confirms earlier reports that exercise seems to be safe with relatively few adverse events occurring within the cancer survivor population during exercise testing and interventions. Further, this review found that among the qualified studies the average measured VO_{2peak} improved 2.3 ml/kg/min and the average estimated VO_{2peak} improved 3.4 ml/kg/min. Although each of these increases was significant, they were still lower than the average 15% improvement in VO_{2peak} among non-cancer clinical populations (Jones et al., 2012). Why is this so? Could it be that current prescription methods in the cancer survivor population are inadequate to sufficiently stimulate the cardiovascular system for improvement? This study begins to answer that question.

This provides some insight into the necessity of developing accurate and valid exercise testing protocols in the cancer survivor population. Of these, how many conducted identical VO_{2peak} exercise testing? The answer to this question is beyond the scope of this study, but again confirms the reason for developing reliable and accurate exercise testing protocols that can be used repeatedly among the cancer survivor population for consistency both within and between studies.

The American College of Sports Medicine (ACSM) first developed exercise guidelines for cancer survivors in 2010 (Schmitz et al., 2010). The research group lead by Schmitz reviewed in depth the current literature and concluded with recommendations both generally and cancer-site specific for cancer patients such as breast, prostate and colon. In general, the recommendations were to ‘avoid inactivity’ and strive for the US Department of Health and Human Services (DHHS) Physical Activity Guidelines for Americans which are 150 min/week of moderate intensity physical activity or 75 min/week of vigorous physical activity. Blanchard et al. (2008) found that nearly 70% of cancer patients report not meeting these guidelines prior to a cancer diagnosis.

The review covered six of the most commonly studied cancer sites, but for the purposes of this paper, only the data for breast cancer is presented. Due to the quantity of literature regarding specifically breast cancer studies, the authors had seven stringent criteria with which to include previous studies. After combing through the literature, 54 breast cancer intervention studies were selected as eligible. Of these 54 studies, ‘all surmised that exercise was safe' before and during treatment for breast cancer. Only 28 reported adverse events and the events were 'rare, mild and expected on the basis of the activity prescribed' such as plantar fasciitis from walking. One particular note the authors make is that 25% of participants in a home-based exercise intervention for shoulder rehabilitation had to discontinue due to symptoms or swelling. The recommendations conclude that exercise is both safe and feasible for breast cancer patients during and after primary treatment.

A total of 22 studies that assessed aerobic fitness were identified as eligible for the review. All but two of these found statistically significant improvements in aerobic fitness and as we know, higher cardiorespiratory fitness is associated with reduced all-cause and cancer mortality (Gulati et al., 2003; Holmes et al., 2005; Myers et al., 2002; Peel et al, 2009; Sawada et al., 2003). Physical function was also measured in six randomized controlled trials using exercise as the intervention and all but two observed a statistically significant positive effect.

The review concludes that although there are specific risks associated with exercise for cancer survivors, there is consistent evidence that exercise during and after cancer treatment is safe (Schmitz et al., 2010).

A meta-analysis performed by Jones et al. (2011) reviewed numerous studies with the intention of examining the effect of exercise training on peak oxygen consumption in cancer patients. This meta-analysis however only accepted randomized controlled trials that contained supervised exercise training and that used a cardiopulmonary exercise test (CPET) with gas exchange analysis to assess cardiorespiratory fitness. The results returned six eligible studies involving a total of 571 adult cancer patients (exercise, n=344; usual care, n=227). The pooled data indicate that exercise training significantly improved VO_{2peak} approximately 2.90 ml/kg/min however again this is lower than the average increases seen with apparently healthy adults undergoing similar training volumes. The analysis concluded that there is no higher incidence of adverse events with exercise training, although safety was not rigorously monitored or reported during the reviewed studies.

Jones et al. (2011, 2012) and Schmitz et al. (2010) have concluded through their reviews that exercise is feasible and seems to be safe for cancer survivors; it can improve aerobic fitness with minimal adverse events and will generally improve physical function and quality of life in this population. The field of exercise oncology will continue to grow to include less studied cancer types, studies examining specific exercise responses, and as the results from larger prospective studies continue to mount, the accuracy of exercise prescriptions will improve in this population.

Section 5: The Importance of Cardiorespiratory Fitness on All-Cause and Cancer Mortality

Aerobic fitness is the number one parameter used to identify fitness level and all cause mortality among adults. Greater maximal VO_2 is known to be associated with reduced risk of all cause mortality in both men and women (Gulati et al., 2003; Myers et al., 2002). Research groups found significant reductions in mortality for patients with exercise capacities above 5 Metabolic Equivalents (METS). Gulati's group found a 17% reduction in mortality for each 1-MET increase in exercise capacity. Myers' group found similar outcomes in that each 1-MET increase contributed an additional 12% reduction in mortality. Peel et al. (2009) found an inverse relationship between cardiorespiratory fitness and dying from breast cancer. Women with moderate fitness levels had a 33% lower risk of dying from the disease and women with the highest VO_2's had a 55% lower mortality risk. Sawada et al. (2003) found groups with the highest cardiorespiratory fitness had a 59% lower risk of cancer mortality compared to those with the lowest cardiorespiratory fitness. Cancer survivors may have a greater risk of declining aerobic fitness due to the negative consequences cancer treatment can elicit. Declines in physical function can manifest at the first treatment and continue years into recovery and can be markedly greater without exercise intervention. Exercise has been shown to mitigate many of the side effects seen with cancer treatment (Burnham et al., 2002; Courneya et al., 2003; Daley et al., 2007; Herrero et al., 2006; Ingram et al., 2007). Cancer rehabilitation programs and certified cancer exercise specialists are growing in number to deliver these exercise interventions, but standardized testing must be implemented to provide the most beneficial exercise prescription possible.

Section 6: Oncology Exercise Testing

The current literature regarding physical activity and cancer is growing. However the literature concerning exercise testing and cancer is sparse. Jones et al., (2008) contributed a systematic review of the literature concerning several types of exercise testing including submaximal and maximal, sample characteristics, end points and adverse event reporting. They concluded the current literature is so broad in scope and methods that standardization among researchers is essential. Intervention studies often used set-workload treadmill protocols, where most cardiopulmonary exercise testing (CPET) used a cycle ergometer and set-workloads. Jones et al. (2008) reported that most studies did maximal exercise testing and only 13 of 90 studies used age-predicted submaximal exercise testing. Most CPET and intervention studies reported peak VO_2 while others reported submaximal training parameters. The research in this area has grown exponentially in the past decade but is far from developing standardized, safe guidelines for exercise testing and prescription. Due to the heterogeneity of the research involving exercise testing and cancer survivors, it is difficult to provide detailed guidelines for this population, thus the need to increase accessibility and standardize testing among cancer survivors.

Disseminating the research reveals another strong reason for validating submaximal exercise testing standardization. Many maximal VO_2 tests involving cancer patients end prematurely due to low self-motivation and/or poor physical function of the subjects. Peak testing requires a level of physical activity above and beyond what most cancer patients regularly perform. As previously mentioned nearly 70% of cancer patients reported not meeting the ACSM guidelines for physical activity prior to a cancer diagnosis. These patients do not have the physical capability to perform this level of intensive work nor do they feel comfortable doing it.

Myelosuppression is a major concern from cancer treatment. Reduced hemoglobin levels cause anemia and possibly add to the fatigue many patients experience. Considering 70% of patients experience fatigue and may have chemotherapy induced anemia, pushing above and beyond daily activity is a foreign concept to them. It is quite likely they will be unable to give maximum effort, possibly another reason for reporting peak instead of maximal outcomes in the literature.

Despite the quantity of literature investigating exercise tolerance in cancer patients, only a few studies have directly examined the correlation between submaximal and maximal exercise testing in cancer patients (De Backer et al., 2007; Jones et al., 2006; May et al., 2010). May et al. (2010) found that submaximal testing did provide a reasonable alternative to exhaustive maximal testing in evaluating exercise intervention for a group of 147 cancer survivors. The mode of testing was on a cycle ergometer so the results cannot be compared to treadmill testing. However, May's group found that only in the group of survivors whose HR peak reached 140 bpm or higher was moderately correlated (r=-0.51) with peak testing. The group who did not get to 140 bpm was only weakly correlated with peak outcomes. The take home point is that submaximal exercise testing provides a safe, inexpensive and generally well accepted form of exercise intervention evaluation for this population.

De Backer's group found that cycle ergometer submaximal exercise testing was moderately (r=0.71) correlated with maximal exercise testing, but they were more interested in a steep ramp test which proved to be slightly higher correlated with maximal exercise testing. A major limitation of this study was the lack of designated termination criteria for the maximal test. The researchers termed the test maximal when the subject reached exhaustion or could no longer maintain a predetermined cadence. This reiterates the point that maximal exercise tests are difficult to reliably obtain in this population. They are more often peak tests. Both May and De Backer agree that submaximal exercise testing needs to be validated for a variety of reasons. Submaximal tests are inexpensive, lower in risk to the subject, well received by cancer survivors and can be used to evaluate exercise intervention whereas maximal tests are used as more of a diagnostic tool in determining pulmonary or cardiac limitations requiring electrocardiogram (ECG) and physician presence.

In other clinical populations such as cardiac and pulmonary rehabilitation, submaximal exercise testing has shown moderate to high correlations with maximal exercise capacity (Cahalin et al., 1996; Guyatt et al., 1985; Riley et al., 1992; Thompson et al., 2010). This is promising considering the similar insults many cancer patients experience through treatment. Chemotherapy and radiation can cause cardiac and pulmonary implications as mentioned earlier. Either of these adverse impacts can directly influence dysfunction of the oxygen cascade leading to further CRF decline.

Summary

Cancer treatment poses a number of challenges to the cancer patient. Without experienced exercise specialists and cancer rehabilitation programs, exercise can pose quite a psychological burden to the patient. Cancer patients clearly have many more obstacles to overcome to initiate an exercise program than healthy adults, but the benefits may be of greater magnitude to this population. Barriers need to be removed to allow for quick exercise intervention among this group. Maximal testing poses a greater risk in already diseased populations, makes testing difficult in non-clinical settings and may cause psychological distress for the cancer patient. Although submaximal testing may over-predict VO_2 max in apparently healthy populations, it may have benefit for diseased populations unable to give their best effort during an exercise test (De Backer et al., 2007; May et al., 2010; Noonan et al., 2000). Submaximal testing can be performed in a non-clinical setting, does not require direct physician presence, and may give the patient more confidence in performing the test. Being able to accurately predict maximum VO_2 using submaximal protocols will open the door for more patients to participate in various exercise programs. By creating evidence based standards from which to draw exercise prescriptions, the utilization of exercise in cancer rehabilitation will be safer and provide more reliable parameters leading to improved fitness and reduced cancer recurrence risk.

Chapter III

Methodology

Subjects

Nine subjects in the breast cancer survivor group included women who were diagnosed with early stage (I-III) breast cancer, have completed all primary cancer treatment including surgery, radiation and chemotherapy within the past 3 to 6 months, and who were relatively sedentary (i.e., have not participated in regular exercise within the past year). Subjects in the breast cancer survivor group were recruited from the North Carolina Cancer Hospital on the campus of the University of North Carolina at Chapel Hill (UNC-CH). Subjects in the control group included nine women who did not have a history of cancer diagnosis or treatment, were relatively sedentary (i.e., had not participated in regular organized physical activity within the past year), and were healthy enough to participate in aerobic exercise. All attempts were made to match the control group with subjects in the breast cancer survivor group on both age and physical activity level. Subjects in the control were recruited from the faculty, staff, and student populations at UNC-Chapel Hill, as well as from the surrounding areas of the Triangle Region of North Carolina.

The inclusion criteria for participation in the breast cancer survivor group included: A confirmed diagnosis of early stage (I-III) invasive breast cancer, must have completed all major cancer treatments at least three months prior to participation in the study, patients receiving adjuvant hormonal therapy or adjuvant trastuzumab were eligible, no presence of metastatic disease, female between the ages of 40 and 70 years of age, not involved in regular organized physical activity for at least 1 year prior to enrollment. The inclusion criteria for participation in the control group included: being a female between the ages of 40 and 70 years of age, no history of cancer diagnosis or treatment, did not regularly use anti-inflammatory medications, were either post-menopausal or had not experienced a menstrual cycle for approximately one year and not involved in regular organized physical activity for at least one year prior to enrollment.

All subjects were required to complete a comprehensive medical questionnaire, a physical screening by either a physician or certified professional, and a 12-lead resting electrocardiogram (ECG).

Instrumentation

A medical history questionnaire was used to record information about the subjects medical and cancer history including treatment type, physical activity level over the past year, age, race, and menopausal status. A portable stadiometer (Perspective Enterprises, Portage, MI) was used to measure height to the nearest 0.01 cm. A mechanical scale (Detecto, Webb City, MO) was used to measure body mass to the nearest 0.1 kg. A GE Case Cardiosoft V. 6.6 ECG diagnostic system (General Electric, Palatine, IL) was used to assess cardiac function during rest and exercise. A Littman Stethoscope (3M, St. Paul, MN) was used to auscultate the heart and lungs during the physical screening, as well as for measurement of blood pressure during rest and exercise. A sphygmomanometer (American Diagnostics Corporation, Hauppage, NY) was used to measure blood pressure during rest and exercise. A Lode electronically-braked cycle ergometer (Lode, Gronigen, The Netherlands) was used as the mode for the VO_{2peak} test. Respiratory gas analysis and oxygen uptake (VO_2) was measured using a Parvo Medics TrueMax 2400 Metabolic System (Parvo Medics, Salt Lake City, UT). A Polar telemetry system (Polar Electro Inc., Lake Success, NY) was used to measure heart rate. The rating of perceived exertion (RPE) was measured using Borg's 6-20 Rate of Perceived Exertion (RPE) Scale.

Research Design Overview

This retrospective study used data collected from previous study IRB #11-1405 conducted by Mrs. Elizatbeth Evans. Subjects were divided into two groups: a breast cancer survivor group and a control group which consisted of women with no history of cancer. Each subject visited the lab a total of three times (Orientation/familiarization, Visit 1 (VO_{2max} test) and Visit 2 (collection of 24hr post exercise blood sample), however for this study, the procedures and data analyzed were collected during only the laboratory visit 1 (VO_{2max}). All laboratory visits occurred in the Integrative Exercise Oncology Research Laboratory (IEORL) in the department of Exercise and Sport Science at UNC-Chapel Hill. Approval from the Institutional Review Boards in the Department of Exercise and Sport Science, Lineberger Comprehensive Cancer Center, and the School of Medicine at UNC-CH were obtained before subject recruitment and testing.

General Procedures

Orientation/ Familiarization Session

All subjects underwent an orientation and familiarization session of the study protocol which was administered a few days prior to visit 1. Once all questions had been answered, each subject signed an informed consent. Each subject also completed a comprehensive medical and cancer history questionnaire, underwent a 12-lead ECG, and a physical examination performed by a physician or a member of the research team who was certified to perform physical exams. Further screening for exclusion was based on the criteria set forth by the ACSM as contraindications to exercise testing (Thompson et al., 2010).

Upon clearance for participation in the study, several demographics were collected such as race, height, weight and age. Height and weight were collected using equipment in the IEORL. The comprehensive medical questionnaire was used to collect age, race, menopausal status, physical activity level and cancer treatment type.

During the orientation subjects received in depth information about all the study protocols and participated in a familiarization of the study which included cycling with all the metabolic equipment set up for approximately 10 minutes. During the familiarization all adjustments to the equipment were recorded and reproduced during visit 1, the VO_{2max} test day. This familiarization was conducted to get subjects used to the equipment and alleviate any anxiety or discomfort of being exposed to the equipment, which could influence the VO_{2max} test. During the orientation/familiarization visit to the laboratory, subjects were also provided with pre-assessment guidelines that included: to refrain from eating at least 2 hours prior to testing, refrain from exercise and caffeine at least 12 hours prior, refrain from alcohol use at least 48 hours prior and to maintain adequate hydration, and were asked to follow those guidelines before reporting to the laboratory for the VO_{2max} testing (visit 1). During laboratory visit 1, each subject performed a maximal oxygen consumption cycle ergometer test from which VO_{2max} was obtained.

Laboratory Visit 1: VO_{2max} Test

During visit 1 to the IEORL, subjects received further explanation of the VO_{2max} test protocol and were given the opportunity to ask any questions they might have at that time. After all questions were answered, all subjects underwent a VO_{2max} test. Maximal oxygen uptake (VO_{2max}) was determined using the Astrand Cycle Ergometer Maximal Test Protocol (Heyward, 2002). The VO_{2max} test was performed on an electronically-braked cycle ergometer. Subjects began by sitting quietly on the cycle ergometer for three minutes while resting metabolic data were collected. The first stage of the test was initiated and required the subject to cycle at 50 Watts for three minutes. The subjects were allowed to pedal at a comfortable cadence, as the resistance on the cycle-ergometer adjusted to maintain the set workload for each stage. At the end of the first stage, the workload was then increased by 25 Watts every three minutes until volitional fatigue. Heart rate, rating of perceived exertion (RPE), 12-lead ECG monitoring, and expired gas collection were performed throughout the test. Heart rate and RPE were recorded at the end of each minute. The subjects VO_{2max} was determined as the highest VO_2 recorded during the last stage of the protocol and the corresponding workload was also recorded as the subject's peak workload. A cool down period was initiated upon completion of the

VO_{2max} test and consisted of cycling at a very low workload (<20 Watts), while ECG and blood pressure were monitored continuously until they had returned to near baseline levels.

For the estimation of VO_{2max}, data obtained during the VO_{2max} test was used. The Karvonen Formula for determining target heart rate was used to find 85% of heart rate reserve (HRR) and was calculated using the following equation: 85% HRR=(((220-age) – RHR)*.85)+RHR. This 85% HRR calculation signals what would pertain to test termination during a submaximal exercise test and was used for the estimation of VO_{2max} from the VO_{2max} test. Estimated VO_{2max} was then calculated after completion of the VO_{2max} test using the last two consecutive stages in which steady state was reached with heart rates between 110 and 150 bpm. The estimated VO_{2max} was calculated using the American College of Sports Medicine equation as follows:

$$VO_{2max} = (2^{nd}\ VO_2) + [((2^{nd}\ VO_2 - 1^{st}\ VO_2) / (2^{nd}\ HR - 1^{st}\ HR)) \mathbf{x} (HRmax - 2^{nd}\ HR)].$$

Where:

1^{st} VO_2 = The VO_2 measurement obtained in the second to last stage of the test in which a steady-state HR was reached within 110 to 150 bpm.

2^{nd} VO_2 = The VO_2 measurement obtained in the last stage of the test in which a steady-state HR was reached within 110 to 150 bpm.

1^{st} HR = The HR obtained during the second to last stage of the test in which a steady-state HR was reached within 110 to 150 bpm.

2^{nd} HR = The HR obtained during the last stage of the test in which a steady-state HR was reached within 110 to 150 bpm. This data point should be close to the previously calculated 85% HRR as possible.

HRmax = The theoretical maximum of a person's heart rate. It is calculated by using the equation: 220-age = x.

Statistical Analysis

All statistical analyses were performed using SPSS software version 20.0 for Windows. Statistical significance was set a priori at an alpha level of 0.05. Descriptive statistics, including means and standard deviations were calculated for demographic data and performance scores.

Dependent samples t-tests were used to test for comparisons between the dependent variables of estimated and directly measured VO_{2max}. Dependent samples t-tests were also used to compare the estimated and measured wattages of 40%, 60%, 70% and 80% of VO_{2max}. The variables that were used to represent the wattage corresponding to 40%, 60%, 70%, and 80% of VO_{2max} were calculated for both groups using a simple linear regression model (y = mx + B) shown in Figure 2.

Exploratory analyses were conducted using the data of the control subjects. Specifically comparing estimated and measured VO_2 outcomes with the breast cancer survivor group as well as comparing each of the training thresholds between groups.

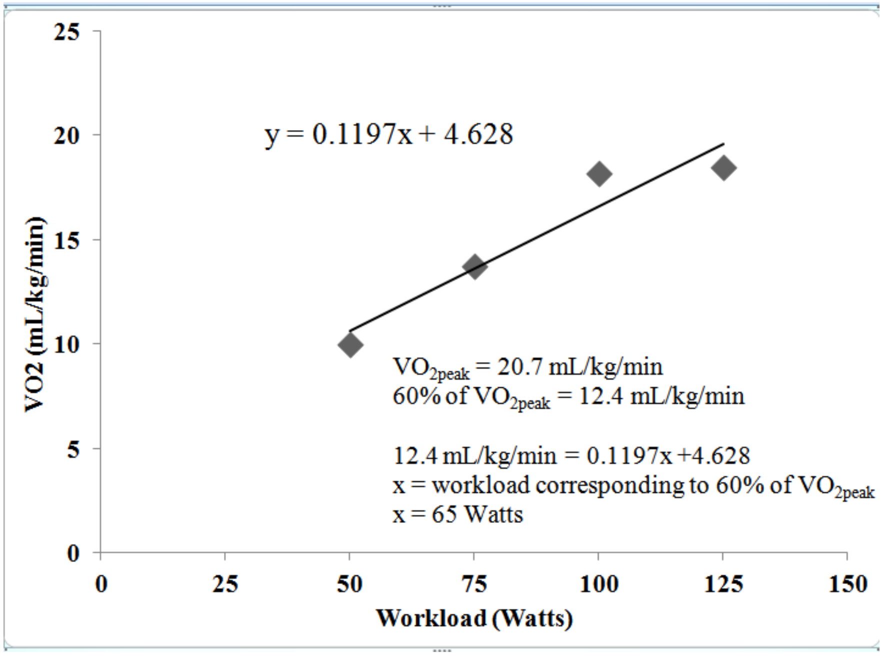

Figure 1: Example regression model for determining workload corresponding to 60% of VO_{2peak}.

Chapter IV

Results

The primary purpose of this study was to compare the results of maximal oxygen uptake (VO_{2max}) between estimated and directly measured VO_{2max} values obtained during maximal cycle ergometer testing in breast cancer survivors. A secondary purpose was to compare training thresholds devised from estimated and direct measurements of VO_{2max}, using watts, at 40%, 60%, 70%, and 80% of maximal oxygen uptake. All data were entered into an electronic database for analysis. All data were analyzed on SPSS version 20.0 for Windows, a statistical software program. An alpha level of 0.05 was used for all statistical procedures, and descriptive statistics were presented in the form of means and standard deviations (SD). No statistical adjustments for performing multiple t-tests were made for the analyses of the data. Confidence intervals of the means are also provided, as well as an analysis of effect size for each statistical test. The effect size of each t-test analysis was computed via the Cohen's *d* method (small effect size, d = .2 - .5: medium effect size, d = .5 - .8: large effect size, d > .8). (Cohen, 1988). It should be noted that Cohen's *d* is a method originally formulated for physiological research but has been used extensively within exercise science research to inform of physiological data as well.

Subjects

This study included a total of 18 subjects, with 9 subjects in the breast cancer survivor group and 9 subjects in the control group. Physical characteristics for all subjects are presented in Table 2. Descriptive statistics are presented as mean ± standard deviation (SD).

Table 2. Subject physical characteristics (mean ± SD)

Characteristic	Breast Cancer Survivor Group (n=9)	Control Group (n=9)
Age (years)	50 ± 6*	59 ± 5*
Height (cm)	164.7 ± 5.8	163.8 ± 5.9
Weight (kg)	76.9 ± 12.6	77.7 ± 13.3

*$p < 0.05$ for comparing age between groups

All subjects in the breast cancer survivor group received surgery, chemotherapy and radiation therapy as part of their major treatment and completed those treatments within 3 to 6 months prior to enrollment in the study. The breast cancer survivor group treatment characteristics are presented in Table 3.

Table 3. Breast Cancer Survivors Treatment Characteristics

Treatment Characteristic	Number of subjects
Surgery	9
Mastectomy	4
Lumpectomy	5
*ACT	6
ACT + Carboplatin	1
Carboplatin + Taxotere	2
Adjuvant Hormonal Therapy	6
Tamoxifen	5
Femara	1
Adjuvant Trastuzumab	2

*Combination of Adriamycin, Cytoxan and Taxol; Two subjects received additional medications concerning their cancer treatments, with one receiving Lapatinib and the other one Bevacizumab.

Descriptive statistics for VO_2 and workload and training thresholds devised from direct and estimated VO_2 measurements for all subjects are presented in Table 4.

Table 4. Measured and estimated VO_2 and training thresholds (mean ± SD).

	Breast Cancer Survivor Group (BCS)	Control Group (CNT)
Measured VO_{2peak} (ml/kg/min)	18.13 ± 2.7*	18.51 ± 5.1
Estimated VO_{2max} (ml/kg/min)	16.36 ± 3.6*	18.80 ± 6.1
Measured 40% Watts	25 ± 33	37 ± 43
Estimated 40% Watts	18 ± 31	38 ± 41
Measured 60% Watts	57 ± 23	68 ± 35
Estimated 60% Watts	48 ± 18	70 ± 31
Measured 70% Watts	73 ± 19#	84 ± 32
Estimated 70% Watts	63 ± 12#^	85 ± 27^
Measured 80% Watts	90 ± 17	99 ± 30
Estimated 80% Watts	77 ± 9^	101 ± 23^

*Significant difference between MVO_{2peak} and EVO_{2max} in BCS group ($p<0.05$).
#Significant difference between M70% and E70% in BCS group ($p<0.05$).
^Significant difference between BCS and CNT groups at both E70% and E80% ($p<0.05$).

Hypothesis 1, there will be a significantly higher maximal oxygen uptake (VO_{2max}) estimated from a submaximal oxygen uptake exercise evaluation when compared with the directly measured maximal oxygen uptake test in a group of breast cancer survivors, was measured using a dependent samples t-test. The mean predicted and measured VO_{2max} values were used in the analysis. Significant differences were found between the directly measured and estimated VO_2 values in breast cancer survivors (18.1± 2.7 ml/kg/min, 16.3 ± 3.6 ml/kg/min, respectively, p=0.01, Effect size (Cohen's d)

=0.56, and 95% of CI of mean lower = .25, upper = 3.30). No significant differences were observed between direct and estimated measurements in the control group.

Hypothesis 2, there will be a significant difference in training thresholds expressed in watts at 40%, 60%, 70%, and 80% of VO_{2max} devised from the directly measured and estimated maximal oxygen uptake testing evaluations, with higher wattage resulting at all percentages of VO_{2max} from the estimated maximal oxygen uptake evaluation versus directly measured maximal oxygen uptake values, was measured using 4 dependent samples t-tests. The mean wattage values at each percentage of VO_{2max} were used in the analysis. The results of the analyses of hypothesis 2 are presented in Table 5.

Table 5. Results of the Analyses of Hypothesis 2

Training Thresholds (Watts at % VO_{2max})	Std. Error Mean	95% Confidence Interval of the Difference		Effect Size (Cohen's d)	T	df	Sig.
		Lower	Upper				
40% VO_{2max}	3.17	-2.553	12.108	0.15	1.50	8	0.08
60% VO_{2max}	4.72	-3.558	18.224	0.37	1.55	8	0.07
70% VO_{2max}	5.15	-1.003	22.781	0.70	2.11	8	0.03
80% VO_{2max}	6.36	-4.999	24.332	0.67	1.52	8	0.08

* Significant difference between directly measured and estimated training thresholds at 70% of VO_{2max}.

No significant differences were found between the directly measured and estimated training threshold in watts at 40%, 60%, and 80% of VO_{2max} in the breast cancer survivor group analyzed in the study. At 70% of VO_{2max} significant difference in the determination of training threshold expressed in watts devised from directly measured vs. estimated VO_{2max} was observed (73.4 ± 19 Watts, 62.5 ± 12 Watts, $p=0.03$ respectively).

No significant differences were found between estimated and directly measured training thresholds devised from watts within the control group ($p>0.05$ within each training threshold).

Chapter V

Discussion

Review

A systematic review conducted by Jones et al., (2008) revealed that most studies in the field of exercise oncology conducted maximal exercise testing, as well as age-predicted submaximal exercise testing, for the assessment of cardiopulmonary function. The review further identifies the different methods, termination endpoints, reporting of outcomes and differences in testing used in exercise oncology research. The final conclusion from Jones's systematic review is that the current guidelines for oncology exercise testing vary too greatly between studies to make many evidence-based recommendations at this time other than maximal exercise testing for the assessment of cardiorespiratory function is feasible and safe to perform in oncology patients. Many questions concerning exercise testing in cancer survivors still exist. For example; how do the insults that occur from treatment affect the outcome of oxygen uptake capacity and its influence on the design of exercise prescriptions in oncology patients? Are the current prescription techniques accurately stimulating an optimum training response that maximizes improvements in maximal oxygen uptake in oncology patients? Many cancer patients have difficulty in performing any level of exercise due to the cancer treatment related side effects, fatigue and other physiological alterations that occur such as reduced oxygen carrying capacity and decreased muscular strength (Irwin 2012). Asking them to perform a maximal exercise test may not yield the best results due to their reduced cardiopulmonary, muscular, or both, capacities in performing such tests. A possible alternative may be performing a submaximal exercise test where VO_{2max} is estimated. Cancer patients may be more prone and able to perform such tests, require less equipment, is less time consuming, does not require medical personnel on site, and it is more applicable to gyms and clinics that may not possesses the capability to run maximal cardiopulmonary exercise tests.

Current research in the field of oncology exercise testing is quite minimal. Only a few studies have been conducted and none, to our knowledge, directly examined the difference between submaximal and maximal aerobic exercise testing in cancer survivors with the exact same protocol. Previous studies have compared different cycle ergometer maximal exercise testing protocols from the one used in the current study (DeBacker et al., 2007; May et al., 2010). The results of those studies found that submaximal exercise testing was weakly to moderately correlated with maximal exercise testing.

Therefore the purpose of this study was to examine whether submaximal and maximal cardiopulmonary testing protocols elicit similar results in breast cancer survivors who suffer physiological alterations as a result of having and receiving treatment for cancer. More specifically, this study compared the results of maximal oxygen uptake (VO_{2max}) between estimated and directly measured VO_{2max} values obtained during maximal cycle ergometer testing in breast cancer survivors. A secondary purpose was to compare training thresholds devised from estimated and direct measurements of VO_{2max}, measured in watts, at 40%, 60%, 70%, and 80% of maximal oxygen uptake.

Aerobic capacity outcomes in breast cancer survivors

The current study found that estimated VO_{2max} was significantly lower than measured VO_{2peak} in a group of post-treated breast cancer survivors. The results were somewhat surprising considering that in healthy, non-clinical population's submaximal exercise testing typically overestimates VO_{2max} (Thompson, 2010). Earlier studies using cancer survivors have found weak to moderate correlation between submaximal and maximal cycle ergometer testing however those studies used different exercise protocols than the current study and were designed to assess an intervention outcome (DeBacker et al., 2007; May et al., 2010). In the study by May et al., (2010) there was a caveat that the subject needed to obtain a heart rate of at least 140 bpm in order to be included in the correlational analyses between submaximal and maximal exercise testing. May's group used the 140 bpm threshold because in healthy subjects Astrand and Rodahl recommended a heart rate up to or above 140 bpm to generate the best estimate of aerobic capacity (May et al., 2010). Psychological and emotional influences such as test anxiety, fear, or excitement, may cause a marked elevation in submaximal heart rate without either VO_{2peak} or performance being affected (Burnham et al., 2002). The initial theory was that submaximal testing would overestimate VO_{2max} even more so in this population compared with healthy controls. Common functional barriers found in the breast cancer population who have received treatment for cancer include reduced physical fitness, reduced cardiopulmonary capacity and muscular weakness would contribute to the inability of the survivors to reach true maximal exertion, defined previously, on a maximal aerobic capacity exercise test (Courneya et al., 2003, 2011; Irwin 2012). The early test-termination that would result, thus determined as VO_{2peak}, would correspond with lower than maximal heart rate responses giving the impression the individual is more physically fit thus inflating the estimated VO_{2max} outcomes. Another possible explanation for the underestimation of VO_{2max} in the breast cancer survivors in this study could be attributed to large heart rate variations in response to exercise observed during testing. In this population we have seen large day-to-day heart rate variations and considerable elevated resting heart rates when compared to age-matched healthy, sedentary control subjects, likely due to the cancer treatments and reduced fitness level. Cardiotoxic chemotherapy agents, reduced physical activity, muscle atrophy and sarcopenia would all play a role in reducing aerobic energy system utilization or interference with the normal oxygen cascade that is directly responsible for determining aerobic capacity outcomes (Irwin 2012; Jones et al., 2011; Shapiro et al., 2001). At some point during their treatment, they were likely exposed to an agent that has direct cardiac side effects such as reducing ejection fraction, or indirectly through reduced physical activity leading to further functional decline.

The nature of the mode and test protocol in this experiment could have also implicated the surprising results of this study. As fitness level and muscular strength and endurance decline through the cancer experience, the ability to power the pedals on a cycle ergometer will inevitably decline as well. Since cycle ergometry is a more localized mode of exercise, using primarily the lower limbs, a quicker localized muscular fatigue could contribute to a premature termination of the test by some of the breast cancer survivors during the study. This limitation would reduce the ability of the subjects to perform maximally on a cycle ergometer test, which appeared to be the case in some of the tests performed during the study. Quite a few of the breast cancer survivors during the study terminated their cardiopulmonary tests because of their inability to pedal at a higher wattage (lack of strength to power the pedals), and not because their heart rates or oxygen uptake had reached their potential maximal capacities. This is all speculation at this time, however, due to the fact that the increase in heart rate observed from the initial stage of the test to the subsequent stages of the protocol appeared to be much greater in the BCS group when compared to the control group; a factor that could influence the regression model used for the estimation of VO_{2max}. Therefore, it is recommended that this study be reproduced using treadmill protocols to see if the localized nature of the cycler ergometer test may have influenced the results of this current study. Despite the localized fatigue limitation that may have occurred using cycle ergometry, this mode of testing is still preferred because of the balance and peripheral neuropathy that is common among cancer patients (Irwin 2012). Cycle ergometry provides a reasonably safe alternative in testing patients who may experience the aforementioned side effects.

Another factor that was observed during the current study that may have influenced the results was that some breast cancer survivors experienced hot flashes during testing, which could have altered their heart rate response during the test and consequently the estimation of VO_{2max}, since heart rate is a major variable in the prediction of the maximal oxygen uptake value. Since hot flashes are a common side-effect from cancer treatments, this increase in temperature during test can alter heart rate response significantly, which could partly explain some of the surprising elevated jumps in heart rate observed for some subjects when moving through some stages of the maximal test. For these subjects, re-scheduling of the test should be considered for future trials comparing the results of maximal oxygen uptake evaluation using directly measured and estimated testing protocols.

When the study was initially designed the criteria for termination of the submaximal exercise test was 85% of heart rate reserve (HRR), Due to the nature of this retrospective study, and after evaluating the data obtained for analyses, it was noted that several subjects in the BCS group did not reach 85% HRR during the maximal oxygen uptake test, thus the VO_{2max} estimations were calculated using an exercise termination of 75% HRR. Likewise, four of the sedentary controls were unable to reach even 75% HRR which became a major limitation of this study. This modification itself points to the possibility of a larger problem within the cancer population, regarding the precision of exercise prescriptions devised from cardiopulmonary exercise testing protocols, posing interesting questions such as: are the current testing techniques, which are mostly based on healthy adults, appropriate for cancer patients? Do the current length of stages to reach steady-state heart rate (HR) and the workload increases allow those with heart rate variations and physiological alterations affecting the oxygen cascade allow for a true steady-state HR to be reached? Many of the subjects in the study did not reach a steady-state HR on the last stage of the test used for the estimation of VO_{2max}, despite finishing the stage; also, as previously mentioned, the jump in HR was significantly greater than expected considering the relatively low 25 Watts increase between workloads. Longer stages or smaller increases in workload may be considered when designing specific cardiorespiratory exercise testing for cancer patients. The current study used 25 Watts increases between workloads and three minutes per stage. Using 15 Watts increases and allowing for 3 to 5 minute stage lengths might allow for steady-state HR to be reached and a better prediction of maximal oxygen uptake.

Another potential limitation that could have impacted the results of the study was the nature of the assessment of maximal oxygen uptake using a metabolic system. Many of the breast cancer survivors felt overwhelmed with the mask during the test. Even though a familiarization session was used to get subject used to the equipment, most of them felt that the mask made them feel too hot and they would rather have participated in the test without having to use it. Most likely, the combination of the effort along with the discomfort of using the mask could have also influenced the results.

The average VO_{2peak} found in the breast cancer group was 18.13 ml/kg/min which is considered very poor for healthy adult females 70 to 79 years old (Thompson et al., 2010). The greatest VO_{2peak} found in this group was 21.3 ml/kg/min and is still considered poor in the 70 to 79 age classification. The Modified Bruce Treadmill Exercise Test was developed for diagnosis of coronary risk patients whose aerobic capacity was severely diminished (Noonan et al., 2000). The same guidelines should correspond to cancer patients whose aerobic capacity is considered below average or worse. Currently, many studies and programs around the country use the Modified Bruce Treadmill Test, but unfortunately due to balance issues and peripheral neuropathy which are very common side effects of cancer treatment, not all patients can safely or fully perform a treadmill exercise test. Developing a standardized cycle ergometer protocol with longer stages and/or smaller increments in workload for the patients who are of lower physical function may prove more appropriate. Regardless of which method of exercise testing is used, the consideration for the standard error of measurement of any metabolic system should be realized. The metabolic system used in this study has a standard error of approximately +/- 2% which could influence the results of future testing where power is inadequate or differences in the means are just significant.

Despite numerous studies citing the safety of maximal exercise testing in cancer patients (Irwin 2012; Jones et al., 2006, 2008, 2012), there is still a psychological barrier many of these patients have in performing maximally during a test or during general exercise. As a professional who has worked with many cancer patients, I have observed that motivation to push past a certain limit is lacking in this population due to the fear of injury or other negative consequences. Not all patients respond this way and in fact many, whose cardiorespiratory fitness is above average, may be able to perform a true maximal exercise test.

The current study found four of the nine breast cancer subjects, and only three of the sedentary controls reached maximal termination criteria defined as: 1) A respiratory exchange ratio (RER) of >1.10, 2) A rating of perceived exertion (RPE) of ≥18, 3) Peak heart rate (HR) within 10 beats of age-estimated maximum, 4) A 150 ml/min or less rise in VO_2 with an increase in workload. Lactate reading was excluded from this list as it was not taken during the study. Because only four termination criteria points were set, in order to be termed a maximal test, at least three must have been reached. The four breast cancer subjects and three sedentary controls that reached maximum were also the only subjects who obtained at least 125 Watts during the cycle ergometer exercise test. This might suggest that a certain level of fitness may be needed to even consider performing a maximal test or it could point to a physiological difference between the two subsets (<125 Watts and >125 Watts) that was either present before the test or developed as a result of undergoing a different type of cancer treatment. Is it possible those who reached maximum did not undergo cardiotoxic therapy or was there another difference in type, length or combination of treatment that contributed to the better response to the maximal cardiopulmonary exercise test in the breast cancer group? A follow up study could analyze this question further.

In the control group no significant difference was found between estimated VO_{2max} and measured VO_{2peak} ($p=0.87$), however when the data for the subjects who did not reach 75% HRR is excluded (3/9), the remaining six data points found statistical significance and is nearly identical to the results of the breast cancer group where estimated VO_{2max} is significantly lower than measured VO_{2peak} ($p=0.03$). This again suggests that either a certain level of physical function is needed to obtain an accurate VO_{2max} using this particular protocol for this particular group of deconditioned subjects or that modifications to this protocol would allow for a more accurate aerobic capacity outcome, such as longer stages or smaller increases in workload between stages.

Using submaximal exercise testing to estimate VO_{2max} in early stage breast cancer survivors who had completed major cancer treatment between 3 and 6 months may not be the most appropriate method based on the results of this study. If estimated VO_{2max} is lower than actual VO_{2peak} and prescriptions are then developed using the estimated value, workloads will be under-represented, for example: 60% VO_{2max} might correspond to a lower actual workload of maybe 50% VO_{2peak}. This could possibly be one of the reasons for the less than 1 MET increases in aerobic capacity that are usually observed in cancer patients after aerobic training interventions of 12 to 16 weeks (Jones et al., 2012).

Aerobic training thresholds in breast cancer survivors

The secondary purpose of the study was to examine whether workloads expressed in watts as a percentage of measured VO_{2peak} were different from workloads at identical percentages calculated from estimated VO_{2max}. The wattage at 40%, 60%, and 80% were not significantly different between the estimated VO_{2max} and measured VO_{2peak} (p=0.08, 0.07, and 0.08, respectively); however significant difference was observed at the wattage devised from 70% estimated VO_{2peak} vs. measured VO_{2max} (p=0.03). It is quite possible that using a larger sample size would produce statistical significance among the other percentages. The trend toward significance and the small effect size of the analyses suggests that the analyses were underpowered when evaluating the differences in the determination of training thresholds at 40%, 60% and 80% of VO_{2max} where the standard deviations are even larger than the mean. However, at 70% of VO_{2max}, the moderate to high effect size (d=0.70), with smaller standard deviations, showed significantly different training thresholds. When further examining the data, and results of the analyses, besides the small sample size and large standard deviations at 40% and 60% of VO_{2max}, the heart rate response of the cancer patients during the first stages of the test, may also help explain the non-significant difference between the training thresholds devised using the results of the directly measured and estimated VO_{2max} values.

The raw data from this study show that during the first stage of each cycle ergometer test, the breast cancer survivors' heart rates remained relatively stable, however at the second and third stages when a load of 25 Watts was added for each stage, there was a large jump in heart rate for many of the subjects compared with the relatively small increase of 25 Watts when compared to the control group. This suggests that the workload increase was quite significant for the subjects and the relative intensity was such that the subjects did not have the lower limb strength to adjust to the new workload easily. These large jumps in heart rate, due to the lower limb strain, produce a sharp divergent point on the regression line where maximal exertion or fatigue will set in sooner, compared with oxygen uptake. The data also show that less than half of the subjects reached true maximal exertion and when the VO_2 data is evaluated, we notice that only two of the subjects who reached maximal exertion actually had a plateau in VO_2. This again suggests that the workloads used for this population either begin at too high of an intensity or the change in watts between stages is too great to allow for a comparable heart rate response compared with oxygen uptake. As the workload increases the subjects are unable to sustain the increased muscular demand due to reduced lower limb strength, a possible reduction in the oxygen cascade where oxygen uptake within the muscle is altered, test anxiety, and discomfort with the metabolic equipment on their face. A familiarization session was conducted to reduce the effects of test anxiety and discomfort, but an adjustment to the actual test protocol may help to eliminate the issue of reduced lower limb strength.

Not all breast cancer survivors respond the same way to an exercise test. Differential treatments, stage of cancer, previous physical activity levels, age, and body composition will vary between patients and thus will likely have an impact on the ability of the survivor to perform the exercise test.

Conclusions

The results of this study suggest that using a cycle ergometer testing protocol for the estimation of VO_{2max} in breast cancer survivors may underestimate maximal oxygen uptake, and therefore, training thresholds devised from submaximal tests should be evaluated with caution. Further, the administration of maximal oxygen uptake tests in this specific population utilizing cycle ergometry may be negatively influenced due to the localized lower limb muscular fatigue that is quite common among breast cancer survivors who have undergone treatment for cancer.

Recommendations for future research

Many of the subjects in this study were unable to reach 85% HRR. A lower submaximal termination endpoint may need to be used. Due to the inability of many subjects to reach the predetermined end point, it is possible that in the subjects mind there may be little to no difference between terminating the test at 85% HRR or maximal exertion. If the field of exercise oncology would like to continue utilizing cycle ergometer exercise testing for fitness classification or for the evaluation of interventions, modifications to the current submaximal testing procedures may need to be developed for breast cancer survivors, such as lowering the test termination criteria of HR threshold, or increasing length of stages, and/or decreasing the amount of change between stages to allow for a steady-state HR to be reached. These changes may also allow for more subjects to reach defined maximal exertion on cycle ergometer testing due to the ability to pedal for longer durations before lower limb fatigue sets in. As not all subjects reached

85% HRR, less than half of the subjects reached true max, as defined earlier, in this study.

Future studies should also evaluate a larger sample size and ensure the study is properly powered and to allow for perhaps examination of the stratification of the sample based on age, different cancer treatments patients underwent, and also the physical activity level prior to testing. All of these factors could influence the results of the maximal oxygen uptake evaluation in this population.

Comparing these results with similar findings using a treadmill exercise protocol would be another great recommendation. By utilizing a treadmill test for exploration between estimated and directly measured maximal oxygen uptake, we may find different results, due to walking being a more natural exercise, which might then suggest that unless the subject is a trained cyclist, using a cycle ergometer protocol is inadequate in the breast cancer population. Further, using the same cycle ergometer protocol and then lower limb strength training the subjects between maximal oxygen uptake tests would also help to identify whether the lower limb strength is truly a limitation of this particular protocol.

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