THE EFFECT OF MODERATE INTENSITY INTERMITTENT EXERCISE ON METABOLIC BIOMARKERS IN BREAST CANCER SURVIVORS

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ABSTRACT

MICHELLE M. PEBOLE: The Effect of Moderate Intensity Intermittent Exercise on Metabolic Biomarkers in Breast Cancer Survivors

(Under the direction of Dr. Anthony C. Hackney)

PURPOSE: To examine the effect of one bout of exercise on the metabolic biomarkers responses of breast cancer survivors (BCS) and healthy sedentary women controls (SW). METHODS: 9 women who completed major treatments for Stage I-III invasive breast cancer within 3-6 months and 9 SW without a history of cancer diagnosis completed a 30-minute bout of intermittent cycle ergometry exercise at 60% of VO_{2peak}. Blood was taken pre-exercise, immediately post-exercise, and 2 hr post-exercise and analyzed for blood lactate, glucose and free fatty acid (FFA) concentrations. RESULTS: Peak exercise lactate responses of BCS were significantly lower than SW ($p<0.01$). No differences existed in glucose responses for BCS and SW. BCS FFA response at 2 h post exercise was greater than SW ($p<.05$). CONCLUSIONS: Findings support that BCS do not have the same metabolic responses to exercise as non-cancer patients. The reason for the differing metabolic responses is unclear.

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CHAPTER ONE

Introduction

In 2014, an estimated 232,670 new breast cancer cases will occur in females, with 7,580 of those cases occurring here in North Carolina (American Cancer Society [ACS], 2014). Breast cancer treatment typically involves breast-conserving surgery or mastectomy. With early detection, long term survival is similar among women treated with breast-conserving surgery plus radiation therapy and those treated with a mastectomy. Normally, with a diagnosis of breast cancer comes an array of treatment options including surgery, radiation therapy, chemotherapy, hormone therapy, and targeted therapy. Local therapies, such as surgery and radiation, are intended to treat tumor without affecting the rest of the body (Abeloff, et al., 2008). Contrastingly, systematic therapy such as chemotherapy, hormone therapy, and targeted therapy, refers to administered drugs which can reach cancer cells throughout the body (ACS 2014). With efficiency of current treatment options rising steadily, breast cancer survival is on the rise.

For all stage diagnoses of breast cancer, relative survival rates at 10 and 15 years after diagnoses are 83% and 78%, respectively. Currently, approximately 61% of breast cancer diagnoses are made at a localized stage, for which the 5 year survival rate is 99%. If the cancer has spread to lymph nodes of the arm or other tissues, survival rate slightly decreases to 84%. However, if the diagnosis is made at the late stage, where the cancer has spread to the collarbone or distant lymph nodes and organs, survival rate drops dramatically to 24%, (ACS 2014). Therefore, there is a large population of breast cancer survivors across the US; and with modern advances in diagnosis and treatment, that number will continue to increase. One way to promote

healthy lifestyles in this population is physical activity. Exercise is important in this population in that it helps with prevention of relapse as well as increasing quality of life. Many studies have shown breast cancer survivors diagnosed in the early stage who are more physically active are less likely to die from breast cancer, as well as lowering all-cause mortality (Avis et al., 2005).

Research has shown that exercise programs improve aerobic capacity, muscular strength, flexibility, body composition, quality of life, physical functioning, and body image (Battaglini et al., 2014; Schmitz, 2010). These improvements have been accompanied by decreases in body size, fatigue, depression, anxiety and pain (Battaglini et al., 2009; Battaglini et al., 2014; Schmitz, 2010). Furthermore, exercise before and after breast cancer diagnosis is associated with a decreased risk of recurrence and/or death from breast cancer (Friedenreich et al., 2009; Holmes et al., 2005; Irwin, 2009). The benefits of physical activity in this populations may come from multiple interrelated biologic pathways involving decreasing adiposity, sex hormones insulin resistance, adipokines, and chronic inflammation (Friedenreich et al., 2011). Despite research showing that exercise elicits many positive outcomes for these patients, little is known about exercise metabolism in breast cancer survivors. More studies on the acute metabolic adaptations to exercise in this population may lead to a better understanding of their underlying physiology. Currently, only a few studies have examined energy metabolism and substrate utilization in breast cancer survivors. Those that have, found significantly lower lactate levels following various intensity exercises when compared to age-matched healthy controls, suggesting alterations in carbohydrate-lipid metabolism and substrate utilization in this population (Evans et al., 2009; Tosti 2010). Considering the growth in this population, as well as benefits of physical activity, additional research in this area is warranted. This research may aid in the development of how best to prescribe exercise to these patients and improve health.

Statement of purpose

The purpose of this study was to examine the effect of a 30 minute acute bout of moderate-intensity (60% VO_{2peak}) intermittent exercise on metabolic biomarkers of energy metabolism (blood lactate, glucose and free fatty acid concentrations) in female breast cancer survivors versus sedentary controls.

Research Questions

RQ1: Will the acute exercise bout result in different lactate responses in the breast cancer group as compared to the controls?

RQ2: Will the acute exercise bout result in different blood glucose responses post exercise when compared to the control group?

RQ3: Will the acute exercise bout result in different blood free fatty acid responses post exercise when compared to the control group?

Hypotheses

H1: The acute exercise bout will result in decreased lactate production post exercise in the breast cancer group when compared to the control group.

H2: The acute exercise bout will result in decreased blood glucose concentrations post exercise when compared to the control group.

H3: The acute exercise bout will result in increased blood free fatty acid concentrations post exercise when compared to the control group.

Terms

Early Stage Breast Cancer: Breast cancer that has not spread beyond the breast or the axillary lymph nodes.

Advanced breast cancer: Breast cancer that has spread beyond the breast and lymph nodes under the arm or other parts of the body, also known as metastatic breast cancer.

Lobules: Gland of the breast that produces milk.

Ducts: Part of the breast that carry milk from the lobules to the nipple; the majority of breast cancers start in the ducts of the breasts.

Stroma: Surround the ducts and lobules with fatty tissue, blood vessels, and lymphatic vessels.

Breast cancer survivor: For the purpose of this study, breast cancer survivors have diagnosis of stage I, II, or III invasive breast cancer, have received chemotherapy, and completed all planned surgery, chemotherapy, and radiation 3-6 months prior to enrollment.

Assumptions

1. All subjects enrolled in the study followed the pre-exercise guidelines prior to reporting for laboratory for exercise.
2. VO_{2peak} tests accurately approximate a patient's $VO_{2max.}$

Limitations

1. The control group was, on average, older than the experimental group.
2. Small sample size.
3. Occasional inability to obtain blood samples, leading to limited availability of samples.
4. Recruitment only from UNC Hospitals limits the sample diversity.

Delimitations

1. Subjects were between 40-70 years old.
2. Subjects could not be regular users of anti-inflammatory medications.
3. Subjects must not have experienced a menstrual period for approximately 1 year prior to enrollment.
4. The exercise bout was intermittent, which may be atypical for other exercise formats.
5. Subjects must have been diagnosed with stage I, II, or III invasive breast cancer, had received chemotherapy, and completed all planned surgeries, chemotherapies, and radiation therapy 3-6 months prior to enrollment.
6. The control group did not have a history of cancer diagnosis or treatment. Controls were also sedentary and free from cardiovascular and musculoskeletal disease that would make them unfit for exercise.

Significance

Breast cancer survival is on the rise. This population is one that stands to gain many health advantages from physical activity and exercise. Exercise is an intervention that has shown in other cancer populations to alleviate many negative effects of treatment, allowing patients to lead a healthier, higher functioning, and more active lifestyle (Battaglini et al., 2014). However, despite positive research findings, only 28% of breast cancer survivors exercise during treatment, with about 32% of survivors meeting ACSM's exercise recommendations (Irwin, 2009). Therefore, more knowledge about exercise energy metabolism in this population will be highly beneficial in that it will give fitness professionals a more precise exercise prescription. More knowledge about lactate metabolism in this population also has several practical implications.

Previous research has shown suppressed lactate levels in this population following exercise. That being said, these findings suggest blood lactate responses post exercise are not a good indicator of exercise intensity in breast cancer patients, contrary to findings in healthy populations where lactate responses are frequently used as indicators of exercise intensity. Furthermore, carbohydrate metabolism during exercise may be diminished in breast cancer patients. Since carbohydrates are used during high intensity exercise, this may also have implications for exercise prescriptions in this population in that higher intensity exercise may be more challenging to perform. More research on blood lactate, blood glucose and free fatty acid content will reveal more insight into substrate metabolism. This will be beneficial in considering exercise intensity for the use of exercise prescription in this population.

CHAPTER TWO: REVIEW OF LITERATURE

Cancer is the second leading cause of death in the United States, following heart disease (Siegel et al., 2013). The lifetime probability of being diagnosed with cancer is slightly higher in men (45%) than women (38%). While it is projected that 1,658,370 new cases of cancer will be diagnosed in 2015, incidence rates are decreasing for all four major cancer sites (lung, breast, colorectal, prostate), with the exception of female breast (American Cancer Society, 2015). Furthermore, cancer death rates are steadily decreasing at slightly less than 2% per year according to the recorded data from 2005-2009 (Siegel et al., 2013).

Modern medicine, coupled with the decreasing mortality rate, suggests more individuals are successfully living longer with a prior diagnosis—either through remission or more effective palliative care. Chances of survival increase when diagnosis is early, effective primary treatment is prescribed, and proper secondary treatments and therapies are used to encourage better overall quality of life (Smith et al., 2013). This holds true with breast cancer. With increasing survival rates, it is important to comprehend the underlying physiology of cancer survivors as well as promote healthy lifestyles in this population.

For the purpose of organization, this literature review is divided into the following sections: 1) Breast Cancer Overview, 2) Breast Cancer Pathophysiology, 3) Breast Cancer Survivors and Exercise as a Treatment 4) Breast Cancer and Exercise Metabolism 5) Summary and Conclusions.

Section 1: Breast Cancer Overview:

As of January 1, 2012, approximately 14.5 million people in the United States are living with a history of cancer, (American Cancer Society, 2015). While it is projected that 1.6 million cases will be diagnosed in 2015, incidence rates are decreasing for all four major cancer sites, with the exception of female breast cancer (American Cancer Society, 2015). Cancer is the second leading cause of death in the United States, and accounts for about 1 of every 4 deaths (Siegel et al., 2013). Fortunately, the 5-year survival rate for all cancer diagnoses made from 2003 until 2009 has increased to 68%; a significant increase from 49% in 1975-1977, (ACS, 2014). This improvement signifies both a progression in diagnosing and treating cancer, while also indicating increasing proportions of the population are living as cancer "survivors" (ACS, 2014). This study will focus on one of the most prevalent types of cancer in the United States, breast cancer.

In 2014, an estimated 232,670 new breast cancer cases will occur in females, with 7,580 of those cases occurring here in North Carolina (ACS, 2014). Risk factors for breast cancer include weight gain after the age of 18, being overweight or obese, use of hormone replacement therapy, alcohol consumption, long term smoking, and physical inactivity, (ACS, 2014). Risk is also increased with a family history of breast cancer diagnoses, although many researchers have concluded most familial breast cancer results from a mixture of both genetics and lifestyle choices. That is, inherited mutations in breast cancer susceptibility genes BRCA1 and BRCA2 occur much less than 1% in the population, but account for an estimated 5%-20% of all female breast cancers (ACS, 2014). Factors associated with decreased risk of breast cancer include breastfeeding, regular moderate or vigorous physical activity, and maintaining a healthy body

weight, (ACS, 2014). Even with taking preventative measures, it is important to take necessary breast cancer screening precautions.

Early detection is paramount in both treating and preventing breast cancer. For women at average risk, breast cancer screening includes clinical breast cancer exams as well as mammography (ACS, 2011). Early detection with mammography can catch breast cancer in an early stage, when there are more treatment options. Declines in breast cancer mortality among women since 1989 have been attributed to both improvements in early detections (like the mammogram), as well as increases in treatment efficiency, (ACS, 2014). Annual screening for breast cancer with both mammography and an MRI is recommended to start at the age of 40 (ACS, 2014).

Breast cancer treatment typically involves breast-conserving surgery or mastectomy. With early detection, long term survival is similar among women treated with breast-conserving surgery plus radiation therapy and those treated with a mastectomy. To determine if the tumor has spread beyond the breast, underarm lymph nodes are usually removed and evaluated during surgery (ACS, 2014). In early stage breast cancer patients, a sentinel lymph node biopsy may be performed whereupon only the first lymph nodes to which cancer would have likely spread is removed. This results in a lower change of long-term side effects such as lymphedema (ACS, 2014). Treatment involves several options.

Normally, with a diagnosis of breast cancer comes an array of treatment options including surgery, radiation therapy, chemotherapy, hormone therapy, and targeted therapy. Local therapies, such as surgery and radiation, are intended to treat the tumor without affecting the rest of the body (Abeloff, et al., 2008). Contrastingly, systemic therapy such as chemothereapy, hormone therapy, and targeted therapy, refers to administered drugs which can

reach cancer cells throughout the body, (ACS 2014). With effectiveness of current treatment options rising steadily, breast cancer survivorship is on the rise.

For all stages of breast cancer, relative survival rates at 10 and 15 years after diagnoses are 83% and 78%, respectively. Currently, approximately 61% of breast cancer diagnoses are made at a localized stage, for which the 5 year survival rate is 99%. If the cancer has spread to lymph nodes of the arm or other tissues, survival rate slightly decreases to 84%. However, if the diagnosis is made at the late stage, where the cancer has spread to the collarbone or distant lymph nodes and organs, survival rate drops dramatically to 24%, (ACS 2014). Therefore, there is a large population of breast cancer survivors across the US; and with modern advances in diagnosis and treatment, that number will only increase. It is therefore very important to monitor and consider the health of the population as measured by both prevention of relapse as well as their quality of life. One way to promote healthy lifestyles in this population is physical activity. Many studies have shown breast cancer survivors who are more physically active, especially after diagnoses, are less likely to die from breast cancer, as well as lowering all-cause mortality (Avis, Crawford, Manual, et al., 2005).

Section 2: Breast Cancer Pathophysiology

Cancer is born as a consequence of DNA damage intertwined with errors in proper cell cycle behavior. All cancer stems from the rapid, uncontrolled growth of abnormally functioning cells (Poste, 1980). The human body habitually produces these abnormally functioning cells; however, safety and repair mechanisms of the genetic cell cycle serve to either correct cellular irregularity or to ensure a discontinuation of cell specific growth. If both cellular missteps occur in concert, the irreparably damaged DNA will replicate and divide rapidly in one part of the body—resulting

in site-specific tumor growth (ACS, 2011). Breast cancer is made of a malignant tumor that starts in the cells of the breast. These tumor cells can invade surrounding tissues and metastasize to distant areas of the body. Breast cancer can be better understood by comprehending and comparing normal versus infected breast structures.

Female breasts are made up of lobules, ducts, and stroma, each with a specific function. Lobules produce milk, ducts carry breast milk from the lobules to the nipple, and stroma surround the ducts and lobules with fatty tissue, connective tissue, blood vessels, and lymphatic vessels (Abeldoff, Wolff, & Weber, 2008). Most breast cancers begin in cells that line the ducts or lobules. Additionally, many lymph nodes are in close proximity to breast tissue, with most lymph vessels in the breast connecting to axillary nodes under the arm (Avis et al., 2005). Other significant lymphatic nodes in this region are located inside the chest and below/above the collarbone. Different forms of breast cancer affect these structures.

The most common forms of breast cancers are ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), invasive ductal carcinoma (IDC), and invasive lobular carcinoma (ILC). DCIS and LCIS are both considered pre-cancer states, whereas IDC and ILC are fully cancerous (ACS, 2013). DCIS is a pre-invasive breast cancer signifying cells lining the ducts have changed to look like cancer cells. However, these cells have not invaded through the walls of the ducts to other breast tissue. Only some cases can go on to become invasive cancers, but currently there are no diagnostic tools to determine which cases will do so (ACS, 2013). LCIS cells look like cancer cell growth in the lobules of milk-producing glands of the breast, but do not grow through the wall of the lobules. It differs from DCIS in that LCIS will not become invasive if the cancer is not treated. However, women with this condition have 7 to 11 fold increased risk of developing invasive cancer in either breast (ACS, 2013).

IDC is the most common type of breast cancer, claiming about 80% of invasive breast cancer cases; it starts in the milk duct of the breast, breaks through the wall of the duct, and grows in the fatty tissue of the breast. This form of cancer is capable of metastasizing to other parts of the body via the lymphatic system and bloodstream (ACS, 2013). Similarly, ILC starts in the lobules and can metastasize to other parts of the body. About 1 in 10 invasive breast cancer cases is an ILC. Less common types of breast cancer include inflammatory breast cancer, Paget disease of the nipple, phyllodes tumor, and angiosarcoma.

Section 3: Breast Cancer Survivors and Exercise as a Supportive Intervention

Presently, with increased detection and treatment methods, breast cancer survivorship has increased dramatically in the past few years. Today, there are roughly 12 million cancer survivors alive in the United States alone, with that number steadily increasing (Hewitt, Greenfield, Stovall, 2006). Historically, doctors advised patients primarily with rest and avoidance of physical activity and exertion. However, recent research in the field of exercise physiology and cancer rehabilitation reveals that exercise can improve physical functioning, quality of life, and cancer-related fatigue in many cancer survivor groups, (Battaglini et al., 2004; Battaglini et al., 2007; Schmitz et al., 2010). Furthermore, treatment for breast cancer is expensive and comes with many deleterious side effects. Thus, non-pharmacologic methods, such as physical activity and exercise, may offer an attractive supplement to traditional therapies and aide to decrease morbidity and increase quality of life (Battaglini et al., 2009; Schmitz, 2010).

Current recommendations from the ACSM regarding cancer survivors focus on maintain physical activity while also emphasizing individualization and appropriate rest and recovery

period. Present recommendations suggest increasing exercise levels to 3-5 days a week with resistance training 2-3 days a week (American College of Sports Medicine [ACSM], 2014). Research currently supports improvements in wellbeing even in patients undergoing systemic cancer treatments with gradual increases in physical activity over one month. Exercise tolerance in these individuals may vary greatly from day to day and person to person. Additionally, heart rate may be a less reliable measure for monitoring exercise intensity in this population. Therefore, using rate of perceived exertion (RPE) along with heart rate reserve (HRR) may be helpful in evaluating intensity (ACSM, 2014). Aerobic exercise intensity should be moderate (40% - 60% VO_{2peak} or HRR; RPE moderate) to vigorous (65%-80% VO_{2peak} or HRR; RPE 12-16). Flexibility exercises should be mindful of range of motion restrictions due to surgery and chemotherapy/radiation therapy. Time recommendations do not differ from those of the healthy population; 75 minutes a week of vigorous physical activity or 150 minutes of moderate intensity activity, or a combinations of the two (ACSM, 2014). Resistance training should be at least 1 set of 8-12 reps with exercises covering large muscle groups throughout the upper and lower body (ACSM, 2014). In this population, slower progression may be needed, and awareness of exercise on cancer-related symptoms in survivorship is needed (ACSM, 2014). Cancer survivors who follow these recommendations will likely experience many health benefits.

There have been many studies examining the safety and efficacy of exercise training in breast cancer survivors who have completed surgery, chemotherapy, and radiation therapy, specifically. Research has shown that exercise programs improve aerobic capacity, muscular strength, flexibility, body composition, quality of life, physical functioning, and body image (Battaglini et al., 2009; Schmitz, 2010). When using estimated measurements derived from a submaximal treadmill testing protocol, significant improvements in cardiorespiratory function

have been observed for breast cancer exercise groups, at improvements from baseline of 3.54 mL/kg/min, (Battaglini et al., 2014). These improvements have been accompanied by decreases in body size, fatigue, depression and anxiety and pain (Battaglini et al., 2014; Spector et al., 2014; Schmitz, 2010). Specific positive body composition changes with exercise training include significant decreases in body fat percentage and increase in lean body mass (Battaglini et al., 2014). Furthermore, exercise before and after breast cancer diagnosis is associated with a decreased risk of recurrence and/or death from breast cancer, as well as dramatic increases in quality of life (Friedenreich, et al., 2009; Holmes, et al., 2005; Irwin, 2009).

Yet, despite the numerous benefits of physical activity in cancer survivors, a large proportion of cancer survivors do not perform regular physical activity, with many survivors decreasing physical activity levels after diagnosis (Irwin, 2009). Only about 28% of breast cancer survivors exercise during treatment, with about 32% of survivors meeting ACSM's exercise recommendations (Irwin, 2009). Therefore, it is important to advocate physical activity in cancer counselling as well as prescription by medical professionals.

Section 4: Exercise Metabolism

Throughout the day, and especially during exercise, the body meets energy needs via substrate oxidation of primarily carbohydrates and lipids. During exercise, it is especially important the body is efficient at utilizing these substrates for ATP production. However, recent research suggests that there are several differences between exercise metabolism and substrate oxidation in the healthy population as compared to breast cancer survivors.

Regulation of plasma glucose concentrations is one of the most tightly regulated physiological variables in the body. Normal human blood glucose concentrations are about 100

mg/dl (Brooks et al., 2005). This is required for central nervous function as well as other glucose requiring systems, organs, and cells. During exercise, skeletal muscle greatly increases the amount of glucose it uptakes in order to meet energy demands. Therefore, maintenance of blood glucose homeostasis becomes a major physiological challenge during exercise (Brooks et al., 2005). In healthy adults, glucose is stored as glycogen primarily in the liver, but also in the skeletal muscle. To mobilize glucose, glycogenolysis occurs. Epinephrine and norepinephrine secretion from the adrenal medulla at the start of exercise help stimulate muscle glycogenolysis by activating the adenylate cyclase mechanism. Catecholamine secretion also stimulates hepatic glycogenolysis in the liver. Therefore, increased catecholamine release is strongly associated with increased glucose appearance in the blood (Brooks et al., 2005). The resulting glucose is then used by working skeletal muscle. Normally, glucose rises at the start of exercise, and for the remainder of the exercise bout, glucose may fall, but will remain within approximately 10% of the normative value until exercise ends (Brooks et al., 2005). Additionally, it is well established that with increases in exercise intensity comes greater reliance on carbohydrate as fuel, and reductions in free fatty acid (FFA) utilization, in part due to rapid rises in norepinephrine levels. Additionally, during hard exercise, inactive tissues become glucose resistant, leaving glucose to be taken up by active muscle. (Brooks et al., 2005). Changes in FFA oxidation result in changes in blood FFA concentrations.

Blood FFA concentrations change during exercise in healthy populations. During prolonged moderate intensity exercise (above 50% VO_2max), blood FFA levels rise continuously (Brooks et al., 2005). Fasting increases the mobilization of triglyceride to FFA and glycerol almost doubling the FFA concentrations in the blood. During more high intensity exercises, during which blood lactate concentrations and secretion of cortisol from the adrenal cortex and

catecholamines increase and pH declines, lipolysis is inhibited, and the esterification of FFA to triglyceride is promoted (Brooks et al., 2005). Because of this, at higher intensity exercise (65% VO_2max or higher), blood FFA concentrations decline. This limits the amount of FFA for use as fuel sources. Further, products of CHO catabolism inhibit mitochondrial enzymes that allow FFA derivatives into mitochondria for oxidation (Brooks et al., 2005).

Lactate production also plays a key role in exercise metabolism. Lactate is produced as a by-product of metabolism. During exercise metabolism, glucose is broken down into pyruvate, which then quickly gets converted into lactate by the muscle lactate dehydrogenase isoform (LDH-M) (Brooks et al., 2005). At rest and during light intensity exercise, lactic acid is produced and removed at equal rates. In healthy adults, lactate turnover happens very rapidly (Brooks et al., 2005). As exercise intensities increase, so do blood lactate levels; metabolic clearance rate of lactate is also increased at these higher exercise intensities. However, at these higher intensities lactate production outpaces lactate clearance, ultimately resulting in more lactate accumulation (Brooks et al., 2005). Therefore, lactate removal is concentration dependent; its levels must rise to force its removal. When exercise intensity increases, there is greater reliance on carbohydrate as an energy substrate, thus increasing lactate production through glycolytic mechanisms (Brooks, et al., 2005; Gladden 2004; van Loon, Greenhaff, Constantin-Teodosiu 2001). Blood lactate levels increase non-linearly, and concentrations will rise steadily beginning at about 60% VO_2max. These elevated lactate levels may contribute to altering several other physiological mechanisms in order to combat lactate build up and buffer a decreased pH (Brooks et al., 2005). These mechanisms include increased ventilation, neuroendocrine responses, as well as fast-twitch muscle fiber recruitment. However, evidence

supports that substrate oxidation and lactate metabolism differs in clinical populations such as breast cancer survivors.

Section 5: Exercise Metabolism in Breast Cancer Survivors

Despite the small number of studies that have examined energy metabolism issues in cancer patients, several differences have still been identified. For instance, research has shown glucose intolerance is more frequent in cancer populations (Brooks et al., 2000; Edmonson, 1966; Glicksman & Rawson, 1956). Additionally, insulin resistance and greater levels of fasting insulin are associated with breast cancer (Larsson et al., 2007). These findings suggest alterations in carbohydrate metabolism in this population. Similarly, Evans and associates indirectly examined carbohydrate metabolism during exercise by measuring blood lactate responses (Evans et al., 2009). Results found post-treated breast cancer patients had significantly lower lactate levels following high intensity exercise (70%VO_2max) when compared to age-matched healthy controls.

Additionally, Tosti et al. found significantly lower blood lactate responses to exercise at various intensities including low (40% VO_2max), moderate (60% VO_2max), and high (70% VO_2max) (Tosti et al., 2010). Lower blood lactate concentrations during exercise suggest alterations in carbohydrate metabolism in breast cancer survivors. This finding is new, and needs more research to comprehend fully. In the same study, Tosti et al. found reduced carbohydrate oxidation and greater fat oxidation in the cancer survivors as compared to healthy controls. These alterations in lactate metabolism are in line with Tosti's findings on substrate utilization. If less carbohydrate is being utilized, then less lactate should be produced. However, magnitude of these differences between populations is seldom reported. Mechanisms behind the

reduction in carbohydrate metabolism and lactate responses in the cancer population are unknown with speculations pointing towards altered endocrine responses, irregular glucose metabolism, and treatment effects in this population.

Section 6: Summary and Conclusions

With efficiency of current treatment options rising steadily, breast cancer 10 and 15 year survival rates are increasing steadily. Along with these increases come increasing breast cancer survival populations. Therefore, it is important to monitor and comprehend the health of these survivors as well as how this relates to their quality of life. One efficient way to promote healthy lifestyles while improving quality of life is through physical activity and exercise. Many studies have shown breast cancer survivors who are more physically active, especially after diagnoses, are less likely to die from breast cancer, as well as lowering all-cause mortality (Avis et al., 2005). Currently, breast cancer survivors are advised to perform physical activity 3-5 days a week, with resistance training 2-3 days a week (ACSM, 2014). During these exercise bouts, aerobic intensity is advised to be from moderate to vigorous intensities (40% - 80% VO_2R; RPE 10-16) (ACSM, 2014). Time recommendations are the same as for healthy populations: 75 minutes of vigorous physical activity or 150 minutes of moderate intensity activity per week (ACSM, 2014).

Following these recommendations leads to many health benefits including improved aerobic capacity, muscular strength, flexibility, body composition, quality of life, physical functioning, and body image (Schmitz, 2010). These improvements have been accompanied by decreases in body size, fatigue, depression and anxiety and pain (Schmitz, 2010). Finally,

exercise before and after breast cancer diagnosis is associated with a decreased risk of recurrence and/or death from breast cancer (Friedenreich et al., 2009; Holmes et al., 2005; Irwin, 2009).

Despite knowledge of the many benefits, little is known about exercise metabolism in breast cancer survivors. Previous research has found that breast cancer survivors experience reduced carbohydrate oxidation and greater fat oxidation as compared to healthy controls (Tosti et al., 2010). Additionally, studies have found that in breast cancer populations, lactate production is decreased at low, moderate, and high intensities (Evans et al., 2009; Tosti et al., 2010). These findings suggest alterations in carbohydrate metabolism in this population. However, mechanisms behind the reduction in carbohydrate metabolism and lactate responses in the cancer population are unknown. This study aims to add to knowledge regarding acute metabolic responses to exercise in breast cancer survivors.

CHAPTER THREE: METHODOLOGY

Participants

Research participants included a control and experimental group. The experimental group included 9 women who completed major treatment for stage I-III invasive breast cancer (BC) within 3-6 months of enrollment. The control group consisted of 9 sedentary women without a history of cancer. All subjects were between the ages of 40-70 years, were not regular users of anti-inflammatory medications, and had not experienced a menstrual cycle for approximately 1 year prior to enrollment; they were recruited from the University of North Carolina at Chapel Hill and the surrounding areas after obtaining approval from the Institutional Review Board at UNC in the Department of Exercise and Sports Science and School of Medicine, as well as the Protocol Review Committee of the UNC Lineberger Comprehensive Cancer Center. Inclusion criteria for the breast cancer survivor group included:

- Diagnosis of stage I, II, or III invasive breast cancer
- Had received chemotherapy
- Completed all planned surgery, chemotherapy, and radiation 3-6 months prior to enrollment

Whereas, inclusion in the control group included:

- No history of cancer diagnosis or treatment

- Sedentary, defined by not meeting ACSM's guidelines
- Free from cardiovascular and musculoskeletal disease that would render aerobic exercise participation unsafe

Research Design Overview

All blood analyses were done retrospectively as samples were obtained in an earlier study conducted by Dr. Elizabeth Evans (2012). This paper will outline procedures subjects went through prior to blood analysis, as consistent with Evans reporting. Throughout this study, each subject completed three laboratory visits. During visit 1, subjects were given background regarding the study, signed all IRB-approved written informed consent documents, received a comprehensive medical and physical screening, and completed a peak oxygen uptake test (VO_{2peak}) on the cycle ergometer to assess maximal aerobic power. During visit 2, subjects performed a 30-minute intermittent exercise bout on the cycle ergometer at 60% of VO_{2peak}. Immediately pre-exercise, immediately post-exercise, and 2 hours post-exercise blood samples were obtained. Lastly, one resting blood sample was obtained at 24 hours post-exercise during visit 3. However, these latter 24 hour post-exercise blood samples were not used in this analyses. Pre-assessment guidelines included the following: fasting for at least 2 hours prior to testing, no exercise for at least 12 hours prior to testing, maintaining adequate hydration, no caffeine for at least 12 hours prior to testing, and no alcohol use for at least 48 hours prior to testing.

Visit 1: Medical/Physical Screening and VO_{2peak} test

To determine if subjects were healthy enough to proceed with the study protocol, each completed a comprehensive medical history questionnaire, a 12-lead resting electrocardiogram (ECG) and a physical examination (Whaley et al., 2006). After being cleared for participation, the subject's height and body mass were taken using a portable stadiometer (Perspective Enterprises, Portage, MI) and a calibrated balance-beam scale (Detecto, Webb City, MO). Body mass index (BMI) was calculated from height (cm) and body mass (kg) measurements. A Discovery Dual Energy X-ray Absorption (DEXA) scanner (Hologic, Inc., Bedford, MA) reported body fat percentages for each subject. For the breast cancer survivor group, medical treatment details were recorded. These treatments included surgery type, chemotherapy, whether or not radiation therapy was received, along with other relevant cancer treatment and medication.

VO_{2peak} was then measured via the Åstrand Cycle Ergometer Maximal Test protocol on a Lode electronically-braked cycle ergometer (Lode, Groningen, The Netherlands) (Heyward, 2006). This protocol called for the subject to begin pedaling at a workload of 50 Watts for 3 minutes, and progressively added increments of 25 Watts every 3 minutes until volitional fatigue. At the end of every minute of the test, heart rate and rating of perceived exertion (RPE) were recorded (Borg, 1982). Expired gases were collected and analyzed using a TrueMax 2400 Metabolic System (Parvo Medics, Salt Lake City, UT). Minute-by-minute heart rates were obtained from 12-lead ECG monitoring (GE CASE Cardiosoft V. 6.6 ECG diagnostic system, General Electric, Palatine, IL). The highest VO_2 measured by the metabolic system during the last stage of the test was declared the VO_{2peak}. The workload on the cycle ergometer that corresponded to the subject's VO_{2peak} was peak work load. After test completion, subjects cooled down by pedaling at a very light, self-selected workload. Research assistants monitored vitals for a minimum of 5 minutes post-exercise, until heart rate and blood pressure returned to near-

baseline levels (Whaley, Brubaker, Otto, 2006). Results obtained from the Åstrand test were used to calculate the submaximal workload at which subjects exercised during visit 2.

Visit 2: Aerobic Exercise Session

The acute bout of moderate-intensity aerobic exercise (30 minutes) on the cycle ergometer corresponded to 60% of the subject's VO_{2peak}. This intensity and duration combination was comparable to protocols used in similar studies examining the effects of aerobic exercise in breast cancer patients. Thus, this protocol is representative of exercise prescriptions that are appropriate and used frequently in this population according to the literature (Jones et al., 2011; Payne et al., 2008). However, previous testing with breast cancer survivors at UNC-CH revealed cycling for 30 continuous minutes at 60% of VO_{2peak} was difficult for many breast cancer patients. To make sure all subjects could complete the exercise session while maintaining the 60% of VO_{2peak} workload, an intermittent protocol was utilized. This protocol had subjects' alternate 3-minute intervals of exercise (10x) with 1.5 minutes of rest, for a total of 30 minutes of exercise in a 43.5-minute period. All exercise sessions started between 7:00-10:00 am to control for daily physiologic variation in the research between patients.

For the purpose of blood sampling, an angiocatheter was positioned in an antecubital vein in the arm of the subject at the beginning of the laboratory visit. Subjects then laid supine for approximately 20 minutes. A pre-exercise (Pre-Ex) blood sample was drawn into two 3-mL K_3EDTA Vacutainer® tubes. Following the rest, subjects sat calmly on the cycle ergometer for 3 minutes while pre-exercise metabolic data was collected. Subjects then warmed up for 4-5 minutes. After the warm up, subjects could stretch the lower body muscles in a self-selected mode. After this, subjects performed the 30-minute aerobic exercise bout. Expired gases were

monitored during the first, third, seventh, and tenth exercise interval. To ensure subjects maintained an exercise intensity as close as possible to 60% of VO_{2peak}, workload was adjusted throughout the exercise bout based off data from the metabolic system. Heart rate and RPE were recorded every 3 minutes. The subject immediately dismounted the cycle ergometer when the exercise bout was complete, and assumed supine position. An immediate post-exercise (0hPost) blood sample was drawn into two 3-mL K_3EDTA Vacutainer® tubes.

Subjects relaxed in the laboratory for the remainder of the visit. Ingestion of any food or beverages was not permitted, with the exception of water. At 2 hours post-exercise (2hPost), another blood sample was obtained in the same manner as previously described. Lastly, the angiocatheter was removed and subject was bandaged.

Visit 3: 24-hour Follow-up Session

24 hours after completion of the aerobic exercise session the subjects returned to the applied physiology lab (APL) in order to obtain the 24hourPost a resting blood sample. Standard venipuncture procedures were used to transfer blood into two 3-mL K_3EDTA Vacutainer® tubes. Blood was taken from an antecubital vein in the arm. However, none of these bloods were used in the analyses of the current study.

Determination of Plasma Blood Lactate, Glucose, and Free Fatty Acid

Following laboratory visits 2 and 3, whole blood samples were centrifuged at 4°C at 3000 rpm for 10 minutes using an IEC Centra-8R refrigerated centrifuge (International Equipment Company, Needham Heights, MA). The plasma portion of the blood was removed and stored in cyrofreeze vials at -80°C until the time of analysis. Blood glucose and free fatty acid concentrations were analyzed from these samples using an ELISA assay (Abnova Corp, China).

Lactate was analyzed using the DT60 Johnson & Johnson automated blood analyzer (Rochester, NY).

Calculation of Plasma Volume Shifts

Plasma volume shifts during exercise were calculated utilizing the Dill and Costill equation (Dill, Costill, 1974). Complete blood counts were analyzed at each study time point using a COULTER® Ac•T diff ™ Hematology Analyzer (Beckman Coulter, Inc., Brea, CA). This generated hematocrit and hemoglobin values used in plasma volume shift calculations. Plasma volume shifts were calculated to evaluate the effect of exercise on fluid shifts in the blood, which can affect concentrations of lactate, glucose, and free fatty acids.

Statistical Analyses

Statistical analyses were performed using SPSS version 19.0 with significance set *a priori* at $p \leq 0.05$. Blood glucose, free fatty acid, and lactate levels will be analyzed with a 2 (group) X 3 (measurement time) mixed model ANOVA to compare data sets. If significant F-ratios are found with the ANOVA, a Bonferroni post-hoc test will be used to determine individual mean differences.

Additionally, outcomes were converted to a percent change of pre exercise levels and statistically analyzed with a 2 X 2 mixed model ANOVA. If significant F- ratios are found, a Bonferroni post-hoc test was used to determine individual mean differences.

CHAPTER FOUR: RESULTS

Subjects

There were 18 subjects who participated in the study, 9 women in the breast cancer survivor group, and 9 in the control group. Physical characteristics for all 18 subjects are detailed in table 1. All the women in the breast cancer survivor group had a diagnosis of stage I-II invasive breast cancer, had received chemotherapy, and completed all planned surgery, chemotherapy, and radiation 3-6 months prior to enrollment. At the time of blood collection, 4 subjects in the survivor group were receiving additional adjuvant therapies, including Herceptin, Femara, or Tamoxifen (Evans 2012). All women in the control group were sedentary, did not possess any counter indications to exercise, and had never had a previous cancer diagnosis. Subjects were matched on physical characteristics, with no significant differences between the groups in physical characteristics, physical activity level, or menopausal status. However, it was found that the control group was significantly older than the breast cancer survivor group ($p=0.013$). Descriptive characteristics are presented in the form of mean ± standard deviation In Table 1, which can be found on the next page.

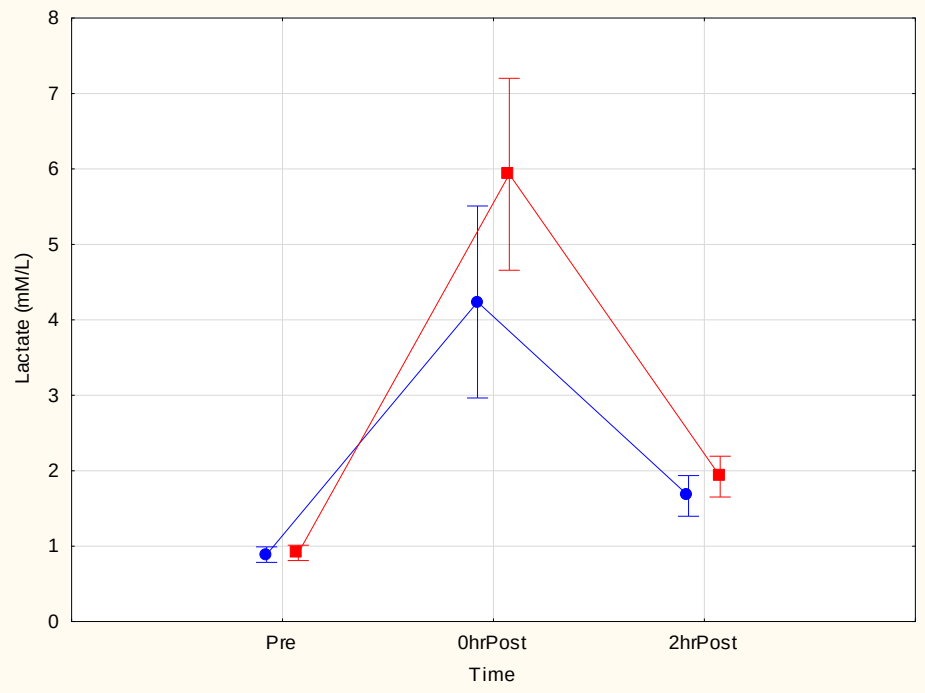
Table 1. Subject physical characteristics (mean ± SD).

Characteristic	Breast Cancer Survivor Group (n = 9)	Control Group (n = 9)	p-value
Age (years)	50 ± 6	59 ± 5	0.013
Race (# of women)	Caucasian (8) African American (1)	Caucasian (9)	--
Height (cm)	164.7 ± 5.8	163.8 ± 5.9	0.931
Weight (kg)	76.9 ± 12.6	77.7 ± 13.3	0.931
Body Mass Index (kg/m^2)	28.4 ± 5.0	28.9 ± 4.6	0.862
Percent Body Fat (%)	41.6 ± 4.5	42.1 ± 4.0	0.761
VO_{2peak} (mL/kg/min)	18.1 ± 2.7	18.5 ± 5.1	0.862
Peak Workload (W)	107 ± 19	106 ± 17	0.897

Blood lactate responses

Lactate responses are displayed in Figure 1. Resting Pre-Ex blood lactate levels did not differ significantly between groups and exercise caused lactate to increase in both groups ($p<0.001$). However, the 0hrPost blood lactate levels of the groups differed significantly, with the level in the cancer patients being lower ($p<0.01$). At 2hrPost there were no group differences observed and levels were not different from respective resting Pre-Ex values.

Figure 1. Blood lactate responses Pre-Ex, 0hrPost, and 2hrPost exercise bout. Mean ± 95% CI is depicted. Blue circles are cancer patients, red squares are control subject responses.



Blood glucose responses

Blood glucose levels Pre-Ex, 0hrPost, and 2hrPost are presented in Table 2. There were no statistically significant differences in the response to exercise or between the control and breast cancer group ($p>0.05$).

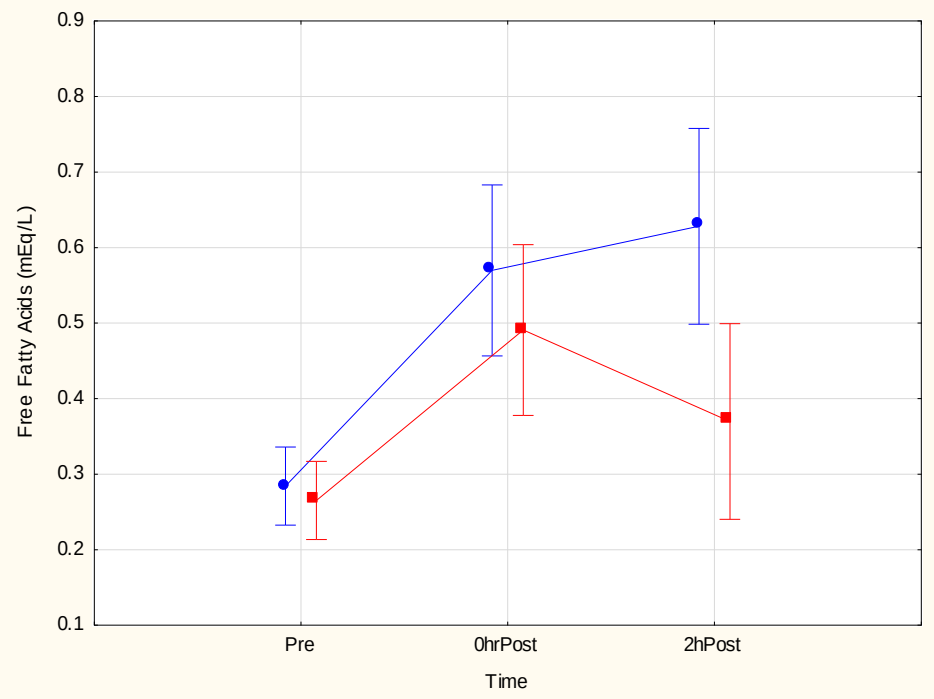
Table 2. Blood glucose responses Pre-Ex, 0hrPost and 2hrPost exercise bout. Mean ± 95% CI are reported.

Group	Time	Mean (mg/dl)	-95% (mg/dl)	+95% (mg/dl)
Cancer	Pre-Ex	97.8	92.0	103.6
Cancer	0hrPost	93.5	87.0	100.0
Cancer	2hrpost	86.0	71.6	100.4
Control	Pre-Ex	92.8	87.0	98.6
Control	0hrPost	83.3	76.8	89.7
Control	2hrpost	91.7	77.2	106.1

Blood free fatty acid responses

Blood free fatty acid responses immediately Pre-Ex, 0hPost, and 2hrPost are presented in Figure 2. No group differences existed at Pre-Ex. Exercise caused free fatty acid concentrations to increase in both groups significantly ($p<0.01$). At 2hrPost exercise, the cancer group's free fatty acid concentrations were still elevated from its respective Pre ($p<0.01$), while the control was not significantly elevated and had returned to Pre-Ex levels. Furthermore, the cancer group responses were significantly greater than the control responses at 2hrPost ($p<0.01$).

Figure 2. Blood free fatty acid responses Pre-Ex, 0hrPost, and 2hrPost exercise bout. Mean ± 95% CI are depicted. Blue circles are cancer patients, red squares are control subject responses.



Plasma Volume Shifts

Plasma volume shifts during exercise and recovery were similar between groups and did not differ significantly (p= 0.87 – 1.00).

Percent Change Analysis

All data were also statistically analyzed using percent change values, as noted in the Methodology chapter. The results and the understanding of the data analysis did not change with this analysis; the significance was found at the same time points in both situations.

CHAPTER FIVE: DISCUSSION

The purpose of this study was to examine the effect of an acute, 30 minute bout of moderate-intensity intermittent exercise on metabolic biomarkers of energy metabolism in female breast cancer survivors. More specifically, this study examined blood lactate, glucose, and free fatty acid concentrations in response to an intermediate 30 minute bout of cycling at 60% VO_{2peak}. For the purposes of this document, the discussion section will be delimited to only the variables discussed here regarding exercise energy metabolism (blood lactate, glucose, and free fatty acids). Details and discussion of all other aspects of the study have been reported elsewhere (Evans 2012).

Resting and Exercise Biomarker Responses

Resting values from both the control and experimental group for all biomarkers are within normal resting reference values, suggesting this data is valid, and is comparable to those in previous research studies. In general, the changes in the biomarkers in response to exercise also agree with physiological responses in the healthy population (Brooks et al., 2005). Specifically, resting blood glucose levels typically range from about 70 mg/dL to 110 mg/dL, with the mean being approximately 100 mg/dL, (American Diabetes Association, 2000). Resting blood glucose data from our subjects were within this range, with the means for the cancer group being 97.8 mg/dL and 92.7 mg/dL in the control group. Resting free fatty acid levels and blood

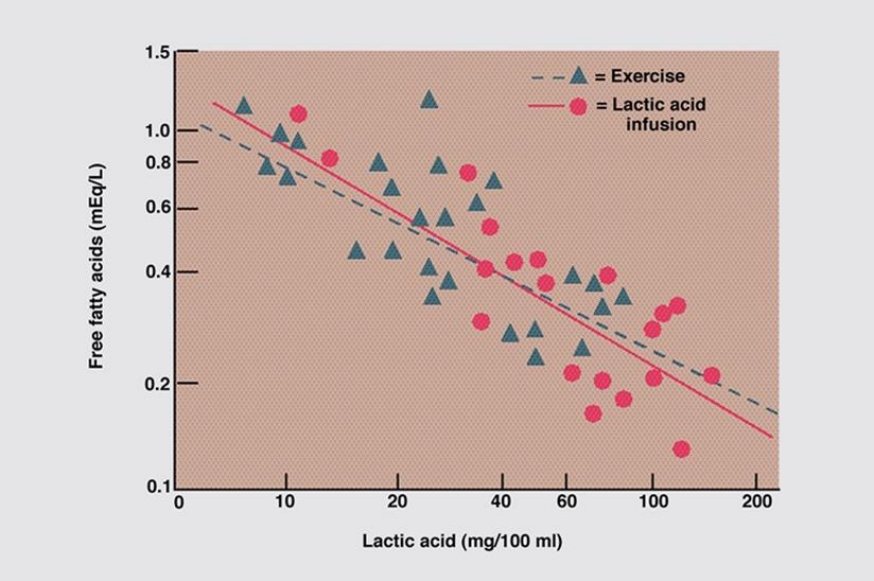
lactate levels in healthy populations have been reported to range from 0.1 to 0.6 mEq/L and 0.5 to 2.0 mM/L, respectively (Brooks et al., 2005; Gollnick et al., 1986; McGee et al., 1992). In the present study, mean resting free fatty acid concentrations were 0.28 mEq/L in the cancer group and 0.23 mEq/L in the control group. Resting blood lactate values were also within reference range, with the means being 0.8 mM/L in the cancer group and 0.9 mM/L in the control. Not only do the resting values here align with previous research, but also the changes found in response to exercise for each measurement do as well (Brooks et al., 2005).

During exercise, blood glucose rises at the start and remains within approximately 10% of the normative value until exercise ends (Brooks et al., 2005). Data from this study yielded no significant blood glucose findings. However, blood glucose did remain relatively constant, staying within 10% of resting values from immediately Pre-Ex to 2 hours post exercise. Additionally, in response to this moderate intensity exercise bout, blood FFA levels should rise continuously (Brooks et al., 2005). In both the control and cancer group, exercise caused free fatty acid concentrations to significantly increase. Furthermore, at 2 hours post exercise, the cancer group's free fatty acid concentrations were still elevated from its respective Pre, while the control was not significantly elevated (see discussion below). Blood lactate levels increase non-linearly in response to exercise, with a steady rise beginning at about 60% VO_2max (Brooks et al., 2005). In both groups, blood lactate responses followed this model. Both groups yielded significantly higher immediately post blood lactate concentrations when compared to resting values, suggesting increased lactate accumulation. Although these findings did follow the expected responses to exercise, several differences were found between the breast cancer and control group responses that correspond with previous research.

Exercise Energy Metabolism: Control versus Cancer

Several differences are known between exercise energy metabolism in healthy individuals and breast cancer survivors. Research has found significantly decreased blood lactate responses to exercise following low, moderate, and high intensity exercise in post-treated breast cancer survivors when compared to age-matched healthy controls (Evans et al., 2009; Tosti et al., 2010). Additionally, research has identified reduced carbohydrate oxidation and greater fat oxidation during exercise in the cancer survivors (Tosti et al., 2010). The present findings support this previous research, while also expanding on it. Although there were no significant differences between the two groups in blood glucose, there were differences in blood FFA responses as well as blood lactate. Our data shows significantly higher FFA concentrations 2 hours post exercise in the post-treated cancer survivors when compared to the control group, signifying a potentially greater fat oxidation in the cancer group. Although Tosti's exercise was 9 continuous minutes, FFA concentrations were significantly increased immediately post exercise. Both studies suggest increased fat oxidation in the breast cancer survivors (Tosti et al., 2010). It is well recognized that when there are elevated FFA levels, this can inhibit glycolysis and the metabolism of glucose hence, decreased lactate production (Brooks et al., 2005). The strength of this relationship between blood lactate and FFA concentrations is illustrated in Figure 3.

Figure 3. The *in vivo* inter-relationship between blood FFA and lactate concentrations in exercise situations and with exogenous lactate infusion (r = 0.90; Brooks et al., 2005).



The current analysis therefore supports previous research findings, while also expanding on them. This study is the first to measure free fatty acid concentrations directly in the blood of exercising breast cancer patients. Though our blood lactate findings are not novel, they do align themselves with previous research, suggesting there is a difference in cancer energy metabolism during exercise (Evans et al., 2009; Tosti et al., 2010). Together, these studies suggest decreased blood lactate accumulation during exercise in breast cancer survivors when compared to healthy controls – possibly due to compromised glycolytic processes. Additionally, our FFA findings are new and novel. Although previous studies have found decreased carbohydrate oxidation and increased fat oxidation in exercising cancer patients, this has been determined through expired gas analysis. This is perhaps the first study to report these findings from direct FFA biomarker measurements in the blood. These findings also suggest lower carbohydrate oxidation and greater fat oxidation in the breast cancer group. Reasons for why the glucose did not change significantly in response to exercise and support the lactate and FFA responses are unknown; but in light of the comments of Brooks et al. (2005) this lack of significant change in glucose is not entirely unexpected.

Possible Mechanisms of Responses

Reduced blood lactate and carbohydrate oxidation, paired with increased fat oxidation use in this cancer population has been documented several times. These findings could be expected; decreased lactate production would signify decreased reliance on carbohydrate and increased reliance on fat-lipid metabolism, (Brooks et al., 2005; Rasmussen & Winder, 1997). However, the difference in the fat biomarker response between the study groups is a new research finding, and nonetheless suggests that more research is needed to expand the body of knowledge. Mechanisms behind the apparent increased fat oxidation in the breast cancer patients are unknown, though it has been speculated differing hormonal status between the breast cancer and healthy population groups may contribute (Evans 2012).

That is, Evans found in her doctoral dissertation research work different endocrine hormones responses to a moderate intensity exercise bout, which may have implications for regulations of exercise energy metabolism in breast cancer survivors. Normally, epinephrine levels would increase during exercise; however, Evans found breast cancer survivors showed no significant change in epinephrine in response to the exercise (Evans 2012). This irregular epinephrine response may be a possible mechanism for the alteration in exercise metabolism in breast cancer survivors. Epinephrine plays a role in stimulating muscle glycogenolysis during exercise (Brooks et al., 2005; Hackney 2006). Thus decreased levels of epinephrine in the blood may potentially delimit the availability of glucose in the muscle cell, therefore limiting the body's ability to use glycolysis for energy (Brooks et al., 2005; Konatska et al., 1990). This finding would suggest that an increased reliance on lipids to meet energy demands would be needed. Evans also found increased cortisol in the breast cancer survivors in response to

exercise; this hormone plays a large role in increasing the lipolysis rate, further stimulating lipid metabolism (Hackney 2006).

Additionally, cancer is often associated with hyperglycemia, glucose intolerance, and insulin resistance, which may affect energy metabolism (Edmonson 1966; Glicksman & Rawson 1956; Marks & Bishop 1956; Tosti et al., 2010). These complications may reduce the body's capacity to use glucose as an energy substrate during exercise. Cancer treatments may also be contributing to alterations in exercise metabolism (Lane & McKenzie, 2005; Kaur et al., 2010). The ultimate goal of cancer treatment is termination of malignant cancer cells and destroying their carbohydrate metabolic capacities to halt tumor growth. Therefore, most treatments target diseased tissue with the ultimate goal of affecting only diseased tissues (ACS, 2014). However, some healthy cells are inevitably affected (Kaur et al., 2010). Perhaps these treatments, by unintentionally affecting healthy cells, significantly diminish the breast cancer patient's ability to perform carbohydrate metabolism. It is important to note, these explanations are only speculation. More research on cancer exercise energy metabolism is needed to discern and pinpoint these physiological mechanisms and explain these occurrences.

Clinical Significance

Regardless of the mechanism behind these responses, the findings have clinical significance. These findings provide evidence that blood lactate responses to exercise are not a valid indicator of exercise intensity in breast cancer survivors. In healthy populations, blood lactate levels are a somewhat common parameter off which to base exercise prescriptions. However, these results suggest exercise prescriptions written with lactate in this population may not be appropriate. Additionally, this population has a reduced capacity to metabolize

carbohydrates during exercise, suggesting rapid production of energy via anaerobic pathways may be decreased. Therefore, exercise at high intensities may not be appropriate for long periods of time in breast cancer survivors. Increased research on exercise energy metabolism in breast cancer survivors can provide insight as to what could be more appropriate intensity measurements in the population, as well as uncover more information on breast cancer exercise metabolism.

Limitations and Strengths

This study expanded on the previous body of knowledge, finding several significant differences between healthy and cancer patient energy metabolism via direct metabolic biomarkers in the blood. However, there are several limitations. To begin, the control group was older than the breast cancer group by an average of 9 years. This may have affected metabolism indirectly in the subjects, impacting the biomarkers indirectly. In addition, the sample size was small. With additional subjects, perhaps statistical significance would have been found in blood glucose. Despite a small sample size, statistical significance was still found in blood lactate and free fatty acid concentration. Additionally, the sample was very homogenous, comprised of only post treated breast cancer survivors. Therefore, it is unclear whether these results can be generalized to other cancer diagnoses. Lastly, this study examined only the response to the acute effects of exercise in this group. Thus, based on this limitation in the findings, speculation is not valid on exercise training related effects.

Despite these limitations, this study does have several strengths. First, it supports previous research as expected. Results here add to the increased evidence that breast cancer survivors have a decreased lactate response to exercise, while also adding new novel free fatty

acid findings. No previous study has examined FFA concentrations in response to exercise in post treated breast cancer survivors. Finally, despite having a small sample size, there was statistical significance in two of the three variables, suggesting the magnitude of the difference in these variables is large. It has identified a clear metabolic difference between these two groups, the mechanism for which is unknown. More research is needed to better understand and advocate for these survivors.

Conclusions

This study found a reduced blood lactate response to moderate intensity exercise. More research regarding the physiological mechanism behind this finding is needed to better understand this altered metabolism. Reduced blood lactate responses to exercise also suggest that lactate levels are not an appropriate method to prescribe exercise in this population. Additionally, there were no significant findings with blood glucose. Free fatty acid metabolism was found to be significantly increased in the breast cancer group 2 hours post exercise, suggesting elevated levels of fat-lipid metabolism during exercise. Decreased carbohydrate and increased fat oxidation rates during exercise in these survivors may alter and diminish their ability to exercise at higher intensities. This research is important in educating clinicians and exercise physiologists on the potential of different metabolic responses of cancer patients during exercise, which should be taken into consideration when prescribing different exercise durations and intensities. Therefore, more research is needed to confirm or refute the results of this experiment so more precise and specific exercise prescriptions can be devised for breast cancer patients providing better chances for more pronounced desirable outcomes.

REFERENCES

Abeloff MD, Wolff AC, Weber BL, et al. Cancer of the Breast. In: Abeloff MD, Armitage JO, Lichter AS, et al, eds. Clinical Oncology. 4th ed. Philadelphia, Pa: Elsevier; 2008: pp. 1875–1943.

American Cancer Society. Breast cancer facts and figures 2011-2012. Atlanta, GA: American Cancer Society; 2011.

American Cancer Society, 2013. Breast Cancer; 2013.

American Cancer Society 2014. Treatment and side effects. http://www.cancer.org/treatment/treatmentsandsideeffects/

American Cancer Society. Cancer facts and figures, 2014. Atlanta, GA: American Cancer Society.

American Cancer Society. Cancer Facts & Figures 2015. Atlanta: American Cancer Society; 2015.

American College of Sports Medicine. ACSM's Guidelines for Exercise testing and prescription. 9th edition. Exercise prescription for other clinical populations. 2014; pp. 263- 273.

American Diabetes Association. Screening for Type 2 Diabetes. Clinical Diabetes. 2000; 18(2): 69-74.

Avis N, Crawford S, Manuel J. Quality of life among younger women with breast cancer. J Clin Oncol. 2005; 23: 3322–3330.

Battaglini, CL, Bottaro M, Campbell JS, Novaes J, Simao R. Physical activity and levels of fatigue in cancer patients. Revista Brasileira de Medicina do Esporte. 2004; 2 (10): 98-104.

Battaglini CL, Boltaro M, Dennehy C, Rae L, Shields E, Kirk D, Hackney AC. The effects of an individualized exercise intervention on body composition in breast cancer patients undergoing treatment. Sao Paulo Med. J. 2007; 125: 22-28.

Battaglini CL, Hackney AC, Garcia R, Evans E, Shea T. The effects of an exercise program in leukemia patients. Cancer Ther. 2009. 8(2): 130-138.

Battaglini CL, Mills RC, Phillips BL, Lee JT, Story CE, Nascimento MG, Hackney AC. Twenty-five years of research on the effects of exercise training in breast cancer

survivors: A systematic review of the literature. Wold J Clin Oncol. 2014. 5(2): 177-190.

Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982; 14(5): 377-381.

Betof AS, Dewhirst MW, Jones LW. Effects and potential mechanisms of exercise training on cancer progression: A translational perspective. Brain Behav Immun. 2013; 30: S75-S87.

Brooks GA. The lactate shuttle during exercise and recovery. Med SciSports Exerc. 1986; 18(3): 360-368.

Brooks GA, Fahey, TD, Baldwin KM. Exercise physiology: human bioenergetics and its applications. 3rd Ed: 2000.

Costill DL, Coyle E, Dalsky G, Evans W, Fink W, Hoopes D. Effects of elevated plasma FFA and insulin on muscle glycogen usage during exercise. J Appl Physiol. 1997; 43: 695-699.

Costill DL, Dill DB. Calculation of percentage changes in volume of blood, plasma, and red cells in dehydration. J Appl Physiol. 1974 37(2): 247-248.

Edmonson JH. Fatty acid mobilization and glucose metabolism in patients with cancer. Cancer. 1966; 19: 277-280.

Evans ES. UNC-CH Doctoral Dissertation. The impact of acute aerobic exercise on natural killer cell, catecholamine, and cortisol responses in breast cancer survivors Under the direction of Dr. Claudio L. Battaglini, 2012.

Evans ES, Battaglini CL, Groff DG, Hackney AC. Aerobic exercise intensity in breast cancer patients: a preliminary investigation. Integr Cancer Ther. 2009; 8(2): 139-147.

Friedenreich CM, Gregory J, Kopciuk KA, Mackey JR, Courneya KS. Prospective cohort study of lifetime physical activity and breast cancer survival. Int J Cancer. 2009; 124: 1954–62.

Friedenreich CM. Physical activity and breast cancer: Review of the epidemiologic evidence and biologic mechanisms. Clinical Cancer Prevention. 2011; 188; 125-139.

Gladden LB. Lactate metabolism: a new paradigm for the third millennium. J Physiol. 2004; 558(pt 1): 5-30.

Glicksman AS, Rawson RW. Diabetes and altered carbohydrate metabolism in patients with cancer. Cancer. 1956; 9: 1127-1134.

Gollnick, PD. Bayly WM, Hodgdon DR, Exercise intensity, training, diet, and lactate concentration in muscle and blood. Med Sci Sports Exerc. 1986. 18(3): 334-340.

Gunover A, Felig P, Hagenfeldt L, Hendler R, Wahren J. Substrate turnover during prolonged exercise is man. J Clin Invest. 1974; 53(4): 1080-1090.

Hackney AC. Stress and the neuroendocrine system: the role of exercise as a stressor and modifier of stress. Endocrinol Metab. 2006. 1(6): 783-792.

Hargreaves M. Interactions between muscle glycogen and blood glucose during exercise. Exercise and Sports Science Reviews. 1997; 25: 21-39.

Hewitt M, Greenfield S, Stovall E, editors. From cancer patient to cancer survivors: Lost in translation. Washington (DC): National Academies Press; 2006.

Heyward VH. Assessing cardiorespiratory fitness. In: Heyward VH. *Advanced Fitness Assessment and Exercise Prescription.* 5th edition. Champaign: Human Kinetics; 2006. p. 55-91.

Holmes M, Chen WDF, Kroenke C, Colditz G. Physical activity and survival after breast cancer diagnosis. JAMA. 2005; 293: 2479–2486.

Irwin ML. Physical activity interventions for cancer survivors.Br J Sports Med. 2009; 43: 32–38.

Jones LW, Peppercorn J, Scott JM, Battaglini CL. Exercise therapy in the management of solid tumors. Curr Treat Options Oncol. 2010; 11(1-2): 45-58.

Kaur H, Saini S, Peer S, Singh J. Current therapies and novel targets in treatment of breast cancer. Sys Rev Pharm. 2010; 1: 40-49.

Konarska M, Stewart RE, McCarty R. Habituation and sensitization of plasma catecholamine responses to chronic intermittent stress: effects of stressor intensity. Physiol Behav. 1990. 47(4): 647-52.

Lane K, McKenzie DC. Cancer. In Skinner JS, ed. Exercise testing and exercise prescription for special cases: theoretical basis and clinical application. Philadelphia, PA. Lippincott Williams & Wilkins; 2005: 363-375.

Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer. 2007; 121: 856-862.

Marks PA, Bishop JS. The glucose metabolism of patients with malignant disease and of normal subjects as studied by means of an intravenous glucose tolerance test. J Clin Incest. 1956; 36: 254-264.

McGee DS, Jesse TC, Stone MG, Blessing D. Leg and hip endurance adaptation to three different weight-training programs. J Appl Sport Sci Res 1992, 6(2): 92-95.

Payne JK, Held J, Thorpe J, Shaw H. Effect of exercise on biomarkers, fatigue, sleep disturbances, and depressive symptoms in older women with breast cancer receiving hormonal therapy. Oncol Nurs Forum. 2008:35(4): 635-642.

Rasmusen BB, Winder WW. Effects of exercise intensity on skeletal muscle malonyl-CoA carboxylase. J Appl Physiol. 1997;38: 1104-1109.

Sabiston CM, Brunet J. Reviewing the benefits of physical activity during cancer survivorship. Am J Lifestyle Med. 2012; 6(2): 167-177.

Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, Irwin ML, Wolin KY, Segal RJ, Lucia A, Schneider CM, von Gruenigen VE, Schwartz AL. American College of Sports Medicine Roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010; 42(7):1409-1426.

Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013; 63(1): 11-30

Smith RA, Brooks D, Cokkinides V, Saslow D, Brawley OW. Cancer screening in the United States, 2013: a review of current American Cancer Society guidelines, current issues in cancer. CA: Cancer J Clin 2013; 63(2): 87-105.

Spector, D., Deal A, Amos, K., Yang H, Battaglini**,** CL. A pilot study of a home-based motivational exercise program for african-american breast cancer survivors: clinical and quality of life outcomes. Integr Cancer Ther. 2014. 13(2): 121-32.

Tosti KP, Hackney AC, Battaglini CL, Evans ES, Groff D. Exercise in patients with breast cancer and healthy controls: Energy substrate utilization and lactate responses. Integr Cancer Ther, 2011. 10(1): 6-15.

Van Loon LJC, Greenhaff PL, Constantin-Teodosiu D, Saris WHM, Wagenmakers AJM. The effects of increasing exercise intensity on muscle fuel utilization in humans. J Physiol. 2001; 536: 295-304.

Whaley MH, Brubaker PH, Otto RM. Pre-exercise evaluations. In: Whaley MH, Brubaker PH, Otto RM, editors. ACSM's Guidelines for Exercise Testing and Prescription, 7th edition. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 39-54.