

Substrate Oxidation and Blood Lactate Responses to Varying Exercise Intensities
in Breast Cancer Patients and Healthy Controls

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ABSTRACT

Karen P. Tosti: Substrate Oxidation and Blood Lactate Responses to Varying Exercise Intensities in Breast Cancer Patients and Healthy Controls
(Under the direction of Anthony C. Hackney, Ph.D., D.Sc.)

Post-treated breast cancer patients were matched with healthy women based on age, physical fitness level and menopausal status. Subjects participated in low, moderate, and high intensity submaximal exercise sessions that corresponded with 40% VO_{2max} , 60% VO_{2max} , and 70% VO_{2max} . Oxygen uptake and respiratory exchange ratio were taken during submaximal exercise sessions to determine substrate oxidation. Blood lactate and blood glucose were measured before and after submaximal exercise sessions. The breast cancer patients had a significantly ($p \leq 0.05$) lower carbohydrate oxidation rate and higher fat oxidation rate at all exercise intensities compared to healthy women. The breast cancer patients had a significantly ($p \leq 0.05$) lower blood lactate response to exercise at all intensities compared to the healthy women. The results indicate that post-treated breast cancer patients have augmented lipid metabolism and reduced carbohydrate metabolism during submaximal exercise.

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CHAPTER I

BASIS OF STUDY

Introduction

Over the past 35 years breast cancer has been the most prevalent type of cancer diagnosed in women in the United States (Jemal et al. 2009). Although this serious disease is very common, mortality rates are currently decreasing and survival rates are increasing (Jemal et al. 2009). The decreased mortality rate can be attributed to earlier detection and more aggressive treatments (Battaglini et al. 2008; Humpel & Iverson 2005; Jones et al. 2007; Kim et al. 2009). These efforts have resulted in there being over 2.4 million breast cancer survivors in the United States in 2009 (White et al. 2009).

Treatment of breast cancer is multi-faceted and varies individually based on the type tumor and other individual risk factors (Jones et al. 2007). Treatment typically consists of removal of a tumor and adjuvant therapies such as radiation, chemotherapy, hormonal therapy, or any combination of these (Segal et al. 2001). Adjuvant treatments for breast cancer can have many acute and long-term debilitating side effects including but not limited to: a decrease in energy expenditure, weight gain, fatigue, increased risk of cardiovascular disease, decreased cardiopulmonary function, and decreased quality of life (Dimeo et al. 1998; Evans et al. 2009; Kim et al. 2009; Segal et al. 2001). However, recent studies have shown positive benefits of exercise training within breast cancer survivors. A review of studies showed that aerobic exercise training in breast cancer patients during and after adjuvant therapies significantly improved aerobic capacity and

body composition (Kim et al. 2009). Segal et al. (2001) noted benefits in physical functioning for patients undergoing self-directed or supervised exercise when compared to a control group of non-exercising patients. Patients who had not received chemotherapy treatments also significantly improved their aerobic capacity and body weight after supervised exercise sessions when compared to breast cancer controls that had not undergone exercise training (Segal et al. 2001). A study of post-menopausal breast cancer survivors involved in exercise saw a significant increase in quality of life compared to non-exercising patients in the control group (Courneya et al. 2003). Sternfeld et al. (2009) also found that physical activity, including exercise training, in breast cancer survivors decreases the total occurrence of mortality due to all causes including cancer recurrence.

These positive outcomes are promising and in 2003, Brown et al. (2003) published general guidelines for physical activity before and after cancer treatment. The following year the American College of Sports Medicine (ACSM) also established general exercise guidelines for cancer patients in order to provide structure for training programs. These guidelines however were not specific to the type or severity of cancer. Concurrently, the ACSM does not have a definitive “Position Statement” for exercise prescription in cancer patients either during or after treatment (Humpel & Iverson 2005). Some basic guidelines have also been established by several other organizations but there are no clear evidence-based recommendations for any specific cancer population (Humpel & Iverson 2005). For example, a meta-analysis of studies on exercise training in cancer patients showed that aerobic intensities were reported anywhere from 40% of heart rate reserve to 90% of maximal heart rate (Humpel & Iverson 2005). This is an

extremely wide variance in this exercise prescription parameter. Exercising at the proper intensity is important to gain cardiovascular benefits but should be approached cautiously with cancer populations due to the cardiovascular complications that may occur with some types of treatments (Battaglini et al.2006; Gianni et al. 2008). Therefore, it is important to explore and quantify the physiological differences (i.e., cardiovascular, metabolic) between exercising at different intensities in cancer patients in comparison to normal “healthy” controls. This information can contribute to the literature so that accurate guidelines and recommendations for exercise prescription in cancer patients can be devised.

Researchers have extensively explored substrate oxidation levels in normal healthy individuals exercising at varying intensities. There have been only a few studies, however, looking at substrate oxidation issues, specifically carbohydrate metabolism, in cancer patients. One such study showed that diabetes or glucose intolerance was more frequent in cancer populations when compared to healthy controls (Glicksman & Rawson 1956). Another study, however, showed that fasting values of blood glucose and plasma free fatty acids were similar in cancer patients and normal controls (Edmonson 1966). Decreased glucose tolerance was noted in cancer patients compared to the normal controls at rest, which could potentially be the result of increased free fatty acid utilization (Edmonson 1966). A greater incidence of hyperglycemia has also been shown in cancer patients at the time of diagnosis, however it was not determined as to whether this was an effect of the cancer or had been established before developing cancer (Glicksman & Rawson 1956). A recent study has also found that insulin resistance and high fasting levels of insulin are also associated with breast cancer (Larsson et al. 2007).

These studies suggest that there seems to be a strong relationship between altered carbohydrate metabolism and breast cancer disease. However, most of these studies were performed in a resting state and not in response to exercise and also at the time of diagnosis rather than post-treatment.

Very few studies have looked at blood lactate and blood glucose as markers of carbohydrate metabolism in exercising cancer survivors. Dimeo et al. (1998) noted that exercising blood lactate levels significantly decreased after a 6 week training program. Regrettably, this study did not compare blood lactate levels with normal healthy controls. A more recent study looking at blood lactate levels as an indicator of intensity during exercise showed that post-treated breast cancer patients had significantly lower lactate levels during high intensity (70% VO_{2max}) exercise when compared to healthy matched controls (Evans et al. 2009). These results were quite surprising and unexpected. It has been well established that exercising at a higher intensity causes greater reliance on carbohydrate as a substrate and therefore more lactate would be produced through glycolysis (Brooks et al. 2005; Rasmussen & Winder 1997; Romijn et al. 1993; van Loon et al. 2001). Therefore, it was speculated by Evans et al. (2009) that perhaps less carbohydrate was being metabolized as an energy substrate and thus causing lower blood lactate levels.

Purpose

The results of the study performed by Evans et al. (2009) indicates that further research on substrate oxidation and carbohydrate metabolism in cancer patients during exercise is warranted. Therefore, the purpose of this study was to compare substrate

oxidation and blood lactate at low (40% $\text{VO}_{2\text{max}}$), moderate (60% $\text{VO}_{2\text{max}}$), and high (70% $\text{VO}_{2\text{max}}$) intensities in post-treated breast cancer patients to apparently healthy controls. The methodology used was similar to the protocol that was used in Evans et al. (2009). In general, post-treated breast cancer patients (women) completed steady-state exercise for 9 minutes at low (40% $\text{VO}_{2\text{max}}$), moderate (60% $\text{VO}_{2\text{max}}$), and high (70% $\text{VO}_{2\text{max}}$) intensities. Matched control women with no history of breast cancer also performed the same exercise sessions at low, moderate, and high intensities. Respiratory gases, blood lactate, blood glucose, and substrate oxidation measurements were taken during and after exercise testing and compared between the cancer treatment and control groups.

Significance of study

The significance of this study pertains to the development of a better understanding of substrate oxidation (i.e., energy metabolism) at different exercise intensities in post-treated breast cancer patients and how it compares to healthy women. Energy metabolism increases with increasing intensity of exercise (Brooks et al. 2005; McArdle et al. 2007). Concurrently, the amount of carbohydrate used as an energy source also increases with greater exercise intensity. Conversely, the amount of lipid decreases as exercise intensity increases and carbohydrate contribution increases. If carbohydrate metabolism is compromised with increasing exercise intensity, it can make exercise more difficult and result in an earlier onset of fatigue (Manore & Thompson 2000). The fact that carbohydrate metabolism may be altered at rest in cancer patients suggests that exercising carbohydrate metabolism may be altered as well. This

possibility warrants that studies examining exercise energy metabolism are necessary in cancer populations. Such studies can provide information and give insight into issues of exercise intensity so that more accurate guidelines/recommendations can be developed for exercise training prescription in breast cancer patients.

Research questions

1. Is there a difference in substrate (carbohydrate and lipid) oxidation in cancer patients exercising at low (40% VO_{2max}), moderate (60% VO_{2max}), and high (70% VO_{2max}) intensities when compared to apparently healthy controls?
2. Is there a difference in blood lactate response in cancer patients exercising at low (40% VO_{2max}), moderate (60% VO_{2max}), and high (70% VO_{2max}) intensities when compared to apparently healthy controls?
3. Is the relationship between carbohydrate oxidation and blood lactate production (post-exercise) different in breast cancer patients when compared to apparently healthy controls?

Hypotheses

H1. No significant difference in lipid and carbohydrate oxidation will occur between the cancer and control groups during low (40% VO_{2max}) and moderate (60% VO_{2max}) exercise intensities.

H2. Carbohydrate oxidation will be significantly lower and lipid oxidation will be significantly higher during exercise at high (70% VO_{2max}) intensity in the cancer group when compared to controls.

H3. No significant difference in the blood lactate response to exercise will occur between the cancer and control groups during low (40% $\text{VO}_{2\text{max}}$) and moderate (60% $\text{VO}_{2\text{max}}$) exercise intensities.

H4. Blood lactate response will be significantly lower post-exercise at the high (70% $\text{VO}_{2\text{max}}$) intensity in the cancer group when compared to controls.

H5. A significant correlation will exist between carbohydrate oxidation and blood lactate production in both healthy controls and cancer patients in response to exercise; however, this relationship will be significantly stronger in the healthy controls.

Delimitations

Male subjects were excluded from this study and only female subjects were studied due to the high prevalence of the disease in women. All breast cancer patients had completed their major treatments including surgery, chemotherapy, radiation, or any combination of these treatments within 6 months prior to participating in the study. This study was performed in a thermo-neutral environment to control for the effect of increased carbohydrate use due to increased core temperature. Subjects also refrained from consuming any food or beverage two hours before each exercise session to establish more accurate resting blood glucose and blood lactate measurements.

Limitations

This study did include some limitations which may have impacted the results. The study used a submaximal test to predict maximal oxygen consumption ($\text{VO}_{2\text{max}}$) which was not the most accurate measure of $\text{VO}_{2\text{max}}$ because it is based on certain

assumptions (e.g., economy of movement, linear HR response, etc). Protein metabolism was not taken into consideration during this study which may have somewhat confounded the interpretation of the outcomes of the study. Diet was not controlled; therefore differences in the percentage of carbohydrate and fat consumed may have impacted substrate oxidation during exercise. There was a very small sample size which decreased the power of the results. Lastly, the study results can only be generalized to women who have been diagnosed with Stage I – III breast cancer and have completed all major medical treatments within the last 6 months.

CHAPTER II

REVIEW OF LITERATURE

Introduction

The positive prognosis for breast cancer patients has greatly increased over the last decade due to earlier detection and more effective treatments (Battaglini et al. 2008; Jones et al. 2007; Humpel & Iverson 2005; Kim et al. 2009). These improvements however, have increased the number of cancer survivors with lingering side effects from their treatments (McTiernan 2004). Exercise training has been shown to be a positive therapy to increase overall health and quality of life for many cancer patients during and after treatments (Knols 2005). Substrate metabolism during exercise is studied widely in healthy individuals, however currently there is little evidence based information about this topic for cancer survivors.

I. Side effects of breast cancer and treatments

As the number of breast cancer survivors increases, the impact of treatments on long term health and well-being has caused a large population with unique and distinct needs (Sternfeld et al. 2009; Stull et al. 2007; White et al. 2009). The acute and chronic side effects of treatment can cause serious and sometimes fatal consequences for this growing number of breast cancer survivors. Side effects of breast cancer and subsequent treatments can range anywhere from decreased energy expenditure to increased mortality. Most importantly these treatments typically cause a functional decline which increases

the risk of recurrence, and co-morbidities such as cardiovascular disease, diabetes, and osteoporosis, as well as premature death (Lane & McKenzie 2005; Stull et al. 2007; White et al. 2009).

Cardiovascular injury

Almost all of the adjuvant therapies have side-effects which at some level may, directly or indirectly, acutely or chronically impact the cardiovascular system of cancer patients (Jones et al. 2007). For example, anthracycline is an effective form of chemotherapy commonly prescribed to patients; however, it can cause cardiotoxicity which is then further complicated by the interaction of other prescribed drugs and therapies (Gianni et al. 2008). The correlation of drug treatment and side effects seems to be dose dependent, with patients receiving high or extended doses of medication having a greater risk for cardiac complications (McTiernan 2004). Some of the cardiac damage that occurs with these treatments does not result in overt symptomatic events, necessitating the need for identifying signs of cardiac damage earlier on (Gianni et al. 2008). Long term effects of anthracycline chemotherapy treatment can also cause declines in left ventricular function while radiotherapy treatment may cause cardiovascular pathologies including atherosclerosis, coronary artery disease, and thickening of the pericardium (Jones et al. 2007). Endocrine therapies such as Tamoxifen and biological drug therapies such as Herceptin may also have a negative impact on the cardiovascular system including cardiovascular disease and cardiac toxicity (Jones et al. 2007). Courneya et al. (2003) indicate the reduction in cardiopulmonary capacity may lead to substantial reductions in quality of life or even premature death.

These cardiovascular complications that accompany cancer treatment can be chronic and severe and therefore need to be addressed.

Musculo-skeletal symptoms

Another side effect of breast cancer treatment is an increased risk for developing osteoporosis due to medications use, decreases in physical activity and weight-bearing exercises (McTiernan 2004). Lymphedema is also another side effect associated with breast cancer survivors, especially those who have had some lymph nodes removed (McTiernan 2004). Furthermore, both chemotherapy and radiation have been shown to cause changes in muscle physiology at the cellular level (Battaglini et al. 2006). Specifically, a variety of chemotherapy treatments can cause direct injury to muscle cells at the site of treatment while radiation can cause declines in neuromuscular efficiency (Billingham et al. 1977; Kuno et al. 1996; Monga et al. 1997). Inactivity due to fatigue also causes muscle atrophy and loss of muscle strength (Humpel & Iverson 2005).

Fatigue and related symptoms

The most common complaint of all cancer patients is fatigue, with rates occurrence rates ranging as high as 96% (Humpel & Iverson 2005; McTiernan 2004). This can be one of the most distressing and persistent symptoms of the disease in breast cancer survivors (Courneya et al. 2003; Dimeo et al. 1998). Other common symptoms reported by cancer patients include feelings of anxiety and depression, sleep disturbances, decreased physical activity, decreased functional capacity, and decreases in activities of daily living (Humpel & Iverson 2005). Feelings of nausea have also been reported as a side effect of treatments (Segal et al. 2001). Many cancer treatments can also have adverse affects on sleep patterns which is associated with “decrements in learning,

memory, alertness, and immune function, and may exacerbate anxiety and depression” (McTiernan 2004).

Weight gain

Weight gain is a common side effect during and after breast cancer treatments (Demark-Wahnefried et al. 1997; Kim et al. 2009; Saquib et al. 2007). This weight gain has been attributed to many factors including physical inactivity, decreased resting metabolic rate, hormonal changes, overeating, or the disease process itself (Schwartz 2000). Interestingly, many women decrease their level of physical activity because they are fearful of overexertion or unsure of what exercise they can do (Segal et al. 2001). It has been suggested that cancer treatments, may impair the body’s ability to process (i.e., digest, store) nutrients which could have a profound impact on substrate metabolism and weight gain both at rest and during exercise (Battaglini et al. 2006).

Chemotherapy treatment specifically has been linked to an increased weight gain in breast cancer patients although the exact mechanism is not well understood (Demark-Wahnefried et al. 1997; Saquib et al. 2007; Schwartz 2000). One theory is that women typically gain weight as they transition through menopause; as chemotherapy pushes younger women into earlier menopause, there is a substantial increase in body mass (Saquib et al. 2007). Steroid drug use along with chemotherapy is also common which may also enhance weight gain (Saquib et al. 2007). The Women’s Healthy Eating and Living Study reported that women who received chemotherapy were 65% more likely to see a significant weight gain after treatment when compared to women who did not receive either chemotherapy or Tamoxifen drug treatment (Saquib et al. 2007).

To complicate issues, this weight gain typically consists of an increase in adiposity and a decrease in lean body mass, causing an increased percentage in body fat (Battaglini et al. 2008; Doyle et al. 2006). This altered body composition can negatively impact levels of fatigue, rates of survival and re-occurrence as well as have damaging psychological impacts on the patient (Battaglini et al. 2008; Demark-Wahnefried et al. 1997). Furthermore, greater levels of visceral fat, especially intra-abdominal fat, have been associated with increased levels of glucose and insulin (McTiernan 2004). Elevated levels of insulin have “mitogenic effects on breast cells”, which negatively impacts breast cancer prognosis (Larsson et al. 2007; McTiernan 2004). Additionally, weight gain in adulthood has also been shown to increase the risk of developing breast cancer, increased recurrence, and higher mortality rate (Demark-Wahnefried et al. 1997; Kim et al. 2009; Saquib et al. 2007).

Results of a large epidemiologic study also showed that less than 10% of breast cancer survivors were able to return to their pre-diagnosis weight over 6 years of follow-up visits (Saquib et al. 2007). This issue is further complicated by the fact that many cancer survivors were already overweight or obese at the time of diagnosis (Doyle et al. 2006). It has been well documented that overweight and/or obesity in patients can negatively affect their survival rates, especially in breast cancer patients (Kim et al. 2009; McTiernan 2004). Due to the fact that obesity has been strongly associated with breast cancer recurrence as well as decreased survival rates, there is an urgent need to help these survivors maintain or obtain a healthy weight after completing treatments (Doyle et al. 2006).

II. Benefits of exercise after cancer treatment

Although the previously mentioned side effects can be detrimental for breast cancer survivors, exercise can help patients to improve their overall health and well being. Just as exercise has been used as a complementary therapy in other chronic diseases, it has recently been used to help improve quality of life, physical fitness, and overall survival rate in breast cancer patients (McNeely et al. 2006). Historically, physicians were recommending cancer patients to rest, in an attempt to help the increased fatigue that typically coincides with cancer and its related treatments (Dimeo et al. 1998). It is now recognized that such inactivity induces muscular catabolism and was therefore further increasing levels of fatigue and inactivity (Dimeo et al. 1998; Evans et al. 2009). In recent years, studies have consistently shown that exercise during the recovery from cancer treatment can improve cardiovascular fitness, muscle strength, body composition and fatigue levels (Doyle et al. 2006; Humpel & Iverson 2005; Speck et al. 2010). Lifestyle factors, including physical activity (i.e., exercise training), are now recognized as a way to ameliorate side effects from treatment and decrease the chances of recurrence and co-morbidities (White et al. 2009).

Attenuate cardiovascular injury

The serious impact of cardiovascular injury has been shown to be lessened with a combination of exercise and cardiovascular disease drugs. Specifically, these factors have resulted in improved vasodilation, lower oxidative stress, and an increase in endothelial progenitor cells (Jones et al. 2007). Jones et al. (2007) reports exercise training can also increase cardiovascular reserve, exercise capacity, reduce cardiovascular disease mortality, and all-cause mortality. This concept is supported by a meta-analysis of

studies using exercise after breast cancer treatment, which showed improvements in blood pressure and cardiopulmonary measures (Knols et al. 2005). Exercise training in breast cancer survivors is also thought to decrease the risk of cardiovascular disease, just as in other populations, and therefore improve overall prognosis (Sternfeld et al. 2009).

Increase aerobic capacity

Aerobic exercise in a variety of cancer patients, including breast cancer patients, has repeatedly shown to increase aerobic capacity (VO_2) when compared to non-exercising patients (McTiernan 2004). Furthermore, a meta-analysis performed specifically in breast cancer patients, showed a moderate to large improvement in absolute and relative peak oxygen consumption (VO_{2peak}) (Kim et al. 2009). Courneya et al. (2003) demonstrated that moderate to high aerobic exercise 3 times a week for 15 weeks showed a significant improvement in absolute and relative VO_{2peak} in postmenopausal exercising breast cancer patients when compared with a control group who's absolute VO_{2peak} decreased. Although the exact mechanism of this improvement is not well understood in breast cancer survivors, it is assumed to be the same as in other women through skeletal muscle adaptations (improved capillary density, increased oxidative enzymes, ratio of Type I muscle fibers) and increased cardiac output (Courneya et al. 2003). A study similar to that of Courneya et al. (2003) indicated that breast cancer patients not receiving chemotherapy, significantly increased aerobic capacity using a home based aerobic exercise intervention or a supervised aerobic exercise intervention when compared to a control group which saw a decrease in aerobic capacity (Segal et al. 2001).

Exercise intensity may also have an impact on physical functioning, with moderate increases seen with training conducted at 50-60% of VO_{2max} , while more robust increases may be seen after exercise training at 60-85% of VO_{2max} (Segal et al. 2001). However, trying to determine the appropriate exercise intensity to prescribe for cancer patients can be difficult. Most studies have used percentages of heart rate or VO_{2max} or a combination of the two but a few studies have used either RPE or blood lactate measurements (Evans et al. 2009). Dimeo et al. (1998) trained cancer patients on the treadmill 5 days a week for 6 weeks, just below their anaerobic threshold (3.0 ± 0.5 mmol/L) at about 80% of maximum heart rate. To ensure training just below the anaerobic threshold was achieved blood lactate concentrations were checked during exercise at the end of each training week. If lactate concentrations fell below 2.5 mmol/L during exercise, the treadmill speed was increased 0.5 km/h to maintain the appropriate intensity (Dimeo et al. 1998). Results showed a significant decrease in blood lactate after training from 2.6 mmol/L to 1.3 mmol/L at a submaximal workload of 5km/h (Dimeo et al. 1998). This particular study however, only had 5 subjects of varying age and type of cancer and some were still receiving major treatments while others had finished their treatments up to 18 months before beginning the program.

Reduce fatigue and related symptoms

Many psychological benefits have been reported after exercise in cancer survivors including significant improvements in mood, fatigue, depression, anxiety, happiness, self-esteem, and quality of life (Courneya et al. 2003; Doyle et al. 2006; Knols et al. 2005). Courneya et al. (2003) reported similar results with an aerobic exercise intervention in a cancer group compared to non-exercising cancer patients. It is important to note however

that the changes in self-esteem were independent of cardiovascular changes and may be related to social interaction or a sense of accomplishment by completing the exercise program (Courneya et al. 2003). Segal et al. (2001) and McNeely et al. (2006) also report improved degrees of nausea, self-image, and physical functioning in response to exercise training. Increased levels of daily exercise may also be used as a mechanism to control stress after breast cancer treatments to help patients cope with the disease as well as have some self-control during the treatment process (Segal et al. 2001).

Musculo-skeletal improvements

Weight bearing aerobic activity in cancer patients, has been shown to increase muscle mass, increase joint lubrication, and reduce fracture occurrence in elderly patients through improved balance and stability (McTiernan 2004). Weight bearing aerobic exercise has also been shown to significantly decrease the amount of bone density lost in cancer patients when compared with control subjects (McNeely 2006). Exercise training in cancer patients has a positive impact on protein synthesis and muscle regeneration (Battaglini et al. 2006). Specific exercises to increase range of motion for breast cancer survivors may also improve connective tissue integrity and help to decrease joint pain (Battaglini et al. 2006). More research is needed to confirm or refute these preliminary findings.

Increased survival rate

Some studies have reported that physical activity (i.e., exercise) significantly decreases breast cancer recurrence and death rates (Doyle et al. 2006). Although, this was not found in the Life After Cancer Epidemiology (LACE) study, physical activity did seem to have a protective effect on total mortality in breast cancer patients regardless of

stage of cancer, menopausal status, and body mass index (BMI) (Sternfeld et al. 2009). Interestingly, vigorous exercise did not seem to show a protective effect with breast cancer recurrence, mortality or all cause mortality when compared to moderate exercise (Sternfeld et al. 2009). Improved cardiovascular fitness has been associated with decreased all cause mortality in healthy women and therefore may also positively impact breast cancer survivors (McNeely et al. 2006). Exercise training in breast cancer survivors is also thought to improve prognosis through improved immune function (Sternfeld et al. 2009).

Weight management

There is a strong correlation between increased body fat, re-occurrence rates and decreased survival (Battaglini et al. 2008; McTiernan 2004). Decreased total caloric intake during treatment can cause a loss of lean tissue with an increase in percent body fat (Battaglini et al. 2008). Exercise in breast cancer patients during treatment has shown to increase appetite and cause less of an increase in body fat percentage and body mass (Battaglini et al. 2006, 2008; Schwartz 2000). Battaglini et al. (2008) examined patients who participated in aerobic and resistance exercise training throughout their cancer treatment. Patients who exercised had a significantly higher total caloric intake, less of an increase percent body fat and a lower fatigue level at the end of the treatment period when compared with patients who did not exercise. Schwartz (2000) also examined patients who were undergoing treatment and stratified the subjects as exercisers or non-exercisers based on caloric expenditure as measured with an accelerometer. The study found that the non-exercisers had an increase in weight and BMI throughout treatment while the exercisers maintained their weight and BMI (Schwartz 2000). Specifically

during major medical treatments, a combination of exercise and diet may have a greater impact on body composition than exercise alone (McTiernan 2004).

The results of multiple studies indicate that after major medical treatments have been administered, physical exercise alone is not enough to cause a significant decrease in weight (Knols et al. 2005). One study focusing on aerobic exercise in breast cancer patients showed no improvements in body weight or BMI after treatment when compared to controls, but there was a trend toward improved body composition through decreased sum of skinfolds (Courneya et al. 2003). Segal et al. (2001) reported that breast cancer patients undergoing supervised aerobic exercise training program during treatment decreased body weight but it was not significant when compared to a control group. More specifically, the patients that had undergone chemotherapy only saw a small non-significant decrease in body weight with exercise while the control group had an increase in body weight (Segal et al. 2001). A meta-analysis of breast cancer studies also revealed a non-significant reduction in both body weight and BMI after exercise when compared to a control group (McNeely et al. 2006). Another meta-analysis of breast cancer studies showed that exercise intervention significantly decreased body fat percentage but did not have a significant impact on body weight or lean body mass (Kim et al. 2009). Aerobic exercise alone compared to aerobic and resistance training combined showed a smaller effect size on lean body mass and body fat percentage (Kim et al. 2009). Solely aerobic exercise may be more beneficial at reducing body weight in more specific sub-groups that have a higher likelihood of weight gain, such as, younger women receiving chemotherapy (Kim et al. 2009).

Conclusions

Current data show an overall beneficial effect of exercise training in cancer patients on a variety of physiological and psychological markers (Knols et al. 2005; McTiernan 2004). These results however are not found in all trials and therefore the findings should be interpreted carefully (Knols et al. 2005). The benefits of exercise may be affected by mode, intensity, and duration of the exercise program as well as the patient's baseline measurements, lifestyle, motivation, and adherence to the program (Knols et al. 2005). Precise exercise prescriptions for exercise training programs are still unclear due to the variety of types of cancer, stage of cancer, type of treatment, age of patient, and other confounding factors (Humpel & Iverson 2005). Even in breast cancer patients there is a wide variety of exercise prescribed due to the "lack of consensus on optimal exercise prescription for this patient population" (McNeely et al. 2006). More evidence-based research is necessary to help answer these questions as well as develop more precise exercise prescription guidelines (Humpel & Iverson 2005; McTiernan 2004).

III. Substrate metabolism (lipid and carbohydrate oxidation)

A. Healthy individuals during exercise

Exercise energy produced through substrate oxidation has been studied extensively in healthy individuals. Carbohydrate and fat are the primary substrates oxidized during exercise to produce energy and these substrates are used at different rates depending on exercise intensity (Brooks et al. 2005; van Loon et al. 2001). Other factors impacting the rate and amount of substrate oxidation include diet, muscle glycogen content, exercise duration, training status, fiber type make-up, and blood metabolites (Venables et al.

2005). Fuel utilization during exercise is a complex process but it seems as though the amount of substrate available and enzyme activation play the key role in healthy trained individuals (Rasmussen & Winder 1997; van Loon et al. 2001).

Carbohydrate is the primary substrate oxidized with increasing exercise intensity, while free fatty acid oxidation decreases (Rasmussen & Winder 1997). It is believed that the mechanism which causes decreased fat oxidation during high intensity exercise is an increased amount of glycolytic activity, decreased activity in the pyruvate dehydrogenase complex, decreasing the amount of free carnitine available, and limiting the amount of free fatty acids transferred into the mitochondria (van Loon et al. 2001). This decrease in available free carnitine at high intensity may also then limit the amount of carnitine palmitoyltransferase (CPT 1) enzyme activity which would also in turn reduce the amount of fat oxidation (van Loon et al. 2001).

The “crossover concept” has been identified as the point at which the relative amount of carbohydrate (CHO) utilized exceeds the relative amount of fats being oxidized and occurs in most trained individuals at about 65% VO_{2max} (Rasmussen & Winder 1997). However, in untrained men and women, this crossover point occurs much earlier at about 50% VO_{2max} (Venables et al. 2005). Relative to untrained persons, evidence suggests that the crossover point seems to occur at a significantly higher intensity in women, at about 54% VO_{2max} , when compared to men, at about 43% VO_{2max} (Venables et al. 2005).

High amounts of lactate in the blood are also associated with increasing exercise intensity and increasing utilization of carbohydrate as an energy substrate (Rasmussen & Winder 1997). Initially with low to moderate intensity exercise there is a small but linear increase in blood lactate levels. However, as exercise intensity moves from

moderate to hard/heavy, lactate levels tend to increase exponentially (Brooks et al. 2005). Increases in blood lactate can have both direct and indirect effects on limiting fat oxidation and utilization (Venables et al. 2005).

B. Cancer patients

Early studies have indicated that altered carbohydrate metabolism has been consistently recognized in cancer patients (Edmonson 1966; Glicksman & Rawson 1956; Marks & Bishop 1956; Warburg 1956). Warburg (1956) was the first to discover that lack of oxygen or toxic substances can irreversibly destroy cellular respiration in normal cells. Over time, the cells use anaerobic glycolysis to survive and altered cells, otherwise known as cancer cells are formed (Warburg 1956). The phenomenon of cancer tumor cells using anaerobic glycolysis to produce energy even in the presence of oxygen has been termed the “Warburg effect” (Levin & Gevers 1981). This was the first conclusive study stating that cancer cells thrived through altered carbohydrate metabolism.

Multiple studies have shown that glucose intolerance is apparent in 37-60% of cancer patients (Levin & Gevers 1981). A study by Edmonson (1966) indicated that glucose tolerance was significantly reduced and the level of glucose needed to suppress plasma free fatty acids was significantly higher in cancer patients compared to controls. Typically, increases in free fatty acid mobilization are seen after altered carbohydrate metabolism through either fasting or Type II diabetes (Edmonson 1966). Therefore altered carbohydrate metabolism in cancer patients may be impacted by hormonal alterations, much as is seen in diabetes. Glicksman and Rawson (1956) speculate that altered carbohydrate metabolism may come from a hormonal disturbance due to the fact that hyperglycemia is more evident in patients with cancer of endocrine organs. Other

studies have also attributed altered carbohydrate metabolism in cancer patients to insulin resistance (Levin & Gevers 1981). Specifically in breast cancer, high levels of insulin also have direct affects on breast tissue and may also indirectly affect breast cancer through interactions with other hormones (Larrson et al. 2007).

A recent study by Evans et al. (2009) exercised post-treated breast cancer patients and age-matched healthy controls at low (40% VO_{2max}), moderate (60% VO_{2max}) and high (70% VO_{2max}) exercise intensities for 9 minutes. Results indicated that there were no differences in heart rate or rating of perceived exertion between groups across all exercise intensities. There was also no difference in blood lactate results between the groups when exercising at low and moderate intensities. However, breast cancer patients exercising at a high intensity (70% VO_{2max}) produced significantly lower blood lactate of 3.3 mmol/L when compared to age-matched healthy controls with a blood lactate of 7.7 mmol/L (Evans et al. 2009). These results were unexpected and were attributed to subject age, menopausal status, and menstrual cycle phase differences between the subject groups (Evans et al. 2009). Nevertheless, these particular findings suggest that carbohydrate metabolism during exercise may not be similar in breast cancer survivors when compared to apparently healthy controls.

Collectively, the above studies suggest an association between altered carbohydrate metabolism and cancer. Nonetheless, this relationship is not fully understood and therefore more studies investigating this metabolic phenomenon are necessary to elucidate the issue.

IV. Using indirect calorimetry to predict substrate oxidation

A. Healthy individuals during exercise

Indirect calorimetry is used frequently in exercise physiology as a means to determine oxygen exchange within the body. It is assumed that during indirect calorimetry the measured oxygen uptake (VO_2) and carbon dioxide production (VCO_2) are reflective of gas exchange at the tissue level (Romijn et al. 1992, 1993). Specific metabolic calculations can then be used to determine substrate oxidation from these measurements (da Rocha et al. 2006). However, when using indirect calorimetry to predict substrate oxidation, other metabolic processes such as gluconeogenesis, lipogenesis, ketogenesis, and oxidation of lactate need to be considered as they may impact on results (Fraysn 1983; Romijn et al. 1992). Typically during exercise these other metabolic processes are not occurring at any great extent; they occur more so during the recovery period (Romijn et al. 1992). Another limitation of using indirect calorimetry to predict substrate oxidation is that it does not include protein oxidation; however, during high intensity exercise very little energy is elicited from protein oxidation (Romijn et al. 1992).

Using indirect calorimetry to measure VO_2 by the muscle has been verified but there is some controversy that at high exercise intensities increased VCO_2 values through hyperventilation may overestimate the amount of carbohydrates oxidized (Romijn et al. 1993). When exercise intensity goes above the blood lactate threshold, the bicarbonate pool may become unstable, therefore over predicting VCO_2 and carbohydrate oxidation (Romijn et al. 1992). It is assumed that utilization of VCO_2 to predict actual carbon dioxide production in the muscle is only beneficial when a subject is exercising at “low” or “moderate” steady-state intensities with a stable bicarbonate pool (Venables et al.

2005). When lactate is produced and not oxidized, oxygen and carbon dioxide are not directly involved, but the hydrogen ions produced from lactate may displace carbon dioxide from bicarbonate stores (Frayn 1983). During exercise however, lactate is typically oxidized or converted to glucose which is then oxidized therefore resulting in similar respiratory gases (Frayn 1983; Romijn et al. 1992). Romijn et al. (1992) further illustrated this point and validated the use of indirect calorimetry to calculate carbohydrate and fat oxidation in trained healthy men exercising at a “high” intensity above their lactate threshold at 85% of VO_{2max} .

The respiratory exchange ratio (RER) is a ratio of the amount of VCO_2 by the amount of VO_2 . The ratio can be measured through indirect calorimetry procedures. The RER can be assessed during rest or exercise and subsequently used to determine exercise energy metabolism, providing information on substrate oxidation and utilization (Brooks et al. 2005; McArdle et al. 2007). As the values increase from 0.70 to 1.00 more carbohydrate is being oxidized and less fat is being oxidized with equal amounts (i.e., 50% CHO, 50% fat) being oxidized at 0.85 (McArdle et al. 2007). During exercise VO_2 and RER together can be used to calculate how many calories are being utilized for energy production. It is known that carbohydrate contains 4.02 kcal per gram while fat contains 8.93 kcal per gram (McArdle et al. 2007). Therefore carbohydrate and fat oxidation can be determined by multiplying the amount of calories expended each minute by the percentage of each substrate being oxidized. The amount of carbohydrate and fat oxidized each minute is then divided by 4.02 and 8.93 to come up with amount in grams, respectively.

B. Clinical populations at rest and during exercise

Indirect calorimetry has been used extensively in healthy populations but has also been beneficial for clinical populations. Disease states can have significant impacts on nutritional status and therefore indirect calorimetry has been used in clinical populations to determine energy expenditure and substrate oxidation at rest (da Rocha et al. 2006). Indirect calorimetry can be used in a variety of patients including those that are critically ill, such as cancer patients, to use predictive equations of energy expenditure as well as determine substrate oxidation (Holdy 2004; Reeves et al. 2004). This technique is typically used in combination with nutritional counseling in an effort to determine total energy expenditure and substrate utilization in a wide variety of clinical patients (Holdy 2004).

Current work by da Rocha et al. (2006) supports the use of gas exchange to assess metabolic alterations in clinical populations and also to monitor a patient's nutritional status at rest. Demark-Wahnefried et al. (1997) used indirect calorimetry to determine resting metabolic rate in Stage I - II breast cancer patients at various stages throughout their chemotherapy treatments. While most of the previous studies were performed at rest, the American College of Sports Medicine (ACSM) suggests that respiratory gases, specifically $\dot{V}CO_2$ and RER may be used in clinical populations during exercise to determine substrate oxidation (ACSM 2009). Therefore using indirect calorimetry to predict substrate oxidation during exercise in cancer patients seems to be a valid procedure.

Conclusion

It is apparent that exercise has a positive impact on breast cancer survivors in many ways. As research continues however there will be a better understanding of how exercise impacts a cancer survivor's physiology. Yet, some questions still remain as to how cancer or cancer treatments may cause physiological changes which can affect exercise metabolism. More specifically it is unclear if cancer, or treatment of cancer, alters substrate oxidation which could impact a patient's ability to exercise at certain intensities. Therefore the purpose of this study will be to explore how cancer and subsequent treatments may alter substrate oxidation during exercise in an attempt to elucidate this issue.

CHAPTER III

METHODOLOGY

Subjects

Cancer patients for this study were recruited from the *Get REAL and HEEL* program on the UNC – Chapel Hill campus (i.e., treatment group). Participants in the program ranged from 25 – 75 years old and had been diagnosed with Stage I – Stage III breast cancer. All major medical treatments had been completed within the last 6 months prior to enrollment in *Get REAL and HEEL*. Women for the healthy control group were recruited from the Chapel Hill town area and were matched to patients in the treatment group based on age, physical activity, and menopausal status.

This human subjects study was approved by the Internal Review Board (IRB) at UNC – Chapel Hill. Before agreeing to the study, all subjects met with the primary investigator to go over the experimental protocol. Subjects were informed of all risks associated with the study and then were allowed to read and sign the informed consent form. They were also given a physical activity questionnaire (PAQ; modeled after the modifiable activity questionnaire) assessing activity levels over the past year (Kriska 1997). Subjects completed the PAQ (Appendix A) at the first meeting and scores from the questionnaire were used in matching the breast cancer patients with healthy controls. All breast cancer patients were cleared by their personal physician to participate in physical activity while all control subjects completed a physical screening and 12-lead resting ECG at the Applied Physiology Laboratory (APL) for clearance to participate.

All subjects were given pre-assessment guidelines to follow before any exercise testing occurred. The guidelines included no exercise 24 hours prior to testing, no alcohol consumption 48 hours prior to testing, no eating 2 hours prior to testing, and no diuretics taken 7 days before testing unless prescribed by a physician. Subjects were excluded from the study based on the following criteria; an abnormal ECG, a recent history of smoking (quit \leq 2 years ago), any known metabolic disease, acute or chronic illness, elevated resting vitals, physical injury, or inability to complete a submaximal cycle ergometer test.

Instrumentation

Subjects' height and weight were measured on a portable stadiometer (Perspectives Enterprises, Portage, MI) and mechanical scale (Detecto, Webb City, MO), respectively. Lange calipers (Beta Technology, Santa Cruz, CA) were used to take skin fold measurements to estimate body composition. Blood oxygen saturation levels were measured using a 3301 model BCI International pulse oximeter (BCI International, Waukesha, WI). All exercise sessions were performed on a Corival model, "Lode" electronically braked cycle ergometer (Lode BV, Groningen, The Netherlands). Heart rate was obtained through a Polar® heart rate monitor (Polar Electro, Inc., Lake Success, NY). An Oro-Nasal 7400 VMask facemask (Hans Rudolph, Inc., Shawnee, KS) with headgear was used to collect respiratory gases. Respiratory gas was analyzed through indirect calorimetry with a Parvo Medics TrueMax2400 Metabolic System (Parvo Medics, Salt Lake City, UT). An Accu-Chek Softclix Pro lancet device (Hoffmann-LaRoche Ltd., Basel, Switzerland) was used to obtain a small blood sample from the

finger for analysis. A “Lactate Plus” lactate analyzer (Nova Biomedical, Waltham, MA) was used for all blood lactate measurements. A “One Touch Ultra” glucometer (Lifescan, Inc., Milpitas, CA) was used for all blood glucose measurements.

YMCA test (maximal oxygen uptake)

Once the subjects had been cleared for participation they reported to the APL for their first exercise test. This test was used to estimate their VO_{2max} value. Once in the laboratory, subjects sat down with a researcher to record menstrual status and verify that pre-assessment guidelines had been followed. The subjects then underwent a brief orientation with the equipment and reviewed the procedure for that day. Subjects were then fit with a heart rate monitor and asked to rest in a seated position for 5 minutes. After 5 minutes of quiet rest, heart rate (HR), blood pressure (BP), and blood oxygen saturation levels (SpO_2) were recorded. Once resting HR was recorded, 70% of heart rate reserve (HRR) was calculated using the Karvonen formula. Subjects did not continue with the exercise session if any of the following resting vitals were observed:

- $HR \geq 100$ bpm (beats per minute)
- Systolic BP ≥ 140 mmHg
- Diastolic BP ≥ 90 mmHg
- SpO_2 saturation $\leq 90\%$

Age, weight, and height were recorded and then skin fold measurements were taken at 3 sites (triceps, suprailiac, and abdomen) to determine body composition using the Jackson and Pollock equation for women (as reported by ACSM 2009; Evans et al. 2009).

For cycle ergometry, each subject was fit onto the ergometer and the seat height was adjusted so that there was a 5 – 10° bend in the knee of the extended leg. Seat height was recorded at the end of exercise for future sessions. They were also fit with a ‘7400 Vmask’ facemask secured tightly around their head which was worn throughout the testing to collect respiratory gases. Resting respiratory gases were taken for 3 – 5 minutes while the subject was seated in a resting position on the ergometer. The participant then immediately began a 3 – 5 minute warm-up at a low intensity (25 Watts) on the electric cycle ergometer.

The testing protocol consisted of the YMCA submaximal test as described by the American College of Sports Medicine (ACSM) guidelines (2009). All subjects began the first 3 minute stage at 25 Watts (W). Heart rate was recorded during the last 15 seconds of the 2nd and 3rd minute of each stage while the rating of perceived exertion (RPE) was recorded during the last 30 seconds of each stage using Borg’s (6–20) scale. If the subjects’ recorded HR was within 5 bpm between the 2nd and 3rd minute of the stage, the subject then moved on to the next stage. If the subject’s HR was greater than 5 bpm difference between the 2nd and 3rd minute of the stage, they continued for a 4th minute. The HR between the 3rd and 4th minute was compared and had to fall within 5 bpm to proceed to the next stage. This was done to verify that the subject had achieved a steady state response at each stage. The workload of the 2nd stage was determined by the steady-state HR attained in the first stage as seen below:

	STAGE 1: 25 W			
	HR: < 80	HR: 80 - 90	HR: 90 - 100	HR: > 100
STAGE 2	125 W	100 W	75 W	50 W
STAGE 3	150 W	125 W	100 W	75 W

Table 1 – Chart used during the YMCA test to determine workload after the first stage.

The exercise test continued until the subject completed 2 stages in which their HR was between 110 bpm and 70% of their HRR. The exercise test was also terminated if the subject obtained a HR > 150 bpm, they could not maintain the workload, the subject requested to stop, or the investigator felt that the test should be terminated for safety reasons.

Immediately after the exercise test was over the workload was reduced to 20W for a cool down of 3 – 5 minutes. During the cool down period the subject was able to remove the facemask and consume fluids *ad libitum*. Vital signs were continually monitored throughout the recovery period and the subject was able to stop pedaling and dismount the bike when vitals had appreciably decreased and stabilized. Subjects were cleared to leave the APL when HR was ≤ 100 bpm, systolic BP was within 20 mmHg of resting values, SpO₂ was within 5% of resting values, and they were showing no other signs of distress or discomfort.

Calculations

Based on the results of the YMCA submaximal test, the subject’s predicted maximal workload was determined using a regression equation of workload versus HR

response. This workload was then used to predict VO_{2max} using the ACSM equation: Leg cycling VO_2 (ml/kg/min) = $[1.8 \times \text{work rate (kgm/min)}/\text{body mass (kg)} + 3.5$ (ml/kg/min) + 3.5 (ml/kg/min) (ACSM, 2009). A regression of actual and predicted workloads and VO_2 values was used to prescribe workloads for submaximal exercise sessions. Specifically, each subject completed 3 submaximal exercise sessions that corresponded with 40% (low intensity), 60% (moderate intensity), and 70% (high intensity) of their predicted VO_{2max} . The three exercise sessions were randomly assigned to each subject in an attempt to decrease confounding outcomes. Subjects returned 2 – 7 days after the YMCA protocol test to begin their submaximal exercise sessions.

Exercise sessions

For all cancer patients enrolled in the *Get REAL and HEEL* program, the exercise sessions were used as the cardiovascular training portion of their workout for that day. Subjects returned to the APL at least 48 hours after their YMCA test for their first submaximal exercise session. Once at the laboratory, subjects put on a heart rate monitor and sat upright in a resting position for several minutes. During this rest period, they were prompted by the investigator to complete a 24-hour recall of their diet (Appendix B). The information from the dietary recall was entered into the website, <http://www.sparkpeople.com>, to determine total caloric intake, percentage of carbohydrate and percentage of fat consumed in the previous 24 hours. This was performed to ensure that the subjects were in a eucaloric state and that their carbohydrate intake was within a normal range of 45 – 55% of daily caloric intake (Manore & Thompson 2000). The investigator also confirmed that the subjects had been fasting for

the past 2 hours and documented any changes in the subject's menstrual status. Next, the equipment use and exercise protocol for the day was reviewed with the subjects. Resting HR, BP, and SpO₂ were recorded, and just as with the YMCA submaximal test, the exercise session did not progress forward if HR \geq 100 bpm, systolic BP \geq 140 mmHg, diastolic BP \geq 90 mmHg, or SpO₂ \leq 90% were observed. A resting blood lactate and blood glucose sample were then taken using a finger puncture technique and immediately analyzed (described in Blood analysis section).

The subject then positioned themselves on the electric cycle ergometer and secured the facemask tightly around their head to collect resting metabolic data for 3 – 5 minutes. Once the calorimetry system had stabilized, the subject then began a 3 – 5 minute warm-up period at 20W on the electric cycle ergometer. Exercise sessions consisted of 9 minutes of steady-state exercise at the randomly chosen prescribed workload for the day and started immediately after the warm-up (Evans et al. 2009). All subjects were blinded to the specific exercise workload for each session. The exercise protocol lasted for 9 minutes or until the subject could not maintain the workload, the subject requested to stop, or the investigator felt that the exercise session should be terminated for safety reasons. Indirect calorimetry was performed throughout the exercise session with respiratory gas analysis updated every 15 seconds. Heart rate and RPE were taken during the last 15 seconds of every minute during the exercise session to ensure safety.

Following the submaximal exercise, the workload was reduced to 20W for a cool-down of 2 minutes and the facemask was removed. At the end of the 2nd minute of the cool-down the subject was asked to stop pedaling and remain seated on the cycle

ergometer. A final blood lactate and blood glucose measurement were taken during the last 30 seconds of the 3rd minute into recovery. Once the last blood sample had been taken the subject was able to consume fluids and dismount the cycle ergometer. Vital signs were continually monitored throughout the recovery period and the subject was cleared to leave the APL when HR was ≤ 100 bpm, BP was within 20 mmHg of resting values, SpO₂ was within 5% of resting values, and they were showing no other signs of distress or discomfort. *Get REAL and HEEL* participants were then transported to the clinic for the remainder of their exercise session for the day. The same protocol was repeated twice more, with at least 48 hours between sessions, over the next 2 weeks.

Blood analysis

Finger punctures were used throughout the testing for blood analysis. For resting measurements the fingertip was placed in a cup of warm water to increase blood flow to the area. The fingertip was dried and then cleaned with an alcohol pad to remove dirt and debris. The area was then wiped with a sterile gauze pad to remove any residue of sweat or alcohol. A lancet device was set with a depth setting of 3 – 5 for the skin puncture. The finger was punctured using the lancet and the finger was massaged distally until a small bead of blood appeared. A blood lactate measurement was taken first and a blood glucose measurement was taken immediately afterwards from the same site. If possible a duplicate blood lactate sample was also taken. The finger puncture was then covered with a sterile gauze pad and the subject was asked to add some compression for about 1 – 2 minutes or until bleeding stopped. These steps were replicated for the resting and post-exercise blood sampling. After the exercise session additional first-aid care was provided

to the subject as needed. The biochemical basis for the lactate analyzer and glucometer analytical procedures are reported in the appendices (Appendices C and D).

Respiratory gas analysis

Both the oxygen uptake (VO_2) and respiratory exchange ratio (RER) were averaged for the last 5 minutes (min 4 – min 9) of the 40%, 60%, and 70% exercise sessions. If the subject did not complete all 9 minutes, only the minutes completed after 4 minutes were averaged. Based upon these averages the amount of calories expended per minute was calculated. The RER data was then broken down into the percent of lipids and carbohydrates oxidized per minute (McArdle et al. 2007). Finally the total amount of grams oxidized per minute for each substrate was calculated for the 5 minute steady state period (McArdle et al. 2007). An example of these calculations appears in Appendix E.

Statistical analysis

All statistical procedures were performed using version 17.0 of Statistical Package for the Social Sciences (SPSS) software (SPSS Inc, Chicago, IL). Statistical significance was set a priori at an α level of $p \leq 0.05$. A one-way ANOVA was run on the demographic characteristics of the 2 groups. For the metabolic data a 2 x 3 mixed model ANOVA (group x intensity) was applied on the rate of lipid and carbohydrate oxidation (g/min) averaged over the last 5 minutes of steady-state submaximal exercise sessions. A Tukey HSD post hoc test was used to determine mean differences when a significant effect was found (hypotheses - H1, H2). A 2 x 3 x 2 mixed model ANOVA

(group x intensity x time) was also applied on blood lactate measurements. A Tukey HSD post hoc test was used to determine mean differences if a significant effect was found (hypotheses - H3, H4). A Pearson product moment correlation was run between carbohydrate oxidation and recovery blood lactate over all 3 exercise intensities within each of the groups (hypothesis - H5). A Hotelling test was applied between groups to determine if the correlation for each group was significantly different (hypothesis - H5).

CHAPTER IV

RESULTS

Subjects

There were 14 subjects who participated in the study; seven women in the treatment group and seven women in the control group. All women in the treatment group had been diagnosed with breast cancer, undergone surgery and had completed their major medical treatments within the last six months. One woman had been diagnosed with Stage I breast cancer while three subjects had been diagnosed with Stage II and three subjects had been diagnosed with Stage III breast cancer. Four of the women received both chemotherapy and radiation treatment, while one woman received only chemotherapy and two women received only radiation therapy as their major medical treatments. Six out of the seven women in the treatment group were also on adjunctive therapies (i.e., Herceptin, Tamoxifen, Femara) during this research study. All women in the control group did not have a history of cancer or any pre-existing medical conditions that restricted them from exercising and had been essentially sedentary for the last year.

The subject groups were matched on age (± 4 years; range 38 – 66 years), physical activity level and menopausal status. There were no significant differences ($p > 0.05$) between the groups for these characteristics (Table 2). Although the groups were not specifically matched for height, weight, body mass index (BMI), or body fat percentage, there was no significant difference between groups for any of these parameters either (Table 3).

Group	Age (yr)	Activity Level (MET h/wk)	Menopausal status (# of women)
Treatment	50.6 ± 3.3	77 ± 6	Pre-menopausal (1) Peri-menopausal (3) Post-menopausal (3)
Control	50.9 ± 3.6	65 ± 10	Pre-menopausal (3) Peri-menopausal (2) Post-menopausal (2)

Table 2 – Matching factors characteristics (mean ± SE).

Group	Height (cm)	Weight (kg)	BMI (kg/m²)	Body fat (%)
Treatment	166.5 ± 2.6	81.6 ± 4.2	28.6 ± 1.1	31.8 ± 1.6
Control	162.8 ± 1.6	75.4 ± 5.4	28.2 ± 1.9	31.2 ± 2.2

Table 3 – Subject physical characteristics (mean ± SE).

Subjects were asked to consume their typical diet over the course of the research study and a 24 hour dietary recall was administered before each submaximal exercise session to confirm dietary intakes. There were no significant differences ($p > 0.05$) for total caloric intake, percentage of carbohydrates (CHO) consumed, or percentage of fat consumed between groups at each submaximal exercise session (Table 4).

Prescribed Intensity	Group	Total Caloric Intake (kcal)	CHO (%)	Fat (%)
Low (40% VO_{2max})	Treatment	1942 ± 205	51 ± 5	33 ± 4
	Control	1878 ± 298	52 ± 3	34 ± 3
Moderate (60% VO_{2max})	Treatment	1940 ± 166	52 ± 4	31 ± 3
	Control	1813 ± 305	57 ± 4	28 ± 5
High (70% VO_{2max})	Treatment	2207 ± 259	53 ± 5	28 ± 4
	Control	1479 ± 148	56 ± 3	30 ± 4

Table 4 – Subject dietary intake 24 hours prior to each submaximal exercise session (mean ± SE).

YMCA test (maximal oxygen uptake)

The results of the YMCA test to predict VO_{2max} are reported in Table 5. Furthermore, Table 5 also displays the calculated workloads measured in Watts (W) to elicit the low (40% VO_{2max}), moderate (60% VO_{2max}), and high (70% VO_{2max}) submaximal exercise sessions for each of the subjects. The predicted VO_{2max} , the predicted maximal workload, and workloads at all of the submaximal exercise intensities were not significantly different between groups ($p > 0.05$).

Group	VO_{2max} (ml/kg/min)	Wkld_{max} (W)	Low 40% VO_{2max} (W)	Moderate 60% VO_{2max} (W)	High 70% VO_{2max} (W)
Treatment	22.0 ± 1.5	108 ± 6	39 ± 4	61 ± 4	75 ± 5
Control	24.1 ± 1.7	115 ± 10	43 ± 4	69 ± 5	79 ± 6

Table 5 – Maximal aerobic capacity (VO_{2max}), maximal workload (Wkld_{max}), and workload for each submaximal exercise session (mean ± SE).

Submaximal exercise sessions

Table 6 presents the actual measured percentage of VO_{2max} and percentage of Wkld_{max} across the different submaximal exercise intensities. While there are slight variances in the percentage of the exercise sessions when expressed as a percentage of VO_{2max} or maximal workload, no significant differences were noted between the groups for the respective submaximal exercise sessions ($p > 0.05$).

Prescribed Intensity	Group	Actual Intensity (%VO_{2max})	Actual Workload (% Wkld_{max})
Low (40% VO_{2max})	Treatment	41 ± 5	36 ± 4
	Control	45 ± 2	37 ± 2
Moderate (60% VO_{2max})	Treatment	55 ± 4	57 ± 3
	Control	59 ± 2	60 ± 2
High (70% VO_{2max})	Treatment	65 ± 5	70 ± 2
	Control	65 ± 2	69 ± 2

Table 6 – Actual percentage of VO_{2max} and Wkld_{max} during each submaximal exercise session (mean ± SE).

During the submaximal exercise sessions there was a significant ($p \leq 0.05$) main effect of intensity on both heart rate (HR) response and rating of perceived exertion (RPE). However, there was no significant difference between HR response (mean ± SE) for the treatment group (120 ± 6, 130 ± 5, 147 ± 5 bpm) versus the control group (115 ± 4, 135 ± 4, 145 ± 4 bpm; $p > 0.05$) group at the low, moderate, and high submaximal exercise intensities respectively. Similarly, RPE responses (mean ± SE) for the treatment group (11 ± 1, 13 ± 1, 14 ± 1) versus the control group (10 ± 1, 12 ± 1, 14 ± 1; $p > 0.05$) did not differ at the low, moderate, and high submaximal exercise intensities respectively.

The VO₂ and RER values were averaged for the last 5 minutes (min 4 – min 9) of each submaximal exercise session and used to calculate carbohydrate and fat oxidation rates. There were only two subjects, one from each group, who were unable to complete the full 9 minutes of submaximal exercise during the high intensity session. For those subjects, only the minutes completed after minute 4 (i.e., steady-state obtained) were used in the calculations. There was a significant ($p \leq 0.05$) main effect of group and exercise intensity for both carbohydrate and fat oxidation rates (see Figure 1). The treatment group oxidized significantly less carbohydrate and more fat across all exercise intensities when compared to the control group.

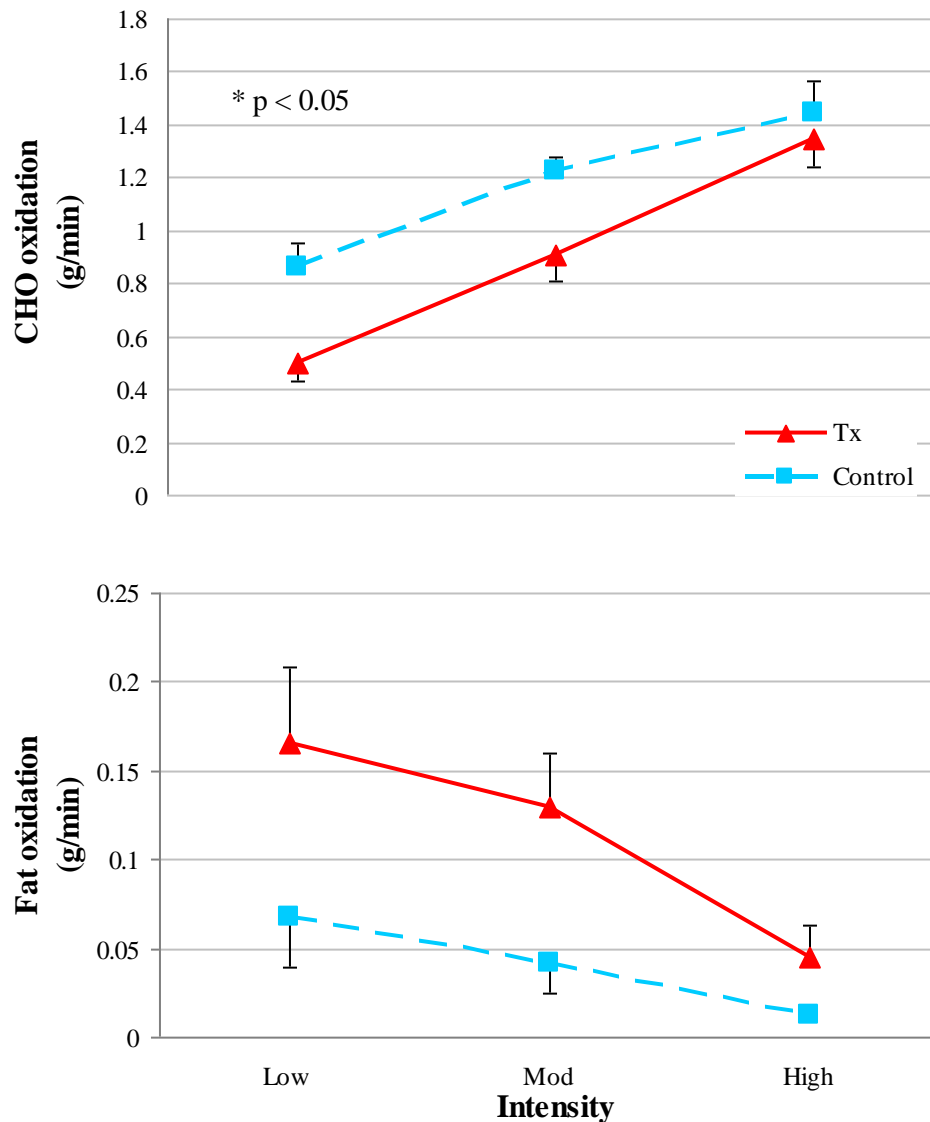


Figure 1 - Carbohydrate (CHO) and fat oxidation rates at different submaximal exercise intensities (mean \pm SE). Mod = Moderate intensity and Tx = Treatment grouping in the figure.

There was a significant interaction effect of exercise intensity and time (i.e., pre vs. post) on blood lactate responses to the submaximal exercise sessions ($p \leq 0.05$). That is, the post-exercise lactate response became greater as exercise intensity increased in both groups. There was also a significant interaction effect for group and time within blood lactate responses (Figure 2). Specifically, the latter finding points to there being a

greater concentration of blood lactate in response to exercise (i.e., post) across all submaximal exercise sessions in the control group compared to the treatment group.

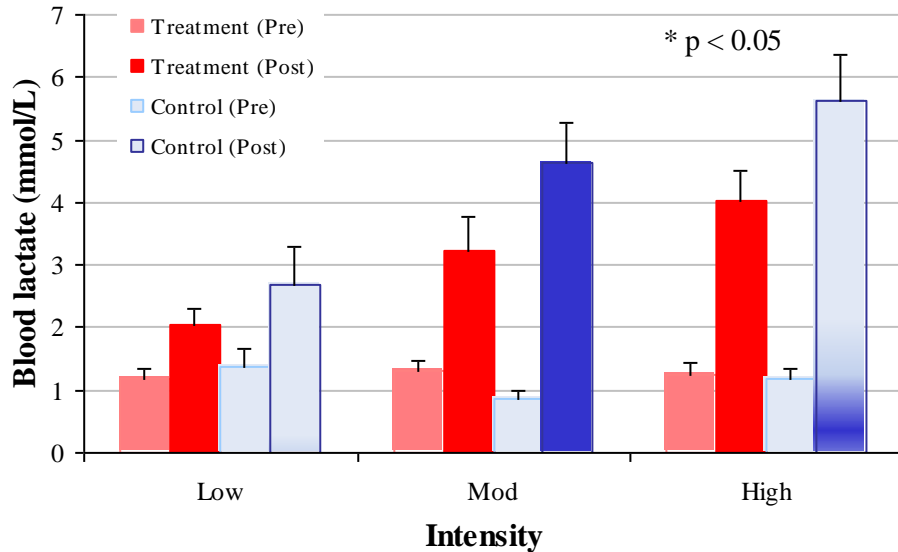


Figure 2 – Pre-exercise and post-exercise blood lactate values at different submaximal exercise intensities. Mod = Moderate intensity in figure.

There was a significant ($p \leq 0.05$) main effect of time on the blood glucose response across all submaximal exercise intensities (Figure 3); i.e., glucose decreased post-exercise. These blood glucose responses also approached significance ($p = 0.079$) for a three-way interaction of group, exercise intensity and time. In this case, the control group tended to have lower resting glucose and a more pronounced and consistent decrease in glucose concentrations post-exercise than the treatment group.

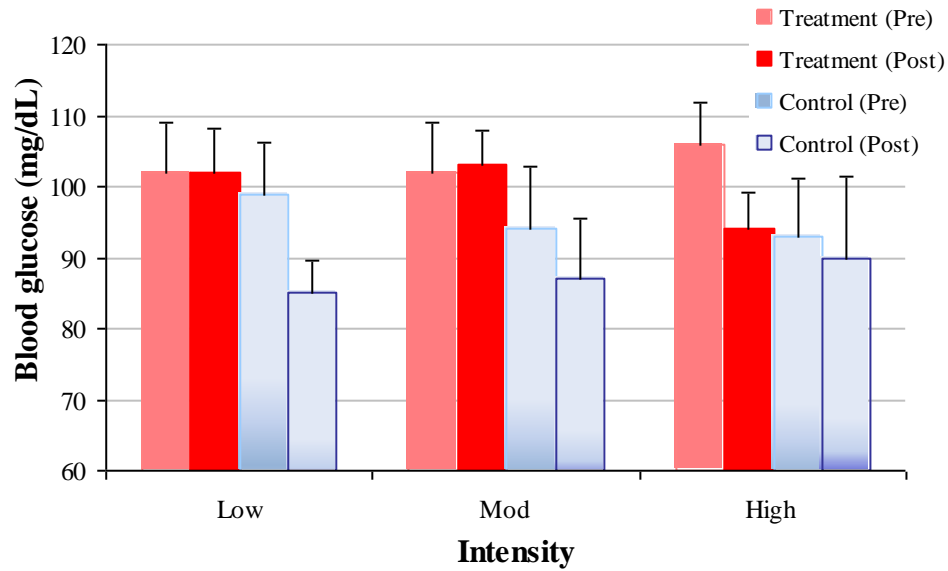


Figure 3 – Pre-exercise and post-exercise blood glucose values at different submaximal exercise intensities. Mod = Moderate intensity in figure.

Carbohydrate oxidation and post-exercise blood lactate responses were significantly correlated ($p \leq 0.05$) for both the treatment ($r = 0.549$) and control groups ($r = 0.635$). Although there was a stronger correlation in the control group, it was not significantly different ($p > 0.05$) from the treatment group coefficient (Figure 4, 5).

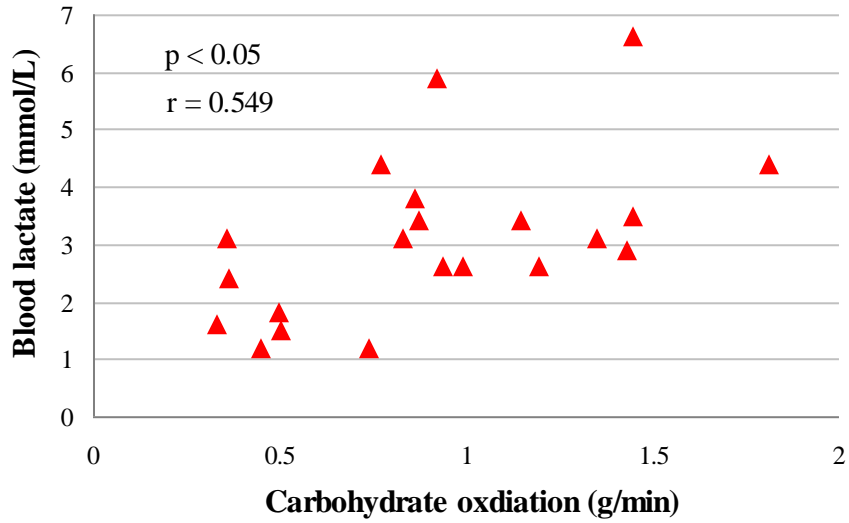


Figure 4 – Carbohydrate oxidation rate and post-exercise blood lactate response at all submaximal exercise intensities in the treatment group.

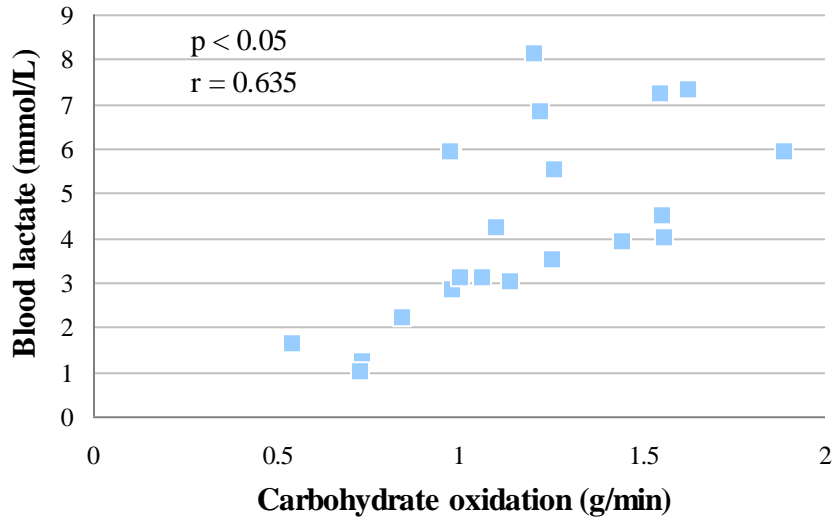


Figure 5 – Carbohydrate oxidation rate and post-exercise blood lactate response at all submaximal exercise intensities in the control group.

CHAPTER V

DISCUSSION

Introduction

The aim of this study was to develop a better understanding of substrate oxidation (i.e., energy metabolism) at different exercise intensities in post-treated breast cancer patients compared to healthy women. The goal of obtaining this information is to provide insight into how to develop more accurate and precise exercise prescriptions for cancer patients. What follows is a discussion of the results and findings from this research study. This chapter contains a brief synopsis of the physiological outcomes, a comparison of the results with previous literature findings, and some possible physiological explanations as to why the results occurred. Finally the practical implications of the findings are discussed.

Exercise responses

The subjects recruited into both study groups were predominantly sedentary in nature. This fact is confirmed by the predicted maximal oxygen uptakes in each group; treatment group = 22.0 ± 1.5 ml/kg/min, and control group = 24.1 ± 1.7 ml/kg/min. According to the American College of Sports Medicine these outcomes classify the groups at low levels of aerobic physical fitness (ACSM 2009).

The subjects of each group responded appropriately to all submaximal exercise sessions (Brooks et al. 2005). Specifically, there was a significant increase in VO_2 , RER,

HR, and RPE from rest to exercise during all submaximal exercise sessions in both groups. Both groups also elicited significant and greater increases in VO_2 , RER, HR, and RPE during exercise as the intensity of the submaximal sessions increased from low (40% $\text{VO}_{2\text{max}}$) to moderate (60% $\text{VO}_{2\text{max}}$) to high (70% $\text{VO}_{2\text{max}}$).

Blood lactate levels also increased from rest to post-exercise and as the exercise sessions became more intense, there were larger increases in lactate. An increase in blood lactate during exercise with greater increases in intensities agrees with previous studies (Brooks et al. 2005; Evans et al. 2009). However, there was a significantly greater overall response in blood lactate to exercise in the control group compared to the cancer treatment group across all exercise intensities. This finding agrees in part with the work of Evans and associates (Evans et al. 2009). In that study the lactate responses of the cancer patients were only significantly less than that of healthy control subjects after high intensity exercise (~ 70% $\text{VO}_{2\text{max}}$). Why the results of the Evans and present studies are somewhat conflicting is uncertain. These differences may be attributed to the mode of exercise (treadmill vs. cycle ergometer), the subject group characteristics, or the small sample sizes used in each of the studies. Regardless of these differences, there is evidence in both studies for decreased blood lactate production during exercise in breast cancer patients when compared to healthy women.

The present findings of overall lower lactate responses at all exercise intensities (low, moderate and high) in cancer patients is a new and novel finding. These lower lactate responses in the cancer group are in line with the reduced carbohydrate oxidation and greater fat oxidation found in this group compared to the control group across all exercise intensities. These physiological events are in agreement, that is, if less

carbohydrate is being oxidized, then a reduced amount of lactate should be produced (Brooks et al. 2005). It is well established that as exercise intensity increases there is a greater reliance on carbohydrate and a reduction in fat as an energy source, which was observed in both study groups (Brooks et al. 2005). But, the finding of between group differences in the magnitude of the oxidation rates of carbohydrate and fat is also a new novel finding, having never been reported in the literature previously. It is unknown whether this reduced oxidation of carbohydrate in the cancer treatment group is resulting in the reduced lactate in the blood due to: substrate (i.e., glucose) being unavailable, a reduced glucose uptake by muscle, or a compromised glycolysis biochemical process in muscle. This last point cannot be determined from the present data, but is in need of evaluation within future studies.

Possible physiological explanations

Why carbohydrate oxidation is reduced and fat oxidation is enhanced in the cancer patients is unknown. Some of the possibilities may be related to pre-existing conditions, the actual disease process itself or the medical treatments administered to the patients. The following discussion will explore some of these explanations and determine if they are plausible or not.

While all of the women were considered healthy, (other than breast cancer in the treatment group), some women were also classified as overweight, obese or menopausal. Metabolic alterations have been displayed in overweight and obese populations which may increase lipolysis (McMurray & Hackney 2005). During exercise, obese populations have blunted sympathetic nervous system and catecholamine response which

may alter the extent of lipolysis; however the rate of fat oxidation does not seem to differ between obese and normal weight individuals (McMurray & Hackney 2005). Figure 1 indicates, however, that there was a significant difference between groups in this study for fat oxidation. Furthermore, there was no significant difference in BMI or body fat percentage between the groups (Table 3); therefore, the difference in substrate oxidation observed cannot be attributed to adiposity related factors.

Women who have begun menopause begin to produce less estrogen from their ovaries which can impact metabolism (McMurray & Hackney 2005). A lower level of circulating estrogen is associated with increased carbohydrate oxidation and blood lactate production during exercise; i.e., opposite of what was seen in the treatment group (Bunt 1990; Evans et al. 2009; McMurray & Hackney 2005). The results of this study show that there was no significant difference between groups for menopausal status; although there were actually more menopausal women in the treatment group than the control group. Therefore a divergent menopausal status between the groups does not seem to explain the difference in fat and carbohydrate oxidation observed between the groups.

The disease process of cancer has been associated with endocrine changes which may impact metabolism (Edmonson 1966; Glicksman & Rawson 1956; Marks & Bishop 1956; Sommers 1955). For example, a study by Sommers (1955) found that the majority of breast cancer patients presented with endocrine abnormalities; in particular, the pituitary and ovaries were found to be in a hyper-functional state. It is believed that these abnormal endocrine gland actions cause an increase in estrogen release from either the ovaries or the adrenal cortex which is stimulated through the pituitary-adrenal pathway (Sommers 1955). Increased circulating levels of estrogen can have large effects on

metabolism. Specifically, estrogen can directly and indirectly increase lipolysis and lipid (fat) oxidation both at rest and during exercise (McMurray & Hackney 2005).

The disease state of cancer has also been associated with mild to moderate hyperglycemia, glucose intolerance, and insulin resistance which may impact metabolism as well (Edmonson 1966; Glicksman & Rawson 1956; Marks & Bishop 1956). There was no significant difference between groups for resting blood glucose in the current study which is consistent with some previous literature (Edmonson 1966; Glicksman & Rawson 1956). However, resting levels of blood glucose were slightly higher in the cancer treatment group compared to the control group. Interestingly, there was less of a decrease in blood glucose after exercise in the cancer group when compared to the control group (Figure 2). Although these glucose findings only approached significance ($p < 0.10$), they nonetheless support the concept of glucose intolerance in cancer populations which could be driven in-part by a developing insulin resistance (Edmonson 1966; Glicksman & Rawson 1956; Marks & Bishop 1956). Perhaps to some degree this effect is persisting even into exercise within the cancer patients and compromises their ability to metabolize carbohydrate. This however is only speculation and would need to be confirmed with an oral glucose tolerance test and hormonal measurements which was not possible in the current study.

Specific cancer treatments may also be impacting metabolism in these breast cancer patients. The goal of cancer treatments is to destroy cancerous tissues and cells (Lane & McKenzie 2005). Radiation therapy is localized and destroys cancerous cells by fracturing their DNA sequence (Kaur et al. 2010). Chemotherapy, anti-hormonal drug treatments such as Tamoxifen and Femara, and biological therapies such as Herceptin,

are all systematic therapies used to treat breast cancer (Kaur et al. 2010). Although these treatments are meant to impact cancerous tissue primarily, they are not always selective and healthy systemic tissue may also be negatively impacted by these harsh treatments causing unwanted side effects (Lane & McKenzie 2005). All of the cancer patients within this study had or were currently receiving some sort of systemic treatment (i.e., chemotherapy, anti-hormonal therapy, biological therapy). It is highly possible that healthy cells are impacted when these systemic treatments target the cancer cells and destroy their metabolic process. Decreasing carbohydrate metabolism ability within the cancer cell is essential to destroy the tumor but consequently it can be detrimental to healthy cells attempting to produce energy during exercise.

Most of the patients (5 out of 7) in the current study were receiving anti-hormonal therapies such as Tamoxifen or drug agents which mimic Tamoxifen. While Tamoxifen, and similar drugs, are meant to work against the negative actions of estrogen at breast tissue, these drugs actually act in the same way as estrogen at many other tissues in the human body (NCI, 2010). As stated earlier, increased amounts of circulating estrogen has both a direct and indirect effect on increasing lipid metabolism and inhibition of carbohydrate metabolism (Bunt 1990). Although estrogen has direct effects on lipolysis it also may directly reduce glucose uptake in the muscle (McMurray & Hackney 2005). The current results support this concept through the observed decreased carbohydrate oxidation as well as less of a change in blood glucose in the cancer group during exercise.

Exogenous estrogen can also have indirect effects on substrate oxidation. Bunt (1990) has reported that estrogen can result in increased levels of cortisol, due to estrogen stimulating the adrenal cortex. In addition, Tamoxifen has been shown to substantially

increase plasma cortisol concentrations in breast cancer patients (Levin et al. 1981). Cortisol is a powerful lipolytic hormone and is connected to increased fat metabolism at rest and during exercise (Hackney 2006). The resulting lipolysis from cortisol elevations can be further enhanced through estrogen (or Tamoxifen acting like estrogen), by promoting growth hormone (hGH) release from the anterior pituitary (Bunt 1990). Growth hormone is likewise known to promote lipolysis and free fatty acid mobilization at rest and in response to exercise (Bunt 1990; Hackney 2006). Furthermore, these actions of cortisol and hGH can promote a reduction in glycogenolysis which in turn decreases glycolytic substrate availability and lactate production (Bunt 1990; McMurray & Hackney 2005).

Additionally, estrogens have been shown to result in a chronic elevation of the insulin:glucagon (I:G) ratio which further reduces the rate of glycogenolysis (Bunt 1990). Such actions on the I:G ratio can lead to decreased insulin sensitivity, promote glucose intolerance and hyperglycemia (Bunt 1990; McMurray & Hackney 2005). Changes in glucose tolerance have been observed in women who receive exogenous estrogen through oral contraceptives or hormone replacement therapy (Bunt 1990). Furthermore, women using oral contraceptives have exhibited higher blood glucose levels, greater hGH and cortisol responses, and slightly greater lipid oxidation and reduced glycogenolysis during submaximal exercise when compared to non-oral contraceptive users (Bunt 1990).

Chemotherapy treatments and the use of Tamoxifen-like drugs may be compounding this myriad of events to further disrupt normal energy metabolism in cancer patients during exercise. This means that some drug therapies used by the cancer patients may result in part for their altered energy metabolism during exercise which

promotes the reduced lactate responses observed in this study. Obviously, without hormonal measurements from this study to confirm this hypothesis, the above must be considered speculation. Nonetheless, this does provide another and highly plausible explanation for the metabolic findings in the study.

It is evident that there is decreased carbohydrate metabolism during exercise in post-treated breast cancer patients when compared to controls. Whether this altered metabolism was evident before cancer was diagnosed or caused by the cancer and/or subsequent treatments is still unclear. Further research needs to be conducted in this area to determine the exact cause of this phenomenon. Regardless, the ultimate finding of decreased carbohydrate oxidation in breast cancer patients during exercise has significant practical implications for clinicians.

Practical implications

These results combined with the results from Evans et al. (2009) suggest that blood lactate levels taken post-exercise are not a good indicator of exercise intensity in breast cancer patients, especially at higher intensities ($\geq 70\%$ VO_{2max}). Furthermore, the ability to produce energy from carbohydrate metabolism during exercise is significantly diminished in breast cancer patients compared to healthy women. Since glucose and glycogen (i.e., carbohydrate) are the predominant choices for energy production during high intensity exercise, this has implications for exercise prescription for this select group (McMurray & Hackney 2005). Clinicians should understand that energy cannot be produced as rapidly through anaerobic glycolytic means in this population, making exercise at higher intensities more difficult. Although there were no significant

differences in RPE between the groups at any intensity, current evidence supports that clinicians should still be conservative when working with breast cancer patients especially at higher exercise intensities. Using a combination of heart rate and RPE may be a more effective and appropriate way to determine exercise intensity in exercising breast cancer patients (Evans et al. 2009).

These are preliminary findings and more research needs to be performed before any specific exercise prescription guidelines can be created. These findings can only be generalized to women who have been diagnosed with Stage I – III breast cancer and have finished all of their major medical treatments within the last 6 months. Still, the results are striking and indicate that there is decreased carbohydrate oxidation and increased fat oxidation in breast cancer patient during exercise. This information further supports the need for a conservative approach to individualized exercise prescription in this population as has been recommended by Battaglini et al. (2006).

CHAPTER VI

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

Summary

Post-treated breast cancer patients and healthy women were matched for age, physical fitness level and menopausal status. Each participant underwent a YMCA submaximal cycle ergometer test to predict their maximal oxygen consumption (VO_{2max}). Based on the subjects VO_{2max} , workloads were prescribed for submaximal exercise sessions at low (40% VO_{2max}), moderate (60% VO_{2max}) and high (70% VO_{2max}) intensities. Heart rate, rating of perceived exertion, oxygen uptake, and respiratory exchange ratio were continuously monitored throughout the exercise sessions. Blood lactate and blood glucose were measured before exercise and 3 minutes into recovery. The breast cancer patients had a significantly ($p \leq 0.05$) lower carbohydrate oxidation rate and higher fat oxidation rate at all exercise intensities compared to healthy women. The breast cancer patients also had a significantly ($p \leq 0.05$) reduced blood lactate response to exercise at all submaximal exercise intensities compared to the healthy women. The results support the concept that post-treated breast cancer patients have a greater capacity for lipid oxidation and a lessened capacity for carbohydrate oxidation during submaximal exercise. This phenomenon results in decreased blood lactate production through glycolysis during exercise. Although the exact mechanisms underlying these findings are unclear, the differences between groups may be attributed to the disease state of cancer and/or the subsequent cancer treatments. Further research

needs to be done in this area to help elucidate the issue as to why this altered energy metabolism is occurring.

Hypotheses (Accept or Reject)

H1. No significant difference in lipid and carbohydrate oxidation will occur between the treatment and control groups during low (40% VO_{2max}) and moderate (60% VO_{2max}) exercise intensities. (Reject)

H2. Carbohydrate oxidation will be significantly lower and lipid oxidation will be significantly higher during exercise at high (70% VO_{2max}) intensity in the treatment group when compared to controls. (Accept)

H3. No significant difference in the blood lactate response will occur between the treatment and control groups during low (40% VO_{2max}) and moderate (60% VO_{2max}) exercise intensities. (Reject)

H4. Blood lactate response will be significantly lower post-exercise at the high (70% VO_{2max}) intensity in the cancer group when compared to controls. (Accept)

H5. A significant correlation will exist between carbohydrate oxidation and blood lactate production in both healthy controls and cancer patients in response to exercise; however, this relationship will be significantly stronger in the healthy controls. (Reject)

Recommendations for future studies

Subjects

A larger sample size and more homogeneous group of breast cancer patients would be recommended for future studies (i.e., same stage of cancer, type of treatment). Studying breast cancer patients who have had similar treatments may help to define if this altered metabolism during exercise is a product of certain treatments being administered. Lastly, exercise training has been shown to decrease estrogen levels but the synergistic effects tend to increase overall fat metabolism in healthy individuals (McMurray & Hackney 2005). Therefore, it would also be interesting to see if similar changes in substrate oxidation occur in breast cancer patients after exercise training.

Exercise sessions

The YMCA submaximal cycle ergometer protocol to predict maximal oxygen uptake (VO_{2max}) was used because it has been validated to be accurate in 20-54 year old healthy women (Beekley et al. 2004). However, when working with some of the older subjects they had a difficult time with the first workload of 25 Watts (150 kgm/min). Therefore it is suggested that when working with a population over the age of 50 years old to begin the VO_{2max} test at a lower workload. If using an electric cycle ergometer, keeping the subjects at a pedal rate of 50 – 60 rotations per minute would also be recommended. Subjects were told to pedal at a comfortable rate and there was a wide range of variability in pedal rate between individual subjects and this appeared to influence the subjects' perception of exercise difficulty.

Biochemical analysis

Future studies should also investigate more physiological markers to determine why carbohydrate oxidation is reduced during exercise in breast cancer patients. Specifically, a more detailed dietary analysis along with an oral glucose tolerance test would be recommended. This would help in-part to determine if energy metabolism was being altered through substrate availability or uptake at the muscle. Furthermore, hormonal analysis of estrogen, cortisol, hGH, and insulin might give more information about how endocrine changes in breast cancer patients may impact substrate oxidation and energy metabolism during exercise.

Appendices

- A. Modified Physical Activity Questionnaire
- B. 24 Hour Recall for Food Intake
- C. Biochemical Analysis for Blood Lactate
- D. Biochemical Analysis for Blood Glucose
- E. Sample Calculations to Determine Substrate Oxidation

APPENDIX A

Physical Activity Questionnaire

(Modeled after the Modifiable Activity Questionnaire)

1. Over this past year, have you spent more than one week confined to a bed or chair as a result of an injury, illness, or surgery? Yes _____ No _____
 If yes, how many weeks over this past year were you confined to a bed or chair? _____ weeks

2. Do you have difficulty doing any of the following activities?
 a. Getting in or out of a bed or chair? Yes _____ No _____
 b. Walking across a small room without resting? Yes _____ No _____
 c. Walking for 10 minutes without resting? Yes _____ No _____

3. Please circle all activities listed below that you have done more than 10 times in the past year:

Jogging (outdoor, treadmill).....1	Football/Soccer.....14	Stair Master.....27
Swimming (laps, snorkeling).....2	Raquetball/Handball/Squash.....15	Fencing.....28
Bicycling (indoor, outdoor).....3	Horseback riding.....16	Hiking.....29
Softball/Baseball.....4	Hunting.....17	Tennis.....30
Volleyball.....5	Fishing.....18	Golf.....31
Bowling.....6	Aerobic Dance/Step Aerobic.....19	Canoeing/Rowing/Kayaking.....32
Basketball.....7	Water Aerobics.....20	Water skiing.....33
Skating (roller, ice, blading).....8	Dancing (Square, Line, Ballrm).....21	Jumping rope.....34
Martial Arts (karate, judo).....9	Gardening or Yardwork.....22	Snow skiing (x-country/Nordic trk).35
Tai Chi.....10	Badminton.....23	Snow skiing (downhill).....36
Calisthenics/Toning exercises.....11	Strength/Weight training.....24	Snow shoeing.....37
Wood chopping.....12	Rock climbing.....25	Yoga.....38
Water/coal hauling.....13	Scuba Diving.....26	Other.....39
Walking for exercise (outdoor, indoor at mall or fitness center, treadmill).....40		

List each activity that you circled in the “Activity” box below, check the months you did each activity over the past year (12 months) and then estimate the average amount of time spent in that activity.

Activity	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Average # of Times Per Month	Average # of Minutes Each Time

4. In general, how many HOURS per DAY do you usually spend watching television? _____ hours
5. Did you ever compete in an individual or team sport (NOT including any time spent in sports during school physical education classes)? Yes_____ No_____
- If yes, how many total years did you participate in competitive sports? _____ years
6. Have you had a job for more than one month over the past 12 months? Yes_____ No_____

List all JOBS that you have held over the past year for more than one month. Account for all 12 months of the past year. Please refer to the next page for job codes and categories. If unemployed/disabled/retired/homemaker/student during all or part of the past year, list as such. Think of your normal job activities of a normal 8 hour day, 5 day week

Job Name	Job Code	Walk or bicycle to/from work	AVERAGE JOB SCHEDULE				Out of the total # of "Hrs/Day" reported working at this "job", how much of this time was usually spent sitting? Enter this # in "Hrs Sitting" column, then place a check in the category which best describes their job activities when they were not sitting.			
			Min/Day	Hrs/Day	Day/Wk	Mos/Yr	Hrs spent sitting at work	Check the category that best describes job activities when not sitting		
								Hrs sitting	A	B

Category A
(Includes all sitting activities)

Sitting
Standing still w/o heavy lifting
Light cleaning – ironing,
cooking, washing, dusting
Driving a bus, taxi, tractor
Jewelry making/weaving
General office work
Occasional/short distance walking

Category B
(Includes most indoor activities)

Carrying light loads
Continuous walking
Heavy cleaning – mopping,
sweeping, scrubbing, vacuuming
Gardening – planting/weeding
Painting/Plastering
Plumbing/Welding
Electrical work

Category C
(Heavy industrial work, construction, farming)

Carrying moderate to heavy loads
Heavy construction
Farming – hoeing, digging
- mowing, raking
Digging ditches/shoveling
Chopping/sawing wood
Tree/pole climbing
Water/coal/wood hauling

JOB CODES

Not employed outside of the home:

1. Student
2. Home Maker
3. Retired
4. Disabled
5. Unemployed

Employed (or volunteer):

6. Armed Services
7. Office worker
8. Non-office Worker

APPENDIX B

The 24-hour Recall for Food Intake

- The 24-hour recall consists of obtaining information on food and fluid intake for the previous day or previous 24 hours.
- The 24-hour recall is based on the assumption that the intake described is **typical** of daily intake.
- Although the 24-hour recall is one of the easiest methods for collecting information regarding the patient's intake, it is prone to error:

1. Patient may not be able to recall the foods eaten.

- It is often helpful to base questioning on the sequence of activities, beginning with questions such as, "What time did you get up in the morning?" and "What did you first eat?" and then proceed methodically in similar fashion through the next 24 hours.
- Alternatively, try starting with the present and work back through the previous 24 hours.
- Patient may have a tendency to forget items like snack foods or sauces and gravies, but further probing of certain food items can jog the patient's memory on these and other points.

2. Patient may not be able to estimate the amounts of each food eaten.

- It may be helpful to have food models or illustrations of usual portion sizes available to provide a basis for comparison.

3. Information given may not be sufficiently specific.

- Use a checklist to provide greater accuracy of items listed by the patient.

4. Patient may not be telling the truth.

- Be careful to avoid suggesting the answers expected and try not to appear judgmental.

5. Intake during the previous 24 hours may not be typical.

- Patient should be asked about this, and if necessary should be further questioned about a more typical day's intake.

Necessary components of the 24-hour recall:

- Time the food or beverage was consumed
- The food or beverage item
- Serving size of the food or beverage item
- How the food was prepared
- Where the patient had the food or beverage item
- Any relevant notes to the meal or food item

Source: Zeman, F.J. and Ney, D.M. Applications in Medical Nutrition Therapy (1996). Prentice Hall: Upper Saddle River, NJ, pp. 53-54.

24-Hour Recall Form			Patient Name:		
General Clinical Research Center			Protocol #:		
School of Medicine, UNC-Chapel Hill 27599			Investigator Name:		
Interviewer:			Medical Record #:		
			Telephone #		
Time	Serving Size	Meals:	How Prepared:	Where	Notes:
		Breakfast			
		Snack			
		Lunch:			
		Snack:			
		Dinner/Supper			
		Snack			
		Other			

Notes and Comments:

APPENDIX C

Biochemical Analysis of Blood Lactate

Methodology: Electrochemical, Lactate Oxidase Biosensor

Test Measured: Blood Lactate

Test Time: 13 seconds

Test Strip Volume: 0.7 μ L

Battery Life (normal): 600 Tests

Data Output Port: Serial

Electrochemical Biosensor: Yes

Calculates Average Results: Yes

Data Storage: Users/Tests: 10/130

Data Transfer Port: Yes

Weight: 2.65 ounces (75g)

Size: 3.6" x 2.3" x 0.9" (91.4mm x 58.4mm x 22.9mm)

Measurement Range: **Lactate:** 0.3 to 25.0 mmol/L

Operating Ranges: **Temperature:** Lactate 41°F to 113°F (5°C to 45°C)

Altitude: 0 to 12,000 feet

Humidity: 10% to 90% relative humidity

On-board Data Storage Files: 1 common file for 20 tests

9 additional files for 10 tests each

2 Quality Control files for 20 tests

Typical Analytical Specifications for Imprecision:				
Within-Run Imprecision n=20, whichever is greater			Day-to-Day Imprecision n=20, whichever is greater	
Analyte	CV%	SD	CV%	SD
Lactate	5.0	0.2 (mmol/L)	7.0	0.3 (mmol/L)

Battery: Coin Type No. 2450

Optional Accessories: Meter to PC data cable, with USB Port Adapter and PC data charting program (Windows® 2000 and beyond)

Meter Warranty: Warranty effective for one year from purchase date.

Certifications and Compliance: EMC (EN 55022 class B, IEC 801-2, EN 61000-4-3, ENV 50204, EN 61000-4-2)

FOR PROFESSIONAL USE ONLY

APPENDIX D

Biochemical Analysis of Blood Glucose

Result Range: 20 to 600 mg/dL

Calibration: Plasma-equivalent

Sample: Fresh capillary whole blood

Sample Size: Minimum 1 microliter

Test Time: 5 seconds

Assay Method: Glucose oxidase biosensor

Power Source: One replaceable 3.0V (#2032 or equivalent) lithium battery

Battery Life: About 1,000 tests (about one year at three tests per day)

Glucose Units: mg/dL

Memory: 150 blood glucose and control solution tests

Automatic Shutoff: Two minutes after last user action

Size: 3.12" x 2.25" x 0.85"

Approximate Weight: 1.5 ounces with battery

Operating Ranges:

Temperature 43 – 111 °F/6 – 44 °C

Relative Humidity 10 – 90%

Hematocrit 30 – 55%

APPENDIX E

Sample Calculations to Determine Substrate Oxidation

60% submaximal exercise session (example data only):

Average VO_2 over last 5 minutes: 1.059 L/min

Average RER over last 5 minutes: 0.90

RER chart at 0.90:

- 4.924 kcal/L O_2
- 67.5 % from carbohydrate
- 32.5% from fat

$4.924 \text{ kcal/L } \text{O}_2 \times 1.059 \text{ L/min} = 5.215 \text{ kcal/min}$

Carbohydrate oxidation:

$5.215 \text{ kcal/min} \times 67.5\% = 3.520 \text{ kcal/min}$

1 g carbohydrate = 4.02 kcal

$(3.520 \text{ kcal/min}) / (4.02 \text{ kcal/g}) = \mathbf{0.876 \text{ g/min}}$

Fat oxidation:

$5.215 \text{ kcal/min} \times 32.5\% = 1.695 \text{ kcal/min}$

1 g fat = 8.93 kcal

$(1.695 \text{ kcal/min}) / (8.93 \text{ kcal/g}) = \mathbf{0.190 \text{ g/min}}$

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