AEROBIC EXERCISE TRAINING EFFECTS ON PHYSICAL FUNCTION, FATIGUE AND MOOD, IMMUNE STATUS, AND OXIDATIVE STRESS IN SUBJECTS UNDERGOING RADIATION TREATMENT FOR BREAST CANCER

by

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DEDICATION

To my husband Joe, and my sons Jon and Chris, whose love allows me to live life to it's fullest.

To the ladies in my study, whose desire to contribute to the body of knowledge surrounding cancer treatment and survivorship inspired me with their dedication, courage, enthusiasm, and hope.

To Barney, whose dedication, vigilance, loyalty, and encouragement provided me with the discipline and strength to complete this project.

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CHAPTER 1

INTRODUCTION

Aerobic exercise is commonly used to promote health and restore physical function (APTA, 2001, ACSM, 2000, Blair, et al., 1996, NIH, 1996, Pate, et al., 1995). In apparently healthy people, and in people with chronic disease, aerobic exercise has been shown to increase physical function, improve immune parameters, mediate depression, improve body composition, and minimize oxidative stress (ACSM, 2000, Powers, et al., 1999, Mackinnon, 1999, APTA, 1998, Green & Crouse, 1995, Petruzello, et al., 1991). The benefits associated with aerobic exercise may also be useful in managing symptoms related to cancer and its treatments.

Females undergoing radiation treatment for breast cancer commonly report symptoms of fatigue, reduced physical function, weight gain, and psychological disturbances. (Pinto & Maruyama, 1999, Ream & Richardson, 1999, Portneoy & Itri, 1999, Friendenreich & Courneya, 1996, Irvine, et al., 1991). These symptoms commonly interfere with a person's ability to perform self-care and household activities, as well as to participate in vocational, social, and recreational pursuits (Berger, 1998, Nail & Jones, 1995, Nail & Winningham, 1995, Irvine et al., 1994, King et al., 1985, Meyerowitz et al., 1983, Kobashi-Schoot, et al., 1979). Early evidence is beginning to support aerobic exercise training as a method to manage some of the symptoms related to cancer (Pinto & Maruyama, 1999, Dimeo, et al., 1999, Segar, et al., 1998,

Mock, et al., 1997, Friendenreich and Courneya, 1996, Winningham & MacVicar, 1989, MacVicar, et al., 1989, Winningham & MacVicar, 1988). While there is evidence that aerobic exercise performed during this time may assist in controlling cancer-related symptoms, there have been few clinical-controlled trials performed to examine this phenomenon (Portenoy & Itri, 1999, Ream & Richardson, 1999, Pinto & Maruyama, 1999, Friendenreich & Courneya, 1996, Irvine, et al., 1991).

While there have been a few studies performed that examined the effect of aerobic exercise training on physical function, body composition, fatigue, and psychological disturbances, these studies were performed during chemotherapy treatments or on cancer survivors (Dimeo, et al., 1999, Segar, et al., 1998, Winningham & MacVicar, 1989, MacVicar, et al., 1989, Winningham & MacVicar, 1988). Only one study was found to date that examined the influence of aerobic exercise training on fatigue and emotional distress in females undergoing radiation treatment for breast cancer (Mock, et al., 1997).

Aerobic exercise training may also have a positive influence on immune parameters and on anti-oxidant defense mechanisms (Powers, et al., 1999, Nieman & Pedersen, 1999, Mackinnon, 1999, Shephard and Shek, 1999, NIH, 1996, Shephard, et al., 1994, Petruzella, et al. 1991). Radiation treatment is known to have a profound impact on immune parameters and to increase oxidative stress (Fairey, et al., 2002, Kovacic & Osuna, 2000, Thompson, et al., 1996). Authors have speculated on the possibility of enhancing immune parameters in people with cancer through aerobic exercise. However only two

studies were found at this time that examined the influence of aerobic exercise on the immune parameters in people undergoing treatment for cancer and neither was performed during radiation treatment (Na, et al., 2000, Shore & Shepherd, 1999, Hoffman-Goetz, 1994, Woods & Davis, 1994, Sternfeld, 1992).

Oxidative stress levels may also have an impact on cancer-related symptoms. Oxidative stress is reported to contribute to fatigue and to chronic disease such as heart disease, diabetes, and cancer (Betteridge, 2000, Niess, et al. 1999, Morrow & Roberts, 1996, Hahn, et al. 1993, Thrush & Kensler, 1991, Southorn, 1988). Regular participation in aerobic exercise has been shown to elevate cellular concentrations of anti-oxidants that may reduce cellular injury, improve physical function, and delay fatigue (Niess, et al., 1999, Powers, et al., 1999). The influence of aerobic training on oxidative stress in subjects undergoing radiation treatment for cancer does not appear to have been examined in earlier studies.

Although aerobic exercise training may be of benefit in managing cancer-related symptoms, studies to describe or explain this phenomenon are relatively rare. Further evidence on the effect of aerobic exercise training during radiation treatment for breast cancer may be of benefit in the management of symptoms related to cancer and its treatments.

Purpose

The purpose of this study was to examine the effects of aerobic exercise training on physical function, body composition, fatigue, mood, immune parameters, and oxidative stress in females undergoing radiation treatment for

breast cancer. This study also examined whether there was a difference between an aerobic exercise trained group (AE) and a placebo-stretching group (PS) on the variables of interest following the treatment intervention.

There were two hypotheses tested in this study. The first null hypothesis was that there would be no significant difference between pre-test and post-test measures in the variables of interest in the treatment group following the moderate intensity aerobic exercise training intervention. The second null hypothesis was that there would be no significant difference in measures of the variables of interest between the AE group and the PS group following the intervention.

Definitions

For the purpose of this study, the following terms are defined.

Aerobic Exercise

Aerobic exercise in this study was moderate-intensity walking, performed for 20-45 minutes, on 3-5 days per week, at 50-70% of the individuals peak heart rate, as measured on a symptom-limited graded exercise test (SLGXT) (ACSM, 2000, Blair, et al., 1996, Pate, et al., 1995).

Cancer-Related Symptoms

The cancer-related symptoms that were measured in this study are physical function, body composition, fatigue and mood.

Physical Function

Physical function is described as a subject's ability to participate in usual activities of daily living such as self-care, household management, and

vocational, social and recreational pursuits (APTA 2001, ACSM, 2000). Physical function was assessed by means of a symptom-limited graded exercise test (SLGXT) that measured peak oxygen consumption (peak VO_2). VO_2 peak is correlated with physical activity capabilities when it is translated into MET levels (ACSM 2000). MET levels describe activities that a person is capable of performing based on their fitness level as defined by either their peak or maximal oxygen consumption.

Body Composition

Body composition describes a subject's relative percentage of fat mass compared to their lean mass, and water content. People undergoing treatment for cancer commonly experience disturbances in body composition by either losing lean mass or gaining fat mass (Osler, 1987, Theologides, 1977). Females undergoing treatment for breast cancer commonly experience an increase in fat mass, which may be linked to a poor prognosis for survival ((Stoll, 1996, Goodwin, et al., 1998, Pujol, et al., 1997, Schapira, 1990). The predictors of body fat that were used in this study were skinfolds, body mass (weight) and the body mass index (BMI) (ACSM, 2000).

Fatigue

According to Irvine et al. (1994), "Cancer-Related Fatigue (CRF) is defined as a self-recognized phenomenon that is subjective in nature and is experienced as a feeling of weariness, tiredness, or lack of energy that varies in degree, frequency and duration." CRF in this study was measured using the Piper Fatigue Scale-Revised (R-PFS).

Mood

Mood disturbances are common complaints of people undergoing treatment for cancer (Spiegel, 1996). The Profile of Mood States test (POMS) was used to provide a total mood score.

Immune Parameters

Four immune parameters will be assessed in this study through serum measures.

CD4+ and CD8+ Cells

CD4+ and CD8+ cells are T-lymphocytes in the immune system. T-lymphocytes participate in the initiation and regulation of most aspects of adaptive immunity. Quite simply, CD4+ cells participate in regulation, activation, recognition and secretion activities of the immune system. Typical CD4+ counts are 800-1300 cells/mm^3. CD8+ cells are cytotoxic, recognize foreign antigens, and provide negative feedback to control CD4+ cells (Mackinnon, 1999, Shephard, et al. 1994).

CD4+/CD8+ Ratio

The CD4+/CD8+ ratio is a measure of the effectiveness of immune function and normal values are between 1.5 - 2.0. When this ratio drops below 1.5, immune function is impaired and there is increased susceptibility to infection (Shephard et al., Int. J. Sports Med., 1994).

Natural Killer Cell Activity (NKCA)

Natural killer cells (NK) are an important first line of defense in the body against microorganisms, certain types of tumor cells, and virus-infected cells.

NK cells can be measured simply by cell counts or by cytolytic activity levels. Cytolytic activity levels for NK cells are termed natural killer cytotoxic activity (NKCA). NKCA is the more important measure since it indicates the effectiveness of the NK cells in their immune defensive role (Nieman et al, 1995, Shephard, 1995). Therefore, this study used NKCA in assessing immune function.

Maximal Heart Rate

The individual's maximal heart rate was the maximum heart rate achieved on the SLGXT. Participants performed the SLGXT approximately one-week before and one-week after a 7-week radiation regimen (ACSM, 2000, Pate, et al., 1995).

Muscle Strength

Muscle strength represents the maximum force exerted by a muscle or group of muscles during a voluntary contraction (ACSM 2002). Muscle strength was assessed though standard technique by means of a hand-held dynamometer.

Oxidative Stress

Oxidative stress occurs when there is an imbalance between the production of oxidants and the body's ability to maintain anti-oxidative defenses (Neiss, 1999, Powers et al., 1999, Rovere, et al., 1996). Physiological processes in the body are capable of managing moderate amounts of oxidative stress, however, beyond certain levels, damage can occur to macromolecules in the cell. (Neiss, et al, 1999, Powers et al., 1999). Oxidative stress also

contributes to the adverse effects of cancer, chemotherapy, and radiation treatments (Kovacic and Osuna, 2000, Thompson, et al., 1996, Binert, et al., 1999, Hahn, et al., 1994). A central component of oxidant injury is peroxidation of lipids. A unique by-product of lipid peroxidation, that can be reliably measured in vivo, is 8-Isoprostane. (Roberts and Morrow, 2000). Oxidative stress in this investigation will be assessed through serum levels of 8-Isoprostanes.

Oxygen Consumption Peak Measures (VO_2 peak)

VO_2 peak is a measure of the highest oxygen consumption level achieved by a participant on a SLGXT. This value is a clinically accepted measure of an individual participant's maximal physical performance (ACSM, 2000). A more accurate measure of maximal physical performance is maximal oxygen consumption (VO_2 max). VO_2 max is not easily achieved by most people, especially those with chronic disease or illness, because it requires an all-out maximum physical performance. To achieve a VO_2 max, a subject must achieve a Respiratory Exchange Ratio (RER) at or above 1.15, their oxygen intake values and the heart rate must fail to increase with increases in the workload, and the 'Rating of Perceived Exertion' (RPE) must be 19 or greater. In clinical trials, graded exercise testing is frequently performed in sedentary subjects unfamiliar with exercise or subjects with illness or chronic disease. In these populations the demanding parameters of maximal testing are seldom achieved. Therefore, in clinical trials the VO_2 peak, which is the best effort

achieved by the subject, is used as an acceptable measure for an individual's maximal physical performance capability (ACSM 2002, ACSM 2000).

Symptom-Limited Graded Exercise Test (SLGXT)

A SLGXT is a method used to assess physical function. The SLGXT provides information on a subject's fitness level, the safety of the subject beginning to participate in an exercise program, and information to enable the development of an individualized exercise prescription such as the maximal heart rate. The SLGXT used in this study was the modified Bruce protocol treadmill test with oxygen analysis. VO_2 peak was measured by oxygen analysis using continuous open circuit spirometry and indirect calorimetry of expired gases. The test was performed according to ACSM guidelines and under physician supervision (2000).

Training Heart Rate Range

The training heart range is the heart rate in beats per minute recommended to acquire health or fitness benefits from aerobic training. The training heart rate range for this study was in the moderate range of 50-70% of a participant's maximal heart rate as measured on the SLGXT. Participants in the walking portion of this study wore heart rate monitors during their exercise sessions in order to maintain the correct heart rate range for training.

The Research Problem and Relevance to the Field

Females undergoing radiation treatment for breast cancer commonly experience symptoms related to their treatment that include diminished physical function, weight gain, fatigue, and mood disturbances (Gerber & Augustine,

2000, Portenoy & Itri, 1999, Ream & Richardson, 1999). These symptoms often interfere with their ability care for themselves, to work, or to participate in recreational pursuits (Berger, 1998, Nail & Jones, 1995, Nail & Winningham, Irvine et al., 1994, King et al., 1985, Meyerowitz et al., 1983, Kobashi-Schoot, et al., 1979). While there is evidence that aerobic exercise performed during this time may assist in mediating cancer-related symptoms, there have been few clinical-controlled trials to examine this phenomenon (Portenoy & Itri, 1999, Ream & Richardson, 1999, Pinto & Maruyama, 1999, Friendenreich & Courneya, 1996, Irvine, et al., 1991).

Although it seems counter-intuitive to perform exercise during a chronic illness or for fatigue, gradual and progressive aerobic exercise training is regularly used in rehabilitation (ACSM 2002, APTA 2001). Aerobic exercise training improves an individual's physical work capacity and thereby increases their physical reserves for activity which delays fatigue (ACSM, 2002). Aerobic exercise has also been found to be of benefit in weight control, in reducing psychological disturbances, and may improve immune parameters and oxidative stress levels (Powers, et al., 1999, Shepherd, 1995, Shepherd, et al., 1994, Petruzella, et al., 1991, Winningham, et al., 1989). Since radiation treatment appears to negatively impact physical function, body composition, psychological states, immune parameters, and oxidative stress, evidence on the impact of aerobic exercise training on these variables will be of benefit to the clinical community. Information from this study will provide clinicians with

evidence on the safety and efficacy of using aerobic exercise as a method to manage symptoms related to radiation treatment in females with breast cancer.

Limitations of the Present Study

The following are limitations of this study in terms of design, reliability, validity, and generalizability.

Study Design

This study is a random-assigned, clinical-controlled design. The placebo-stretching group was used to identify changes that occurred in the variables that were not related to the intervention such as radiation effects, seasonal effects, or historical events. Additionally, participants in both groups were contacted weekly by telephone or in person to attempt to uncover confounding factors, such as acute illnesses, that would have affected the study results. Clinical designs, by their nature, predispose studies to confounding factors from human conditions such as unreported dietary or medical supplements, personal and religious support systems, familial pre-dispositions, and unreported psychological or physical interventions.

Additional confounding factors in this study were related to the different types of cancer treatments, the different ages of the participants, and varying degrees of individual physical activity from activities of daily living. All participants self reported that they were sedentary for 12 weeks prior to entering the study. However, differences in physical fitness could have occurred based on individual variations in activities of daily living. These variations in fitness levels would have influenced the baseline physical fitness

levels and ultimately the degree of training achieved by each participant. Second, age was not controlled in this design and variations in physical status may exist between subjects that are pre, peri, or post-menopausal. These confounding factors are noted, however due to the size of the sample, they were not controlled for in this study. Additionally, not all participants received chemotherapy prior to entering the study, and variations may have occurred in responses based on the individual's cancer treatment regimen.

Finally, the design of the study did not permit double-blind conditions for the participants or the examiner. The subjects and the examiner knew who was in the placebo-stretching group or the aerobic exercising group. This may have produced unintended effects on participation or examination and measurement techniques.

Reliability and Validity

Reliability and validity was addressed by using standardized tests, by using the same examiner for all testing and training, and by having an examiner that was experienced and familiar with the testing and training. Intra-rater variability may have influenced measurement outcomes. All test instruments and protocols have established reliability and validity. Information on the validity, standardization, and error measurements will be described or referenced in the 'Methods' section of this document.

Generalizability

The results of this study apply to females undergoing radiation treatment for Stage 0-III breast cancer. The information from this study is not

generalizable to people with other types of cancer diagnosis or to people with other health problems related to immune suppression. Additionally, the results of this study are not generalizable to other types of cancer treatments such as chemotherapy, hormonal treatments, or surgery.

Lastly, the measures for the immune parameters and for oxidative stress were obtained from the serum, and therefore the results of this study are not generalizable to what is occurring at the site of the neoplasm.

CHAPTER TWO

THEORETICAL FOUNDATIONS AND LITERATURE REVIEW

Exercise in the Maintenance and Restoration of Function

Aerobic exercise is an important component of health and fitness (NIH Consensus Statement, 1996, Blair, et al., 1996, Pate, et al., 1995, American Heart Association, 1992). Aerobic exercise is also used in the maintenance and rehabilitation of physical function in subjects with chronic health problems including cardiovascular and pulmonary disease, neurological and orthopedic conditions, and even in the aging process (ACSM, 2002 APTA 2001). Moderate levels of aerobic exercise are beginning to be linked to improving the status of people undergoing treatment for cancer (Friendenreich and Courneya, 1996, Pinto and Maruyama, 1999).

Exercise prescriptions for aerobic training originally required subjects to perform at high intensities, such as 70-85% of their maximal heart rate, in order to achieve health benefits associated with training. Later studies found that even moderate intensities of exercise, such as 50-70% of maximal heart rates, were sufficient for developing marked improvements in health (NIH Consensus Statement, 1996, Blair, et al., 1996, Pate, et al., 1995). Health benefits are achieved when 30 minutes of moderate intensity aerobic exercise is accumulated on most days of the week (Blair, et al., 1996, NIH Consensus Development Panel, 1996, Pate, 1995, American Heart Association, 1992, Public Health Service, U.S. Department of Health & Human Services, 1991,

Paffenbarger, et al., 1986). By lowering the intensity of exercise required to achieve health benefits from high to moderate levels, more people are able to participate in aerobic exercise to improve their health, even people with physical limitations or chronic diseases. There is also evidence that moderate and regular aerobic exercise can improve certain immune parameters and this may have an impact on the incidence and severity of illness (Nieman & Pedersen, 1999, Shepherd & Shek, 1999, Shepherd, et al., 1994, Nieman, 1994). Studies are beginning to support the usefulness of aerobic exercise as a method to manage cancer-related symptoms in people with cancer or undergoing treatment for cancer (Ream & Richardson, 1999, Portenoy & Itri, 1999, Friendenreich & Courneya, 1996, Irvine et al., 1991).

Symptoms Related to Cancer and Its Treatments

Several authors have described the prevalence and severity of symptoms caused by cancer and its treatments and the methods used by people to manage symptoms primarily related to fatigue and loss of function (Irvine et al., 1998, Woo, et al., 1998, Irvine et al., 1994, Graydon, 1994, Greenberg et al., 1992, King et al., 1985, and Haylock & Hart, 1979). The participants in these studies reported that their primary method for managing fatigue was rest, such as sitting or sleeping (Ream & Richardson, 1999, Portenoy & Itri, 1999, Graydon, et al., 1995). The people in these investigations complained of their inability to participate in self-care, household tasks, as well as career, social and recreational activities. However, resting and lack of activity may, in fact, increase cancer-related fatigue and loss of physical

function through deconditioning (Dimeo, et al., 1998, Winningham, et al., 1994, Winningham and colleagues, et al., 1989).

Anxiety and depression are also common problems associated with cancer and its treatments (Anderson, et al., 1998, Spiegel, 1996). Spiegel (1996) reports that half of all people with cancer have a psychiatric disorder related to depression or anxiety. Relief from depression, through psychotherapy in the Spiegel investigation, was associated with longer survival in people with breast cancer, lymphoma, and malignant melanoma. However, the physiological mechanisms responsible for this phenomenon were not examined, and neither was aerobic exercise training.

Aerobic Exercise Training and Cancer-Related Fatigue

There is some support in the literature for aerobic exercise training as a means to improve cancer-related fatigue (Dimeo, et al., 1998, Winningham, et al., 1994, Winningham, et al., 1989). Exercise was formerly contraindicated in people undergoing treatment for cancer. They were encouraged instead to rest and conserve their limited physical resources in order to fight their disease (Ream & Richardson, 1999). But rest and limiting physical activity are ineffective in managing fatigue and may actually perpetuate a cycle of deconditioning which leads to further loss of function (ACSM, 2002). Physical inactivity causes muscle wasting and diminishes both muscle and cardiorespiratory endurance (Dudley & Ploutz Snyder, 1998, Coyle, 1998). When cardiorespiratory and muscle deconditioning occur, a subject's capacity for physical activity decreases. With lowered physical function, usual activities,

such as stair climbing and household tasks, require a higher percentage of a person's available reserve capacity. When a person performs activities at a higher percentage of their available physical reserve capacity, they fatigue more rapidly (ACSM, 2002). Aerobic exercise training increases maximal functional capacity, or maximal aerobic capacity (VO_2max). This increase in maximal aerobic capacity allows subjects to perform daily activities at a lower percentage of their physical reserve capacity and thereby lengthens their time to fatigue (ACSM, 2002). Aerobic exercise training that increases maximal aerobic capacity is one of the mechanisms that has been proposed to improve fatigue and the diminished physical function in subjects with cancer.

Exercise, NK Cell Counts, and NKCA

Moderate aerobic exercise training appears to decrease the number of sickness days experienced by a person, however there is considerable debate on whether this phenomenon is related to changes in certain immune parameters (Nieman & Pedersen, 1999, MacKinnon, 1999, Shepherd, et al., 1994). There is considerable interest among sports physicians and exercise physiologists in the impact of exercise training on immune parameters. The effects of exercise on immune parameters may also have important consequences for subjects with immune suppression such as cancer and HIV^+/AIDS (Fairey, et al., 2002, Shephard, 1998, Birk, 1996, Rigsby, et al., 1992, LaPerriere, et al., 1990). As more people are living with immune deficiency conditions, several authors have examined the safety of exercise in these populations as well as the impact of exercise on their immune profiles. A

great deal of attention has been focused in recent years on the influence of exercise on NK cells, and NKCA.

NK cells are an important first line of defense against abnormal cells, virus-infected cells, and certain types of tumor cells (Paul, 1999). Some authors suggest that resting levels of NK cell counts and NKCA increase in response to moderate endurance training (Shephard, 1999, MacKinnon, 1999). Improvements in resting NK cell counts and NKCA from moderate aerobic training may be linked to maintaining health (MacKinnon, 1999, Birk, 1996). However, prolonged or intense exercise training has been shown to cause declines in NK number and activity (Shephard, 1999, MacKinnon, 1999).

In a recent review, Shephard and Shek (1999) examined the results of 94 studies on the response of NK cell counts and NKCA to exercise. During moderate intensity exercise, NK cell counts showed statistically significant increases, ranging from 186-344% above resting levels. Post exercise NK counts were significantly lower during the first one to two hours of recovery. Increases in resting levels of NK counts have been reported in response to moderate exercise training. A meta-analysis by Shepherd and Shenk (1999) suggested that the increases seen in resting NK counts in response to aerobic training was small and statistically non-significant. For cross sectional studies, the mean effect was 110% of sedentary control subjects with 95% confidence limits (91 to 131%). For longitudinal training experiments, the increase was smaller at 105% of sedentary controls at a 95% confidence level (94 to 118%).

The NKCA has been described as a more important indicator of the effectiveness of immune function (Shephard & Shek, 1999). Meta-analysis by these same authors, revealed that NKCA values in trained subjects were 17% higher than values in sedentary controls. This difference was described as statistically non-significant, however, the reviewers identified many shortfalls in the research designs including small sample size, analysis techniques, and training volume variations. Additionally, the studies did not examine associations between changes in NK counts or NKCA and clinical presentations such as performance, fatigue, rates of illness or infections. The authors pointed out that a majority of the studies were performed on young male athletes and there was limited information on females, children, the elderly, and people with chronic disease.

A few studies have examined the effect of aerobic training on people who are immunocompromised due to HIV^{+}/AIDS (MacArthur, et al., 1993, Rigsby, et al., 1992, LaPerriere, et al., 1990). The studies that exist are complicated by sample size, compliance, and drop out rates (Shephard, 1998). Assumptions are based primarily on trends in the data. In general, the studies found that moderate intensity physical training may enhance certain aspects of immune function (Shephard 1998, Birk, 1996). In subjects with mild to moderate immune dysfunction, it was generally found that moderate intensity exercise did not diminish their immune function or exacerbate their HIV symptoms. Subjects in this category demonstrated improvements in aerobic power similar to that of seronegative subjects. These subjects also

demonstrated improvements in resting NK counts and NKCA, and a stabilization or increase in CD4+ counts (MacArthur, et al., 1993, Rigsby, et al., 1992). It is theorized that improvements seen in immune profiles are related to a decrease in cortisol production and an increase in opioid production (Shephard, 1999, Birk, 1996). Subjects with severe immune dysfunction (less than 200 cells/mm^3) did not demonstrate improvements in CD4+, NK counts or NKCA, however, exercise appeared to slow their progression from HIV+ to AIDS (Birk, 1996). Exercise training was also shown to diminish anxiety and depression in these subjects and this appeared to be related to an attenuation of anticipated declines in CD4+ counts (Shephard, 1999, Birk, 1996, Rigsby, et al., 1992).

Caution must be observed when attempting to generalize findings on NKCA in the serum to what is happening at the site of a neoplasm. In studies on NKCA and tumor progression in human and animal models, it has been found that high levels of NKCA are correlated with increases in tumor growth rates. In a study by Rowse and colleagues (1995), NKCA and tumor growth rates were examined in response to psychosocial stress in Shionogi mouse mammary tumors. This study found that psychosocially stressed mice had higher NKCA and demonstrated increased tumor growth rates. Studies by Hoffman-Goetz and colleagues (1992) and Strange and colleagues (2000) supported the above findings in animal models. To confound the above findings, a study by Anderson and colleagues (1998) examined levels of stress and NKCA levels in subjects with breast cancer. This study found that as stress

levels in human subjects increased, NKCA levels decreased. Their conclusion was that stress had a significant negative impact on immune function. However, a study described in the section 'Breast Cancer Immunology' below indicates that NKCA may in fact be suppressed by the immune system at the site of a neoplasm in order to suppress tumor growth in humans (Eremin, et al., 1986). NKCA modulates cytokines and other immune substances that promote growth, and healthy tissues at the site of the tumor may downregulate NKCA to slow tumor growth rates.

Exercise Effects on CD4+ and CD8+ counts and CD4+/CD8+ Ratios

Although moderate intensity training has been found to have a beneficial impact on immune function in general, changes in immune parameters vary for different lymphocyte subsets (MacKinnon, 1999, Shephard, Rind & Shek, 1994). CD4+ and CD8+ counts generally rise immediately following acute bouts of moderate or intense exercise. The CD8+ rise is greater, and this results in a decrease in the CD4+/CD8+ ratio causing suppression of the CD4+ cells. CD4+ and CD8+ counts are then depressed during the post-exercise recovery time, but return to baseline levels within 1-2 hours post exercise. This response to acute exercise tends to be similar for trained versus untrained subjects, unless exercise is prolonged (MacKinnon, 1999, Shephard, Rind & Shek, 1994). When exercise is prolonged, both CD4+ and CD8+ counts begin to decrease during exercise, but appear to recover to baseline values within 3 hours after exercise, unless the exercise bout is severe.

Exercise training does not appear to influence resting levels of CD4+ and CD8+ cells, or CD4+/CD8+ ratios unless exercise is both prolonged and severe. This stability in resting levels of T-lymphocytes following aerobic exercise training was also demonstrated in HIV+ patients. The stability of the T-lymphocyte response, among other factors, leads investigators to conclude that aerobic exercise training is safe for this population (MacKinnon, 1999, Stringer, et al., 1998, Shephard, 1998, Birk and MacArthur, 1994, MacArthur, et al., 1993, Rigsby, et al., 1992). The effect of aerobic exercise training on these immune parameters in people undergoing radiation treatment for breast cancer does not appear to have been previously described

Breast Cancer Immunology

T-Lymphocytes, NK Cell Counts and NKCA

In reviewing the literature on breast cancer, it is apparent that there are different immune responses in the peripheral circulation compared to the responses at the site of the neoplasm. The first part of this section will examine studies pertaining to the peripheral circulation, and the second part will review studies on immune function at the site of the tumor.

Although data are inconsistent for subjects with cancer, several authors have suggested an inverse relationship between circulating NKCA and progression of distant metastases (Cunningham-Rundles, et al., 1981, Levy, et al., 1987, Schantz et al., 1986, and Strayer, et al., 1986). In vitro, compromised measures of NKCA have been associated with the progression of cancer (Lewis & McGee, 1992, and Whiteside & Herberman, 1989). In early breast cancer,

NK cell counts and cytolytic activity appear to be near normal however, in advanced disease, NK cell counts and NKCA are depressed (Hadden, 1995, Wei & Heppner, 1996).

In early breast cancer, T-lymphocyte counts in the serum are normal or slightly depressed, and CD4+/CD8+ ratios are decreased (Hadden, 1995, Wei & Heppner, 1996). In advanced breast cancer, both T-lymphocyte counts and CD4+/CD8+ ratios are decreased. Ten-year survival rates in subjects with breast cancer have been associated with higher lymphocyte levels (Tsakraklides, et al., 1974). Observations on the behavior of breast cancers, such as lymphocyte infiltration of primary tumors, sinus histiocytosis, and follicular hyperplasia, suggest that there may be a protective response mounted by the immune system against breast cancer.

Investigations into the response of the immune system early in the disease remain unclear both peripherally and at the site of the tumor. By the time a clinical diagnosis is made, the immune response may be failing (Wei & Heppner, 1996). Observations on general immune status in subjects with breast cancer indicate that, unless subjects have advanced disease, T-cell and B-cell values are typically within normal ranges (Nemoto, et al., 1974, Catalona, et al., 1973). Head and colleagues (1993) examined T & B cells assays of peripheral blood from 142 breast cancer patients prior to surgery and 2-4 weeks post chemotherapy. They found that 58% of the subjects had deficient T-cell reactivity to phytohemagglutin. This response was significantly different from normal subjects as it was within the 25th percentile of the normal range of

values. Following chemotherapy, some patient's values moved into the average range. From this study, it is considered that general measures of immune competence in subjects with breast cancer are not grossly different than those in apparently healthy subjects. However, these studies did not examine associations with clinical symptoms such as diminished function or the number or severity of illnesses or infections. Therefore, it is not known at this time whether there is a relationship between T-cell values and clinical symptoms.

Few studies have been performed on immune status at the site of the actual tumor. One study by Black and Leis (1973) examined in vivo inflammatory responses in cryostat sections of subject's own tumors. They found positive immune reactions in 82% of subjects with pre-cancerous or in situ lesions, 47% reactivity in subjects with node-negative invasive cancer, and 20% responses in node-positive patients. This study is important in demonstrating variations that occur in response to different cancer stages and the importance of examining neoplasms in the host environment.

Wei and Heppner (1996) described three in vitro studies in a review on immune status and neoplasms. Vose and Moore (1979) described tumor infiltrating lymphocytes in 7 breast cancers as primarily T-cells that were functionally deficient and blocked peripheral lymphocytes in cytotoxic assays. Eremin and colleagues (1986) found diminished NKCA in breast tumor infiltrating lymphocytes (TIL) and significant suppression of NKCA when TIL was added to peripheral lymphocyte assays. Whiteside and colleagues (1986)

also found primarily T-cells in their analysis of TIL from breast cancer patients, with CD8+ cells predominating over CD4+ cells, a sign of diminished immune activity. The conclusion from these studies is that TIL appears to contain cytolitic cells, but that tumor environments do not always appear to support effective immune responses.

Interestingly, while increased peripheral serum levels of NKCA are linked to improved immune status in apparently healthy subjects, increased NKCA levels are linked to increased risk for developing breast cancer. Pross, et al., (1984) found a positive correlation between subjects with high risk for developing breast cancer and abnormally high levels of peripheral NKCA. Rowse and colleagues (1995) found a positive correlation between NKCA and tumor size in mouse mammary tumors. A review article by Stewart and Tsai (1993) cautions that specific clinical pathologies must be examined in regard to whether lymphocyte infiltration is associated with a favorable or unfavorable prognosis. These authors also point out that T cells and NK cells promote a variety of cytokines, lymphokines, and peptide hormones and some of these immune factors may have the ability to promote proliferation in normal, pre-cancerous and neoplastic breast epithelial cells.

Wei and Heppner implanted preneoplastic C4 hyperplastic alveolar nodule lines (HAN) into syngeic mice to observe tumor progression and immune response. These investigators found no evidence of an immune response to tumor progression. From their studies they suggest that an increase in immune response may actually stimulate growth in cancer cells and

the likely culprit was NKCA. NK cell counts were present in higher numbers at the tumor site compared to normal mammary epithelium. As NKCA increased, tumor formation progressed, however suppression of NKCA lengthened the latency period and decreased tumor formation. Several other studies support this 'immune stimulation' mechanism in the development and progression of cancer. Eremin and associates (1981) found low NKCA in breast cancers and suppression of NKCA in breast cell infiltrates was possibly linked to an immune control mechanism.

Oxidative Stress

Oxidative stress is related to the ability of the body to maintain a balance between oxidative actions and anti-oxidative defense mechanisms. When this balance fails, oxidative damage may occur in important molecules and vital biological systems, including DNA (Niess, et al. 1999, Powers, et al., 1999, Rovere, et al. 1996). Oxidants, such as free radicals (FR), reactive oxygen species (ROS), and reactive nitrogen species (RNS), are continuously produced during normal human metabolism and play an important role in a variety of normal physiological and pathological processes (Powers, et al., 1999, Neiss, et al., 1999, Papas, 1996). Examples of deliberate production of reactive radicals in normal biological functions include activated phagocytes using ROS to kill bacteria and fungi, and the role of the reactive radical, superoxide, in signaling cellular growth (Papas, 1996).

At high concentrations, FR, ROS, and RNS contribute to oxidative stress and that causes damage to macromolecules and biological systems. Damage

to lipids induces lipid peroxidation that disturbs membrane integrity and function. Oxidation of proteins can impair enzyme function in multiple metabolic processes, cause damage to nucleic acids, such as guanine, and may damage DNA. DNA damage is considered a mechanism in the development of cancer. Oxidative damage has also been implicated in heart disease, diabetes, chronic inflammatory conditions, neurodegenerative diseases, and even the aging process (Betteridge, 2000, Niess, et al., 1999, De Flora, et al., 1996, Morrow & Roberts, 1996, Hahn, et al., 1993, Thrush & Kensler, 1991, and Southorn, 1988). It is not clear at this time whether oxidative stress is a causal factor or an epiphenomenon in the various diseases.

Lifestyle and environmental factors such as smoking, environmental pollutants, diet and dietary supplements, fasting, ultraviolet radiation, medications, and interestingly, radiation treatments and strenuous exercise can also influence oxidative stress levels (De Flora, et al., 1996). Acute exercise increases the generation of FR, ROS, and RNS and therefore, contributes to increasing levels of oxidative stress (De Flora, et al. 1996). The body appears to respond to the elevated levels of oxidative stress from regular endurance training by elevating cellular concentrations of antioxidants that may reduce cellular injury, improve physical function, and delay fatigue. Review articles by Niess and colleagues (1999) and Powers and colleagues (1999) describe salient adaptations that occur in antioxidant defense mechanisms as a result of exercise training. The primary adaptations observed are increases in the concentrations of enzyme and non-enzyme systems, activation of transcription

factors, reductions of oxidant release by leukocytes, and increases in the levels of stress proteins.

The enzymes primarily involved in antioxidant defense include superoxide dismutase (SOD), glutathione peoxidase (GPX), and Catalase CAT. Most of the oxidative damage appears to occur in structures with high oxidative capacity such as the liver, lung, kidney, heart, red blood cells, and Type I and IIa skeletal muscle fibers. Therefore, it is not surprising that the major adaptations in antioxidant defense systems also occur in these structures. SOD is a first line of defense against superoxide radicals and it is most active in highly oxidative muscle fibers such as Type I and Type IIa. Exercise training in animal models has been shown to increase total SOD levels in most studies, however, variations in results may have been due to differences in the training regimens and assay sensitivities. GPX catalyzes hydrogen peroxide and therefore offers important cellular protection to membrane lipids, proteins, and nucleic acids. Most studies offer consistent support for increases in GPX activity as a result of endurance training in active skeletal muscles. CAT is the only enzyme that has not been consistently shown to increase with aerobic training. Increases in the levels of SOD and GPX appear to be positively correlated with the intensity and the duration of exercise in studies where animals exercised at intervals of 30, 60 and 90 minutes and at 55, 65, and 75% of VO_2 max (Powers, et al., 1999)

Non-enzymatic adaptations center on glutathione (GSH). GSH is present in all plant and animal cells and plays multiple roles in cellular

antioxidant defense through the removal of hydrogen peroxide and organic peroxides. GSH is synthesized by the enzyme γ-glutamylcysteine synthtase (GCS). GCS has been shown to increase 1.5 to 2 times as a result of aerobic training in dogs. (Marin, et al. 1993)

Adaptations in stress proteins and transcription activity have also been observed as a result of endurance exercise. Chronic exercise training appears to promote increases in levels of stress proteins, such as heme oxygenase –1 (HO-1) and heat shock protein (HSP-70). HO-1 appears to promote maintenance of the proliferative capacity and survival in cells in response to oxidative stress by reducing the intracellular pool of free iron that opposes the generation of ROS. Both HO-1 and HSP-70 maintain the viability, function, and proliferative capacity in immune cells during and after strenuous exercise. One final adaptation observed in response to chronic exercise is that increased levels of ROS may promote transcription factors that modulate acute and chronic inflammatory processes through promotion of gene expression (Niess, et al., 1999). The effects of these adaptive increases in antioxidant defense mechanisms as a result of endurance training does not appear to have been previously described in subjects undergoing radiation treatment for breast cancer at this time.

In terms of cancer, oxidative stress is implicated in the tissue damage, the malaise and the fatigue that develops in response to both the disease and its treatments. Subjects with neoplastic diseases show increased levels of oxidative stress and free radical activity in their blood compared to healthy

controls (Gerber, et al., 1997, Huang, et al., 1996, Rovere, et al., 1996, Hahn, et al., 1994, Trush & Kensler, 1991). High doses of ionizing radiation and cytotoxic drugs may further increase oxidative stress and contribute to cell damage (Kovacic & Osuna, 2000, Thompson, et al., 1996, Binert, et al., 1999, Hahn, et al., 1994). Several authors have proposed a link between oxidative stress and muscle fatigue (Essig & Nosek, 1997, Lawler & Powers, 1998). Normalizing reactive oxidants through aerobic exercise training has been suggested as a means of managing muscle fatigue. Methods for managing oxidative stress through diet and antioxidant supplements are presently being investigated in healthy subjects and in subjects undergoing treatment for cancer (Papas, 1996, Hahn et al., 1994).

Markers have been used to measure oxidative stress in apparently healthy subjects following exercise, in subjects with cancer, and in subjects undergoing radiation treatment (ACSM, 1998, De Flora, et al. 1996, Morrow & Roberts, 1996). However, markers for oxidative stress have not been previously examined in subjects undergoing radiation treatment for breast cancer and participating in aerobic exercise training.

Several markers have been used to measure oxidative stress including malondialdehyde, lipid hydroperoxides, conjugated dienes, and short chain alkanes. A central component of oxidant injury is peroxidation of lipids. A unique product of lipid peroxidation, that can be reliably measured in vivo, is isoprostane (Roberts and Morrow, 2000, Morrow, et al., 1996). Serum levels of 8-Isoprostane were used to measure oxidative stress in this investigation.

Aerobic Exercise Training Effects on Physical Function in Cancer

There are few random-assigned, clinical-controlled investigations on the effects of exercise training in subjects with cancer (Ream & Richardson, 1999, Portneoy & Itri, 1999, Friendenreich & Courneya, 1996, Irvine, et al., 1991). Buettner and Gavron (1981) performed the earliest reported investigation into the effects of exercise training on people with cancer. Male and female subjects, with a history of cancer, were divided into an exercise or a sedentary control group. Following eight weeks of aerobic exercise training, treatment subjects were compared to sedentary controls on variables of estimated VO_2 max, grip strength, reductions in resting heart rate, weight, skinfold thickness, and several psychological variables. The exercising subjects demonstrated improvements on all variables compared to the sedentary control subjects. However, a limitation of this study was related to generalizability, as only two of the subjects were actively undergoing treatment for cancer during the time of the study and other subjects may have been in remission.

Winningham, MacVicar and colleagues examined the effects of aerobic exercise training in subjects undergoing chemotherapy for breast cancer. These touchstone investigations examined the effects of aerobic exercise training on the variables of functional capacity, nausea, and weight and body composition in subjects with cancer. The first article published by this group examined the effects of aerobic exercise training on symptoms of nausea as measured on the *Derogatis Symptom Check List-90-Revised Somatization* Scale (Winningham and MacVicar, 1988). The subject sample consisted of 42

females receiving adjuvant chemotherapy for breast cancer. Subjects were divided into three groups, an aerobic exercise group, a placebo group that performed flexibility exercises, and a non-exercise control group. Subjects were evaluated for symptoms of nausea before and after a 10-week exercise regimen. Self-monitored, aerobic exercise training was performed three times per week at an exercise intensity of 60-85% of the subject's maximal heart rate. Maximal heart rates were derived from a symptom limited graded exercise test. Data was analyzed using repeated measures ANOVA, Duncan's Multiple Range Test, and the Chi-square test with probability set at $p < .05$. Results for the repeated measures ANOVA supported a significant difference for the group-test interaction with a difference in the post-test results dependent on the assigned group ($F = 2.45$; $p = .0027$). The Duncan Post-Hoc test supported a significant difference for the post-test exercise group ($p < .05$). The primary limitation described in this study by the authors was the inability to generalize their findings to other forms of cancer. The author's concluded that the results of their study supported moderate intensity aerobic exercise as a method to control chemotherapy induced nausea and to promote physical well being.

The second study reported by this group investigated the effect of aerobic exercise training on body weight and body composition in patients undergoing adjuvant chemotherapy for breast cancer (MacVicar, Winningham & Nickel, 1989). 24 female subjects with Stage II breast cancer were randomized to an exercise or a control group. The exercise group performed aerobic exercise for 20-30 minutes, three times per week for 10-12 weeks, at 60-85% of

their maximal heart rates. Covariate analysis, adjusted for age and pre-test values, was used to assess pre-test and post-test comparisons on weight, skinfold measures, % body fat, and lean body mass. Both the treatment group and the control group gained weight during the study. The exercise group gained 0.82 kg. and the control group gained 1.99 kg. However, these differences were not significant ($F = 1.86$, $p = 1.888$). Skinfold measures were significantly different ($F = 8.69$, $p = .001$) with the exercise group losing 3.19 mm. of subcutaneous fat and the control group gaining 9.6 mm. These skinfold measures support a significant difference in lean body weight ($F = 5.26$, $p = .033$) with the exercise group gaining 2.04 kg. of lean mass and the control group losing 1.26 kg. of lean mass. Although the % body fat changes were described as a variable, they were not presented in the data analysis. The author's described the limitations of this study as the small sample size, variations in chemotherapy regimens, variations in medications such as prednisone, and a lack of dietary controls.

The final study reported by this group examined the effects of aerobic exercise training on maximal functional capacity in subjects undergoing chemotherapy for Stage II breast cancer (Winningham, MacVicar et al., 1989). In this study, 45 subjects were stratified by baseline functional capacity (± 1 MET) and then randomized to an experimental, a placebo, or a control group. The experimental group participated in aerobic exercise training three times per week for ten weeks, at 60-85% of their maximal heart rate, while the placebo group performed non-aerobic, flexibility exercises. ANOVA found no significant

difference between the study groups prior to the intervention in terms of age or weight. Analysis of covariance was applied to assess changes in functional capacity for each group, with baseline measurements used as covariates. Post hoc pairwise comparisons were performed between groups using Tukey's multiple comparison method. The dependent variables measured in this study were functional capacity in VO_2 max in liters, heart rate, maximum workload, and maximum test time. Functional capacity was measured by means of oxygen uptake while performing a cycle ergometer test. The exercise group demonstrated significant improvements on VO_2 max in liters, workload, and test time ($p = .05$), while the control group and the placebo group values did not significantly change. Differences between the exercise group and the control and placebo groups were also significant for VO_2max in liters, maximum workload, and test time ($p = .05$). Limitations in this study described by the authors were sample size, and the inability to generalize findings to other stages of breast cancer, other cancer diagnoses, or other treatments. The authors concluded that subjects undergoing adjuvant chemotherapy for Stage II breast cancer were able to improve their functional capacity as a result of aerobic exercise training. The authors suggested that increases in functional capacity might improve an individual's ability to perform self-care activities and activities of daily living and recommended further investigation into this relationship.

In 1989, Decker, Turner-McGlade, and Fehir examined the effects of aerobic exercise training on psychosocial and physiological variables in

subjects undergoing bone marrow transplantation (BMT) for acute leukemia (AL). This study intended to determine if BMT subjects could return to what was described as their original fitness levels following one year of aerobic exercise. The 'original fitness level' was not measured or described in this study. Physical capacity, basal metabolic rates, and emotional status were assessed in 12 subjects before and after BMT. Aerobic capacity was calculated by means of a cycle ergometer, however the test protocol and test end points were not described. Depression and well being were assessed on the Beck Depression Inventory (BDI). Basal metabolic testing was not described. Subjects were given an exercise prescription that consisted of a minimum of 3 exercise sessions each week, for a minimum of thirty minutes at 85% of their maximum heart rate. The subjects were asked to perform the exercise sessions at home. Measurements were planned to be taken one week prior to BMT, one month post BMT, 6 ½ months post BMT, and then annually. A majority of these subjects were unable to complete stress testing until four months post BMT due to what was described as poor physical status. Measurements appear to have been performed at baseline, at 4 months post BMT, and at 8 months post BMT on depression and aerobic capacity only. Descriptive statistics on mean changes were provided, however statistical analyses were not well described. Basal metabolic rates declined from baseline to 4 months from 3.3 to 2.7 ml/ kg/min. Mean aerobic capacity declined from a baseline of 17.51 ml/kg/min. to 15.74 ml/kg/min. at 4 months. It appears that only one subject was tested at 8 months and this subject did experience a

marked improvement in aerobic capacity on a graph, although the specific values were not provided in the study. The only results of the BDI that were reported were that two subjects experienced mild post BMT depression at 4 months. The authors did report that the patients began to tolerate exercise at 4 months post BMT. The authors described aerobic exercise training as beneficial for cardiac patients and commented that exercise may be correlated with reductions in risks for developing breast cancer, but the descriptions of their data were unclear or not provided. The authors concluded that all of the patients in their study had positive subjective responses to the exercise program and felt exercise was worthwhile during this time. The major limitations of this study were lack of a control group, failure to report data on exercise compliance or monitoring, under reporting of data on outcome measures, and unclear interpretations of results.

Four important studies on the effects of aerobic exercise training in subjects with cancer were performed at the Freiberg University Medical Center in Germany under the direction of Fernando Dimeo. In 1996, Dimeo and colleagues examined the effects of aerobic exercise training in patients with hematological malignancies following bone marrow transplantation (BMT). 20 patients performed 6 weeks of treadmill walking beginning 30 ± 6 days following BMT. There was no control group. Significant changes were noted in pre to post test values for all subjects on maximal physical performance, maximum walking distance, and heart rate at specific submaximal workloads ($p = .001$). The authors concluded that their results were different from previous studies

that reported that physical function after BMT would recover only after many months, and that many patients would experience long lasting or permanent decrements in physical function. The authors recommended structured rehabilitation as beneficial in promoting early recovery of function in subjects following BMT.

Dimeo and colleagues (1997) performed a pilot study that examined the feasibility and effects of aerobic training in 16 patients following completion of high dose chemotherapy and autologous peripheral stem cell transplantation. 32 subjects diagnosed with solid tumors or non-Hodgkin's lymphoma were assigned to an exercise group or to a control group. Subjects in the exercise group walked on a treadmill 5 days per week for six weeks at 80% of their predicted maximal heart rate and with a corresponding lactate concentration of 3 ± 0.5 mmol/L. The variables examined were physical function, cardiac function, fatigue, and hemoglobin concentration. Physical function was assessed by maximal walking speed on a treadmill and fatigue was assessed by personal interviews following the exercise intervention. The Wilcoxon-Mann-Whitney U test assessed pre-test values and found no significant differences between groups on walking speed or hemoglobin levels. Prior to training, the walking speed of the exercise group was 6.2 ± 1.1 km./hr. and control group was 6.2 ± 1.3 km./hr. The hemoglobin levels were 10.1 ± 1.4 g. /dL. for the walking group, and 10.1 ± 1.2 g. /dL. for the control group. Following the 6-week intervention, walking speed for the exercise group were 8.3 ± 1.6 km./hr. and 7.5 ± 1.3 km./hr. for the control group. Hemoglobin concentrations were 13

± 1.0 g. /dL. in the exercise group, and 12 ± 1.4 g. /dL. in the control group. Following the intervention, hemoglobin concentration and walking speed values for both groups improved, however the exercise group's values were significantly higher than those values in the control group. The conclusions from this study were that cancer patients recovering from high dose chemotherapy should not be instructed to rest but should instead increase their physical activity in order to reduce fatigue and improve physical function. Limitations of this study included the lack of a standardized tool to evaluate fatigue and well being, and the lack of a more accurate assessment for fitness.

The third study performed by Dimeo's group examined the effects of aerobic exercise on physical performance and on the number and severity of treatment-related complications (Dimeo, et al. 1997). 80 subjects with solid tumors undergoing high dose chemotherapy were selected to participate in this study. Subjects were randomly assigned to a training group or a control group. Subjects were evaluated one week prior to hospitalization and again at discharge. Complete data was collected on 28 subjects in the exercise group and 32 subjects in the control group. Aerobic training was performed for 30 consecutive minutes daily on a supine cycle ergometer at 50% of the subject's maximal heart rate. The physical performance variables included maximal treadmill test speed, maximal exercise heart rate, the percentage of the maximal predicted heart rate achieved, hemoglobin concentration, and hematocrit. The severity of complication variables included the duration of neutropenia and thrombopenia, the number of blood transfusions and platelet

transfusions, the reported intensity of pain, the reported intensity of diarrhea, the severity of infections, the severity of mucositosis, and the duration of the hospitalization.

At discharge, the exercise group had significantly higher maximal physical performance levels than the control group with the loss of physical performance in the control group being 27% greater than the loss measured in the exercise group. Statistical analysis was by means of Fisher's exact test on the nominal data, Student's t-test was used to evaluate normally distributed continuous data, and the Wilcoxon-Mann-Whitney U test was used on the categorical data. P values were set at .05 and all tests were two-tailed. Duration of neutropenia, severity of diarrhea, severity of pain, and duration of hospitalization were significantly reduced in the exercise group as compared to the control group. Multiple regression analysis confirmed that aerobic training, duration of neutropenia and thrombopenia, number of platelet transfusions, intensity of pain, intensity of diarrhea, and duration of hospitalization predicted the loss in physical performance. The authors concluded that aerobic exercise could be safely applied to subjects immediately following high dose chemotherapy treatments to prevent physical performance declines and lessen the severity of some symptoms related to treatment. The major limitations of this study were that the exercise testing methods lacked precision and the method of testing lacked validity as it was different from the training mode.

Dimeo and colleagues also examined the effect of aerobic exercise on the rehabilitation of subjects with profound cancer fatigue. Five cancer patients

suffering with severe fatigue participated in aerobic training that consisted of treadmill walking 5 days per week for six weeks at 80% of their maximal heart rate and a corresponding lactate concentration of 3 ± 0.5 mmol/L. During the first week, each patient walked for 3 minutes five times, with three minutes of slow walking between each training bout to allow recovery. Exercise training bouts gradually increased and rest periods decreased weekly until subjects were able to walk continuously for 30 – 35 minutes. Each subject's maximal heart rate was measured on a symptom limited graded exercise test. Subjects participating in the study had a variety of cancer diagnoses and underwent different cancer treatment protocols. The cancer diagnoses included medulloblastoma of the cerebellum, non-Hodgkin's lymphoma, Hodgkin's lymphoma, disseminated non-small cell bronchial carcinoma, and breast carcinoma. There was also no control condition. The variables evaluated were maximal physical performance, maximal distance walked, heart rate at equivalent submaximal workloads, and lactate concentration at an equivalent submaximal workload. Statistical analysis of data before and after the training program was performed with the Wilcoxon Sign Rank Test with a probability value set at .05. Following training, maximal physical performance measured by distance covered as well as velocity increased significantly from 6.4 ± 0.4 km./hr. to 7.5 ± 0.9 km./hr. and from 1640 ± 724 m. to 3300 ± 953 m. Heart rate and lactate concentrations, at equivalent submaximal workloads, were significantly decreased following training. Heart rates at 5 km./hr. decreased from 138 ± 21 beats per minute to 113 ± 20 beats per minute and the lactate

concentration decreased from 2.6 ± 1.4 mmol./L. to 1.3 ± 0.6 mmol./L. The investigators concluded that all subjects experienced clear reductions in fatigue following the exercise training. Fatigue was assessed anecdotally through subject interviews. Two subjects reported being able to return to school, three patients indicated improved ability to complete daily activities without fatigue, and three of the subjects began jogging regularly. The authors concluded that the loss of energy in some subjects following cancer treatments is related to muscular deconditioning and these patients will benefit from aerobic exercise training in order to relieve fatigue and return to normal activities.

Exercise, NK Cell Counts, NKCA, and T-Cells

Four studies examined the effects of aerobic exercise training on T-cell counts and NKCA in subjects with cancer. Peters et al. (1994) studied the influence of aerobic exercise on NK, NKCA, and personality traits in subjects with breast cancer. 24 females with Stage I or II breast cancer were recruited to participate in this study. Exercise training began six months following surgical procedures. There was no control group. Subjects began cycle ergometer training 5 times per week for the 6 weeks, and then cycled 2 to 3 times per week for 6 additional months at what appeared to be 70% of their maximum heart rate. Variables measured were NK cell counts, NKCA, and personality traits by means of a Freiburger Personlichkeitsinventar questionnaire (FPI-R). All variables were measured prior to, at five weeks, and at the end of the training period. Statistical analysis was through an ANOVA procedure, and the relation between immunological and psychological data was

through linear correlation. Significance was set at .05. The authors reported that the NK cell counts did not change significantly throughout the course of the study, while NKCA increased significantly. The initial measures for NKCA was at 18.9% lysis, although this value was lower than values reported in aerobically trained subjects at 30-35% lysis of target cells, 18.9% is still within normal limits. The final measurement of NKCA in these subjects was 28.3% and this value was close to that measured in apparently healthy aerobically trained subjects. Life satisfaction significantly improved at five weeks but returned to baseline values in the final measurement. The authors reported a connection between training frequency and life satisfaction ($r = .64$). The authors concluded that based on the results of their study, aerobic exercise training enhanced NKCA in survivors of cancer, and that a connection was established between psychological behavior and the immune system. The major limitations of this study included failure to provide information on statistical findings, lack of exercise test measures, and the absence of a control group. A control group would have eliminated questions regarding changes in NKCA related to circ-annual rhythms, nutrition, and merely a recovery phenomenon.

Nieman and colleagues (1995) found a different result in their study than the results found by Peters and colleagues. This study examined the effects of eight weeks of exercise on concentrations of circulating T-cells, NK cells and NKCA. 16 Subjects with a prior diagnoses of breast cancer (3.0 ± 1.2 years prior to the study) were randomly assigned to an exercise or a control group. Supervised aerobics and weight training were performed in the exercise group

for 60 minutes, 3 times per week for 8 weeks. Aerobic training was at 75% of the individual's maximal heart rate. Complete data was obtained on twelve subjects, six in each condition. The measured variables included physical work capacity on a symptom-limited treadmill test, a six minute walk test, leg extension strength on a Kin-Com device, and T-cell, NK cell and NKCA evaluation. Statistical analysis included baseline testing of subject variables using a Student's t-test, and a 2 x 2 repeated measures ANOVA described as one between-subjects factor (exercise vs. non-exercise group) and one within-subject factor (pre and post test time points on the training data). Results of this study indicated no significant difference in the NKCA or circulating T or NK immune cells in the exercise group compared to the non-exercise group following the intervention. The authors suggested that the exercise intensity and the duration in weeks of the study might have been insufficient to cause changes in resting immune factors. Limitations in this study included the length of time since the cancer diagnosis and treatment, the small sample size, and use of the ANOVA statistical analysis with insufficient power for this sample size. The authors noted that the NKCA was in the same range as apparently healthy subjects. The possibility also exists that these subjects were in remission or cancer-free and that the results of the study were not reflective of subjects with cancer.

Na and colleagues (2000) examined the effects of moderate intensity aerobic training on NKCA in subjects immediately following surgery for stomach cancer. Subjects were randomly assigned to an exercise or a usual care group.

Participants in the exercise group performed 30 minutes of supervised activity twice per day, 5 times per week for 2 weeks. The training intensity was described as moderate, and there were no pre-test or post-test fitness assessments performed. NKCA was drawn on post-operative day (POD) 1, 7 and 14. Data analysis was by means of multiple linear regression and t-tests. The authors reported a significant difference between the exercise group and the control group on NKCA measures between post-operative day 7 and 14. NKCA in the exercise group went from 16.2% on POD 1, to 14.6% on POD 7, to 27.9% on POD 14. The control group values were 19.7% on POD 1, 17.9% on POD 7, and 13.3% on POD 14. The authors concluded that physical training immediately following surgery increased NKCA significantly compared to a non-exercising control group.

In contrast, Shore and Shephard (1999) examined acute and chronic responses of T-cell counts, PHA-induced proliferation, body mass, and self-concept in six children with acute lymphoblastic leukaemeia and other types of neoplasms, compared to eleven normal volunteer controls. Three children receiving chemotherapy for cancer completed 12 weeks of aerobic exercise training at 70-85% of their maximal heart rate, as measured on a bicycle ergometer test, to subjective exhaustion. Three children with the same diagnoses served as controls. Two of the controls had completed their treatment and only one of the controls was actively undergoing chemotherapy. Values were compared with previously reported data on 11 healthy subjects. No statistical analyses were reported. Scores on the Peirs-Harris self-concept

inventory were reported to demonstrate a "partial resolution" of anxiety compared to normal children. Body mass index did not change significantly following the 12 weeks of training, and aerobic power improved by a small degree of 2 ml/kg/min. from the baseline of 33.7 ml/kg/min., in the exercise group. Cell counts were initially low in all six subjects and diminished further in the treatment group compared to the control children, who demonstrated no significant change in cell counts following the 12-week study. The authors concluded that children undergoing chemotherapy have low immune parameters, and despite further suppression of immune status related to physical activity, these children still benefit from modest levels of progressive activity, as long as immune status is monitored.

Aerobic Exercise Effects on Depression and Emotional Distress

Aerobic exercise training has some support in the literature as a means to manage anxiety and depression. A meta-analysis was performed by Petruzella and colleagues (1991) of 124 studies on the anxiety reducing effects of both chronic and acute exercise. They concluded that aerobic exercise has a significant influence on reductions in anxiety without the danger or cost of medications or psychotherapy. The studies included in this meta-analysis were primarily performed on apparently healthy subjects but included 2 studies on obese subjects, 4 on cardiac rehabilitation subjects, and 4 on psychiatric subjects. None of the studies included examined subjects with cancer.

Mock and colleagues (1997) examined the effects of a walking program on physical function, fatigue, emotional distress, and difficulty sleeping in

subjects with breast cancer undergoing radiation treatment. This was the only other study found thus far that was performed on aerobic exercise in people undergoing radiation treatment. 46 subjects, with Stage I or II breast cancer, were randomly assigned to an exercise program or a control group. The exercise group performed home-based, self-paced walking while the control group received the usual care. Measures were performed before and after the intervention. Physical function was measured using a 12-Minute Walk Test and a self reported "0 –10 Exercise Rating Scale". Symptoms were measured on the Symptom Assessment Scales and the Piper Fatigue Scale. Subjects walked 20-30 minutes, 4-5 times per week, during six weeks of radiation treatment. Baseline values were assessed by means of the Student-t test and Chi-square analysis for equivalence. Data was assessed by MANCOVA with baseline variables as covariates. Pearson correlation coefficients were used to assess relationships between physical function and symptom intensity. The results of the study indicated significant differences between the two groups on physical function and symptom intensity. Significant differences were found between pre and post-test values in the exercise group on fatigue, anxiety, and difficulty sleeping, but not depression. The primary limitations of this study were related to limitations in reliability. Limitations in this study were related to the use of predictive measures for physical fitness and training, and reliance on self-reports for exercise compliance. The authors concluded that moderate self-paced walking exercise during radiation treatment for breast cancer

improved adaptive responses as demonstrated by improved physical function and lower reported levels of fatigue, anxiety, depression, and sleep disturbance.

Segar and colleagues (1998) examined the influence of aerobic exercise on self-esteem, depression, and anxiety in breast cancer survivors. 24 subjects, who were an average of 3 ½ years post breast cancer surgery, were randomly assigned to an exercise group, an exercise and behavior modification group, or a control group. Aerobic exercise was performed for 30-40 minutes, 4 days per week for 10 weeks at 60% of the subjects predicted maximal heart rate. The variables measured were depression on the Beck Depression Inventory, anxiety on the Speilberger State -Trait Anxiety Inventory, and self-esteem using a Rosenberg Self-Esteem Inventory. Variables were measured pre-and post-intervention, and twelve weeks following post intervention. Exercise compliance was assessed by means of exercise logs that were collected weekly. Statistical analyses was performed by means of two ANOVA procedures, a 2 x 2 (group x time) for pre and post intervention data, and a 2 x 3 for pre, post, and 12 weeks post-intervention data. The results of this study indicated that subjects in the exercise group had significantly less depression and state/trait anxiety then the control group on the post intervention data. Analysis of the data from 12-weeks post intervention revealed no significant differences in the variables. Self-esteem did not change appreciably between the two groups at any sampling time. Limitations in this study included the small sample size, the reliance on self-reports of compliance, and the lack of a fitness test to assess whether training occurred. The recommendations of

these authors from this study were that self-paced aerobic exercise training appears to be safe for breast cancer survivors, and that aerobic training improves symptoms of anxiety and depression in this population.

Dimeo and colleagues (1999) evaluated the effects of aerobic training on fatigue and psychological status in 59 subjects undergoing chemotherapy followed by autologous peripheral blood stem cell transplantation. 27 subjects agreed to participate in the exercise group and 32 subjects who did not exercise were the control group. Exercising subjects trained for 30 minutes daily on a supine bicycle ergometer during their hospitalization. Psychological distress and fatigue were evaluated before and after the training regimen by means of the Profile of Mood States Test (POMS) and the Symptom Checklist 90. The results of the study supported significant increases in fatigue and somatic complaints in the control group but not in the exercising group ($p < .01$). The training group had significant improvements in several values of psychological distress ($p < .05$). The authors concluded that aerobic training during chemotherapy could reduce fatigue and improve symptoms of psychological distress compared to those reported in a non-exercising group.

The effects of exercise training on symptoms of anxiety and fatigue are relevant for two reasons. First, improvements in immune function have been noted in subjects that experience relief from psychological distress from either counseling or from aerobic training (Petruzella et al., 1991, ACSM, 1998). Relief from anxiety or depression has also been linked with lowering circulating levels of corticosteroids and catecholamines and these circulating factors

influence T-helper cell effectiveness (Shephard, 1999, Birk, 1996). Therefore, improvements in immune function may occur directly from the aerobic exercise training, and indirectly through the impact of exercise on circulating factors that influence immune function.

Anthropometry in Subjects with Cancer

Unlike the cachexia seen in subjects with cancers of the lung or visceral organs, subjects with breast cancer typically gain weight or body mass (Stoll, 1996, Osler, 1987, Huntington, 1985, Theologides, 1977). The reasons for this increase in body mass in females undergoing treatment for breast cancer are not clear. Such factors as medications, diet, sedentary lifestyle, depression, and genetics are being examined as contributing factors to the increases in body mass seen in this population (Pujol, et al., 1997, Stoll, 1996). Excess fat mass is a known risk factor for diabetes and coronary artery disease (ACSM 1998). Obesity is also being examined as a risk factor in the development of breast cancer and as a prognosticator for survival in females diagnosed with breast cancer (Goodwin, et al., 1998, Pujol, et al., 1997, Schapira, 1990). The results of current studies are unclear as the influence of obesity on cancer risk and cancer survival may also be related to other factors such as age and menopausal status.

In general, obesity in post-menopausal women is related to an increased risk of breast cancer, however, in pre-menopausal women the reverse has been found (Pujol, et al., 1997). The distribution of fat tissue also appears to influence the development of breast cancer and its prognosis. While obese

women have a slightly higher risk for developing breast cancer, women with android obesity are at a markedly higher risk (Pujol, et al., 1997, Schapira, et al., 1990). Schapira and colleagues describe females with android obesity as having lower levels of sex hormone binding globulin and higher levels of free testosterone and non-protein-bound estrogen than do females with gynoid obesity or non-obese controls. These abnormal hormonal levels may contribute to increased risk of developing breast cancer. Interestingly, these abnormal hormonal levels reverse when subjects lose fat weight (Kopelman, et al., 1981).

Exercise is an established component in successful weight management programs in apparently healthy subjects (ACSM 2002, ACSM 2000). There was only one study found thus far that investigated the role of aerobic exercise training in controlling weight gain in females undergoing treatment for breast cancer. The study by Winningham, MacVicar and others was previously reviewed in this document under the section on 'Clinical Investigations on Exercise in Subjects with Cancer'. Briefly, these authors found that a group of breast cancer patients, who exercised during adjuvant chemotherapy, experienced a significant decrease in body fat compared to a non-exercising control group. These authors concluded that exercise could be safely used in subjects undergoing adjuvant chemotherapy for breast cancer to stabilize body weight and reduce body fat gains at this time.

People with cancer present a unique challenge in the measurement of body fat. The most recognized method for accurate body composition measurement is hydrostatic weighing, which is based on Archemedes Buoyant

Principle (ACSM 2000, ACSM 1998). Because people undergoing treatment for cancer suffer from immune suppression, underwater weighing is contraindicated since it poses an increased risk for acquiring infections (Winningham, et al., 1985). Additionally, since body density norms have not been established in this population, anthropometric techniques that rely on prediction equations based on body density, like skinfold measures and bioelectric impedence, are not valid at this time (ACSM 2002). Anthropometric measures that have been applied to this population previously include Waist-Hip Ratios (WHR), the Body Mass Index (BMI) and the sum of skinfolds measures (Goodwin, et al., 1998, Pujol, et al., 1997, Tornberg & Carstensen, 1994, Schapira, et al., 1990, Winningham, et al., 1989)

Estimates of broad categories of obesity such as the Waist-Hip Ratio (WHR) and the Body Mass Index (BMI) have been used to assess risk in the breast cancer population. The WHR is a simple method that divides the circumference of a subject's waist by the circumference of their hips. Subjects are considered to be at increased risk for developing obesity related diseases at ratios above .95 for males and above .86 for females (ACSM 2000). The BMI, or Quetelet Index, uses four broad categories to assess obesity and desirable weight based on body weight, or mass, and height ratio. A subject's weight in kilograms is divided by their height in meters squared (wt/ht^2). BMI has been used in population based studies as a relatively good indicator of total body composition and the categories of obesity have been a useful reflection of health outcomes. Limitations of the BMI include difficulty interpreting the values

into useful information for patients, inability to determine distributions of body fat such as android or gynoid, and values that are inappropriate in muscular, athletic populations. Using the BMI, 20-24.9 kg/m^2 is considered desirable for men and women, while numbers greater than 25 kg/m^2 are placed into three categories of obesity that are high, very high, and extremely high (ACSM 2000).

The sum of skinfolds measures is simply the total sum of skinfolds measured from various named sites using a skin caliper technique. These measures are typically used in prediction equations to predict or estimate a subject's body fat percent (ACSM 2000). The prediction equations are population specific and frequently rely on norms for body density. Therefore, these equations are not accurate when they are applied to groups other than those for which the equations were developed (ACSM 1998). Population specific equations and body density measures have not been developed or validated for predicting body composition in the females undergoing treatment for breast cancer at this time. In lieu of the equations, clinicians can simply report the sum of the skinfolds as an measure over time to examine change.

Summary of the Theoretical Foundations and Literature Review

Aerobic exercise is a method that has support in the literature for the maintenance and restoration of physical function in subjects with a wide variety of diseases and disabilities. Early studies on aerobic exercise training in people with cancer provide limited support that it is safe and effective for restoring physical function and alleviating cancer-related symptoms of fatigue, anxiety, nausea, and depression. Evidence on the effect of aerobic exercise training on

immune parameters during treatment for breast cancer is inconclusive and there do not appear to be any investigations on cancer treatment, aerobic exercise and oxidative stress.

CHAPTER THREE

METHOD

Participants

After receiving approvals from the Human Investigation Committees at Wayne State University and the Karmanos Cancer Institute, 60 sedentary females with a diagnosis of Stage 0 - III breast cancer were to be recruited through physicians at the Karmanos Cancer Institute to participate in this study. Screening and safety considerations specific to exercise in cancer patients as described in Winningham, MacVicar and Burke (1986) and by the ACSM, (2000) would be followed. Baselines for inclusion were: medical clearance, signed consent forms, prior surgical treatment and histologically established stage 0 - III breast cancer, absence of uncontrolled cardiac or hypertensive disease, and willingness to participate in this study and be randomly assigned to either the PS protocol or the AE protocol. Additionally, subjects were to be between the ages of 20 and 65 years old and to not have participated in aerobic exercise for three months prior to entry into the study.

Medical clearance for participation in this study was determined by the participant's physician, the results of a routine MUGA scan on heart function, and the individual's responses to a symptom limited graded exercise test in accordance with the guidelines for exercise testing of the ACSM (2000).

Participants were given verbal and written information on the study, signed informed consent forms, and then were randomly assigned by random number chart to the aerobic training protocol or to a placebo-flexibility protocol.

Materials

Descriptions of the test instruments used in this study and evidence of their validity and reliability are described in the following sections. Measurements on the variables of interest were performed within one week before and within one week following a 7-week radiation treatment. Subjects were asked to report to the testing sessions in a post-absorptive and a well-rested state, having refrained from caffeine or nicotine consumption for four hours prior to testing.

Fatigue Assessment

Fatigue was assessed by means of the Revised Piper Fatigue Scale (R-PFS) (Piper, et al., 1998). The R-PFS is a self-reported survey, developed specifically to assess fatigue in subjects with breast cancer. The R-PFS consists of 22 items that provide a total fatigue score and four subscale scores. The subscales assess aspects of fatigue related to behavioral/severity, affective meaning, sensory, and cognitive/mood. The total fatigue score was used to assess fatigue in this study. Face and content validity for the R-PFS were determined through literature review and an 11-member panel of national experts on fatigue. Concurrent validity was assessed and established by significant correlations with the subscales and mood disturbance scores on the POMS, and the Fatigue Symptom Checklist (FSCL) scales. Internal

consistency was assessed through the standardized alpha (Cronback's alpha) and found to be 0.97 for the entire scale and above 0.92 for each sub-scale. The authors indicate that some redundancy may continue to exist and are currently appraising revisions to this instrument.

Mood Assessment

The Profile of Mood States inventory (POMS) is a psychological questionnaire designed to assess 6 identifiable mood or affective states: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment (McNair, et al., 1992). The instrument consists of 65 adjectives rated on a 5-point scale. This instrument has been extensively studied and utilized in the assessment of mood and fatigue across widely diverse disciplines such as drug trials, psychological interventions, and sports medicine. Internal consistency was assessed at or near .90 or above. Factorial validity was established through six-factor analytic replications in the development of the POMS. The authors indicate that this test instrument has predictive and construct validity through evidence from studies in other disciplines including cancer research and sports medicine. Concurrent validity was reported by the authors to be established through significant correlations with the Hopkins Symptom Distress Scales and the Manifest Anxiety Scale. Test-retest reliability ranges from .65 to .74 on each of the subscales.

Physical Function Measures

The physical function measures performed in this study were aerobic fitness as measured by peak aerobic power (VO_2 peak), muscle strength as

measured by grip tests, and anthropometric measures by skin caliper technique, body mass, BMI, and WHR.

Aerobic Fitness

The measure for aerobic fitness was peak aerobic power (VO_2 peak). Oxygen uptake was measured continuously using open circuit spirometry and indirect calorimetry of expired gases using an automated metabolic cart (Jaeger, Model: Oxycon-Alpha, Hoechberg, Germany). Calibration was performed each day. The exercise test was the modified Bruce protocol (ACSM, 2000). The treadmill used was the Trotter Treadmill (Model 6586). Heart rate and ECG were monitored continuously by means of a 12-lead configuration using an electrocardiograph (Jaeger, Model Oxycon-Alpha, Hoechberg, Germany), and blood pressure was assessed through auscultation. Measurement of VO_2 peak allowed for the functional capacity to be assessed by conversion to MET levels and associated functional tasks.

Muscle Strength

Muscle strength was measured through handgrip testing using a Jaymar Dynamometer. The subject was seated and stabilized during all muscle testing using the positions recommended by the American Society of Hand Therapists (Mathiowetz, et al. 1984). Subjects were familiarized with the test dynamometer and given two practice tests prior to actual testing. Subjects performed a total of five trials lasting five seconds each with one-minute of rest between each trial, the first two trials were practice tests, and the final three trials were average to assess the peak torque (Mathiowetz, et al. 1984).

Anthropometry

The anthropometric measurements that were performed in this study were the Waist-Hip Ratio (WHR), the Body-Mass Index (BMI), and the sum of 7 skinfold thicknesses (triceps, suprailium, subscapular, axilla, calf, thigh, and abdomen). A single investigator familiar with these techniques performed all measurements. The same Lange caliper, calibrated each day, and the same tape measure were used for all tests. Regression equations have not yet been developed in this population to enable prediction of body fat percent through skin caliper technique. Therefore, the sum of the skinfolds will be reported. Additionally, since this population is immune compromised, hydrostatic weighing is contraindicated due to the risk of infection from the water.

Training Procedures

Placebo-Flexibility Group Protocol & Monitoring

Subjects in the placebo group were provided with a general stretching program that they performed three to five days per week, during the course of their radiation treatment. Each subject was given written and verbal instructions, as well as one training session on proper stretching techniques by a licensed physical therapist. The stretching activities were typical of flexibility exercises provided to patients by a physical therapist following breast surgery for cancer. Participants in the PS group were also given a training diary to record the number of participation days as well as any feelings of fatigue, nausea, or sleep disturbances. The principle investigator communicated with all subjects weekly, either in person or by telephone. Weekly communications

were performed to promote compliance, monitor training, answer questions, and oversee safety issues and concerns related to the stretching protocol. Participants were also advised to contact their physician in the event that they developed any unusual signs or symptoms related to the radiation treatment or the exercise.

Aerobic Exercise Training Protocol

Following administration of the symptom-limited graded exercise test (SLGXT), an individualized exercise prescription was developed for each participant in the AE group. The exercise prescription consisted of the intensity, duration, frequency and mode for aerobic exercise training. The intensity was 50-70% of the maximal heart rate the participant achieved during the SLGXT, the duration of exercise was 20-45 minutes per session, the frequency was 3-5 times per week, and the mode was walking.

Participants in the AE group monitored their training time and intensity by means of the Polar Heart Rate Monitor® (POLAR Heart Rate Monitors, Model: Pacer, Woodbury, N.Y.). These devices provided a simple method for participants to monitor their exercise intensity and duration. The heart rate monitors have a programmable target heart zone with an alarm that signals when the participants heart rate is above or below their training range. The monitors also record the time spent in the training heart zone during each workout to allow improved reliability in reporting quantitative data related to exercise compliance, exercise intensity and exercise duration.

These subjects were also given a training journal to assist in recording training compliance. The training journals enabled subjects to record their intensity, duration, frequency, and mode of training, as well as subjective feelings of mood, fatigue, nausea, or sleep disturbances experienced that day. The training journals were a back up to the heart rate monitors for reporting exercise compliance, exercise intensity and duration.

The principle investigator communicated with the participants in the AE group weekly, either in person or by telephone. The purpose of these weekly conversations was the same as in the PS group, to promote compliance, monitor training, answer subject questions, and oversee safety issues and concerns about the aerobic exercise training. Like the participants in the PS group, participants in the AE group were advised to contact their physician in the event that they developed any unusual signs or symptoms related to the radiation treatment or the exercise.

The subjects performed the self-monitored walking exercise in their own homes on a treadmill or by walking in their neighborhood. This method was determined to be safe and effective in people undergoing treatment for breast cancer (Winningham, et al. 1990, Mock, et al. 1994). Additionally, there is support in the professional literature for the examination and development of self-monitored exercise programs that promote self-reliance and enhance lifestyle changes (Gerber & Augustine, 2000, Pinto & Maruyama 1999).

All subjects were informed that they were free to leave this study at any time of their own determination without any penalty to them or changes in their usual cancer treatment.

Laboratory Analysis

Blood specimens were drawn approximately 1 hour prior to testing and subjects were instructed to refrain from food, tobacco, and caffeine for at least four hours prior to testing. Blood draws were performed by hospital personnel certified and experienced in these techniques. Blood was drawn from an antecubital vein while the subject was seated. The University Laboratories at Wayne State University Medical School performed routine complete blood counts. The Immunology Laboratory in the University Laboratories of Wayne State University assessed the CD4+ and CD8 counts by means of flow cytometry techniques (Nieman, et al., 1991). NKCA was assessed by chromium release assay (Whiteside, et al., 1990). Analysis of 8-Isoprostane was performed in the Biochemistry Laboratory at the Karmanos Cancer Institute by means of enzyme linked immunoassay assay analysis (ELISA) (Roberts & Morrow, 2000).

Data Analysis

Analysis of the data was performed using the Statistical Package for the Social Sciences software program (SPSS/PC+ release 10.0.5, SPSS, Chicago Illinois). This study originally planned to use multivariate analysis of covariance (MANCOVA) in order to examine differences among the scores on the variables of interest between the two conditions as well as to examine the influence of

aerobic exercise training on the variables of interest. It was then planned to use discriminant analysis to examine whether the AE group and the PS group could be predicted and explained by differences in the variables of interest. However, due to the resulting small sample size, unequal numbers in each condition, and outliers, the appropriate test became the Wilcoxon Sign-Rank test (WSRT).

The WSRT examined whether aerobic exercise caused a significant difference between the baseline and final scores on the variables of interest in either the AE group or the PS group and thus examined the influence of aerobic training on the variables of interest. The WSRT is robust to outliers, in terms of Type I errors, and outperforms parametric tests under conditions of non-normal distributions (Sawilowsky, 1990, 1988, Blair & Higgins, 1985).

Following WSRT analysis of each variable, the Stouffer's Z meta-analysis was performed to determine whether there was a significant difference for multiple scores for each condition. The Stouffer's Z test is a meta-analytic procedure that combines information from all the variables for each condition into a single statistic for each group to determine whether their was a significant change in either group (Sawilowsky, et al., 1994, Stouffer et al., 1949). The Stouffer's Z analysis examined whether there was a difference between groups on the variables of interest following the intervention.

In 1988, Walton Braver and Braver noted that "Although meta-analytic techniques are typically applied to the results of many different studies, nothing prevents their application to several different tests of the same effect within but one study...". Sawilowsky and colleagues (1994) note that the Stouffer's Z

analysis provides a "non-parametric omnibus test of the null hypothesis" that tests whether "there is no treatment effect in any of the studies included in the analysis". The Stouffer's Z provided a method to assess whether there was a significant change in either the AE group or the PS group following the intervention on the variables of interest.

The Wilcoxon-Mann-Whitney U (W-MWU) was used to compare baseline scores between the AE and the PS groups to determine whether the variables of interest for each group were statistically similar prior to the intervention. The W-MWU was also used to examine post-test scores to determine whether changes resulting from the intervention were statistically different between the treatment and the placebo groups.

Statistical significance for all tests was set at a probability level of $p<.05$. This probability value improved power and limited Type I errors. All variables are described using means and standard deviations (SD) unless otherwise indicated. Since there is prior research support for this investigation, a one-tailed test was used for all assessments.

CHAPTER FOUR

RESULTS

Participants

Thirty-eight subjects were referred by their physicians to participate in this study. Twenty-three subjects consented to participate and fifteen declined participation. Twenty-one subjects completed the study, thirteen in the AE group and eight in the PS group. Two participants in the PS group did not return for the final testing session.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences software program (SPSS/PC+ release 10.0.5, SPSS, Chicago Illinois).

Between Group Pre-Test and Post-Test Comparisons

W-MWU analysis of pre-test scores indicated that there was no significant difference between the AE group and the PS on all of the variables except for NKCA. NKCA was significantly higher in the AE group prior to the start of the study ($p = .04$). Post-test scores were significantly different between the treatment and the placebo group on measures of VO_2 peak ($p = .01$) and skinfolds ($p = .04$), all other post test variable scores, including NKCA, were not statistically different between the two groups. Table 1 on the following page summarizes the statistics from the W-MWU analysis.

Table 1
W-MWU Comparison of Pre-Test and Post Test Values Between Groups

Variable		Pre-Test	Post-Test
VO_2 peak	W-MWU	39.000	26.000
	Z	-1.358	-2.197
	Asym. Sig. (1 tail)	.0875	.014*
Grip	W-MWU	54.500	58.500
	Z	-.356	-.098
	Asym. Sig. (1 tail)	.368	.461
Skinfolds	W-MWU	45.500	41.000
	Z	-.937	-1.227
	Asym. Sig. (1 tail)	.175	.110
BMI	W-MWU	55.000	56.000
	Z	-.323	-.258
	Asym. Sig. (1 tail)	.374	.398
Body Mass	W-MWU	54.500	54.500
	Z	-.355	-.355
	Asym. Sig. (1 tail)	.361	.361
NKCA	W-MWU	21.000	42.000
	Z	-1.748	-.000
	Asym. Sig. (1 tail)	.040*	.500
CD4+	W-MWU	29.000	38.000
	Z	-1.072	-.330
	Asym. Sig. (1 tail)	.142	.370
CD8+	W-MWU	31.000	29.000
	Z	-.907	-1.073
	Asym. Sig. (1 tail)	.182	.142
CD4+/CD8+ Ratio	W-MWU	38.000	35.500
	Z	-.330	-.536
	Asym. Sig. (1 tail)	.370	.296
8-Isoprostane	W-MWU	23.000	17.000
	Z	-.245	-.980
	Asym. Sig. (1 tail)	.400	.1635
R-PFS	W-MWU	57.500	51.500
	Z	-.162	-.549
	Asym. Sig. (1 tail)	.436	.291
POMS	W-MWU	52.000	37.000
	Z	-.517	-1.487
	Asym. Sig. (1 tail)	.303	.069

*Significant

Within Group Pre-Test to Post-Test Comparisons

WSRT analysis was performed to examine whether post-test scores were significantly different than pre-test scores in either the AE group or the PS group following the intervention. WRST analysis indicated that values in the AE group changed significantly for VO_2 peak ($p = .000$), skin caliper measures ($p = .001$), BMI ($p = .004$), body mass ($p = .005$), NKCA ($p = .004$), CD4+ ($p = .000$), and CD8+ ($p = .000$). There was no significant change in the AE group for grip strength ($p = .065$), the CD4+/CD8+ ratio ($p = .191$), 8-Isoporstane ($p = .166$), the R-PFS ($p = .300$), or the POMS scores ($p = .368$). The PS group also demonstrated significant changes for the immune parameters of CD4+ ($p = .02$) and CD8+ ($p = .02$), but all other values did not significantly change in this group following the intervention. Table 2 below summarizes the results of the WSRT statistical analysis.

Table 2
WSRT Comparison of Pre to Post Test Scores within Each Group

Variable	Exercise Group	Placebo Group
Peak VO_2		
Z	-3.181	-.560
Asymp. Sig. (1 tail)	.0005*	.2875
Grip		
Z	-1.527	.704
Asymp. Sig. (1 tail)	.0635	.2410
Skinfold		
Z	-3.059	-.339
Asymp. Sig. (1 tail)	.0010*	.3675
BMI		
Z	-2.691	-.840
Asymp. Sig. (1 tail)	.0035*	.2005
Body Mass		
Z	-2.622	-.840
Asymp. Sig. (1 tail)	.0045*	.2005
NKCA		
Z	-2.675	-.272
Asymp. Sig. (1 tail)	.0035*	.3925
CD4+		
Z	-3.180	-2.366
Asymp. Sig. (1 tail)	.0005*	.009*
CD8+		
Z	-3.180	-2.366
Asymp. Sig. (1 tail)	.0005*	.009*
CD4+/CDD8+ Ratio		
Z	-.874	-1.183
Asymp. Sig. (1 tail)	.1910	.1185
8-Isoprostane		
Z	-.970	-.135
Asymp. Sig. (1 tail)	.166	.447
R-PFS		
Z	-.524	-.338
Asymp. Sig. (1 tail)	.300	.3675
POMS		
Z	-.699	-1.051
Asymp. Sig. (1 tail)	.2425	.1465

* Significant

Treatment Effects Between Groups

The Stouffer's Z meta-analysis was performed separately for each group to determine whether there was a significant difference on all variables between groups following the intervention. Interestingly, when all of the variables for each group were used in the analysis, both the AE group (Z_{meta} = .0000) and the PS group (Z_{meta} = .0009) were significantly different. However, when variables were grouped by similarity, such as all of the variables that represented physical function, or all of the variables that represented body composition, the findings were quite different.

When the groupings were used, the AE group demonstrated significant changes in physical function (Z_{meta} = .0026), body composition (Z_{meta} = .0001) and immune status (Z_{meta} = .0000), but not in fatigue and mood (Z_{meta} = .2912), or in oxidative stress (Z_{meta} = .1170). The PS group, like the AE group, demonstrated a significant difference in immune parameter values (Z_{meta} = .0010), but no significant differences were found for physical function (Z_{meta} = .1711), body composition (Z_{meta} = .3874), fatigue and mood (Z_{meta} = .2483) or oxidative stress (Z_{meta} = .4483). A summary of the Stouffer's Z analysis appears in Table 3 below.

Table 3.
Meta-Analysis of All Variables & Variable Groupings for Each Condition

	Exercise Group	Placebo Group
All Variables		
Σ Z scores	25.182	10.0895
Resulting Z	7.2694	2.9126
Z meta	.0000*	.0018*
Physical Function (Peak VO_2 & Grip)		
Σ Z scores	4.708	-1.264
Resulting Z	3.3291	-.8938
Z meta	.0005*	.1867
Body Composition (Skinfolds, Mass & BMI)		
Σ Z scores	-8.3720	-2.019
Resulting Z	-4.8336	-.1.1657
Z meta	.00003*	.1230
Immune Status (NCKA, T-Cells)		
Σ Z scores	-9.9090	-6.1870
Resulting Z	-4.9500	-3.0935
Z meta	.00003*	.0010*
Fatigue & Mood (R-PFS, POMS)		
Σ Z scores	1.2230	1.3890
Resulting Z	.8648	.9822
Z meta	.1949	.3365
Oxidative Stress (8-Isoprostane)		
Σ Z scores	1.2190	-.1350
Resulting Z	1.2190	-.1350
Z meta	.1131	.4483

*Significant

CHAPTER FIVE

DISCUSSION

Participants

Thirty-eight multicultural females were originally referred to participate in this study by three radiation oncologists from the Karmanos Cancer Institute during the period of May to December of 2001. Subjects were recruited on a rolling admission based on the start date of their individual radiation regimen.

Of the original thirty-eight subjects referred to the study, twenty-three agreed to participate. Twenty-one subjects completed the study with thirteen in the AE protocol and eight in the PS group. Two participants in the PS group did not return for the final testing session. The reasons they left the study were not given, however, one subject was working two jobs and the other was balancing a full-time job and caring for a family. The reasons that people declined participation are described in Table 4 below.

Table 4.
Reasons for Declining Participation

Lack Transportation	3
Lack Child-Care	1
Anxious/Too Busy	3
Orthopedic Condition	2
Refused Randomization	1
Not Interested	2
Already Exercising	3

Participants were given written and verbal information about the study. They signed informed consent forms and were then randomly assigned, by

random number table, to either the aerobic exercise training (AE) group or the placebo-stretching protocol (PS). Participant demographics are in Table 5 below.

Table 5.
Participant Demographics

	AE Group	PS Group
Age	49.4 ± 7.0 *	51.9 ± 10.0 *
Culture	7 African-Americans 6 Caucasians	6 African-Americans 2 Caucasians
Surgery Only	3	2
Surgery and Chemotherapy	10	6
Adriamyacin-Cytoxan	9	6
Taxitere	1	0
Staging	DCIS – 3 I – 2 II – 4 III – 4	DCIS – 2 I – 1 II – 1 III – 4

*Not Significantly Different

When this study was designed, the radiation oncologists referring people to this study predicted that there would be 6 to 12 subjects referred during each week of the recruitment phase. However, once the study began, a marked decline was seen in the number of patients coming to their facility in a major urban center for radiation treatment. The referring physicians indicated that the decline in patient numbers was probably related to the opening of several suburban radiation treatment centers that coincided with the start of this study. It was thought that people elected to receive their radiation treatments at centers closer to their homes.

Test and Training Procedures

Testing was performed approximately one week before and one week after a participant's seven-week radiation regimen. Participants were instructed not to exercise for 24 hours prior to testing, and not to eat, drink caffeine, or smoke for 4 hours prior to the testing. Blood draws were approximately one hour prior to testing. Each test session took approximately one hour and fifteen minutes. The measurements performed during each test session were the VO_2 peak on a SLGXT with oxygen analysis, anthrompometrics, grip test, and the fatigue and mood scales. All tests were administered by the same evaluator according to the standards described in Chapter 3 of this document.

Following baseline testing, the participants were given directions on either the walking protocol or the stretching exercises. Participants in the AE protocol were given an exercise prescription based on the results of their individual performance on the SLGXT. The exercise prescription consisted of walking for 20-45 minutes at 50-70% of their maximum heart rate on 3-5 days each week. The AE participants were provided with a heart rate monitor and a training diary. The heart rate monitor provided the participants in the AE group with a simple method for assessing and recording their training heart rate and their exercise duration. The training journal was a convenient means to record and track the training. One participant in the AE group was on β-blocking hypertensive medications. This participant appeared to perform a maximal VO_2 test (RER = 1.16, oxygen leveling with increases in the workload, and RPE = 19), however, she did not exhibit the appropriate increases in heart rate during

the SLGXT. This subject trained using the RPE scale at a level of 11-13 as her training stimulus (Birk & Birk, 1987). This method of training appeared to be effective for this participant as she demonstrated the expected 11.0% improvement in her VO_2 peak following training. There were no other abnormal responses to the SLGXT during baseline testing.

Subjects in the PS protocol received identical assessments and blood draws, however, following their test battery, the PS participants were given a booklet on stretching and received an individual training session by a licensed physical therapist on how to properly perform the general stretching protocol.

All participants in both groups were given verbal and written instructions on normal and abnormal responses to their training protocol. They were also advised to contact the principal investigator or their physician if they developed any unusual signs or symptoms related to the exercise or the radiation treatment. All participants received a weekly telephone call or a personal visit during their radiation treatment appointment by the principal investigator. The weekly communication was designed to monitor the participant's progress and safety, as well as to encourage adherence to their protocol. Regular communication with patients participating in conditioning programs have been shown to improve adherence (Tardivel, 1998, Lieberman et al., 1998). Both groups of participants received reimbursement for each fitness session they completed.

Blood draws were performed at the Karmanos Cancer Institute. Blood was drawn from an antecubital vein with the participants in a seated position.

Blood draws were primarily in the morning with only two exceptions. Blood could not be drawn from one subject in the PS group who had bilateral breast surgery and collapsing veins. Blood analysis techniques are described in Chapter 3.

Pre-Test and Post Test Variable Analysis

A summary of all mean and median pre-test and post-test scores, as well as the mean and median change scores, are reported in Table 7 & Table 8.

VO_2 peak

VO_2 peak in the AE group increased significantly ($p = .000$) by a mean score of 9.1% from 20.9 ± 6.8 ml/kg/min. to 22.6 ± 6.2 ml/kg/min. All of the participants in the AE group increased their VO_2 peak levels following the intervention. There were two participants in the AE group that may have been close to their aerobic ceiling when they entered the study. Their VO_2 peak levels at baseline were 35.4 and 30.4 ml/kg/min. These subjects demonstrated modest improvements in the range of 0.3 to 1.3%. If these apparent outliers were removed from the analysis, then the mean baseline value for this group would have been 18.8 ml/kg/min, the final value would have been 20.6 ml/kg/min. and the mean improvement would have been 10.7%.

VO_2 peak in the PS group did not significantly change ($p = .288$) from a mean of 16.9 ± 2.9 ml/kg/min. to 16.6 ± 2.2 ml/kg/min. However, there was one outlier in this group whose VO_2 peak values increased by 41% from 13.8 to 19.5 ml/kg/min. At the time of the initial evaluation, this subject was suffering from marked swelling in her arms and legs. Although she was cleared to exercise to

improve her circulation and decrease her swelling, it appeared that this condition markedly impacted her performance on the initial test. It is unlikely that training alone would provide her with the profound improvement in her VO_2 peak values in just 7 weeks. If her VO_2 peak values are not included in the analysis, then the mean VO_2 peak values for the PS group would have decreased by 3.99% from 17.37 to 16.55 in the 7 weeks of the study. The median decline both with and without this outlier score was 4.1%.

Pre-test scores were not significantly different between the AE group and the PS group ($p = .213$). However, post-test scores were significantly different between the AE and the PS groups ($p = .014$). Indicating a significant improvement in physical function in the AE group as a result of the aerobic exercise training.

Both groups were instructed to perform their activity 3-5 days per week during the 7 weeks of their radiation regimen. Out of a possible 35 days of exercise (7 weeks), the AE participants performed a mean of 25.8 ± 10.1 days or 3.68 ± 1.4 days per week, of exercise. The PS participants performed 29.2 ± 7.7, or 4.16 ± 1.1 days per week of stretching activities. Therefore, raw data indicate that the PS group demonstrated slightly better compliance to the exercise regimens.

Participants in the AE group demonstrated a 9.1% mean increase in physical function as measured by VO_2 peak. This measure is approximately what was expected as the improvement demonstrated by apparently healthy subjects following 12 weeks of aerobic exercise training is 10-30% (ACSM

2000). Only four other studies reported data that could be compared to the oxygen analysis reported in this study. The 9.1% improvement in this study was slightly less than the 12.2% improvement reported by Dimeo and colleagues (1997), and is substantially less than the 40% improvement reported by MacVicar and colleagues (1989) and the 57% improvement reported by Dimeo and colleagues (1996). The differences between the present study and the other studies can be accounted for by variations in training procedures and in testing. Shore and Shephard (1999) also reported an approximate 5-6% increase over baseline measures for the three children in their study undergoing chemotherapy. Baseline values for their subjects were reported in the mid 30 ml/kg/min. range. However, it is difficult to compare the present study with the Shore and Shepherd study as children have typically exhibited higher VO_2 max levels than adults do. It can be generally noted that the oxygen consumption levels in the children with cancer were markedly lower than expected values in young people and these participants also demonstrated an improvement in test performance following training.

In regard to differences in the physical function assessments, it is difficult to directly compare this study with the previous studies. Only one reported using oxygen analysis as a means to assess fitness (MacVicar, et al., 1989), and that study reported values in liters per minute rather than the standardized values of ml/kg/min.

In terms of training, the previous studies used higher training intensities of 60 to 80% of a participant's heart rate maximum compared to the 50-70%

used in this study. Although the percent improvement in this study was less than the improvements reported in the other studies, none of the participants in this study dropped out because of the aerobic exercise training. Dimeo and colleagues (1996) reported 6 of 20 subjects (30%) did not complete exercise training and MacVicar and colleagues reported a total attrition of 27%, although it is difficult to determine how many of these subjects were in the aerobic exercise training group.

The participants in this study also tolerated the symptom-limited graded exercise testing very well. 14 of 23 participants (60.9%) met the more stringent criteria and performed true VO_2 max tests with RER values > 1.15 for both pre and post-test measures, while 67% of the subjects tested had RER values above 1.10. Only one subject in the PS group demonstrated electrocardiographic irregularities (ST segment depression), without accompanying clinical signs or symptoms, such as dypnea, confusion or chest pain, on the post-test. This subject was referred back to her physician for follow up.

Although the subjects tolerated exercise testing well, the baseline mean VO_2 peak for all participants was very low at 19.8 ± 4.8 ml/kg/min. with the median score for both groups at 17.5 ml/kg/min. This VO_2 peak measure represents a value that is below the 10^{th} percentile rank for a 60+ year-old female and as such, these participants demonstrated markedly low physical work capacities (ACSM 2000). In functional terms, these participants would be limited to maximum exercise activities such as moderate intensity walking or

golfing with a cart. They would most likely be out of breath or probably unable to walk up one flight of stairs.

Therefore, based on the results of this study, moderate intensity aerobic exercise training can significantly improve physical function in females undergoing radiation treatment for breast cancer. Participants in this study demonstrated improved compliance to the moderate intensity aerobic exercise compared to more vigorous intensities of training used in other investigations. This improved compliance would enable participants to gain benefits associated with aerobic exercise training. Also, the symptom-limited graded exercise testing appears to be safe and it appears to be effective for assessing fitness and developing exercise prescriptions for this population.

Grip Strength

Values for grip strength were not significantly different between the AE group and PS group on baseline ($p = .368$) or post test measures ($p = .461$). Grip strength for the AE group increased 5.4% from 29.8 ± 5.7 kg. to 31.3 ± 6.5 kg. and 3.6% from 30.8 ± 4.0 to 32.0 ± 6.4 kg. for the PS group. These changes were not significant in either the AE group ($p = .064$) or the PS group ($p = .241$). Grip strength was not expected to change in this study, as specificity of training indicates that endurance training does not improve strength measures (ACSM, 1998). However, 11 of 12 subjects in the AE group and 5 of 8 in the PS group improved their grip strength following the intervention. Further study would be of benefit in this population to examine whether improvements in physical function or flexibility lead to maintaining or

improving strength in this population. It would also be of benefit to examine the effects of strength training compared to endurance training or flexibility training in this population.

Body Composition

Body Mass

Baseline body mass values were not significantly different between groups ($p = .361$). Following the intervention, body mass in the AE group declined significantly ($p = .005$) by 2.2% from 81.6 ± 21.6 to 79.9 ± 20.9 kilograms as 11 of 13 participants in the AE group lost body mass. The PS group had a non-significant ($p = .459$) decrease of 1.3% from 84.1 ± 16.6 to 83.3 ± 18.2 kilograms as 5 of 8 PS participants lost weight. The significant decline in body mass in the AE group supports the use of aerobic exercise as a method to control weight gains in females during radiation therapy.

These results are different from the study by Winningham and colleagues (1989) who found that the exercise group in their study gained 0.82 kilograms and the control group gained 1.99 kilograms following a 10-week intervention. However, body mass alone is not a very meaningful method for examining health. In order to obtain more meaningful assessments, weight measures should be examined along with measures for fat mass such as skin caliper measures or measures related to health such as the BMI.

Skin Caliper Measures

Baseline skin caliper measures were not significantly different between groups ($p = .175$). Skin caliper measures for the AE group decreased

significantly (p = .001) by 12.6% from 202.4 ± 72.6 mm. to 180.4 ± 72.2 mm. while the PS group values increased non-significantly (p = .368) by 0.1% from 230.3 ± 58.7 to 234.0 ± 69.5 mm. The decrease in skin caliper measures for the AE group reflects a decrease in skin caliper measures reported by Winningham and colleagues (1989). However, it is difficult to directly compare skinfold values since the other study reported only mean changes in the skinfold measures and the body fat percents, rather than the total skinfold measures. The earlier study reported a decrease of 3.19 mm. for three sites in the exercise group, and an increase of 9.6 mm. in their control group, which supports an increase in lean body mass in their exercise group and an increase in fat mass in their control group. In the present study, the AE group and the PS group both demonstrated mean declines in skin caliper measures, although only the AE group decreases were significant.

Body fat percent was not calculated in this study, since measures for body density and regression equations for prediction of body fat have not been established for this population. Based on the results of the current study aerobic exercise training significantly decreases skin caliper measures compared to stretching exercises in females undergoing radiation treatment for breast cancer.

BMI

Baseline BMI measures between groups were not significantly different (p = .374) BMI measures in the AE group declined significantly (p = .004) by 2.2% from 30.8 ± 7.6 to 30.1 ± 7.3 while BMI for the PS group increased non-

significantly ($p = .398$) by 1.2% from 32.0 ± 5.6 to 31.7 ± 6.1. These measures reflect the findings of the skinfold measures and the body mass measures that the AE group experienced a significant improvement in body composition compared to the PS group following the intervention.

WHR

WHR was not used in this analysis, as it was found to be insensitive to changes that occurred in the participants in this study. The WHR was developed as an estimation of central obesity, since people with truncal fat (apple shaped) are at a higher risk for developing cardiovascular disease, diabetes, and possibly breast cancer. The WHR is calculated by dividing the waist girth in cm. by the hip girth measure in cm. Since this is a ratio measure any change that causes the denominator to be proportionally smaller will increase the WHR number and give the appearance of increased truncal fat and therefore, decreased health. Several participants in this study lost only hip girth, or had an equal decrease in centimeters at the hip and the waist, therefore their WHR ratio values increased. This increase in WHR did not reflect the improvements seen for these participants in other body composition measurements such as body mass, skinfold measures, and BMI and made them appear to have worsened in their body composition values. Further study is recommended to examine the efficiency of using the WHR as a measure of body composition in this population.

Body Composition Summary

In summary, the results of this study support moderate intensity aerobic exercise as having a significant and positive effect on body composition when performed during radiation treatment for breast cancer. This study mirrored the positive effect of aerobic exercise on body composition that was found by Winningham and colleagues (1989) in subjects undergoing chemotherapy treatment for breast cancer. Since weight gain is a common complaint for females undergoing radiation treatment for breast cancer, and because increased fat weight is related to poor health and possibly poor outcomes, the results of this study provide an effective method for managing weight gain at this time.

Immune Parameters

T-Cells

Baseline measures for CD4+, CD8+ and the CD4+/CD8+ ratios were not significantly different between the AE and PS groups ($p = .142$, $p = .182$, and $p = .370$ respectively). Baseline mean and median T-cell values were also clinically within normal limits.

Following the radiation treatment and the intervention, both groups demonstrated statistically significant declines in CD4+ and CD8+ counts, but not in the CD4+/CD8+ ratio. The AE group's CD4+ measures declined a mean of 48.6% ($p = .001$) from 888.9 ± 366.7 to 444.4 ± 175.6 and the PS group declined a mean of 46.6% ($p = .009$) from 1142.9 ± 723.5 to 528.9 ± 214.3. The CD8+ values also declined significantly in both groups. The AE group CD8+

values declined significantly (p = .001) by 49.7% from 450.4 ± 214.6 to 203.1 ± 95.4. The PS group CD8+ values declined significantly by 37% from 560.7 ± 229.1 to 378.9 ± 221.3. The CD4+/CD8+ ratio increased non-significantly in the AE groups 14.0% from 2.3 to 2.5 (p = .328) and declined non-significantly in the PS group by 13.4% from 2.0 to 1.8 (p = .250). The values for the CD4+/CD8+ ratio are considered to be within the normal range.

Surgery and chemotherapy treatments are typically reported to cause marked declines in immune function that may persist for 6 months following treatment (Fairey, et al., 2002). The normal baseline T-cell values measured in the present study are of interest since they are different from values reported in other studies for subjects following surgery or chemotherapy treatments (Braga, et al., 1996, Head, et al., 1993, Consoli, et al., 1998, Goodman, et al., 1996, Sabbiono, et al., 1999, and Sewell, et al., 1993). Participation in this study began within one week to four weeks following surgery, or surgery and chemotherapy. Four of six participants that received only surgery and 7 of 16 subjects that received both surgery and chemotherapy had baseline CD4+ counts above the normal value of 800, and baseline CD4+/CD8+ ratios above 2.0. The chemotherapy treatments described in the other studies were different from the Adriamycin and Cytoxan used by subjects in this study. Perhaps the difference in drug regimens contributed to the normal mean and median baseline values measured in the present study.

Both the AE group and the PS group demonstrated significant declines in final CD4+ and CD8+ counts, and these declines were not significantly different

between the AE and the PS group ($p = .370$, and $p = .142$). This similarity in declines seen in both the AE group and the PS group indicates that the AE protocol did not maintain or improve the immune parameters, however, AE did not cause further impairments in the T-cell counts. There were no other studies found that examined T-cell counts following radiation treatment and aerobic exercise training. The marked declines seen in this study in the T-cell values following radiation treatments are similar to those reported by other authors (Tisch, et al., 1998, Uh, et al., 1994). Interestingly, the final CD4+/CD8+ ratio for the AE group improved while the PS group value declined. Even though these changes were not significant, this phenomenon requires further investigation in a larger sample.

Therefore, since the final T-cell counts measured in this study were not significantly different between the AE and the PS group, this study supports the safety of performing moderate intensity aerobic exercise during radiation treatment for breast cancer. Additional studies are recommended to examine whether the modest improvement in the CD4+/CD8+ ratios in the AE group compared to the PS group is of clinical importance.

NKCA

NKCA will be more difficult to interpret in this study due to differences in clinical significance and statistical significance. Normal values for NKCA are described as above 17-20 lytic units and values for aerobically trained subjects can be 30 lytic units and higher (Shephard, et al., 1995, Peters, et a. 1994). Prior investigations provide evidence that NKCA decreases significantly

following radiation therapy (Garzetti et al., 1994, Blomgren, et al., 1980). It was the intention of this study to examine whether aerobic exercise training would increase or preserve NKCA levels compared to a non-exercising control group.

Although the mean baseline values for NKCA between the AE group and the PS group were significantly different ($p = .040$) prior to the start of this study, median values for both groups were below what is considered clinically normal at 10 lu. for the AE group and 5 lu. in the PS group. Additionally, the AE group mean value appeared to be in the normal range at 26.1 ± 25.8 lu. although 10 of 14 participants were below normal values. The higher mean value in the AE group was related to outlier values of 87 and 54 lu. in two of the participants.

Following the radiation treatment, the mean NKCA decreased significantly ($p = .004$) in the AE group by 38.1% from 22.8 ± 24.8 to 8.5 ± 9.2 lu., while in the PS group NKCA decreased non-significantly ($p = .3925$) by a mean of 4.6% from 6.7 ± 4.7 to 6.6 ± 4.2. The NKCA for both participants with outlier scores declined markedly to > 5 lu. Although NKCA values for the AE group were found to decrease significantly following the intervention, examination of the median values indicates that NKCA was clinically below normal in both groups prior to the intervention with the AE median at 10 lu. and the PS median at 5 lu. Following the intervention, median values for both groups were 5 lu., therefore the final NKCA measures between the AE group and the PS group were not clinically or statistically different following the intervention. The changes seen in the NKCA values in the AE group are most likely related to the radiation treatment and not to the exercise (Fairey, et al.

2002). Therefore, based on the results of this study, AE was not able to preserve or improve NKCA values during radiation treatment for breast cancer. However, since final NKCA values were not significantly different between the AE and the PS group following the intervention, aerobic exercise does not appear to impair the immune function more than a non-exercising control group (Shephard, et al., 1995, Peters, et al., 1994).

The effect of aerobic exercise on NKCA during radiation requires further study as NKCA levels may be influenced by circ-annual rhythms and by nutritional status (Nieman, et al., 1995, Barone, et al., 1989, Rose, et al., 1982). Neither of these conditions was controlled in this study. Future investigations on NKCA should control for seasonal changes and for participant's nutritional status to improve the reliability of the findings.

Fatigue and Mood

R-PFS

Baseline scores on the R-PFS were not significantly different between the AE and PS groups ($p = .436$). R-PFS scores in the AE group improved non-significantly by 13.2% from 3.8 ± 2.4 to 3.4 ± 1.9 following the intervention. In the PS group, fatigue scores also improved non-significantly by 17.7% from 4.0 ± 2.7 to 3.9 ± 2.4. Although the mean and median scores indicated an improvement in fatigue, further examination demonstrated that fatigue was not consistently improved in either group following the intervention. 7 of 14 participants in the AE group reported their fatigue improved, while 3 of 8 participants in the PS group reported an improvement in their fatigue levels. It

is difficult to measure a construct like fatigue. In prior studies, aerobic exercise training appeared to significantly improve fatigue scores in people undergoing treatment for cancer. Mock and colleagues (1997) reported significant improvements in fatigue scores following an aerobic exercise training intervention in females undergoing radiation treatment for breast cancer compared to a control group. The non-significant findings in this study may be a factor of the small sample size. However, it is recommended that further research be performed on this phenomenon. It is important to understand why some subjects experience relief from their fatigue through aerobic exercise training as well as why others do not experience these improvements.

Mood

Analysis of pre-test scores revealed no significant difference between the AE and the PS group ($p = .243$) for mood as measured on the POMS. The POMS mean scores for the AE group improved non-significantly ($p = .243$) by a mean of 86.0% from 18.5 ± 41.7 to 5.1 ± 22.1 while the PS mean POMS score improved non-significantly ($p = .1465$) by 7.9% from 38.9 ± 48.0 to 23.9 ± 32.0. Post-test scores were not significantly different between the two groups ($p = .069$) in this study.

The mean improvements in both groups were not significant and there was a wide range of scores as well as large standard deviations. In the AE group 11 of 13 participants had improvements in mood, and 2 of 8 subjects in the PS group reported improvements in mood. The improved values in the AE group mirror the values found by Mock and colleagues (1997), whose subjects

demonstrated significant improvements in scores for depression and anxiety with aerobic exercise training during radiation treatment for breast cancer. Segar and colleagues (1998) found significant improvements in self-esteem and state and trait anxiety in exercising breast cancer survivors. A direct correlation between studies in not possible since neither of the prior studies directly measured physical function, and different assessment tools were used to assess psychological symptoms. Mock and colleagues used the Symptoms Assessment Scale, and Segar and colleagues (1998) used the Beck Depression Inventory and the Speilberger State-Trait Anxiety Inventory.

Dimeo and colleagues (1999) examined a relationship between fitness levels and the POMS in cancer patients undergoing chemotherapy treatments. The Dimeo study examined whether a relationship could be found between fitness levels and mood on a one-time fitness and mood test not influenced by a training program. The Dimeo study found a non-significant difference between the total mood score and subjects in the high vs. the low fitness categories. The Dimeo study, like the present study, also had a wide range of scores and large standard deviations on the POMS for both groups. The wide range of scores supports the difficulty of consensus and therefore measurement of constructs such as mood. Although this study did not find significant improvements in mood, this phenomenon merits further study to examine the reasons that aerobic exercise improves mood in some subject but not in others undergoing radiation treatment for breast cancer.

It is also of interest that participants in the PS group demonstrated modest mean improvements in mood and fatigue during this study. All of the participants in the PS group reported that the stretching activities "relieved tension" or "helped get rid of neck and shoulder stiffness" following radiation treatments. The PS group also demonstrated improved compliance to their protocol compared to the AE group. On average participants in the PS group performed the flexibility exercises 4 times per week compared with 3 times per week in the AE group. Therefore, even though participants in the PS group did not experience a physiological change in their aerobic capacity, they demonstrated modest non-significant improvements on the POMS and on the R-PFS. Further study is recommended to examine the effect of flexibility exercises either alone or in combination with the aerobic exercise training.

Oxidative Stress

Baseline measures were not significantly different between the AE and the PS group ($p = .400$). In the AE group, pre-test and post-test 8-Isoprostane values were obtained for 10 subjects. Mean oxidative stress values in this group increased non-significantly ($p = .116$) by 10.5% from 238.2 0 ± 190.0 to 244.0 ± 132.6. 6 subjects in the AE group had increased oxidative stress levels and 4 subjects had decreased values following the intervention. In the PS group, pre-test and post-test 8-Isoprostane values were obtained for 5 subjects. Mean oxidative stress values increased non-significantly ($p = .447$) from 302.6 ± 221.0 to 316.4 ± 118.3 following the intervention. In the PS group three subjects demonstrated increased values and 2 had decreased values following

the intervention. The final values for oxidative stress were not significantly different between the two groups (p = 1635). Therefore, from these preliminary results, aerobic exercise does not appear to significantly increase oxidative stress levels in females undergoing radiation treatment for breast cancer as compared to a non-exercise control group.

Table 6
Descriptive Statistics for Baseline and Final Scores**

	AE Group		PS Group	
	Baseline	Final	Baseline	Final
Physical Function				
Peak VO_2 (ml/kg/min)	20.9 ± 6.8 (17.5)	22.6 ± 6.2* (20.7)	16.9 ± 2.9 (16.6)	16.9 ± 2.2 (17.5)
Grip (kg)	29.8 ± 5.7 (30.0)	31.3 ± 6.5 (32.4)	30.8 ± 4.0 (32.0)	32.0 ± 6.4 (32.0)
Body Composition				
Skinfolds (mm)	203.9 ± 74.7 (208.0)	179.8 ± 71.6* (177)	230.3 ± 58.7 (239.0)	234.0 ± 69.5 (237.5)
BMI	30.8 ± 7.6 (28.4)	30.1 ± 7.3* (28.2)	32.0 ± 5.6 (32.7)	31.7 ± 6.1 (33.2)
WHR	.822 ± .058 (.821)	.801 ± .055* (.797)	.851 ± .038 (.861)	.813 ± .061* (.805)
Weight (kg)	81.6 ± 21.6 (76.0)	79.9 ± 20.9* (74.6)	84.1 ± 16.6 (83.1)	83.3 ± 18.2 (83.1)
Fatigue and Mood				
R-PFS	3.8 ± 2.4 (3.4)	3.4 ± 1.9 (3.3)	4.0 ± 2.7 (3.8)	3.9 ± 2.4 (4.4)
POMS	18.5 ± 41.7 (7.0)	5.1 ± 22.1 (-1.0)	38.9 ± 48.0 (36.0)	23.9 ± 32.0 (33.0)
POMS-Fatigue	8.5 ± 7.4 (6.0)	7.7 ± 6.2 (5.0)	11.4 ± 10.0 (9.5)	13.5 ± 7.8 (14.5)
Immune Status				
NKCA	22.8 ± 24.8 (10.0)	8.5 ± 9.2* (5.0)	6.7 ± 4.7 (5.0)	6.6 ± 4.2 (5.0)
CD	888.9 ± 366.7 (800.0)	444.4 ± 175.6* (396.0)	1142.9 ± 693.2 (1036.0)	528.9 ± 214.3* (549.0)
CD8+	450.4 ± 214.6 (387.0)	203.1 ± 95.4* (207)	560.7 ± 229.1 (680)	378.9 ± 221.3* (350.0)
CD4+/ CD8+	2.3 ± 1.1 (2.1)	2.5 ± 1.1 (2.3)	2.1 ± 1.0 (2.0)	1.8 ± 1.0 (2.3)
Oxidative Stress				
8 –Iso-prostane	238.2 ± 190.0 (140.2)	244.0 ± 132.6 (132.5)	302.6 ± 221.0 (215.1)	316.4 ± 118.3 (306.0)

* Significant Change (p = .05) Wilcoxon Sign Rank Test
**Median Score in Parenthesis

Table 7
Mean/Median** Change Following Treatment

	AE Group	PS Group
Physical Function		
Peak VO_2 (ml/kg/min)	9.1 ± 7.4%* (6.3%)	1.7 ± 0.2% (-4.0%)
Grip (kg)	5.4 ± 12.8% (5.7%)	3.6 ± 14.9% (3.1%)
Body Composition		
Skinfolds (mm)	-12.6 ± 6.8%* (-10.8%)	0.1 ± 6.3% (0.1%)
BMI	-2.2 ± 2.3%* (-1.5%)	-1.2 ± 3.7% (-1.1%)
WHR	-2.5 ± 3.7%* (-2.7%)	-4.6 ± 4.8%* (-4.7%)
Weight (kg)	-2.1 ± 2.4%* (-1.7%)	-1.3 ± 3.6% (-1.2%)
Fatigue and Mood		
R-PFS	13.2 ± 57.6% (9.3%)	17.7 ± 71.5% (2.5%)
POMS	-86.0 ± 117.5 % (-98.3%)	-7.9 ± 40.5% (+7.9%)
Immune Status		
NKCA	-38.1 ± 36.1%* (-37.5%)	4.6 ± 29.3% (0.0%)
CD4+	-48.6 ± 10.1%* (-48.0%)	-46.6 ± 15.6%* (-46.9%)
CD8+	-51.2 ± 15.5%* (-49.7)	-32.9 ± 25.8%* (-37.0%)
CD4+/CD8+	14.0 ± 41.52% (7.7%)	-13.4 ± 21.6% (-16.1%)
Oxidative Stress		
8 – Isoprostane	10.5% ± 0.3% (20%)	5.5%± (NA)

* Significant (p = .05) Wilcoxon Sign Rank Test
** Median Change in Parenthesis

Overtraining Precautions

Participants in the AE group appeared to tolerate the moderate intensity aerobic exercise training very well and none of the participants in the AE group left the study due to the rigor of the exercise. However, one subject in the AE group appeared to overtrain and demonstrated marked decrements in her final values for fatigue and mood as well as grip strength. This participant exercised on every day of the study but one. Frequently this subject walked and bicycled on the same day. This participant demonstrated only a 1.0% improvement in her VO_2 peak values compared to the mean increase of 9.1% demonstrated by other participants in the AE group. She was also one of only two participants in the AE group to report a worsening of fatigue and she experienced a 67% increase in mood disturbances as measured on the POMS. Additionally, this participant developed marked shoulder tendonitis and experienced a 19% decrease in her final grip strength measure. Based on this case study, over-training during radiation treatment for breast cancer appears to be associated with increased fatigue and mood disturbances, decrements in strength, and a damping of improvement in physical work capacity.

Conclusions and Recommendations

Primary Conclusions

The first goal of this study was to examine the effects of aerobic exercise training on physical function, body composition, immune parameters and oxidative stress in subjects undergoing radiation treatment for breast cancer. Based on the results of the WRST analysis of changes in pre-test to post-test

scores, this study supports the following. Moderate intensity aerobic exercise training performed by females with breast cancer during radiation treatment significantly improves measures of physical work capacity and body composition. Aerobic exercise training during this time was not able to preserve immune parameters, and subjects in the AE group experienced significant declines in T-cell and NKCA values following the intervention. Aerobic exercise training measures in the AE group was found to cause modest but non-significant mean improvements in grip strength, fatigue and mood.

The second goal of this study was to examine whether there was a significant difference between the AE group and a PS group for changes seen in the variables of interest following the intervention. Stouffer's Z meta-analysis was used to assess differences between both groups. This analysis found a significant difference in the AE group on measures of physical function, body composition, and immune parameters but not in oxidative stress, or in fatigue and mood following the intervention. In the PS group, this analysis found a significant difference only for the immune parameters. These results indicate that the changes seen in the AE group on the variables related to physical function and body composition were a result of the aerobic exercise intervention since the PS group did not demonstrate significant changes in these variables at this time. This analysis also indicates that the changes seen in the immune parameters for the AE group were related to something other than the exercise intervention since both the AE group and the PS group had significant changes for these values. The significant declines seen in the immune parameters in

both groups were most likely related to the radiation treatments. Based on this analysis, fatigue, mood and oxidative stress were not found to change significantly following the intervention in either group. This lends support for further study on fatigue and mood in these subjects. It also provides early evidence that the changes in oxidative stress were not significantly different in the exercise group compared to the non-exercise condition.

Secondary Findings

There were several findings of interest that occurred during the course of this study and many of these findings would benefit from further examination. First, the Stouffer's Z meta-analysis appeared to be super-powerful under the conditions of this study. When all of the 12 variables were grouped together for each group, the Stouffer's Z test found that both groups significantly changed following the intervention. However, when the variables were grouped for similarity and the meta-analysis was performed, the result was markedly different. Further examination of this statistical method would be beneficial in understanding how this analysis performs under conditions with multiple variables.

Moderate intensity aerobic exercise also appears to be safe and effective for people undergoing radiation treatment for breast cancer. All of the subjects in the AE group experienced an improvement in their physical function and none of them left the study because the exercise was to demanding. However, in one subject, who appeared to over-train, improvements in physical function were damped, fatigue and mood disturbances increased, and grip strength

decreased. Subjects also tolerated the exercise testing very well as 60% of the participants performed true VO_2 max tests.

Interestingly, subjects in the PS group had modest improvements in their fatigue and mood. Participants in this group reported that the stretching exercises relieved stress and stiffness following the radiation treatments. These anecdotal comments were further supported by improved compliance to in the PS group compared to the AE group. Further investigations would be of interest to examine the effects of flexibility exercises alone, or in combination with other exercises, on cancer-related symptoms during radiation treatment.

Many of the participants reported that the weekly telephone call or visit was very much appreciated during this time. Several participants reported that it was the "best part of the study". Health care professionals would benefit from further investigations on the importance of regular communication with people undergoing radiation treatment for cancer.

Finally, the WHR was found to be an inconsistent measure of change in body composition for this population. This finding, in conjunction with the absence of prediction equations for body fat percent in this population, indicates a need for further studies to develop effective tools in order to assess body composition in this population.

Limitations of this Study

The primary limitations of this study were related to the small sample size and various uncontrolled factors related to nutrition, the timing of the study, and variations in cancer treatments. The original intent of this study was to

perform all measures during a single season, however the study covered several seasons and variations in seasons may have affected the results of the immune parameters, as well as mood and fatigue. Diet and supplements were not controlled in this study and variations in nutrition could have had an impact on immune parameters, mood and fatigue, as well as physical performance. Finally, not all subjects received the same treatments prior to radiation therapy and these variations may have affected the final results.

Summary of Conclusions and Recommendations

Based on the results of this study, moderate intensity aerobic exercise is recommended as a safe and effective method to improve physical function and body composition in females during radiation treatment for breast cancer. Moderate intensity aerobic exercise training does not appear to preserve or improve immune parameters or oxidative stress during this time. However, the declines seen in immune parameters and oxidative stress were not significantly different from those in the placebo-stretching group. Therefore, aerobic exercise training does not appear to cause decrements in the immune function that are greater than in a non-exercising group. Finally, modest but non-significant improvements were seen in the mean values for fatigue and mood in both the AE and the PS group. Further studies would be of benefit to explain the reasons behind this phenomenon.

APPENDIX A

HUMAN INVESTIGATION COMMITTEE APPROVALS

WAYNE STATE UNIVERSITY

HUMAN INVESTIGATION COMMITTEE
4201 St Antoine Boulevard - UHC-6G,
Detroit Michigan 48201
Phone: (313) 577-1628
FAX: (313) 993-7122
www.orsps.wayne.edu

NOTICE OF FULL BOARD APPROVAL

TO: Jacqueline Drouin, MS, PT
Physical Therapy
439 Shapero Hall

FROM: Manuel Tancer, M.D. M Tancer
Chairperson, Medical Institutional Review Board (M01)

DATE: August 3, 2000

RE: Protocol #: 07-11-00(M01)-FB "Aerobic Training in Subjects Undergoing Radiation Treatment for Breast Cancer." No funding requested

The above-referenced protocol and consent form (revision dated 07/31/00) were APPROVED following Full Board Review by the Wayne State University Institutional Review Board (M01) for the period of **August 3, 2000 through July 5, 2000.**

EXPIRATION DATE: July 5, 2001

This approval does not replace any departmental or other approvals that may be required.

Federal regulations require that all research be reviewed at least annually. **It is the Principal Investigator's responsibility to obtain review and continued approval before the expiration date.** You may not continue any research activity beyond the expiration date without HIC approval.

- If you wish to have your protocol approved for continuation, please submit a completed Continuation Form at least six weeks before the expiration date. It may take up to six weeks from the time of submission to the time of approval to process your continuation request.
  *****Failure to receive approval for continuation before the expiration date will result in the automatic suspension of the approval of this protocol on the expiration date. Information collected following suspension is unapproved research and can never be reported or published as research data.*****
- If you do not wish continued approval, please submit a completed Closure Form when the study is terminated.

All changes or amendments to your protocol or consent form require review and approval by the Human Investigation Committee (HIC) **BEFORE** implementation.

You are also required to submit a written description of any adverse reactions or unexpected events on the appropriate form (Adverse Reaction and Unexpected Event Form) within the specified time frame.

WAYNE STATE UNIVERSITY

HUMAN INVESTIGATION COMMITTEE
4201 St Antoine Boulevard - UHC-6G,
Detroit Michigan 48201
Phone: (313) 577-1628
FAX: (313) 993-7122
www.hic.wayne.edu

NOTICE OF FULL BOARD CONTINUATION APPROVAL

TO: Jacqueline Drouin, PT, ABD
(Physical Therapy)
University of Michigan-Flint
101 Lapeer Street Annex
Flint, MI 48502-1950

FROM: Manuel Tancer, M.D. M. Tancer /CR
Chairman, Medical Institutional Review Board (M01)

DATE: June 7, 2001

RE: Re-review of Protocol #: 07-11-00(M01)-FB "Aerobic Training in Subjects Undergoing Radiation Treatment for Breast Cancer" Source of Funding: Elsa U. Pardee Foundation/The Max & Victoria Dreyfus Foundation

The above Protocol and Continuation Form, submitted on 05/06/01, were APPROVED following Full Board Review *by the Wayne State University Institutional Review Board (M01) for the period June 7, 2001 through June 6, 2002.*

EXPIRATION DATE: June 6, 2002

This approval does not replace any departmental or other approvals that may be required.

Federal regulations require that all research be reviewed at least annually. **It is the Principal Investigator's responsibility to obtain review and continued approval before the expiration date.** You may not continue any research activity beyond the expiration date without HIC approval.

- If you wish to have your protocol approved for continuation for another year, please submit a completed Continuation Form at least six weeks before the expiration date. It may take up to six weeks from the time of submission to the time of approval to process your continuation request.

  Failure to receive approval for continuation before the expiration date will result in the automatic suspension of the approval of this protocol on the expiration date. Information collected following suspension is unapproved research and can never be reported or published as research data.

- If you do not wish continued approval, please submit a completed Closure Form when the study is terminated.

All changes or amendments to your protocol or consent form require review and approval by the Human Investigation Committee (HIC) BEFORE implementation.

You are also required to submit a written description of any adverse reactions or unexpected events on the appropriate form (Adverse Reaction and Unexpected Event Form) within the specified time frame.

BARBARA ANN
KARMANOS
CANCER INSTITUTE

Clinical Trials Core
Charles A. Schiffer, M.D.
Director of Clinical Research
Margaret Ferrara, M.S.
Manager

Protocol # C-2194

TO: Jacqueline Drouin, MS, PT

FROM: Protocol Review Committee (PRC)

DATE: June 1, 2000

Your protocol, **Aerobic Training in Subjects Undergoing Radiation Treatment for Breast Cancer** has been reviewed by the chairman of the Protocol Review Committee and determined to be **EXEMPT** from PRC review.

You will be required to submit continuation forms and other required paperwork to the Clinical Trials Office.

Please submit a copy of this letter to the HIC. The HIC will not review the study without evidence of prior CCCTC approval or exemption.

Maha Hussain, M.D., Chairman
Protocol Review Committee

A United Way
Clinical Trials Core
4160 John R, Rm. 711
Detroit Michigan 48201
(313)745-4704

Michigan Cancer Foundation
The Detroit Medical Center
Wayne State University

NCI CCC Meyer L. Prentis Comprehensive Cancer Center of Metropolitan Detroit

APPENDIX B

WRITTEN CONSENT FORM

Aerobic Training in Subjects Undergoing Radiation Treatment for Breast Cancer
Jacqueline Drouin, MS, PT

INFORMED CONSENT

Introduction/Purpose
You have been invited to be a subject in a research investigation to examine the effects of exercise on subjects undergoing radiation treatment for breast cancer. The results obtained from this study will help determine the benefits of performing exercise during radiation treatment.

Procedure
Your physician has already given you medical clearance to participate in this study which may include either gentle stretching activities or moderate intensity walking or cycling in your neighborhood.

On two occasions you will complete some simple tests, one test will be within one week of starting your radiation treatment, and the second will be one week after you complete your radiation treatment. The tests will include paper and pencil tests to examine mood and fatigue. You will have a small amount of blood drawn (about 2 Tablespoons) at these two testing sessions and you will have your hand strength tested and your fitness level measured on a treadmill. Your body fat classification will also be measured with a tape measure and a skinfold caliper. The skinfold caliper measures fat folds at various sites.

The exercise test will be performed on a motor-driven treadmill. During this test you will wear a clear mask over your mouth and nose to measure the air you are breathing. A valve on the mask will allow you to breathe in room air, and will take measures of the air you are breathing. The exercise intensity will begin at a level that you can easily do and will slowly advance in stages depending on your fitness level. You may stop the exercise test at any time you wish because of feelings of fatigue or discomfort.

Risks and Discomforts
Professionals familiar with exercise testing will monitor you during all tests to minimize any risk or unusual responses. Exercise testing can cause fatigue or muscle soreness, however, the intensity and progression of the exercise will be kept at a level that will minimize fatigue and muscle soreness. There exists a possibility of certain changes occurring during the testing such as abnormal blood pressure, fainting, or abnormal heartbeat, and in rare instances, death. Every effort will be made to minimize these through the preliminary examination and by observations during testing. Emergency equipment and trained personnel are available to deal with unusual situations that may arise.

Experienced and trained personnel will perform the blood draws and it is unlikely that you will experience a problem. Risks of having blood drawn include bruising or hematoma in the antecubital area, bleeding for more than 2 but less than 5 minutes, and a rare chance of infection.

Exercise training at a moderate intensity is known to be safe and has many positive effects. Before beginning the walking/cycling or stretching program you will receive clearance from your physician, and you will be evaluated for your safety to exercise on the treadmill test described above.

You agree to alert the study personnel if you have any side effects of any kind, or if you seek or receive any medical treatment.

Benefits
You will experience the benefits that accompany participation in exercise such as improved flexibility or endurance. Participation in the physical tests will provide you with information on your grip strength, your fitness level, and your body fat classification. The mood and fatigue tests will allow you to know how you compare to other subjects during this time.

Voluntary Participation/Withdrawal
You will be free to discontinue the test or participation in this study at any time of your own decision. If you choose not to participate in this study there will be no penalties of loss of benefits to which you are otherwise entitled. Your doctor or physical therapist may also discontinue your study participation if it is determined to be in your best interest.

Questions
Any questions about this study are encouraged. If you have any questions now or in the future please call Jacqueline Drouin at (810) 762-3373. If you have any questions about your rights as a research subject, contact the Chair of the Human Investigation Committee at (313) 577-1628.

Confidentiality
Specific information about you and your tests will be confidential. Only the numbers obtained from this study will be documented and shared with the medical community, but your name will not be disclosed in any way.

Compensation
You will be paid $25.00 for each of the two testing sessions. Therefore, if you complete two testing sessions you will be paid a total of $50.00. Testing will be performed at the beginning and at the end of the study.

Costs
There will be no cost to you for participation in this study or to receive all of these tests. Your insurance company or another third party payer will pay for the treatment that is considered standard treatment. Your physician will not receive any compensation from this study. It is unlikely that you will sustain an injury, if you are injured as a result of taking part in this study, treatment will be offered to you, but you or your insurance company will be responsible for payment. Your will be told where you may receive additional treatment for injuries. Wayne State University or the Detroit Medical Center offers no reimbursement, compensation, or free medical treatment.

Aerobic Training in Subjects Undergoing Radiation Treatment for Breast Cancer
Jacqueline Drouin, MS, PT

Alternatives
People that choose not to participate in this study will be provided with the usual care, and will be entitled to any of the treatments that are considered customary care as determined by their physician.

Consent to Participate
By signing this consent form, you agree that you have read all of the above information about this research study, including possible risks and likely benefits. You also agree that the content and meaning of this information has been explained to you and that you understood, and all your present questions have been satisfactorily answered. You will receive a signed copy of this form.

I hereby consent and voluntarily offer to follow the study requirements and take part in this study.

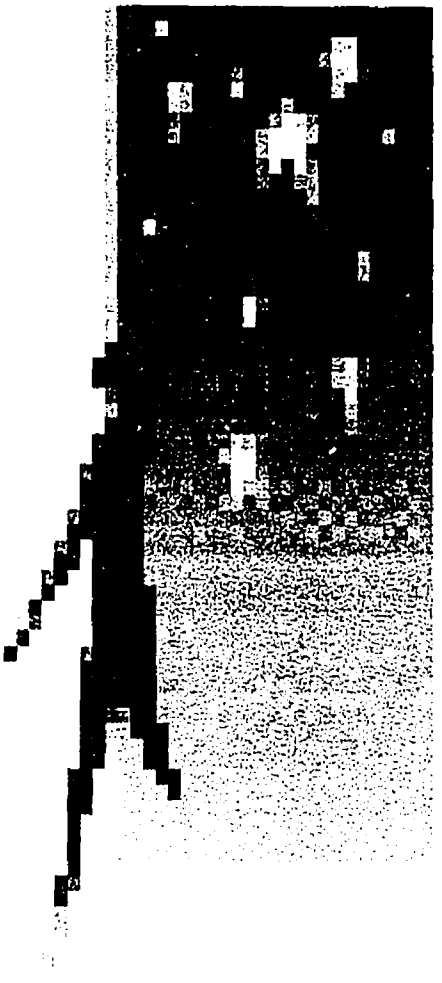
Participant	**Date**
Witness	**Date**
Principle Investigator	**Date**

APPENDIX C

TRAINING PROTOCOLS

FLEXIBILITY PROTOCOL

REACHING FOR THE STARS



A RESEARCH INVESTIGATION ON EXERCISE AND CANCER

EXERCISE AND CANCER

Exercise training has become an important component in the treatment and recovery from breast cancer.

Many studies support exercise as a method to manage fatigue, improve fitness, and relieve depression or anxiety at this time.

There are some things that we do not know about exercise. We would like to know why people that exercise during their radiation treatment report that they feel better and that is what this study is all about.

DESCRIPTION OF THE STUDY

Thank you for agreeing to participate in this study on exercise and its effects on radiation treatment.

This study is being performed through the cooperation of the Karmanos Cancer Center and Wayne State University. This study is being directed by Jacqueline Drouin an assistant professor in the Physical Therapy Departments at Wayne State University and at the University of Michigan. If you have any questions about this study please call her at (810) 762-3373.

PROGRAM DESCRIPTION

This study will be examining the benefits of two different types of exercise that you will perform during your radiation treatment. The two types of exercise are stretching or walking.

You will be assigned to either a stretching or a walking group during your radiation treatment time.

You will be asked to perform the walking or the stretching activities most days of the week, and record your workouts on the enclosed calendar.

TESTING

Before and after the seven weeks of radiation treatment, you will be asked to do the following tests:

a. A Blood Test
b. An Exercise Test
c. A Hand-grip Strength Test
d. A Body Composition Profile
e. Two Pencil and Paper Tests

REIMBURSEMENT

You will be given $25.00 for the first tests and $25.00 again when you repeat the second set of tests.

CONFIDENTIALITY

The information in this study will be confidential. At the beginning of the study, you will be given a subject number. All of the data from this study will be identified by your subject number; at no time will the data from this study be linked with your name.

BENEFITS OF THIS STUDY

Participation in the exercise regimens will provide you with improvements either in you flexibility or your endurance. You will also learn some interesting things about your strength, your endurance, your body composition, and your blood studies. In addition, you will be contributing to the body of knowledge on the best exercise methods during radiation treatment for breast cancer.

GENTLE STRETCHING

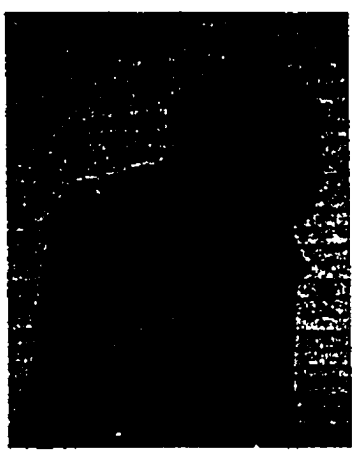
The following are general flexibility exercises for ladies following surgery of the breast. You will be instructed by a physical therapist on the proper way to perform these gentle stretches. Perform only those stretches that the physical therapist has determined are right for you.

Do these exercises five days per week. Perform each gentle stretch three times and hold it for 15-30 seconds. Do not go for a burn. Gentle stretching should make you feel good all over!

GENTLE NECK STRETCHES

BACK

FRONT

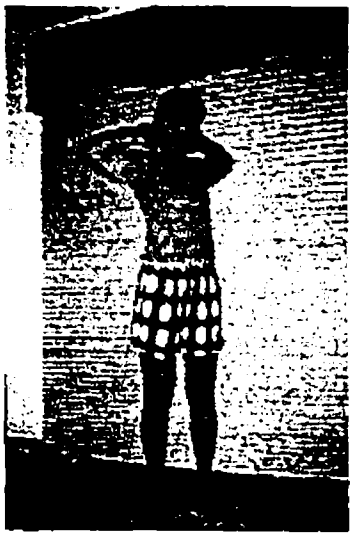


SIDE TO SIDE

RIGHT TO LEFT

GENTLE SHOULDER STRETCHES

SHRUG UP



BUTTERFLY

EASY BUTTERFLY

EASY PULL BACK

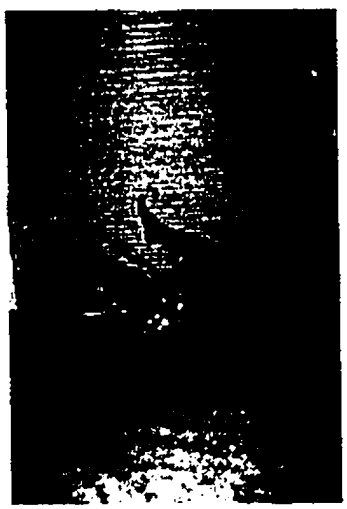
PULL BACK

GENTLE TRUNK AND SHOULDER STRETCHES

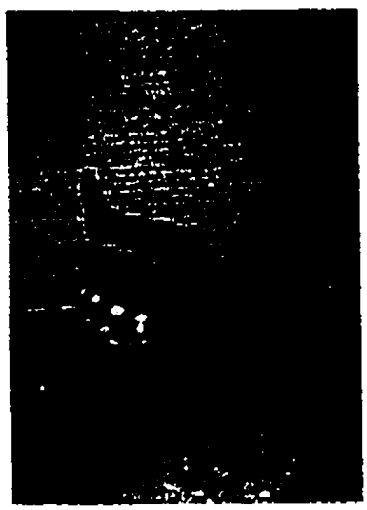
GENTLE SIDE BEND

GENTLE TWIST

GENTLE BACK AND THIGH STRETCHES



KNEE TO CHEST



BOTH KNEES TO CHEST

GENTLE LEG STRETCHES

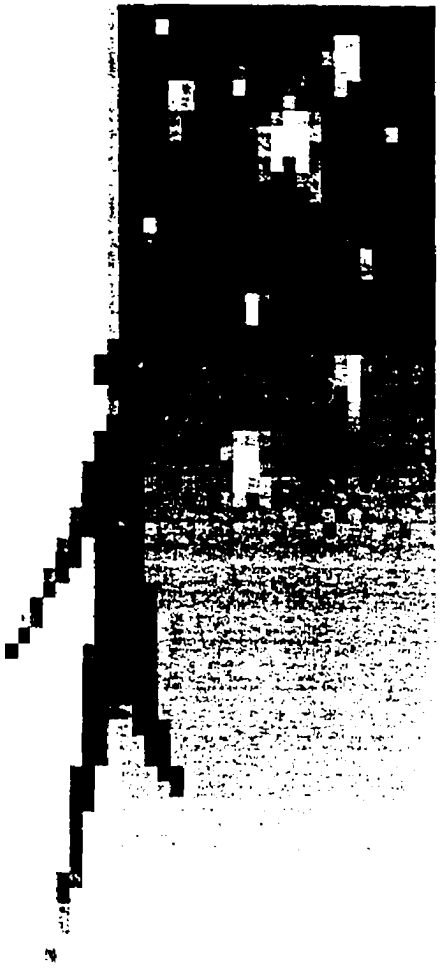
QUAD STRETCH

CALF STRETCH

HAMSTRING

AEROBIC EXERCISE WALKING PROTOCOL

REACHING FOR THE STARS



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BENEFITS OF THIS STUDY

Participation in the exercise regimens will provide you with improvements either in you flexibility or your endurance. You will also learn some interesting things about your strength, your endurance, your body composition, and your blood studies. In addition, you will be contributing to the body of knowledge on the best exercise methods during radiation treatment for breast cancer.

WALKING PROGRAM

You have been selected to participate in the walking program. You will be walking 20-30 minutes per day at the training heart given to you during your exercise test.

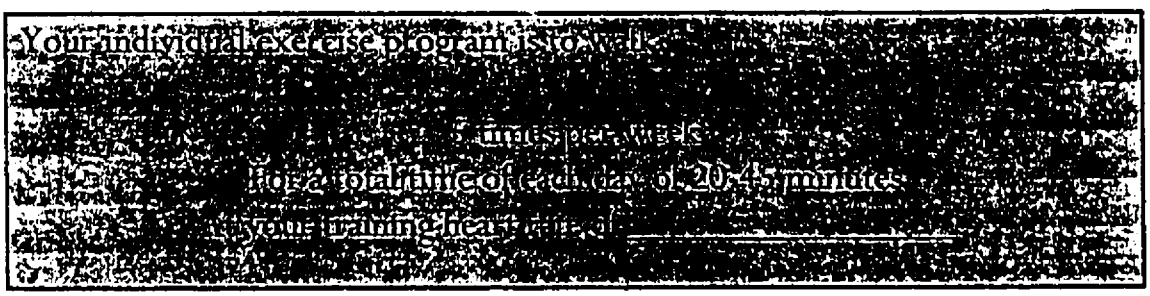
Your exercise session each day should consist of:

1. 10 minutes of slow walking to warm-up
2. 20-45 minutes of walking at your training heart rate
3. 10 minutes of slow walking as a cool down

You will be given a heart rate monitor to wear during your exercise session. It will record measure your heart rate response during exercise for you. It will also keep track of the amount of time you are exercising for the study.

If you experience any unusual responses to the exercise session, please notify your physician, or call Jacqueline Drouin at 810-762-3373.

Please record your exercise time in your journal each day.



TRAINING DIARY

Name

Week	SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
1							
2							
3							
4							
5							
6							
7							
8							
9							

Record each day:

1. Minutes of Exercise
2. Average Exercise Heart Rate
3. Any good feelings or problems such as sleeping, fatigue, nausea, or dizziness

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ABSTRACT

AEROBIC EXERCISE TRAINING EFFECTS ON PHYSICAL FUNCTION, FATIGUE AND MOOD, IMMUNE STATUS, AND OXIDATIVE STRESS IN SUBJECTS UNDERGOING RADIATION TREATMENT FOR BREAST CANCER

by

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Aerobic exercise is associated with improvements in health status however, little is known about its effect during radiation treatment. The purpose of this study was to measure the effects of moderate intensity aerobic exercise training on physical function, body composition, fatigue, mood, immune parameters, and oxidative stress in females undergoing radiation treatment for breast cancer. Following approval by the Human Investigation Committees at Wayne State University and the Karmanos Cancer Institute, 23 females (50.0 ± 8.2 years old) with breast cancer (Stage 0-III) agreed to participate in this study. Participants signed informed consent and were randomly assigned to a moderate intensity aerobic exercise group (AE) or a placebo-stretching group (PS). The AE group performed self-monitored walking, at 50-70% of their maximal heart rate on 3-5

days per week during a 7-week radiation regimen. Measurements were performed one-week before and one-week after the radiation treatments. 21 subjects completed the study, 13 in the AE group and 8 in the PS group. Physical function was measured by peak oxygen consumption (VO_2 peak), and grip strength by dynamometry. Fatigue was measured on the Revised-Piper Fatigue Scale and mood by the Profile of Mood States. Body composition was examined by skin caliper technique, body mass and body mass index (BMI). Immune parameters were measured by CD4+ and CD8+ counts and Natural Killer Cell Activity, and oxidative stress by 8-Isoprostane analysis. Following treatment, the Wilcoxan Signed Rank Test revealed a significant improvement in the AE group, but not in the PS group, on VO_2 peak ($p = .00$), skin caliper measures ($p = .00$), body mass ($p = .00$), and BMI ($p = .00$). Immune parameters declined in both groups but final values were not significantly different between groups. Fatigue, mood, and grip strength improved modestly but not significantly in both groups while oxidative stress declined non-significantly in both groups. This study supports moderate intensity aerobic exercise training as a means to improve physical function and body composition during radiation treatment for breast cancer. Additionally, immune parameters and oxidative stress values were not further compromised in the exercise group compared with the placebo group.

AUTOBIOGRAPHICAL STATEMENT

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The author is an Assistant Professor in the Physical Therapy Department at the University of Michigan – Flint. She holds a Baccalaureate degree in Physical Therapy and a Master of Science in Exercise Science, both from Oakland University in Rochester, Michigan. Her research interests are centered on exercise training in special populations. It is her intent to develop fitness programs to enhance the quality of life in people who are undergoing treatment for cancer and to continue to contribute to the body of knowledge in this area. A bicycle trail in Michigan is also calling her name.