Examination of Static and Dynamic Balance in Breast Cancer Survivors

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ABSTRACT

Daniel Clayton Tysinger: Examination of Static and Dynamic Balance in Breast Cancer Survivors
(Under the direction of Dr. Claudio Battaglini)

This study compared static and dynamic balance between a group of post-treated breast cancer survivors (BCS) and a group of apparently healthy age and body weight-matched sedentary women control (CO). Sixty-five subjects participated in the study (BCS, n=40; CO, n=25). Static balance was assessed using the Single Limb Stance (SLS) while dynamic balance was assessed using the Timed 360° Turn and the Four Square Step Test (FSST). No significant differences were observed between the BCS and CO for static (p=.290) or dynamic balance (p=.396) measured via the Timed 360° Turn test. No associations between muscular fitness and balance were found in either group suggesting that the possible balance issue in BCS may be associated with neurological impairment instead of muscular fitness decline following treatment.
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Chapter I

Introduction

Breast cancer is the second most common form of cancer among women, with an estimated 182,460 cases in the U.S. in 2009 (American Cancer Society, 2009). Of these, 40,170 were expected to die from the disease (ACS, 2009). Approximately one in eight women in the U.S. will be diagnosed with breast cancer in their lifetime (ACS, 2009). This is a disease that has a profound impact on the physiology and psychology of patients, and its treatments are believed to impair their ability to function at the same level as prior to having cancer (Battaglini et al., 2006). Some alterations in physical and psychological functioning can last many years post treatment, compromising overall functionality in some patients, which may lead to significant reductions in quality of life.

Advances in technology and treatment have increased survival rates to 89% at five years post diagnosis (ACS, 2009). Even though new technology has given great hope to many patients, it has come with a multitude of side effects that can be acute (occurs immediately after the initiation of treatment) or chronic (side-effects that can linger for years after completion of treatment). The severity of these side effects is dependant on many factors such as age, stage of disease, Nevertheless, the majority of patients that undergo any kind of treatment, regardless of age, disease stage, and type of treatment such as chemotherapy, radiation and hormonal therapy do experience different side effects that are bothersome, compromising the patients’ ability to function at a minimal required level needed to perform the simplest daily task (Battaglini et al., 2006; Broeckel et al., 2000;
Courneya et al., 2003). Common side effects experienced by breast cancer patients include fatigue, decreased immune function, changes in body composition (decrease in muscle mass with concomitant increases in fat mass), osteopenia, decreased cardiorespiratory endurance, and decreased muscular strength (Courneya et al., 2003; Galvao & Newton, 2005; Shapiro & Recht, 2001; Visovsky, 2006). Some common side effects of a psychological nature include depression, anxiety and decline in cognitive function (Ahles et al., 2002; Mar Fan et al., 2005; Van Dam et al., 1997). Fatigue is often cited as one of the most common and debilitating side effects reported by breast cancer patients (Bower et al., 2000; Broecker et al, 1998; Dimeo, 2001; Schwartz et al., 2001). Debilitating fatigue often leads to a state of deconditioning, which contributes to decreased physical activity levels. This can lead to a decline in muscular endurance and cardiorespiratory endurance and can directly affect the ability to perform basic and instrumental activities of daily living (Battaglini, et al., 2006). Activities of daily living are often taken for granted by healthy people, but for someone in the midst of breast cancer treatment or even those who have completed treatment and are still coping with the side-effects, performing the simplest daily tasks presents a tough challenge. One of the side effects that has been minimally examined and may occur in the breast cancer population is the decline in the ability to balance. Balance impairment is linked to cancer treatments such as radiation and chemotherapy, not the cancer itself. In the breast cancer rehabilitation program (Get REAL & HEEL Breast Cancer Research Program) at the University of North Carolina at Chapel Hill, breast cancer survivors continue to anecdotally report that cancer treatments have impacted their ability to balance. According to their
reports, the ability to stand still or to change direction post-completion of breast cancer treatment has decreased, leading to the hypothesis that cancer patients have significantly altered static and dynamic balance when compared to a normal population. Studies that have looked at the effect of cancer treatment on balance in breast cancer patients are scant (Silverman et al., 2006; Wampler et al., 2007). In a study conducted by Silverman et al. (2006), the authors looked at the impact of chemotherapy 5 to 10 years post-completion of treatment in breast cancer survivors and found significant alterations in the frontal cortex, cerebellum and basal ganglia activity. Although balance was not directly measured, the brain structures that were tested are all involved in postural control. In another study conducted by Wampler and colleagues (2007), their preliminary findings supported the findings of Silverman and colleagues by finding significant differences in static and dynamic balance in a group of Taxane treated breast cancer patients when compared to a group of healthy controls. However, in addition to the possible impact of cancer treatment on the vestibular system (one part of the nervous system that is important for postural control), decreases in muscular fitness and development of peripheral neuropathies commonly observed in cancer patients post treatment may be another factor. Wampler and colleagues suggested these as other potential factors that could impact balance in the breast cancer population. Data from the NIH also indicates that as people age, balance may be compromised by vestibular disorders that include symptoms such as vertigo, dizziness and labyrinthitis.

Previous studies have examined the relationship between muscular fitness, fatigue and balance (Tisdale, 1999; Al-Majid & McCarthy, 2001). The overall results of these studies suggest that muscle weakness and fatigue have a significant effect on balance ability. The reduction in muscular fitness and muscle endurance may contribute to a decrease in
motor functioning, therefore impairing proper control of postural stability. Muscle waste from cancer treatment can decrease strength and endurance (Tisdale, 1999; Al-Majid & McCarthy, 2001).

Given preliminary evidence that cancer treatment contributes to decreased muscular fitness, development of debilitating fatigue and possible impairments of vestibular system function, balance difficulties in the breast cancer population may exist beyond anecdotal reports by patients. The scarcity of data that addresses the potential balance issue in the breast cancer population precludes our ability to fully understand this potential side effect from cancer treatment. Therefore, studies designed to investigate balance in this population are warranted.

**Statement of Purpose**

The purpose of this study was to compare static and dynamic balance between a group of post-treated breast cancer survivors (BCS) and a group of apparently healthy age, height and body weight-matched sedentary women control group (CO). A secondary purpose was to explore the relationship between static and dynamic balance and overall muscular endurance (OME) in both the BCS and CO groups. Finally, the relationship between fatigue and static and dynamic balance was explored in the BCS group.

**Research Questions**

1. Does a) static balance, measured using the single limb stance test, and b) dynamic balance, measured using the Timed 360° Turn test and the Four Square Step tests, differ between groups?

**Hypothesis 1a.** The CO group will have significantly better static balance, measured using the Single Limb Stance test, than the BCS group.
**Hypothesis 1b.** The CO group will have significantly better dynamic balance, measured using the Timed 360° Turn test and the Four Square Step test, than the BCS group.

2. Does muscular endurance correlate with a) static and b) dynamic balance in both BCS and CO groups?

**Hypothesis 2a.** There will be a significant positive relationship between static balance and overall muscular endurance in both the BCS and CO groups.

**Hypothesis 2b.** There will be a significant inverse relationship between dynamic balance and overall muscular endurance in both the BCS and CO groups.

Since alterations in muscular fitness (muscle deconditioning or even muscle mass loss) may occur with administration of anti-cancer treatments, and the ability of the muscle to contract over a period of time (muscular endurance) may be impacted. This potential reduction in muscular endurance capacity may play a role in the ability of patients to balance; meaning that those with less muscular endurance may have a decreased ability to balance.

3. Does cancer treatment-related fatigue in the BCS group correlate with a) static balance and b) dynamic balance?

**Hypothesis 3a.** There will be a significant inverse relationship between fatigue scores assessed using the Revised Piper Fatigue Scale and static balance assessed using the Single Limb Stance test in the BCS group.

**Hypothesis 3b.** There will be a significant inverse relationship between fatigue scores assessed using the Revised Piper Fatigue Scale and dynamic balance assessed using the Timed 360° Turn test and the Four Square Step tests in the BCS group.
Definition of Terms

Breast Cancer Survivors: A group of breast cancer patients who have completed their major treatment (chemotherapy, radiation therapy, or combination of these treatments) within 6 months and were undergoing hormonal therapy at the time of data collection.

Static Balance: The ability to control the body while in a stationary position (Thibodeau & Patton, 1996).

Dynamic Balance: The ability to maintain the center of gravity over a constantly changing base of support (Thibodeau & Patton, 1996).

Overall muscular endurance: A variable created by summing the number of repetitions recorded from the assessment of push-ups, partial curl-ups, biceps brachii curls, latismuss dorsi pulldown, leg extension and leg curls.

Assumptions

1. Both the BCS and CO groups abided by the pre-testing guidelines prior to reporting for testing.

2. The BCS subjects were honest and accurate in answering the questionnaire that was used to assess fatigue.

3. Not all testing was conducted by the same researcher; therefore tester effect must be taken into account as well.

Limitations

1. The different types of treatments that subjects in the BCS group underwent for the treatment of their disease could have affected the outcome variables measured in this study.

2. Even though all subjects in the BCS group had completed their major treatments within 6 months, those who had completed treatment most recently (i.e: within a week) may have
been experiencing more severe side-effects than those who had completed their treatment earlier. This fact may have influenced the results of the study.

**Delimitations**

1. All subjects in the BCS group were participants in the Get REAL & HEEL Breast Cancer Program and were recruited via different hospitals and breast cancer clinics around the Chapel Hill, Durham and Raleigh areas and through the program web page.
2. All subjects in the BCS group were diagnosed with stage I, II, or III breast cancer and had completed their major cancer treatment within six months.
3. All subjects in the BCS group had undergone some type of chemotherapy and/or radiation as part of their major treatment plan.
4. All subjects in the CO group had no contraindication for exercise and were not engaged in regular physical activity for the past year.

**Significance of the Study**

Breast cancer survival rates have increased the past decade due to early detection and new forms of treatments that are now available to patients. Treatment for breast cancer is harsh but necessary. However, a multitude of side effects develop during treatment and may last for many years after the completion of treatment. Even though the medical community attempts to alleviate some of the side effects derived from treatment, by using pharmacological treatment, many others are still under-treated and under-examined. One issue reported by many breast cancer patients that enroll in the Get REAL & HEEL Breast Cancer Rehabilitation Research program is the inability to balance the same way they once could prior to undergoing cancer treatment. Currently, minimal information concerning this possible impairment in this population is available in the literature. To date, there is only one
available published study that suggests that this may be an under-treated issue in the breast cancer population, and that the balance issue should be further investigated (Wampler et al., 2007). If balance is in fact a problem, it can make it difficult for this population of breast cancer patients to carry out their normal daily activities. Balance impairment can also put an individual at a greater risk for falls and consequently injury. In the cancer population, the decrease in physical activity levels associated with negative physiological changes commonly observed in patients who undergo cancer treatment may compromise even further their ability to control their posture and ability to balance. Loss of muscular fitness, the development of treatment-induced peripheral neuropathies and potential treatment damage to the vestibular system are among many theories that may be associated with the patients’ reports of reduced balance post treatment. Therefore, the potential issue of balance impairments in cancer patients is an area that needs to be explored further.
Chapter II

Review of Literature

This review of literature is organized into 6 sections: Section 1 presents the definition of breast cancer and provides current statistics on disease incidence and death rates in the U.S; Section 2 discusses the most common treatments currently available; Section 3 presents information on the most common side effects observed post diagnosis and during/after completion of treatment; Section 4 presents the current understanding on the physiology of balance (postural control); Section 5 discusses the possible mechanisms associated with decline in balance in post-treated breast cancer patients.

Breast Cancer and Current Disease Statistics

Breast cancer is defined as the uncontrolled growth of cells within the breast that form a malignant tumor (American Cancer Society, 2009). The malignant tumor may then metastasize into other parts of the body. The cancer begins in either the ducts or lobules of the breast, and spreads from there (American Cancer Society, 2009).

Breast cancer is classified in stages ranging from 0 to 4, with 4 being the most severe. Stage 0 is called carcinoma in situ, and is the least dangerous. It involves only the lobule lining or duct, and is not always invasive. Even so, it is possible for stage 0 to metastasize (National Cancer Institute, 2009). Stage I is the earliest form of invasive cancer, and is characterized by a tumor that is less than 2 centimeters in diameter. The
tumor is also still enclosed within the breast tissue. Stage II encompasses a few descriptors. The tumor can be between 2 and 5 centimeters in diameter and has not spread to any lymph nodes in the under arm; must be between 2 and 5 centimeters and have spread to lymph nodes under the arm; be larger than 5 centimeters in diameter and contained within the breast; or be no larger than 2 centimeters but have spread to a lymph node in the under arm.

Stage III is called locally advanced cancer and is further subdivided into 3 categories: stage IIIA, stage IIIB and stage IIIC. Stage IIIA is classified by a tumor that is less than 5 centimeters in diameter but has proliferated to underarm lymph nodes and is attached to other immediate structures, or else the tumor is greater than 5 centimeters in diameter and has spread to underarm lymph nodes. Stage IIIB is defined by a tumor that has metastasized to lymph nodes behind the breastbone and under the arm, or the cancer has spread to lymph nodes above or under the collarbone. Stage IIIC is a tumor of any size that has proliferated to the lymph nodes at the rear of the breastbone and under the arm or has spread to lymph nodes above or under the collarbone. Stage IV is the most severe form that has metastasized to other regions of the body (National Cancer Institute, 2009).

Outside of skin cancer, breast cancer is the most commonly diagnosed cancer among women, and accounts for one in four cases of cancer in women in the U.S. (American Cancer Society, 2009). It was estimated that 192,370 new cases were diagnosed in 2009 alone in the U.S., and that 40,170 women would die from the disease (American Cancer Society, 2009). A woman born in the U.S. has about a 3% chance of dying from breast cancer (American Cancer Society, 2009).

**Common Treatments for Breast Cancer**

Common cancer treatments include chemotherapy, radiation, hormonal therapy,
surgery or a combination of the above. Treatments can be further broken down into local, systemic, adjuvant and neoadjuvant. Local therapy is meant to treat a tumor at the site without affecting the rest of the body. Radiation and surgery are both localized types of treatments. Systemic therapy refers to drugs which can be administered orally or intravenously to reach cells anywhere in the body. Chemotherapy, hormone therapy and targeted therapy are systemic treatments. Adjuvant therapy occurs when a patient has no detectable cancer after a surgery and is treated with systemic methods to prevent the cancer from reoccurring in another part of the body. This is done because doctors believe that in some cases cancer cells may break away from the primary tumor and spread via the bloodstream in the early stages of the disease. Since it is nearly impossible to detect if this has happened, adjuvant therapy acts as an insurance plan to kill any leftover cancer cells. Neoadjuvant therapy occurs when systemic therapy, such as chemotherapy, is done before surgery to shrink a tumor to allow for less extensive surgery (National Cancer Institute, 2009). Chemotherapy, a systemic treatment, is treatment with cancer killing drugs that are given intravenously or orally. The drugs travel via the bloodstream to reach the affected area. Chemotherapy is given in cycles, which usually last several months. Each treatment period is followed by a recovery period. Chemotherapy is most effective when used in combination with more than one drug. Chemotherapy can be used as an adjuvant or neoadjuvant method (National Cancer Institute, 2009).

Radiation therapy uses high-energy rays that kill cancer cells. It is used to kill remaining cells in the breast, chest wall, or underarm after breast conserving surgery. Radiation therapy uses 2 methods, external beam radiation and brachytherapy. External beam radiation is the most common form and uses a focused beam from a machine directly on the
affected area of the body. Treatment usually runs 5 days a week for roughly 6 weeks. The
dose of radiation is dependent upon the severity of the tumor and whether lymph nodes are
involved. Treatment may include the entire breast, the chest wall, and underarm area.
Brachytherapy involves radioactive seeds or pellets that are placed directly into the breast
tissue next to the cancer. It is often used in combination with external radiation to augment
the amount of treatment at the site (National Cancer Institute, 2009).

Hormonal therapy is another type of systemic therapy that is most commonly used as
adjuvant therapy, as well as to treat cancer that has come back after treatment or has
metastasized. The hormone estrogen promotes the growth of about 2 out of 3 breast cancers.
Cancer that contains estrogen receptors, are called ER positive cancers, and cancers that
contain progesterone receptors are called PR positive cancers. Hormone therapy seeks to
block the effect or lower the amounts of estrogen within the body. There are 5 common drugs
for hormone therapy. Tamoxifen and toremifene are types of Fareston’s. These drugs work
by temporarily inhibiting estrogen receptors on breast cancer cells, stopping estrogen from
binding to them, and are taken as a daily pill. Felvestrant works by eliminating estrogen
receptors, but instead of blocking reception of estrogen, it eliminates it. This drug is
administered via an injection once a month. Aromatase inhibitors work by stopping estrogen
production in post-menopausal women via blocking the enzyme aromatase, which is
responsible for creating estrogen. These drugs only work in post-menopausal women and are
taken once daily in pill form. Another method is ovarian ablation, which basically shuts
down the ovaries and eliminates much of the body’s source of estrogen production. This drug
has the capability of turning a pre-menopausal woman into a post-menopausal state, and
allows for other hormone therapies to work more effectively. Ovarian ablation can be
achieved by removing the ovaries via an oophorectomy, or more commonly through the use of drugs called luteinizing hormone releasing hormone (LHRH). These drugs stop the signal from the body to the ovaries to produce estrogen. This method of treatment is often used in conjunction with tamoxifen in pre-menopausal women. Finally there is an older less common drug called megestrol acetate. This drug is most used in advanced stages of cancer when the patient has not responded to other types of hormone therapy (National Cancer Institute, 2009).

The oldest treatment and most invasive is surgery. Over the years, surgery has become more refined, less invasive, and an effective way to treat breast cancer, especially if it has not spread to other areas of the body. Most people with cancer will have some type of surgery, which will be discussed below. Preventive surgery is done to remove tissue that is not yet cancerous, but is likely to become so. Women with a family history of breast cancer and who have a mutation in the DNA of a breast cancer gene may consider this surgery to avoid the risk of getting cancer all together. Next there is diagnostic surgery, which aims to diagnose what type of cancer is present by taking a tissue sample and examining it under a microscope. Another type is staging surgery, which determines how much cancer there is and how far it has spread. Curative surgery describes a procedure in which the entire tumor is removed at once, in theory eliminating the cancer from the body totally. Debulking surgery removes some, but not the entire tumor and is performed when removal of the whole tumor is too dangerous to the patients’ health and may harm nearby organs or tissue. Finally, palliative surgery does not seek to cure the cancer, but rather aims to alleviate other problems that are caused by the cancer. An example would be a large tumor that is inhibiting another organ from functioning correctly (National Cancer Institute, 2009).
Commonly Observed Side Effects of Breast Cancer Treatment

Chemotherapy

All forms of treatment carry with them a myriad of side effects, some of which can be severely debilitating. Common side effects from chemotherapy include fatigue, muscle weakness, compromised immune system function, nausea, cardiomyopathies, vomiting, hair loss, problems concentrating, exercise intolerance and psychological disturbances such as depression and anxiety (American Cancer Society, 2009; Battaglini et al., 2006; Dimeo, 2001; Galvao and Newton, 2005; Hsish et al., 2008; National Cancer Institute, 2009). Fatigue is the most commonly reported side effect associated with chemotherapy and radiation treatment, with nearly 70% of patients reporting this (Battaglini, 2006). A less well known side effect includes chemotherapy induced peripheral neuropathy (CIPN) and damage to the vestibular system, both of which could lead to disturbances in postural stability and balance. CIPN occurs due to damage to the peripheral nervous system when a patient receives a neurotoxic chemotherapeutic treatment. Common sensory deficits associated with CIPN include mild to moderate numbness, tingling and stabbing/burning sensation in the hands and/or feet. Motor effects include distal muscle weakness and decreased deep tendon reflexes. Wampler and colleagues (2007) have shown that peripheral neuropathy can have negative effects on visual, somatosensory and vestibular feedback, all which aid in balance control. Potential damage to the vestibular system may come from vestibular toxicity induced by drugs containing platinum compounds (Sergi et al., 2003).
Radiation Therapy

Radiation therapy also poses many issues such as vomiting, nausea, fatigue, coronary and carotid artery arteriosclerosis and skin changes (American Cancer Society, 2009; Hsieh et al., 2008). Primary short-term side effects include swelling and heaviness of the breast and sunburn-like damage to the treated area. The patient may also be advised to avoid exposing treated skin to the sun, as this may worsen the condition. However, these changes usually go away in 6 to 12 months. In some cases, the breast may shrink and become firmer after treatment. Radiation therapy may also hinder a woman’s chances to have breast reconstruction surgery. Radiation therapy of auxiliary lymph nodes can also cause lymphedema. More rare side effects include weakened ribs and toxicity of the heart and lungs. Finally, radiation may cause angiosarcoma, another rare form of cancer, which can grow and spread very fast (American Cancer Society, 2009).

Hormonal Therapy

Hormonal therapy can lead to headaches, blood clots, hot flashes, vaginal dryness or discharge, mood swings and early menopause (American Cancer Society, 2009). Blood clots, which usually occur in the legs, pose a serious threat to a person’s health. Clots can lead to heart attacks, stroke or pulmonary embolism. A blood clot is usually identifiable by pain, swelling, redness in the calf, shortness of breath, chest pain and sudden severe headache. Hormone therapy can also lead to a ‘tumor flare’ if the cancer has spread to the bone. A tumor flare will consist of pain and swelling in the muscle and bones, and usually settles quickly. However, in some cases this may cause a patient to develop a high calcium level in the blood that is uncontrollable, which may cause hormonal treatment to end prematurely. Another rare but serious side effect of hormone therapy is cancer of the uterus. Unusual
vaginal bleeding is a common symptom of uterine cancer and should receive prompt attention (American Cancer Society, 2009).

**Surgery**

Surgery at the chest region may lead to impaired range of motion at the shoulder, fluid buildup at the wound, infection, pain, scar tissue and deformation of the breast tissue (American Cancer Society, 2009; Hsieh et al., 2008). Surgery will sometimes require the removal of lymph nodes and may cause a condition known as lymphedema. Lymphedema is a swelling of the arm due to excess fluid in the arms that usually travels back to the bloodstream through the lymphatic system. Removal of the lymph nodes inhibits this pathway and causes fluid to build up in the arm. This condition affects up to 30% of women who have lymph nodes removed. As with any surgery, infection of the site is always a threat, and if not recognized and treated promptly can lead to further complications. Numbness of the upper and inner part of the arm is another effect since the nerve that controls this region is located within the lymph node area. Hematoma, a buildup of blood in the wound, and seroma, a buildup of clear fluid in the wound, are also potential troublesome side effects.

**Physiology of Balance (Postural Control)**

Balance is a very dynamic process that incorporates many different inputs from the visual and vestibular systems in conjunction with receptors located in joints and muscles that are constantly feeding back and relaying information to the brain about the proprioception of the body. Balance involves the use of the vestibular, visual, and somatosensory systems, including both peripheral and central nervous system components (ASHA, 2009). Research has also shown that a relationship between muscular endurance and balance exist. More specifically, acute bouts of exercise can lead to decreased motor performance and
compromise the ability to balance (Nardone et al., 2007). Much of the control of balance from the inner ear comes from an organ called the labyrinth. The labyrinth communicates with visual and musculoskeletal systems to maintain balance. For example, visual inputs are sent to the brain, where they are then compared to information from the muscle and joint receptors and the vestibular system. This helps explain why it is much more difficult to balance when someone’s eyes are closed. The lack of visual data telling the brain where the body is in relation to its surroundings takes away a vital piece of information that the brain uses to help balance the body. Two examples of the relationship between the visual and vestibular systems are the vestibular ocular reflex (VOR) and nystagmus. The VOR consists of reflexive eye movement that stabilize the visual image on the retina during head movement, allowing the image of whatever someone is looking at to stay in the center of the field of vision. When the head is moved to the right, the VOR moves the eyes to the left. When the head is turned without making any attempt to focus on an object, the vestibular ocular reflex will keep the eyes centered in a neutral position. This enables the eyes to respond quickly in response to any further movement. If the head is moving too fast for the eyes to keep up, vertigo and dizziness will ensue. Nystagmus is a rapidly occurring eye movement that happens when the head is rotated side to side and then comes to a sudden stop, or for normal speed head movements as well. It consists of the rhythmic oscillation of the eyes in either a vertical, horizontal or rotary direction that occurs when the head is moved. There are three forms of nystagmus: pendular, jerk and physiologic. Pendular nystagmus occurs when the rhythmic oscillation is symmetrical and the eyes are oscillating from one side to the other at the same speed. Pendular nystagmus can be caused by poor central vision due to color blindness, cataracts or corneal scarring. Jerk nystagmus occurs
when eye movement is not symmetrical and the speed differs when the eye is oscillating. Jerk nystagmus can occur due to motor defects caused by lesions on the cerebellum, vestibular nerve or brainstem. It can also be induced physiologically by objects crossing the field of vision very quickly, causing the eyes to jerk back and forth to remain focused. Both pendular and jerk nystagmus can be caused by damage to the eyes or vestibular system, but can also occur involuntarily (Butterworth-Heinemann). Physiologic nystagmus will occur if a person deliberately interferes with the movement of the eyes to focus on an object. This can prevent dizziness and vertigo. To avoid losing balance, ballerinas and figure skaters use this technique. This reflex enables the eyes to maintain a correct position, and allows for information from the visual system to still be accurate even though the head is moving rapidly (Sharp & Barber, 1993).

The labyrinth contains three semicircular canals, the superior, posterior and horizontal, that tell the body where it is in rotary motion. Each canal is filled with fluid called endolymph. The motion of the fluid within the canal is a signal that the body is moving. The three canals converge in an area of the inner ear called the vestibule. From here the vestibular system works in conjunction with visual system to keep objects in focus when the body is moving. While in movement, joint and muscle receptors supplement the information from the vestibular system, and together it is all sent to the brain stem and cerebellum (NIDCD, 2009).

Fluid movement in the canals tell the brain about the direction and velocity of rotation of the head, which enables the brain to determine if the head is nodding up and down or shaking left and right. Each canal has a bulbed end that contains hair cells, which are entrenched in a jelly like substance called the cupula. Rotation of the head causes displacement of fluid, which in turn stimulates and displaces these hair cells. Once the hair
cells are stimulated they send nerve impulses to the brain via the vestibular portion of the acoustic nerve (VIII cranial nerve). The impulses are then processed in the brain stem and cerebellum. These organs are primarily responsible for detecting rotational movement of the head (ASHA, 2009). Two other organs, called the utricle and saccule, are responsible for monitoring acceleration or deceleration in a linear fashion, and to sense head position relative to gravity. Together these are known as the otolithic organs. The hair cells of the otolithic organs are covered with a jelly like layer that houses small calcium stones called otoconia. When the head is sloped or the body’s position is altered with respect to gravity, the stones are displaced, causing the hair cells to bend, which again sends nerve impulses to the brain the via the vestibular portion of the acoustic nerve (ASHA, 2009).

**Balance in Cancer Patients**

Cancer and its treatment have many side effects, which may affect the different mechanisms that control balance.

**Chemo Brain**

Chemo brain describes the phenomenon of decreased cognitive function that some cancer patients experience during and after their chemotherapy treatments. Chemo brain can be defined as decreased cognitive abilities, speed of information processing or response speed and organizational skills (Staat & Segatore, 2005). Cognitive dysfunction has been reported in as many as 50% of breast cancer patients undergoing chemotherapy (Paraska & Bender, 2003). Since chemotherapy is a form of neurotoxin, it can damage the CNS, and therefore has the potential to impair balance. For example, the drug 5-fluorouracil (5-FU) has been reported to impair cerebellar function. The drug is a neurotoxic metabolite, which can readily cross the blood brain barrier (BBB), and cross into the cerebrospinal fluid and brain.
Common symptoms of this include ataxia (a gross lack of coordination and muscle movements), dysmetria (the inability to judge distance or scale), pathological nystagmus, vertigo, limb incoordination, and diplopia or double vision. A study by Silverman and colleagues (2006) demonstrated altered blood flow to the cerebellum 5-10 years post chemotherapy treatment. All subjects were former breast cancer patients treated with adjuvant chemotherapy. The subjects received a PET scan, which was compared to PET scans from control subjects. Silverman found that subjects who underwent chemotherapy had alterations in basal ganglia, cerebellum and the frontal cortex. In 2007, Wampler et al. conducted a study in regards to the effect of Taxane chemotherapy on postural stability. They noted that peripheral neuropathy was a common side effect, and that diabetic peripheral neuropathy has been associated with postural instability and increased risk of falls. Therefore, their hypothesis was that chemotherapy induced peripheral neuropathy might also have similar effects as diabetic peripheral neuropathy. This is the only study to date that has investigated this potential relationship in cancer patients. Wampler and colleagues (2007), collected data on breast cancer patients using quantitative and clinically feasible measurements of balance. The study consisted of 20 women between the ages of 30 and 60 who had complete taxane therapy for breast cancer. The tests included center of pressure (COP) using a force plate, sensory organization testing (SOT), the Fullerton Advanced Balance Scale (FABS) and the timed up and go (TUG) test. The COP testing involved the subjects standing on a force plate which measured stability in four different static positions: eyes open with head straight, eyes open with head back 40°, eyes closed with head straight, and eyes closed with head back 40°. The sensory organization test asked the subjects to complete 3 trials of 6 conditions that increased in difficulty each time. The first condition
consisted of the subject standing on a stable platform with eyes open and a non-moving visual surround. The test then advanced by either modifying visual feedback by closing eyes, or by moving the visual surround, and altering somatosensory feedback by moving the platform in the sagittal plane. The authors indicated that the clinically feasible FABS and TUG test correlated moderately with the COP and SOT quantitative tests. In all four test modes, all breast cancer patients recorded significantly lower scores when compared to age matched healthy controls. Another possible reason for balance decrements in the breast cancer population is damage to the visual system. Some women with breast cancer have been found to have lower contrast vision. Paclitaxel (a mitotic inhibitor), and cyclophosphamide (a nitrogen mustard alkylating agent that slows or stops cell growth) have been associated with spontaneous side effects such as scotoma (area of lost vision surrounded by normal vision), photopsia (appearance of flashes due to retinal irritation), and blurred vision (Griffin & Garnick, 1981; Kende, Sirkin, Thomas & Freeman, 1979; Scaioli et al., 2006; Tan & Walsh, 1998). However, these side effects have been reported in patients with and without peripheral neuropathy, so it is not clear if these visual changes are associated with peripheral neurotoxicity to the optic nerve, changes to the cornea, or vascular changes at the retina (Scaioli et al., 2006). It is still possible that chemotherapy induced ocular modifications may contribute to postural instability issues in the breast cancer population, but little is known for certain.

Taxane therapy is currently not associated with vestibular toxicity; however, platinum compounds, another type of chemotherapy drug that causes peripheral neuropathy, has been associated with vestibular toxicity (Sergi, 2003). The data from the Wampler study suggests a link between balance and vestibular toxicity. On conditions 5 and 6 of the sensory
organization test, in which the patients were on an unstable surface and had either absent or conflicting visual feedback, there were large differences between the breast cancer and control group. Peterka and Loughlin (2004) suggest that these types of conditions reflect the ability of vestibular system to preserve postural stability. On conditions 5 and 6 of the SOT test, the breast cancer group also scored lower than a group of patients with type I diabetes and peripheral neuropathy. Recall that diabetic induced peripheral neuropathy has been associated with postural instability. Another hypothesis is that somatosensory system changes induced by Taxane therapy may cause postural instability. While the peripheral neuropathy in the breast cancer patients was described as mild, force plate COP velocities and SOT scores for 3 conditions were similar to patients with severe peripheral neuropathy secondary to diabetes (Wampler, 2007). Balance in breast cancer patients was compromised just as much as it was in patients with diabetes.
Chapter III
Methodology

The purpose of this study was to compare static and dynamic balance between a group of post-treated breast cancer survivors (BCS) and an apparently healthy age-, height- and body weight-matched comparison group (CO). The secondary purpose was to explore the relationship between static and dynamic balance and overall muscular endurance in both the BCS and CO group. Lastly, the relationship between fatigue and static and dynamic balance in the BCS group was explored.

Study Design

This was a cross-sectional study comparing two groups; one group composed of women breast cancer survivors (BCS group) and a control group composed of apparently healthy, age, height and body weight-matched sedentary women (CO group). The main outcome variables of the study included: static and dynamic balance, muscular endurance, and fatigue. All the data for the BCS group were retrieved from the Get REAL and HEEL database for patients that were enrolled in the program between 2006 and 2008. For the control group, the data were collected prospectively.

Subjects

Subjects for this study consisted of 65 females, 40 breast cancer survivors (BCS group) and 25 healthy, sedentary women (CO group) who were age, height and weight matched with the BCS group, ages 25 to 75 years old. Age was matched within five years, weight was matched within five kilograms, and height was matched within five centimeters.
The exclusion criteria for the BCS group included: Acute or chronic bone, joint, or muscular abnormalities that would compromise the patient’s ability to participate in the exercise rehabilitation program, renal function with creatinine <1.5 mg/dl, immune deficiency that would compromise the patient’s ability to participate in the exercise rehabilitation program, Absolute Neutrophil Count < 1.5 per uL or blood, Platelet Count Test <90,000 per uL of blood, blood hematocrit <30%, or metastatic disease. The aforementioned criteria were determined by reviewing the assessment of the Physical Activity Readiness Questionnaire (Par-Q), Medical History Questionnaire, and CBC panel provided by an oncologist.

The Inclusion Criteria for the CO group included: Apparently healthy sedentary women with no history of chronic disease, ages between 25-75 years, not participating in structured regular exercise or diet program for the past year, no orthopedic problems and no known vestibular problems that may cause balance issues, and classified as low risk per ACSM guidelines. The exclusion criterion for the CO group included any known contraindications to exercise. The aforementioned criteria were determined by reviewing the assessment of the Physical Activity Readiness Questionnaire (Par-Q), and Medical History Questionnaire following recommendations of the American College of Sports Medicine.

**Recruitment Process**

The patients in the BCS group had already completed participation in the Get REAL & HEEL Breast Cancer Program, and therefore, archived data from these subjects were used for this study. Data on demographic information (age, body weight, height, % body fat and type of treatment received) and results of the baseline assessments for static and dynamic balance, muscular endurance tests and fatigue were retrieved from the Get REAL & HEEL patient’s files and used for comparisons with the CO group in this study.
For the subjects in the CO group, recruitment to participate in the study occurred via fliers that were posted around the University of North Carolina at Chapel Hill. To increase the ability to match CO subjects to the BCS group, recruitment of CO subjects also occurred through approaching potential subjects and inviting them to visit the GET REAL & HEEL facility to undergo a screening for participation in the study. After the screening and approval for participation was confirmed, subjects in the CO group were asked to sign an informed consent and the HIPAA authorization for use and disclosure of health information for research purposes approved by the UNC Biomedical IRB# 05-2785. These subjects were then scheduled for testing.

Instrumentation

Body weight and height were assessed using a physician’s balance beam scale equipped with height rod Health-o-Meter 402KL (Rye, NY). Static and dynamic balance were measured using a stopwatch model Accusplit Pro Survivor (San Jose, CA) to time each test. Cardiorespiratory endurance was tested on a StarTrac Treadmill Model 4500 Series, Unisen, Inc., (Irvine, CA). Muscular fitness tests were performed using weight machines by Magnum Fitness Retro Series (South Milwaukee, WI) and dumbbells by Power System Sports (Knoxville, TN). A metronome Seiko Model SQ50V, Seiko Sports Life CO., LTD. (Tokyo, Japan) was used to monitor cadence during the muscular fitness test. The Revised Piper Fatigue Scale is a self-administered questionnaire consisting of 22 questions in 4 subscales: behavioral/severity, affective meaning, sensory, and cognitive/mood. It has been shown to be an effective measurement for assessing fatigue in breast cancer patients (Piper, Dibble, Dodd, Weiss, Slaughter, Paul 1998). Scores for the Revised Piper Fatigue Scale range from 0-10 with 0 being no fatigue and 10 being the greatest amount of fatigue possible.
General Procedures

All the balance, muscular fitness and fatigue data for the BCS group were retrieved from the Get REAL and HEEL database; however the control group data were collected prospectively. In order to allow for accurate comparisons between the BCS group and the CO group, the CO group underwent the exact same battery and order of administration of fitness assessment that the BSC underwent. Even though cardiorespiratory endurance, body composition and flexibility tests were part of the battery of tests that the BCS and CO groups underwent, these variables were not relevant to this study and therefore not used in the analysis of the data with the exception of the assessment of fatigue. Fatigue for the BCS group was assessed through the Revised Piper Fatigue Scale, which was given to the BCS subjects at the initial meeting with the GR&H directors. They were then instructed to complete the questionnaire at home, and return it filled out on the day they were scheduled for their initial fitness assessment.

The initial visitation/screening meeting with CO subjects occurred at the Get REAL & HEEL facility. Individuals who qualified were enrolled in the study and received pre-assessment guidelines that they were asked to follow strictly prior to reporting to the facility for testing. These pre-assessment guidelines included: no eating 2 hours prior to testing; void completely prior to testing; maintain proper hydration prior to testing; wear appropriate clothing for physical activity; and no alcohol consumption 48 hours prior to testing (Heyward, 2006).

After verifying that subjects followed the pre-assessment guidelines by their own report, resting vital signs (heart rate, blood pressure, and oxygen saturation) were taken after subjects sat quietly for approximately 5 minutes. After the resting vitals were assessed,
height and height were measured. Body composition was then assessed using skin fold method.

Upon completion of body composition measurements, assessment of static balance and dynamic balance was administered. Static balance was measured using the Single Limb Stance test (Goldie, Bach & Evans 1998; Lipsitz et al, 1991; Weiss, Suzuki, Bean, & Fielding, 2000). This test was assessed barefoot in all subjects. The tester demonstrated the test procedure and then asked the subjects to stand on one leg for 30 seconds with arms folded across the chest and eyes closed. The tester also informed the subjects that they could stand on the limb of preference. The test was terminated and time stopped when the subject lifted the ankle, touched the supporting leg, the supporting leg moved on the floor, the lifted foot touched down, either arm moved from the start position, or the eyes opened. A stopwatch was used to measure to the nearest hundredth of a second the time that the subjects were able to maintain a single limb stance. The tester started the stopwatch when the subjects achieved the appropriate position. The test was started and timed once the subject assumed the proper position of standing on one leg, arms crossed and eyes closed. Three trials were performed, with the mean time being recorded as the test time. If a subject was unable to achieve single limb stance, the time was recorded as 0.00 seconds.

Dynamic balance was assessed immediately after the conclusion of the static balance test. It was assessed using the Timed 360° turn (Gill, Williams, & Tinetti, 1995) and the Four Square Step test (Dite & Temple, 2002). The time required for patients to turn 360° in their preferred direction while standing was recorded using a digital stopwatch that measured the nearest hundredth of a second. Subjects were instructed to complete the turn “as quickly as possible”. Two trials were performed and the best (fastest time = lower time) was recorded.
For the Four Square Step test, subjects were asked to change direction quickly while stepping forward, backward, and sideways over canes, which create 4 squares on the floor. The sequence subjects were asked to step in each square was as follows: 2 – 3 – 4 – 1 – 4 – 3 – 2 – 1 (See appendix A). They were asked to step as fast as possible into each square, with both feet while facing forward. If the subject stepped on a cane, lost balance, or did not touch both feet in any of the squares, the trial was repeated. A digital stopwatch was used to measure to the nearest hundredth of a second the time required to complete the sequence. Two trials were performed and the best (fastest) time was used for analysis.

The Four Square Step test was chosen because it mimics movements that people engage in during their everyday activities like stepping over, back and from side to side. It has been validated as a measurement of dynamic balance predicting dynamic balance just as well as the Timed Up and Go test, the Step Test and the Functional Reach test in other populations (Dite & Temple, 2002). Both the Four Square Step test and the Timed 360° Turn tests were chosen because they are valid measurements of balance, they are very simple to administer, require no expensive equipment, and as mentioned above, they reproduce similar real life movements that require balance.

After static and dynamic balance tests were concluded, subjects were asked to participate in a cardiovascular endurance test using the Modified Bruce Protocol. The Modified Bruce Protocol is a graded-exercise test that can last up to seven stages, each three minutes long (Heyward, 2006). The test ended whenever the subject reached 75% of heart rate reserve using the Karvonen Method [Target HR = ((HRmax-HRrest)(.75)) + HRrest]. Following the cardiovascular endurance assessment, muscular endurance was evaluated using a standardized push-up and partial curl-up test (Heyward, 2006) and a sub-maximal
testing protocol developed at the Rocky Mountain Cancer Rehabilitation Institute (RMCRI, Greeley, CO) (Schneider, Dennehy, & Carter, 2003). The standardized push-up test consisted of the subject in the down position with arms shoulder width apart and knees and lower legs on the floor, while keeping the back flat and the head up. The subjects were then instructed to push up from the down position until arms were fully extended, then lower back down to the original position while keeping the back flat the entire time. Repetitions were counted until the subject could no longer maintain proper form on two consecutive push-ups. The partial curl-up test consisted of the subject lying on a mat with the back flat, and knees bent at 90 degrees. With their arms lying palm down at their sides, subjects were asked to place their middle finger over a piece of tape placed on the mat. A second piece of tape was placed 10 centimeters beyond the first piece. A metronome was then set for 50 beats per minute, and the subjects were instructed to curl up and down to the beat until they could no longer sustain the movement.

For the assessment of muscular endurance developed at the RMCRI and used in the current study, subjects were asked to perform repetitions of arm curls, lat pulldown, leg extension, and leg curl exercises until reaching a Rate of Perceived Exertion (RPE) of 7 on the modified Borg Perceived Exertion Scale (0-11 scale) (Borg, 1982). The lat pulldown, leg extension, and leg curl were all performed on machines. The subjects were appropriately fitted to each machine, with only repetitions that encompass the full range of motion being counted. The arm curl exercise was performed using dumbbells, and was also counted only if a full range of motion repetition was completed. The determination of the weights for each of the exercises was based on a predetermined % of their body weight calculated according to their age and sex established by the RMCRI protocol (Schneider, Dennehy, & Carter, 2003).
An overall muscular endurance score was calculated from the sum of the number of repetitions performed on each of the resistance exercises. Finally, flexibility of the hamstrings and lower back was measured. For the BCS group, fatigue was measured upon entering the program before any type of exercise or recreation intervention.

**Statistical Analysis**

All data were entered into an electronic database for analyses. All data were analyzed using SPSS version 17.0 for Windows, a statistical software program. Statistical significance was set *a priori* at an alpha level of 0.05. Descriptive statistics, including means and standard deviations, were calculated for demographic and physical performance variables.

For the analyses including comparison of static and dynamic balance between groups and relationships between static and dynamic balance and overall muscular endurance (research questions 1 & 2), 25 subjects per group were used. Independent samples t-tests were used for between-group comparisons of static and dynamic balance (research question 1). Simple linear regression was used to address the second research question concerning the relationship between static and dynamic balance scores and overall muscular endurance.

For examination of relationships between fatigue and static and dynamic balance in the BCS group (research question 3), retrospective data on 40 subjects were used. Simple linear regression was used to determine the relationship between scores on the Revised Piper Fatigue Scale and scores on the static and dynamic balance tests.
Subjects

Volunteers for this study consisted of 40 females in the breast cancer survivors group (BCS) and 25 apparently healthy, sedentary females who were age, height and weight matched to the breast cancer survivors that acted as the control group (CO). Subject characteristics for both groups are presented in Table 1.

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Age (Years) Mean ±SD</th>
<th>Height (Centimeters) Mean ±SD</th>
<th>Weight (Kilograms) Mean ±SD</th>
<th>Body Composition (% Body Fat) Mean ± SD</th>
<th>Overall Muscular Endurance (Repetitions) Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCS Group N=25</td>
<td>53.48 ± 9.73</td>
<td>165.50 ± 6.75</td>
<td>71.08 ± 13.08</td>
<td>27.35 ± 4.37</td>
<td>*52.76 ± 20.25</td>
</tr>
<tr>
<td>CO Group N=25</td>
<td>54.08 ± 9.48</td>
<td>162.87 ± 5.44</td>
<td>69.66 ± 13.68</td>
<td>25.94 ± 4.65</td>
<td>*82.28 ± 27.91</td>
</tr>
</tbody>
</table>

*Significant difference between groups (p = .000)

Cancer treatment received in the BCS consisted of 31 patients who underwent chemotherapy, 29 who had radiation and 39 who had surgery. Out of the 31 patients that underwent chemotherapy, 28 were on Taxanes, 15 on Antracyclin, 3 on Cyclophosmide and 10 on Flouracil. Only 4 subjects reported peripheral neuropathies. Our of the 25 BCS subjects that were used to compare to the CO group, all had surgery, 22 had radiation and 23 had chemotherapy. All subjects in the BCS group underwent at least one type of treatment, while many had multiple treatment types.
The first research question addressed between-group differences in balance performance. Hypothesis 1a, which stated that subjects in the BCS and CO groups would differ significantly on measures of static balance using the Single Limb Stance test, was not supported. The descriptive statistics for the independent samples t-test analysis are presented below in Table 2.

### Table 2. Descriptive statistics of BCS and CO groups for Single Limb Stance

<table>
<thead>
<tr>
<th></th>
<th>Mean (Sec)</th>
<th>SD</th>
<th>Std. Error</th>
<th>95% CI upper</th>
<th>95% CI lower</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCS group</td>
<td>4.81</td>
<td>3.28</td>
<td>.66</td>
<td>.89</td>
<td>-2.91</td>
</tr>
<tr>
<td>CO group</td>
<td>5.82</td>
<td>3.39</td>
<td>.68</td>
<td>.89</td>
<td>-2.91</td>
</tr>
</tbody>
</table>

Using independent samples t-test, no significant difference was found between the mean scores of single leg stance between the BCS and CO groups (p = .290). The Cohen’s $d$ score was -.30 indicating a small effect size ($r = -.15$).

Hypothesis 1b, which stated that there would be significant between-group differences in the average time taken to complete the $360^\circ$ Turn test and the FSST, also was not supported. The descriptive statistics for the independent samples t-test analysis for the $360^\circ$ Turn and the FSST are presented in Table 3 and Table 4, respectively.

### Table 3. Descriptive statistics of BCS and CO groups for Timed $360^\circ$ Turn test

<table>
<thead>
<tr>
<th></th>
<th>Mean (Sec)</th>
<th>SD</th>
<th>Std. Error</th>
<th>95% CI upper</th>
<th>95% CI lower</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCS group</td>
<td>1.70</td>
<td>.45</td>
<td>.09</td>
<td>-.12</td>
<td>.30</td>
</tr>
<tr>
<td>CO group</td>
<td>1.61</td>
<td>.27</td>
<td>.05</td>
<td>-.12</td>
<td>.30</td>
</tr>
</tbody>
</table>

### Table 4. Descriptive statistics of BCS and CO groups for the Four Square Step test

<table>
<thead>
<tr>
<th></th>
<th>Mean (Sec)</th>
<th>SD</th>
<th>Std. Error</th>
<th>95% CI of mean upper</th>
<th>95% CI of mean lower</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCS group</td>
<td>5.68</td>
<td>.98</td>
<td>.20</td>
<td>-.160</td>
<td>-.26</td>
</tr>
<tr>
<td>CO group</td>
<td>6.61</td>
<td>1.36</td>
<td>.27</td>
<td>-.160</td>
<td>-.26</td>
</tr>
</tbody>
</table>
No significant difference was found for the mean scores of the Timed 360° Turn test between the BCS and CO groups (p = .396). The Cohen’s d score was .24 indicating a small effect size (p = .12). However, a significant difference was found between the mean scores of the Four Square Step test between the BCS and CO groups (p = .008) indicating that the BCS group had a faster time (better performance) than the CO group subjects. The Cohen’s d score was -.78 indicating a small effect size (p = -.37).

The second research question examined the relationship between overall muscular endurance and balance in the BCS and CO groups. Hypothesis 2a was not supported, as there was no significant relationship between OME and static balance in the BCS group (r (39) = 0.247, p = 0.125); or the CO group (r (24) = 0.126, p = .545).

Hypothesis 2b also was not supported, as overall muscular endurance was not related to dynamic balance scores for either group. No significant relationship was found in the BCS group between overall muscular endurance and the results of the Timed 360° Turn test, (r (39) = 0.090, p = 0.578); or for the results of the Four Square Step test (r (39) = 0.124, p = 0.450). For the CO group, the values for the Timed 360° Turn test and Four Square Step Test were (24) = 0.009, (p = 0.964) and r (24) = 0.261, (p = 0.286), respectively.

Finally, the third research question examined relationships between fatigue and balance scores in the BCS group. Hypothesis 3a, which stated that there would be a significant inverse relationship between fatigue scores assessed using the Revised Piper Fatigue Scale and static balance assessed using the Single Limb Stance test in the BCS group, was not supported. The results for static balance were (39 = 0.017, p = 0.915).

Hypothesis 3b, which stated that there would be a significant inverse relationship between fatigue scores assessed using the Revised Piper Fatigue Scale and dynamic balance
in the BCS group using the Timed 360° Turn test and the Four Square Step tests, was not supported. For the Timed 360° Turn test, \((r (39) = 0.090, p = 0.579)\) or for the Four Square Step test, \((r (39) = 0.031, p = 0.851)\).
Chapter V

Discussion, Conclusion, and Recommendations

Balance impairments in the breast cancer population may be an issue. Anecdotal information by patients expressing concerns about their ability to balance after conclusion of treatment has received little attention. Only one study published to date has examined the potential balance issue in cancer patients (Wampler et al. 2007). It has been suggested by previous research that common cancer treatments like radiation and chemotherapy can negatively impact the nervous and vestibular systems (Silverman et al., 2006), which could in turn have negative implications on the ability of cancer patients to balance. Furthermore, the deleterious effects of anti-cancer treatment on different physiological systems including the musculoskeletal system (decreased muscle mass due to treatment toxicities and reduced physical activity levels during and post treatment), and the development of chemotherapy and radiotherapy induced neuropathies, may be postulated as other mechanisms that could potentially influence the ability of cancer patients to balance. Therefore, with the intent of furthering the scant body of knowledge in the area of balance in cancer patients, the purpose of this study was to compare static and dynamic balance between a group of post-treated breast cancer survivors (BCS) and a group of apparently healthy age and body weight-matched sedentary control group (CO). A secondary purpose explored the relationship between static and dynamic balance and overall muscular endurance in both the BCS and CO groups.
Finally, the relationship between fatigue and static and dynamic balance was explored in the BCS group. No significant differences or relationships were found between groups that suggested the BCS group had a compromised ability to balance when compared to the CO group. Therefore no statements can be made, from the data in this study, that the BCS group had impaired postural control due to their cancer treatments. However, very little data about this subject exist, so more research in the area would be welcomed.

**Static Balance**

No significant difference was observed between the BCS and CO groups for the assessment of static balance measured via the Single Limb Stance test. However, when compared to other data, both groups fall short of the 19.9-second average for the 50-59 age range (similar age of subjects examined in the current study) (Truijen, Van de Heyning, Vereeck, & Wuyts, 2008). The BCS group averaged a time of 4.81 seconds, while the CO group averaged 5.82 seconds per trial. A clear reason for the dramatic difference is not readily present. One possible reason may have been the fact that the subjects in the Truijen study were able to wear shoes while performing the test, which was stated in the study. All subjects in the current study were tested while barefoot. Also, a meta-analysis performed by Bohannon on individuals of 60-99 years of age found an average Single Limb Stance time of 15.7 seconds, which is still much greater than the current study. Research by Springer et al., also suggests that Single Limb Stance is more dependent upon age rather than sex, since men and women scored equally as well in each age group. While the Springer study did not have enough subjects to establish true normative values, their findings were congruent with similar research that had also researched Single Limb Stance data among varying age groups and across sexes.
In the only other study that has examined balance in cancer patients to date, Wampler and colleagues (2007) found that breast cancer patients who underwent Taxane therapy performed significantly worse at static and dynamic balance tasks when compared to healthy controls. The decrements in balance may have been caused by the development of a condition known as chemotherapy-induced peripheral neuropathy (CIPN), which occurs between 50% and 71% of people treated with Taxanes (Wampler, 2006). CIPN describes the injury to the peripheral nervous system by a patient who as received a chemotherapeutic agent known to be neurotoxic. CIPN symptoms include mild to moderate tingling, numbness, and a burning/stabbing pain in the hands and feet. These symptoms can worsen with increased doses. CIPN can also reduce or disable the Achilles tendon reflex. The control group in Wampler and colleagues study consisted of 20 females, ages 30-60, who were age, height and weight matched to the breast cancer group. All control group subjects were also pre-screened for any vestibular, visual, somatosensory, orthopedic and neurologic disease prior to entering the study. It was not stated if the subjects in the Wampler study had been diagnosed with peripheral neuropathies or not. Peripheral neuropathy in patients with type II diabetes has been reported in the literature to correlate with deficits in the ability of these types of patients to balance (Wampler et al., 2007).

The results of the current study do not agree with those from Wampler et al., (2007), who found significant differences between breast cancer patients and healthy controls in regards to static balance. However, measures used to assess were quite different. Differences in results may be attributed to the difference in testing methods used. The Wampler research used extremely sensitive equipment such as a forceplate, to measure center of pressure while subjects had their eyes opened or closed, and head tilted back or looking straight ahead. They
also used sensory organization testing that consisted of six different balance assessments.

The current study used three clinical balance assessments that, when compared to the Wampler study, were much less sensitive.

Another factor to consider when attempting to explain the disagreement between the current and Wampler and colleagues (2007) study may be the sample of patients enrolled in these two studies. In the study by Wampler et al. (2007), all subjects had undergone Taxane therapy; although how long they were post-treatment when the study began was not stated. Taxane is a class of anti-cancer drugs, which has been shown to be associated with the development of peripheral neuropathies. In the current study, the majority of the subjects in the BCS group had also undergone Taxane treatment; however, 30% of the sample did not. Perhaps the fact that not all patients were treated with Taxane may have confounded the results of this study. For future studies, subgroups of breast cancer patients undergoing different types of treatment would allow for comparisons that may help clarify not only the effects of Taxane based chemotherapeutic agents on the development of peripheral neuropathy, but also other treatment regimens that may also be associated with peripheral neuropathies, vestibular system impairment, and loss of muscular fitness.

Another factor that could have confounded the results of the current study and is worth commenting on may be the fact that 25 out of the 40 cancer patients had completed their cancer treatment within two months of data collection, 7 had completed their treatment within 3 to 4 months, and 8 subjects had completed their treatment for cancer 5 to 6 months prior to participating in the study. The further away patients are from completing their cancer treatment, the less likely they will be experiencing the same intensity of some treatment-related symptoms compared to how they felt during treatment. For example, some of the
conditions that may be associated with impaired balance, such as peripheral neuropathy and muscular fitness deconditioning, may not be as severe.

**Dynamic Balance**

Dynamic balance was assessed via the Four Square Step test and the Timed 360° Turn test.

*The Timed 360° Turn test*

No significant difference was found between groups in the Timed 360° Turn test. The mean difference between groups was only .09 seconds, with the BCS group recording the slower time, meaning a less efficient test. Possible reasons for the non-difference between groups for static balance may be attributed to the overall functionality of the subjects in the BCS group in this study and perhaps the sensitivity of the test.

Since all subjects in the BCS group were outpatients who had completed their treatment. They may have gone back to resuming a lifestyle similar to the one they lived prior to treatment. Resuming these activities may prevent them from declining in their overall functional capacity (ability to perform their normal daily tasks), which might be very different from patients who are still hospitalized or are still in treatment. Patients hospitalized or who are in treatment usually experience symptoms such as fatigue and overall body deconditioning that are much more pronounced than outpatients or patients who have already completed their treatment (Battaglini, et al., 2007).

Fatigue is yet another factor that might have influenced the results of the current study, hence the exploration of the associations of fatigue and balance have also been included in the current study. As expected in any cancer population that undergoes chemotherapy and radiation therapy, fatigue is usually a debilitating process that is reported
by the majority of patients; even by patients that have completed their treatment a few years ago. In the current study, subjects in the BCS group averaged a score of 4.21 on the Revised Piper Fatigue Scale. While this does indicate mild fatigue, it does not appear that this mild fatigue in this group of breast cancer patients was severe enough to compromise their ability to balance.

According to normative data for the Timed 360° Turn test, which states that a time greater than four seconds to complete a full revolution puts a person at a greater risk of falling, neither group presented dynamic balance deficits. This perhaps supports the assumption that the side effects from treatment are not as severe as once they could have been (e.g. while these patients were undergoing treatment), and therefore, the task of performing a 360 degree rotation could be performed with no significant complications in controlling balance.

It is very important to interpret the results of this study with caution. The sensitivity of the Timed 360° Turn test may have also confounded the results of the current study. When comparing the results of the current study with the only other experiment that has examined balance in post-treated breast cancer patients to date (Wampler et al. 2007), the results were different. However, due to differences in the methods of assessing dynamic balance between these studies, true comparisons cannot be made at this time. Assumptions can, however, be generated, which are of extreme importance for developing future experiments in this area of research. In Wampler and colleagues (2007) study, the authors used the Fullerton Advanced Balance Scale (FABS) as well as the Timed Up and Go test (TUG) as the measurements for the assessment of dynamic balance. The FABS consisted of standing with feet together and eyes closed, reaching forward to grasp a pencil held at shoulder height, turning 360° in a
right then a left direction, stepping up and over a 15.2cm (6-in) bench, tandem walking, standing on one leg, standing on foam with eyes closed, two-footed jumping for distance, walking with head turns, and responding to an unexpected trunk perturbation. The FABS challenges the visual, somatosensory and vestibular systems, all of which are used for postural control and may be more sensitive to balance impairments in subjects with chemotherapy induced peripheral neuropathy. The TUG test consisted of timing a person’s ability to stand up from a chair, walk three meters, turn around and walk back to the chair and sit down. Wampler and colleagues (2007) found significant differences in both the FABS and TUG scores between the breast cancer and control groups. Wampler attributed the difference between groups to several different factors. One was the effect of peripheral neuropathy due to cancer treatment, even though the severity of the neuropathy was only described as mild. Another possible effect was changes in the visual system. Although visual changes are not associated with Taxane therapy, she found that patients in the breast cancer group had significantly worse contrast vision than the control group. Also, chemotherapy treatments like taxol and cyclophosphamide have been associated with decrements in vision and side effects such as scotoma, photopsia, and blurred vision. It should also be noted that these visual side effects have been found in patients with and without peripheral neuropathies, so it is not clear if the symptoms are a result of damage to the optic nerve, or to the eye structure itself. Due to the fact that the FABS test alone consisted of eleven different procedures to test postural stability, it may be more sensitive to smaller differences in postural control and balance thus explaining the differences between Wampler and colleagues study and the current study.
Four Square Step Test

A very interesting finding of the current study was that the BCS group performed better than the CO on the Four Square Step Test (FSST) with a mean time of 1.07 seconds faster than the CO group. One possible explanation for this is that the BCS group was just as capable at balancing as the CO group, and that their previous cancer treatment did not adversely affect their performance. Even though this was a surprising finding based on the hypothesis that the CO group would perform better than the BCS group on the FSST, clinically the difference between groups is not of relevance. The better time for the BCS group may be attributed to the fact that they were more motivated than participants in the CO group. Overcoming their disease and wanting to prove that they are just as able as their CO group counterparts may have given them more incentive to complete the task faster. A study by Dite & Temple in 2002 examined falling in older adults over the age of 65, and used the FSST as test method. They found that a time to complete the test of greater than 15 seconds resulted in a greater fall risk for these subjects. The scores obtained by both groups were well under this cutoff value. Although the average age of subjects in the current study was under 65, their scores were roughly 10 seconds faster than the 15 second cutoff and were able to complete the test without much difficulty.

To confirm or refute the suppositions that time from completion of treatment to testing of balance and sensitivity of different procedures may have contributed to the discrepancies between the results of Wampler et al. and the current study, future research should examine the effects of anti-cancer treatment on dynamic balance in groups of patients during different times throughout the cancer continuum process (from diagnosis through
completion of treatment, and recovery from treatment) as well as to design studies that can compare different methods for the assessment of balance.

**Relationship between Overall Muscular Endurance and Static Balance**

No significant relationship was found between overall muscular endurance and static balance in either the BCS or CO groups. Previous studies have examined the relationship between postural stability; motor control and muscular endurance and muscular fatigue (Bigland & Woods, 2004; Johnson et al., 1998; Ohira et al., 2005) in other populations but none have examined this relationship in cancer patients.

One possible relationship between muscular endurance and balance could be muscle wasting, or muscle atrophy, during cancer cachexia. Cachexia is associated with disruptions in protein metabolism that causes wasting of proteins in tissue via excessive protein catabolism. Since muscle is composed primarily of protein, this is the site where most of the degradation occurs. Significant wasting affects approximately 50% of cancer patients (Tisdale, 1999). The process of muscle wasting also has an additive effect, because muscle wasting leads to fatigue, while fatigue further contributes to inactivity and can further accelerate muscle wasting as well, creating a damaging cycle. Atrophy of the muscles causes side effects such as fatigue and muscle weakness. Lower extremity muscle weakness has been shown to have a negative effect on balance, more so in older subjects (Al-Majid & McCarthy, 1990). Even though some of the subjects in the current study are not in the same age range as those tested in the aforementioned trials, they may still be experiencing the same condition of muscle weakness and atrophy that older adults also experience. Although not directly supported by any evidence from the current study, muscle atrophy may have an effect on a breast cancer patients’ ability to balance either statically or dynamically. Studies
have also shown that a way to combat postural instability due to muscle weakness and is through physical activity, and that strengthening weak muscles would improve motor control and reduce the risk of falls, especially in the older population (DiBrezzo et al., 2005; Judge et al., 1993; Visovsky, 2006). DiBrezzo et al., (2005) specifically identified that decreased lower limb strength is a primary fall risk factor. Woollacott and Shumway-Cook (1990), found weak ankle dorsiflexors to be one of the primary muscular contributors to falling. All of this information is relevant to the breast cancer population since many women post treatment are deconditioned and likely have experienced treatment-related side effects such as fatigue, decreased muscular strength, osteopenia, increases in fat mass and decreases in lean muscle mass (Courneya et al., 2003; Galvao & Newton, 2005; Shapiro & Recht, 2001; Visovsky, 2006); factors that are associated with poor balance in other populations (Barnett et al., 2005; DiBrezzo et al., 2005; Judge et al., 1993). Subjects in the current study reported experiencing all of these side effects.

The overall muscular endurance score in the CO group was significantly higher than the BCS group in this current study. It should be noted that this score included upper extremity and trunk muscles and not just lower limb muscles that would be used in balance during walking and standing. However, it did not seem that these higher scores translated into an increased ability to balance statically or dynamically for the CO group, since the scores for the static and dynamic balance tests were very similar between groups. When comparing the OME scores between the BCS and CO groups for lower body only, there is no statistical difference between the groups, which may also in part explain the non-difference. It is important to note that several studies examining balance in other populations are often conducted on how well a person can balance after the muscle being tested undergoes some
sort of fatigue, usually in the form or exercise. This is much different than the current study, where the subjects completed all the balance testing prior to undergoing any sort of exercise. Breast cancer patients often complain about balance problems while performing daily tasks and not necessarily when they are fatigued due to physical exertion. Because of the significant difference in OME between groups and the non significant difference between groups on balance, the results of this study suggests that muscular fitness does not appear to be a factor affecting the ability of post-treated breast cancer patients to balance.

**Relationship between Static and Dynamic Balance and Fatigue in the BCS Group**

No significant relationship was found between static or dynamic balance and fatigue assessed using the Revised Piper Fatigue Scale within the BCS group. Battaglini and colleagues (2006) state that fatigue in cancer patients is not the same as in a healthy population. Fatigue in a healthy population is most commonly associated with a tired feeling due to exercise or long days of physical and/or mental work, which generally subside with rest. Fatigue in the breast cancer population is a different phenomenon. Fatigue is believed to be a multifactorial process caused by a variety of permanent and transient side effects of cancer treatment including but not limited to lack of sleep, nausea, psychological stress, cardiovascular and pulmonary dysfunction, muscle weakness, and immune system dysregulation (Battaglini et al., 2006; Dimeo et al., 2004). The relationship between fatigue and all three balance variables was very poor in the current study, suggesting that fatigue had a minimal effect on the ability to balance in the BCS group. The actual amount of fatigue the subjects in the BCS group were experiencing at the time of the study may explain in part the non-correlation analyses. The Revised Piper Fatigue Scale grades fatigue on a scale of 1 to 10, with 10 being the most severe fatigue. The mean fatigue of the subjects in the BCS group
was around 4 points, indicating mild-moderate fatigue. Other studies involving cancer patients and the use of the Revised Piper Fatigue Scale had similar yet slightly higher scores for subjects’ following treatment. In a study by Turner, Hayes, and Reul-Hirche (2004), subjects recorded a mean score of 4.9. Hsieh and colleagues (2008) recorded means of 4.89 and 5.40 in two different groups of breast cancer patients. Even though the scores from the Revised Piper Fatigue Scale in the current study is slightly less when compared with studies that measured fatigue in similar groups of breast cancer patients, fatigue scores of between 4-5 may not be enough to preclude the ability of these patients to perform activities of daily living. Therefore, the results of this study suggest that fatigue may not be a major factor in affecting the ability of these patients to balance. However larger studies with more homogeneous samples of patients regarding type of treatment and patients within specific window of time from completion of treatment are recommended. Also the use of more sensitive measurements for the assessment of balance should be explored.

**Conclusion**

Subjects in the CO group did not significantly outperform the BCS group in any balance measurement, and actually performed worse than the BCS group on the FSST. This may suggest that breast cancer survivors do not have decreased balance abilities compared to sedentary healthy women of a similar age, height and weight. A possible explanation for this may be that some of the subjects who were three to six months post treatment may have recovered from the side effects of their treatment, thus enabling them to perform better than subjects who were closer to completion of their treatment. The current study suggests that neither muscular fitness nor fatigue seem to be associated with balance in this population of post-treated breast cancer patients. The results of the study also suggest good news for breast
cancer patients, since it appears that their balance abilities are just as good as those women who have never had breast cancer. Based on the results of this current study, below are recommendations for future experiments to be designed to continue the exploration of the potential issue of balance in breast cancer patients.

**Recommendations for Future Research**

The following are recommendations for future research concerning cancer treatment and balance in breast cancer patients:

1. A larger sample size.
2. The use of more homogeneous groups of patients (e.g: patients undergoing similar cancer treatment; patients at a similar window of time of treatment completion, patients suffering from similar symptoms, etc.).
3. The use of specific assessment tools to examine potential causes of balance deficit (e.g: the use of Neurocom Pro Balance Master for the assessment of vestibular dysfunction).
4. Studies comparing different types of balance assessment (e.g: sophisticated tests that are more sensitive to small balance alterations vs. less expensive and less sensitive tests that can be administered in clinics and fitness settings).
5. Studies comparing different subgroups of breast cancer patients (e.g: groups with different diagnosis as well as groups of patients undergoing different types of treatments; homogenous groups of patient in-treatment vs. similar patients who have completed their treatment).
6. Collect data on CIPN in breast cancer patients.
APPENDIX A: FOUR SQUARE STEP TEST DIAGRAM
References


