A TAILORED EXERCISE PROGRAM FOR BREAST CANCER SURVIVORS: AN EXAMINATION OF BODY WEIGHT AND HEALTH-RELATED QUALITY OF LIFE

By

ANNA MARIE DAVENPORT

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Approved By:

Shannon L. Mihalko, Ph.D., Advisor _____

Examining Committee:

Peter H. Brubaker, Ph.D. _____

Gary D. Miller, Ph.D. _____

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ABSTRACT

Anna Marie Davenport

A TAILORED EXERCISE PROGRAM FOR BREAST CANCER SURVIVORS:

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Thesis under the direction of Shannon L. Mihalko, Ph.D., Department of Health and Exercise Science.

As breast cancer survival rates improve, more women will have to cope with the long term effects of breast cancer treatment. Weight gain, a common long term side effect of treatment, negatively affects breast cancer outcomes (Chlebowski, Aiello, & McTiernan, 2002; Rock et al., 1999). Very few studies have investigated the effect of physical activity on body weight in breast cancer survivors, and even fewer studies have examined the relationship between body weight and health-related quality of life (HRQL) in this population. The purpose of this study was to examine the longitudinal effect of a physical activity intervention on weight maintenance in breast cancer survivors and to analyze the relationship between body weight and HRQL in this population. One hundred and four women who had been surgically treated for Stage I-III breast cancer were recruited and randomized into either a comprehensive tailored exercise program (CTEP), or a usual care group (UC). The CTEP group underwent a training program including both aerobic exercise and resistance training, and the usual care group received patient education. Body weight, self-reported physical activity (via CHAMPS) and self-reported HRQL (via the FACT-B) were collected at baseline, 6, 9, 15, and 18 months. Neither group gained more than 2.3 kg over 18 months indicating weight maintenance in

both groups. Pearson correlations demonstrated a negative correlation between physical activity and BMI, which was significant at both 9 months and 18 months. Likewise, repeated measures ANCOVA revealed that the participants in the intervention group had a significant decrease in BMI at both 6 and 9 months ($p=0.02$ and $p=0.01$, respectively) and that participants in the control group had a significant increase in BMI at 18 months ($p=0.01$). Repeated measures ANCOVA also revealed that post-baseline BMI was significantly lower in the intervention group when compared to the control group ($p=0.01$). Pearson correlations demonstrated a significant association between BMI and FACT-B over the course of 18 months ($p<0.05$). Weight gain is a deleterious side effect of breast cancer treatments that can lead to adverse outcomes. These results not only suggest that physical activity is related to BMI in breast cancer survivors but also show that BMI is negatively correlated with HRQL in this population. Consequently, weight management should be one of the primary goals in the rehabilitation of breast cancer, and health care providers should consider the role of physical activity as part of the standard treatment regimen for breast cancer survivors.

INTRODUCTION

Accounting for one out of four cancer diagnoses, breast cancer is the most frequently diagnosed cancer among women in the United States (American Cancer Society [ACS], 2007). Although it is the second most fatal cancer in women, the rate of death from breast cancer has been steadily decreasing. The decline in breast cancer mortality is thought to be a result of improvements in both diagnosis and treatment of the disease. A steady increase in the five-year survival rate may also be a direct result of these improvements, and today, approximately 89% of the women diagnosed with breast cancer will live for at least five years following diagnosis (ACS, 2009a; Jemal et al., 2009). Collectively, a decrease in mortality and an increase in the five-year survival rate will result in more women having to cope with the long term effects of breast cancer treatments.

Weight gain is a common side effect experienced by breast cancer survivors (Rock et al., 1999). Several studies have measured body weight in breast cancer survivors from one to four years postdiagnosis (Goodwin et al., 1999; Irwin et al., 2005; Rock et al., 1999), and reported that over 50% of the women in the studies gained weight (81.4%, 68%, and 60%, respectively) with the mean weight gain ranging from 1.6 kg – 3.9 kg. The effect of an unhealthy weight in breast cancer survivors is detrimental. A review of the literature by Chlebowski et al. (2002) found an association between an unhealthy weight, both at the time of diagnosis and postdiagnosis, and increased risk of recurrence and decreased survival.

While adjuvant chemotherapy is thought to be the primary cause of weight gain in breast cancer survivors, decreased physical activity levels may also play a role in weight gain, particularly in breast cancer survivors who undergo adjuvant chemotherapy (Demark-Wahnefried et al., 2001; Irwin et al., 2009; Pinto & Maruyama, 1999). The first step in the prevention of weight gain is weight maintenance, which occurs when there is an energy balance (Jakcic, 2009). Engaging in physical activity aids in achieving energy balance, and increasing physical activity levels may be an effective means of stabilizing body weight in breast cancer survivors. Nonetheless, very few studies have investigated the effect of physical activity on body weight in breast cancer survivors.

Weight gain has also been shown to negatively affect Health-Related Quality of Life (HRQL) in the general population (Fontaine & Barofsky, 2001). Jia & Lubetkin (2005) assessed the relationship between obesity and HRQL in a random sample of the U.S. population. The results, which are in accordance with other studies, revealed an inverse relationship between body weight and HRQL. As BMI increased, HRQL decreased, and those categorized as class II/severe obesity had the greatest decreases in scores when compared to those of normal weight. Although it has been shown that weight gain is a common problem experienced by breast cancer survivors, there is a paucity of research examining the relationship between body weight and HRQL in this population.

Weight gain, an acute and long term effect of breast cancer treatments, has been shown to negatively impact breast cancer outcomes. Decreased physical activity is a modifiable factor that may influence weight gain in breast cancer survivors, yet research examining the effect of physical activity on body weight in breast cancer survivors is

scarce. An unhealthy weight has also been shown to negatively affect HRQL in the general population; however, research examining the relationship between body weight and HRQL in breast cancer survivors is lacking. Therefore, the purpose of this study was to examine the longitudinal effect of a physical activity intervention on weight management in breast cancer survivors and to analyze the relationship between body weight and HRQL in this population.

REVIEW OF LITERATURE

Pathophysiology of Breast Cancer

Cancer is a collection of diseases involving the uncontrolled and unregulated growth of abnormal cells (ACS, 2007). The rampant growth of abnormal cells often leads to the formation of a mass called a tumor, which can be either benign or malignant. Benign tumors are noncancerous, and although they can grow very large and can damage adjoining areas within the body, they do not have the ability to metastasize to other areas of the body. Conversely, malignant tumors are cancerous, which are not only capable of becoming large but are also capable of metastizing throughout the body. Metastasis occurs when cells become separated from the primary tumor and spread throughout the body via the circulatory and lymphatic systems (Newton, Hickey, & Marrs, 2009; Schneider, Dennehy, & Carter, 2004).

Cancer is named after the site where the primary tumor originates; thus, breast cancer arises in the tissue of the breast. Breast tissue includes lobules, which are the milk producing glands, and ducts, which connect the lobules to the nipple, as well as fatty, connective, and lymph tissue (ACS, 2007). Cancer which begins in the lobules or ducts of the breast is known as a carcinoma whereas cancer which begins in the fatty or connective tissue of the breast is known as a sarcoma. Ductal and lobular carcinomas are classified as either in situ or invasive. Ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) are considered early stage cancers in which the cancer cells remain confined to either the ducts or lobules (ACS, 2009c). On the other hand, invasive ductal carcinoma (IDC) or invasive lobular carcinoma (ILC) signifies that the cancer cells

have broken through the walls of the ducts or lobules and have invaded surrounding tissue (Bucholz, 2009). Whereas one out of ten cases of breast cancer is diagnosed as ILC, eight out of ten cases of breast cancer are diagnosed as IDC making it the most common type of breast cancer. There are, however, many less common types of breast cancer such as inflammatory breast cancer, Phyllodes tumors, and Paget's disease of the nipple (ACS, 2009c).

Epidemiology of Breast Cancer

Breast cancer is the most frequently diagnosed cancer among women in the United States. It is estimated that 192,370 women will be diagnosed with invasive breast cancer in 2009. Likewise, invasive breast cancer is expected to account for approximately 27% of all new cancer cases in women. The incidence rate for invasive breast cancer among women has increased steadily over the last two decades; however, between 1999-2005, it decreased by 2.2% per year. This decrease is likely the result of two factors: a reduction in the use of postmenopausal hormone therapy, which has been shown to increase the risk of both heart disease and breast cancer, and a reduction in mammography screening, which may delay the diagnosis of breast cancer. Although the incidence rate for in situ breast cancer has remained steady since 2000, it is estimated that 62,280 women will be diagnosed with in situ breast cancer in 2009 (ACS, 2009a; Jemal et al., 2009).

Age, the most important risk factor for breast cancer with the exception of being female, has a linear relationship with breast cancer incidence (ACS, 2009a; Newton et al., 2009). Therefore, as women grow older, their risk of developing breast cancer increases.

95% of new breast cancer cases during 2000-2004 occurred in women 40 years and older, with the lowest incidence rate occurring in women 20-24 years old and the highest incidence rate occurring in women 75-79 years old. Additionally, the median age at the time of diagnosis during 2000-2004 was 61 years (ACS, 2009a).

Breast cancer is the second most fatal cancer in women. It is estimated that 40,610 women will die from breast cancer in 2009 (ACS, 2009a; Jemal et al., 2009). However, since 1990, the rate of death from breast cancer in women has steadily decreased. This decline in breast cancer deaths was larger for younger women. From 1990-2006, the mortality rate decreased 3.2% per year for women who were less than 50 years old as opposed to 2.0% per year for women 50 years and older. The overall decline in mortality from breast cancer is thought to be the result from improvements in both diagnosis and treatment of the disease (ACS, 2007).

Likewise, improvements in both diagnosis and treatment may have resulted in improvements in the five-year survival rate for breast cancer, which has been steadily increasing (Schwartz, 2008). From a rate of 63% in the early 1960s, the five-year survival rate increased to 75% in the 1970s and to 79% in the 1980s. Today, approximately 89% of the women diagnosed with breast cancer will live for at least five years after diagnosis (ACS, 2009a; Jemal et al., 2009). Nevertheless, there is a correlation between the five-year survival rate of breast cancer and the stage of disease at diagnosis. Women diagnosed with in situ breast cancer have a five-year survival rate of 98%. On the other hand, the five-year survival rate decreases if the cancer has spread. Women diagnosed with invasive breast cancer, which has spread to the lymph nodes, have a five-year survival rate of 84%, and women diagnosed with invasive breast cancer, which has

spread beyond the lymph nodes to other areas of the body, have a five-year survival rate of 27% (ACS, 2007).

Breast Cancer Treatments

Treatment for breast cancer includes local therapies, such as surgery and radiation therapy as well as systemic therapies, such as chemotherapy, hormonal therapy, and targeted/biological therapies. The goal of local therapy is not only to remove cancerous tumors but also to destroy any remaining cancer cells that may be lingering within the surrounding area. On the other hand, the goal of systemic therapy is to destroy cancer cells that may have spread throughout the body. Whereas in situ breast cancer is most often treated with local therapies, invasive breast cancer is typically treated with a combination of both local and systemic therapies (Bucholz, 2009; Newton et al., 2009). For example, surgical removal of a tumor along with assessment of the axillary lymph nodes via either sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND) may be followed by any or all of the above mentioned systemic therapies as well as adjuvant radiation therapy (Bucholz, 2009). Alternatively, systemic therapies may also be given neoadjuvantly in order to shrink large tumors (>2cm) (ACS, 2009b).

The length of treatment varies depending on which treatment is chosen. While radiation therapy may be administered for approximately six to seven weeks (Hulvat, Hansen, & Jeruss, 2009), chemotherapy may be administered for approximately six months, and hormonal therapies, such as antiestrogens and aromatase inhibitors, are usually taken for several years (Schneider et al., 2004). Thus, treatment for breast cancer can entail two months to several years of a patient's life. Likewise, breast cancer

treatments may produce late effects, which may occur months or years following treatment; acute effects, which occur during treatment and dissipate upon completion of treatment; and long term effects, which occur during treatment and remain upon completion of treatment (Courneya, Mackey, & Jones, 2000; Doyle et al., 2006; Mayo Clinic, 2009).

Late Effects of Breast Cancer Treatments

Late effects of breast cancer treatments most commonly arise from their toxicity, which can damage various organs in the body. Since radiation therapy is a localized treatment, it tends to affect organs located in or near the area of the body that is being radiated (Newton et al., 2009). With breast cancer survivors, the goal of radiation therapy is to target the breast while excluding the heart and lungs. Improvements in radiation techniques have helped to minimize the toxicity from radiation to these organs; nevertheless, it is not always possible to exclude these organs from the radiation field when treating breast cancer (Bucholz, 2009). Thus, breast cancer survivors treated with radiation therapy are at risk for pericarditis, pericardial effusion, premature coronary artery disease, pneumonitis, and pulmonary fibrosis. Radiation therapy in the axilla region can also damage nerves resulting in peripheral neuropathy of the limb on the affected side (Burstein & Winer, 2000; Ganz, 2001). The appearance of late effects from radiation therapy is associated with the total dose of radiation, the length of individual treatments and the number of treatments (Schneider et al., 2004).

Unlike radiation therapy, chemotherapy is a systemic treatment, and thus, the possibility of damage to other organs is not confined to a specific location in the body.

Depending upon the type, the dose and the regimen of chemotherapy, different organs may be affected (Newton et al., 2009). Several chemotherapy agents used to treat breast cancer may affect the heart and lungs resulting in cardiomyopathy, congestive heart failure, and pneumonitis. Likewise, other chemotherapy agents used to treat breast cancer may cause renal failure and peripheral neuropathy (Ganz, 2001). Chemotherapy may also induce ovarian failure resulting in the sudden onset of menopause. The rapid reduction of estrogen levels (as opposed to the gradual reduction of estrogen levels which is seen with the natural occurrence of menopause) resulting from ovarian failure places premenopausal breast cancer survivors at high risk for osteoporosis (Burstein & Winer, 2000).

Acute and Long Term Effects of Breast Cancer Treatments

Reduced Physical Fitness

In addition to late effects, there are several acute and long term effects associated with breast cancer treatments. A low level of physical fitness is commonly seen in breast cancer survivors both during and following treatment (Burnham & Wilcox, 2002; Mutrie et al., 2007; Schwartz, 2008). Several randomized controlled trials (RCTs), which examined the effect of exercise on physical fitness in cancer survivors, used maximal or peak oxygen uptake (VO_2max/VO_2peak) to measure physical fitness. VO_2max/VO_2peak is the accepted standard measure of cardiorespiratory fitness, and normative values specific to age and gender have been established (American College of Sports Medicine [ACSM], 2010). Likewise, research suggests that the risk of all cause mortality is

increased when VO_2max falls below the 20th percentile for age and gender (ACSM, 2010).

In a group of breast cancer survivors (mean age 49.2 of years) who were undergoing adjuvant chemotherapy, mean VO_2peak at baseline was 25.2 ml/kg/min, which placed them between the 5th and 10th percentile when compared to normative values for females aged 40-49 (ACSM, 2010; Courneya et al., 2007). Low levels of physical fitness have also been noted in cancer survivors who have completed treatment. In a group of breast cancer survivors (mean age of 59 years), Courneya et al. (2003) observed a mean VO_2peak of 18.2 ml/kg/min at baseline, which placed them below the 1st percentile when compared to normative values for females aged 50-59 (ACSM, 2010). Likewise, in a group of both men and women (mean age of 39 years) who had been diagnosed with either breast cancer, gynecologic cancers, lymphomas, or testicular cancer, Thorsen et al. (2005) observed a mean VO_2max of 29.9 ml/kg/min at baseline. Although a VO_2max of 29.9 ml/kg/min placed the women in the 20th percentile when compared to normative values for females aged 30-39, it placed the men between the 1st and 5th percentile when compared to males aged 30-39 (ACSM, 2010).

Reduced Health-Related Quality of Life

Health-Related Quality of Life (HRQL) is a term that focuses on the impact of a disease or medical condition on one's functional status and well-being. It is defined as "a multidimensional construct, encompassing emotional, physical, psychological, social and subjective feelings of well-being which reflect an individual's subjective evaluation and reaction to health or illness" (Fontaine & Barofsky, 2001, p. 174). It may also include other constructs such as cognitive function, sexual function, symptoms of illness, effects

of treatments, body image, and self-esteem (Rejeski and Mihalko, 2001). Thus, HRQL is considered to be the most appropriate assessment of Quality of Life in medical and health care research as it provides relevant information that is beneficial in the understanding of different responses to the same condition (Fontaine & Barofsky, 2001).

Fatigue. Some effects of breast cancer treatment can lead to a reduction in HRQL (Mutrie et al., 2007; Thorsen et al., 2005). Fatigue is one of the most common side effects of breast cancer treatments, which has been shown to negatively affect HRQL (Hann, Jacobsen, Martin, Azzarello, & Greenberg, 1998; Jacobsen et al., 2007; Schwartz, 2000; Windsor, Potter, McAdam, & McCowan, 2009). Although fatigue encompasses a general feeling of tiredness and overall exhaustion, it is distinct from feeling sleepy or tired in that it is also characterized by a lack of motivation and energy as well as lethargy, weakness and irritability. It is often associated with a reduction in both physical and mental abilities (Hann et al., 1998; Schwartz, 2000), and depending upon the stage of cancer and the type of treatment, it can affect approximately 40% - 100% of breast cancer patients (Schwartz, 2000). In fact, several studies have shown that almost 99% of breast cancer patients will experience fatigue during the course of treatment with more than 60% rating their fatigue level as moderate to severe (Bower et al., 2000).

Some breast cancer survivors have reported fatigue upon completion of treatment. For example, in a sample of 752 adult cancer survivors who participated in the Study of Cancer Survivors-I (SCS-I), Baker, Denniston, Smith and West (2005) investigated the problems adult cancer survivors endure one year after diagnosis. They reported that approximately 2/3 of the sample (67.1%) continued to suffer from fatigue one year post-diagnosis. Conversely, Windsor et al. (2009) assessed fatigue in cancer patients, who

underwent either chemotherapy or radiation therapy, at baseline, upon completion of treatment, and at two follow-up visits (1st follow-up visit was 4-6 weeks following completion of treatment/2nd follow-up visit was 2-4 months following completion of treatment). As expected, fatigue scores, reported via the Brief Fatigue Inventory, increased from baseline to the end of treatment. Although fatigue scores had declined by the first follow-up visit, they were still greater than baseline scores. However, by the second follow-up visit, fatigue scores were similar to baseline scores suggesting that fatigue diminishes soon after the completion of treatment.

Decreased Physical Function. Decreased physical function, another common side effect of breast cancer treatment which can lead to decreased HRQL, is most often an acute effect whereby the largest decrease typically occurs immediately following treatment and improves over the course of time. However, other effects of breast cancer treatment, such as pain and comorbidities may render decreased physical function a long or late term effect (Demark-Wahnefried, Aziz, Rowland & Pinto, 2005). Ganz et al. (2004) measured HRQL via the Medical Outcomes Study (MOS) SF-36 in 558 women at the end of treatment. The end of treatment was defined as one month following surgery (either lumpectomy or mastectomy) in cases where neither radiation therapy nor chemotherapy was prescribed; three weeks following radiation therapy in cases where it was the final component of treatment; and three weeks following chemotherapy in cases where it was the final component of treatment. With all treatments, physical function scores reported by breast cancer survivors were much lower than those reported in the general population. Additionally, among women who had surgery only, statistically

significant lower physical function scores were reported by women who had a mastectomy versus those who had a lumpectomy (70.5 and 78.7 respectively, $P = 0.02$).

Broeckel, Jacobsen, Balducci, Horton, & Lyman (2000) observed lower physical function scores many months after completion of adjuvant chemotherapy. They compared HRQL in a group of breast cancer survivors who had completed adjuvant chemotherapy 3-36 months (mean = 16 months) prior to the study with an age-matched group of women who had no history of breast cancer. In comparison to the noncancer group of women, breast cancer survivors reported statistically significant lower physical function scores (85.85 and 70.33 respectively, $p \leq 0.001$). It can be seen that decreased physical function may persist beyond the completion of treatment leading to further reduction in HRQL.

Weight Gain

Weight gain is another common problem experienced by breast cancer survivors (Rock et al., 1999). The amount of weight gained typically ranges from 2 kg to 6 kg; however, weight gains greater than 10 kg are not uncommon (Demark-Wahnefried, Winer, & Rimer, 1993; Demark-Wahnefried et al., 2001; Irwin et al., 2005). Goodwin et al. (1999) measured body weight following breast cancer diagnosis in a cohort of 535 breast cancer survivors who were diagnosed with invasive breast cancer. Baseline body weight was measured four to eight weeks post-surgery, and one year body weight was measured 13-14 months post-surgery. Over the course of a year, 81.4% of all women gained weight (mean weight gain = 1.6 kg), and the mean weight gain for those who received adjuvant chemotherapy was 2.5 kg.

Irwin et al. (2005) examined change in weight from diagnosis to three years post-diagnosis in a cohort of 514 breast cancer survivors involved in the Health, Eating, Activity and Lifestyle Study (HEAL). Adjuvant treatment for this cohort included surgery only, surgery + radiation, and surgery + chemotherapy (with or without radiation). Body weight was measured at baseline (within the first year following diagnosis) and at two years after the baseline visit (within the third year following diagnosis). 68% of the women gained weight with a mean weight gain of 3.9 kg and a range of 0.1 kg – 27.0 kg. Among the women who gained weight, 31% gained less than 2.5kg; 19% gained between 2.5 – 4.9kg; and 18% gained 5kg or more. These results denoted a larger weight gain than has been observed in studies of healthy women.

Similar results were found in two studies involving breast cancer survivors who participated in the Women's Healthy Eating and Living Study (WHEL). Participants in the WHEL study had undergone either lumpectomy or mastectomy and completed adjuvant therapies prior to entering the study. Rock et al. (1999) followed change in weight from one year prior to breast cancer diagnosis to four years following diagnosis in a group of 1,116 WHEL participants. Following the diagnosis of breast cancer, 60% of the women gained weight with a mean weight gain of 2.7 kg. Data from this study suggested that both behavioral and physiologic factors may continue to influence energy balance for up to four years following breast cancer treatment. Likewise, Saquib et al. (2007) followed a sample of WHEL participants (n = 3,045) for six years in order to determine the proportion of women who gained weight while undergoing chemotherapy and returned to pre-cancer weight following completion of chemotherapy. Weight was measured at baseline and every year thereafter, and pre-cancer weight (one year prior to

diagnosis) was self-reported. Only 10% of the subjects returned to pre-cancer weight at any time during the six years, and the highest proportion of subjects (< 5%) that returned to pre-cancer weight was seen at the four year follow-up visit. It can be seen that weight gain may not only occur during and immediately following treatment but may persist for several years upon completion of treatment. However, it is important to note that none of the aforementioned studies included a healthy, comparison group. Thus, it cannot be determined if the amount of weight gain experienced by breast cancer survivors is greater than the amount of weight gain which gradually occurs with age in healthy women.

The acute and long term effects of breast cancer treatments can be detrimental. Fatigue and reduced physical function may negatively impact HRQL and may contribute to reduced physical fitness. Both poor physical fitness and weight gain have been shown to increase the risk for all cause mortality. Additionally, weight gain is a major risk factor for the development of several chronic diseases and has been shown to negatively affect breast cancer outcomes.

Impact of Weight Gain in the General Population

A classification of overweight or obese signifies an unhealthy weight for a given height. The most common method used to define overweight and obese is Body Mass Index (BMI), which divides body weight in kilograms by height in meters² and which is correlated with percent body fat. A BMI range of 25.0 kg/m² to 29.9 kg/m² classifies one as overweight, and a BMI ≥ 30 kg/m² classifies one as obese (Centers for Disease Control and Prevention [CDC], 2009a; Okay, Jackson, Marcinkiewicz, & Papino, 2009).

Overweight/obesity has been steadily rising for the past 25 years, and as of 2005-2006, more than 72 million adults in the U. S. were obese (Ogden, Carroll, McDowell, & Flegal, 2007). This trend is alarming considering the fact that overweight/obesity is a major risk factor for several chronic diseases. For example, the adverse effects of overweight/obesity on cardiovascular health include coronary heart disease, heart failure, systolic and diastolic dysfunction and endothelial dysfunction. Likewise, overweight/obesity can also affect blood pressure and cholesterol levels resulting in hypertension and dyslipidemia, which are risk factors for cardiovascular disease (CVD) (Lavie, Milani, & Ventura, 2009). Other adverse effects of overweight/obesity include type 2 diabetes and metabolic syndrome, characterized by a cluster of CVD risk factors including hypertension and dyslipidemia (Koopman, Swofford, Beard, & Meadows, 2009) as well as stroke, liver disease, gallbladder disease, osteoarthritis, and some cancers (endometrial, colorectal, breast) (CDC, 2009b). An analysis of 57 prospective studies involving nearly 900,000 participants reported that all-cause mortality was the lowest in individuals with a BMI ranging from 22.5 kg/m² to 25 kg/m², yet for every increase in BMI of 5 kg/m² above this range, there was a correlation of approximately 30% higher all-cause mortality (Whitlock et al., 2009).

Impact of Weight Gain in Breast Cancer Survivors

An unhealthy weight prior to the diagnosis of breast cancer has been shown to increase the risk of the development of breast cancer in postmenopausal women. A high level of free circulating estrogen, which is thought to be one of the mechanisms in the pathogenesis of breast cancer, is associated with obesity in postmenopausal women. In

postmenopausal women of normal weight, androstenedione, an androgen produced by the adrenal glands, is converted to estrogen via two enzymes (aromatase and 17 β hydroxysteroid dehydrogenase). The estrogen then binds to sex hormone-binding globulin (SHBG), which not only regulates its access to estrogen sensitive tissues, such as breast tissue, but also reduces the level of free circulating estrogens. However, several factors lead to increased levels of free circulating estrogen in obese postmenopausal women. First, increased body fat results in higher levels of aromatase and 17 β hydroxysteroid dehydrogenase; second, the synthesis of estrogen occurs primarily in adipose tissue; and third, the production of SHBG is inhibited (Chlebowski et al., 2002; Clemons & Goss, 2001; Demark-Wahnefried et al., 1993). Cauley et al. (1999) measured serum estrogen levels in a group of 97 women with breast cancer and a randomly chosen group of 247 women who did not have breast cancer. All women were participants in the Study of Osteoporotic Fractures; were at least 65 years old; and had provided serum samples at baseline. When compared to women who had the lowest levels of bioavailable estradiol, women with the highest levels of bioavailable estradiol were 3.6 times more likely to develop breast cancer (95% CI, 1.3-10.0).

An unhealthy weight, at the time of diagnosis, can have a negative impact on the outcomes of breast cancer. In a review of the literature, Chlebowski et al. (2002) examined the effect of weight at the time of diagnosis. 34 studies investigated the association between obesity and risk of recurrence or survival. 26 of the 34 studies, including 26,460 women, concurred that there is a statistically significant association between obesity and recurrence or survival, whereas eight studies, including 3,727 women, found no such association. Likewise, in a review of 51 studies which examined

the association between obesity and the prognosis of early stage breast cancer, a majority of the studies found that obesity had a negative effect on breast cancer prognosis. 20 of the 51 studies reported on the effect of obesity on breast cancer recurrence with over half noting that obesity increased the risk for recurrence (McTiernan, 2006).

Weight gain following diagnosis has also been found to have an adverse effect on breast cancer outcomes. Three out of four studies reviewed by Chlebowski et al. (2002) found an association between postdiagnosis weight gain and risk of recurrence or decreased survival. McTiernan (2006) reviewed seven studies that examined the effect of postdiagnosis weight gain on risk of recurrence or survival. Only three of the seven studies reported that weight gain negatively affected these outcomes. However, the average amount of weight gained in all of the studies ranged from 1.2 kg to 10 kg over the course of a year, and the three studies that identified a positive association between weight gain and adverse outcomes had the highest average weight gain ranging from 5.9 kg to more than 10 kg over the course of a year. This suggests that adverse effects on outcomes only occur when a substantial amount of weight is gained postdiagnosis.

Using the amount of weight gained at 60 weeks, Camoriano et al. (1990) analyzed the relationship between weight gain and risk of recurrence and survival. This point in time was chosen because it not only corresponded to the completion of treatment for all of the patients but also was the point in time when median weight gain was maximal for all three groups. After a median follow-up of 6.6 years, the results showed that premenopausal women who gained more than the median weight (5.9 kg) at 60 weeks had 1.5 times greater risk of recurrence when compared to women who gained less than the median weight at 60 weeks ($P = 0.02$ univariate analysis). However, the significance

of this risk was diminished when factors such as lymph node status, estrogen receptor status, tumor size and age were taken into account (P = 0.17 multivariate analysis). Likewise, there was a 1.6 times greater risk of death for premenopausal women who gained more than the median weight at 60 weeks when compared to women who gained less (P = 0.01 univariate analysis; P = 0.04 multivariate analysis). Although a similar trend for both risk of recurrence and risk of death was seen in postmenopausal women who gained more than the median weight (3.6 kg), neither univariate nor multivariate analyses resulted in statistical significance. Additionally, an analysis of 5,204 Nurses' Health Study (NHS) participants, who had been diagnosed with invasive breast cancer, found that an unhealthy body weight pre-diagnosis was associated with an increased risk of death from breast cancer, all-cause mortality and breast cancer recurrence in premenopausal women and non-smokers. Likewise, weight gain after diagnosis was associated with risk of recurrence as well as increased risk from breast cancer death and all-cause mortality in non-smokers (Kroenke, Chen, Rosner, & Holmes, 2005).

Factors Influencing Weight Gain

Although weight loss is associated with other types of cancer, research has shown that weight gain is a problem among breast cancer survivors (Demark-Wahnefried et al., 1993; Demark-Wahnefried et al., 2001; Irwin et al., 2005), and it is thought that adjuvant chemotherapy may be the primary cause. Despite the acute effects of chemotherapy such as nausea, vomiting, and mucositis, many breast cancer survivors who receive adjuvant chemotherapy have been shown to gain weight (Demark-Wahnefried et al., 2001; Holmes,

Chen, Feskanich, Kroenke, & Colditz, 2005). Weight gain in breast cancer survivors who undergo adjuvant chemotherapy treatment may be related to the type of chemotherapy and the length of treatment. It has also been suggested that treatment involving multiple chemotherapy agents leads to higher weight gains than single agents alone. Another factor which may influence weight gain while undergoing adjuvant chemotherapy is menopausal status. Several studies have shown that women who are premenopausal at the time of diagnosis are more likely to gain weight than those who are postmenopausal at the time of diagnosis (Demark-Wahnefried et al., 1993). Camoriano et al. (1990) examined weight gain in a group of 545 premenopausal and postmenopausal women who received adjuvant chemotherapy following a mastectomy with positive lymph nodes and who were part of two separate prospective studies. The study involving postmenopausal women included two groups – a group who received adjuvant chemotherapy and a control group who had a mastectomy but did not receive adjuvant chemotherapy. At 60 weeks (the end of treatment), all three groups gained weight; however, the premenopausal group gained significantly more weight than either the postmenopausal group receiving adjuvant chemotherapy or the control group (5.9 kg, 3.6 kg and 1.8 kg respectively [$P < .0001$]).

There are several other factors which may affect weight gain during adjuvant chemotherapy. For example, both reduced metabolic rates (Chlebowski et al., 2002) and hyperphagia, as either a means of coping with a cancer diagnosis or due to an increased appetite (breast cancer patients receiving adjuvant chemotherapy have reported cravings similar to those experienced during pregnancy), have been examined as possible contributors to weight gain (Demark-Wahnefried et al., 1993;, Kroenke et al., 2005;

Levine, Raczynski, & Carpenter, 1991). Likewise, decreased energy expenditure resulting from decreased physical activity levels may contribute to weight gain particularly since many breast cancer survivors suffer from fatigue and reduced physical function during the course of treatment (Demark-Wahnefried et al., 1993; Pinto & Maruyama, 1999).

Effect of Physical Activity on Body Weight in the General Population

Decreased physical activity is a modifiable risk factor for weight gain. Many of the United States' public health agencies and medical associations including the National Heart, Lung and Blood Institute (NHLBI), the CDC, the ACSM, and the American Heart Association (AHA) agree that physical activity is an important component of weight management (Donnelly et al., 2009). Overweight and obesity are the result of an energy imbalance in which a positive energy balance induces weight gain. Conversely, a negative energy balance, which occurs when energy expenditure is greater than energy intake, induces weight loss. Engaging in physical activity contributes to a negative energy balance by increasing energy expenditure (Jakicic & Otto, 2006). Although exercise can lead to a reduction in body weight, a majority of the research shows that the effect of exercise alone on weight loss is typically less than 3% of baseline weight (Donnelly et al, 2009). Nonetheless, weight maintenance, the first step in the prevention of weight gain, is another important element of weight management, and engaging in physical activity can also contribute to energy balance, which is necessary for weight maintenance (Jakicic, 2009). Unlike overweight/obesity, there is not a standardized definition for weight maintenance. Stevens, Truesdale, McClain, & Cai, (2006), defined

weight maintenance as "a weight change of less than ± 3% of a designated body weight" (p. 397). It has also been defined as "a change of ≤ 5 lb (2.3 kg)" (Donnelly et al, 2009, p. 461). Despite the fact that physical activity alone does not result in significant reduction in body weight, it plays an important role in weight maintenance thereby aiding in the prevention of weight gain.

In an eight to nine month intervention, Slentz et al. (2004) investigated the effects of exercise amount and intensity on body weight in a group of 120 sedentary, overweight men and women (aged 40-65 years). Participants were randomized into one of three exercise groups or into a non-exercising control group. Exercise interventions for the three exercise groups included: 1) low amount/moderate intensity (LA/mod) - caloric equivalent of approximately 12 miles/week of walking at 40%-55% of VO_2peak, 2) low amount/vigorous intensity (LA/vig) - caloric equivalent of approximately 12 miles/week of jogging at 65%-85% of VO_2peak, and 3) high amount/vigorous intensity exercise (HA/vig) - equivalent to approximately 20 miles/week of jogging at 65%-85% of VO_2peak. Each group gradually increased the amount and intensity of exercise during the first two to three months until the appropriate exercise level was attained and continued exercising at that level for the next six months. Modes of exercise included cycle ergometers and elliptical trainers as well as walking and jogging. All participants were counseled to maintain their current dietary habits throughout the intervention. Although the results showed that exercise intensity did not affect body weight, there was a clear dose-response relationship between the amount of exercise and change in body weight resulting in weight maintenance for both of the LA exercise groups and

significant weight loss for the HA exercise group (LA/mod [-1.3 kg], LA/vig [-1.1 kg], and HA/vig [-3.5 kg]).

Effect of Physical Activity on Body Weight in Breast Cancer Survivors

Decreased energy expenditure resulting from decreased physical activity levels may contribute to weight gain following a diagnosis of breast cancer, particularly in breast cancer survivors who undergo adjuvant chemotherapy (Demark-Wahnefried et al., 2001; Irwin et al., 2009; Rock et al., 1999). However, as previously stated, decreased physical activity is a modifiable risk factor for weight gain, and increasing physical activity levels may be an effectual component of weight maintenance in this population. Nevertheless, few studies have examined the effect of physical activity on body weight in breast cancer survivors (Irwin, 2006; Irwin et al., 2009).

Body weight was a secondary outcome in several RCTs (Burnham & Wilcox, 2002; Courneya et al., 2003; Courneya et al., 2007; Demark-Wahnefried et al., 2008; Matthews et al., 2007; Segal et al., 2001). Most of the studies (Burnham & Wilcox, 2002; Courneya et al., 2003; Demark-Wahnefried et al., 2008; Matthews et al., 2007) employed small sample sizes (n = 18, n = 36, n = 53, n = 90), and all of the studies utilized interventions of short durations (10 weeks – six months) and low volumes of exercise (≤ 150 minutes/week). One study failed to report the volume of exercise that was to be achieved during the intervention (Segal et al., 2001). In all of these studies, both the intervention groups and the control groups maintained body weight. The mean change in body weight for the intervention groups ranged from -1.4 kg to +2.3 kg, and the mean change in body weight for the control groups ranged from -0.2 kg to +1.7 kg.

However, these studies had several limitations including small sample sizes, short duration, low volumes of exercise, poor adherence and lack of follow-up testing.

More recently, Irwin et al. (2009) investigated the effect of a six month exercise intervention on body weight as a primary outcome in a group of 75 sedentary, postmenopausal breast cancer survivors who had completed adjuvant therapy. The exercise intervention employed a combination of both supervised and home-based aerobic exercise with participants exercising three days/week at a local health club and two days/week at home for 30 minutes/session. According to weekly physical activity logs, participants in the exercise group engaged in an average of 120 minutes of physical activity per week over the course of six months. Both the intervention group and the control group maintained weight at 6 months. However, there was a trend of decreasing weight in the intervention group (mean weight change of -0.55 kg) and a trend of increasing weight in the control group (mean weight change of +0.1 kg).

The effect of a 12 month exercise intervention on body weight was also reported as a secondary outcome in a subsample of the participants (n=50). Results showed that both groups maintained body weight at 12 months. Likewise, there was a trend of decreasing weight in the intervention group (mean weight change of -0.39 kg), and a trend of increasing weight in the control group (mean weight change of +0.65 kg). Nevertheless, this study exhibited several of the same limitations as the previous studies, and the volume of exercise during months 6-12 was not reported.

Relationship between Body Weight and HRQL in the General Population

The effects of weight gain are not limited to increased risk for disease and increased risk of mortality as weight gain has also been shown to negatively affect HRQL (Fontaine & Barofsky, 2001; Jia & Lubetkin, 2005). However, very few studies have looked at the relationship between overweight/obesity and HRQL in either the U.S. general population or in obese people who are free from chronic conditions commonly associated with obesity (Jia & Lubetkin, 2005). Using the physical and mental component summary scales (PCS-12 and MCS-12, respectively) of the Short-Form 12 (SF-12) to measure HRQL, Jia & Luetkin (2005) assessed the relationship between obesity and HRQL in a random sample (n = 13,646) of the U.S. population from the 2000 Medical Expenditure Panel Survey (MEPS). The MEPS included information on six self-reported chronic conditions allowing this analysis to focus on those who did not report any of the six chronic conditions. The results revealed an inverse relationship between body weight and HRQL. In other words, as BMI increased, HRQL decreased. Those categorized as class II/severe obesity (BMI $\geq$ 35 kg/m^2) had the greatest decreases in scores for both subscales when compared to those of normal weight (BMI of 18.5-24.9 kg/m^2) (average PCS-12 score decrease was 4.00, $P < 0.0001$; average MCS-12 score decrease was 1.07, $P = 0.0303$). A significant reduction of PCS-12 scores was also seen for those categorized as class I/moderate obesity (BMI of 30-34.9 kg/m^2) (average score decrease was 1.86, $P < 0.0001$) as well as those categorized as overweight (BMI of 25-29.9 kg/m^2) (average score decrease was 0.73, $P = 0.001$) when compared to those of normal weight. However, there was no significant reduction in MCS-12 scores for either the class I/moderate obesity or the overweight categories.

These results are in accordance with other studies. A review of the literature by Fontaine and Barofsky (2001) found that obese people tend to have significant decreases in HRQL measurement scores; that there appears to be an inverse relationship between body weight and HRQL; and that the physical component of HRQL tends to be affected by body weight more so than the mental component of HRQL. Hassan, Joshi, Madhavan and Amonkar (2003) analyzed data from the CDC's 2000 Behavioral Risk Factor Surveillance Survey (BRFSS), which includes a HRQL component comprised of physical health, mental health and activity limitations (n = 183,372). As BMI increased, scores decreased in all three of these areas. However, statistical significance was seen in the obese and severely obese groups but not in the overweight group. Also, when compared to the normal weight group, the severely obese had higher odds ratios for physical health and activity limitations (1.87 [CI 1.64-2.12]; 1.73 [CI 1.50-1.99], respectively) than for mental health (1.41 [CI 1.26-1.59]. Conversely, when compared to the normal weight group, odds ratios for the obese group were similar for both physical and mental health.

Relationship between Body Weight and HRQL in Breast Cancer Survivors

Although obesity has been shown to negatively affect HRQL in the general population and weight gain has been found to be a common problem following a diagnosis of breast cancer, research examining the relationship between body weight and HRQL in breast cancer survivors is scarce. Bardwell et al. (2004) utilized the RAND 36-Item Health Survey Physical and Mental Health scales to measure HRQL, and examined factors associated with HRQL in a group of women (n = 2582) who had been treated for early stage breast cancer. Although lower BMI was significantly correlated with better

physical HRQL ($p \leq 0.001$), it was not significantly correlated with better mental HRQL. A significant association between lower BMI and better physical HRQL was also found in a multivariate analysis ($p \leq 0.001$), whereas no association between BMI and mental HQRL was found. These results are supported by Mosher et al. (2009), who analyzed the relationship between body weight and HRQL in a group of older breast, prostate, and colorectal cancer survivors (age ≥ 65 years). Results from this study found that poorer physical HRQL was significantly associated with a greater BMI ($p < 0.0001$), and the association remained significant after adjusting for age, race, level of education, type of cancer, and comorbidities ($p < 0.001$). However, there was no significant association between mental HRQL and BMI either before or after adjustments.

Limitations in the Research

It has been established in the literature that an unhealthy weight not only increases the risk of developing breast cancer (Chlebowski et al., 2002; Clemons & Goss, 2001; Demark-Wahnefried et al., 1993) but also increases the risk of recurrence and decreases survival in breast cancer survivors (Camoriano et al., 1990; Chlebowski et al., 2002; McTiernan, 2006). Additionally, many of the nation's public health agencies and medical associations agree that physical activity is an important component in weight management (Donnelly et al., 2009). Nonetheless, very few RCTs have measured the effect of physical activity on body weight in breast cancer survivors, and those that have investigated this relationship employed small sample sizes and utilized short interventions (10 weeks – six months) with low volumes of exercise (typically ≤ 150 minutes/week). Likewise, due to a lack of follow-up testing, these studies do not provide

enough data to determine the long term effect of physical activity on body weight in this population. Finally, it has been suggested that interventions including both a physical activity component and a diet component may afford better results than physical activity interventions alone (Matthews et al., 2007). However, the feasibility and safety of diet interventions in this population has not been studied, and only one RCT to date has examined the effect of both physical activity and diet education on body weight in breast cancer survivors (Demark-Wahnefried et al., 2008). Thus, future research should include larger clinical studies utilizing longer physical activity interventions that incorporate higher volumes of exercise as well as follow-up testing. Dietary interventions should also be studied in order to determine the safety and feasibility of such interventions in this population.

Future research should also focus on the relationship between an unhealthy body weight and HRQL in breast cancer survivors. Even though an unhealthy body weight has been shown to negatively affect HRQL in the general population (Fontaine & Barofsky, 2001; Jia & Lubetkin, 2005), there is a paucity of research assessing this relationship in breast cancer survivors. Additionally, studies that have examined this relationship in breast cancer survivors are limited due to cross-sectional design.

Objectives

An unhealthy weight is a common problem among breast cancer survivors that has been shown to negatively impact breast cancer outcomes. Although physical activity is an important component of weight management, current research examining the effect of physical activity on body weight among breast cancer survivors is scarce. Likewise, an

unhealthy weight has been shown to negatively affect HRQL in the general population, yet even less research has examined the relationship between body weight and HRQL in breast cancer survivors. Thus, the objectives of this study were 1) to examine the longitudinal effect of the comprehensive tailored exercise program (CTEP) group versus the usual care (UC) group on weight maintenance and 2) to analyze the relationship between body weight and HRQL in breast cancer survivors to determine if a greater BMI is correlated with poorer HRQL at both baseline and over the 18 month course of the RESTORE study.

Hypotheses

Hypothesis 1: Participants randomized to the comprehensive tailored exercise program will maintain body weight over time as compared to the usual care group.

Hypothesis 2: BMI will be negatively correlated with HRQL at both baseline and over the course of 18 months.

METHODS

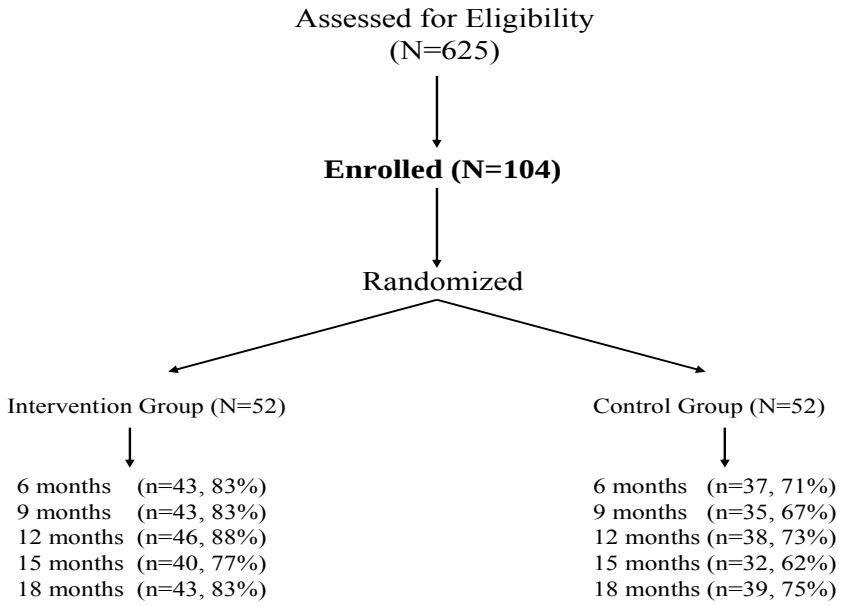
Study Design and Participants

Research on Optimal Recovery Practices in Breast Cancer (RESTORE) was a randomized, controlled, single-blind trial involving women who had recently been diagnosed with and surgically treated for Stage I-III breast cancer were recruited from Wake Forest Baptist Medical Center and Forsyth Medical Center. Eligibility criteria included: 1) no previous history of breast cancer, 2) ≥ 18 years old, 3) lived within 30 miles of the study site, and 4) able to participate in a moderate exercise program. Ineligibility criteria included: 1) uncontrolled or unstable angina, 2) a history of myocardial infarction, 3) cardiac conduction disturbances, 4) diagnosed or suspected dementia, 5) peripheral arterial disease, 6) any chronic disease which significantly reduces four year survival, 7) physical immobility or dependent on a wheelchair for mobility, and 8) reoccurrence of breast cancer. A total of 625 women were assessed for eligibility. Of these, 409 women were excluded because they did not meet inclusion criteria, and 112 women refused to be contacted by study staff.

Eligible women were made aware of the study during their post-operative visit by their surgeon or during their medical oncology visit by their oncologist. They received an informational brochure about the study, and if they were interested in participating, they were introduced to a member of the study staff. The staff member provided a detailed explanation of the study, answered questions, and scheduled a baseline visit. Eligibility was verified and informed consent was obtained during the first baseline visit. Once participants were enrolled in the study and had completed baseline testing, they

were randomized into either a comprehensive tailored exercise program (CTEP) or a usual care group (UC) via a web-based randomization process. Randomization status of the participants was known only to the interventionist. See Figure 1 for participant randomization.

Figure 1. Participant Randomization



Procedures

Staff members contacted participants via telephone to schedule testing visits. Forty-eight hours prior to each visit, participants received a reminder call to remind them of the visit and answer questions. Participants were scheduled for a baseline visit (BV) one to twelve weeks post-surgery. The BV included a demographic questionnaire, a self-report physical activity history, arm measurement, grip strength, shoulder range of motion (ROM), body composition, and fitness testing. Additionally, physical function,

nutrition and psychosocial status were assessed at the BV1. Follow-up testing visits occurred at 6, 9, 15, and 18 months post-surgery and included fitness testing, nutrition assessment, and several psychosocial measures. All testing visits were conducted at the Wake Forest University Reynolda campus.

CTEP Group

Exercise Component. Participants randomized to the CTEP group participated in a tailored exercise program, which was customized to meet their baseline aerobic and strength capacity and which began approximately three months post-surgery. Due to its safety for a broad range of function levels, aerobic exercise emphasized walking. Total exercise time for each session was approximately 60 minutes. Each session included a five minute aerobic warm-up, 30 minutes of moderate to somewhat hard (14-16 on the RPE scale) walking, 20 minutes of strength training using both hand weights and Nautilus resistance machines, and 10 minutes of stretching.

Participants were instructed to begin exercising at a low level and to progress slowly. Those who were unable to walk for 30 minutes consecutively began by following the discontinuous walking progression used in the Wake Forest Cardiac Rehabilitation Program until 30 minutes of continuous walking was achieved. Participants recorded total walking time, RPE, and number of laps walked on exercise logs, and they were instructed to maintain exercise logs for both center-based and home-based exercise.

Like walking, strength training was also begun at a low level and progressed slowly. Upon completion of strength testing, an initial weight (50% of established one repetition max) was assigned to each participant. When necessary, strength training

exercises were completed with none or little weight for the first two weeks. The initial weight was used until the participant was able to lift that weight, using the correct form, for 12 repetitions. When these criteria had been met, weight was increased by one to two pounds for upper body exercises and by three to five pounds for lower body exercises. Once participants were able to complete 12 repetitions of a specific weight for two consecutive exercise sessions, they were instructed to progress to the next appropriate weight. Strength training consisted of one set of 8-12 repetitions for the following exercises: leg press, leg extension, leg curl, overhead press, incline press, compound row, seated abdominal crunch, lower back extension, dumbell bicep curls, and dumbbell tricep extensions. Participants were instructed on proper breathing technique for strength training (exhalation during concentric contractions and inhalation during eccentric contractions) at the start of the program, and strength training logs were used to record the amount of weight lifted as well as the number of repetitions.

For the first three months of the intervention, participants attended two exercise sessions per week at the Wake Forest University Clinical Research Center (CRC). During months four through six, supervised exercise was transitioned to home-based exercise, and exercise sessions tapered to once per week at the CRC. Participants were educated on the current recommended physical activity guidelines (30 minutes of moderate intensity physical activity on most days of the week), and throughout the intervention they were encouraged to either exercise at home or at a community center in order to meet these guidelines. During months seven through twelve, participants were not required to attend supervised exercise sessions; however, if they chose to do so, they could continue exercising twice a week at the CRC. Likewise, the exercise specialist

contacted participants via telephone on a monthly basis during this time to discuss adherence/barrier issues, answer exercise and/or nutrition questions and to modify exercise prescriptions as needed.

Exercise sessions were led by an individual certified by the ACSM as an Exercise Specialist and certified by the AHA for Advanced Cardiac Life Support. The exercise leader and staff members were also certified in CPR, and at least two staff members were present at each exercise session. Staff members walked with participants during the exercise sessions to determine whether exercise prescriptions were appropriate, to gauge how participants were feeling, to answer questions, and to make home based exercise recommendations. Throughout the program participants were directed to report any problems or symptoms incurred during exercise and to rest as needed.

Lymphedema Prevention Component. Intervention participants also participated in a lymphedema prevention program consisting of two parts, an educational session and an individual assessment conducted by a physical therapist. During the educational session, participants were provided with basic knowledge regarding the physiology, signs, and symptoms of lymphedema; what to do if signs and symptoms appear; and how to prevent lymphedema. Each participant was then assessed by the physical therapist for range of motion (ROM) and strength/weight resistance of the affected arm. They were then provided with an individualized regimen to promote lymph flow and increase flexibility and were given compressions sleeves to wear during exercise, heavy arm use, and air travel as a preventive measure.

Individual Information Sessions. In addition to exercise and lymphedema components, participants in the CTEP group were required to attend five 60 minute

individual information sessions during the first three months of the intervention. The sessions, led by a registered dietician and an exercise specialist, focused on making healthy nutrition and physical activity lifestyle changes. Topics for individual sessions included: 1) Goal Setting, 2) The FITT Principle, 3) Introduction to the Food Guide Pyramid, 4) Barriers, Obstacles and Setbacks, and 5) Self-Confidence.

Usual Care Group

Participants randomized to the UC group received quarterly newsletters that included general information about nutrition and physical activity. Additionally, they received information regarding lymphedema risk and prevention. At the end of the study, they met with the interventionist, who provided them feedback on their physical fitness level as well as recommendations on how to improve their fitness and strength.

Measures

Although RESTORE utilized many physical and psychosocial measures, only measures analyzed for this thesis will be described. The measures for this thesis include a demographic questionnaire, a self-report physical activity history, body weight, height, body mass index (BMI), and HRQL. Demographic information was obtained at baseline only.

Body Weight

Body weight was measured using a beam scale with moveable weights. Participants were weighed in light clothing, without shoes, with pockets emptied, and with weight distributed evenly between the feet. Body weight was recorded to the nearest 0.5 lb. Currently, there is not a standardized definition for weight maintenance in

the breast cancer survivors. For the purposes of this study, weight maintenance was defined as "a change of ≤ 5 lb (2.3 kg)" (Donnelly et al., 2009, p. 461). The five pound criterion was chosen based on a review of previous literature as well as analyses of normal weight change patterns in healthy adults (St Jeor et al., 1997). It should be noted that this definition is applicable to healthy adults but may not be appropriate for the breast cancer population.

Height

Height was measured using a stadiometer attached to the beam scale. Participants were measured without shoes, with weight evenly distributed between the feet, with their back to the stadiometer, and with head erect and eyes looking straight ahead. The horizontal bar of the stadiometer was lowered to the most superior point on the head, compressing the hair. Height was measured to the nearest 0.5 cm.

Body Mass Index (BMI)

BMI assesses an individual's weight relative to their height and is correlated with percent body fat (ACSM, 2010). BMI was calculated by dividing the participant's body weight in kilograms by her height in meters^2.

Physical Activity

The Community Health Activities Model Program for Seniors (CHAMPS) was used to assess each participant's physical activity level. The CHAMPS questionnaire begins with three multiple choice questions that are designed to gauge an individual's overall social and physical activity level as well as how many flights of stairs he/she climbs in a typical day. Responses for the social and physical activity questions range

from “not at all active” to “extremely active,” and responses for the number of flights of stairs question range from “none” to “five or more flights.”

Next, participants report both the number of times per week and the number of hours per week they spend engaging in 32 social and physical activities. Social activities include spending time with family/friends, participation in recreational activities and hobbies, and doing housework. Physical activities include mild, moderate and vigorous activities such as walking, jogging, bicycling, strength training, and yoga. Responses for number of hours per week range from “less than one hour/week” to “nine or more hours/week.” Frequency per week in moderate activities was calculated for all exercise related activities.

Health-Related Quality of Life (HRQL)

The Functional Assessment of Cancer Therapy – Breast (FACT-B) was used to assess HRQL. This is a 37 item multidimensional questionnaire designed to measure HRQL in breast cancer patients. It is comprised of four subscales related to HRQL (physical, emotional, social and functional well-being) as well as the Breast Cancer Subscale, which consists of nine items specific to HRQL in breast cancer patients (Brady et al., 1997). Responses are scored using a 5 point Likert scale which includes 0 = Not at all, 1 = A little bit, 2 = Somewhat, 3 = Quite a bit, and 4 = Very much. Reversed scoring is used for some questions. A higher score indicates better overall HRQL (range = 0-144) as well as better well-being for each of the subscales: physical, social and functional well-being (range = 0-28), emotional well-being (range = 0-24), and BCS (range = 0-36).

Analytic Plan

Descriptive statistics (mean, median, and standard deviation) were used to characterize demographic and disease variables. Demographic variables included age, race, education, employment status, and BMI. Disease variables included stage of disease, type of surgery and adjuvant therapy. Descriptive statistics were also used to characterize the variables of interest including body weight, BMI, FACT-B, and CHAMPS for each time point. Adjusting for baseline BMI, repeated measures ANCOVA was applied to analyze change in BMI over time within each group as well as to analyze change in BMI over time between the groups. Pearson correlations were run to assess the relationship between BMI and FACT-B. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). A two-sided P-value < 0.05 was considered to be statistically significant.

RESULTS

Participant Characteristics

Table 1 describes the baseline participant characteristics of the total sample and of each group after randomization. The final sample consisted of 104 women. Age ranged from 32 to 82 years (mean = 53.7 years, SD = 11.7). Eighty-eight percent of the participants were Caucasian, and 12% were African-American. A majority of the sample was highly educated. Fifty-one percent of the participants had graduated from college, 28% had some college, and 17% had a high school education. Most of the participants were overweight (43%) with 28% of the participants being obese and 29% of the participants being normal weight. There were no significant differences between groups at baseline. The characteristics were normally distributed with the exception of BMI, which was positively skewed.

Table 1. Participant Characteristics [N=104; N(%)]

Characteristic	Total Sample	Usual Care	Intervention
Age (yrs)			
<50	44(42)	23(44)	21(40)
50 - 65	42(40)	19(37)	23(44)
>65	18(18)	10(19)	8(16)
Race			
White	92(88)	47(90)	45(87)
African American	12(12)	5(10)	7(13)
Education			
High School Graduate or less	18(17)	9(17)	9(17)
Some college	29(28)	19(37)	10(19)
College Graduate (4 yr) +	53(51)	22(42)	31(60)
N/A	4(4)	2(4)	2(4)
BMI (kg/m^2)			
Normal (18.5 - 24.9)	30(29)	14(27)	16(31)
Overweight (25 - 29.9)	45(43)	23(44)	22(42)
Obese (≥30)	29(28)	15(29)	14(27)

Disease Characteristics of Participants

Table 2 describes the disease characteristics of the sample as a whole and of each group after randomization. Almost half of the women (49%) had been diagnosed with Stage I disease while 38% were diagnosed with Stage II disease and 12% were diagnosed with Stage III disease. Surgical treatment included lumpectomy for 46% of the women and mastectomy for 50% of the women. In addition to surgical treatment, most of the women received some type of adjuvant therapy (chemotherapy 60%, tamoxifen 47%,

radiation 64%). There were no significant differences between groups at baseline, and the data were normally distributed.

Table 2. Disease Characteristics [N(%)]

Characteristic	Total Sample	Usual Care	Intervention
Stage of Disease			
I	51(49)	26(50)	25(48)
II	40(38)	21(40)	19(37)
III	12(12)	4(8)	8(15)
N/A	1(1)	1(2)	0
Type of Surgery			
Lumpectomy	48(46)	25(48)	23(44)
Mastectomy	52(50)	24(46)	28(54)
N/A	4(4)	3(6)	1(2)
Adjuvant Therapy			
Chemotherapy	62(60)	31(60)	31(60)
Tamoxifen	49(47)	23(44)	26(50)
Radiation	67(64)	36(69)	31(60)

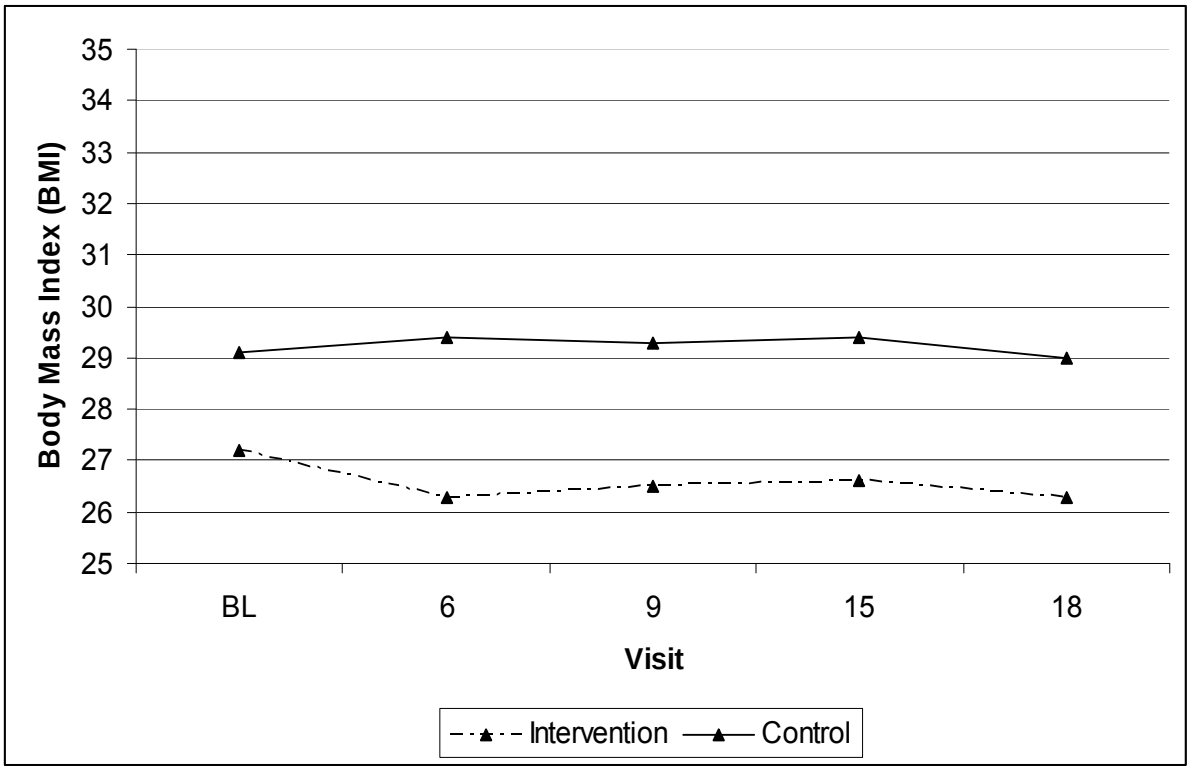
Descriptive Statistics for Variables of Interest

Table 3 describes the variables of interest. Means and standard deviations are reported for each group at each time point. The data for body weight, FACT-B, and CHAMPS were normally distributed, and there were no significant differences between groups at baseline ($p = 0.26$, $p = 0.62$, and $p = 0.17$, respectively). The data for BMI was

positively skewed, and results from the Wilcoxon Signed Ranks Test showed there was no significant difference in BMI between groups at baseline ($p = 0.11$).

At present, there is no operational definition for weight maintenance in breast cancer survivors. For the purposes of this study, weight maintenance was defined as a change of $\leq$ 5 lb (2.3 kg) (Donnelly et al., 2009, p. 461). Participants in both the intervention group and the control group maintained body weight over the course of 18 months. The mean weight change for body weight from baseline to 18 months was -0.38 kg (SD = 4.5 kg) for the intervention group and 1.7 kg (SD = 5.8 kg) for the control group. BMI calculations revealed that participants in both groups were on average overweight (see Figure 3).

Figure 2. Mean BMI by Group



The normative value for the FACT-B total score in breast cancer survivors is 112.8 (Deshields et al., 2005). Participants in both the intervention group and the control group reported a relatively high HRQL at baseline. Scores for the intervention group progressively increased from baseline to 15 months with a slight decrease in scores at 18 months. Scores for the control group progressively increased from baseline to nine months with scores decreasing at both 15 months and 18 months.

As shown by the CHAMPS questionnaire, participants in both groups engaged in similar amounts of moderate-intensity physical activity. Participants in the intervention group reported that they engaged in moderate-intensity physical activity an average of 7.4 (SD = 4.4) times per week over the course of 18 months. Participants in the control group reported that they participated in moderate-intensity physical activity an average of 7.2 (SD = 4.9) times per week over the course of 18 months.

Table 3. Descriptive Statistics for Variables of Interest (Mean ± SD)

Variable/Time	BL	6mos	9mos	15mos	18mos
BW (kg)					
Intervention	72.4 ± 15.4	71.3 ± 15.6	72.5 ± 17.9	72.4 ± 18.8	71.0 ± 16.2
Control	75.9 ± 17.1	76.3 ± 16.6	76.2 ± 15.8	76.2 ± 16.6	75.1 ± 14.9
BMI (kg/m²)					
Intervention	27.2 ± 5.9	26.3 ± 6.2	26.5 ± 7.0	26.6 ± 7.4	26.3 ± 6.8
Control	29.1 ± 6.1	29.4 ± 6.8	29.3 ± 6.8	29.4 ± 7.0	29.0 ± 6.5
FACT-B (0-144)					
Intervention	102.6 ± 16.4	112.8 ± 16.7	116.0 ± 17.2	119.4 ± 14.0	117.3 ± 17.4
Control	104.0 ± 22.7	107.0 ± 23.2	117.6 ± 15.7	116.7 ± 17.9	113.7 ± 20.8
CHAMPS (times/wk)					
Intervention	4.9 ± 2.8	7.6 ± 4.6	8.6 ± 4.5	8.2 ± 5.2	7.7 ± 4.8
Control	6.7 ± 4.2	8.0 ± 5.2	7.2 ± 4.7	7.1 ± 5.1	6.9 ± 5.3

Body Mass Index (BMI)

Repeated measures ANCOVA was also run to analyze differences in BMI over time for each group. Within the intervention group, participants randomized to the intervention group had a significant decrease in BMI at 6 and 9 months ($p = 0.02$ and $p = 0.01$, respectively), and there was a trend towards decreased BMI at 15 and 18 months ($p = 0.07$ and $p = 0.07$, respectively). Within the control group, participants randomized to the control group had a significant increase in BMI at 18 months ($p = 0.01$) with a trend towards increased BMI at 15 months ($p = 0.06$), but no significant increase was seen at 6 or 9 months.

Adjusting for baseline BMI in analysis of the total sample, repeated measures ANCOVA revealed that post-baseline BMI was significantly lower (p=0.01) in the intervention group (27.7 kg/m², SE = 0.27) when compared to the control group (28.3 kg/m² , SE = 0.24) [F(1, 87) = 6.20, p = 0.0147]. The mean difference over time between groups was -0.900 (95% CI = [-1.617, -0.182]) (see Table 3). Since the BMI data were not normally distributed, Signed Ranks tests were also considered, and the conclusions were the same.

BMI and FACT-B

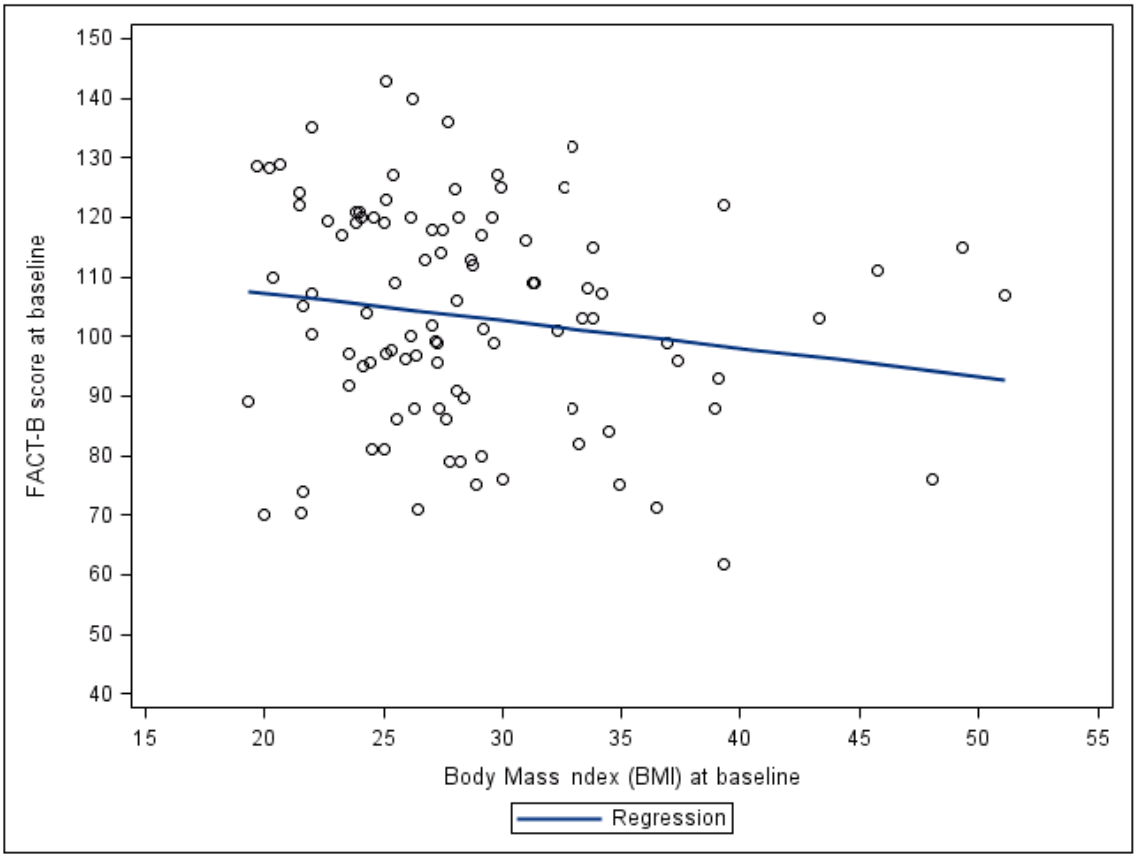
Correlations between BMI and FACT-B are shown in Table 4. Pearson product moment correlations revealed a significant association between BMI and FACT-B at baseline, 6, 9, and 18 months. It should be noted that the significance of this association was borderline at 15 months (p = 0.052). Since BMI data were not normally distributed, Spearman correlations were also considered, and the conclusions were the same. Linear trend plots showed a negative correlation at baseline (Figure 2) and over time (Figure 3).

Table 4. Correlations between BMI and FACT-B

BMI/FACT-B	BL	6 mos	9mos	15mos	18mos
BL	-0.23 <0.0001***	-0.29 0.0091**	-0.31 0.0066**	-0.25 0.0420*	-0.38 0.0007***
6mos	-	-0.30 0.0076**	-	-	-
9mos	-	-	-0.32 0.0055**	-	-
15mos	-	-	-	-0.24 0.0521	-
18mos	-	-	-	-	-0.33 0.0057**

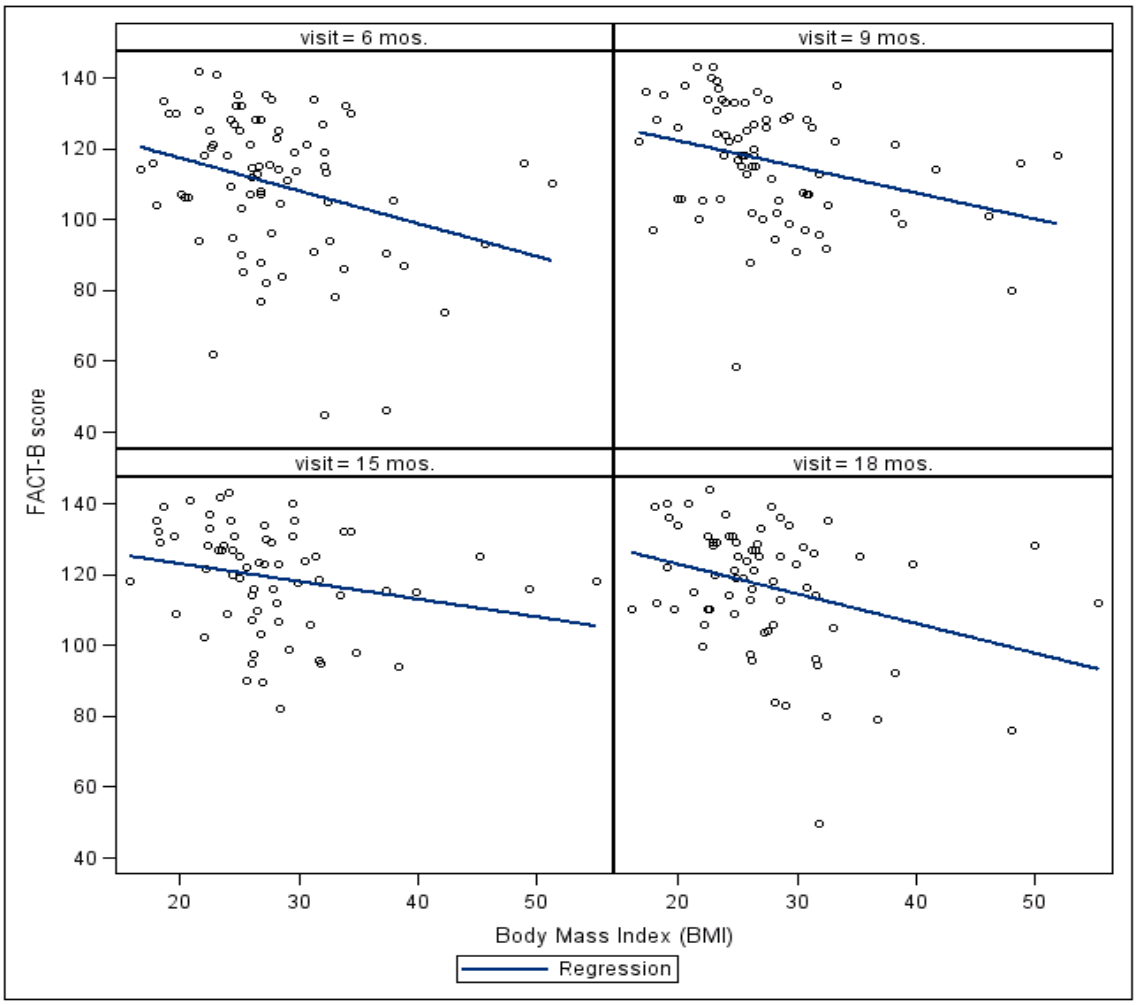
***p < 0.05 **p < 0.01 ***p < 0.001**

Figure 3. Linear Trend Plot for BMI and FACT-B at Baseline



r = -0.23, p <0.0001

Figure 4. Linear Trend Plot for BMI and FACT-B Over Time



6 months: r = -0.30, p = 0.0076

9 months: r = -0.32, p = 0.0055

15 months: r = -0.24, p = 0.0521

18 months: r = -0.33, p = 0.0057

Figure 5 depicts a visual representation of the mean FACT-B scores for each BMI classification at each time point in the intervention group. Overweight participants reported lower FACT-B scores than normal weight participants at each time point. When compared to normal weight participants, obese participants reported lower FACT-B scores at each time point. With the exception of baseline, obese participants reported lower FACT-B scores than overweight participants.

Figure 5. FACT-B Scores by BMI – Intervention Group

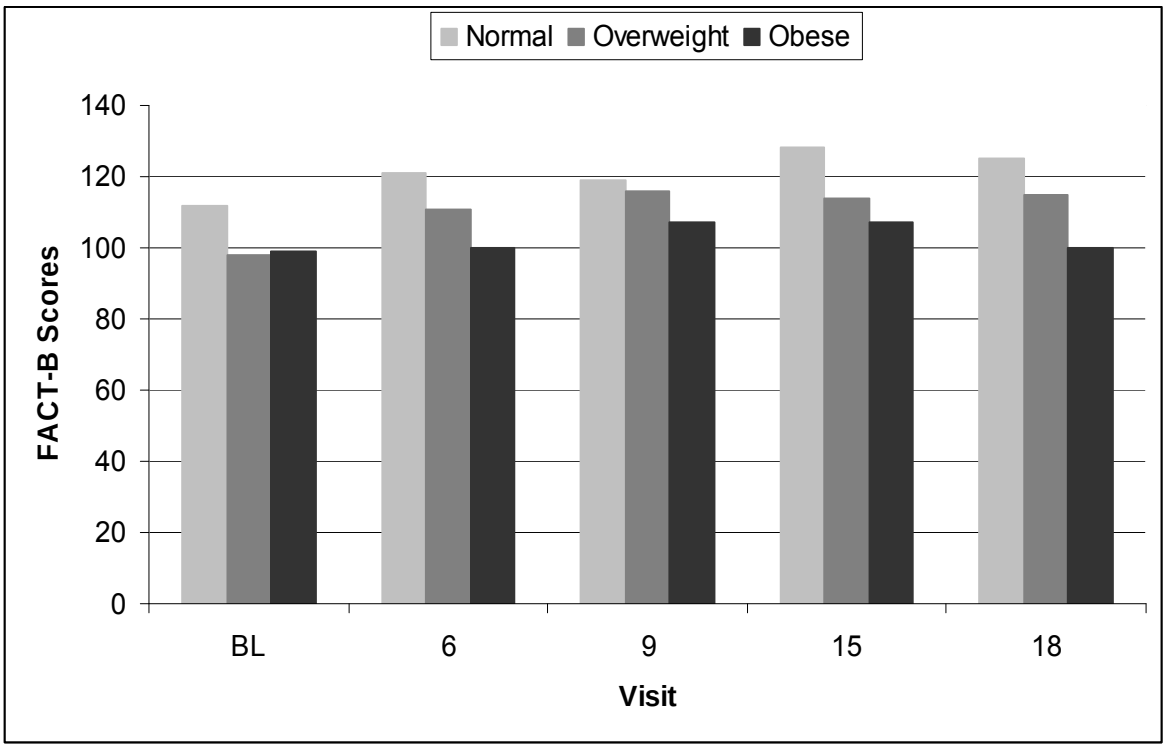
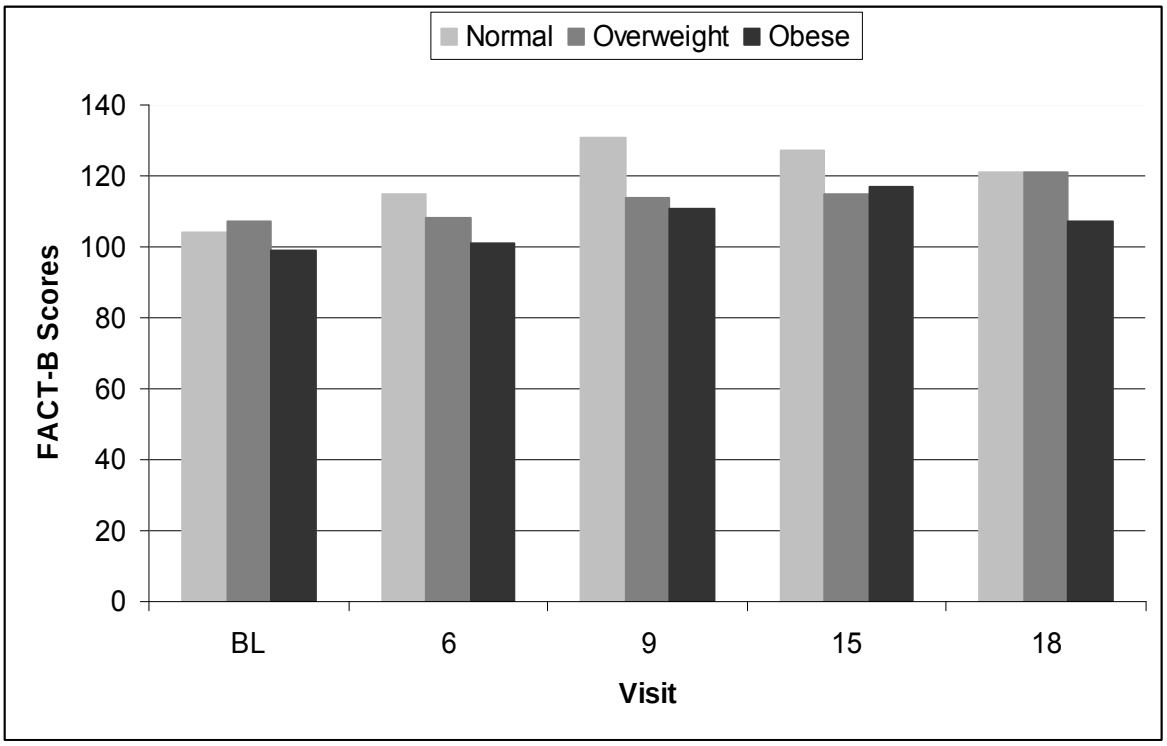


Figure 6 depicts a visual representation of the mean FACT-B score for each BMI classification at each time point in the control group. With the exception of baseline and 18 months, overweight participants reported lower FACT-B scores than normal weight participants. Obese participant reported lower FACT-B scores than normal weight participants at each time point. With the exception of 15 months, obese participants reported lower FACT-B scores than overweight participants.

Figure 6. FACT-B Scores by BMI – Control Group



DISCUSSION

Although breast cancer is the second most fatal cancer in women, the mortality rate has been steadily decreasing due to improvements in both diagnosis and treatment (ACS, 2009a; Jemal et al., 2009; Schwartz, 2008). However, this means more women are left to cope with the side effects of breast cancer treatments. Breast cancer treatments are intensive and result in several acute and long term side effects. Whereas acute side effects resolve quickly upon the completion of treatment, long term side effects, such as weight gain, may persist for years following treatment (Matthews et al., 2007).

It has been well established in the literature that weight gain is a common side effect of breast cancer treatments (Goodwin et al., 1999; Irwin et al., 2005; Rock et al., 1999). Weight gain can be detrimental to breast cancer survivors. An unhealthy weight at both the time of diagnosis and post-diagnosis is associated with increased risk of recurrence and decreased survival (Chlebowski et al., 2002) as well as other chronic conditions such as diabetes, heart disease, and orthopedic problems (CDC, 2009b; Koopman et al., 2009; Lavie et al., 2009). Additionally, two studies have shown that an unhealthy weight negatively affects HRQL in this population (Bardwell et al., 2004; Mosher et al., 2009).

Decreased energy expenditure resulting from decreased physical activity levels may play a role in weight gain (Demark-Wahnefried et al., 2001; Irwin et al., 2009; Pinto & Maruyama, 1999), and increasing physical activity levels may promote weight maintenance in breast cancer survivors. However, few studies have examined the effect of physical activity on body weight in breast cancer survivors, and even fewer studies

have assessed the relationship between an unhealthy weight and HRQL in this population. Thus, there is a need to investigate both the effect of physical activity on body weight as well as the relationship between body weight and HRQL in breast cancer survivors. The objectives of this study were to examine the longitudinal effect of a comprehensive tailored exercise program versus usual care on weight maintenance in breast cancer survivors and to analyze the relationship between body weight and HRQL in order to determine if a greater BMI is correlated with poorer HRQL in this population.

Body Weight and BMI

It was hypothesized that participants randomized to the intervention group would maintain their body weight over time as compared to the usual care group. The results of this study did not support this hypothesis. Currently, there is no definition of weight maintenance for breast cancer survivors. For the purposes of this study, weight maintenance was defined as "a change of ≤ 5 lb (2.3 kg)" (Donnelly et al., 2009, p. 461). According to this definition, participants in both the intervention group and the control group maintained their body weight over the course of 18 months.

A possible explanation for these results may be the fact that the total sample for this study included more overweight participants (43%) than obese participants (28%). Likewise, each group included more overweight participants (Intervention = 44%, Control = 42%) than obese participants (Intervention = 29%, Control = 27%). Research has shown that there is a significant association between physical activity and BMI in breast cancer survivors (Blanchard, Stein, and Courneya, 2010; Irwin et al., 2004; Milne, Gordon, Guilfoyle, Wallman, & Courneya, 2007). In an analysis including 806 breast

cancer survivors, Irwin et al. (2004) found that obese participants engaged in less moderate-intensity physical activity when compared to both overweight ($p = 0.05$) and normal weight ($p = 0.05$) participants.

The current study supports these findings. An analysis of this relationship within the total sample revealed a negative correlation between physical activity and BMI, which was significant at both 9 months and 18 months ($p = 0.01$ and $p = 0.01$, respectively). Consequently, since 71% of the participants in the control group of the current study were either normal weight or overweight, it is possible that this group was more active than sedentary thereby leading to weight maintenance. This is further supported by the fact that the control group reported similar amounts of moderate-intensity physical activity as was reported by the intervention group.

Nonetheless, even though both groups maintained body weight over the course of 18 months, BMI decreased over time in the intervention group, and when compared to baseline, was significantly lower at both 6 and 9 months. On the other hand, BMI increased over time in the control group and was significant at 18 months. Additionally, post-baseline BMI was significantly lower in the intervention group when compared to the control group. A five year follow-up study of the RESTORE participants is currently in progress, and results from this study will provide information as to whether or not this trend continued over time.

Since adjuvant chemotherapy is thought to be one of the primary causes of weight gain in the breast cancer population, a secondary analysis of participants who underwent chemotherapy ($n = 62$) was conducted. This analysis revealed that post-baseline BMI was significantly lower ($p=0.01$) in the intervention group (28.2 kg/m², SE = 0.43) when

compared to the control group (29.6 kg/m², SE = 0.33), and the mean difference over time between groups was -1.44 (95% CI = [-0.35, -2.53]) in women undergoing chemtherapy. On the other hand, an analysis of participants who did not undergo chemotherapy revealed no significant difference between groups in post-baseline BMI. These results suggest that a comprehensive tailored exercise program may be beneficial for weight maintenance in breast cancer survivors who received adjuvant chemotherapy versus breast cancer survivors who did not receive adjuvant chemotherapy.

Relationship between BMI and HRQL

It was hypothesized that BMI would be negatively correlated with HRQL at baseline and over the course of 18 months. This hypothesis was supported by the results of this study. BMI was significantly correlated with HRQL at baseline, 6, 9, and 18 months. BMI was also correlated with HRQL at 15 months; however, the significance of the association was borderline at this time point. Linear trend plots depicted a negative correlation between BMI and HRQL, which means a greater BMI was associated with poorer HRQL. These results not only contribute to the paucity of research in this area but also support the results of previous studies. Bardwell et al. (2004) found that a lower BMI was significantly correlated with better physical HRQL in breast cancer survivors, and Mosher et al. (2009) found that poorer physical HRQL was significantly associated with a greater BMI in older breast, prostate, and colorectal cancer survivors.

These results also demonstrate that the difference between baseline FACT-B scores and post-intervention FACT-B scores in the current study is clinically meaningful. It has been reported that a change of seven to eight points on the FACT-B denotes a

clinically meaningful difference (Eton et al., 2004). Although this is a minimal change, research has shown that a relatively small improvement in HRQL signifies a large benefit in cancer patients (Cella, Hahn, & Dineen, 2002). In the current study, the average difference in FACT-B scores between baseline and 18 months was an increase of 14.7 points for the intervention group and an increase of 9.7 points for the control group. It is interesting that the control group experienced a clinically significant improvement in HRQL. However, as previously mentioned, the control group was comprised of mostly overweight participants who appeared to be more physically active than sedentary, which may have resulted in a better HRQL.

Results from the current study also found that overweight participants most often reported lower FACT-B scores than normal weight participants and that obese participants most often reported lower FACT-B scores than both normal weight and overweight participants. These results support recent findings of Blanchard et al. (2010), who analyzed the relationship between BMI and HRQL in a group of breast, prostate, colorectal, bladder, uterine and skin melanoma cancer survivors (n = 3,241). The sample included 1,013 breast cancer survivors. The RAND-36 Health Status Inventory was used to measure HRQL, and results were reported for each cancer type. Healthy weight and overweight breast cancer survivors had higher Physical Composite Summary Scores (51.2 ± 10.9 and 50.5 ± 11.6, respectively) than obese breast cancer survivors (47.7 ± 12.1) ($p < 0.01$). In other words, as weight increased, physical HRQL decreased.

Limitations and Future Directions

This study has contributed relevant information to the literature in regard to the effect of physical activity on body weight in breast cancer survivors and the association between body weight and HRQL in this population. Nonetheless, there are several limitations and recommendations for future research studies that should be acknowledged. First, the sample in this study was comprised of predominantly middle-aged, highly educated, Caucasian women with early stage disease. The homogenous nature of the study sample limits the generalizability of the results. For example, both physical activity levels and the association between body weight and HRQL may differ for women of different races/ethnicity due to cultural norms. Future studies should include a more diverse population to increase the generalizability of the findings.

There was also a considerable difference in the retention rate between the intervention group and the control group as evidenced by the percentage of participants who completed follow-up testing visits. The percentage of participants randomized to the intervention group who completed follow-up testing visits ranged from 77% - 88%. Conversely, the percentage of participants randomized to the control group who completed follow-up testing visits ranged from 62% - 75%. This is not surprising as participants randomized to control groups often do not feel it is necessary to return for follow-up testing visits since they are not participating in the intervention. Providing an incentive, such as a yoga class once per week, may alleviate a feeling of exclusion from the study among control group participants thereby resulting in an improved retention rate for this group. Future studies should consider the incorporation of incentives for the control group as part of the intervention.

Next, both the intervention group and the control group reported similar amounts of moderate-intensity physical activity throughout the course of the study. A control group that was more physically active than sedentary could explain the lack of a significant increase in body weight over time in this group. However, the CHAMPS questionnaire may not be the best means of assessing physical activity as there are several elements of the questionnaire which may result in an overestimation of physical activity. First, subjects are asked to recall physical activity participation in the past four weeks. Many subjects may not remember the exact amount of physical activity in which they engaged over the past four weeks and thus, will report an estimate. The amount of physical activity participation is more likely to be overestimated than underestimated as people are inclined to report what they think the investigators want to hear. Subjects are also asked to report both the number of times per week as well as the average total time per week spent in engaging in various activities, and there are several activities which may be construed by the subjects as being the same activity. Both of these elements could also result in an overestimation of physical activity. Finally, the CHAMPS questionnaire was designed for a senior population and includes more mild activities than moderate/vigorous activities. Since the mean age of the sample was 54 years and since the current study assessed the frequency of moderate physical activity, CHAMPS may not have been the best means of assessing moderate physical activity for this sample. Future studies should include physical activity measurements relative to the study population, and ultimately, objective measures of physical activity such as accelerometers should be considered.

Additionally, like a majority of the studies which have examined the effect of physical activity on body weight in breast cancer survivors, body weight was a secondary outcome of the RESTORE trial. The primary outcomes of RESTORE were physical fitness, arm volume, and HRQL. Thus, the intervention was not designed to promote weight maintenance in breast cancer survivors. For example, the literature suggests that greater amounts of moderate-intensity physical activity (150–250 minutes/week) are necessary to effectively manage body weight (Donnelly et al., 2009). Through a combination of supervised and home-based exercise, participants in the intervention group in the current study were encouraged to meet the recommended physical activity guidelines of 30 minutes of moderate-intensity physical activity on most days of the week. It is possible that a greater volume of exercise would have led to a larger difference in BMI between the groups over time. In the future, studies examining the effect of physical activity on body weight in breast cancer survivors should include interventions designed to promote weight management in this population.

It has been noted that interventions which include the promotion of a healthy diet (increasing fruit and vegetable intake, decreasing fat intake) as well as physical activity may help achieve a negative energy balance necessary for weight loss in this population (Demark-Wahnefried et al., 2005). Although this intervention included one 60 minute informational session on healthy eating habits, there was no further promotion of healthy eating throughout the study and participants were not required to keep food logs. Thus, no conclusions can be drawn in regard to the effect of both a healthy diet and physical activity on body weight in breast cancer survivors. Future studies should include interventions that incorporate both physical activity and the promotion of healthy eating

behaviors to determine if the combination of two weight-related lifestyle behaviors is a more effective means of achieving weight management in breast cancer survivors.

Implications and Conclusions

Weight gain is a common problem experienced by breast cancer survivors which may persist for years following diagnosis. An unhealthy weight has not only been shown to negatively affect breast cancer outcomes but has also been shown to be negatively correlated with HRQL in breast cancer survivors. Although it cannot be assumed that an unhealthy body weight causes poorer HRQL, prevention of further weight gain may improve HRQL in breast cancer survivors (Bardwell et al., 2004). Consequently, weight management should be a priority in this population. Findings from this study not only illustrate that physical activity is related to BMI in breast cancer survivors but also show that BMI is negatively correlated with HRQL. These findings provide the rationale for promoting physical activity in this population.

Unfortunately, it has been reported that a majority of breast cancer survivors do not meet the American Cancer Society's recommended physical activity guidelines of 150 minutes per week of moderate to vigorous intensity physical activity (Irwin et al., 2003; Irwin et al., 2004). Blanchard, Courneya, & Stein (2008) conducted a study that examined the prevalence of physical activity among six major cancer survivor groups. They found that only 37.1% of breast cancer survivors (n = 2,885) met the recommendation for physical activity. Therefore, interventions should include components designed to promote adherence to weight-related lifestyle behaviors.

Another means of promoting physical activity stems from the diagnosis of breast cancer. A cancer diagnosis has been referred to as a teachable moment in that it is a prime opportunity to encourage cancer survivors to adopt healthy lifestyle changes. Research has shown that physicians are a powerful influence in regard to mammography screening, and thus, may also be influential in the promotion of healthy lifestyle behaviors (Demark-Wahnefried et al., 2005). Jones, Courneya, Fairey, and Mackey (2004) conducted a RCT that looked at the effect of an oncologist's recommendation to exercise versus usual care immediately following the diagnosis of breast cancer. Participants in the recommendation group reported a mean of 10.1 ± 10.7 MET hours per week compared to a mean of 6.7 ± 8.9 MET hours per week in the usual care group (p = 0.011). Thus, health care providers should consider the role of physical activity as part of the standard treatment regimen for breast cancer survivors and should not only recommend physical activity participation but also assess physical activity levels of breast cancer survivors.

Weight gain is a harmful side effect of breast cancer treatments that adversely affects breast cancer outcomes and contributes to poorer HRQL in breast cancer survivors. With the number of breast cancer survivors increasing, further examination of the rehabilitation process for this population is imperative. Weight management should be one of the primary goals in the rehabilitation process. The literature has demonstrated that engaging in physical activity plays an important role in weight management and that BMI is negatively correlated to HRQL. Results from the current study further support these findings. Thus, physical activity should be included in the rehabilitation process for

breast cancer survivors, and future research in regard to the optimal physical activity intervention for the rehabilitation of breast cancer survivors is warranted.

APPENDIX A

WAKE FOREST UNIVERSITY SCHOOL OF MEDICINE
AND
FORSYTH REGIONAL CANCER CENTER
WINSTON-SALEM, NC

INFORMED CONSENT

STUDY TITLE: Research on Optimal Recovery Practices in Breast Cancer (RESTORE)

PURPOSE OF THIS RESEARCH STUDY: The purpose of this study is to see whether receiving patient education about safe exercise and participating in a customized exercise program can significantly improve quality of life and physical fitness of women in the months following surgery for breast cancer. A second goal of this study is to see whether a special lymphedema prevention program is effective in helping prevent you from developing swelling in your arm(s) in the months following surgery for breast cancer.

HOW YOU WERE SELECTED TO PARTICIPATE: You were selected to participate in this study because you were recently diagnosed and treated for breast cancer. Your surgeon or oncologist is taking part in this study and has given us permission to invite you.

We believe that being physically active through exercise can help women limit possible declines in functioning after surgery and may enhance quality of life in women of all ages with breast cancer. This study will also be looking at preventing lymphedema. Lymphedema is a condition that some women may get following breast cancer treatment and is characterized by swelling and/or pain in the arm and/or hand on the same side as surgery. There is no cure for lymphedema and currently there are no *scientifically proven preventive* strategies. Although we do not know exactly how many women develop lymphedema following breast cancer treatment, it is a common condition. There is some evidence that women who maintain good skin care, engage in proper post-operative arm exercises and avoid injury and infection in the affected arm and hand may be less likely to develop the condition.

WHAT YOU WILL BE ASKED TO DO IF YOU PARTICIPATE IN THIS STUDY: If you agree to participate, you will be randomly assigned (similar to the flip of a coin) to either: (i) a patient education program about lymphedema prevention, including safe exercises you can do on your own; or (ii) a more involved exercise and lymphedema program, which includes exercise sessions to attend, a class on lymphedema, and a visit

with a physical therapist to learn more about lymphedema exercise for your arms. Both groups will receive dietary information and advice.

All participants will attend an initial (baseline) visit at the Wake Forest University Reynolda campus. This will be followed by visits at 3 months, 6 months, 9 months, 15 months and 18 months after surgery. We will provide limited transportation to and from the campus for those who need it. At each of these visits we will ask you to fill-out questionnaires on your quality of life, physical and emotional well-being. Physical fitness assessments will include flexibility, range of motion, cardiovascular endurance, body composition, and strength. All participants will also receive nutritional assessments at 3, 6, 9, 15 and 18 months. You will be asked to keep a 4-day food log in order to assess your nutrition. In addition, 12 months after surgery we will contact you by telephone to collect data.

At approximately 3-months and 18-months after surgery you will be asked to visit the WFU School of Medicine campus in order to undergo a scan of your body that measures the amount of bone, muscle and fat tissue using a Dual Energy X-Ray Absorptiometry machine (DEXA). This procedure is a type of x-ray but involves much less radiation exposure. Radiation exposure information can be found in the risks section of this document below.

Resting metabolism and diet will also be assessed for all participants during the visit to the WFU School of Medicine campus at 3 months and 18 months. Resting metabolism testing requires an 8-hour fast (no drinks containing calories or caffeine, or food) prior to the GCRC visit. If you feel you are placing yourself at risk from this condition or are uncomfortable driving during this state, we suggest that a friend of family member drives you, or alternatively, it is possible that transportation may be arranged by the GCRC. You will be asked to lie still in a reclined position for 30 minutes in a quiet, temperature control room to establish baseline and resting conditions. For an additional 30 minutes, you will wear a neoprene mask interfaced with a MedGraphics Metabolic Cart for the determination of gas exchange. Once the procedure is performed, snacks will be provided to you prior to leaving the testing facility.

All of the information that we collect on you in this study will be kept confidential, and will not be shared with others.

If you are assigned to the more involved program, you will first receive instruction on three lymphedema preventive strategies: range of motion exercises; lymph flow exercises; and use of an elastic sleeve. A trained therapist will assess your arm and hand strength and provide an individualized exercise plan for you to follow. You will be given an elastic sleeve, shown how to put it on and instructed on appropriate times to wear it. The therapist will instruct you on both exercise techniques and how often to use them. You will be asked to complete a diary noting how often each week you used the three preventive strategies. Three months after receiving the educational materials, physical

therapy assessment, and instruction, you will be asked to turn in the diary and complete a questionnaire about lymphedema.

In addition, if you are assigned to the more involved program, you will attend exercise sessions twice a week at times that are convenient for you. After 3 months you will be taught how to complete the appropriate exercises at home by walking and performing strength training. Gradually the center-based exercise program will taper off to a home-based exercise program. In the exercise program, you will participate in a 3-month center based program of exercise that includes a warm-up, muscle strengthening, stretching, walking or cycling and a cool down. All study participants will receive information and advice on resuming an active lifestyle, reducing your risk for disease, and a physical fitness evaluation approximately every three months to tell how fit you are.

Once you have completed the 18-month visit your participation in this study will end.

RISKS: We believe there is minimal risk from participating in this study. Some of the questionnaires may seem personal to you, such as questions about mood, emotions, and sexual activity following treatment for breast cancer. These kinds of questions are commonly asked in studies on cancer and quality of life, and we have found that most people are not bothered by answering them. Your answers will be kept private. There will be a loss of the personal time it takes you to fill out questionnaires and to attend testing sessions and the exercise program. Testing sessions will be scheduled at your convenience to minimize interruption of daily responsibilities. To minimize the amount of time the exercise program will detract from other activities and responsibilities, it is being offered at several times during the week so that you may choose the most convenient time for you. Potential negative effects from fitness testing include muscle soreness, fatigue, injury and pain. However, study personnel will take all possible precautions to prevent these negative effects. There is also a slight risk that you may experience a fall during the walking test or the walking portion of the exercise program. Steps will be taken to clear the walking path of debris and distractions so that this risk remains minimal. Potential negative effects may occur if the exercise program is performed incorrectly. These are: arm strain; soreness; pain; swelling; exacerbation of an existing joint problem; or stiffness. However, the exercises are developed for your particular level of strength and flexibility; therefore, if performed as instructed, we expect no negative effects. If at any time following your breast cancer surgery, you develop pain and/or swelling in the affected arm and/or hand, you should notify your physician immediately. While we believe that the exercise program will be safe for those eligible to participate, if your health changes or should you become pregnant during the study period, you should discuss your continued participation with your physician.

As mention before, if you are assigned to the more involved program, you will be given a sleeve to wear to help prevent lymphedema. It is possible that if you have skin sensitivity to the garment you could develop a rash, sensitive skin, or a skin infection. Any participant developing these conditions will be instructed not to wear the sleeve and to see their physician for treatment. Those who have an allergic reaction will be released

from the study, and those women with a skin infection will be instructed not to wear the sleeve until the condition has resolved and their physician states that they can safely wear the garment. If you experience decreased sensitivity of the limb or skin, you will be cautioned to immediately remove the sleeve and report any problems that arise as a result of wearing the sleeve.

The only radiation dose that you will receive as a result of participating in this study is radiation from the DEXA machine. You may experience other radiation exposure as a result of your regular medical care outside of this study. The amount of radiation you will receive from each DEXA scan is 1.5 millirem. This is equal to slightly more than 1% (1.25%) of the amount of natural background radiation that the average person in the United States receives each day. The annual background radiation the average person receives each year in the United States is 360 millirem. The risk of this procedure is small. Other than minimal exposure to radiation, there are no risks associated with DEXA scans. The amount of radiation that you would be exposed to is equivalent to a flight departing from Winston-Salem, North Carolina and arriving in Denver, Colorado. The incremental health risk that you would potentially face from this exposure would be about the same as smoking four cigarettes in your lifetime. Thus, the risk to you, if any, is estimated to be slight.

Should new information be learned about risks in participating in the study, or studies like this one, you will be notified and this new information will be discussed with you. Presently, the researchers conducting this study are not aware of the existence of or potential for any risks other than those listed above.

BENEFITS: By participating in this study you will help researchers and health providers better understand how to help women treated for breast cancer improve their quality of life and well-being. Other benefits include receiving important information about lymphedema, a condition for which you are at risk based on having had surgery for breast cancer. You will also receive instruction on possible preventive techniques and have the opportunity to employ them for the prevention of lymphedema. Information will be given about your resting metabolism, level of body fat and bone density. All instruction, instructional materials and the elastic sleeve will be provided to you free of charge. You will also receive important information about the role of exercise and lifestyle change in improving quality of life after treatment for breast cancer. Although we do not offer compensation for participating in this study, we do not anticipate that you will have any costs associated with your participation.

COMPENSATION FOR ILLNESS OR INJURY: Should you be injured as a result of participating in this research project, you will be provided medical care, at no cost to you, for that injury. You will not receive any injury compensation, only medical care. You should also understand that this is not a waiver or release of your legal rights. You should discuss this issue thoroughly with the principal investigator before you enroll in the study.

REVIEW OF RESEARCH RECORDS: It should be noted that representatives of the U.S. Army Medical Research and Materiel Command (who are funding this research project) are eligible to review research records as a part of their responsibility to protect human subjects in research.

RIGHTS OF HUMAN SUBJECTS: For additional information about your rights as a participant in this study, contact the Chairman, Institutional Review Board, through the Office of Research, Wake Forest University School of Medicine, at (336) 716-4542.

FOR MORE INFORMATION: For more information about this research, contact the Principal Investigator of the study, Dr. Roger Anderson, Department of Public Health Sciences, Wake Forest University School of Medicine at (336) 716-7057 or Kathy Bokeno, RN, the Project Manager, at (336) 713-0398.

RIGHT TO WITHDRAW: Participation in this study is completely voluntary and while we encourage you to continue to the end of this study, you may, of course, withdraw from the study at any time. Refusal to participate will not compromise or affect the quality of care that you receive from the Wake Forest University School of Medicine, North Carolina Baptist Hospital, or Forsyth Medical Center. If you choose not to participate you will receive the usual treatment for breast cancer follow-up. The researcher may decide to take you off this study if it is in your medical best interest, your condition worsens, or new information becomes available.

CONFIDENTIALITY: None of the medical information gathered from this study will become a part of your hospital record. All of your information will be kept confidential. Information of a sensitive personal nature will not be put on your medical record but will be noted in the investigator's research file and identified only by an identification number. The list of identification numbers connecting the patients' names to the numbers will be kept in a separate secure location. If information gathered from this study is used for a publication in medical journals or for teaching purposes, no names will be used. The study staff, principal investigators, institutional review board or representatives of the U.S. Army Medical Research and Materiel Command (who are funding this research project), may however, review your record for this study. To that extent confidentiality isn't absolute. Information from your DEXA scan may be used in other research but your identifying information will not be included with the scans. Please indicate whether you wish to have your data shared in this way by checking one box and initialing in the space below.

☐ **Yes** – I authorize the use of data from my DEXA scan for other research.
___*(initials)*

☐ **No** – I do not authorize the use of data from my DEXA scan.
___*(initials)*

SUBJECT CONSENT: I have read and understand the consent form. The principal investigator has explained the study purpose, procedures, risks and benefits to me, and all my questions have been answered. Alternatives to my participation in this study have been discussed. Based on the above, I consent to participate in the research and have received a copy of the consent form.

I agree to take part in this study.

Signature of Subject_____ Date_____

Printed name of Subject_____ Date_____

Permanent Address of Subject _____

_____

Signature of Person Administering Consent_____ Date_____

Printed name of Person Administering Consent_____ Date_____

APPENDIX B

CHAMPS QUESTIONNAIRE

This questionnaire is about activities that you may have done in the past 4 weeks. Before you begin, please review the following steps and examples:

Step #1: Number of times each week

- For each activity, write on the line provided how many times each week, on average you did that activity.
- If you did an activity less than once a week or not at all, please write a zero "0" on the line provided.

For example, if you did not do the activity at all or did it less than once a week during the past 4 weeks:

Example A Step #1

Activities:	**Number of times a week** (If none, write "0")	Less than 1 hour a week	1-2.5 hours a week	3-4.5 hours a week	5-6.5 hours a week	7-8.5 hours a week	9+ hours a week
Mow Lawn……	Times a week 0	* When "Times a week" is "0", skip this part ○	○	○	○	○	○

Step #2: Total time, on average, each week

- If you did the activity at least once a week, fill in the corresponding circle that represents how much total time, on average, you spent doing it each week.

For example, if you did the activity on average 3 times a week for a total of 1.5 hours each week:

Example B Step #1 Step #2

Activities:	**Number of times a week** (If none, write "0")	Less than 1 hour a week	1-2.5 hours a week	3-4.5 hours a week	5-6.5 hours a week	7-8.5 hours a week	9+ hours a week
Go to the senior center…..	Times a week 3	* When "Times a week" is "0", skip this part ○	●	○	○	○	○

Think about the past 4 weeks. For each activity, please write **HOW MANY TIMES** each week, on average, you did it. Next, please fill in the circle representing how much **TOTAL TIME**, on average, you spent doing that activity each week.

Social Activities:	**Number of times a week** (If none, write "0")	Less than 1 hour a week	1-2.5 hours a week	3-4.5 hours a week	5-6.5 hours a week	7-8.5 hours a week	9+ hours a week
a. Visit with friends and family (other than those you live with)…	Times a Week _____	○	○	○	○	○	○
b. Go to the senior center……	Times a Week _____	○	○	○	○	○	○
c. Do volunteer work…….	Times a Week _____	○	○	○	○	○	○
d. Attend church or take part in church activities….	Times a Week _____	○	○	○	○	○	○
e. Attend other club or group meetings….	Times a Week _____	○	○	○	○	○	○

Recreation and Hobbies:	**Number of times a week** (If none, write "0")	Less than 1 hour a week	1-2.5 hours a week	3-4.5 hours a week	5-6.5 hours a week	7-8.5 hours a week	9+ hours a week
f. Use a computer…..	Times a Week _____	○	○	○	○	○	○
g. Dance (such as square, folk, line, ballroom)(do not count aerobic dance here)…	Times a Week _____	○	○	○	○	○	○
h. Do wood-working, needlework, drawing, or other arts or crafts…	Times a Week _____	○	○	○	○	○	○
i.Play golf,riding a cart (count walking time only)…	Times a Week _____	○	○	○	○	○	○
j. Play golf, carrying/ pulling your equipment (count walking time only)…	Times a Week _____	○	○	○	○	○	○
k. Attend a concert, movie, lecture, or sport event…	Times a Week _____	○	○	○	○	○	○
l. Play cards, bingo, or board games with other people…	Times a Week _____	○	○	○	○	○	○

Recreation and Hobbies:	**Number of times a week** (If none, write "0")	Less than 1 hour a week	1-2.5 hours a week	3-4.5 hours a week	5-6.5 hours a week	7-8.5 hours a week	9+ hours a week
m. Shoot pool or billiards	Times a Week _____	○	○	○	○	○	○
n. Play singles tennis (do not count doubles)…	Times a Week _____	○	○	○	○	○	○
o. Play doubles tennis (do not count singles)…	Times a Week _____	○	○	○	○	○	○
p. Skate (ice, in-line, roller)…	Times a Week _____	○	○	○	○	○	○
q. Play a musical instrument…	Times a Week _____	○	○	○	○	○	○
r. Read…	Times a Week _____	○	○	○	○	○	○
Work Around the House:	**Number of times a week** (If none, write "0")	Less than 1 hour a week	1-2.5 hours a week	3-4.5 hours a week	5-6.5 hours a week	7-8.5 hours a week	9+ hours a week
s. Do Heavy work around the house (such as washing windows, cleaning gutters)…	Times a Week _____	○	○	○	○	○	○

Work Around the House:	**Number of times a week** (If none, write "0")	Less than 1 hour a week	1-2.5 hours a week	3-4.5 hours a week	5-6.5 hours a week	7-8.5 hours a week	9+ hours a week
t. Do light work around the house (such as sweeping or vacuuming)…	Times a Week _____	○	○	○	○	○	○
u. Do heavy gardening (such as spading, raking)...	Times a Week _____	○	○	○	○	○	○
v. Do light gardening (such as watering plants)…	Times a Week _____	○	○	○	○	○	○
w. Work on your car, truck, lawn mower, or other machinery…	Times a Week _____	○	○	○	○	○	○
Walking & Jogging, Including Treadmill**:**	**Number of times a week** (If none, write "0")	Less than 1 hour a week	1-2.5 hours a week	3-4.5 hours a week	5-6.5 hours a week	7-8.5 hours a week	9+ hours a week
x. Walk uphill or hike uphill (count only uphill part)…	Times a Week _____	○	○	○	○	○	○
y. Walk leisurely for exercise or pleasure…	Times a Week _____	○	○	○	○	○	○

Walking & Jogging, Including Treadmill**:**	**Number of times a week** (If none, write "0")	Less than 1 hour a week	1-2.5 hours a week	3-4.5 hours a week	5-6.5 hours a week	7-8.5 hours a week	9+ hours a week
z. Walk to do errands (such as to/from a store or to take kids to school (count walk time only)…	Times a Week _____	○	○	○	○	○	○
aa. Walk fast or briskly for exercise (do not count walking leisurely or uphill)…	Times a Week _____	○	○	○	○	○	○
bb. Jog or run…	Times a Week _____	○	○	○	○	○	○
Other Types of Exercise:	**Number of times a week** (If none, write "0")	Less than 1 hour a week	1-2.5 hours a week	3-4.5 hours a week	5-6.5 hours a week	7-8.5 hours a week	9+ hours a week
cc. Ride a bicycle or stationary cycle using legs only…	Times a Week _____	○	○	○	○	○	○
dd. Do aerobic machines involving arms and legs (such as rowing or cross-country ski machines)…	Times a Week _____	○	○	○	○	○	○

Other Types of Exercise:	**Number of times a week** (If none, write "0")	Less than 1 hour a week	1-2.5 hours a week	3-4.5 hours a week	5-6.5 hours a week	7-8.5 hours a week	9+ hours a week
ee. Do stair or step machine…	Times a Week _____	○	○	○	○	○	○
ff. Swim gently…	Times a Week _____	○	○	○	○	○	○
gg. Swim moderately or fast…	Times a Week _____	○	○	○	○	○	○
hh. Do water exercises (do not count other swimming)…	Times a Week _____	○	○	○	○	○	○
ii. Do stretching or flexibility exercises (do not count yoga or Tai-chi)…	Times a Week _____	○	○	○	○	○	○
jj. Do yoga or Tai-chi…	Times a Week _____	○	○	○	○	○	○
kk. Do aerobics or aerobic dancing…	Times a Week _____	○	○	○	○	○	○

Other Types of Exercise:	**Number of times a week** (If none, write "0")	Less than 1 hour a week	1-2.5 hours a week	3-4.5 hours a week	5-6.5 hours a week	7-8.5 hours a week	9+ hours a week
ll. Do moderate to heavy strength training (such as hand-held weights of more than 5 lbs., weight machines, or push ups)…	Times a Week _____	○	○	○	○	○	○
mm. Do light strength training (such as hand-held weights of 5 lbs. or less, or elastic bands)…	Times a Week _____	○	○	○	○	○	○
nn. Do general conditioning exercises, such as light calisthenics or chair exercises (do not count strength training)…	Times a Week _____	○	○	○	○	○	○
oo. Play basketball, soccer, or racquetball (do not count time on sidelines)…	Times a Week _____	○	○	○	○	○	○

Other Types of Exercise:	**Number of times a week** (If none, write "0")	Less than 1 hour a week	1-2.5 hours a week	3-4.5 hours a week	5-6.5 hours a week	7-8.5 hours a week	9+ hours a week
pp. Do other types of physical activity not previously mentioned (please specify), _____	Times a Week _____	○	○	○	○	○	○

APPENDIX C

FACT-B QUESTIONNAIRE

Below is a list of statements that other people with your illness have said are important. By circling one (1) answer per line, please indicate how true each statement has been for you during the past 7 days.

I. Physical Well-Being

During the past 7 days:

a. I had a lack of energy

Not at all A little bit Somewhat Quite a bit Very much

b. I had nausea

Not at all A little bit Somewhat Quite a bit Very much

c. Because of my physical condition, I had trouble meeting the needs of my family

Not at all A little bit Somewhat Quite a bit Very much

d. I had pain

Not at all A little bit Somewhat Quite a bit Very much

e. I was bothered by side effects of treatment

Not at all A little bit Somewhat Quite a bit Very much

f. I felt ill

Not at all A little bit Somewhat Quite a bit Very much

g. I was forced to spend time in bed

Not at all A little bit Somewhat Quite a bit Very much

II. Social/Family Well-Being

During the past 7 days:

a. I felt close to my friends

Not at all A little bit Somewhat Quite a bit Very much

b. I got emotional support from my family

Not at all A little bit Somewhat Quite a bit Very much

c. I got support from my friends

Not at all A little bit Somewhat Quite a bit Very much

d. My family has accepted my illness

Not at all A little bit Somewhat Quite a bit Very much

e. I was satisfied with family communication about my illness

Not at all A little bit Somewhat Quite a bit Very much

f. I felt close to my partner (or the person who is my main support)

Not at all A little bit Somewhat Quite a bit Very much

ff. Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box. ☐

g. I was satisfied with my sex life

Not at all A little bit Somewhat Quite a bit Very much

III. Emotional Well-Being

During the past 7 days:

a. I felt sad

Not at all A little bit Somewhat Quite a bit Very much

b. I was satisfied with how I'm coping with my illness

Not at all A little bit Somewhat Quite a bit Very much

c. I was losing hope in the fight against my illness

Not at all A little bit Somewhat Quite a bit Very much

d. I felt nervous

Not at all A little bit Somewhat Quite a bit Very much

e. I worried about dying

Not at all A little bit Somewhat Quite a bit Very much

f. I worried that my condition would get worse

Not at all A little bit Somewhat Quite a bit Very much

IV. Functional Well-being

During the past 7 days:

a. I was able to work (include work at home)

Not at all A little bit Somewhat Quite a bit Very much

b. My work (include work at home) was fulfilling

Not at all A little bit Somewhat Quite a bit Very much

c. I was able to enjoy life

Not at all A little bit Somewhat Quite a bit Very much

d. I have accepted my illness

Not at all A little bit Somewhat Quite a bit Very much

e. I was sleeping well

Not at all A little bit Somewhat Quite a bit Very much

f. I was enjoying things I usually do for fun

Not at all A little bit Somewhat Quite a bit Very much

g. I was content with the quality of my life right now

Not at all A little bit Somewhat Quite a bit Very much

V. Additional Concerns

During the past 7 days:

a. I was short of breath

Not at all A little bit Somewhat Quite a bit Very much

b. I was self-conscious about the way I dressed

Not at all A little bit Somewhat Quite a bit Very much

c. My arms were swollen or tender

Not at all A little bit Somewhat Quite a bit Very much

d. I felt sexually attractive

Not at all A little bit Somewhat Quite a bit Very much

e. I was bothered by hair loss

Not at all A little bit Somewhat Quite a bit Very much

f. I was worried that other members of my family might someday get the same illness I have

Not at all A little bit Somewhat Quite a bit Very much

g. I worried about the effect of stress on my illness

Not at all A little bit Somewhat Quite a bit Very much

h. I was bothered by a change in weight

Not at all A little bit Somewhat Quite a bit Very much

i. I felt like a woman

Not at all A little bit Somewhat Quite a bit Very much

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SCHOLASTIC VITA

ANNA MARIE DAVENPORT

Personal Information

Birthplace: Atlanta, Georgia
Birth Date: August 22, 1966

Undergraduate Study

1984-1986 Oxford College of Emory University
Oxford, Georgia
A.A. Liberal Arts

2005-2008 University of Wyoming
Laramie, Wyoming
B.S. Kinesiology and Health Promotion
Summa Cum Laude

Graduate Study

2008-2010 Wake Forest University
Winston-Salem, North Carolina
M.S. Health and Exercise Science
Advisor: Shannon L. Mihalko, Ph.D
Thesis: A Tailored Exercise Program for Breast Cancer Survivors: An Examination of Body Weight and HRQL

Professional Experience

2009-2010 Morning Program Coordinator & Senior Exercise Leader
Healthy Exercise and Lifestyle ProgramS
Wake Forest University
Winston-Salem, North Carolina

2009-2010 Research Assistant
Breast Care Clinic Strength and Flexibility Study
Wake Forest University
Winston-Salem, North Carolina

2009-2010 Research Assistant
RESTORE Study
Wake Forest University
Winston-Salem, North Carolina

2009-2010 Exercise Leader
Action Health Weight Loss Program
Wake Forest University
Winston-Salem, North Carolina

2008-2010 Graduate Teaching Assistant, Course Instructor
Department of Health and Exercise Science
Wake Forest University
Winston-Salem, North Carolina

2008-2010 Research Assistant
IDEA Study
Wake Forest University
Winston-Salem, North Carolina

2008-2009 Exercise Leader
Healthy Exercise and Lifestyle ProgramS
Wake Forest University
Winston-Salem, North Carolina

2008 Research Assistant
AML Mobility Study
Wake Forest University
Winston-Salem, North Carolina

2008 Cardiac Rehabilitation Internship
Cardiovascular Health Clinic
Mayo Clinic
Rochester, Minnesota

Professional Affiliations

2007-Present American Association of Cardiovascular and Pulmonary Rehabilitation

2006-Present American College of Sports Medicine

2008-Present American College of Sports Medicine
Southeastern Regional Chapter

2006-2008 American College of Sports Medicine
Rocky Mountain Regional Chapter

Certifications

2009-Present	American College of Sports Medicine Clinical Exercise Specialist
2009-Present	American College of Sports Medicine Cancer Exercise Trainer
2007-Present	American Heart Association Basic Life Support for Healthcare Providers