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Difference in physiological parameters following an exercise intervention in breast cancer survivors on a single chemotherapy drug versus combination chemotherapy drugs

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THE DIFFERENCE IN PHYSIOLOGICAL PARAMETERS FOLLOWING AN EXERCISE INTERVENTION IN BREAST CANCER SURVIVORS ON A SINGLE CHEMOTHERAPY DRUG VERSUS COMBINATION CHEMOTHERAPY DRUGS

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ABSTRACT

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Exercise has become an important part of cancer rehabilitation as the incidence of breast cancer is increasing and the mortality rate is decreasing. Breast cancer chemotherapy treatment induces a physical demand on the body while exercise counter balances symptoms of chemotherapy treatment. The purpose of this investigation was to determine the effects an exercise intervention has on breast cancer survivors who have received a single chemotherapy drug versus combination chemotherapy drugs. A secondary purpose was to determine any differences in chemotherapy categories. Participants were chosen that had single drug treatment (n = 34) and combination drug treatment (n = 20). Groups completed a pre-physiological assessment followed by an exercise intervention. Following the exercise intervention, a post-assessment was obtained. The protocol for all assessments was the same for all breast cancer survivors, but each exercise intervention was individualized. Within single and combination chemotherapy groups pre- to post-assessment, results showed significant improvement ($P<0.05$) in pulmonary function [FVC% - Single – change (2.04%) and Combination – change (5.66%)] and [FEV_1% - Single – change (3.87%) and Combination – change (6.60%)], chest press [Single – change (6.50%) and Combination – change (6.50%)], lat pulldown [Single – change (9.70%) and Combination – change (6.90%)], shoulder press [Single – change (9.20%) and Combination – change (9.75%)], and sit-and-reach [Single – change (0.40%) and Combination – change (0.55%)]. Resting heart rate was

significantly ($P<0.05$) improved only in the combination group – change (-6.60%). The data suggest that exercise is beneficial for breast cancer survivors whether on a single chemotherapy drug or on a combination of multiple chemotherapy drugs. Additionally, no significant differences were found between chemotherapy categories or the interaction between therapy and drug categories.

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INTRODUCTION

Breast cancer is the most common cancer among women, accounting for roughly 1 in 4 cancers diagnosed in women in the United States, with the exception of skin cancer. (Breast Cancer Facts & Figures, 2009-1010) Since 1990, women in the United States under the age of 50 have shown a drop in death rates of 3.2% per year and those 50 and older have shown a drop of 2% per year. (Cancer Facts and Figures, 2010) In addition, from 1999-2005, the incidence of female breast cancer has declined 2.2% per year, after incessantly increasing for over two decades. (Cancer Facts & Figures, 2010) Risk factors include age, gender, family history, postmenopausal obesity, alcohol consumption, physically inactive, and the use of combined estrogen and progestin menopausal hormones. (Breast Cancer Facts & Figures, 2009-2010)

Chemotherapy treatments with single-agent, sequential single-agent, and combination chemotherapy regimens have had a significant physiological and psychological impact on breast cancer survivors. In a review by Cardoso, Bedard, Winer, Pagani, Senkus-Konefka, Fallowfield, et al. (2009), it was suggested that there is an improvement in overall survival rate ($P<0.001$) with combination versus single-agent chemotherapy in metastatic breast cancer. Francis, Crown, Di Leo, Buyse, Balil, Andersson, et al. (2008) found that the use of sequential chemotherapy treatment was better in disease-free survival compared to concurrent chemotherapy treatment. Carlson & Telli, (2009) suggested that while combination chemotherapy is associated with greater toxicity than with sequential chemotherapy, sequential chemotherapy is the preferred approach for most patients. Mauri, Polyzos, Salanti, Pavlidis, and Ioanndis (2008) found

that anthracycline regimens compared with single-agent chemotherapy with nonanthracycline drugs had a 22-33% relative risk reduction in mortality. Jones (2008) suggested superior survival outcomes with taxane-based regimens, nonanthracyclines, and trastuzumab. In a study by Miles, von Minckwitz, and Seidman (2002), combination versus sequential chemotherapy was found to show significant ($P<0.05$) improvement in response rate, median time to progression, and median overall survival. However, there has not been enough evidence to establish a universal consensus on which chemotherapy treatment regimen is the most effective.

Exercise interventions used in cancer rehabilitation settings have had a physiological impact on breast cancer survivors. In a review by Spence, Heesch, and Brown (2009), improvements were found in physical performance ($P<0.05$) and walking ($P<0.01$). Vallance, Plotnikoff, Karvinen, Mackey, and Courneya (2010) found that breast cancer survivors who met the physical activity guidelines at baseline ($P<0.001$) and post intervention ($P<0.001$), had a greater likelihood of meeting the physical activity guidelines at 6 months follow-up. Sprod, Hsieh, Hayward, and Schneider (2010) found significant ($P<0.05$) improvements in cardiovascular endurance in breast cancer survivors undergoing 3- and 6-month individualized exercise interventions. Additional improvements ($P<0.05$) were shown for breast cancer survivors exercising for 6-months in pulmonary function and muscular endurance.

Exercise has also been found to reduce many of the psychological side effects associated with breast cancer. Blanchard, Courneya, and Laing (2001) found that acute exercise was an effective intervention in reducing ($P<0.03$) the state anxiety in breast cancer survivors. Brown et al. (2009) found improvements in quality of life and fatigue,

while Vallance et al. (2010) found significant improvements in physical activity behavior ($P<0.001$), psychosocial functioning ($P<0.001$), and motivation ($P<0.001$), and Sprod et al. (2010) found significant ($P<0.05$) improvements in fatigue and symptoms of depression.

The combination of chemotherapy and exercise treatment with breast cancer survivors has a significant impact on physiological and psychological parameters and side effects. However, more information is needed regarding chemotherapy regimens, chemotherapy categories, and exercise to determine any significant effects on breast cancer. Additionally it is necessary to establish whether one chemotherapy treatment regimen is better in regards to the outcomes of exercise assessments.

Statement of Purpose

The purpose of this research was to determine the differences in physiological parameters following an exercise intervention in female breast cancer survivors on a single chemotherapy drug versus combination chemotherapy drugs. A secondary purpose was to determine any differences in chemotherapy categories.

Research Hypotheses

H1: The main hypothesis for this investigation was that breast cancer survivors receiving single-agent and sequential single-agent chemotherapy treatment would show significantly greater results in physiological parameters measured in pre- and post-exercise assessments compared to breast cancer survivors receiving combination chemotherapy.

H2: The chemotherapy categories will show significant differences in physiological parameters.

H3: Exercise will enhance performance pre- to post-exercise intervention.

Assumptions

This study was conducted under the assumption that participants did not engage in activities other than those exercises performed under the supervision of a cancer exercise rehabilitation specialist at the Rocky Mountain Cancer Rehabilitation Institute.

Limitations

There were several limitations with this study. First, the breast cancer survivors weren't all at the same stage of recovery. The exercise intervention was individualized and therefore clients did not perform the same exercises.

Significance of the Study

The relationship between single-agent, sequential single-agent, and combination chemotherapy treatment with female breast cancer survivors and overall survival, progression-free survival, disease-free survival, and time to treatment failure has been established (Biganzoli et al., 2002; Chan et al., 1999; Citron et al., 2003; Forbes et al., (2008); Henderson et al., 2003; Jones et al., 2006; Jones et al., 2005; Mamounas et al., 2005; Marty et al., 2005; Miller et al., 2007; Nabholtz et al., 2003; Paridaens et al., 2000; Piccart-Gebhart et al., 2006; Robert et al., 2006; Seidman et al., 2008; Slamon et al., 2001; Sledge et al., 2003; Sparano et al., 2008). The physiological benefits of an exercise intervention for female breast cancer survivors receiving chemotherapy treatment have also been established (Campbell et al., 2005; Courneya et al., 2003; Drouin et al., 2006; Hsieh et al., 2008; Kolden et al., 2002; Matthews et al., 2007; Mock et al., 2004; Mutrie et al., 2007; Nikander et al., 2007; Pinto et al., 2003; Schneider et al., 2007).

However, no research has been found that determines the physiological differences in response to single-agent, sequential single-agent, and combination chemotherapy treatment or determining if differences exist between categories of chemotherapy drugs. Therefore, this study was designed to determine the physiological alterations that occur with exercise in breast cancer survivors who received varying regimens and categories of chemotherapy drugs.

Definition of Terms

Adenocarcinoma (AC). A cancer histotype that originates in glandular tissue – the part of an epithelial tissue which includes skin, glands, and other tissues that line the organ/body's cavities.

Adjuvant setting. Additional treatment given after surgery.

Apoptosis. Digestion by phagocytes of cell fragments from destroyed cells.

Anaphase. Third stage of mitosis in which a full set of daughter chromosomes move toward each pole of a cell.

Anaplasia. A reversion of differentiation in cells and is characteristic of malignant tumors.

Antineoplastics. Drugs that inhibit neoplasms.

Arthralgias. Joint pain due to injury, infection, illnesses, or allergic reaction to medication.

Axillary lymph nodes. Small oval-shaped organs of the immune system located in the armpit region of the body.

Biopsy-confirmed hyperplasia. The increase of cells especially atypical hyperplasia.

Bone marrow. Soft substance inside bones.

Cachexia. Weight loss.

Cell proliferation. Rapid cell reproduction.

Chemotherapy. Administration of cytotoxic chemicals to destroy malignant tumor cells.

Comorbidity. The appearance of multiple illnesses.

Cytokinesis. The division of cytoplasm that occurs after the cell nucleus has divided.

DNA (deoxyribonucleic acid). A nucleic acid found in all living cells; it carries the organism's hereditary information.

Drop Foot. Deficiency in dorsiflexion of the ankle and toes.

Dyspnea. Shortness of breath.

Filgrastim. A granulocyte colony-stimulating factor (G-CSF) analog used to stimulate the proliferation and differentiation of granulocytes.

Forced Expiratory Volume (FEV1). Is the volume of air exhaled in the first second after maximal inhalation.

Forced Vital Capacity (FVC). The maximal amount of air a person can expel from the lungs after a maximum inspiration.

Genome. Entirety of an organism's heredity.

Granulocytopenia. Neutrophil deficiency that reduces fight against infection, basophils, and eosinophils.

Hematopoietic. Blood cell component formation.

High breast tissue density. A mammographic measure of the amount of glandular tissue relative to fatty tissue in the breast.

High bone mineral density. A routinely measured to identify women at increased risk for osteoporosis.

Hyperplasia. An enlargement caused by increased cells.

Kinase. An enzyme that transfers phosphate groups from high-energy donor molecules to specific substrates.

Leucopenia. Low white blood cell count.

Lymphatic system. Vessels transporting lymph.

Lymphedema. Swelling of subcutaneous tissues caused by obstruction of lymphatic drainage.

Lymphocytes. Type of white blood cells.

Malignant tumor. An invasive tumor that has the competence to form metastic colonies.

Mammogram. An x-ray of the breast.

Mastectomy. Surgical breast cancer treatment involving the removal of the breast tissue while leaving the skin, nipple, pectoral muscles and lymph nodes.

Melanocytes. Malignant pigment-producing cells.

Metaphase. Second stage of mitosis.

Metastasis. The manifestation of a malignancy in a secondary growth in a new location arising from the primary growth.

Mitosis. Process during which the chromosomes are redistributed to two daughter nuclei; nuclear division. Consists of prophase, metaphase, anaphase, and telophase.

Myalgias. Muscle pain from diseases and disorders.

Nadir. Low blood counts.

Necrosis. Cell death.

Neurons. Nerve cell.

Peripheral neuropathy. Nerve damage caused by injuries, infections, metabolic problems and exposure to toxins.

Prophase. The first stage of mitosis, consisting of coiling of the chromosomes accompanied by migration of the two daughter centrioles toward the poles of the cell, and nuclear membrane breakdown.

Radiation. The process by which ionization displaces an electron form the nucleus of an atom, resulting in an unstable atom, followed by the free atom being accepted by another atom, thus becoming unstable.

RNA (ribonucleic acid). Nucleic acid that contains ribose and the bases A, G, C, and U. Carries out DNA's instructions for protein synthesis.

Sequential chemotherapy. Chemotherapy in which several agents are administered one at a time rather than concurrently to optimize dosage and increase patient tolerance.

Tachypnea. Rapid breathing.

Telophase. The final phase of mitosis; begins when migration of chromosomes to the poles of the cell has been completed and ends with the formation of two daughter nuclei.

Topoisomerase. Enzyme that unwind and wind DNA.

CHAPTER II

REVIEW OF LITERATURE

Introduction

Cancer is a disease characterized by an abnormal regulation of cell growth and reproduction that has the capability of metastasizing throughout the body. (Brooks, Fahey, & Baldwin, 2005; Marieb & Hoehn 2007; Schneider, Dennehy, & Carter, 2003) A number of factors need to be considered regarding the cause for cancer. External factors are preventative determinants such as tobacco, infectious organisms, chemicals, smoke, fumes, and radiation. On the other hand, internal factors consist of inherited mutations, hormones, immune conditions, and mutations arising from metabolic processes, which are all influential determinants of cancer. (Cancer Facts & Figures, 2009)

Cancer Incidence

Approximately 77% of all cancers are diagnosed in persons 55 years of age and older, yet anyone at anytime can be susceptible to cancer. (Cancer Facts & Figures, 2009) The good news is that, according to The National Cancer Institute, approximately 11.1 million Americans with a history of cancer were alive in 2005 and the number of cancer survivors is steadily increasing. According to Cancer Facts and Figures (2009), approximately 1,479,350 new cases of cancer are expected in the United States.

Cancer is often referred and classified as benign or malignant tumors. Tumors are an abnormal growth of cells caused by abnormal regulation of cell division. Benign tumors grow slowly and rarely cause death but are capable of

damaging adjacent areas. Unlike malignant tumors, benign tumors don't possess the destructive potential and are well differentiated and well organized. (Brooks et al., 2005; Schneider et al., 2003)

On the other hand, malignant tumors contain cancer cells and are very unpredictable and unsettled in terms of organization compared to normal cells. These tumors consist of a widely assorted arrangement of cells, cells with loss of differentiation, anomalous (irregular) mitotic characteristics, increased invasiveness throughout the body (metastasis), and a decreased sensitivity to drug exposure. (Schneider et al., 2003) Malignant tumors are commonly susceptible to metastasizing, where a secondary tumor from it's original origin develops but its location resides in another tissue elsewhere in the body. (Marieb & Hoehn, 2007; Schneider et al., 2003) The process of metastasis arises due to the release of attached tumor cells from the primary tumor, allowing entry into the circulation or lymphatic system. (Marieb & Hoehn, 2007; Schneider et al., 2003) Next, the sub-endothelial basement membrane of the distant tissue has the tumor cells adhere to it and the entrance into new tissue is then permitted and proliferation and reproduction of new cells form in the new tissue. Malignant tumors are also designed to pursue aggressive cell proliferation, affect normal tissue and eventually terminate the host tissue. (Brooks et al. 2005; Schneider et al., 2003) Malignant tumors are of a disproportionate form and contain considerable amounts of necrotic areas because of the compromised blood flow supply and lack of apoptosis. (Schneider et al., 2003) The understanding of how a normal cell develops must first be established in order to understand how cancer develops.

Cell Division and Carcinogenesis

A normal cell in the body consists of two major parts, the nucleus and the cytoplasm. The nucleus is the control center where chemical reactions and reproduction of the cell are orchestrated. Vast quantities of deoxyribonucleic acid molecules (DNA) called genes, reside in the nucleus of the cell. Genes control the heredity passed on from parents to children. (Marieb & Hoehn, 2007) The body contains somatic cells that can sustain trauma, disease, or damage to the cell. The body is also capable of reproducing new cells in order to replace the compromised cells. In addition, there is a large amount of cell reproduction that continuously occurs in places like bone marrow and skin. Conversely, neurons and striated muscle cells either have infrequent or no reproduction of new cells. The normal cell growth and division consists of a cell cycle, which involves two phases, the interphase and cell division (mitosis or M phase). (Schneider et al., 2003) The interphase is the period beginning from cell formation to cell division consisting of 90% of the cell cycle. Cell division is vital to the body's growth and repairing of tissue and in most body cells consists of two events, mitosis and cytokinesis. (Marieb & Hoehn, 2007) Mitosis consists of a number of eloquent events where two daughter cells develop from the mother cell. This goes into four phases involving the prophase, metaphase, anaphase, and telophase where all of the phase's transition into the other at a continuous rate and the duration varies according to the type of cell. (Marieb, & Hoehn, 2007) Cytokinesis, starts at a later time during the anaphase, and is finished after the mitosis phase ends. The body's cells contain pairs of chromosomes. Within these pairs of chromosomes are genes made up of DNA molecules. These genes are

responsible and considered the backbone for the creation of life through sending messages to the chromosomes periodically instructing the body's process of growth and function. However, this isn't always the case and unfortunately errors arise and pose threats to reproduction. The body is capable of repairing some of the errors yet, if they occur while in the stages of cell division, the cell's genes can be compromised causing mutations. This destructive shift can ultimately cause an abnormality among the chromosome within the cancer cell and the cancer then starts to develop as the abnormal chromosome begins to reproduce. (Schneider et al., 2003)

Carcinogenesis, which is defined as the steps in converting a normal cell into a cancerous cell, is suggested to occur in two stages (initiation and promotion) with the branching of substages. (Schneider et al., 2003) The effects carcinogens have on the chromosomes components during the pre-initiation stage are protected. During the first stage, which is the initiation phase, a carcinogen attacks a normal cell within the genome of the cell, and the consequential mutated cell resorts to uncontrolled cell division. (Cowan & Talaro, 2009; Schneider et al., 2003) Therefore, causing an alteration or destruction among the DNA molecules of the cell or inhibition and ultimately complete failure of the cell's DNA repair system. (Cowan & Talaro, 2009; Schneider et al., 2003) However, an accumulation of up to ten mutations may have to occur in order for a cell to become cancerous. (Schneider et al., 2003) The DNA mutation is expressed as soon as the division of the cell takes place and the second stage (promotion) is then initiated. (Schneider et al., 2003) Unrestrained cell division, along with the promotion of tumor development begins and the cell genetic information can be expressed or repressed. (Cowan & Talaro, 2009; Schneider et al.,

2003) In the repressed state of a mutated gene, a normal function can take place but the potential of expression is always in consideration. Cancer cells can reproduce at any pace and the formation of tumors is the result. These tumors then form throughout the body's tissues and organs where a classification for the actual cancer is then established. (Schneider et al., 2003)

Characteristics of Cancer Cells

There are a number of types of cancer, where tumors are named according to the invaded tissue or organ within the body and the level of cell differentiation. Specifically, there are five classes of cancer types and each has a very extensive background. Carcinomas are tumors that originate in the epithelial cells (lining of all tissues). (Saladin, 2010; Schneider et al., 2003) Melanomas are malignant tumors of melanocytes that are commonly on the skin, but can be seen throughout the body. Sarcomas are solid tumors that originate in connective tissue, bone, muscle, cartilage, or fat. Leukemia is a cancer of the blood or bone marrow due to abnormal white blood cell (leukocyte) proliferation. (Saladin, 2010; Schneider et al., 2003) Lastly, lymphomas are malignant cancers of the lymphocytes resulting in an amplification of lymph glands as well as other organs where the development of lymphocytes normally occurs. (Saladin, 2010; Schneider et al., 2003)

Grading and Staging of Cancer Cells

The grading of tumors is established according to the tumor cells microscopic appearance. This presents the level of undifferentiation (anaplasia) that exists within the cells, where the less the cells are differentiated, the more malignant the cancer. (Schneider et al., 2003) There are four classes of grading starting with grade I (low-

grade) to grade IV (highest grade) when identifying the state of a tumor cell. A grade I tumor cell is identified as a tumor with cells that are well differentiated, resemble normal cells, are slow growing, and not very aggressive. Grades II and III tumors have a moderate and poor status of differentiated cells. Grade IV tumors are poorly differentiated, their cells are immature in nature, they complicate the pinpointing of origin location within the tissue, are fast growing, and extremely aggressive.

The term TNM Staging (tumor, nodes, metastasis) in cancer research is widely used for clinical and pathological purposes in determining the cancer's extent and progression. (Schneider et al., 2003) In order to determine the proper therapy for a cancer patient, the cancer's anatomic status and extent must be established. Through the use of TNM Staging, the higher the stage, the more the progression of the cancer. The TNM Stage is categorized by the following: the letter (T) represents the local tumors size, (N) represents the spread of the cancer to regional lymph nodes, and (M) represents the presence or absence of distant metastasis. (Schneider et al., 2003) According to Schneider et al. (2003), the TNM System has four stages recognized within it involving the following:

- Stage I signifies a mass limited to the organ of origin, no lymph node involvement, and no metastasis.
- Stage II signifies that the original tumor has spread into immediate surrounding tissue and there is some lymph node involvement.

- Stage III signifies that tumors show an extensive primary lesion with fixation to deeper structures, and lymph nodes exhibit malignant invasion.
- Stage IV signifies that distant metastases beyond the local site of the primary tumor are evident.

Table 1 below displays the staging of the tumor; it's size, lymph node involvement, and whether there is metastasis.

Table 1. Basic Staging of the TNM System (Schneider et al., 2003)

Tumor Stage	Tumor Size	Lymph nodes?	Metastasis
I	<2 cm	None	None
II	2-5 cm	No, or yes on same side	None
III	>5 cm	Yes on same side	None
IV	Does not matter	Does not matter	Yes

Breast Cancer

Breast cancer is an uncontrolled growth of breast cells, as a result of mutations, or abnormal changes in the genes responsible for regulating the growth of cells. (Schneider et al., 2003) There are two main types of breast cancer, first, a ductal carcinoma, which forms in the tubes (ducts) and transports milk from the breast to the nipple. The second type, lobular carcinoma, forms in the lobules of the breast where milk is formed. It has been suggested that over 95% of breast cancers originate from the epithelial elements of the mammary gland and are adenocarcinomas. (Manton, Akushevich, & Kravchenko, 2009) In 2009, the United States had 192,370 new cases of breast cancer in women and 1,910 in men. Deaths are projected at 40,170 females and 440 males. (Cancer Facts & Figures, 2009) According to Cancer Facts & Figures (2009), breast cancer with the exception of skin

cancers, is the most commonly diagnosed cancer among women in the United States. Breast cancer is ranked as the second leading cause of death among women second to lung cancer. However, from 1999-2005, incidences of female breast cancer have declined 2.2% per year, after increasing for over two decades. In addition, since 1990 women under the age of 50 have shown a drop in death rates of 3.2% per year, and those 50 and older a drop of 2% per year. (Cancer Facts & Figures, 2009) According to Cancer Facts and Figures (2009), this decrease is due to the reduction in the use of menopausal hormone therapy (MHT), formerly known as hormone replacement therapy. This is due to the publication of results from the Women's Health Initiative in 2002, which associated MHT use to the increase of breast cancer and heart disease.

Risk factors for breast cancer consist of age, family or personal history (inherited genetic mutations in the breast), overweight or obesity after menopause, the use of MHT (especially combined with estrogen and progestin therapy), physical inactivity, smoking, and consumption of one or more alcoholic beverages per day. (Cancer Facts & Figures, 2009; Marieb & Hoehn, 2007; Martini & Bartholomew, 2007; Saladin, 2010) In addition to these risk factors, there are other factors considered to increase the risk for breast cancer. These involve high breast tissue density, high bone mineral density, biopsy-confirmed hyperplasia, and high-dose radiation to the chest, typically related to a medical procedure. (Saladin, 2010; Cancer Facts & Figures, 2009)

Categories and Staging of Breast Cancer

The detection of breast cancer is typically seen on a mammogram in an early abnormal state, even before the possibility of it being physically felt by the woman or health care professional. There are two types of mammograms that are available. The first being a screening mammogram which is used to check for breast cancer in women who have no signs or symptoms of the disease, and second a diagnostic mammogram which is used to check for breast cancer after a lump or other sign or symptom of the disease has been found. (Saladin, 2010; www.radiologyinfo.org) In the case of a large tumor, the mass may be painless to the person in benign conditions. (Cancer Facts & Figures, 2009) Less common symptoms involve continual change in the breast, such as thickening, swelling, distortion, tenderness, skin irritation, redness, or scaliness, or nipple abnormalities, such as ulceration, retraction, or spontaneous discharge. (Saladin, 2010; Cancer Facts & Figures, 2009) Table 2 describes the stage of breast cancer beginning with lowest, Stage 0 to the highest, Stage IV, and a description of each stage. (www.breastcancer.org)

Table 2. Breast Cancer Stages (www.breastcancer.org)	
Stage	Definition
0	Cancer cells remain inside the breast duct, without invasion into normal adjacent breast tissue.
I	Cancer is 2 centimeters or less and is confined to the breast (lymph nodes are clear).
IIA	No tumor can be found in the breast, but cancer cells are found in axillary lymph nodes (the lymph nodes under the arm) OR the tumor measures 2 centimeters or smaller and has spread to the axillary lymph nodes OR the tumor is larger than 2 but no larger than 5 centimeters and has not spread to the axillary lymph nodes.
IIB	The tumor is larger than 2 but no larger than 5 centimeters and has spread to the axillary lymph nodes OR the tumor is larger than 5 centimeters but has not spread to the axillary lymph nodes.
IIIA	No tumor is found in the breast. Cancer is found in axillary lymph nodes that are sticking together or to other structures, or cancer may be found in lymph nodes near the breastbone OR the tumor is any size. Cancer has spread to the axillary lymph nodes, which are sticking together or to other structures, or cancer may be found in lymph nodes near the breastbone.
IIIB	The tumor may be any size and has spread to the chest wall and/or skin of the breast AND may have spread to axillary lymph nodes that are clumped together or sticking to other structures, or inflammatory breast cancer is considered at least Stage IIIB.
IIIC	There may either be no sign of cancer in the breast or a tumor may be any size and may have spread to the chest wall and/or the skin of the breast AND the cancer has spread to lymph nodes either above or below the collarbone AND the cancer may have spread to axillary lymph nodes or to lymph nodes near the breastbone.
IV	The cancer has spread – or metastasized – to other parts of the body.

Chemotherapy Treatment and Breast Cancer

Chemotherapy, also known as anti-cancer and antineoplastics, for it's use in cancer treatment began in the 1940's with the use of nitrogen mustard therapy. Dougherty, Gilman, Goodman, and Lindskog (1942-1943) first established nitrogen mustard therapy as a cancer treatment however, there were no published studies because of wartime military security considerations. Chemotherapy is designed and used for curing a specific cancer; controlling tumor growth; tumor shrinkage before

surgery or radiation therapy; and destroying cancer cells of microscopic proportion that may be present after the known tumor is removed by surgery (adjuvant therapy for preventing recurrence). The ultimate goal is to destroy the entirety of the tumor cells with very little damage to the normal cells along with limiting destructive effects on a normal cells function. However, it is very difficult to narrow down specifications among cells because of the large similarities involved with a normal cell and a cancer cell. Chemotherapy's antineoplastic effects are most distinctive throughout the proliferation phases of the cell cycle and these effects jeopardize the malignant cells growth potential. (Schneider et al., 2003) Therefore, due to the higher amount of proliferation among cancer cells versus normal cells, a higher percentage of cancer cells are destroyed compared to normal cells with chemotherapy drugs. (Schneider et al., 2003)

There are two major classes of antineoplastic agents with chemotherapy that are classified according to their structure or cell cycle activity. They are cell cycle phase-specific agents and cell cycle phase-nonspecific agents. (Barton-Burke, Wilkes, & Ingwerson, 2001) Cell cycle phase-specific agents are designed to destroy proliferating cells that reside in only the specific phase of the cell cycle (phases G_1 through M). (Brown, 1987) Cell cycle phase-nonspecific agents are designed not to depend on the cell cycle's phase to be active. (Barton-Burke et al., 2001) In addition, chemotherapy drugs are categorized based on their function and the cancer destruction process. For this investigation, the following chemotherapy categories in Table 3 are the most common in breast cancer survivors at Rocky Mountain Cancer

Rehabilitation Institute. (Delgin & Vallerand, 2009; Schneider et al. 2003; www.chemocare.com)

Table 3. Chemotherapy Categories	
Alkaloids	Designed to prevent cell duplication by interrupting the formation of chromosomes.
Alkylating Agents	Designed to attack all cells in a tumor, whether they are reproducing or not by binding with the DNA in the cells to prevent reproduction.
Antimetabolites	Designed to attack the cells during cell division. These chemotherapy drugs imitate normal cell nutrients so the cell consumes the drug but eventually starves to death.
Antitumor Antibiotics	Designed to insert into strands of DNA, either breaking the chromosomes or inhibiting the synthesis of RNA, which plays an important role in synthesis within cells.
Anthracyclines	Designed to insert into strands of DNA, either breaking the chromosomes or inhibiting the synthesis of RNA, which plays an important role in synthesis within cells. Forms free-oxygen radicals that destroy DNA and cell membranes.
Aromatase Inhibitors	Designed to synthesize estrogen during treatment for breast and ovarian cancer in postmenopausal women.
Estrogen Inhibitors	Inhibits topoisomerase and kinase, and interferes with DNA transcription, replication, and function to prevent DNA super coiling.
Monoclonal Antibodies	Designed to bind only to cancer cell-specific antigens and induce an immunological response against the target cancer cell.
Progestin	Designed to mirror progestinic effects of progesterone.
Taxanes	Interrupt interphase and mitosis.

The use of a single chemotherapy drug is effective throughout cancer treatment however; the usage of a mixture (cocktail) of chemotherapy drugs appears to be more effective. (Schneider et al., 2003) The benefits include paramount cell

tissue death, where the normal tissue has a higher tolerance of the drugs due to the lower dosage being used. (Schneider et al., 2003) Another benefit consists of an expanded realm of drug exposure to the wide assortment of resilient cells. (Schneider et al., 2003) Yet another benefit consists of a gradual decrement of development among cancer cells that are resilient to specific treatments during the therapy process. (Schneider et al., 2003**)**

Single-agent chemotherapy is the use of one chemotherapy drug throughout the whole treatment process, while sequential single-agent chemotherapy is the use of one chemotherapy drug for a period, then switching to a different chemotherapy drug for another period, and may continue on with other drugs. However, combination chemotherapy treatment uses two or more chemotherapy drugs at one time throughout the duration of treatment. Waterhouse, Gelmon, Klasa, Chi, Huntsman, Ramsay et al. (2006) suggest that the design of combined chemotherapy drugs should contain the development of certain principles consisting of the following:

1. Each agent in the combination has proven activity as a single agent.
2. Each drug should have a different mechanism of action such that the combination is additive or synergistic.
3. Toxicities, particularly those that are dose limiting, should not overlap in order to give the full therapeutic dose of each drug.
4. The best schedule developed for each drug should also be used in the combination, optimizing the timing of each dosing and minimizing the time between doses.
5. Resistance mechanisms for each drug should be non-overlapping.

However, combined chemotherapy is still under continual refinement in the adjuvant setting for breast cancer and treatments vary by the extent of the disease. (Waterhouse et al., 2006) In addition, there are a number of patient disease-related factors to consider when determining whether sequential or combination chemotherapy treatment is going to be used. Cardoso et al. (2009), suggest that these factors consist of the following in Table 4 below.

Table 4. Factors to Consider When Choosing Single or Combination Chemotherapy

Patient related	Disease related
Menopausal status	Endocrine responsiveness
Biological age and comorbidities (including organ dysfunction)	HER2 status
Performance status and adverse effects of prior therapy	Disease-free interval
Socioeconomic and psychological factors	Previous therapies and response obtained
Patient preference	Tumor burden (defined as number and site of metastases)
Available therapies in the patient's country	Need for rapid disease and/or symptom control

A significant factor to take into consideration when making the selection of an appropriate therapeutic strategy in the metastatic setting is the differences in tumor biology. (Telli & Carlson, 2009) Not only has single and combination chemotherapy treatment been effective, but also the use of a sequential single-agent chemotherapy treatment has been suggested to be even more effective than combination chemotherapy treatment. (Cardoso et al., 2009) However, many studies comparing combination chemotherapy treatments to single-agent therapy have been limited by the lack of sequential treatment comparisons. (Telli & Carlson, 2009) Tellie & Carlson (2009) also suggest that in metastatic breast cancer there are many actively

used single-agent chemotherapeutic agents, with the majority of the data favoring an anthracycline- or taxane-based approach.

According to NCCN Clinical Practice Guidelines in Oncology (2010), in the situation of recurrent or metastatic breast cancer, anthracyclines are considered the most influential chemotherapy agent in terms of efficacy in breast cancer and are extensively used in the adjuvant treatment of early-staged breast cancer. Taxanes (Paclitaxel & Docetaxel) along with anti-metabolites are also preferred categories for single-agent use. (NCCN Clinical Practice Guidelines in Oncology, 2010) For the sake of this investigation, the most effective anthracycline drug suggested for metastatic breast cancer treatment is doxorubicin (adriamycin). (NCCN Clinical Practice Guidelines in Oncology, 2010; Telli & Carlson, 2009)

Table 5 displays the preferred single-agents and chemotherapy combinations in an adjuvant chemotherapy setting and for recurrent or metastatic breast cancer, according to NCCN Clinical Practice Guidelines in Oncology, (2010). For the sake of this investigation, the chemotherapy single-agents and combinations will only consist of drugs used with the breast cancer survivors from RMCRI.

Table 5. Preferred Chemotherapy Regimens in the Adjuvant and Recurrent or Metastatic Breast Cancer Setting. (NCCN Clincial Practice Guidelines in Oncology, 2010)	
Adjuvant Chemotherapy	
Non-Trastuzumab	-TAC (docetaxel/doxorubicin/cyclophosphamide) -Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks -AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel -TC (docetaxel and cyclophosphamide) -AC (doxorubicin/cyclophosphamide)
Trastuzumab	-AC followed by T+ concurrent trastuzumab (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules) -TCH (docetaxel, carboplatin, trastuzumab) -AC followed by docetaxel + trastuzumab
Other Adjuvant Regimens	-AC followed by docetaxel every 3 weeks -A followed by T followed by C (doxorubicin followed by paclitaxel followed by cyclophophamide) every 2 weekly regimen with filgrastim support
Recurrent or Metastatic Breast Cancer	
Single Agents	-Doxorubicin (Adriamycin) -Paclitaxel -Docetaxel -Cyclophosphamide
Agents with Bevacizumab	-Paclitaxel
Chemotherapy Combinations	-AC (doxorubicin/cyclophosphamide) -AT (doxorubicin/docetaxel; doxorubicin/paclitaxel)
First-Line Agents for HER2-Positive Disease	-Trastuzumab + paclitaxel ± carboplatin -Trastuzumab + docetaxel

NCCN Clinicial Practice Guidelines in Oncology (2010) recommends preferred dosages with other chemotherapy drugs and regimens used. The selection, administration, and modification of these regimens are far too extensive for the sake of this investigation and will not be discussed. The intervention involved with each agent and combination for an individual is based on expected toxicities, prior

treatment, patient individuality, and comorbidity. These regimens have been modified over time and used in an effective manner and have shown better outcomes for breast cancer survivors. The following studies suggest evidence for overall survival, time to treatment failure, disease-free survival, and progression-free survival in regards to single-agent, sequential-single agent, and combination chemotherapy regimens used with breast cancer survivors.

Single-Agent vs. Single-Agent Chemotherapy

Sparano et al. (2008) found that the estimated 5-year survival rates were 76.9% for the group receiving paclitaxel every 3 weeks, 81.5% for the group receiving docetaxel every 3 weeks, and 77.6% for the group receiving weekly docetaxel. In comparison to the paclitaxel every 3 weeks group, there was a significantly better disease-free survival in the group receiving weekly paclitaxel (P=0.006), and in the group receiving docetaxel every 3 weeks (P=0.02), but not in the group receiving weekly docetaxel (P=0.29). Sparano et al. (2008) also found that the estimated overall 5-year survival rates were 86.5% for the every 3 weeks paclitaxel group, 89.7% for the weekly paclitaxel group, and 87.3% for the every 3 weeks docetaxel group. The overall survival was significantly better in the weekly paclitaxel group (P=0.01) compared to the every 3 weeks paclitaxel group, but not in the groups receiving docetaxel every 3 weeks (P=0.25) or weekly docetaxel (P=0.80).

Seidman et al. (2008) found that the median time to cancer progression for patients receiving weekly paclitaxel was prolonged by 4 months (9 vs. 5 months; P<0.0001), and the addition of trastuzumab to paclitaxel in patients with HER2-2-normal breast cancer was not associated with significantly longer time to progression

(7 vs. 6 months; P=0.28). The adjustment of the line of therapy for the 3-weekly to weekly paclitaxel showed a significant impact to the overall survival (P=0.009), but the addition of trastuzumab did not have a significant impact on overall survival.

Forbes et al. (2008) found that over a 5-year adjuvant treatment period, the time to recurrence was significantly lower for the arimidex group (P=0.002) compared to the tamoxifen group, and at the 5 year mark, the arimidex group was at a significantly lower risk (P=0.0001) than the tamoxifen group. However, there were no differences noted in the overall survival with either group.

Piccart-Gebhart et al. (2006) found that disease-free survival was significantly greater (85.8%) with the trastuzumab group compared to (77.4%) with the observational (control) group (P<0.0001), and there was no significance between the groups regarding the overall survival.

Jones et al. (2005) found that the median time to progression was significantly longer in the docetaxel every 3 weeks group than in the paclitaxel every 3 weeks group (P<0.0001), and the median overall survival was significantly longer in the docetaxel group than in the paclitaxel group (P=0.03).

Paridaens et al. (2000) found that progression-free survival (during and/or after treatment) in first-line therapy was significantly longer for doxorubicin than for paclitaxel (median, 7.5 months vs. 3.9 months, respectively; P=0.0001). They also found that there was no significant difference in the overall survival between the two study arms (P=0.38), with a median survival of 18.3 months with the doxorubicin arm and 15.6 months with the paclitaxel arm.

Chan et al. (1999) found that the median time to treatment failure was significantly longer in the docetaxel group (22 weeks) than in the doxorubicin group (18 weeks) using the Wilcoxon test (repeated measures on a single sample) (P=0.01). They also found that the median overall survival was similar with both treatment groups (docetaxel, 15 months; doxorubicin, 14 months) with no significant difference.

The single-agent versus single-agent chemotherapy studies had conflicting results regarding significant differences in regimen and duration. Sparano et al. (2008) found that the groups who received paclitaxel and docetaxel every 3 weeks had a significantly longer duration of disease-free progression compared to the paclitaxel given weekly. On the other hand, Seidman et al. (2008) found that paclitaxel given weekly was significantly better in disease-free progression compared to the group receiving paclitaxel every 3 weeks. However, both studies found that the weekly paclitaxel group had a significantly longer overall survival period.

Similarly, Jones et al. (2005) and Chan et al. (1999) found that docetaxel given every 3 weeks produced significantly longer median times to progression, but Jones et al. (2005) found docetaxel also had a longer overall survival and Chan et al. (1999) found no significant difference in overall survival. However, Paridaens et al. (2000) found that doxorubicin given every 3rd week produced a significantly longer progression-free survival compared to the every 3rd week paclitaxel, but no significant differences in overall survival.

Forbes et al. (2008) found that arimidex produced significantly less time to recurrence compared to tamoxifen and no significant difference in overall survival.

While Piccart-Gebhart et al. (2006) found that trastuzumab produced a significantly higher disease-free survival compared to the observational group. Sparano et al. (2008), Seidman et al. (2008) and Jones et al. (2005) were the only studies that found a significant difference in overall survival.

Combination vs. Combination Chemotherapy

Jones et al. (2006) found that there was a significant increase in disease-free survival with the docetaxel + cyclophosphamide group (86%) compared to the doxorubicin + cyclophosphamide group (80%) (P=0.01), but no significant difference between the groups in overall survival.

Robert et al. (2006) found that the median progression-free survival was significantly longer in patients receiving trastuzumab + paclitaxel + carboplatin compared to the trastuzumab + paclitaxel group (P=0.005), and no statistical significance in overall survival rate.

Romond et al. (2005) found that the trastuzumab + doxorubicin + cyclophosphamide + paclitaxel group had a greater disease-free survival (87.1%) compared to the control group using doxorubicin + cyclophosphamide + paclitaxel (75.4%). However, there was a significantly greater overall survival with the trastuzumab group (62 deaths) compared to the control group (92 deaths) (P=0.01).

Nabholtz et al. (2003) found that the time to treatment failure was significantly longer with the docetaxel + doxorubicin group compared to the doxorubicin + cyclophosphamide group (median, 25.6 weeks vs. 23.7 weeks; respectively, P=0.04). Overall survival was not different between docetaxel +

doxorubicin and doxorubicin + cyclophosphamide (median, 22.5 vs. 21.7 months; respectively).

Henderson et al. (2003) found that there was a significantly greater disease-free survival rate with the paclitaxel + cyclophosphamide + doxorubicin group compared to the cyclophosphamide + doxorubicin group (P=0.002), and a significantly lower death rate for the paclitaxel group compared to the non-paclitaxel group (adjusted P=0.006; unadjusted P=0.009).

Biganzoli et al. (2002) found that the median progression-free survival was 6 months in the doxorubicin + paclitaxel and doxorubicin + cyclophosphamide arms, with no significant difference (P=0.65). They also found that the median overall survival was 20.6 months in the doxorubicin + paclitaxel group compared with doxorubicin + cyclophosphamide group (20.5 months) with no significant difference (P=0.49).

All of the studies found significant differences with combination versus combination chemotherapy except for Biganzoli et al. (2002). Jones et al. (2006) and Nabholtz et al. (2003) compared 2 regimens with only 2 drugs and had docetaxel in their regimen. They found significantly longer times to treatment failure, but neither found significant differences in overall survival.

Robert et al. (2006), Romond et al. (2005) and Henderson et al. (2003) compared three combined chemotherapy drugs with only two combined chemotherapy drugs in their studies and all had a significantly longer disease-free survival period compared with the regimens consisting of only two drugs. In addition Romond et al. (2005) and Henderson et al. (2003) had significantly longer

overall survival times with the three drug regimens compared to the two drug regimens with the exception of Robert et al. (2006). Biganzoli et al. (2002) found no significant differences with the comparison of two drug regimens.

Combination vs. Single-Agent Chemotherapy

Miller et al. (2007) found that combined chemotherapy (paclitaxel + bevacizumab) versus single-agent chemotherapy (paclitaxel) significantly increased the 1-year survival rate (81.2% vs. 73.4%, P=0.01) however; the median overall survival was similar between the two regimens paclitaxel (26.7 months) and paclitaxel + bevacizumab (25.2 months) (P=0.16). They also found that the combined chemotherapy significantly prolonged the progression-free survival compared to the single chemotherapy (P<0.001).

Marty et al. (2005) found that there was statistical significance in overall survival for trastuzumab + docetaxel (P=0.03) versus docetaxel alone, and the median time to treatment failure was significantly greater for combined chemotherapy (median, 9.8 vs. 5.3 months; P=0.0001) versus single-agent chemotherapy.

Mamounas et al. (2005) found that there was a significant reduction in the disease-free survival with the paclitaxel + doxorubicin + cyclophosphamide group by 17% compared to the doxorubicin + cyclophosphamide group (P=0.006), and there was no significant difference between the overall survival rate.

Citron et al. (2003) found that overall survival was significantly prolonged with dose-dense regimens (II and IV) (*P*=0.01), (II) Doxorubicin every 2 weeks for 4 cycles followed by paclitaxel every 2 weeks for 4 cycles followed by cyclophosphamide every 2 weeks for 4 cycles and (IV) Doxorubicin plus

cyclophosphamide every 2 weeks for 4 cycles followed by paclitaxel every 2 weeks for 4 cycles. They also found that disease-free survival was significantly prolonged with dose-dense regimens (II and IV) compared with the every 3-week regimen (*P*=0.01).

Sledge et al. (2003) found that overall survival had no significant differences with median survivals of 19.1 months (doxorubicin), 22.4 months (doxorubicin + paclitaxel), and 22.5 months (paclitaxel). However, the time to treatment failure was statistically significant with a longer median for doxorubicin + paclitaxel (8.2 months) compared to either single-agent doxorubicin (6 months) (*P*=0.002) or single-agent paclitaxel (6.3 months) (*P*=0.05).

Slamon et al. (2001) found that chemotherapy treatment (paclitaxel + doxorubicin + cyclophosphamide) combined with trastuzumab compared with chemotherapy treatment alone (paclitaxel + doxorubicin + cyclophosphamide) had a significantly longer time to treatment failure (median, 6.9 vs. 4.5 months; P<0.001), and a significantly longer median survival time 25.1 vs. 20.3 months (P=0.04).

There are conflicting results with the studies mentioned regarding single-agent and sequential single-agent versus combination chemotherapy regimens. Sledge et al. (2003) found that single agents doxorubicin and paclitaxel compared to doxorubicin and paclitaxel combined show significantly longer times to treatment failure, but no significance in overall survival. While Citron et al. (2003) found that sequential single-agent regimens given every 2 weeks show significantly longer overall survival and disease-free survival compared to sequential single-agent regimens given every 3 weeks.

Mamounas et al. (2005) and Slamon et al. (2001) found that 3 or more drugs involved with combination regimens given every 3 weeks show significant improvement in disease-free survival, while Slamon et al. (2001) found results suggesting a significantly longer overall median survival time.

Miller et al. (2007) and Marty et al. (2005) found that the two drug combination regimens significantly prolonged time to treatment failure and progression-free survival compared to single-agent treatment. Miller et al. (2007) found a significantly longer 1-year survival rate but not overall survival with the combination regimen. Marty et al. (2005) found significantly longer overall survival with the combination regimen.

Among all of the studies mentioned regarding single-agent, sequential single-agent, and combination chemotherapy treatment, the results show positive evidence for all treatment regimens at different times with different dosages. It has been shown that the treatment seems to be most effective for single-agent, sequential single-agent, and combination chemotherapy treatment in 3-week intervals (Chan et al., 1999; Henderson et al., 2003; Jones et al., 2006; Jones et al., 2005; Mamounas et al., 2005; Marty et al., 2005; Nabholtz et al., 2003; Paridaens et al., 2000; Robert et al., 2006; Slamon et al., 2001; Sledge et al., 2003; and Sparano et al., 2008). It has also been suggested that 4-week (Miller et al. 2007) and 2-week intervals (Citron et al. 2003), as well as weekly intervals (Seidman et al. 2008 and Sparano et al. 2008) have been effective.

In addition to the parameters found in the previous research many others such as toxicities, side effects, mental impairments, and physical impairments are generally addressed as detrimental factors placed on the body by chemotherapy.

Side Effects and Toxicities

There are substantial side effects with chemotherapy and this plays a significant role in everyday activities. The most common side effect with chemotherapy is fatigue (Byar, Berger, Bakken, & Cetak, 2006; De Jong, Courtens, Abu-Saad, & Schouten, 2002; Donovan, Jacobsen, Andrykowski, Winters, Balducci, Malik et al., 2004; Patrick, Ferketich, Fram, Harris, Hendricks, Levin et al., 2004) Fatigue is not a consistent symptom and may appear throughout the cancer treatment and even months after the treatment process. (Wu, Dodd, & Cho, 2008) Fatigue is a controversial symptom that hasn't been fully understood in regards to the mechanisms. (Wu et al., 2008) However, studies have shown significant improvement in fatigue with exercise. (Davidson et al., 2005; Hsieh, Sprod, Hydock, Carter, Hayward, & Schneider, 2008; Schneider, Hsieh, Sprod, Carter & Hayward, 2007; Schwartz, Mori, Gao, Nail, & King, 2001, and Wu et al., 2008)

Throughout the cancer therapy process whether it involves chemotherapy, hormonal therapy, radiation therapy, or surgery, there is extensive toxicity (side-effects) involved. Toxicities involved with therapy can occur in the cardiovascular, immune, pulmonary, gastrointestinal, musculoskeletal, neuroendocrine, and hepatic systems. (Schneider, Dennehy, Roozeboom, & Carter, 2002) Schneider et al. (2002) reported that radiation has acute and chronic effects on the cardiovascular systems involve the pericardium, myocardium, and coronary arteries. In addition,

chemotherapy agents specifically doxorubicin has been shown to damage the heart by way of cardiomyopathies (i.e. ischemic, dilated, hypertrophic, restrictive). (Schneider et al., 2002) Hematopoietic toxicity involves damage to tissues that produce bone marrow, leucopenia, and granulocytopenia. (Schneider et al., 2002) Pulmonary toxicity symptoms involve coughing, dyspnea, low-grade fever, fatigue, low tolerance to exercise, restlessness, and tachypnea. (Schneider et al., 2002) Abdominal radiation symptoms involved with gastrointestinal system toxicity include vomiting, nausea, and loss of appetite. Chemotherapy symptoms include nausea and vomiting which lead to increased energy requirements, nutritional deficiency, dehydration, electrolyte imbalance, diarrhea, abdominal pain and intestinal disease. (Schneider et al., 2002) The musculoskeletal effects with radiotherapy and chemotherapy consist of muscle wasting and cachexia, and tissue necrosis, while hepatic toxicity symptoms include rapid weight gain, increases in abdominal girth, fatigue, and anorexia. (Schneider et al., 2002) Neuroendocrine toxicities that stem from radiotherapy may include cell necrosis and atrophy when relating to thyroid tissue impairment, while chemotherapy symptoms involve anything from confusion, memory loss, hearing loss, and drop foot. (Schneider et al., 2002) Lastly, dermatological toxicities can consist of hair loss, specifically with chemotherapy drugs. (Schneider et al., 2002)

Exercise Training in Breast Cancer Survivors

Exercise has become increasingly important in our everyday lives and there has been a plethora of research in regards to its health benefits. Exercise has been shown to reduce obesity, strengthen cardiovascular capacity, reduce cardiovascular disease,

increase lung capacity and pulmonary function, strengthen bone and muscle, reduce the effects of aging, increase quality of life, and other alterations. (Brooks et al., 2005) Exercise programs can also benefit the cancer survivor similar to the healthy individual but can also improve fatigue, depression, and other debilitating side effects. (Schneider et al., 2003)

There have been a substantial amount of studies conducted on the effects of exercise in breast cancer survivors who were currently undergoing chemotherapy treatment. However, there is limited research investigating the effects of exercise on cancer survivors taking varying categories of chemotherapy drugs. Most research has collectively combined all breast cancer survivors regardless of the chemotherapy treatment. Therefore, the purpose of this investigation was to group survivors according to their chemotherapy agent and compare exercise test results among the different categories. The studies in Table 6 show evidence of the effects of exercise, pre- & post- (aerobic & resistance training) during and/or after chemotherapy with female breast cancer survivors.

Table 6. Exercise Research and Benefits				
Study & Type	Matthews et al. 2007 (Randomized Control Trial)	Drouin et al. 2006 (RCT)	Courneya et al. 2003 (RCT)	Hutnick et al. 2005 (Controlled Clinical Trial)
Subjects	36	21	53	36
Age	51-57	35-65	50-69	29-69
Treatment	Chemotherapy, Radiation, Surgery, Combination	Chemotherapy, Radiation, Surgery, Combination	Chemotherapy, Radiation, Hormone, Surgery, Combination	Chemotherapy, Radiation, Surgery, Combination
Cancer Treatment Status	Within last 12 months	Radiation 5 d/wk for 7 wks	12 months before study	Study done 2 wks after treatment
Exercise Treatment	12 wks	7 wks	15 wks	12 wks
Assessment	Baseline measurements from current activity levels	Modified Bruce treadmill test	Cycle ergometer test (60 rpm, 2-min workloads at 30 W w/↑ of 15 W until pVO2max met	Not applicable
Exercise Intervention	1st 4 wks (3 times/wk, 20-30 min/session) Last 5 wks (5 times/wk, 30-40 min/session)	20-45 min/session, walking & treadmill	Cycle ergo, 15 min/session for wks 1-3, ending at 35 min/session for wks 13-15	40-90 min/session, aerobic & resistance exercise
Intensity	Moderate, RPE (11-13)	50-70% (HRM)	70-75% pVO2max	60-75% (HRM)
Frequency	See intervention	3-5 days/wk	3 days/wk	3 days/wk
Results	Significant (P=0.01) ↑in self-reported walking Significant (P<0.01)↑ in total walking time (min/wk)	Significant (P<0.001) 6% median measure improvement in pVO2max w/exercise group	Significant (P<0.001) ↑ in pVO2max w/exercise group	Increase in VO2max & strength, not significant

Study & Type	Kolden et al. 2002 (Before & after, w/out control)	Mock et al. 2004 (RCT)	Mutrie et al. 2007 (RCT)	Campbell et al. 2005 (RCT)
Subjects	40	108	177	19
Age	45-76	30-69	29-76	E = 48 (± 10) C = 47 (± 5)
Treatment	Chemotherapy, Radiation, Hormone, Surgery, Combination	Chemotherapy, Radiation, Surgery	Chemotherapy, Radiation, Combination	Chemotherapy, Radiation, Combination
Cancer Treatment Status	Post-surgery	58% received RT 42% received CT	~24 wks after diagnosis	Before & during study
Exercise Treatment	16 wks	Either 6 wks for RT or 12 to 24 wks for CT	12 wks, w/24 wk follow-up	12 wks
Assessment	Single-stage submax treadmill test, estimated 1-RM bench & leg press test	12-minute walk test (Larson et al., 1996)	12-minute walk test	12-minute walk test (McGavin et al., 1976)
Exercise Intervention	60 min/session, Aerobic & resistance exercise	15-minute walk to 30-minute walk over time	45 min/session, low level aerobics	30 minutes (warm-up, aerobic/anaerobic exercise, cool-down)
Intensity	40-60% pVO2max, ↑ to 70% by wk 16	~50-70% (HRM)	50-75% (HRM)	60-75% (HRM)
Frequency	3 days/wk	5-6 times/wk	2 days/wk	Unknown
Results	Significant ($P<0.001$) ↑ in VO2max, bench & leg press tests	Significant ($P<0.01$) improvement in increased functional capacity	Significant ($P<0.0001$) improvement in 12-minute walk	Significant ($P<0.01$) improvement in 12-minute walk

Study & Type	Pinto et al. 2003 (RCT)	Segal et al. 2001 (RCT)	Thorsen et al. 2005 (RCT)	Turner et al. 2004 (RCT)
Subjects	24	99	111	10
Age	M (52.5)	M (~51)	18-50	33-63
Treatment	Chemotherapy, Radiation, Surgery	Chemotherapy, Radiation, Hormonal, Combination	Chemotherapy, Radiation, Surgery	Chemotherapy, Radiation, Surgery
Cancer Treatment Status	Post-surgery	During study	Before study	M (17 months prior to study) Range 4-60 months
Exercise Treatment	12 wks	26 wks	14 wks	8 weeks, (6 week & 3 month follow-up)
Assessment	Cycle ergometer peak test (50 rpm, w/↑of 25 W every 2 minutes	Modified Canadian Aerobic Fitness Test (mCAFT)	Cycle ergometer, 50 rpms.	Submax bicycle ergometer test
Exercise Intervention	60 min/session, aerobic training, Last month, strength training	Unknown min/session, progressive walking program	30 minutes (walking, resistance training, cycling, aerobics, water activities, jogging)	40-60 minutes, Low-impact aerobics, Resistance training: 2-3 sets, 8-12 reps
Intensity	60-70% (HRM)	50-60% pVO2max	60-70% (HRM)	Aerobic: 70-90% (HRM) Resistance: moderate
Frequency	3 days/wk	5 days/wk	2 times/wk	1 time/wk
Results	Significant ($P<0.05$ & .01) ↓ in SBP, DBP; SBP, DBP, & HR at 75 W workload	3% & 2% ↑ in pVO2max with SDEG & SEG respectively	VO2max increased 23% in intervention group	No significant results regarding fitness

Study & Type	Nikander et al. 2007 (RCT)	Hsieh et al. 2008 (Pre-test & Post-test)	Schneider et al. 2007 (Pre-test & Post-test)
Subjects	30	96	113
Age	41-65	58	56
Treatment	Chemotherapy, Radiation, Endocrine, Combination	Chemotherapy, Radiation, Surgery, Combination	Chemotherapy, Radiation
Cancer Treatment Status	Post-treatment	Complete	96 completed RT and/or CT 17 during
Exercise Treatment	12 wks	24 wks	24 wks
Assessment	Figure-8 running test (Gillquist et al., 1986)	Bruce treadmill test	Bruce treadmill test
Exercise Intervention	50 min/session, aerobic exercise	60 min/session, whole-body exercise	60 min/session, whole-body exercise
Intensity	RPE (11-16)	40-75% (HRR)	40-75% (HRR)
Frequency	1 day/wk	2-3 days/wk	2-3 days/wk
Results	Significant ($P<0.05$) improvement in Figure-8 running & CMJ power	Significant ($P<0.05$) improvement in treadmill time & pVO2max	Significant ($P<0.05$) improvement in treadmill time & pVO2max

Exercise and Breast Cancer

The studies in Table 6 show research completed on exercise and breast cancer survivors. Every study involved female breast cancer survivors who had either been on chemotherapy or were currently receiving chemotherapy treatment before and/or during the study. Additionally Table 6 shows the results of the exercise tests. As can be seen other treatments were involved (i.e. radiation, surgery, hormone and endocrine therapy, and combinations) with these studies, along with different treatment times.

All of the studies in Table 6 were conducted by a randomized control trial with the exception of Hutnick et al. 2005 (Controlled Clinical Trial); Kolden et al. 2002 (Before & After w/out a control); Hsieh et al. 2008 (Pre- vs. Post-test); and Schnieder et al. 2007 (Pre- vs. Post-test). Hsieh et al. 2008 and Schneider et al. 2007 used a pre- versus post-test design, while Kolden et al. 2002 also used a pre- versus post-test design. Hutnick et al. 2005 used a controlled clinical trial, not randomized because the attempt of a blind study wasn't applicable to their study.

Most of the independent variables with the studies consisted of the effect on VO2max (Courneya et al., 2003; Drouin et al., 2006; Hsieh et al., 2008; Hutnick et al., 2005; Kolden et al., 2002; Schnieder et al., 2007; Segal et al., 2001; Thorsen et al., 2005; and Turner et al., 2004). While Matthews et al. 2007; Mock et al. 2004; Mutrie et al. 2007; and Campbell et al. 2005 measured walking time, and Hsieh et al. 2008; and Schneider et al. 2007 measured treadmill time in addition to $\dot{V}O_2max$ and Nikander et al. 2007 measured running & counter-movement jump (CMJ) power. Hutnick et al. 2005 and Kolden et al. 2002 also measured strength in addition to $\dot{V}O_2max$. Lastly, Pinto et al. 2003 measured systolic and diastolic blood pressure, heart rate, and rate of perceived exertion.

Significant increases in $\dot{V}O_2max$ were found by Drouin et al. (2003), (6% increase, $P<0.001$); Courneya et al. (2003), (0.24 ml/min increase, $P<0.001$); Kolden et al. (2002), (4.62 ml/kg increase, $P<0.001$); Hsieh et al. (2008), ($P<0.05$); and Schneider et al. 2007, (15% increase, $P<0.05$); while Hutnick et al. (2005), Segal et al. (2001), and Thorsen et al. (2005) had increases in $\dot{V}O_2max$ but not significant. Significant increases in meters walked were found by Mutrie et al. (2007), (3% increase, $P<0.0001$) and

Campbell et al. (2005), (+328 [± 145], P<0.01) in a 12-minute walk test, while Matthews et al. (2007) found significant differences in self-reported walking (P=0.01) and total walking time (from 103 to 134 to 147 min/week, P<0.01). Nikander et al. (2007) found significant increases in Figure-8 running and counter movement jump (CMJ) (~5% and ~10% respectively, P<0.05) and Hsieh et al. 2008 and Schneider et al. 2007 found significant increases in treadmill time (37.16%, 27.03%, 28.57%, 33.54% and 1.03 & 1.30 minutes respectively, P<0.05). Mock et al. (2004) found a significant increase in functional capacity (P<0.01) and Pinto et al. (2003) found significant decreases in baseline systolic and diastolic blood pressure (-13.55 & -8.89 respectively, P<0.05), heart rate (-10.78 bpm, P<0.05), and systolic and diastolic blood pressure (-36.45, P<0.01, -7.77, P<0.05 respectively) at a 75-watt workload. Kolden et al. (2002) found significant improvement in bench and leg press (11.68 & 60.08 lbs respectively, P<0.001), while Hutnick et al. (2005) found improvement in muscle strength but not significant. With the exception of Hutnick et al. (2005), Segal et al. (2001), Thorsen et al. (2005), and Turner et al. (2004), all of the studies found a significant improvement/increase in exercise pre- versus post-intervention.

Summary

Breast cancer is the second leading cause of death for women in the U.S. however; death rates are declining because of modifications in chemotherapy treatment. Toxicities, physical and mental symptoms will continue to decline as chemotherapy treatment advances, along with the incorporation of exercise and a healthy diet. Exercise has been found to be a vital part of the rehabilitation process for breast cancer survivors and will only continue to support health benefits, wellness, and quality of life.

CHAPTER III

METHODOLOGY

Experimental Design

There is much research regarding the effects of chemotherapy treatment on breast cancer survivors. For the sake of this investigation, research concerning specific chemotherapy drugs used at the Rocky Mountain Cancer Rehabilitation Institute and suggested evidence for results regarding overall survival; disease-free survival, progression-free survival, and time to treatment failure will be used. In addition, the research concerns single-agent, sequential single-agent, and combination chemotherapy treatments involving the chemotherapy drugs used at RMCRI. Moreover, single-agent and sequential single-agent will be grouped together and compared to combination chemotherapy treatment because of the small portion of sequential single-agent chemotherapy-treated breast cancer survivors who were involved with this investigation from RMCRI.

The purpose of this research was to determine the differences in physiological parameters following an exercise intervention in breast cancer survivors on a single chemotherapy drug versus combination chemotherapy treatment. A secondary purpose was to determine if differences exist between categories of chemotherapy drugs. The data for this investigation came from the Rocky Mountain Cancer Rehabilitation Institute database.

Participants

The study was conducted on fifty-four female breast cancer survivors who had received either single-agent (n = 34) or combination (n = 20) chemotherapy treatment for

breast cancer, before, during or after their exercise intervention. The participants were a convenient sample chosen from the RMRCI database that had completed specific physiological parameters and pre- and post-exercise assessment. Parameters collected were age, height, weight, blood pressure, heart rate, forced vital capacity (FVC), forced expiratory volume (FEV_1), predicted $\dot{V}O_2$max (ml/kg/min), time on treadmill, chest press, latissimuss dorsi pull-down, shoulder press and sit-and-reach.

Exercise Training

The exercise intervention consisted of 3 to 6 months of exercise training between pre- and post-assessments and included 1-hour sessions, 2-3 days per week, at moderate intensities involving aerobic and resistance training, flexibility, range of motion, balance, and stretching. Equipment used during the intervention included the Cybex Exercise Equipment® (chest press, lat-pull down, shoulder press), Exerstrider® walking poles, Quinton Q60® treadmill, NuStep, resistance machines, dumbbells, therabands, bosu balls, fitballs, medicine balls, wall-wheel, wall rope-pulley, dyna disks, and balance pads.

The equipment specifically used for the pre- and post-assessments were the Cybex Exercise Equipment® (chest press, lat-pull down, shoulder press), Quinton Medtrack ® treadmill, Spirometrics, Inc. Flowmate Plus pulmonary spirometer, sit-and-reach scale, heart rate monitor, blood pressure cuff, stethoscope, pulse-oximeter, and a metronome.

Collection of Data

The cardiovascular endurance test was conducted using a Bruce Treadmill Protocol to measure the client's cardiorespiratory fitness. Table 7 displays the design of the Bruce Treadmill Protocol VO_2peak Test including the stage, speed, and grade. The

test was terminated based upon the client's volitional fatigue, whether they asked to stop, or the assessor's determination for the termination. In addition, the following is RMCRI's guidelines to stop the treadmill test:

1. ACSM's indications for terminating exercise testing (page 106, 7th edition).
2. Heart rate does not increase with increased intensity.
3. Systolic blood pressure does not increase with increased intensity.
4. Diastolic blood pressure fluctuates more than 10 mmHg from baseline.
5. Oxygen saturation drops below 80 (pulse oximeter).
6. Heart rate exceeds maximum heart rate using the following formula:

   HRmax = 205.8 – (0.685 x age).

The time is recorded in the form of a decimal by dividing the seconds by 60 and the time does not include the warm-up.

Table 7. Bruce Treadmill Protocol VO_2peak Test		
STAGE	SPEED (MPH)	GRADE (%)
Warm up	1.7	0
1	1.7	10
2	2.5	12
3	3.4	14
4	4.2	16
5	5.0	18

Pulmonary function test involved FEV_1% (the amount of exhalation in the first second) and FVC% (the total volume of air the client can exhale), which are measured through a dry spirometer. The client is instructed to exhale as forcefully as possible and then continue exhaling as long as possible without bending at the waist and wearing a nose clip to prevent any air from passing through the nose. Two test values are obtained and if the second FVC% score is more than 5% higher or lower than the first FVC% score, the test must be repeated for a third time. The highest value is used for both

FVC% and FEV_1%. The following standards (norms) are adapted from the American College of Sports Medicine's (ACSM) pulmonary function prediction equations:

≥ 95% = Excellent

81-94% = Within normal limits (WNL)

75-80% = Lower limit of normal (LLN)

< 75% = Low

The weight machine protocols (chest, lat-pull down, shoulder) are listed in Table 8 with the predetermined weight percentages for each modality.

Table 8. Percentage of Body Weight To Be Lifted (RMCRI, 2009)

Exercise	Age: < 45		Age: 45-60		Age: 60-70		Age: > 70	
	Men	Women	Men	Women	Men	Women	Men	Women
Shoulder press	.300	.225	.280	.210	.265	.200	.250	.185
Lat Pulldown	.500	.375	.470	.350	.440	.330	.410	.310
Chest Press	.500	.375	.470	.350	.440	.330	.410	.310

The client was instructed to perform a couple of repetitions in order to establish if more, less, or no weight was to be adjusted. For the weight machine tests, a metronome was set at 25 bpm (beats per minute). The optimal number of repetitions was established between 8 and 12 and did not exceed 15. The following exercise tests were instructed by the assessor to the client for each modality.

A. Shoulder Press

1. Adjust the seat so that when the client grasps the handles, the elbows are at less than or equal to a 90-degree angle.
2. Have client sit on seat with back and buttocks against the backrest.
3. Feet should be placed flat on the floor and shoulder-width apart.

4. Full repetition:

   UP: Raise training arm until arms are at near full extension.

   DOWN: Lower training arm until elbows are at a 90-degree angle.

B. Lateral Pull-Down

1. Have client sit on bench seat with thighs positioned comfortably underneath the pad.
2. Adjust seat so client's shoulders line up with the line on the machine.
3. Client's torso should remain upright throughout the lift (not leaning forward or backward).
4. Full repetition:

   DOWN: Pull training arm down until elbows are at a 90-degree angle.

   UP: Allow training arm to rise until arms are at near full extension.

C. Chest Press

1. Adjust the seat so the handles are at mid-chest height.
2. Have client sit on seat with back and buttocks against backrest.
3. Feet should be placed flat on the floor approximately shoulder-width apart.
4. Full repetition:

   UP: Press outward until arms are at near full extension.

   DOWN: Lower training arm until elbows are at a 90-degree angle.

D. Modified Sit and Reach Procedure

For the modified sit and reach test, the client sits on the floor with shoulders, head, and buttocks against a wall and legs straight out in front.

A 12-inch sit and reach box was placed against the soles of the feet with the zero end of the yardstick toward the client. The client held her arms straight forward from the shoulders toward the box, placing one hand on top of the other and keeping the head and shoulders against the wall. The yardstick was positioned so that the zero end was touching the fingertips. The client bent forward, sliding the fingertips along the top of the yardstick. The client's knees did not bend and the hands stayed together. The inches were used at the farthest tip of the fingertips and recorded.

Drug Treatment

The drugs used with the breast cancer survivors for this investigation are described in Table 9.

Table 9. Chemotherapy Drugs Used With Breast Cancer Survivors at RMCRI.

Drug	Type	Side Effects	How it Works
Arimidex (Anastrozole)	Aromatase Inhibitor	Hot flashes, nausea, decreased energy and weakness, bone pain, & cough	Blocks the enzyme aromatase used to convert androgens into estrogen. Tumors dependent on this hormone for growth and will shrink

Avastin (Bevacizumab)	Mono-clonal Antibody	Generalized weakness, pain, abdominal pain, nausea, vomiting, poor appetite, constipation, diarrhea upper respiratory infection, headache, hair loss	Interferes with angiogenesis by targeting and inhibiting human vascular endothelial growth factor (VEGF).
Carboplatin (Paraplatin)	Alkylating Agent	Low blood counts, nadir, nausea, vomiting, taste changes, hair loss, weakness, & blood test abnormalities	Cell-cycle non-specific (resting phase of the cell)
Cytoxan (Cyclophos-phamide, Neosar)	Alkylating Agent	Low blood counts, nadir, hair loss, nausea, vomiting, poor appetite, loss of fertility, discoloration of the skin or nails	Cross-links DNA Cell-cycle non-specific (resting phase of the cell); inhibits DNA synthesis
Doxyrubicin (Adriamycin, Rubex)	Anthracycl ine	Pain on side where medication was given, low blood counts, nadir, nausea, vomiting, mouth sores, hair loss	Non-cell-cycle specific (multiple phases of the cell), affects cells only when they are dividing
Exemestane (Aromasin)	Aromatase Inhibitor	Fatigue, nausea, hot flashes, depression, bone pain, insomnia, anxiety, shortness of breath	Blocks the enzyme aromatase used to convert androgens into estrogen. Tumors dependent on this hormone

Faslodex (Fulvestrant)	Estrogen Inhibitor	Nausea, vomiting, weakness, hot flashes, headache, bone pain, constipation, abdominal pain, diarrhea, cough	Blocks estrogen (interferes with cell growth) from going into the cancer cell
Femara (Letrozole)	Aromatase Inhibitor	Hot flashes, bone/back/joint pain, nausea, fatigue, shortness of breath, coughing	Blocks the enzyme aromatase used to convert androgens into estrogen. Tumors dependent on this hormone
Herceptin (Trastuzumab)	Monoclonal Antibody	Fever, body pain, weakness, nausea, headache, shortness of breath	Targets the HER2/neu receptor on cancer cells and prevents cells from multiplying
Megace (Megestrol, Megestrol Acetate)	Progestin	Weight gain, edema, menstrual bleeding	Stops hormone production, blocks hormone receptors
Tamoxifen (Novaldex)	Estrogen Inhibitor	Hot flashes, vaginal discharge, swelling, loss of libido	Stops hormone production, blocks hormone receptors; Interacts with protein kinase C and stimulation of human NK cells

Taxol (Paclitaxel, Onxal)	Taxane	Low blood counts, arthralgias & myalgias, hair loss, nausea, vomiting, diarrhea, hypersensitivity reaction	Mitotic inhibitor; Cell-cycle non-specific (resting phase of the cell)
Taxotere (Docetaxel)	Taxane	Low white & red blood cell count, nadir, nausea, hair loss, diarrhea, mouth sores, fatigue, weakness, nail changes, peripheral neuropathy	Mitotic inhibitor; Cell-cycle non-specific (resting phase of the cell)

Table 10 displays the single and combination chemotherapy treatment regimens used with the breast cancer survivors for this investigation.

Table 10. Single & Combination Chemotherapy Treatment	
Single-Agent (n = 34)	Combination (n = 20)
Tamoxifen = 23	Adriamycin + Cytoxan = 2
Arimidex = 8	Cytoxan + Femara = 1
Taxol = 2	Carboplatin + Herceptin = 1
Taxotere = 1	Cytoxan + Taxotere = 2
	Tamoxifen + Megace = 1
	Adriamycin + Cytoxan + Taxotere = 6
	Adriamycin + Cytoxan + Tamoxifen = 2
	Adriamycin + Cytoxan + Taxol = 2
	Adriamycin + Cytoxan + Taxotere + Herceptin = 1
	Adriamycin + Cytoxan + Taxotere + Taxol = 1
	Adriamycin + Cytoxan + Avastin + Faslodex = 1

Statistical Analyses

The statistical analysis included the dependent variables systolic/diastolic blood pressure, resting heart rate, treadmill time, predicted $\dot{V}O_2max$, FVC%, FEV_1%, chest press, lat-pull down, shoulder press, and sit-and-reach for single-agent and combination

chemotherapy clients, pre- versus post-assessment results. Paired t-tests (unequal variance) were run between single and combination chemotherapy group's participant characteristics and significance was established at the 95% confidence interval ($P<0.05$). The data analyses were performed with SAS 9.2 and Microsoft Excel.

A Principle Components Analysis (PCA) was conducted to group the variables into appropriate components based off of a four-factored rotated factor pattern. There were four variable groups used in the PCA and MANOVA including Pre- and Post-Blood Pressure (BP), Cardio, Oxygen, and Muscle. Each variable group consisted of the appropriate physiological variables with the greatest variance among each other. The first principal component represents for as much of the variability in the data as possible, and each following component accounts for as much of the remaining variability as possible.

A Multivariate Analysis of Variance (MANOVA) was performed to determine change over time for the pre- and post-assessment results between overall therapy category, therapy (Single vs. Combination), and drug (i.e. Taxol vs. Cytoxan + Femara) categories. A MANOVA was used to find the optimal combination of the dependent variables and account for the variance associated with the independent variables, which were then separated out, and each one and interaction on the linear composite was tested. (Thomas, Nelson, & Silverman, 2005) Differences were considered significant at the 95% level of confidence ($P<0.05$) and obtained with the Wilks' Lambda distribution.

The FACTOR Procedure Rotation Method: Varimax for the Pre- and Post-test data and each variable are presented in Table 14. This statistical method was used to describe variability among observed variables in terms of a potentially lower number of unobserved variables (factors). (Thomas et al., 2005)

CHAPTER IV

RESULTS

INTRODUCTION

The purpose of this research was to determine the differences in physiological parameters following an exercise intervention in female breast cancer survivors on a single chemotherapy drug versus combination chemotherapy drugs. A secondary purpose was to determine any differences in chemotherapy categories.

Data obtained from breast cancer survivors concerning their breast cancer stage, chemotherapy treatment, exercise test results pre- versus post-training was compiled from the Rocky Mountain Cancer Rehabilitation Institute at the University of Northern Colorado. These research data were used in order to answer more questions about exercise as a therapeutic measure for cancer survivors.

Participant Characteristics

The population used in this investigation included current, past, and deceased breast cancer survivors who participated in the rehabilitation program at the Rocky Mountain Cancer Rehabilitation Institute. The study consisted of data from fifty-four participants who were chosen based on completed physiological results. A combined fifty-four breast cancer survivors were selected with thirty-four single-agent chemotherapy treated subjects and twenty combination chemotherapy treated subjects. Table 11 displays the participant characteristics including the mean of age (years), height (inches), and weight (pounds). There were no significant differences between single-agent and combination chemotherapy treated groups with the participant's characteristics.

All of the pre- and post-assessment results consisted of either three to six-month exercise interventions.

Table 11. Participant Characteristics			
	Single-Agent (n = 34)	Combination (n = 20)	p-value
Age (yrs.)	55.80 ± 8.75	53.48 ± 6.73	0.12
Height (in.)	64.40 ± 2.66	63.72 ± 2.40	0.19
Weight (lbs.)	161.92 ± 37.93	159.20 ± 30.21	0.67

Note. Values are means ± standard deviation (SD).

Table 12 displays single-agent and combination chemotherapy categories associated with the chemotherapy drugs used by the breast cancer survivors. Clients were categorized into one of three therapy categories. The combination group therapy category 1 had anthracycline, alkylating agent, and taxane drugs. Therapy category 2 had anthracycline and alkylating agent drugs. Therapy category 3 had no required drug and was a combination of various drugs. Therapy category 1 was established due to the drug effect that anthracyclines, alkylating agents, and taxanes have on the body's physiological parameters. Therapy category 2, unlike the first, did not involve taxanes, and therapy category 3 consisted of different combined chemotherapy drugs.

Table 12. Chemotherapy Categories For Single and Combination Treatments	
Single-Agent (n = 34) Drug Category = 1	Combination (n = 20) Drug Category = 2
Estrogen Inhibitor = 23 (Therapy Category = 1)	Anthracycline + Alkylating Agent + Taxane = 8 Anthracycline + Alkylating Agent + Taxane + Taxane = 1 Anthracycline + Alkylating Agent + Taxane + Monoclonal Antibody = 1 (Therapy Category = 1)
Aromatatse Inhibitor = 8 (Therapy Category = 2)	Alkylating Agent + Anthracycline = 2 Alkylating Agent + Antrhacycline + Estrogen Inhibitor = 2 Alkylating Agent + Anthracycline + Estrogen Inhibitor + Monoclonal Antibody = 1 (Therapy Category = 2)
Taxane = 3 (Therapy Category = 3)	Alkylating Agent + Monoclonal Antibody = 1 Alkylating Agent + Taxane = 2 Alkylating Agent + Aromatase Inhibitor = 1 Estrogen Inhibitor + Progestin = 1 (Therapy Category = 3)

Analysis of Data

Table 13 displays the physiological parameters measured for single and combination chemotherapy treated breast cancer survivors. The values are presented as means ± SD and significance is indicated by the p-value. Significance was found in single and combination groups for FVC%, FEV1%, chest press, lat pulldown, shoulder press, sit-and-reach, and resting heart rate (combination only). No significant difference was found in systolic or diastolic blood pressures, resting heart rate for single, treadmill time, or predicted $\dot{V}O_2max$.

Table 13. Physiological Parameters						
VARIABLE	SINGLE (Mean) (n = 34)			COMBINATION (Mean) (n = 20)		
	Pre-Test	Post-Test	p-value	Pre-Test	Post-Test	p-value
Systole (mm/Hg)	124.62 ± 19	124.24 ± 14	0.86	124.65 ± 15	122.20 ± 11	0.27
Diastole (mm/Hg)	78.24 ± 8	77.15 ± 8	0.48	78.20 ± 8	75.30 ± 9	0.21
Resting Heart Rate (beats/minute)	83.53 ± 11	81.60 ± 11	0.28	94.35 ± 13	87.75 ± 11	0.04*
FVC%	93.25 ± 15	95.29 ± 14	0.001*	96.90 ± 15	102.56 ± 12	0.006*
FEV1%	83.37 ± 15	87.24 ± 14	0.004*	91.20 ± 15	97.80 ± 12	0.01*
Treadmill (minutes)	5.81 ± 2	6.84 ± 2	0.39	7.00 ± 2	8.20 ± 2	0.10
VO2max (ml/kg/min)	22.00 ± 5	24.00 ± 5	0.40	22.60 ± 6	27.54 ± 7	0.15
Chest Press (reps)	9.82 ± 6	16.32 ± 7	0.001*	9.85 ± 4	16.35 ± 7	0.006*
Lat Pulldown (reps)	14.40 ± 8	24.10 ± 14	0.001*	16.30 ± 11	23.20 ± 14	0.01*
Shoulder Press (reps)	8.10 ± 7	17.30 ± 12	0.001*	7.75 ± 6	17.50 ± 8	0.001*
Sit-and-reach (inches)	12.60 ± 4	13.00 ± 3	0.01*	11.64 ± 3	12.19 ± 4	0.04*

Note. Values are means ± SD. * = Differs significantly from pre-test values ($P<0.05$).

Figures 1 and 2 show the change in pre- to post-assessments for single and combination chemotherapy treatment regimens, respectively. There was a significant difference in RHR (combination only), FVC%, FEV%, chest press, lat pulldown, shoulder press, and sit-and-reach.

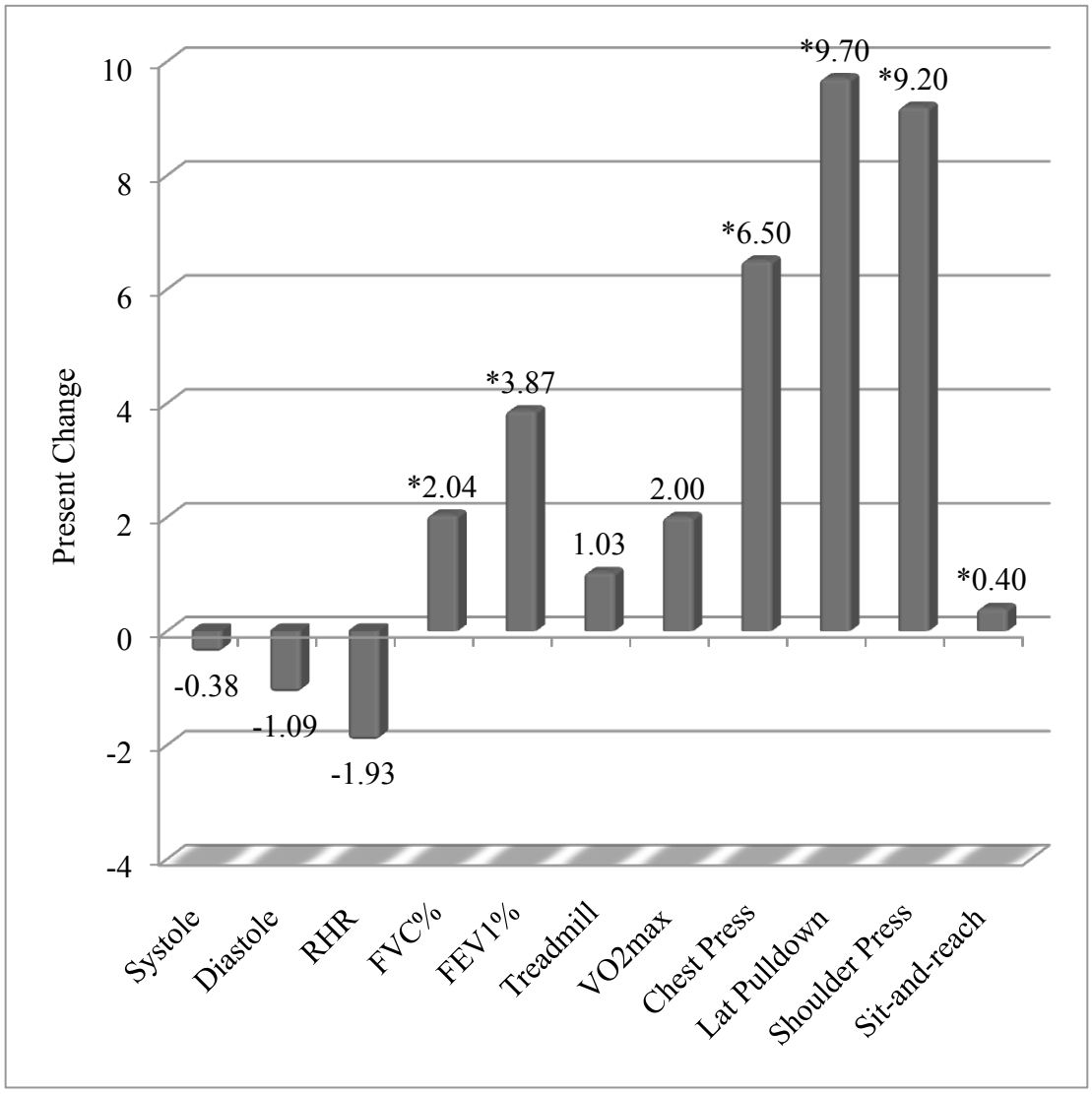

Figure 1. Single Chemotherapy (n=34) Present Change Pre- to Post-Assessment.

Note. * = Significance at P<0.05.

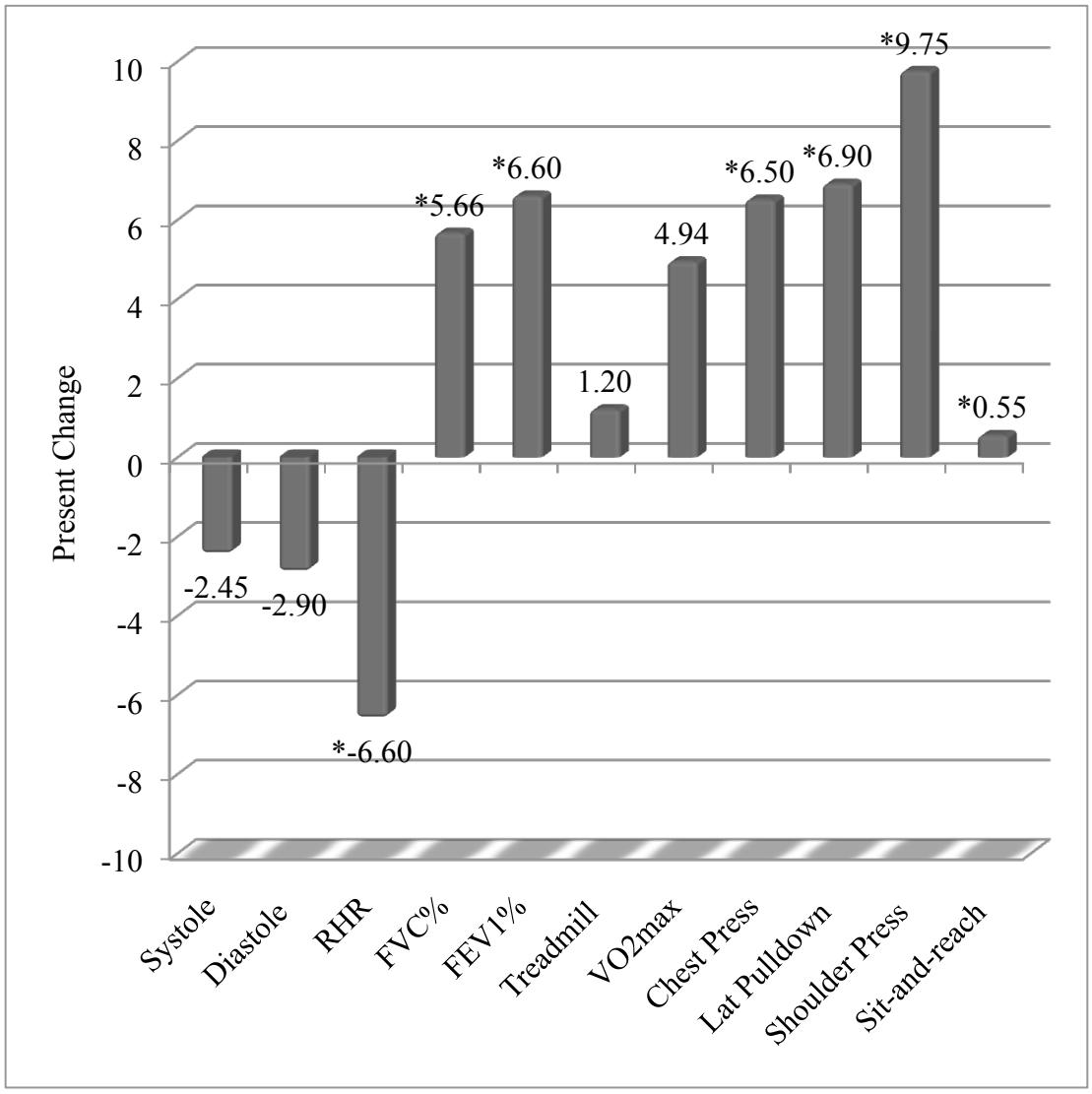

Figure 2. Combination Chemotherapy (n=20) Present Change Pre- to Post-Assessment.

Note. * = Significance at P<0.05

Table 14 displays the rotated factor pattern for every variable measured. This statistical method was used to describe variability among observed variables in terms of a potentially lower number of unobserved variables (factors). The underlined values represent the variables with the greatest association between each, in each column.

Table 14. Rotated Factor Pattern				
VARIABLE	FACTOR 1	FACTOR 2	FACTOR 3	FACTOR 4
PreBench	0.84970	-0.00762	0.07643	-0.21134
PreLats	0.64599	0.10892	0.08537	-0.04005
PreShoulder	0.63113	0.31693	0.03642	-0.10785
PreSitnreach	0.49203	0.16247	-0.07899	0.04480
PreVO2max	0.32855	0.79911	0.02827	-0.05770
PreTreadmill	0.15472	0.79263	-0.11857	-0.16368
PreFVC	0.04061	0.05559	0.75513	-0.02876
PreFEV	0.20493	0.03203	0.74361	0.04948
PreRHR	-0.15299	-0.17966	0.47781	0.11978
PreExDiastole	-0.14634	-0.00207	0.17362	0.68389
PreExSystole	-0.00362	-0.36504	-0.07966	0.54577
PostTreadmill	0.85954	0.05888	-0.16904	0.00725
PostVO2max	0.84113	0.05877	-0.18282	0.03517
PostSitnreach	0.38934	-0.06245	-0.23875	-0.09422
PostFEV	-0.01597	0.80759	0.02423	-0.01121
PostFVC	0.14330	0.80634	-0.03871	-0.09299
PostRHR	-0.16558	0.37981	0.13591	0.33111
PostExSystole	-0.26394	-0.06570	0.78268	-0.00542
PostExDiastole	-0.19942	0.09612	0.76890	-0.03978
PostLats	0.13001	-0.00477	0.02929	0.67625
PostShoulder	0.02017	0.02674	-0.08226	0.61184
PostBench	-0.14660	-0.05262	0.01534	0.49665

Table 15 displays the overall means and standard deviations of the four variable group's factors compared for both single and combination chemotherapy subjects. The four variable group's factors consisted of the following:

Blood Pressure (BP) = Systole and Diastole

Cardio = FVC%, FEV1%, and RHR

Oxygen = Predicted $\dot{V}O_2max$ and Treadmill

Muscle = Bench, Lats, Shoulder, and Sit-and-reach

Table 15. Means of Four Factor Groups			
N	VARIABLE	MEAN	STD DEV
54	PreBP	101.61	11.33
	PostBP	99.97	10.32
	PreCardio	89.46	14.05
	PostCardio	90.98	12.35
	PreOxygen	14.22	3.87
	PostOxygen	16.13	4.44
	PreMuscle	9.02	4.13
	PostMuscle	14.02	5.39

Table 16 displays the means and standard deviations for all therapy and drug categories for single and combination chemotherapy subjects pre- and post-assessment.

Table 16. Means By Therapy and Drug Category					
THERAPY CATEGORY	DRUG CATEGORY	N	VARIABLE	MEAN	STD DEV
1 (Single)	1	23	PostBP	102.32	10.27
			PreBP	102.90	12.66
			PostCardio	85.82	13.40
			PreCardio	84.84	12.96
			PostOxygen	14.73	3.39
			PreOxygen	13.50	3.94
			PostMuscle	14.03	5.52
			PreMuscle	9.40	4.16
	2	8	PostBP	101.12	10.62
			PreBP	102.31	6.81
			PostCardio	91.83	9.07
			PreCardio	91.37	14.83
			PostOxygen	14.58	4.74
			PreOxygen	13.95	3.77
			PostMuscle	15.89	7.57
			PreMuscle	7.75	3.95
	3	3	PostBP	87.00	7.00
			PreBP	87.66	10.26
			PostCardio	94.77	15.69
			PreCardio	88.55	9.24
			PostOxygen	19.52	4.54
			PreOxygen	16.59	4.15
			PostMuscle	10.16	4.81
			PreMuscle	9.00	4.41

2 (Combination)	1	10	PostBP	97.35	11.00
			PreBP	102.45	12.77
			PostCardio	95.90	7.76
			PreCardio	91.83	16.29
			PostOxygen	19.87	4.74
			PreOxygen	17.08	3.79
			PostMuscle	13.23	4.17
			PreMuscle	11.02	3.12
	2	5	PostBP	96.90	9.73
			PreBP	101.70	5.78
			PostCardio	99.60	13.44
			PreCardio	102.40	10.89
			PostOxygen	16.33	2.92
			PreOxygen	12.87	1.40
			PostMuscle	14.04	3.83
			PreMuscle	7.30	4.18
	3	5	PostBP	103.40	6.06
			PreBP	101.10	11.24
			PostCardio	92.66	11.33
			PreCardio	90.53	13.94
			PostOxygen	15.37	5.41
			PreOxygen	12.14	3.13
			PostMuscle	14.85	5.64
			PreMuscle	7.08	5.66

Figure 3 displays the results from the MANOVA analyses including the overall therapy category (single versus combination), overall drug category (i.e. single 1 versus combination 1) and overall therapy category x drug category interaction. No significant difference was found with any of the MANOVA analyses.

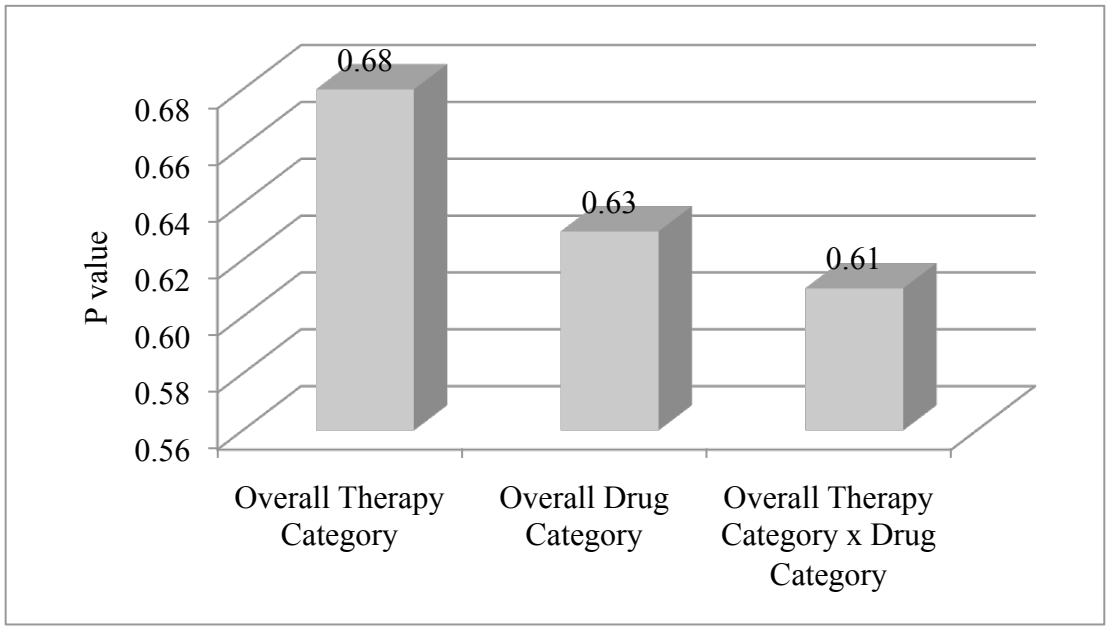

Figure 3. Single Versus Combination Chemotherapy MANVOA Results Pre- and Post-Assessment.

Summary

The main hypothesis (H1) for this investigation was that breast cancer survivors receiving single-agent and sequential single-agent chemotherapy treatment would show significantly greater results in physiological parameters measured in pre- and post-exercise assessments compared to breast cancer survivors receiving combination chemotherapy. H1 was rejected. There were no significant differences between single or combination chemotherapy treatment pre- and post-assessments. Additionally, H2 was rejected. There were no significant differences in the chemotherapy categories between single and combination chemotherapy treatment regimens. H3 was accepted. There were significant differences ($P<0.05$) in exercise performance with the single pre- to post-exercise assessment and with the combination pre- to post-exercise assessment. The single and combination groups showed improvements on FVC%, FEV1%, chest press, lat pulldown, shoulder press, sit-and-reach, and resting heart rate (combination only).

CHAPTER V

DISCUSSION

Effect of Exercise Training on Breast Cancer Survivors

Many researchers have studied the impact of exercise training on breast cancer survivors receiving chemotherapy. This investigation is in agreement with Pinto et al. (2003) concerning a significant decrease in heart rate after exercise. Pinto et al. (2003) found a significant (-10.78 bpm, $P<0.05$) decrease in heart rate at a 75-Watt workload, while this study found a significant (-6.60 bpm, $P<0.05$) decrease in resting heart rate with only the combination group. This investigation is also in agreement with Kolden et al. (2002) concerning a significant (+11.68 lbs, $P<0.001$) increase in bench press while this investigation found a significant (Single – change (6.50%) reps, $P<0.001$; Combination – change (6.85%) reps, $P<0.006$) increase in chest press repetitions. This investigation is in agreement with Hutnick et al. (2005), Thorsen et al. (2005), and Segal et al. (2001) concerning an increase in $\dot{V}O_2max$ but not significantly.

This investigation is not in agreement with Hsieh et al. (2008), Schneider et al. (2007), Drouin et al. (2006), Courneya et al. (2003), and Kolden et al. (2002) concerning a significant increase in predicted $\dot{V}O_2max$ or treadmill time (Hsieh et al. 2008 & Schneider et al. 2007). This investigation is not in agreement with Pinto et al. (2003) concerning a significant decrease in systolic and diastolic blood pressure.

However, no research was found in relation to the purpose of this investigation and whether or not the effect of a single chemotherapy drug regimen versus a combination chemotherapy drug regimen is more or less effective in response to exercise tests. This study examined the impact single versus combination chemotherapy regimens

have on physiological parameters involved with exercise. There were significant differences ($P<0.05$) found between pre- and post-assessments within the single and combination chemotherapy treatment regimens for pulmonary tests FVC% and FEV1%, chest press, lat pulldown, shoulder press, sit-and-reach, and resting heart rate (combination only). These findings suggest a beneficial impact exercise has on physiological parameters measured with breast cancer survivors who have received either single or combination chemotherapy treatment. These findings also suggest the similarities between the specific parameters found to be significant with both chemotherapy treated subjects.

Effect of Single and Combination Chemotherapy Drugs

No significant difference was seen between single and combination chemotherapy drugs. However, the significant differences found pre- to post-assessment were similar between single and combination chemotherapy treatment regimens therefore; the physiological changes were similar between therapy categories pre- to post-assessment. The following studies found significant differences with breast cancer survivors and exercise treatment before, during, and after treatment.

Thorsen et al. (2005), Turner et al. (2004), and Courneya et al. (2003) conducted their studies before treatment and found no significant differences, but Courneya et al. (2003) found significant ($P<0.001$) difference in $\dot{V}O_2max$.

Schneider et al. (2007) and Campbell et al. (2005) conducted their studies before and during treatment and Schneider et al. (2007) found significant difference in treadmill time and $\dot{V}O_2max$ ($P<0.05$) and Campbell et al. (2005) in 12-minute walk ($P<0.01$).

Mutrie et al. (2007), Drouin et al. (2006), Mock et al. (2004), and Segal et al. (2001) conducted their studies during treatment. All but Segal et al. (2001) found significant differences in (12-minute walk, $P<0.0001$; $\dot{V}O_2max$, $P<0.001$; and Functional capacity, $P<0.01$), respectively.

Hsieh et al. (2008), Matthews et al. (2007), Nikander et al. (2007), Hutnick et al. (2005), Pinto et al. (2003), and Kolden et al. (2002) conducted their studies after treatment. All but Hutnick et al. (2005) found significant differences in (Treadmill time & $\dot{V}O_2max$, $P<0.05$; Self-reported walking, $P=0.01$, Total walking time, $P<0.01$; Figure-8 running & CMJ power, $P<0.05$; Systolic/Diastolic blood pressure, $P<0.05$, Heart rate, $P<0.01$; and $\dot{V}O_2max$, bench & leg press, $P<0.001$), respectively.

The findings of these investigations suggest that an exercise intervention can produce a significant improvement at any time throughout the chemotherapy treatment process. However, no research has been found suggesting significant difference between single chemotherapy and combination chemotherapy treatment. The findings of no significance between therapy categories with this investigation may suggest that the physiological side effects of chemotherapy are similar between therapy categories and that no one therapy category has more impact on physiological parameters involved with exercise.

Effect of Chemotherapy Drug Categories

Although slight improvements were found, there were no findings of significant differences ($P=0.63$) between chemotherapy drug categories single versus combination with this investigation. Physiologically, the aforementioned studies suggest exercise treatment can be found significant at any point in the chemotherapy treatment process.

However, with this investigation, whether any chemotherapy drug(s) existed in the breast cancer survivor at the time of the pre- and post-assessment, and if any side effects had any impact on the breast cancer survivor's exercise performance, and whether significant difference could have been found, remains unclear. There has been no research found concerning chemotherapy drug categories and exercise training with breast cancer survivors and any interaction between each treatment.

Effect of Interaction Between Drug Therapy and Drug Category

Similarly, even though slight improvements were found, there were no findings of significant differences (P=0.61) between the interaction of single therapy and drug categories with combination therapy and drug categories with this investigation. Again, this may suggest whether the existence of chemotherapy drug(s) the breast cancer survivor was on may or may not have had an impact with any physiological side effects and influence on the assessments and intervention. Also, there has been no research found concerning therapy interaction with chemotherapy drug categories and exercise.

Summary and Conclusions

The findings of this investigation indicate there is a significant benefit in an exercise intervention program for breast cancer survivors who have received either single or combination chemotherapy regimens from a pre- to a post-assessment. The findings also suggest that both single and combination chemotherapy are similar in terms of the impact an exercise intervention has on either treatment concerning the physiological parameter's measured (FEV1%, FVC%, heart rate (combination only), chest press, lat pulldown, shoulder press, sit-and-reach). In addition, the findings raise the question of

whether one chemotherapy treatment is more effective than the other and specific research concerning drugs and categories would be valuable.

Future Study

Further research should be performed specifically concerning chemotherapy treatment times and encompassing all possible chemotherapy drugs, categories and combination regimens. In addition, a larger sample size of breast cancer survivors all starting their exercise intervention and pre- and post-assessments at the same time and narrowing down the individualized exercise prescriptions to be as close to each breast cancer survivor as possible should be implemented. Further research should concentrate on the physiological parameters of major muscle groups, treadmill times, pulmonary function tests, blood pressure, heart rate, flexibility, and psychological parameters (fatigue, depression, motivation).

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