Spring 2023

Effect of Resistance Training on White Blood Cell Count and Chemotherapy Efficacy in Triple-Negative Breast Cancer Patients During Adriamycin-Cyclophosphamide Chemotherapy Treatment

Mimi Wassef
Southern Methodist University, mwassef@smu.edu

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Research Proposal
APSM 4305
Fall 2022
Department of Applied Physiology and Wellness
Annette Caldwell Simmons School of Education & Human Development

By
Mimi Wassef
B.S. Applied Physiology & Health Management
B.A. English

Abstract Word Count: 280
Total Word Count: 5,335

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Abstract

Triple-negative breast cancer (TNBC) is one of the most difficult subtypes of breast cancer to treat due to a lack of molecular targets. While chemotherapy (CT) has become the standard form of treatment, the administration of CT depends on adequate white blood cell (WBC) count. When WBC becomes too low, patients risk becoming ineligible for treatment. In the general population, WBC count has been shown to increase as a result of exercise, but little research has been done on the effects of exercise and WBC count in the TNBC population. The purpose of this study is to determine if 12 weeks of resistance training during CT treatment can maintain, or improve WBC count and chemotherapy efficacy in non-metastatic TNBC patients compared to those in a usual care (UC) condition. It is hypothesized that TNBC patients in the exercise intervention group will maintain, or see improvements in WBC count and CT efficacy compared to patients in a UC condition. This study is experimental and longitudinal. The study population will consist of 20 non-metastatic TNBC patients receiving CT treatment. Measurements of WBC count and tumor size will be taken at three points throughout the fourteen-week study period. The groups will be compared at the end of the fourteen weeks. Statistical Package for the Social Sciences will be used to perform statistical analyses. Mean and standard deviation will be utilized to present the descriptive statistics. Statistical analysis of inferential variables will be performed using a 2x3 Analysis of Variance. This study is significant because WBC count maintenance as an effect of resistance training could be monumental to the TNBC population—where the ability to stay eligible for treatment is imperative to patient survival.

Keywords: Triple-negative breast cancer, white blood cell count, chemotherapy efficacy

Chapter I: Introduction

Triple-negative breast cancer (TNBC), one of the most aggressive subtypes of breast cancer, is recognized for its unique molecular profile (negative estrogen, progesterone, and human epidermal growth factor 2, or HER2, receptors), high rate of metastasis, and poor prognosis in response to treatment (Aysola et al., 2013). Although the prevalence of TNBC is low (approximately 15-20%) compared to other breast cancer subtypes, TNBC patients have few treatment options (due to negative target receptors) and face aggressive tumor growth and low survival rates (Wahba & El-Hadaad, 2015). Due to the cancer's aggressive course, it is imperative that patients have effective treatment plans, and that clinicians and researchers further explore TNBC pathophysiology and its subtype-specific therapies.

Chemotherapy is historically known as the gold standard and most effective treatment option for early and advanced stages of TNBC; it can be administered clinically in neoadjuvant and/or adjuvant settings (Bergin & Loi, 2019). Neoadjuvant chemotherapy (NACT) is administered pre-operative treatment, whereas adjuvant chemotherapy (ACT) is administered post-operative treatment—TNBC therapies often favor NACT approaches because it allows for surveillance of tumor growth and response to chemotherapeutic treatment prior to exploring surgical options (Gupta et al., 2020). Neoadjuvant chemotherapy is typically administered in four cycles: each cycle consists of three weeks (drugs are given at the beginning of each cycle), for a total of 12 weeks (although some chemotherapy treatments can run as long as six months) (Lohman et al., 2018). Prior to receiving a cycle of chemotherapy, patients undergo lab testing to determine white blood cell (WBC) counts, which subsequently determine whether treatment can be safely administered—if WBC counts are too low, patients can be exposed to life-threatening toxicity, which is why they may be denied treatment (Lohman et al., 2018). Low WBC count prior to, or as a result of chemotherapy, is particularly threatening to TNBC patients with few treatment options. When chemotherapy treatment is denied, delayed, or reduced, the potential for detrimental outcomes increases, including infection, metastasis, critical care, and mortality (Karvinen et al., 2014).

Studies on the general population have shown increases in WBC count and improvements in immune function following exercise, but there is little research on this topic in the TNBC population and in individuals with compromised cell counts (Jamurtas et al., 2018). Additionally, exercise is often encouraged to cancer patients as a way to mitigate declines in energy, physical function, and quality of life, but generally has not been discussed in regard to improving hematological outcomes (Campbell et al., 2019). As research specific to resistance training has developed, there has been evidence supporting that increases in circulating WBC can result from resistance exercises (McCarthy et al., 1991). These immunologic research advancements can serve as a basis for exploring further the implications of a resistance training program on chemotherapy eligibility, and subsequently, its effects on tumor reduction and total chemotherapy efficacy.

Moreover, it is critical to understand that TNBC patients will experience adverse synergistic effects in response to treatment (e.g., peripheral neuropathy, cognitive function, fall risk, pain, fatigue) that may affect their ability to participate in a resistance training intervention (Campbell et al., 2019). For this reason, prescribing appropriate resistance exercises to TNBC patients in chemotherapy treatment is vital to obtaining and understanding the responses of WBC count and CT efficacy as a result of the intervention. Guidelines specific to cancer exercise prescription have been outlined and implemented in this study, per the American College of Sports Medicine (ACSM) 2010 cancer exercise guidelines and 2018 Roundtable discussion.

With proper exercise prescription and execution, an association between resistance exercise, WBC count, and chemotherapy efficacy could be monumental to TNBC treatment, reoccurrence, and survival outcomes.

The purpose of this study is to determine if 12 weeks of resistance training during combination Adriamycin-cyclophosphamide (AC) chemotherapy treatment can maintain, or improve white blood cell (WBC) count and chemotherapy efficacy in non-metastatic triple-negative breast cancer (TNBC) patients compared to those in a usual care (UC) condition, or not engaging in resistance training during the same AC chemotherapy treatment. It is hypothesized that TNBC patients who engage in resistance exercises during AC chemotherapy treatment will maintain, or see improvements in WBC count and chemotherapy efficacy compared to participants with no prescribed exercise intervention.

Chapter II: Review of Literature

Overview

Only 15-20% of breast cancer patients are diagnosed with triple negative breast cancer (TNBC), a form of breast cancer characterized by a lack of molecular targets: estrogen and progesterone hormone receptors, and human epidermal growth factor 2 (HER-2) (Patel et al., 2019). Due to the lack of molecular targets present, TNBC is one of the most aggressive forms of BC and can be one of the hardest to treat due to an increased risk of metastasis and relapses (Wahba & El-Hadaad, 2015). Because hormone and HER-2 targeted therapies are not viable options for TNBC patients, chemotherapy and surgery are standard clinical treatment choices (Wahba & El-Hadaad, 2015). Traditionally, when treating other forms of breast cancer, chemotherapy is administered in adjuvant settings (after initial treatment), but triple-negative cancers have reported higher response-rates to neoadjuvant chemotherapy (before initial treatment), in addition to greater long-term outcomes (Wahba & El-Hadaad, 2015). While neoadjuvant CT is often an effective first line of defense for TNBC, there can be detrimental effects on white blood cell (WBC) count, resulting in CT administration delays, reductions in dosage, and patient ineligibility for receiving treatment altogether, furthering the risk of metastasis and mortality (Karvinen et al., 2014). Since there are few cancer treatment options for TNBC patients, WBC count is vital to receiving chemotherapy treatments, suppressing tumor growth, and increasing patient survival (Karvinen et al., 2014). In general, physical exercise has been shown to increase immune function and circulating WBCs in healthy populations, but little research has been done to examine the effects of physical exercise and hematologic outcomes in cancer patients (Freidenreich & Volek, 2012). Specifically, in the TNBC population, WBC counts are compromised as a side effect of CT, and the effects of regular exercise during CT treatment are poorly known in regard to chemotherapy efficacy and subsequent tumor response.

Triple-Negative Breast Cancer Characteristics and Interventions

Triple-Negative Breast Cancer is a subtype of breast cancer (BC) that is characterized by its molecular profile: a negative estrogen (ER) receptor, negative progesterone (PR) receptor, and negative human epidermal growth factor 2 (HER-2) receptor, making it one of the most rare and aggressive subtypes of breast cancer (Aysola et al., 2013). Following a TNBC diagnosis, several factors are taken into account regarding the type of treatment regimen given to a patient (including tumor size, cancer stage, metastasis, status of lymph nodes), but often chemotherapy is advised as systemic option—due to a lack of other therapeutic options (Gupta et al., 2020). A typical CT regimen for TNBC patients involves a combination of CT drugs in the neoadjuvant setting in order to reduce tumor size and evaluate chemo efficacy before subsequent treatment and surgical steps are taken (Gupta et al., 2020). Treatments generally consists of four cycles of drug administration; chemotherapy drugs are given once every three weeks, for a total of twelve weeks, and are only administered to patients who meet adequate white blood cell and neutrophil counts (Lohman et al., 2018). Because neoadjuvant chemotherapy is often one of the best options available for TNBC patients, studies on chemo sensitivity in the TNBC population revealed the most effective outcomes were in response to anthracycline/taxane-based chemo regimens—such as Cyclophosphamide (Aysola et al., 2013).

White Blood Cell Count and Chemotherapy Efficacy

Reduction in WBC count is often associated with complications in chemotherapeutic eligibility, such as increased risk of illness, infection, and inability to tolerate agents of treatment (Moses & Brandau, 2016). Although chemotherapy is often the first line of defense to reduce tumor size in TNBC patients, white blood cells are also the body's first line of defense against the cytotoxic effects of CT, often leading to increased susceptibility of additional infection and weakening immune function (Crawford et al., 2004). Because chemotherapy drugs are extremely cytotoxic, especially families of taxane drugs often used in TNBC treatment, the subsequent hematological effects may impact CT treatment efficacy (Moses & Brandau, 2016). As a result of chemotherapy treatments, the body's immune system becomes suppressed by toxic chemicals, which may impact patient tolerance and ability to receive treatment. When a patient's ability to receive treatment is compromised by infection, reductions in circulating WBCs, and protective mechanisms, treatment outcomes may also be compromised (Crawford et al., 2004).

Cancer and Exercise

Prior to research in the early 1990's and 2000's, cancer patients were advised to avoid physical activity, but in 2010, the American College of Sports Medicine developed the first set of exercise guidelines for cancer survivors and concluded exercise as generally safe for patients, even during treatment (Campbell et al., 2019). Today, a myriad of scientific evidence supports and agrees that cancer patients should continue to be physically active throughout cancer therapy treatments and remission (Schmitz et al., 2019). In addition to emerging evidence linking exercise, improved immune function, and reduction in tumor growth, research in mouse models has shown that exercise in conjunction with chemotherapy also helps slow tumor growth (Patel et al., 2019). While the area of research relating WBC count, resistance training, and CT efficacy is less explored, randomized control trials have reported preliminary evidence showing that exercise performed during cancer treatment may improve treatment efficacy (Patel et al., 2019), (Freidenreich & Volek, 2012). Nonetheless, resistance, or strength training exercises and outcome effects on cancer patients continues to be understudied (Patel et al., 2019).

In addition to the benefits of exercises, components of physical activity, including type, intensity, duration, and frequency are crucial to assessing and prescribing physical exercise for cancer patients, which includes understanding a patient's limitations and restrictions, treatment timeline, and physical status (Patel et al., 2019). It is also important to keep in mind the possibility of adverse events when working with cancer patients who are receiving treatment, which may include strokes, hospitalizations, increasing weakness, and weight loss (Karvinen et al., 2014).

White Blood Cell and Immune Responses to Exercise

In the general population, physical exercise and general physical activity is associated with improvements in immune system functions—including WBC functions (Bartlett et al., 2021). Following chemotherapy, WBCs become suppressed by cytotoxic agents of treatment, and though limited data exists in relation to TNBC, WBC count, and exercise, data has shown that WBC function and resistance to infection may improve as a result of physiological changes in the quality and quantity of WBCs following exercise (Bartlett et al., 2021). Rises in WBCs immediately following exercise and later, post-exercise, is a mechanism of exercise-induced leukocytosis (Jamurtas et al., 2018). Although not many studies have researched in-depth types of physical exercise (aerobic, resistance, intense bouts, etc.) in correspondence to changes in WBC count, exercise-induced leukocytosis has been reported for short and long submaximal, and resistance training exercises (Jamurtas et al., 2018). Additionally, there is a large space for didactic growth regarding WBC response to exercises in populations in compromised WBC conditions.

Cancer Exercise Prescription and Guidelines

In 2018, ACSM hosted a Roundtable on Physical Activity and Cancer Prevention and Control in order to update (in light of new research and studies) the 2010 ACSM Roundtable recommendations and guidelines for cancer and exercise (Campbell et al., 2019). Though the 2010 Roundtable discussion deemed exercise safe for cancer patients (which remains conclusive), the 2018 Roundtable discussion highlights that cancer exercise studies and their sample populations are largely based on willing participants, which may accurately represent the entire, or typical cancer patient population (Campbell et al., 2019). Variance in patient physical capability is important to keep in mind when prescribing strenuous exercises, especially for those enrolled in treatment—as their exercise tolerance may be affected by the side effects of chemotherapy (Campbell et al., 2019). Medical clearance (approval from an oncologist or medical professional) and exercise testing (body composition, muscle strength and endurance, cardiorespiratory endurance, flexibility) should be implemented in respect to a patient's cancer diagnosis, treatment modality, and current health status (Campbell et al., 2019).

The FIIT Principle is used to develop exercise prescriptions and is based on the frequency, intensity, time, and type of exercise (Campbell et al., 2019). For resistance exercises specifically, the FITT Principle recommends training 2-3 days per week for 20 to 30 minutes (Schmitz et al., 2019). Baseline exercise level and individual classification as an "exerciser" or "non-exerciser" should be determined in order to accurately adjust any cancer diagnosis recommendations. The Leisure Score Index (LSI), derived from the Godin-Shepard Leisure-Time Physical Activity Questionnaire (GSLTPAQ) assesses physical activity frequency and intensity (light, moderate, vigorous) (Karvinen et al., 2014). According to LSI scores, individuals can be classified as an "exerciser" or "non-exerciser" using ACSM's recommendations for exercise: 150 minutes of moderate-to-vigorous exercise per week, or 60 minutes of vigorous exercise per week (Karvinen et al., 2014). If the aforementioned variables are met, an individual is considered an "exerciser." Exercise prescription should be adjusted for any exercise intolerance, side effect of cancer treatment, impairment, and patient limitation.

Summary

The unique molecular profile of TNBC breast cancer makes it one of the rarest, and hardest subtypes of breast cancer to control and treat. Because of limited molecular targets, there are few treatment options available to TNBC patients. While neoadjuvant chemotherapy has become a part of the standard regimen of treatment, administration of CT drugs is dependent on adequate WBC counts. TNBC patients with low blood counts risk experiencing reduced dosages in treatment, delays, and even complete ineligibility of treatment. Due to the aggressive nature of TNBC, it is vital that patients are able receive every chemotherapy treatment. An association exists between increases in WBC count and exercise in the general population, but little research points to this evidence in the TNBC or WBC-compromised populations. Thus, the purpose of this study is to determine if 12 weeks of resistance training using stretch bands during combination Adriamycin and cyclophosphamide (AC) chemotherapy treatment can maintain white blood cell (WBC) count and chemotherapy efficacy in non-metastatic triple negative breast cancer (TNBC) patients compared to those in a usual care condition, i.e., not engaging in the prescribed resistance training protocol during AC chemotherapy treatment.

Chapter III: Methods

Selection of Participants

Twenty non-metastatic triple-negative breast cancer (TNBC) patients in combination Adriamycin and cyclophosphamide (AC) chemotherapy (CT) will be selected for this study through patient referrals, disseminating trial information to clinics, and communication with cancer centers in the Dallas/Fort-Worth metroplex. The study will also be posted on clinicaltrials.gov to increase public awareness and knowledgeability of study criteria and purpose. Inclusion criteria for subject participation includes a histologically confirmed diagnosis of TNBC currently in a stable non-metastatic disease state, AC chemotherapy with curative intent, and approval by oncologist to exercise and participate in the study. Exclusion criteria will include refusal to give individual informed consent or obtain consent from an oncologist, possession of a metastatic disease-state, receival of any previous chemotherapy treatment, smokers, individuals with congenital bone marrow defects, autoimmune disorders, rheumatoid arthritis, Kostmann's syndrome, Hypersplenism, HIV/AIDS, aplastic anemia, previous splenectomy, and individuals taking lithium, corticosteroids, beta-agonists, and long-term antibiotics.

Participants will be eligible for the study regardless of exercise status and knowledge unless prohibited by any of the aforementioned exclusion criteria. The study sample will be obtained through convenience sampling. Random processes will not be used to select participants due to the specific disease state of individuals eligible for the study. Because participants will be selected through accessibility and convenience (and willingness to participate), it is important to reiterate that subjects will be included regardless of exercise status and knowledge—contributing to a larger sample of individuals with traits representative of the non-metastatic TNBC population. Extraneous variables may include natural WBC production, diet, hormone concentration, and menopause status. Subjects will be asked to keep a food log for review throughout the study. Menopausal status will also be recorded as a component of subject demographics.

Study Design

Prior to intervention, each participant will complete the Godin-Shepard Leisure-Time Physical Activity Questionnaire (GSLTPAQ) to determine physical activity. Participants will also be classified as "exercisers" or non-exercisers" based on the American College of Sports Medicine (ACSM) Physical Activity Guidelines. The results of the GLAQ Subject demographics will be obtained from patient records (age, weight, height, sex, race, comorbidities, menopausal status). A resistance exercise program will be randomly assigned to half of the participants, and the other half will undergo a usual care condition, i.e., no administered participation in resistance training during chemotherapy administration. The exercise intervention group will begin the resistance training protocol two weeks before the first AC-CT treatment and conclude the exercises during the last week of treatment (exercises performed for a total of 12 weeks). The usual care group, or control group, will participate in data collection but will not be given an exercise intervention. Participants of the usual care group will be advised to continue activities of daily living during treatment as they see fit. The usual care group will not be told to discontinue exercise if it is a part of their normal routine.

White blood cell (WBC) count and tumor response, determined by changes in tumor size, will be measured in both groups pre-intervention (baseline), mid-intervention (week 7), and post-intervention (week 14). Chemotherapy efficacy will be regarded as a secondary measurement of tumor response, and will be determined by changes in tumor size throughout treatment. The final chemotherapy treatment for all participants will take place week 9. The entirety of the study runs for 14 weeks with a 12-week exercise intervention or usual care condition. WBC count will be objectively determined by routine complete blood count measurements at the chemotherapy center. Tumor responses will be assessed by PET-CT scans and read subjectively by a radiation oncologist. PET-CT scan readings will be quantitatively transformed to standard uptake value (SUV) and reported as ratios. SUV values are representative of cancer activity and response to treatment and will be used to semi-quantitatively determine chemotherapy efficacy in subjects of the control and intervention groups (Kinahan et al., 2010). WBC count, changes in tumor response, and subsequent chemotherapy efficacy will be compared between groups.

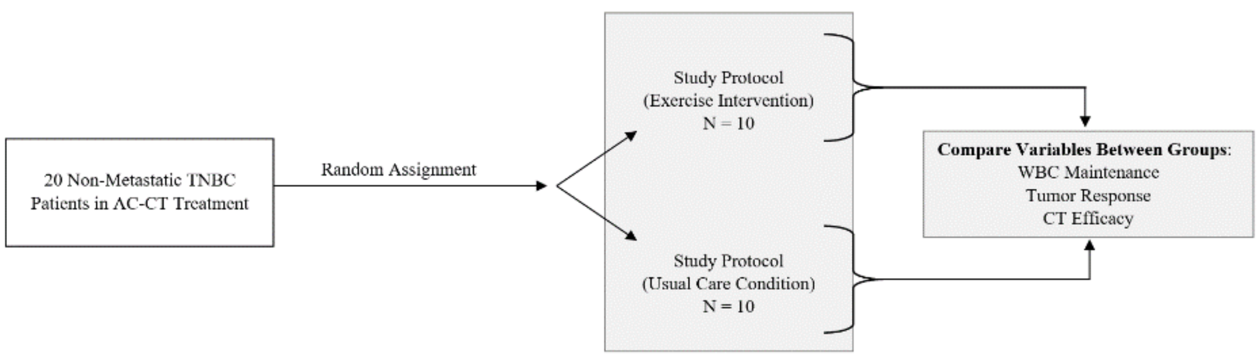


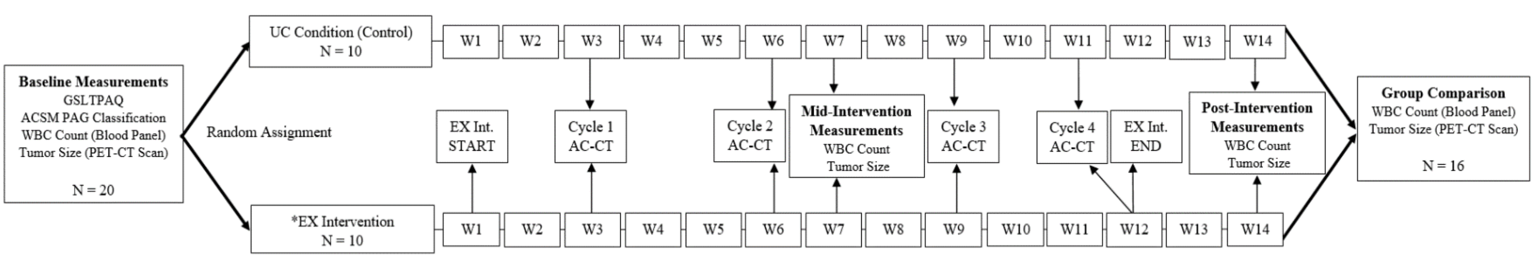
Figure 1: Study Design

Study Protocol

This study is designed as a randomized control trial. Non-metastatic TNBC subjects will be randomly assigned to participate in either an exercise intervention group or usual care, or control group. Subjects randomized to the exercise intervention group will participate in a 12-

week resistance training protocol starting one week prior to the first AC-CT treatment until the last week of treatment (CT is administered in four cycles, treatment received once every three weeks). Exercises will be performed seated, and participants will use stretch bands for resistance. Based on the FITT principle and cancer exercise guidelines established by ACSM, subjects will be prescribed resistance exercises three times per week for a total of 20-30 minutes. Each exercise session will be followed by a rest day, and exercises will not be performed in conjunction with CT treatment days. Resistance exercises prescribed to subjects will consist of total body movements that are easy for subjects to replicate at home and adjust resistance with bands. These will include bicep curls, triceps extensions, seated rows, scapular retractions, chest press, knee extensions, hip abductions and adductions, heel raises, chair squats, and seated sit-ups. Stretch bands will be utilized for exercise because they are generally safer than dumbbells and widely used in geriatric and vulnerable populations (Karvinen et al., 2014). Total body exercises with stretch bands can be performed from a variety of seated positions. Cancer patients in CT may experience extreme bouts of fatigue and nausea as a side effect of treatment, so it is important to administer exercises that are safe, convenient, and effective. Resistance training with bands is practical for cancer patients because tension can be adjusted for a variety of patient physical capability and adjustments in bodily function throughout treatment (Karvinen et al., 2014).

Over the 12-week exercise intervention subjects will perform one of the three weekly exercise sessions under supervision of a trainer. The other two exercise sessions will be completed by the participant on their own. Subjects will be given PDF access to a file with the exercises along with video instructions and demonstration of each movement. While performing exercises on their own, subjects will be reminded to maintain band tension so that the exercises are strenuous and moderately challenging. The exercise prescription will be constructed of warm-up exercises, a strength portion, and subsequent cool-down/stretching period. Targeted muscle groups will vary across the three exercise sessions. The warmup will consist of three movements, performed for three sets of ten repetitions. The subsequent strength portion will consist of six movements, targeting major muscle groups, performed for three sets of twelve repetitions. Lastly, the cool-down/stretching period will be completely seated and be comprised of full body flexibility exercises. Flexibility exercises will be performed for one set and each position should be held for 15-20 seconds each. Outside of supervision, subjects will be asked to keep a journal record of their exercises to review with the trainer during their weekly in-person session. Participants assigned to the usual care condition (control group) will not perform or be given access to exercises prescribed to the exercise intervention group. Subjects of the control group will be instructed to continue daily activities and lifestyle habits throughout treatment. After all post-intervention measures have been obtained, control subjects will be given access to the exercise prescription tools developed for the study (PDF file, and video instruction/demonstration access).



*Exercise Intervention: 12-week resistance training protocol, performed 3x weekly, 20–30-minute sessions

GSLTPAQ = Godin-Shepard Leisure-Time Physical Activity Questionnaire
ACSM PAG = American College of Sports Medicine Physical Activity Guidelines

N = Number Participants
UC = Usual Care Condition (Control Group)
EX Intervention = Exercise Intervention Group

AC-CT = Adriamycin-Cyclophosphamide Chemotherapy Treatment

Figure 2: Protocol Design

Selection of Test Instruments/Data Collection

Researchers and radiation oncologists will be blind to whether participants are in the exercise intervention or usual care group. There will be no placebo group. White blood cell count of each participant will be determined by routine complete blood counts (CBC) performed at the chemotherapy center. A hematology analyzer (HA) is used to obtain the measurements at the CT center (Karvinen et al., 2014). The results are recorded and will be obtained from each subject's patient chart. CBC is typically administered before every CT treatment to perform a quantitative analysis of several hematologic components: red blood cells (RBCs), WBCs, and platelets. WBC count is considered low if it is less than 4,000 cells/microliter; typically, a WBC count of 3,000-4,000 cells/microliter is the minimum WBC count for receiving CT (Trujillo-Santos et al., 2008). HAs are used almost virtually in every medical setting and are the standard basis for determining follow-up procedures to medical therapy, disease course, and further intervention (Vis et al., 2016).

Chemotherapy efficacy and tumor responses will be recorded via positron emission tomography and x-ray computerized tomography (PET-CT) scan. Radiation oncology imaging tracers utilized in PET-CT scan devices are commonplace for detecting cancer activity; PET-CT imaging is widely used in the cancer medical setting to monitor tumor responses to treatment and changes in tumor size (Kinahan et al., 2010). Subjective readings of PET-CT imaging can be quantitatively transformed into standardized uptake values (SUVs) and semi-quantitatively representative of chemotherapy efficacy. SUVs attained from PET-CT imaging has become increasingly important in clinical practice for assessing individual patient response early in treatment (Kinahan et al., 2010).

Statistical Analysis

SPSS (Statistical Package for the Social Sciences) will be used to perform all statistical analyses. The alpha level of probability will be 0.05. Mean and standard deviation will be utilized to present the descriptive statistics of independent variables. These variables include subject demographics (age, height, weight, sex, comorbidities, menopausal status), GSLTPAQ data, and classification of participants as exercisers and non-exercisers. Statistical analysis of inferential variables will be performed using a 2x3 Analysis of Variance (ANOVA). Variables include the obtained measures of WBC Counts obtained by routine complete blood counts and tumor responses obtained from quantitatively transformed SUV values (from PET-CT scan readings). A post-hoc analysis will be performed using Tukey's HSD (honestly significant difference) test if a statistically significant F-statistic is obtained from the 2x3 ANOVA.

Anticipated Outcome

It is anticipated that subjects randomized to the exercise intervention group will see consistent maintenance, or improvements in WBC count and chemotherapy efficacy throughout chemotherapy treatment. The usual care group (control group) is anticipated to see declines in WBC count as a result of chemotherapy toxicity and subsequent depletion of immune function. In the usual care condition, chemotherapy efficacy may decline with decreases in WBC count—making it more likely that participants in the control group will experience chemo administration reductions and delays as a result of low WBC count, leading to an advanced disease state.

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