EFFECTS OF PHYSICAL ACTIVITY ON FATIGUE IN BREAST CANCER PATIENTS UNDERGOING CURRENT RADIATION AND/OR CHEMOTHERAPY TREATMENT

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ABSTRACT OF THESIS

OBJECTIVE: To critically analyze the current research and address how physical activity affects fatigue among breast cancer patients undergoing current chemotherapy and/or radiation therapy.

DESIGN: Academy of Nutrition and Dietetics (AND) Evidence Analysis Library (EAL) Project

METHODS: AND's EAL Methodology, which is an objective and transparent process of systematic reviews used to evaluate, synthesize, and grade the strength of current nutrition research. The process incorporates five steps: 1) Formulate Evidence Analysis Question, 2) Gather and Classify Evidence, 3) Critically Appraise Each Article, 4) Summarize the Evidence and, 5) Write and Grade the Conclusion Statement.

RESULTS: Seven studies were analyzed following a PubMed search, which identified 27 articles relating to breast cancer and physical activity. However, several studies did not include patients undergoing current treatment, did not measure fatigue as an outcome measurement, provided no exercise intervention, or were excluded for other various reasons. Exercise interventions within the studies utilized an aerobic intervention in each case, some with additional anaerobic exercise. Of the five RCTs, only one study using an intent-to-treat protocol was able to detect a significant difference in fatigue between intervention and control groups. However, several studies were able to detect a significant difference when utilizing an analysis approach of separating participants into low- verses high-walk/exercisers. Notably, these studies lost randomization and therefore were only able to conclude an association between fatigue and physical activity rather than causality.

CONCLUSION: Physical activity effectively manages fatigue levels in breast cancer patients undergoing current chemotherapy and/or radiation treatment, with the majority of evidence showing significant reductions in fatigue levels. Breast cancer patients should be counseled to participate in aerobic activity, such as walking, and may be advised to include anaerobic exercise. This conclusion was graded *Fair, II*.

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CHAPTER 1: INTRODUCTION

Cancer is a term that describes a group of neoplastic diseases, or the abnormal new growth of tissue. If left untreated, cancer may lead to death (Leser, Ledesma, Bergerson, & Trujillo, 2013). There are over 100 different types of cancer and each has its own etiology, progression, treatment, and prognosis. Cancer can develop in response to both external and internal factors. External factors include not only lifestyle habits such as smoking, but also infectious organisms, chemicals, and radiation (American Cancer Society, 2014). Internal factors include inherited mutations, hormones, immunological conditions, and mutations resulting from metabolism (American Cancer Society, 2014). Internal and external factors may work together or separately to initiate uncontrollable cell growth and promote cancer development (American Cancer Society, 2014).

It has been predicted that in the year 2014, there will be 1,665,540 new diagnosable cases of cancer in the United States alone (American Cancer Society, 2014). Of the 1.6 million cancer cases in 2014, breast cancer will be the second most frequently diagnosed cancer in women after skin cancer and the second leading cause of death amongst women, surpassed only by lung cancer (Leser et al., 2013). Treatment for breast cancer, similar to most other cancers, may consist of a combination of surgery, radiation treatment (RT), chemotherapy (CT), or hormonal therapy. Each treatment type presents many challenges and side effects, which may be acute or chronic. Side effects of treatments may include, but are not limited to: fatigue, alopecia, nausea and vomiting, taste changes, low blood counts, neuropathy, mouth sores, and diarrhea. Of these common symptoms, cancer-related fatigue (CRF) is the most commonly reported side

effect of cancer treatment. CRF is defined as a "multifaceted subjective and physiologic state characterized by persistent, overwhelming exhaustion and a decreased capacity for physical and mental work, which are not relieved by rest" (Mustian et al., 2011). Furthermore, reports suggest that 60% to 99% of patients undergoing cancer treatment experience CRF (Mustian et al., 2011). According to the Cancer Rehab Partners (ORP), not only is CRF the most common distressing symptom among cancer patients, often times it is not evaluated properly and is undertreated.

The pathophysiology of CRF is not well understood, but becomes pathologic when it occurs during normal, daily activities; it lasts for long periods of times; and does not respond to rest (Dimeo, 2001). Mustian et al. (2001), reports that CRF may be due in part to physical deconditioning which may result from decreased physical activity itself, the cancer itself, and/or the treatment (Mustian, et al., 2011). Furthermore, other common causes may include anemia, pain, infection, hormonal imbalance, emotional distress, medication side effects, poor sleep, poor nutrition, and comorbidities (Oncology Rehab Partners, 2015).

Treatments for CRF may consist of patient education, pharmaceutical agents, non-pharmacologic therapies, and etiology-specific interventions (Mustian, et al., 2001). Nonpharmacologic treatments to treat CRF may include education, counseling, optimal sleep, nutrition, physical activity, and reducing stress. ORP suggests that the two best nonpharmacologic treatment interventions for CRF include physical activity and utilizing psychosocial interventions (i.e. massage, muscle relaxation, etc.) Current research has begun to look at physical activity as a modality to improve CRF. Past recommendations for CRF included the discouragement of physical activity as it seemed counterintuitive to

helping with CRF (Physical Activity and the Cancer Patient, 2014). However, further research is needed to conclude more specifics of exercise prescriptions for patients with different types of cancers and treatments, including breast cancer patients.

Therefore, the findings of this research have the potential to significantly alter the current recommendations related to physical activity and fatigue. If fatigue levels are decreased, not only may it increase QOL, it may positively influence nutrition intake and thus lead to decreased weight loss, which is common with severe fatigue. Staggeringly, a weight loss of as little at 6% predicts a reduced response in treatment, reduced QOL, and overall a reduction in survival rate (Leser et al., 2013). Thus, it is important to critically analyze current research and address how physical activity affects fatigue among breast cancer patients undergoing current RT and/or CT treatment.

Research Question

The research question used to conduct this Evidence Analysis Library (EAL) project, is as follows: How does purposeful, regular physical activity affect fatigue levels in breast cancer patients undergoing current chemotherapy and/or radiation treatment?

Sub-Problems

An inherent component that exists within this problem is that of physical activity and what level of activity should be reached to decrease fatigue levels. How does a high level of physical activity affect fatigue? How does a low level of activity affect fatigue? In turn, how will the physical activity level affect the fatigue levels of those undergoing cancer treatment? Furthermore, it may be difficult to define physical activity. Should purposeful, continuous movement define physical activity? Or, would an accumulation of

steps walked, perhaps recorded by a pedometer, contribute to what is considered physical activity?

Limitations, Delimitations, and Assumptions

Boundaries, or limitations, can be set forth by outside factors other than the researcher. Limitations to this research project include the availability of research that already exists related to physical activity, breast cancer, and fatigue. A second potential limitation is that of available resources for the researcher to conduct a literature search. Although the clinical search engine, PubMed, will be used it will therefore incorporate a majority of the available research. However, it may not encompass the entirety of available research. Not to be forgotten are the limitations of subjective measurements of fatigue and the fact that research articles may use different measurements of fatigue.

Delimitations, or those set by the researcher, include the inclusion of randomized control trials, observational, and cohort studies and thus excluding other types of research. In addition, studies to be included are those who are undergoing active chemotherapy and/or radiation, limiting those studies focused on post-treatment fatigue. Ultimately, the studies must include breast cancer patients but may include other types. Thus, the study will somewhat assume generalization to the breast cancer population despite the inclusion of other cancer diagnoses. Lastly, the study will assume good integrity and honesty of the patient participating in the study.

Definitions

Adjuvant: Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy. (NCI, n.d.)

Aerobic Exercise: Physical activity that increases the heart rate and the body's use of oxygen. It helps improve a person's physical fitness. (NCI, n.d.)

American Joint Committee on Cancer: A committee that has established the way that cancer is communicated. Co-created the most comprehensive anatomic staging data, known as TNM (AJCC, n.d.).

Anaerobic Exercise: strengthening muscles by forcing them to work very hard for a brief time; not using oxygen (Merriam-Webster.com, 2015)

Brief Fatigue Inventory: an assessment tool used to rapidly assess CRF. This tool is focused on QOL measurements and its purpose is to "assess the severity of fatigue and the impact of fatigue on daily functioning" (The Brief Fatigue Inventory, 2015).

Cancer: Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death (American Cancer Society, 2014).

Functional Assessment of Cancer Therapy—Anemia (FACT—An, FACT—F): An example of a FACIT questionnaire commonly used in fatigue studies is FACT-An, which is a 47-question assessment used for patients with anemia and/or fatigue (Overview of FACIT, 2015).

Functional Assessment of Chronic Illness Therapy (FACIT): a measurement system of questionnaires designed to assess QOL with a target population of those with chronic illness (Overview of FACIT, 2015).

In situ: An early stage cancer in which the cancerous growth or tumor is still confined to the site from which it started, and has not spread to surrounding tissue or other organs in the body. When cancer in situ involves cells that line the internal organs, or epithelial cells, it is called carcinoma in situ (Glossary, n.d.).

Neoadjuvant therapy: Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy. (NCI, n.d.)

Pathologic: relating to or caused by disease (Merriam-Webster.com, 2015)

Piper Fatigue Scale (PFS): a survey initially created to assess fatigue in cancer patients, but it is now used throughout several medical areas. It focuses on four areas of fatigue,

including behavioral, affective meaning, sensory, and cognitive/mood (Scoring Piper Fatigue Scale (PFS), 2015).

Union for International Cancer Control: A membership organization that exists to help the global health community accelerate the fight against cancer. Co-developed the staging system known as TNM (AJCC, n.d.).

CHAPTER 2: LITERATURE REVIEW

Introduction

Cancer is a term that describes a group of neoplastic diseases, or the abnormal new growth of tissue. If left untreated, cancer may lead to death (Leser, Ledesma, Bergerson, & Trujillo, 2013). There are over 100 different types of cancer and each has its own etiology, progression, treatment, and prognosis. Cancer can develop in response to both external and internal factors. External factors include not only lifestyle habits such as smoking, but also infectious organisms, chemicals, and radiation (American Cancer Society, 2014). Internal factors include inherited mutations, hormones, immunological conditions, and mutations resulting from metabolism (American Cancer Society, 2014). Internal and external factors may work together or separately to initiate uncontrollable cell growth and promote cancer development (American Cancer Society, 2014). In 2014, The American Cancer Society predicted 1,665,540 diagnosable cases of cancer in the United States alone (American Cancer Society, 2014).

Of the 1.6 million cancer cases in 2014, breast cancer will be the second most frequently diagnosed cancer in women after skin cancer and the second leading cause of cancer death amongst women, surpassed only by lung cancer (Leser et al., 2013). Furthermore, it is estimated that 1 in 8 women will be diagnosed with breast cancer during their lifetime (Leser et al., 2013). The most recent data suggests the 5-year survival rate for women diagnosed with breast cancer has reached 90% (American Cancer Society, 2013), which is up from 63% in the early 1960s (Leser et al., 2013). Risk factors for breast cancer include, but are not limited to: increasing age, weight gain after the age of 18, being overweight or obese, and the use of combined estrogen and

progesterone hormone therapy in conjunction with smoking or when over the age of 35 (Leser et al., 2013).

Treatment for breast cancer, similar to most other cancers, may consist of a combination of surgery, radiation treatment (RT), chemotherapy (CT), or hormonal therapy. Each treatment type presents many challenges and side effects, which may be acute or chronic. Side effects of treatments may include, but are not limited to: fatigue, alopecia, nausea, vomiting, taste changes, low blood counts, neuropathy, mouth sores, and diarrhea. Of these common symptoms, cancer-related fatigue (CRF) is the most commonly reported side effect of cancer treatment. CRF is defined as a "multifaceted subjective and physiologic state characterized by persistent, overwhelming exhaustion and a decreased capacity for physical and mental work, which are not relieved by rest" (Mustian et al., 2011). Furthermore, reports suggest that 60-99% of patients undergoing cancer treatment experience CRF (Mustian et al., 2011). The pathophysiology of CRF is not well understood; however, Mustian et al. (2011) suggests it may be due in part to physical deconditioning which may result from decreased physical activity itself, the cancer itself, and/or the treatments. Treatments for CRF may consist of patient education, pharmaceutical agents, non-pharmacologic therapies, and etiology-specific interventions (Mustian, et al., 2001). In addition, current research has begun to look at physical activity as a modality to improve CRF. Not only has current research found that physical activity reduces CRF, it may also improve aerobic capacity, emotional distress, immunologic parameters, flexibility, body composition, and quality of life (QOL) (Mustian, et al., 2001). Thus, the purpose of this literature review is to critically analyze the evidence of

how physical activity affects fatigue among breast cancer patients undergoing current RT and/or CT treatment.

Background

Carcinogenesis is the process that occurs when normal cells transform into cancer cells. This transformation is typically due to accumulating damage to genetic material by internal and external factors. The human body, under normal conditions, can repair these damaged cells through DNA repair genes. If the damage cannot be repaired, apoptosis, or programmed cell-death, may occur in result. Both the repair of these cells and apoptosis are critical cellular processes. Still, genetic damage can occur within the genes that provide DNA repair, and thus lead to dysfunction of the normal repair processes and consequently lead to uncontrolled cell growth, or cancer (Leser, et al., 2013).

Breast cancers are considered either *in situ*, meaning in its original place, or invasive. Ductal carcinoma *in situ* (DCIS) is the most common type of *in situ* breast cancer making up 83% of *in situ* cases between 2006 and 2010 (American Cancer Society, 2013). DCIS breast cancer begins in the cells lining the breast ducts and has not grown beyond its original site. DCIS may or may not progress to invasive cancer. Invasive breast cancers break through their site of origin and invade surrounding breast tissue. The prognosis of invasive breast cancer is dictated by the stage of the disease. Staging is commonly classified using the TNM system, which was developed and is maintained by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC). The system is used as a standardized tool for physicians to stage different types of cancer. This system considers the tumor size (T),

the extent of spread to nearby lymph nodes (N), and the presence or absence of distant metastasis (M). Table 1 describes the current TNM classification system.

Table 1: AJCC and UICC TNM Staging System (AJCC, n.d.)

TNM Staging System	
T: Describes the original (primary) tumor.	
TX	Primary tumor cannot be evaluated
T0	No evidence of primary tumor
Tis	Carcinoma in situ (early cancer that has not spread to neighboring tissue)
T1-T4	Size and/or extent of the primary tumor
N: Describes whether or not the cancer has reached lymph nodes.	
NX	Regional lymph nodes cannot be evaluated
N0	No regional lymph node involvement (no cancer found in the lymph nodes)
N1-N3	Involvement of regional lymph nodes (number and/or extent of spread)
M: Tells whether there are distant metastases (spread of cancer to other parts of the body).	
M0	No distant metastasis (cancer has not spread to other parts of the body.
M1	Distant metastasis (cancer has spread to distant parts of the body)

Since breast cancer is one of the most studied types of cancer, there are many known risk factors. Sex, age, family history, early menarche, and late menopause are risk factors that cannot be modified. Modifiable risk factors include postmenopausal obesity, use of hormones, cigarette smoking, and alcohol consumption. Hormones are believed to increase breast cancer risk related to increasing cell proliferation and thus the increase in likelihood of DNA damage with the possibility of cancer growth. These known risk factors have been specifically associated with hormone positive breast cancers, such as estrogen and progesterone. Little is known about hormone negative breast cancers and their associated risk factors. Several strategies to reduce breast cancer risk have been studied. Recommendations include: avoiding weight gain throughout adulthood, maintaining a BMI < 30 kg/m^2, regular physical activity, and limiting alcohol intake. In addition, breastfeeding for an extended period of time (at least one year) may also reduce a woman's risk for developing breast cancer (American Cancer Society, 2013).

The American Institute for Cancer Research (AICR) and the World Cancer Center Research Fund (WCRF) published the "Food, Nutrition, Physical Activity, and Prevention of Cancer: A Global Perspective" in 2007 as the most comprehensive report on diet and its association with cancer ever completed. The AIRC and WCRF are continuously working on updating reports for several types of cancer each year. A completely updated comprehensive report is expected in the year 2017. Table 2 describes the top 10 recommendations below, in addition to not smoking or chewing tobacco.

Table 2: Recommendations Drawn from the WCRF/AICR Second Expert Report (Research Science Expert Report, n.d.)
1. Be as lean as possible without becoming underweight.
2. Be physically active for at least 30 minutes every day. Limit sedentary habits.
3. Avoid sugary drinks. Limit consumptions of energy-dense foods.
4. Eat a larger variety of vegetables, fruits, whole grains, and legumes such as beans.
5. Limit consumption of red meats (such as beef, pork, and lamb) and avoid processed meats.
6. If consumed at all, limit alcoholic drinks to 2 for men and 1 for women a day.
7. Limit consumption of salty foods and foods processed with salt (sodium).
8. Don't use supplements to protect against cancer.
9. It is best for mothers to breastfeed exclusively for up to 6 months and then add other liquids and foods.
10. After treatment, cancer survivors should follow the recommendations for cancer prevention.

Treatment of breast cancer is determined by several factors, including the stage, biological characteristics, patient's age, risks verses benefits of treatment, and finally, patient and physician consideration. Most women with breast cancer will undergo some type of surgery in combination with RT, CT, and/or hormone therapy. Chemotherapy is "the use of chemical agents or drugs to systemically kill cancer cells" (Leser et al., 2013). This therapy is used to kill rapidly dividing cells and thus includes both cancer and

normal, healthy cells. Normal cells, which are vulnerable to CT, include bone marrow, hair follicles, gonads, and gastrointestinal mucosa. Side effects of CT include, but are not limited to: low blood counts, alopecia, nausea and vomiting, mouth sores, and fatigue.

Radiation therapy may be used alone or in combination with other therapies. Radiation "utilizes high-energy x-rays (ionizing radiation) or other radioactive particles such as electrons, neutrons, protons, beta particles, or gamma rays…to eradicate tumor cells while minimizing injury to healthy, normal tissues in a specific area of treatment" (Leser et al., 2013). Side effects are typically dependent on the site of treatment; however, fatigue is the most common side effect throughout all radiation treatment fields (Leser et al., 2013).

Additionally, hormone therapy is used with hormone sensitive cancers, including breast, ovarian, and prostate. This type of therapy works to stop or reduce the body's ability to produce certain hormones, interfere or block hormone receptors, and/or substitute agents that are chemically similar to the active hormone but cannot be used by the tumor (Leser et al., 2013). Side effects of hormone therapies are dependent on the type of hormone and its mechanism of action.

Side effects from treatment are mitigated using several strategies including patient education, pharmaceutical agents, non-pharmacologic therapies, and etiology-specific interventions. Cancer related fatigue, which was previously noted as the most common unmanaged symptom of patients undergoing cancer treatment, may be treated with interventions of nutrition, pharmacologic, non-pharmacologic, or physical therapy. Evidence has shown that exercising during and post-treatment is considered safe and may even improve physical functioning, exercise tolerance, body composition,

cardiopulmonary fitness, muscular strength, depression, anxiety, and QOL (Leser et al., 2013). Early studies have suggested that exercise can decrease CRF, along with other common symptoms, during RT and CT (Mock et al., 2001). Often times, cancer patients are discouraged to exercise due to severe fatigue with beliefs that exercise will promote or increase their fatigue level. Thus, the previous approach to mitigate CRF by clinicians was rest and decreased physical activity (Physical Activity and the Cancer Patient, 2014).

Tools for Assessing Cancer Related Fatigue

The National Cancer Institute (NCI) describes the assessment of fatigue as being multidimensional in nature. Therefore, multiple tools have been developed for research to be conducted on fatigue. Due to limited time in clinical practice, many screening tools for fatigue are a single-item fatigue intensity rating, with scores of 1 to 10, with 10 being very severe fatigue. Assessment of fatigue is necessary, as it is known for affecting pain, emotional distress, anemia, sleep, nutrition, and level of activity. A single-item screening tool may be appropriate for initial screening to help identify patients that require further comprehensive screening of symptoms. However, there are several more comprehensive tools that have been developed to assess fatigue, which is also commonly assessed with QOL instruments. The NCI identifies selected assessment tools of fatigue, including: Brief Fatigue Inventory (BFI), the Functional Assessment of Cancer Therapy—Anemia (FACT—An), the Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT—F), the Piper Fatigue Scale (PFS, long and short versions), the Schwartz Cancer Fatigue Scale, Fatigue Symptom Inventory, and several others (Fatigue (PDQ®), 2015).

The Functional Assessment of Chronic Illness Therapy, or FACIT, is a measurement system of questionnaires designed to assess QOL with a target population of those with chronic illness. The measurement system was first developed in 1987 and has continued to grow encompassing multiple disease states, treatments, conditions, and non-cancer specific subscales. There are now more than 50 different FACIT scales which are intended to capture clinically-relevant issues associated with a specific disease or associated symptoms with comparison across different medical conditions, as appropriate. The FACIT questionnaires are commonly used among national and international research settings and have been demonstrated to be reliable, valid, and sensitive to change. An example of a FACIT questionnaire commonly used in fatigue studies is FACT-An, which is a 47-question assessment used for patients with anemia and/or fatigue. FACIT also offers a 40-question questionnaire related to fatigue in chronic illness called FACIT-F. See *Appendix A* for a copy of both assessments (Overview of FACIT, 2015).

The BFI is an assessment tool used to rapidly assess CRF. This tool is focused on QOL measurements and its purpose is to "assess the severity of fatigue and the impact of fatigue on daily functioning" (The Brief Fatigue Inventory, 2015). Its focus is on patients with fatigue specifically related to cancer and focuses on fatigue in the previous 24 hours. It utilizes the method of self-report, an interview with research staff, or an interactive voice response system, all within about five minutes. In addition, the PFS is a commonly used questionnaire among medical researchers to measure fatigue of patients in clinical studies. This questionnaire contains 22 questions and takes approximately two minutes to complete. The survey was initially created to assess fatigue in cancer patients, but it is

now used throughout several medical areas. It focuses on four areas of fatigue, including behavioral, affective meaning, sensory, and cognitive/mood (Scoring Piper Fatigue Scale (PFS), 2015). Within clinical research studies, there are several validated questionnaires that may be appropriate to the clinical study. Choosing the correct questionnaire is dependent on the purpose of the study, the desired outcome per patient report, and the validity of the questionnaire.

Understanding Fatigue

Cancer-related fatigue can have a profound effect on the daily lives of cancer patients. Often times, fatigue limits the life of a patient not just at home, but also within areas of their life including work, community, social activities, and recreational activities. According to the Cancer Rehab Partners (2015), fatigue may reduce the ability of a patient to participate in activities of daily living, instrumental activities of daily living, returning to work, participating in premorbid social commitments, and physical activity or exercise.

As previously described, CRF is fatigue that is persistent and interferes with functioning. Normal fatigue and CRF are not the same as CRF refers to fatigue that does not respond to rest and becomes pathologic (Oncology Rehab Partners, 2015). This type of fatigue is a complex symptom and may present for several different reasons. The biochemical reasons to why fatigue may occur is unclear at this time, however, it may be due to electrolyte imbalances, immune dysregulation, abnormal cortisol secretion, metabolic syndrome, and pro-inflammatory cytokine activity (Oncology Rehab Partners, 2015). It is thought that cytokines, defined by the Oncology Rehab Partners as “a diverse group of polypeptide regulators such as proteins, peptides, and glycoproteins that are

secreted by the immune system in response to pathogens (infections) and malignancies (tumors)" may plan an active role in CRF (Oncology Rehab Partners, 2015). Cytokines may stimulate the growth of the cancer tumor while also causing fatigue. However, fatigue may also be affected by mood disorders, problems with sleep, dietary issues (malnutrition), medication side effects, and/or untreated pain. It is clear that CRF is multifactorial and complex.

Fatigue in Breast Cancer Patients

Fatigue incidence and severity may vary amongst the cancer population depending on the specific diagnosis, whether the cancer is a chronic condition, the type and duration/length of treatment, when the treatments were administered, and whether or not appropriate measures were taken for fatigue intervention. Reinertsen, Cvancarnova, Loge, et al. (2010) investigated long-term fatigue in breast cancer survivors. The study found that women may experience fatigue for up to 10 years following treatment. The authors found three predictors of chronic fatigue, including: psychological distress, treatment-related pain, and high body mass index. Based on this study, the authors also suggested that addressing these contributing factors early in the course of treatment may help prevent the development of CRF.

Noal, Levy, Hardouin, et al. (2010) conducted a longitudinal study with women who had localized breast cancer and received adjuvant treatment. The researchers found that CRF was the most common symptom reported among the women, regardless of therapy type. In addition, the fatigue was linked to the patient's psychological status and was also persistent over time. Notably, even after one year, 40% of women reported significant fatigue.

Treating Fatigue in Cancer Patients

There are two categories of interventions to treat CRF; these include pharmacological and nonpharmacological interventions. Pharmacologic interventions are those that are medications prescribed by physicians or other providers with prescribing rights. The physician works to identify any underlying conditions that may be contributing to the development of fatigue. Medications may be prescribed to treat fatigue or specifically treat the underlying condition, for example, pain. According to the National Comprehensive Cancer Network and its guidelines for CRF (Version 1.2014), specific medications, which may be used to treat the fatigue itself, include psychostimulants, such as methylphenidate (Ritalin) or modafinil (Provigil), after ruling out other causes of fatigue.

Nonpharmacologic interventions typically begin with education and counseling which begins at the start of treatment. Patients are counseled regarding side effects of the treatments, including fatigue, and providers typically recommend resting appropriately and avoiding unnecessary chores and nonessential activities (Oncology Rehab Partners, 2015). Two intervention categories include physical activity, which is being extensively studied and the primary focus of this EAL project, and utilizing psychosocial interventions. Psychosocial interventions include attention-restoring therapy, massage, yoga, muscle relaxation, biofeedback, mindfulness-based stress reduction, and acupressure.

Improving diet and nutrition is another nonpharmacologic intervention to help manage fatigue. A study conducted by Huang, Zhang, Kang, et al. (2001) found a correlation between better nutritional status and less severe fatigue. Proper nutrients are

needed for the body to function properly; carbohydrates and fat are utilized for energy, and protein is necessary for maintaining muscle. Additionally, vitamins, minerals, and water in their adequate amounts are required for several different bodily functions. Without proper nutrition, the body cannot function efficiently which can lead to an increase in fatigue. There is a current, ongoing study being conducted regarding the efficacy of diet and physical activity interventions in prostate cancer patients. This study may provide further nutrition recommendations for cancer survivors. Although there is limited research on the role of specific dietary recommendations on fatigue, the evidence related to physical activity and how it relates to fatigue is becoming more abundant.

Programmed Aerobic Exercise and Fatigue

Aghili, Farhan, and Rade (2007) conducted a prospective, non-randomized, parallel designed pilot study for the purpose of assessing aerobic exercise and its affect on severity of fatigue in RT patients. The study included breast and head/neck cancer patients from two cancer centers who were hospitalized for supervision throughout the study. Inclusion criteria encompassed patients 18-65 years old receiving at least five weeks of RT, and with at least three months of disease duration. Exclusions consisted of those with a history of cardiac disease or diabetes and patients with anemia, reduced white blood cells, dyspnea, severe bone pain, and metastasis (Aghili, Farhan, & Rade, 2007).

The study assessed fatigue levels using the BFI one week prior to the start of RT and again daily for the following 28 days. The aerobic training program consisted of 20 minutes of daily walking, beginning during the second week of RT, and lasted throughout the duration of treatment. Relaxation methods followed the exercise. The control group

did not participate in an exercise program and completed the BFI just as the training group did. Fifteen participants were required for each the intervention and control group in order to detect a 70% reduction in fatigue with a one-sided 5% significance level and 80% power (Aghili et al., 2007).

There were no significant differences between baseline characteristics or baseline fatigue scores among the intervention and control groups. At the four-week mark of the study, 44% of patients in the intervention group reported mild fatigue, whereas 57% of patients in the control group reported severe fatigue ($p=0.011$). The median fatigue rating between weeks two and four showed no change in the severity of fatigue amongst the intervention group. However, a significant increase was found in fatigue severity with the control group ($p=0.039$). The results of this pilot study showed that physical training may have had a positive impact on fatigue severity with patients undergoing RT. Notably, fatigue was more severe with a longer duration among those who did not exercise in comparison to those who did. This study shows that it may be more appropriate to recommend exercise along with sufficient rest rather than reduced activities and increased rest that has been commonly advised to cancer patients undergoing current treatment (Aghili et al., 2007).

Fatigue and Quality of Life Outcomes of Exercise

Mock et al. (2001) conducted a multi-institutional pilot study that encompassed 52 women from five outpatient cancer departments. Patients were randomly assigned to the experimental group that consisted of a walking program, or the control group that consisted of usual care during adjuvant CT or RT for breast cancer. Inclusion criteria consisted of patients with recent surgery for stage I, II, or IIIA breast cancer who were

expected to undergo outpatient adjuvant CT or RT. Patients were excluded if concurrent medical issues contraindicated the exercise program. The purpose of this study was to assess a home-based moderate exercise walking routine to help improve fatigue levels experienced by patients undergoing CT and RT (Mock et al., 2001).

This prospective, controlled, and randomized study assessed fatigue, physical function, emotional distress, and QOL outcomes prior to and at the end of CT and RT. Personnel for the study was given training in order to maximize consistency of evaluation amongst study sites. Study participants included patients between the ages of 28-75 years, with a make-up of patients who were 70% married, 66% employed, 86% white, with a mean of 15 years of education, an average BMI of 25.66, and 95% who were either stage I or II. The intervention consisted of an individualized walking program based on age, level of fitness, and type of cancer. Sessions started with the initiation of RT or CT. The program was initiated with 10-15 minutes of exercise, five to six times per week. Participants were then advanced to 30-minute sessions. Participants were instructed to keep diaries in order to measure adherence to the program. The validated PFS assessed fatigue along with the Profile of Moods States measuring emotional distress. Physical functioning was measured with Medical Outcomes Study Short Health Form (MOS), a 12-minute walk test, and an activity level rating scale (Mock et al., 2001).

The study followed an intention-to-treat protocol, which included all subjects in the final analysis regardless of adherence. It was found that almost 50% of subjects in the usual-care, or control group, exercised during therapy. Additionally, almost 33% of women in the treatment group were not completely adherent to the exercise program. The study found no significant difference amongst post-test data. This may have been related

to low adherence and a high number of exercisers in the control group. Further analysis was conducted to compare a low-walk verses high-walk group between the subjects from both the intervention and control group. The low-walk group consisted of those who exercised less than 90 minutes per week and the high-walk group included those who exercised more than 90 minutes per week. Amongst this data, fatigue was slightly lower among the low-walk group at pretest and significantly higher at post-test compared to the high-walk group. Furthermore, higher fatigue levels were found among CT patients compared to RT patients. The 12-minute walk test demonstrated decreased physical functioning among the low-walk group. Additionally, QOL decreased 48% in the low-walk group verses 16% in the high-walk group, which was found to be statistically significant. Overall, these results suggest an association between a home-based walking program and a reduction in fatigue and emotional distress, with an increase in QOL, during RT and CT (Mock et al., 2001).

Aerobic and Resistance Exercise Program During Radiation Therapy

Mustian et al. (2009) performed a clinical trial that was two-armed, randomized, and controlled. The purpose of this pilot study was to measure the effectiveness of a home-based aerobic and resistance exercise program. The study assessed its effectiveness based on aerobic capacity, strength, muscle mass, CRF, and QOL. Participants included breast cancer and prostate cancer patients who would undergo RT. Those who were included in the study had a primary diagnosis of breast or prostate cancer, a completion of a baseline assessment, at least 30 treatments, and a sedentary lifestyle. Patients were excluded if the disease was recurrent, with disease metastasis, or a presence of study contraindication (Mustian et al., 2009).

Forty patients were randomized to either the control or treatment group. The control participants were instructed not to begin any new formal exercise program. The treatment group was provided with an individually tailored home-based, progressive walking, and therapeutic resistance band exercise program. The program consisted of moderate aerobic exercise aimed at 60-70% of resting heart rate, seven days a week, along with encouragement to meet at least 10,000 steps per day or a 5-20% increase each week. Resistance training consisted of resistance band exercises seven days per week. All patients were provided a diary and were instructed through a 45-minute instructional training session. Assessments were completed at baseline, four weeks, and three months. Cancer related fatigue, QOL, and functional status were measured. Adherence was measured with daily diaries that logged activity and time. Pedometers were also used to measure steps (Mustian et al., 2009).

A significant difference was found between the two groups in aerobic capacity, which was measured by a six-minute walk test. A t-test showed the treatment group took a greater amount of steps and completed more resistance training, demonstrating adherence to the intervention. Cancer related fatigue improved among the treatment group at both week four and the three-month follow-up. Fatigue was also improved in the control group at week four, but worsened at three-months. At week four and the three-month follow-up, there was no significant difference in aerobic capacity, strength, and muscle mass between groups. A significant difference was found in QOL scores with improvement in the treatment group compared to the control group. Although the intervention did not show improvement in fitness levels, improvement was found in QOL and CRF, which was the primary goal of the intervention (Mustian et al., 2009).

Exercise Managed Fatigue During Breast Cancer Treatment

Mock et al. (2004) addressed the management of fatigue by exercise in a randomized, controlled trial. The study sought to determine the effects of exercise on fatigue levels during current treatment for breast cancer based on previous findings that toxic cancer treatments with the addition of decreased levels of activity during treatment reduced a patient's capacity for physical performance. Patients were randomized to either the exercise or usual care group. The study took place at National Cancer Institute designated Cancer Centers. A woman qualified for the study if she was between the ages of 18-70 years, being treated for Stage 0-III breast cancer, and scheduled to receive outpatient radiation therapy or adjuvant chemotherapy. Patients were excluded if current major health problems had potential to affect participation in an exercise program or if the patients already engaged in regular exercise (defined as more than 45 minutes per week) (Mock, et al., 2004).

The home-based exercise program or usual care took place at initiation of treatment through completion of therapy, which ranged from six weeks for RT or three to six months for CT. An assessment of physical status and fitness level was conducted as an initial assessment. The exercise group was instructed to walk a moderate pace five to six times per week, as tolerated. Each walking session consisted of a 15-minute brisk walk, which progressed to 30 minutes. Exercise participants were instructed to keep daily diaries of exercise. The control group, or usual care, was encouraged to maintain their current levels of activity (Mock, et al., 2004).

The study focused on fatigue as the primary outcome, which was measured by the Total Score of the PFS. The 12-minute Walk Test, the Medical Outcomes Study Short

Health Form, and the Physical Activity Questionnaire assessed the outcome measures of physical functioning and activity levels. Both the control and intervention groups completed the outcome measure assessments prior to the start of treatment and at the completion of treatment (Mock, et al., 2004).

Of the 119 total participants, 91% completed the study with an attrition rate of only 9%. A total of 60 patients were assigned to the intervention, while 59 were assigned to usual care. Taking into account attrition, 54 participants in both groups completed the trial and were included in the primary analysis. Fatigue levels, as measured by the PFS (fatigue scored on scale of 0-10, 10 being the greatest), were low at baseline (2.43, SD 2.46) and increased over the course of both RT and CT treatment, with no significant differences between the two therapies. The intention-to-treat analysis found no group differences between the intervention and usual care participants. However, when the data was analyzed using instrumental variables with principal stratification (IV/PS) to take into account adherence and high-exercisers verses low-exercisers (between the intervention and control groups) a moderate-intense exercise was found to be effective in managing fatigue levels. For those in the high-walk group, fatigue scores increased only slightly from baseline, remaining at a mild level (2.92; SD 2). However, fatigue levels were increased significantly for low-walkers and reached a moderate level at post-test (4.28; SD 2.70). Overall, it was found that the effect of exercise on fatigue levels had a significant difference from pre-test to post-test ($p = 0.03$). Therefore, a walking exercise program may effectively manage high levels of CRF that occurs during cancer treatment (Mock et al., 2004).

Effects of Aerobic and Resistance Exercise in Chemotherapy Breast Cancer Patients

A multi-centered randomized controlled trial sought to evaluate the relative merits of aerobic and resistance exercise in blunting the effects of unfavorable changes in physical functioning, body composition, psychosocial functioning, and QOL. Eligible participants included non-pregnant women 18 years of age or older, stage I to IIIA breast cancer, and those starting first-line adjuvant chemotherapy. Courneya et al. (2007) conducted a three-arm prospective study. Patients were randomly assigned to supervised aerobic exercise training (AET), supervised resistance training (RET), and usual care (UC).

Exercise among participants began one to two weeks after starting CT and ended three weeks post-chemotherapy. The AET group was instructed to aerobically exercise three times per week beginning at 60% VO_{2max} for weeks one to six, progress to 70% in weeks seven to 12, and 80% beyond week 12. Exercise length started at 15 minutes in weeks one to three and increased by five minutes every three weeks until reaching 45 minutes at week 18. Resistance training participants were asked to exercise three times per week and include nine different exercises, each for two sets with eight to 12 repetitions at 60-70% of their estimated one-repetition maximum. The UC participants were asked not to start an exercise program. Outcomes were assessed at baseline, at midpoint, after completion of treatment, and at a six-month follow-up. Cancer related fatigue and QOL were assessed using FACT-An, while psychosocial outcomes were assessed using the Rosenberg Self-Esteem Scale, the Center for Epidemiological Studies Depression Scale, and the Spielberger State Anxiety Inventory (Courneya et al., 2007).

The study evaluated follow-up data on 223 of 242 patients (92.1%). The groups were not significantly different in demographic data at baseline. In patient-related outcomes, self-esteem was found to be superior in the AET ($p = .015$) and RET ($p = .018$) compared to UC. However, all other patient-related outcomes, including FACT-An, fatigue, anxiety, and depression did not reach statistical significance even after adjusting for covariates, which was contrary to the researchers hypothesis. Aerobic exercise was found to be superior to usual care as it found a significant improvement in self-esteem, preserved aerobic fitness, and maintained body fat levels. Whereas, RET showed significant improvements in self-esteem, muscular strength, and lean body mass. In addition, the study found improvements in chemotherapy completions rates among RET (Courneya et al., 2007).

The authors of the study discussed that the failure of the interventions to improve CRF was possibly in part due to variability in QOL scores reported during chemotherapy, with a standard deviation of 25. Chemotherapy treatment creates many uncontrollable factors that may affect QOL. Results of the study may have also been affected by unsatisfactory adherence to the exercise interventions. Although changes in fatigue, depression, and anxiety showed improvement with physical activity, statistical significance was not found. Limitations of the study included a 70% adherence rate to the exercise interventions, a 33% recruitment rate, and a participant sample that was found to be similar in education and racial demographics. Strengths of the research included the analysis of both aerobic and anaerobic exercise training, the largest sample size at the time of the study, supervised exercise, intent-to-treat analysis, and validated measures to assess primary and secondary outcomes. Although this trial lacked significant findings on

the important outcomes of fatigue and QOL, improvements were found among self-esteem, physical fitness, body composition, and chemotherapy completion rates.

Effects of Supervised Exercise Intervention on Treatment in Breast Cancer Survivors

Hsieh et al. conducted a quasi-experimental study design, which lacks random assignment, to investigate the effects of a supervised exercise program on the outcome measurements of function and fatigue in breast cancer patients undergoing various types of clinical treatment. The 96 participants were divided into groups based on the type of clinical treatment, including surgery alone, surgery and CT, surgery and RT, and surgery with RT and CT. Assessments were completed by trained and certified cancer exercise specialists. Study participants were assessed with an initial medical examination prior to the start of the study, which specifically assessed cardiovascular endurance, pulmonary function, and fatigue. Fatigue was assessed by a revised PFS on the domains of behavioral, affective, sensory, cognitive and mood, and total fatigue. Based on the initial medical examination, individualized exercise programs were designed to meet the needs of each participant. The intervention participants were to attend individually supervised exercise sessions two or three days per week for six months and lasted for 60 minutes with a “whole body approach”. The session typically included a warm-up, aerobic exercise, resistance training and stretching, and concluded with a cool-down (Hsieh et al., 2008).

This study assessed 96 participants and was found to have no significant differences found among age, height, and weight between groups based on the type of clinical treatment received. Post-intervention, the exercise intervention improved

predicted VO_{2max} and length of time on the treadmill ($p < 0.05$) in all four groups. Surgery, chemotherapy, and radiation patients experienced reduced resting heart rates ($p < 0.05$) and increases in forced expiratory volume (FEV_1). The intervention was found to result in significant reductions in all four domains of fatigue and total fatigue for the surgery and chemotherapy; surgery and radiation therapy; and surgery, chemotherapy, and radiation therapy groups ($p < 0.05$). However, surgery only patients were found to have significant reductions on behavioral, affective, and total fatigue ($p < 0.05$), but not on sensory, cognitive, and mood fatigue ($p < 0.05$). There were no significant differences found between treatment groups on any of the fatigue domains. The authors concluded that a moderate intensity, individualized, and supervised exercise program may create improvements, or maintenance, of cardiopulmonary function and reductions in fatigue during treatment for breast cancer (Hsieh et al., 2008).

Effects of Non-Traditional Exercise in Women Receiving RT for Breast Cancer

Reis et al. (2013) conducted a randomized clinical trial with the purpose to trial a 12-week exercise program of Nia, which is considered nontraditional exercise, compared to usual home care. The study would investigate the outcomes of fatigue, QOL, aerobic capacity, and shoulder flexibility in women with breast cancer undergoing radiation therapy. This nontraditional exercise takes a cardiovascular and whole-body approach that works on strength, flexibility, mobility, agility and stability. The exercise art incorporates martial arts, dance arts, and healing arts (i.e. yoga) while focusing on facilitating positive adaptation (Reis et al., 2013).

The study included women aged 18 years and older who would receive radiation therapy for stage I, II, or III for breast cancer. Participants were stratified by stage of

disease. Assessment of fatigue, QOL, aerobic capacity, and shoulder flexibility were assessed at baseline, 6-weeks, and 12-weeks. The intervention instructed participants to participate at home in Nia exercise for 20-60 minutes at least three times per week for 12-weeks. Their activity was to be recorded in an exercise log. The intervention participants also met with the principal investigator (PI) at 6-weeks and 12-weeks to discuss variations of movement within the Nia practice. The control group was asked to continue their current exercise regime while also recording their activities in a log and meeting with the PI. The PI discussed topics of physical, emotional, mental, and spiritual well-being with the participant. Quality of life and fatigue were assessed using the FAICT-F questionnaire. Aerobic capacity was measured using the six-minute walk test and shoulder flexibility was assessed using a goniometer (Reis et al., 2013).

The study found no statistical differences among demographic data, exercise history, or cancer history; however, differences existed between age and employment status. The intervention group was found to be, on average, five years younger and more likely to be employed full-time. Adherence, per exercise logs, was not uniformly maintained between the two groups. Both the intervention and control groups reported aerobic exercise outside of the Nia intervention. With that, the intervention group was found to be more active (four days per week) than the control group (three days per week). Furthermore, because outcome variables may not necessarily be credited to the Nia intervention, statistical analysis was assessed on outcome variables comparing the 12 women who practiced Nia to the 17 women in the control group (Reis et al., 2013).

After controlling for a baseline assessment of fatigue, a significant difference was found between the two groups. The intervention group experienced an average increase

of 17 points in the FACIT-F scale between weeks six and 12, which was significantly higher than the control group, which experienced an average 4-point increase; the higher the score, the less fatigue ($p = 0.05$). There was no significant difference found in QOL, aerobic capacity, or shoulder extension between the groups. Overall, a significant improvement was found over time in the physical, social, emotional, functional well-being, and fatigue in the intervention group. These results support the idea that Nia exercise can positively affect CRF experienced by breast cancer patients. (Reis et al., 2013)

Summary and Conclusions

Results of the studies showed significant reductions of fatigue among breast cancer treatment patients in comparison to the control group when utilizing an intent-to-treat protocol in three of the seven studies. Possibly due to lack of adherence in three of the studies, an intent-to-treat protocol found no significant difference. However, an analysis of a high-exercise to a low-exercise group did find positive impacts on fatigue in the exercise groups. One study failed to find significant differences in fatigue between the control and intervention groups, but did find positive impacts on self-esteem, aerobic fitness, muscular strength, and chemotherapy completion rate. In this study, changes in QOL, fatigue, depression, and anxiety favored the exercise groups. Many of the studies faced limitations of small sample size, adherence, and the inevitable weakness of self-reporting.

These studies demonstrate that exercise programs, either aerobic or aerobic and resistance training, may help mitigate fatigue in breast cancer patients undergoing cancer treatment, specifically CT and/or RT. Not only did the studies find improvements in

fatigue, but also physical functioning, emotional distress, and QOL. Although these studies faced limitations in sample size and adherence, they provide insight on the effect of exercise on cancer related fatigue. Therefore, these studies help to create a better understanding of physical activity and fatigue to create evidence based guidelines for registered dietitians and other clinicians in oncology care. The seven studies discussed contribute to the available evidence to answer the EAL question presented. The Evidence Analysis methodology created by the Academy of Nutrition and Dietetics will be used to create the guidelines surrounding this question.

CHAPTER 3: METHODS

The Evidence Analysis Library (EAL), created by the Academy of Nutrition and Dietetics (AND), is an online website with the "best, most relevant nutritional research on important dietetic practice questions" (Academy of Nutrition and Dietetics Evidence Analysis Library, 2012). The EAL methodology is an objective and transparent process of systematic reviews used to evaluate, synthesize, and grade the strength of current nutrition research. Developed by the AND for AND members, detailed methods and electronic tools are used throughout the process to allow objectivity, transparency, and reproducibility of the entire process. The process has been recognized by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and adapted by the Food and Drug Administration (FDA) to assess health claims placed on food labels. The process incorporates five steps: 1) Formulate Evidence Analysis Question, 2) Gather and Classify Evidence, 3) Critically Appraise Each Article, 4) Summarize the Evidence and, 5) Write and Grade the Conclusion Statement. This objective and transparent process has been used to summarize the current relevant research related to fatigue and physical activity in breast cancer patients during current cancer treatment (Academy of Nutrition and Dietetics Evidence Analysis Library, 2012).

Step One: Formulate Evidence Analysis Question

In order to identify what research is relevant to the practical needs of nutrition research, it is imperative to ask focused questions. Asking focused questions can help make clear connections between what knowledge is needed for practice and what scientific research already exists. For nutrition practice, the nutrition care process (NCP), which incorporates the four phases known as ADIME (assessment, diagnosis,

intervention, monitoring and evaluation), can be a helpful tool to help formulate questions for the EAL. The NCP allows us to keep in mind what outcomes are expected from the particular intervention, in this case, if fatigue is reduced with physical activity. After the relationship of the intervention and outcome has been identified, the relationship needs to be expressed as a focused question using the PICO format (population, intervention, comparison intervention, and outcome of interest). In this format, the population describes the group of patients, the intervention in consideration, the alternative intervention, and finally, what the outcome of the intervention may affect. It is notable that the comparison intervention may not be necessary in all cases. The EAL question addressed with this project is: How does physical activity affect fatigue levels in breast cancer patients undergoing current radiation and/or chemotherapy treatments? Table 1 demonstrates the PICO elements of this question.

Table 3: Evidence Analysis Question using PICO Format

Population (P): Patient or Problem	Breast cancer patients during current radiation and/or chemotherapy treatment
Intervention (I): Cause, treatment, or prognostic factor.	Purposeful, regular physical activity
Comparison Intervention (C), if necessary	N/A
Outcomes (O)	Fatigue

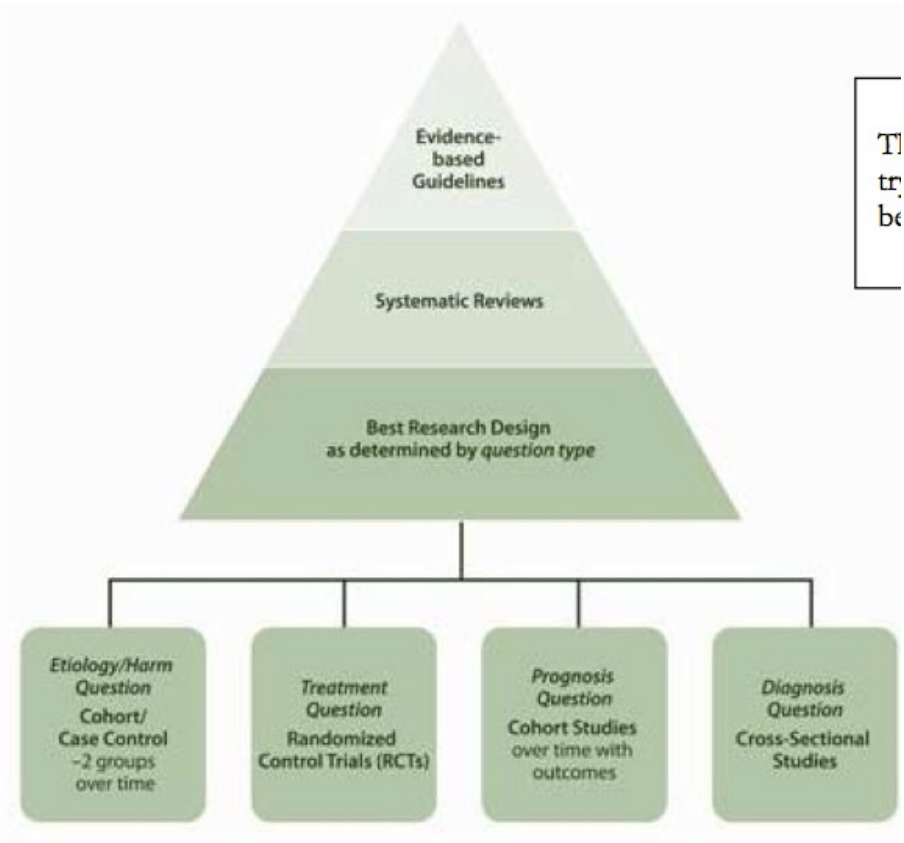
EAL questions should be focused questions that are neither too broad nor. A proper formulated question can lead to a more effective and efficient way to sort through the abundant available research (Academy of Nutrition and Dietetics Evidence Analysis Library, 2012).

Step Two: Gather and Classify Evidence

Following the development of the research question, the research begins. This research includes several steps, including: develop a search plan with inclusion and exclusion criteria, conduct the search, review citations and abstracts, gather articles meeting the specific criteria, and construct a Search Plan & Results. The goal of this step is to find the best available research to answer the EAL question and produce a final list of articles to be abstracted along with those excluded and for what reason. (Academy of Nutrition and Dietetics Evidence Analysis Library, 2012)

Following the planning, the search is conducted followed by reviewing article titles and abstracts to identify the remaining articles that will be critically reviewed. This EAL project used PubMed as its clinical journal source to identify the best available research. The analysis of articles then begins with classifying the articles based on research design. The best research design is largely determined by the question being asked. In this case, a randomized control trial (RCT) is the most appropriate type of research design for this EAL question because it is treatment based. Figure 1 shows the hierarchy of evidence by research design based on question type (Academy of Nutrition and Dietetics Evidence Analysis Library, 2012). In addition, the Search Plan & Results for this project can be found in full at the conclusion of this chapter.

Figure 1: Hierarchy of Evidence by Research Design



(Academy of Nutrition and Dietetics Evidence Analysis Library, 2012)

Also during this step, the research is divided into primary and secondary research. This particular project only encompasses primary research articles. The primary research articles are then classified with a letter grade to describe the level of evidence available in this research area. This step also helps organize the articles used in step three of the process: critical appraisal of each article. Table 2 demonstrates the hierarchy and classification of studies. Furthermore, the AND provides an algorithm to help classify the research design of the studies (Academy of Nutrition and Dietetics Evidence Analysis Library, 2012). *(See Appendix B)*

Table 4: Hierarchy and Classification of Studies

A	Randomized Controlled Trial Cluster Randomized Trial Randomized Crossover Trial
B	Prospective Cohort Study Retrospective Cohort Study
C	Non-Randomized Controlled Trial Non-Randomized Crossover Trial Case-Control Study Time Series Study Diagnostic, Validity or Reliability Study
D	Non-Controlled Trial Case Study or Case Series Other Descriptive Study Cross-Sectional Study Trend Study Before-After Study

(Academy of Nutrition and Dietetics Evidence Analysis Library, 2012)

Step Three: Critically Appraise Each Article

An Evidence Worksheet developed by the AND is used to critically review each research article. The purpose of this worksheet is to abstract key information for future reference, identify study details to determine study quality, summarize the major findings, record the conclusion, note the funding source, note study limitations, and identify how findings may be applicable to clinical practice. Next, a quality criteria checklist is used to determine a rating for each research article. This step helps to identify concepts used for sound scientific investigation and enables a systematic, objective

method of rating. The Evidence Analysis Manual provides instructions and tips to using the Evidence Worksheet and quality criteria checklist (Academy of Nutrition and Dietetics Evidence Analysis Library, 2012).

Step Four: Summarize Evidence

The fourth step is made of up two parts, the Overview Table and the narrative synthesis, both which are intended to combine the information identified through research into a simple summary allowing you to compare studies at a glance. The information in the overview table can largely transfer from the Evidence Worksheets. The table captures the author(s), publication year, primary outcomes, important sample characteristics and comparison factors, implications for practice, and the limitations of findings.

The last portion of step four encompasses writing an evidence summary. This summary considers how the different articles compare and contrast. Components of the evidence summary include: overall summary statement, comparison factor statements, methodological statements with the types of research designs used, identification of factors that may have affected outcomes, and brief definitions of key terms for the reader (Academy of Nutrition and Dietetics Evidence Analysis Library, 2012).

Step Five: Write and Grade the Conclusion Statement

The final step is to grade the strength of the evidence found through the project's research. Essentially, the research is combined into a "bottom line" conclusion statement, or what is the answer to the evidence analysis question. The statement must be clear and concise. Once the conclusion statement is finalized, the strength of the evidence supporting the conclusion statement is given a grade. Table 4 is used to assist in properly assigning a grade to the conclusion statement.

Table 5: AND's Grade Definitions and Conclusion Grading Table

Strength of Evidence Elements	Grades				
	I Good/Strong	II Fair	III Limited/Weak	IV Expert Opinion Only	V Grade Not Assignable
Quality • Scientific rigor/validity • Considers design and execution	Studies of strong design for question Free from design flaws, bias and execution problems	Studies of strong design for question with minor methodological concerns, OR Only studies of weaker study design for question	Studies of weak design for answering the question OR Inconclusive findings due to design flaws, bias or execution problems	No studies available Conclusion based on usual practice, expert consensus, clinical experience, opinion, or extrapolation from basic research	No evidence that pertains to question being addressed
Consistency Of findings across studies	Findings generally consistent in direction and size of effect or degree of association, and statistical significance with minor exceptions at most	Inconsistency among results of studies with strong design, OR Consistency with minor exceptions across studies of weaker design	Unexplained inconsistency among results from different studies OR single study unconfirmed by other studies	Conclusion supported solely by statements of informed nutrition or medical commentators	NA
Quantity • Number of studies • Number of subjects in studies	One to several good quality studies Large number of subjects studied Studies with negative results have sufficiently large sample size for adequate statistical power	Several studies by independent investigators Doubts about adequacy of sample size to avoid Type I and Type II error	Limited number of studies Low number of subjects studied and/or inadequate sample size within studies	Unsubstantiated by published research studies	Relevant studies have not been done
Clinical impact • Importance of studied outcomes • Magnitude of effect	Studied outcome relates directly to the question Size of effect is clinically meaningful Significant (statistical) difference is large	Some doubt about the statistical or clinical significance of the effect	Studied outcome is an intermediate outcome or surrogate for the true outcome of interest OR Size of effect is small or lacks statistical and/or clinical significance	Objective data unavailable	Indicates area for future research
Generalizability To population of interest	Studied population, intervention and outcomes are free from serious doubts about generalizability	Minor doubts about generalizability	Serious doubts about generalizability due to narrow or different study population, intervention or outcomes studied	Generalizability limited to scope of experience	NA

(Academy of Nutrition and Dietetics Evidence Analysis Library, 2012)

Search Plan & Results

This step is critical to help identify the highest quality pieces of research pertaining to physical activity and fatigue in breast cancer patients undergoing current treatment. The following search plan and results, which is a portion of step two in the EAL methodology, distinguishes research that meets the inclusion and exclusion criteria specific to the EAL question being researched.

EAL Question

How does purposeful, regular physical activity affect fatigue levels in breast cancer patients undergoing current chemotherapy and/or radiation therapy?

Date of Literature Review for Evidence Analysis

December 2014

Inclusion Criteria

Age: Adult Population (18 years and older)

Setting: Current Chemotherapy and/or Radiation Therapy

Health Status: Breast cancer patients

**Note:* Studies may include other cancer types, but must include breast cancer patients.

Nutrition Related Problem/Condition: Fatigue

Intervention: Must include exercise as an intervention

Study Design: Randomized Control Trial, Clinical Trial, Cohort, or Observational

*Note: Must be a prospective study

Size of Study Groups: The sample size must equal at least 10 individuals.

Year Range: 2000-2014

Languages: English

Exclusion Criteria

Age: Less than 18 years of age, infants, children, and adolescents

Setting: Those not receiving current chemotherapy and/or radiation therapy.

Health Status: Those studies that do not include breast cancer patients.

Nutrition Related Problem/Condition: Those that do not assess fatigue.

Study Design: Retrospective, Meta-Analysis, and Reviews

Size of Study Groups: <10 individuals

Year Range: Prior to 2000

Language: Articles not published in English.

Search Terms: Search Vocabulary

Health Condition:
breast cancer, fatigue, chemotherapy, radiation

Intervention:
exercise, physical activity

Type of Study Design:
RCT, Clinical Studies, Observational Studies, Cohort, Case-Control Studies

Electronic Databases

Database Used: Pubmed

Search Terms: (((((Chemotherapy) OR Radiation)) AND Fatigue) AND Physical Activity) AND Breast cancer AND ((Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp] OR Observational Study[ptyp]) AND ("2000/01/01"[PDat] : "2014/12/31"[PDat]) AND Humans[Mesh])

Hits: 27

Total Articles to Review: 7

List of Articles Included from Electronic Database

Aghili, M., Farhan, F., & Rade, M. (2007). A pilot study of the effects of programmed aerobic exercise on the severity of fatigue in cancer patients during external radiotherapy. *European Journal of Oncology Nursing, 11*, 179-182.

Courneya, K., Segal, R., Mackey, J., Gelmon, K., Reid, R., Friedenreich, C., ... McKenzie, D. (2007). Effects of Aerobic and Resistance Exercise in Breast Cancer Patients Receiving Adjuvant Chemotherapy: A Multicenter Randomized Controlled Trial. *Journal of Clinical Oncology, 25*(28), 4396-4404.

Hsieh, C., Sprod, L., Hydock, D., Carter, S., Hayward, R., & Schneider, C. (2008). Effects of a Supervised Exercise Intervention on Recovery From Treatments Regimens in Breast Cancer Survivors. *Oncology Nursing Forum, 35*(6), 909-915.

Mock, V., Frangakis, C., Davidson, N., Ropka, M., Pickett, M., Poniatowski, B., ... McCorkle, R. (2004). Exercise Manages Fatigue During Breast Cancer Treatment: A Randomized Controlled Trial. *Psycho-Oncology, 14*, 464-477.

Mock, V., Pickett, M., Ropka, M., Lin, E., Stewart, K., Rhodes, V., ... McCorkle, R. (2001). Fatigue and Quality of Life Outcomes of Exercise During Cancer Treatment. *Cancer Practice, 9*(3), 119-127.

Mustian, K., Peppone, L., Darling, T., Palesh, O., Heckler, C., & Morrow, G. (2011). A 4-Week Home-Based Aerobic and Resistance Exercise Program During Radiation Therapy: A Pilot Randomized Clinical Trial. *Journal of Supportive Oncology, 7*(5), 158-167.

Reis, D., Walsh, E., Young-McCaughan, S., & Jones, T. (2013). Effects of Nia Exercise in Women Receiving Radiation Therapy for Breast Cancer. *Oncology Nursing Forum, 40*(5), 374-382.

List of Excluded Articles with Reason

Article	Reason
Dieli-Conwright CM, Mortimer JE, Schroeder ET, Courneya K, Demark-Wahnefried W, Buchanan TA, Tripathy D, Bernstein L. (2014). Randomized control trial to evaluate the effects of combined progressive exercise on metabolic syndrome in breast cancer in breast cancer survivors: rationale, design, and methods. *BMC Cancer*, doi: 10.1186/1471-2407-14-238.	No therapy
Pickett, M., Mock, V., Ropka ME, Cameron, L., Coleman, M., Podewils L. (2002). Adherence to moderate-intensity exercise during breast cancer therapy. *Cancer Practice*, 10(6):284-92. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12406050?log$=activity.	No outcome measurement of fatigue
Daley, A.J., Crank, H, Saxton, J.M., Mutrie, N., Coleman, R., Roalfe, A. (2007). Randomized trial of exercise therapy in women treated for breast cancer. *Journal of Clinical Oncology*, 25(13):1731-21. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17470863?log$=activity.	No current treatment
Thorsen, L., Skovlund, E., Stomme, S.B., Hornslein, K., Dahl, A.A., Fossa, S.D. (2005) Effectiveness of physical activity on cardiorespiratory fitness and health-related quality of life in young and middle-aged cancer patients shortly after chemotherapy. *Journal of Clinical Oncology*, 23(10):2378-88. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/15800330.	No current treatment
Courneya, K.S., McKenzie, D.C., Reid, R.D., Mackey, J.R., Gelmon, K., Friedenreich, C.M., Ladha, A.B., Proulx, C., Lane, K., Vallance, J.K., Segal, R.J. (2008). Barriers to supervised exercise training in a randomized controlled trial of breast cancer patients receiving chemotherapy. *Annals of Behavioral Medicine*, doi: 10.1007/s12160-007-9009-4.	No outcome measurement of fatigue
Payne, J.K., Held, J., Thorpe, J., Shaw, H. (2008). Effects of	Not radiation and/or

exercise on biomarkers, fatigue, sleep disturbances, and depressive symptoms in older women with breast cancer receiving hormonal therapy. *Oncology Nursing Forum,* doi: 10.1188/08.ONF.635-642.	chemotherapy
Battaglini CL, Mihalik JP, Bottaro M, Dennehy C, Petschauer MA, Hairston LS, Shields EW. (2008) Effect of exercise on the caloric intake of breast cancer patients undergoing treatment. *Braz J Med Biol Res.*, 41(8):709-15. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18797706.	No outcome measurement of fatigue
Windsor PM, Potter J, McAdam K, McCowan C. (2009). Evaluation of a fatigue initiative: information on exercise for patients receiving cancer treatment. *Clin Oncol (R Coll Radiol),* doi: 10.1016/j.clon.2009.01.009.	No exercise intervention
Berger AM, Wielgus K, Hertzog M, Fischer P, Farr L. (2010). Patterns of circadian activity rhythms and their relationships with fatigue and anxiety/depression in women treated with breast cancer adjuvant chemotherapy. *Support Care Cancer*. doi: 10.1007/s00520-009-0636-0.	No exercise intervention
Penttinen HM, Saarto T, Kellokumpu-Lehtinen P, Blomqvist C, Huovinen R, Kautiainen H…Hakamies-Blomqvist L. (2010). Quality of life and physical performance and activity of breast cancer patients after adjuvant treatments. *Psychooncology,* doi: 10.1002/pon.1837.	No current treatment
Yang CY, Tsai JC, Huang YC, Lin CC. (2010). Effects of a home-based walking program on perceived symptom and mood status in postoperative breast cancer women receiving adjuvant chemotherapy. *Journal of Advanced Nursing,* doi: 10.1111/j.1365-2648.2010.05492.x.	No outcome measurement of fatigue
van Waart H, Stuiver MM, van Harten WH, Sonke GS, Aaronson NK. (2010). Design of the physical exercise during adjuvant chemotherapy effectiveness study (PACES): a randomized controlled trial to evaluate effectiveness and cost-effectiveness of physical exercise in improving physical fitness and reducing fatigue. *BMC Cancer,* doi: 10.1186/1471-2407-10-673.	Ongoing study
Newton MJ, Hayes SC, Janda M, Webb PM, Obermair A, Eakin EG, Wyld D, Gordon LG, Beesley VL. (2011). Safety, feasibility and effects of an individualized walking intervention for women undergoing chemotherapy for ovarian cancer: a pilot study. *BMC Cancer* doi: 10.1186/1471-2407-11-389.	Not breast cancer patients
Ma H, Sullivan-Halley J, Smith AW, Neuhouser ML, Alfano CM, Meeske K, George SM, McTiernan A, McKean-Cowdin R, Baumgartner KB, Ballard-Barbash R, Bernstein L. (2011). Estrogenic botanical supplements, health-related quality of life, fatigue, and hormone-related symptoms in breast cancer survivors: a HEAL study report. *BMC Complement Altern Med,*	No exercise intervention

doi: 10.1186/1472-6882-11-109.	
Cho MH, Dodd MJ, Cooper BA, Miaskowski C. (2012). Comparisons of exercise dose and symptom severity between exercisers and nonexercisers in women during and after cancer treatment. *J Pain Symptom Manage*, doi: 10.1016/j.jpainsymman.2011.05.016.	Includes post-treatment
Schmidt ME, Wiskemann J, Krakowski-Roosen H, Knicker AJ, Habermann N, Schneeweiss A, Ulrich CM, Steindorf K. (2013). Progessive resistance versus relaxation training for breast cancer patients during adjuvant chemotherapy: design and rationale of a ransomized controlled trial (BEATE study). *Contemp Clin Trials*, doi: 10.1016/j.cct.2012.10.006.	Ongoing study
Kwiatkowski F, Mouret-Reynier MA, Duclos M, Leger-Enreille A, Bridon F, Hahn T, Van Praagh-… Bignon YJ. (2013). Long term improved quality of life by a 2-week group physical and educational intervention shortly after breast cancer chemotherapy completion. Results of the 'Programme of Accompanying women after breast Cancer treatment completion in Thermal resorts' (PACThe) randomised clinical trial of 251 patients. *Eur J **Cancer***, doi: 10.1016/j.ejca.2012.12.021.	No current treatment
Potthoff K, Schmidt ME, Wiskemann J, Hof H, Klassen O, Habermann N, Beckhove P, Debus J, Ulrich CM, Steindorf K. (2013). Randomized controlled trial to evaluate the effects of progressive resistance training compared to progressive muscle relaxation in breast cancer patients undergoing adjuvant radiotherapy: the BEST study. *BMC **Cancer***, doi: 10.1186/1471-2407-13-162.	Ongoing study
Carayol M, Romieu G, Bleuse JP, Senesse P, Gourgou-Bourgade S, Sari C,…Ninot G. (2013). Adapted physical activity and diet (APAD) during adjuvant breast cancer therapy: design and implementation of a prospective randomized controlled trial. *Contemp Clin Trials*, doi: 10.1016/j.cct.2013.09.016.	Ongoing study
Hu HF, Li TC, Liu LC, Wu CT, Wang YJ. (2013). [Effects of a walking program on fatigue and exercise capacity in post-surgery breast cancer women]. *Hu Li Za Zhi*, doi: 10.6224/JN.60.5.53.	Chinese language; No current treatment

Summary of Articles Identified to Review

Total Number of Articles Considered: 27

Number of Articles Considered but Excluded: 20

Number of Included Primary Articles Identified from Search: 7

Total Number of Included Articles: 7

Based on the search and results plan, seven articles were identified to be included in the analysis. The analysis of each article, step three, was conducted using quality checklists and evidence worksheets, which can be found in *Appendix C*. Step four and five of the EAL methodology can be found in chapters four and five, respectively.

CHAPTER 4: RESULTS

The current research regarding the effects of physical activity on fatigue levels during active treatment for breast cancer is limited, but continuously growing. This literature review incorporates seven studies focused on physical activity as the intervention and fatigue as an outcome measurement in patients undergoing current treatment for breast cancer between the years 2000-2014. Some studies went beyond the measurement of fatigue and also measured physical fitness, QOL, and other measurements associated with wellness. Among the studies, four of the seven studies focused on a home-based exercise program. Three of the studies utilized a walking program, whereas three of the studies incorporated both aerobic and resistance training. One study focused on a non-traditional form of exercise, Nia, which took a "whole body" approach and also incorporated aerobic and resistance training. All but two studies developed a randomized approach with a usual care or control group with only one study lacking a control group. Each of the seven studies used a fatigue assessment identified by the NCI, all with established validity and reliability. Since fatigue is a subjective measure, it is critical to use these tools that have demonstrated validity and reliability. In addition, each of the studies assessed fatigue at baseline, or start of treatment, and at post-treatment.

Relevant Findings: Aghili, et al., 2007

This pilot study sought to assess the incidence and severity of fatigue in both breast and head and neck cancer patients through a radiation course, which lasted four weeks. Although this study did not provide results based on diagnosis, a significant difference among fatigue was found. The intervention group participated in a walking

program of 20 minutes, whereas the comparison group did not engage in an exercise program. At initiation of treatment, both groups were assessed with having moderate fatigue (p = 0.632). At the end of treatment, 44% of patients in the training group had mild fatigue while 57% of the comparison group reported severe fatigue (p =0.011). This study revealed a discernible increase in the severity of fatigue in those who did not participate in the exercise program (p = 0.039) (Figure 2). Overall, the preliminary findings of this pilot study suggest an exercise program, specifically one focused on 20 minutes of daily walking, can have positive results on breast cancer (including head and neck) patients undergoing current cancer treatments.

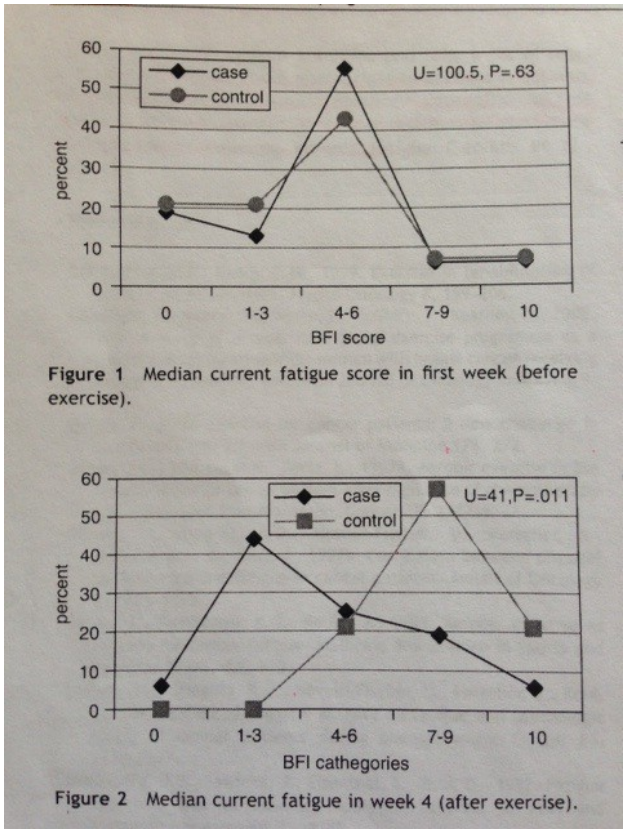


Figure 2: Aghili, et al., 2007

Relevant Findings: Mock, et al., 2001

Due to limited evidence-based interventions to manage fatigue, this study sought to explore the effect of exercise intervention on fatigue. Not only did this 2001 study assess a home-based walking program and its effects on fatigue in breast cancer patients undergoing current treatment, it also explored the effects on physical functioning, emotional distress, and QOL. The exercise intervention was individualized for patients based on a baseline walk test and the specific type of treatment; however, most programs

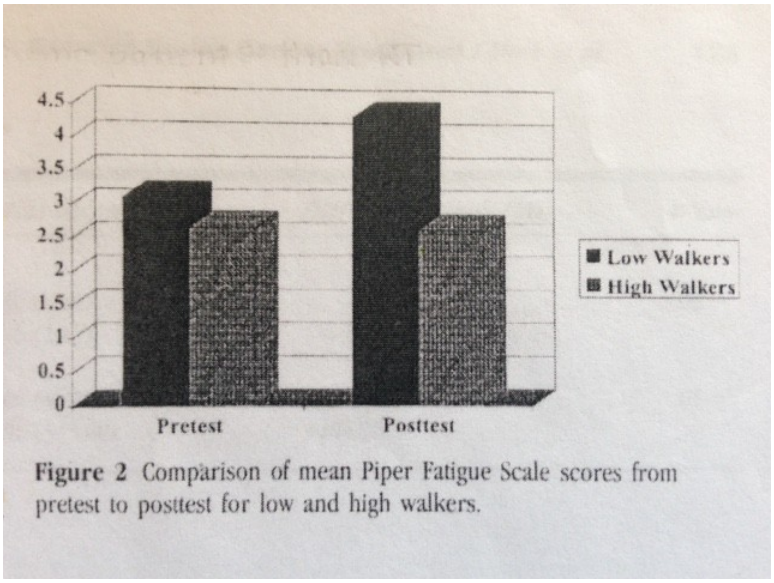


Figure 2 Comparison of mean Piper Fatigue Scale scores from pretest to posttest for low and high walkers.

Figure 3: Mock, et al., 2001

began with 10 to 15 minutes of exercise five to six days per week with advancement to 30 minutes. The usual care group was provided what was considered standard practice for the cancer center. However, possibly because those who were in the usual group were found to be exercising and many of those in the intervention group did not adhere to the protocol, an intent-to-treat analysis found no statistical difference among the groups. An analysis conducted breaking groups into low- verses high-walk groups found mean fatigue scores decreased for patients in the high-walk group during treatment, while scores for the low-walk group increased ($p = .001$). Also notable, the walking exercise program made positive impacts on physical functioning and QOL while decreasing emotional distress. This study suggests that a walking program, which is low-cost, can help reduce fatigue in breast cancer patients undergoing current treatments, along with other symptoms.

Relevant Findings: Mustian, et al., 2009

This clinical trial focused on the feasibility and efficacy of a home-based aerobic and progressive resistance exercise intervention in breast cancer radiation patients while looking at outcomes in aerobic capacity, strength, muscle mass, CRF, and QOL. Patients were randomized to the control group or the intervention group, which consisted of both an aerobic and resistance training program. The exercise intervention showed

improvement on the outcome variable of CRF from baseline to post-intervention and even showed continued improvement from baseline to the three-month follow-up. Additionally, the control group showed a slight improvement from baseline to post-intervention, but an increasingly negative effect from baseline to three-month follow-up.

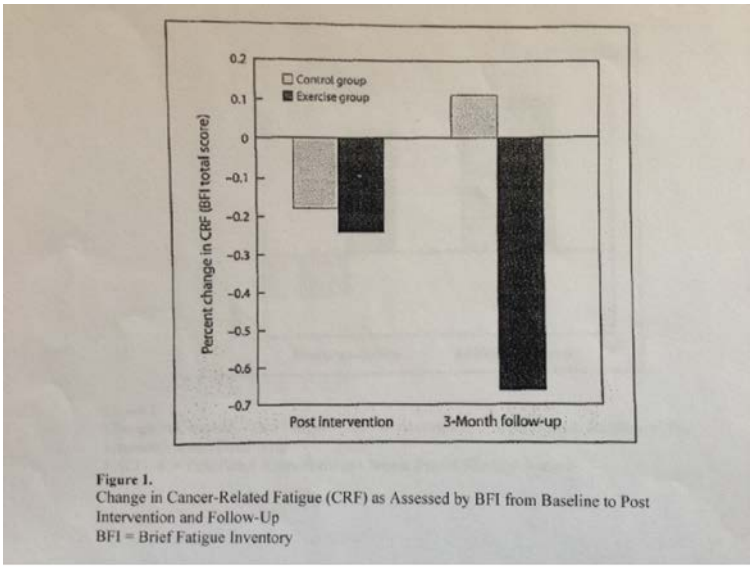


Figure 4: Mustian, et al., 2009

An ANCOVA analysis showed a trend towards a significant difference in lower CRF in the exercise group than the control post-intervention ($p = 0.07$), with a significant difference at three-month follow-up ($p < 0.05$). Notably, this study found that participants demonstrated good adherence and compliance to the intervention. Improvements were also found in other outcomes, but lacked significant difference. This clinical trial demonstrates that an exercise intervention involving both aerobic and anaerobic training can positively influence CRF. Also important, this intervention is safe, easy to implement, and well adhered to by breast cancer patients undergoing radiation therapy.

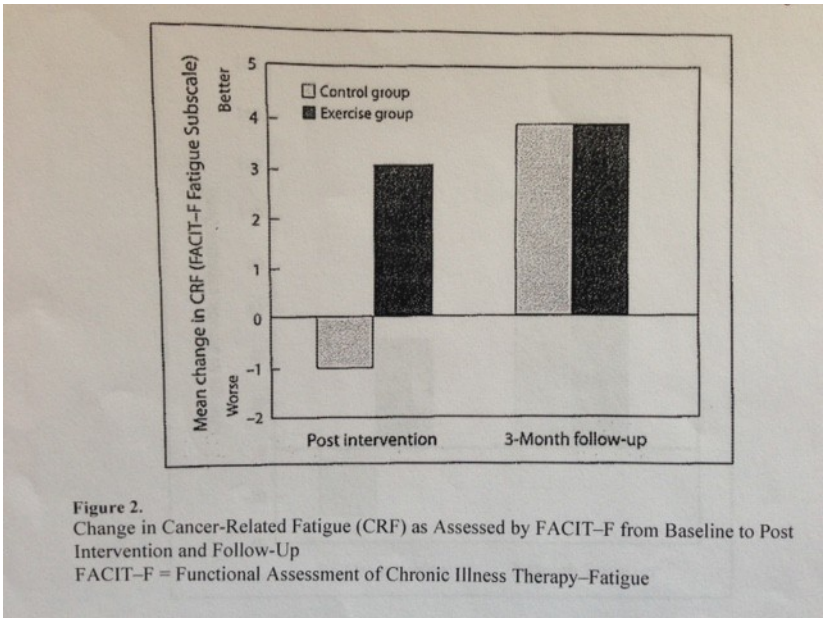


Figure 2.
Change in Cancer-Related Fatigue (CRF) as Assessed by FACIT–F from Baseline to Post Intervention and Follow-Up
FACIT–F = Functional Assessment of Chronic Illness Therapy–Fatigue

Figure 5: Mustian, et al., 2009

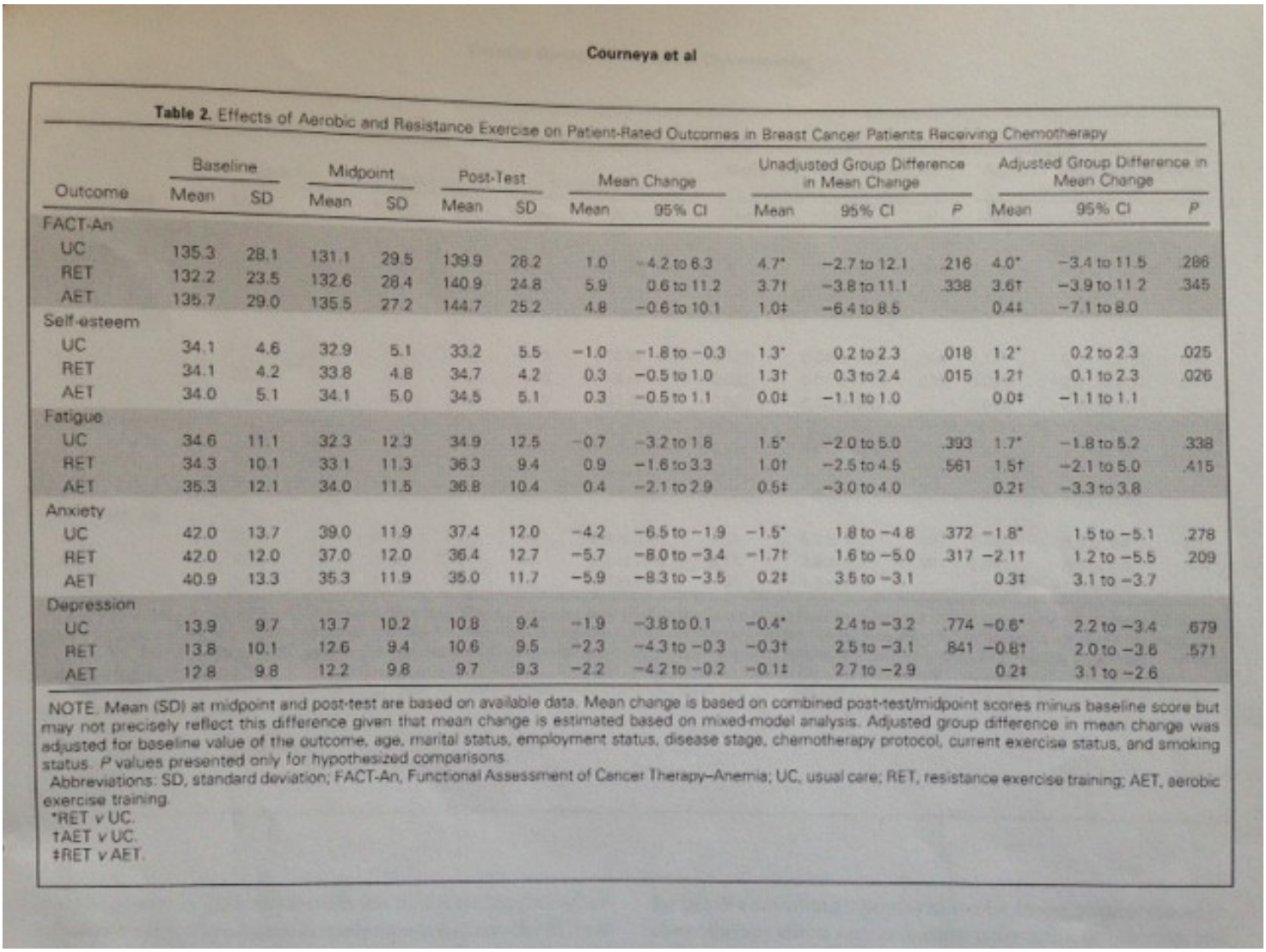
Relevant Findings: Mock, et al., 2004

A randomized controlled trial conducted in 2004 sought to study the effects of exercise on fatigue levels in breast cancer patients undergoing current treatment. The intervention included a walk-based program instructing participants to walk five to six times per week at a moderate pace (50-70% of maximum heart rate), as tolerated. The program began with a 15-minute walk and increased to 30-minutes, progressively. Usual care participants were instructed to continue normal levels of activity. The primary outcome measurement of fatigue demonstrated fatigue at low-levels at baseline but increased over the course of treatment in both radiation and chemotherapy. Due to a lack of compliance, a high-walk verses low-walk group analysis was conducted. Mean fatigue scores increased only slightly from baseline in the high-walk group, whereas fatigue increased significantly for the low-walk group ($p < 0.01$), reaching a moderate level at post-test. In addition, 17% of low-walk participants reported severe levels of fatigue,

while no high-walk participants reported severe fatigue. This study demonstrates that a moderate-intensity home-based walking program can have a positive impact on managing fatigue levels in breast cancer patients undergoing radiation and/or chemotherapy.

Relevant Findings: Courneya, et al., 2007

The 2007 published study assessed the effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy. Fatigue was assessed as a secondary endpoint as the study focused on cancer-specific QOL, and included psychosocial functioning, physical fitness, body composition, chemotherapy completion rate, and lymphedema. Although the results of this study did not demonstrate significant improvements in fatigue with aerobic or resistance exercise training, trends did favor the exercise groups, in addition to other outcome measurements. Although this study does not demonstrate significant improvements in fatigue, it does demonstrate a positive association between physical activity and survival in breast cancer patients undergoing adjuvant chemotherapy.



Courneya et al

Table 2. Effects of Aerobic and Resistance Exercise on Patient-Rated Outcomes in Breast Cancer Patients Receiving Chemotherapy

Outcome	Baseline		Midpoint		Post-Test		Mean Change		Unadjusted Group Difference in Mean Change			Adjusted Group Difference in Mean Change		
	Mean	SD	Mean	SD	Mean	SD	Mean	95% CI	Mean	95% CI	P	Mean	95% CI	P
FACT-An														
UC	135.3	28.1	131.1	29.5	139.9	28.2	1.0	−4.2 to 6.3	4.7*	−2.7 to 12.1	.216	4.0*	−3.4 to 11.5	.286
RET	132.2	23.5	132.6	28.4	140.9	24.8	5.9	0.6 to 11.2	3.7†	−3.8 to 11.1	.338	3.6†	−3.9 to 11.2	.345
AET	135.7	29.0	135.5	27.2	144.7	25.2	4.8	−0.6 to 10.1	1.0‡	−6.4 to 8.5		0.4‡	−7.1 to 8.0	
Self-esteem														
UC	34.1	4.6	32.9	5.1	33.2	5.5	−1.0	−1.8 to −0.3	1.3*	0.2 to 2.3	.018	1.2*	0.2 to 2.3	.025
RET	34.1	4.2	33.8	4.8	34.7	4.2	0.3	−0.5 to 1.0	1.3†	0.3 to 2.4	.015	1.2†	0.1 to 2.3	.026
AET	34.0	5.1	34.1	5.0	34.5	5.1	0.3	−0.5 to 1.1	0.0‡	−1.1 to 1.0		0.0‡	−1.1 to 1.1	
Fatigue														
UC	34.6	11.1	32.3	12.3	34.9	12.5	−0.7	−3.2 to 1.8	1.5*	−2.0 to 5.0	.393	1.7*	−1.8 to 5.2	.338
RET	34.3	10.1	33.1	11.3	36.3	9.4	0.9	−1.6 to 3.3	1.0†	−2.5 to 4.5	.561	1.5†	−2.1 to 5.0	.415
AET	35.3	12.1	34.0	11.5	36.8	10.4	0.4	−2.1 to 2.9	0.5‡	−3.0 to 4.0		0.2†	−3.3 to 3.8	
Anxiety														
UC	42.0	13.7	39.0	11.9	37.4	12.0	−4.2	−6.5 to −1.9	−1.5*	1.8 to −4.8	.372	−1.8*	1.5 to −5.1	.278
RET	42.0	12.0	37.0	12.0	36.4	12.7	−5.7	−8.0 to −3.4	−1.7†	1.6 to −5.0	.317	−2.1†	1.2 to −5.5	.209
AET	40.9	13.3	35.3	11.9	35.0	11.7	−5.9	−8.3 to −3.5	0.2‡	3.5 to −3.1		0.3‡	3.1 to −3.7	
Depression														
UC	13.9	9.7	13.7	10.2	10.8	9.4	−1.9	−3.8 to 0.1	−0.4*	2.4 to −3.2	.774	−0.6*	2.2 to −3.4	.679
RET	13.8	10.1	12.6	9.4	10.6	9.5	−2.3	−4.3 to −0.3	−0.3†	2.5 to −3.1	.841	−0.8†	2.0 to −3.6	.571
AET	12.8	9.8	12.2	9.6	9.7	9.3	−2.2	−4.2 to −0.2	−0.1‡	2.7 to −2.9		0.2‡	3.1 to −2.6	

NOTE. Mean (SD) at midpoint and post-test are based on available data. Mean change is based on combined post-test/midpoint scores minus baseline score but may not precisely reflect this difference given that mean change is estimated based on mixed-model analysis. Adjusted group difference in mean change was adjusted for baseline value of the outcome, age, marital status, employment status, disease stage, chemotherapy protocol, current exercise status, and smoking status. *P* values presented only for hypothesized comparisons.

Abbreviations: SD, standard deviation; FACT-An, Functional Assessment of Cancer Therapy–Anemia; UC, usual care; RET, resistance exercise training; AET, aerobic exercise training.

*RET *v* UC.

†AET *v* UC.

‡RET *v* AET.

Figure 6: Courneya, et al., 2007

initial physiological and psychological assessments. The intervention provided supervised “whole body” exercise sessions that included both aerobic and anaerobic exercise two to three days per week for six months. Fatigue was assessed based on five different categories of fatigue, including: behavioral, affective, sensory, cognitive, and mood. The intervention resulted in significant reductions in all fatigue categories ($p < 0.05$). This study also demonstrated positive findings in several other outcome

measurements indicating that an individualized, moderate intensity exercise program reduces fatigue in breast cancers patient regardless of cancer treatment type.

Relevant Findings: Reis, et al., 2013

This randomized clinical trial evaluated a non-traditional exercise program, Nia, compared to usual care on breast cancer patients undergoing radiation therapy. Outcome measurements included fatigue, QOL, aerobic capacity, and shoulder flexibility. The intervention included Nia exercise for 20-60 minutes, three times per week for 12-weeks. The control group was instructed to continue with normal activities. This study assessed fatigue using the FACIT-F assessment where an increase in points indicates less fatigue. Based on this assessment, the Nia exercise group increased their FACIT-F score significantly compared to the control group ($p = 0.05$), again demonstrating the positive effects of physical activity on fatigue in breast cancer radiation patients. The study demonstrated significant improvements only in fatigue and not among other outcome measurements.

Strengths and Limitations

These seven studies, which focus on relevant findings related to the EAL question in research, are found to have several strengths and limitations. Each study was critically analyzed using quality criteria checklists (found in *Appendix C*) and given a rating based on the analysis, as discussed in chapter two. See Overview Template in *Appendix D* for summary of strengths, limitations, study class, and research quality rating. The Quality Criteria Summary in *Appendix E* recaps research quality ratings.

Aghili, et al., 2007

Strengths and Limitations

Limited conclusions can be made from this study due to its small sample size thus limiting its ability to lead to solid, practice-changing solutions. There was also potential for confounding variables, such as other disease-related variables, that could have more significantly impacted the study's results. Strengths of this study included measurements of fatigue assessed at baseline and week four, when fatigue typically peaks during RT. Additionally, fatigue was measured both during "present time" and "in the last 24 hours", which is beneficial as fatigue levels tend to fluctuate greatly throughout the day. Overall, this study indicates that physical activity may improve fatigue levels during RT. Therefore, this study may lead to moderate exercise prescriptions with adequate rest periods becoming common clinical practice among patients undergoing current RT.

Research Quality Rating

This cohort study is classified in study class C. It was given a positive (+) research quality rating.

Mock, et al., 2001

Strengths and Limitations

The study faced limitations in the adherence of participants amongst the treatment group, self-reporting, small sample size, and prior CT and/or RT treatments amongst some participants who may still have been experiencing side effects. Future studies should consider standardizing the treatment process to prevent self-reporting. The study measured several aspects, including fatigue, physical functioning, and QOL making it a

strength of the study. Overall, the results of this study suggest that exercise does improve fatigue and quality of life outcomes during cancer treatment. (Mock et al., 2001)

Research Quality Rating

This randomized controlled trial is classified in study class A and has received a positive (+) quality rating.

Mustian, et al., 2009

Strengths and Limitations

Due to the study's small sample size, there was a reduction in statistical power, limited applicability, was not completely blinded, and adherence was self-reported. Despite the study's small sample size and other weaknesses, this pilot provides insight into the effect of exercise on CRF. Although more complete studies should be pursued, the results of this study demonstrate that there are promising outcomes from a daily exercise routine. An at-home exercise program may be feasible and effective in decreasing fatigue levels while improving QOL among cancer patients undergoing RT.

Research Quality Rating

The randomized controlled trial is placed in study class A and received a positive (+) quality rating.

Mock, et al., 2004

Strengths and Limitations

This randomized controlled trial studied the effects of physical activity on fatigue levels in women undergoing cancer treatment who were sedentary prior to treatment. The study also focused on both objective and self-reported subjective measures. The study demonstrated quality control by providing standardization among study sites with

detailed protocols for intervention and control groups. Although adherence to the prescribed exercise program was a limitation of the study, the researchers analyzed the data using instrumental variables with principal stratification (IV/PS) to take into account adherence and high-exercisers verses low-exercisers. Due to the nature of subjective measures, like fatigue, this study faced limitations regarding the potential bias of under- and/or over-reporting, which may have affected the data. Lack of blinded research staff to the participant's exercise assignment was a limitation of the study. Overall, this study adds to the research suggesting that moderate intense exercise, like walking, may prevent high-levels of fatigue in patients undergoing treatment for breast cancer.

Research Quality Rating

Classified in study class A per a randomized control trial, this study received a positive (+) quality rating.

Courneya, et al., 2007

Strengths and Limitations

The authors of the study discussed that the failure of the interventions to improve CRF was possibly in part due to variability in QOL scores reported during chemotherapy. Chemotherapy treatment creates many uncontrollable factors that may affect QOL. Results of the study may have also been affected by unsatisfactory adherence to the exercise interventions. Although changes in fatigue, depression, and anxiety showed improvement with physical activity, statistical significance was not found. Limitations of the study included a 70% adherence rate to the exercise interventions, a 33% recruitment rate, and a participant sample that was found to be similar in education and racial demographics. Strengths of the research included the analysis of both aerobic and

anaerobic exercise training, the largest sample size at the time of the study, supervised exercise, intent-to-treat analysis, and validated measures to assess primary and secondary outcomes. Although this trial lacked significant findings on the important outcomes of fatigue and QOL, improvements were found among self-esteem, physical fitness, body composition, and chemotherapy completion rates.

Research Quality Rating

This research study's gold standard randomized controlled trial placed this study in study class A and received a positive (+) quality rating.

Hsieh, et al., 2008

Strengths and Limitations

This study was strengthened by the measurement of several fatigue subgroups, which impact the QOL of cancer treatment patients. Along with the strength of several fatigue measurements, the researchers assessed several types and variations of treatment experienced by breast cancer patients. Just as treatment is individualized for each patient, the intervention was created individually based on patient assessment. The study was limited by the use of a convenience sample and women from one geographical area. As a quasi-experiment, the study lacked randomization and further lacked a non-exercise, control group. Future studies may consider a randomized control trial and higher intensity exercise interventions and its effect on CRF.

Research Quality Rating

This quasi-experimental research placed this study in class D and received a neutral (Ø) rating.

Reis, et al., 2013

Strengths and Limitations

The research conducted by Reis et al. (2013) was strengthened by its format of a randomized control trial and incorporating an intervention and usual care group of participants. The researchers assessed a nontraditional approach of exercise that incorporated a program that focuses on strength, flexibility, mobility, agility and stability which are all important aspects to a whole-body exercise program. In addition, the study was strengthened by using outcome measurements associated with reliable scales. This study was limited by the study participant's variable amount of exercise during the 12-week period in addition to other exercise methods, making it difficult to isolate the specific impact on study outcomes by the Nia exercise. It was also noted by the participants that the exercise logs provided a daily exercise reminder to the patients, possibly affecting the outcome of the control group. In addition, specific p-values were not listed within the study. Despite these limitations, the study adds knowledge to the current research regarding the positive effect of physical activity on CRF among breast cancer patients undergoing current treatment.

Research Quality Rating

This randomized controlled trial is classified in study class A and received a neutral (ø) research quality rating.

CHAPTER 5: SUMMARY AND CONCLUSIONS

Evidence Summary

Evidence from the seven studies generally agreed that fatigue was one of the most common symptoms during cancer treatment, and that it is found among almost 100% of cancer patients undergoing treatment. In several studies, fatigue was not the only outcome measurement. Other measurements included aerobic capacity, strength, body composition, and QOL. Although fatigue was not the primary outcome measurement in each article it was a measure in each study using a validated measurements of fatigue. The evidence from these studies has overwhelmingly found that physical activity, typically a home-based walking program, has a positive impact on fatigue. Most articles found a significant difference and thus decreasing fatigue levels in patients undergoing current chemotherapy and/or radiation therapy.

Each study from this project's search included breast cancer patients undergoing current treatment. Most studies exclusively focused on breast cancer patients, whereas two studies included other diagnoses, including prostate cancer along with head and neck cancer patients. An additional focused topic was the type of exercise intervention. All studies included a form of aerobic exercise (walking or in one instance Nia exercise) or aerobic plus anaerobic exercise. Many of these exercise programs were individualized for each patient and consisted of at-home exercise. In one case, patients were hospitalized for observation. In addition, all studies incorporated the exercise intervention for at least the duration of treatment.

As typical in clinical research, the gold standard study is a randomized control trial (RCT) to test if the intervention works by comparing it to a control group. Of the

seven studies, five utilized the RCT method, whereas a cohort and quasiexperimental protocol were also used. Of the five RCTs, only one study using an intent-to-treat protocol was able to detect a significant difference. However, several studies where able to detect a significant difference when utilizing an analysis approach of separating participants into low- verses high-walk/exercisers. Notably, these studies lost randomization and therefore were only able to conclude an association between fatigue and physical activity rather than causality. Many studies had difficulty with adherence to study protocol as some of the intervention group was not exercising, and some in the control group were exercising. Adherence tended to be a limitation among these studies focused on physical activity and fatigue. Overall, only one randomized control trial was unable to detect a significant difference in fatigue when implementing a physical activity intervention.

Not only does lack of adherence contribute to limitations of these studies, limitations also exist within the design of the exercise intervention. Individualized and self-administered exercise programs may be difficult to measure actual differences in fatigue as each intervention would therefore be different. Although validated fatigue assessments were utilized, fatigue remains a subjective measurement. Similar to several nutrition-related studies, a potential bias of under-reporting and over-reporting related to physical activity participation exists. In addition, a control group was not utilized in each study, limiting a comparison group to determine the effect of the intervention.

Despite several limitations, which are often difficult to overcome, this EAL project and the research identified demonstrates that breast cancer patients should be counseled to participate in physical activity throughout the course of treatment to help

mitigate fatigue. A physical activity recommendation should include aerobic exercise training, such as walking, and may include a resistance exercise program. Not only does physical activity likely help alleviate fatigue, it may also have positive impacts on QOL, body composition, and aerobic capacity.

Conclusion Statement

Question:

"How does purposeful, regular physical activity affect fatigue levels in breast cancer patients undergoing current chemotherapy and/or radiation treatment?"

Conclusion:

Physical activity effectively manages fatigue levels in breast cancer patients undergoing current chemotherapy and/or radiation treatment, with the majority of evidence showing significant reductions in fatigue levels. Breast cancer patients should be counseled to participate in aerobic activity, such as walking, and may be advised to include anaerobic exercise.

Of the seven studies reviewed, five received a positive rating while two received a neutral rating. Five studies utilized a randomized control trial research protocol in addition to one quasiexperiemental and one cohort study design. Overall, the majority of the studies demonstrated that patients undergoing treatment for cancer had a positive result from purposeful, regular exercise compared to a control group, either by a reduction in fatigue or a lack of worsening fatigue. One study, a randomized control trial, showed no impact of exercise on cancer related fatigue.

Grade: II, Fair

This study was given a fair grade based on quality concerns related to some inconsistencies within the research along with the loss of randomization among two of the five randomized control trials following ad hoc analyses. In addition, one randomized control trial found no significant difference and two of the seven studies were not of the gold standard design.

Applications to Practice

Although specific physical activity recommendations are not typically primary interventions of RDs within the nutrition care process, the results of this EAL project can make a sizeable impact on oral intake among cancer patients. As previously mentioned, fatigue levels may decrease oral intake as patients experience less desire to plan and cook meals. Thus, fatigue may lead to decreased oral intake resulting in weight loss. As stated earlier, a weight loss of as little as 6% predicts a reduced response in treatment, reduced QOL, and overall reduction in survival rate. In addition, light physical activity may increase appetite in patients experiencing a depressed appetite during treatment. Ultimately, patients counseled in the importance of physical activity and encouraged to regularly participate an aerobic activity may have the potential to positively impact oral intake leading to increased survival rates in breast cancer patients undergoing current chemotherapy and/or radiation therapy.

Recommendations for Future Practice

Though this EAL project demonstrated fair (Grade: II) evidence for providing physical activity recommendations to patients undergoing current treatments, more research is necessary. Future and more complete studies with larger samples sizes must be conducted. Studies may seek to look at more specific physical activity

recommendations for patients and include other diagnoses. If future studies are able to provide more definite data regarding improvements in CRF, further studies may then consider adding a component assessing malnutrition among cancer patients and its relation to physical activity and reduced fatigue. However, at this point, there are promising outcomes from physical activity and its impact on reducing cancer related fatigue in breast cancer patients undergoing current chemotherapy and/or radiation therapy.

REFERENCES

Academy of Nutrition and Dietetics Evidence Analysis Library. (2012). *Evidence analysis manual: Steps in the Academy evidence analysis process*. Academy of Nutrition and Dietetics. Retrieved from http://www.andeal.org/vault/2440/web/files/2012_Aug_EA_Manual.pdf

Aghili, M., Farhan, F., & Rade, M. (2007). A pilot study of the effects of programmed aerobic exercise on the severity of fatigue in cancer patients during external radiotherapy. *European Journal of Oncology Nursing, 11*, 179-182.

AJCC — American Joint Committee on Cancer. (n.d.). Retrieved February 28, 2015, from https://cancerstaging.org/references-tools/Pages/What-is-Cancer-Staging.aspx

American Cancer Society. *Cancer Facts & Figures 2014*. Atlanta: American Cancer Society, Inc.; 2014.

American Cancer Society. *Breast Cancer Facts & Figures 2013-2014*. Atlanta: American Cancer Society, Inc; 2013.

Andrykowski MA, Donovan KA, Laronga C., et al. (2010). Factors predicting clinically significant fatigue in women following treatment for primary breast cancer. *Cancer*. 116(24):5740-48.

Cancer Related Fatigue, Version 1.2014. (2014). Retrieved March 24, 2015, from https://s3.amazonaws.com/pfizerpro.com/fixtures/oncology/docs/NCCNFatigueGuidelines.pdf

Courneya, K., Segal, R., Mackey, J., Gelmon, K., Reid, R., Friedenreich, C., ... McKenzie, D. (2007). Effects of Aerobic and Resistance Exercise in Breast Cancer Patients Receiving Adjuvant Chemotherapy: A Multicenter Randomized Controlled Trial. *Journal of Clinical Oncology, 25*(28), 4396-4404.

Dimeo, FC. (2001) Effects of exercise on cancer-related fatigue. *Cancer*, 92: 1689-93.

Fatigue (PDQ®) | National Institute for Health: National Cancer Society. (n.d.). Retrieved March 5, 2015, from http://www.cancer.gov/cancertopics/pdq/supportivecare/fatigue/HealthProfessional/page4

Glossary. (n.d.). *Cancer Treatment Centers of America*. Retrieved March 21, 2015, from http://www.cancercenter.com/glossary/

Hsieh, C., Sprod, L., Hydock, D., Carter, S., Hayward, R., & Schneider, C. (2008). Effects of a Supervised Exercise Intervention on Recovery From Treatments Regimens in Breast Cancer Survivors. *Oncology Nursing Forum, 35*(6), 909-915.

Huang X., Zhang Q., Kang X, et al. (2010). Factors associated with cancer-related fatigue in breast cancer patients undergoing endocrine therapy in an urban setting: a cross-sectional study. *BMC Cancer*. 10:453.

Leser, M., Ledesma, N., Bergerson, S., & Trujillo, E. (2013). *Oncology Nutrition for Clinical Practice*. Chicago: Oncology Nutrition Dietetic Practice Group of the Academy of Nutrition and Dietetics.

Merriam-Webster Dictionary. (2015). Retrieved April 6, 2015, from http://www.merriam-webster.com/

Mock, V., Frangakis, C., Davidson, N., Ropka, M., Pickett, M., Poniatowski, B., ... McCorkle, R. (2004). Exercise Manages Fatigue During Breast Cancer Treatment: A Randomized Controlled Trial. *Psycho-Oncology, 14*, 464-477.

Mock, V., Pickett, M., Ropka, M., Lin, E., Stewart, K., Rhodes, V., ... McCorkle, R. (2001). Fatigue and Quality of Life Outcomes of Exercise During Cancer Treatment. *Cancer Practice, 9*(3), 119-127.

Mustian, K., Peppone, L., Darling, T., Palesh, O., Heckler, C., & Morrow, G. (2011). A 4-Week Home-Based Aerobic and Resistance Exercise Program During Radiation Therapy: A Pilot Randomized Clinical Trial. *Journal of Supportive Oncology, 7*(5), 158-167.

NCI Dictionary of Cancer Terms. (n.d.). Retrieved April 6, 2015, from http://www.cancer.gov/dictionary

Noal, S., Levy C., Hardouin A., et al. (2010). One-year longitudinal study of fatigue, cognitive functions, and quality of life after adjuvant radiotherapy for breast cancer. *International Journal of Radiation Oncology*. 81(3), 795-803.

Oncology Rehab Partners (2015). Evaluation Fatigue in Survivors, Module 5. *Oncology Rehab Partners: Advancing Survivorship Care*.

Overview of FACIT | FACIT.org. (n.d.). Retrieved March 5, 2015, from http://www.facit.org/FACITOrg/Overview

Physical Activity and the Cancer Patient. (2014, March 3). Retrieved May 6, 2015, from http://www.cancer.org/treatment/survivorshipduringandaftertreatment/stayingactive/physical-activity-and-the-cancer-patient

Reis, D., Walsh, E., Young-McCaughan, S., & Jones, T. (2013). Effects of Nia Exercise in Women Receiving Radiation Therapy for Breast Cancer. *Oncology Nursing Forum, 40*(5), 374-382.

Reinertsen KV, Cvancarnova M, Loge JH, et al. (2010). Predictors and course of chronic fatigue in long-term breast cancer survivors. *Journal of Cancer Survivorship.* 4(4):405-14.

Research Science Expert Report| American Institute for Cancer Research (AICR). (n.d.). Retrieved March 5, 2015, from http://www.aicr.org/research/research_science_expert_report.html

Scoring Piper Fatigue Scale (PFS) | University at Buffalo Libraries. (n.d.). Retrieved March 6, 2015, from https://ubir.buffalo.edu/xmlui/handle/10477/1898

The Brief Fatigue Inventory (BFI) | MD Anderson Cancer Center. (n.d.). Retrieved March 5, 2015, from http://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/symptom-research/symptom-assessment-tools/brief-fatigue-inventory-bfi.html

APPENDIX A: FACIT QUESTIONAIRES

FACIT-F (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACIT-F (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACIT-F (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
H7	I feel fatigued	0	1	2	3	4
H12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

FACT-An (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-An (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GB1	I feel sad	0	1	2	3	4
GB2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GB3	I am losing hope in the fight against my illness	0	1	2	3	4
GB4	I feel nervous	0	1	2	3	4
GB5	I worry about dying	0	1	2	3	4
GB6	I worry that my condition will get worse	0	1	2	3	4

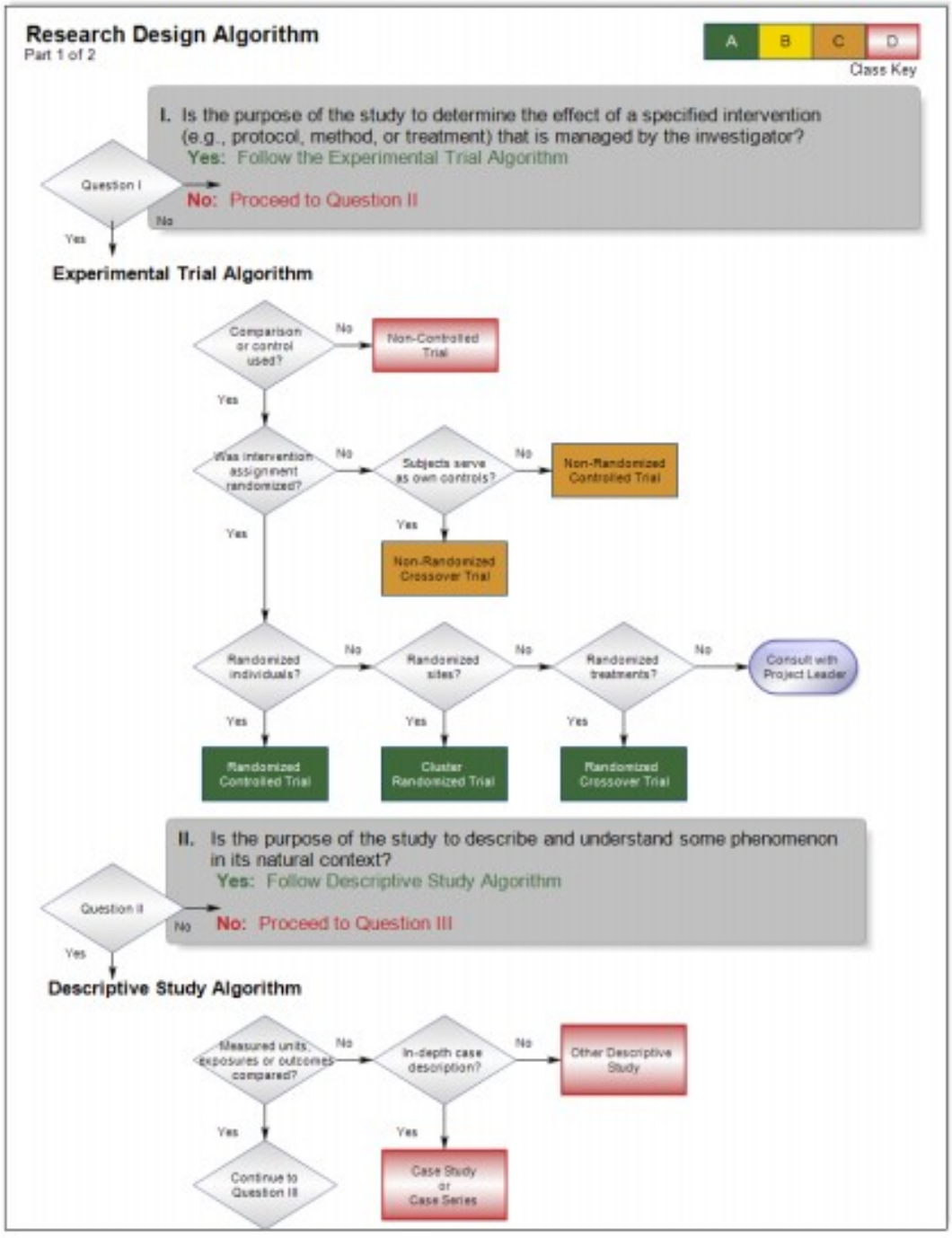
	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

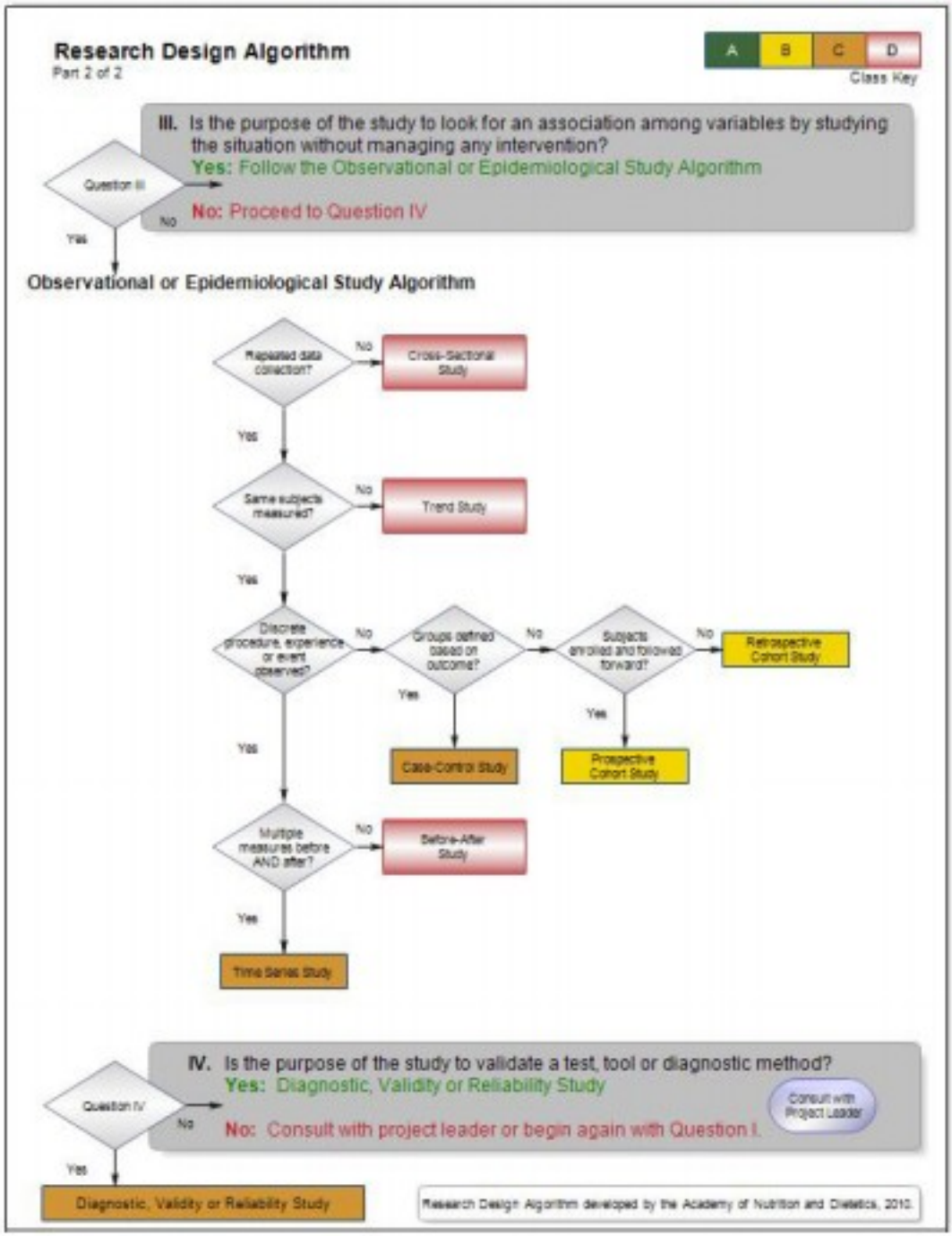
FACT-An (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
H7	I feel fatigued	0	1	2	3	4
H12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An9	I feel lightheaded (dizzy)	0	1	2	3	4
An10	I get headaches	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
An11	I have pain in my chest	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
An13	I am motivated to do my usual activities	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

APPENDIX B: AND ALGORITHM TO CLASSIFY RESEARCH




Research Design Algorithm
Part 2 of 2
A
B
C
D
Class Key
III. Is the purpose of the study to look for an association among variables by studying the situation without managing any intervention?
Yes: Follow the Observational or Epidemiological Study Algorithm
No: Proceed to Question IV
Question III
No
Yes
Observational or Epidemiological Study Algorithm
Repeated data collection?
No
Cross-Sectional Study
Yes
Same subjects measured?
No
Trend Study
Yes
Discrete procedure, experience or event observed?
No
Groups defined based on outcome?
No
Subjects enrolled and followed forward?
No
Retrospective Cohort Study
Yes
Case-Control Study
Yes
Prospective Cohort Study
Yes
Multiple measures before AND after?
No
Before-After Study
Yes
Time Series Study
IV. Is the purpose of the study to validate a test, tool or diagnostic method?
Yes: Diagnostic, Validity or Reliability Study
No: Consult with project leader or begin again with Question I.
Consult with Project Leader
Question IV
No
Yes
Diagnostic, Validity or Reliability Study
Research Design Algorithm developed by the Academy of Nutrition and Dietetics, 2010.

APPENDIX C: QUALITY CRITERIA CHECKLISTS AND EVIDENCE WORKSHEETS

Evidence Worksheet for Primary RESEARCH Article

Citation:	Aghili, M., Farhan, F., & Rade, M. (2007). A pilot study of the effects of programmed aerobic exercise on the severity of fatigue in cancer patients during external radiotherapy. European Journal of Oncology Nursing, 11, 179–182.
Study Design:	Prospective, non-randomized (Cohort)
Study Class (A,B,C,D):	C
Research Quality Rating:	Positive **(+)**
Purpose/Population Studied/Practice Studied	
Research Purpose:	The objective was to assess whether an aerobic exercise intervention during a 4-week course of radiotherapy would reduce the incidence and severity of fatigue in cancer patients undergoing RT.
Inclusion Criteria:	• Aged between 18 and 65 years • Having received at least 5 weeks of radiotherapy • 5 days/week and 2 Gy/day • No previous history of cardiac disease or diabetes • At least 3 months of disease duration
Exclusion Criteria:	• Patients with anemia • Reduced WBCs • Dyspnoea • Severe bone pain and metastasis
Recruitment:	Not noted.
Blinding Used:	Not noted.
Description of Study Protocol:	• Following informed consent, fatigue was assessed before and after the invention • At the first week before initiation of RT, the severity of fatigue was recorded daily at a specified time using the Brief Fatigue Inventory (BFI), establishing baseline fatigue levels. • At the 4th and 5th days of the first week, a 30-minute teaching session for the training group was conducted. The session described fatigue, its causes, its importance and the advantage of walking. • Patients were given a notebook about the training program. • The training program consisted of daily walking for 20 minutes (or 10 minutes daily for frail patients), which began at the second week and last for 21 days.

	• After walking patients laid in bed and took deep breaths with closed eyes for several minutes. • The training group patients were supervised for one week in order to observe them on their walking and after that they walked alone. • Patients were not allowed any training 1–2 hours after RT in the morning and before lunch. • CBCs were checked weekly in both groups in order to exclude patients with reduced blood counts. • The BFI was self-completed by all patients at baseline and daily thereafter for 28 days. • The comparison group did not engage in an exercise program and only completed the BFI as in the training group.
Intervention:	The training program consisted of daily walking for 20 minutes (or 10 minutes daily for frail patients), which began at the second week and last for 21 days.
Statistical Analysis:	• SPSS 10.0 software was used. • General information between the two groups were compared using Exact Fisher and Mann-Whitney U tests. • The severity of fatigue before and after the program was compared with non-parametric tests such as Mann-Whitney U and Wilcoxon tests because both group did not have a normal distribution and the sample size was small.
Timing of Measurements:	Measurements at baseline (first week before initiation of RT) and daily thereafter for 28 days.
Dependent Variables:	Fatigued was measured using the Brief Fatigue Inventory (BFI).

Independent Variables:	Daily walking for 20 minutes (or 10 minutes twice daily for frail patients).
Control Variables:	The comparison is considered usual care, however, the patients were also hospitalized for supervision.
Initial Number (n):	30 total patients, 15 patients in each the control and intervention group
Final Number (n):	30; Attrition was not specifically addressed.
Age:	Between 18-65 years; no range provided.
Ethnicity *(if given)*:	Not provided.
Other Relevant Demographics:	The results indicated that there was no significant difference in demographics, including: age, gender, weight, height, BMI, education, employment, and the type of disease between the two groups.
Anthropometrics:	The results indicated that there was no significant difference in demographics, including: age, gender, weight, height, BMI, education, employment, and the type of disease between the two groups.
Location:	Cancer Institute of Imam Khomeini Hospital (case group) and Jorjani Hosptial (comparison group) in Tehran, Iran.
Summary of Results:	• At the first week of assessment, the percentage of moderate fatigue (scores 4-6) in the training and comparison group patients were 56% and 43%, respectively (U = 100.5, P = 0.632). • At the fourth week, most patients (44%) in the training group had mild fatigue where at 57% of the patients in the comparison group reported severe fatigue (U = 41, P = 0.011). • Results showed that while severity was unchanged in the training group patients, there was a marked increase in the severity of fatigue in the comparison group patients (median score = 8, z = -1.91, P = 0.039).
Author's Conclusions	
Author Conclusion:	Preliminary findings suggest that, similarly to previous research, an exercise program for patients undergoing cancer treatments have positive results. After treatment, rest may be even more ineffective in relieving chronic fatigue.
Reviewer Comments:	**Strengths:** • Patients were hospitalized for observation allowing for control of more confounding variables. • Despite hospitalization, the intervention is a realistic for home-based program. • Fatigue was measured in terms of usual fatigue in the past 24 hours

	and current fatigue at present time since fatigue fluctuates during the day. • BFI is a valid measurement for assessing fatigue, a subjective measure. **Limitations:** • Small sample size • Heterogeneous group of patients • Fatigue is a subjective, self-reported measure • Non-randomized • Hospitalization could also be considered limitation as it does not allow for a typical outpatient radiation therapy patient.

Quality Criteria Checklist: A pilot study of the effects of programmed aerobic exercise on the severity of fatigue in cancer patients during external radiotherapy.				
Questions	**Yes**	**No**	**Unclear**	**N/A**
Relevance Questions				
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group?	X			
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	X			
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to the dietetics practice?	X			
4. Is the intervention or procedure feasible?	X			
Validitiy Questions				
1. Was the research question clearly stated?	X			
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?				
1.2 Was the outcome(s) (dependent variable(s)) clearly indicated?				
1.3 Were the target population and setting specified?				
2. Was the selection of study subjects/patients free from bias?	X			
2.1 Were inclusion/exclusion critieria specified (e.g. risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?				
2.2 Were criteria applied equally to all study groups?				
2.3 Were health, demographics, and other characteristics of subjects described?				
2.4 Were the subjects/patients a representative sample of the relevant population?				

Questions	Yes	No	Unclear	N/A
3. Were study groups comparable?	X			
3.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)				
3.2 Were disribution of disease status, prognostic factors, and other factors (e.g. demographics) similar across study groups at baseline?				
3.3 Were concurrent controls used? (Concurrent preferred over historical controls)				
3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?				
3.5 If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)				
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. 'gold standard')				
4. Was the method of handling widthdrawls described?			X	
4.1 Were follow-up methods described and the same for all groups?				
4.2 Was the number, characteristics of withdrawls (i.e. dropouts, lost to follow-up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow-up goal for a strong study is 80%)				
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?				
4.4 Were reasons for withdrawl similar across groups?				
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?				

Questions	Yes	No	Unclear	N/A
5. Was blinding used to prevent introduction of bias?				
5.1 In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?				
5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)		X		
5.3 In cohort or cross-sectional study, were measurements of outcomes and risk factors blinded?				
5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status?				
5.5 In diagnostic study, were test results blinded to patient history and other test results?				
6. Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?				
6.1 In RCT or other intervention trial, were protocols described for all regimens studied?				
6.2 In observation study, were interventions, study settings, and clinicals/provider described?				
6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	X			
6.4 Was the amount of exposure and, if relevant, subject/patient comliance measured?				
6.5 Were co-interventions (e.g. ancillary treatments, other therapies) described?				
6.6 Were extra or unplanned treatments described?				
6.7 Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?				
6.8 In diagnostic study, were details of test administration and replication sufficient?				

Questions	Yes	No	Unclear	N/A
7. Were outcomes clearly defined and the measurements valid and reliable?				
7.1 Were primary and secondary endpoints described and relevant to the question?				
7.2 Were nutrition measures appropriate to question and outcomes of concern?				
7.3 Was the period of follow-up long enough for important outcome(s) to occur?				
7.4 Was the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	X			
7.5 Was the measurement of effect at an appropriate level of precision?				
7.6 Were other factors accounted for (measured) that could affect outcomes?				
7.7 Were the measurements conducted consistently across groups?				
8. Was the stastical analysis appropriate for the study design and type of outcome indicators?				
8.1 Were statistical analyses adequately described and the results reported appropriately?				
8.2 Were correct statistical tests used and assumptions of test not violated?				
8.3 Were statistics reported with levels of significance and/or confidence intervals?				
8.4 Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	X			
8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g. multivariate analyses)?				
8.6 Was clinical signifiance as well as statistical significance reported?				
8.7 If negative findings, was a power calculation reported to address type 2 error?				

Questions	Yes	No	Unclear	N/A
9. Are conclusions supported by results with biases and limitations taken into consideration?	X			
9.1 Is there a discussion of findings?				
9.2 Are biases and study limitations identified and discussed?				
10. Is bias due to study's funding or sponsorship unlikely?		X		
10.1 Were sources of funding and investigators; affiliations described?				
10.2 Was there no apparent conflict of interest?				

MINUS/NEGATIVE (-)
If most (six or more) of the answers to the above validity questions are "no", the report should be designated with a minus (-) symbol on the Evidence Worksheet.
NEUTRAL (⊘)
If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a (⊘) symbol on the Evidence Worksheet.
PLUS/POSITIVE (+)
If most of the answers to the above validity questions are "yes" (including criteria 2, 3, 6, 7 at at least one additional "yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet)

Citation: Aghili, M., Farhan, F., & Rade, M. (2007). A pilot study of the effects of programmed aerobic exercise on the severity of fatigue in cancer patients during external radiotherapy. European Journal of Oncology Nursing, 11, 179-182.

Evidence Worksheet for Primary RESEARCH Article

Citation:	Courneya, K., Segal, R., Mackey, J., Gelmon, K., Reid, R., Friedenreich, C., ... McKenzie, D. (2007). Effects of Aerobic and Resistance Exercise in Breast Cancer Patients Receiving Adjuvant Chemotherapy: A Multicenter Randomized Controlled Trial. *Journal of Clinical Oncology, 25*(28), 4396-4404.
Study Design:	Randomized Controlled Trial
Study Class (A,B,C,D)	A
Research Quality Rating	**+**
Research Purpose:	To evaluate the relative merits of aerobic and resistance exercise in blunting the effects of unfavorable changes in physical functioning, body composition, psychosocial functioning, and quality of life (QOL) in breast cancer patients undergoing chemotherapy.
Inclusion Criteria:	• English o French speaking, nonpregnant women • > or equal to 18 years old • Stage I through IIIA breast cancer • Beginning first-line adjuvant chemotherapy
Exclusion Criteria:	• Incomplete axillary surgery • Transabdominal rectus abdominus muscle reconstructive surgery • Uncontrolled hypertension • Cardiac illness • Psychiatric illness • Or, otherwise not approved by their oncologist
Recruitment:	Recruited from Cross Cancer Institute (Edmonton, Alberta, Canada), the Ottawa Hospital Integrated Cancer Program (Ottawa, Ontario, Canada), and the British Columbia Cancer Agency (Vancouver, British Columbia, Canada)
Blinding:	The allocation sequence for randomization was generated in Edmonton and concealed from the project directors at each site who assigned participants to groups.
Description of Study Protocol:	Random assignment of breast cancer patients initiating adjuvant chemotherapy to usual care, supervised resistance exercise, or supervised aerobic exercise for the duration of chemotherapy.
Intervention:	• Participants exercised for the duration of their chemotherapy, including delays, beginning 1 to 2 weeks after starting chemotherapy and ending 3 weeks after chemotherapy. • Warm-up and cool-down periods were 5 minutes of light aerobic activity and stretching.

	• **Aerobic Exercise Training (AET):** Exercise 3 times per week on a cycle ergometer, treadmill, or elliptical beginning at 60% of VO_{2max} for weeks 1 to 6 and progression to 70% during weeks 7 to 12 and 80% beyond week 12.
	  o Exercise duration began at 15 minutes for weeks 1 to 3 and increased by 5 minutes every 3 weeks until the duration reached 45 minutes at week 18.
	• **Resistance Exercise Training (RET):** Exercise 3 times per week performing two sets of eight to 12 repetitions of nine different exercises at 60% and 70% of their estimated one-repetition maximum.
	  o Exercises included: leg extension, leg curl, leg press, calf raises, chest press, seated row, triceps extension, bicep curls, and modified curl-ups.
	  o Resistance was increased by 10% when participants completed more than 12 repetitions.
	• **Usual Care:** This group was asked to not initiate an exercise program and was offered a 1-month exercise program after postintervention assessments.

Statistical Analysis:	• 80% power to detect a difference in change scores of 7 points on the Functional Assessment of Cancer Therapy-Anemia scale with a loss-to-follow-up of 10%, a two-tailed $\alpha < 0.05$, and no adjustment for multiple testing. • Baseline comparisons were performed using univariate analysis for variance continuous variables and x^2 analysis for categorical variables. • Mixed-model analysis was used to model each outcome measure at three (or two) time points and compare the differences across groups in changes over time. • Primary analysis was unadjusted, but adjusted analysis was also performed controlling for baseline value of the outcome, age, marital status, and smoking status, using baseline propensity scores for being assigned to the RET and AET groups. • Descriptive data and 95% CIs for all possible comparisons were provided and significant tests (P values) only for hypothesized comparisons. • Intent-to-treat principle • Available data for participants with missing data were included under the missing at random assumption of the mixed-model analysis.
Timing of Measurements:	• Prior to chemotherapy, eligible participants completed a questionnaire, physical fitness test, and dual x-ray absorptiomentry scan (added after the first 23 participants were randomly assigned. • Patient-rated outcomes were assessed at baseline (1-2 weeks after staring chemotherapy), midpoint (middle of chemotherapy), after the intervention (3 to 4 weeks after chemotherapy), and the 6-month follow-up (data not presented). • Objectively measured outcomes were assessed at baseline and after intervention.
Dependent Variables:	• Cancer-specific QOL and fatigue were assessed by the Functional Assessment of Cancer Therapy-Anemia Scale • Psychosocial functioning was assessed by the Rosenberg Self-

	Esteem Scale, the Center for Epidemiological Studies Depression Scale, and the Spielberger State Anxiety Inventory • Aerobic fitness was evaluated using a maximal incremental exercise protocol on a treadmill. • Expired gases were analyzed using a metabolic measurement cart (CPX-D). o Peak oxygen consumption was determined by taking the highest values during a 15-second period. • Muscular strength was assessed by an eight-repetition maximum on the horizontal bench press and leg extension. • Body weight to the nearest 0.1 kg and standing height to the nearest 0.5 cm were assessed without shoes using a balance beam skill. • A dual x-ray absorptiometry scan was obtained for the assessment of whole body fat and lean tissue using the Hologic QDR-4500 in Vancouver and the GE LUNAR EXPERT in Ottawa and Edmonton. • Lymphedema was assessed using standard volumetric arm measurements based on water displacement. • Chemotherapy completion rate was assessed as the average relative dose-intensity (RDI) for the originally planned regime based on standard formulas.

Independent Variables:	• Participants exercised for the duration of their chemotherapy, including delays, beginning 1 to 2 weeks after starting chemotherapy and ending 3 weeks after chemotherapy.
	• Warm-up and cool-down periods were 5 minutes of light aerobic activity and stretching.
	• **Aerobic Exercise Training (AET):** Exercise 3 times per week on a cycle ergometer, treadmill, or elliptical beginning at 60% of VO_{2max} for weeks 1 to 6 and progression to 70% during weeks 7 to 12 and 80% beyond week 12.
	  o Exercise duration began at 15 minutes for weeks 1 to 3 and increased by 5 minutes every 3 weeks until the duration reached 45 minutes at week 18.
	• **Resistance Exercise Training (RET):** Exercise 3 times per week performing two sets of eight to 12 repetitions of nine different exercises at 60% and 70% of their estimated one-repetition maximum.
	  o Exercises included: leg extension, leg curl, leg press, calf raises, chest press, seated row, triceps extension, bicep curls, and modified curl-ups.
	  o Resistance was increased by 10% when participants completed more than 12 repetitions.

Control Variables:	**Usual Care:** This group was asked to not initiate an exercise program and was offered a 1-month exercise program after postintervention assessments.
Initial Number (n):	242 of 736 eligible participants

Final Number (n, *attrition*):	Obtained follow-up data on the patient-rated outcomes from 223 (92.1%) of 242 participants.
Age:	Overall: 25-78 years of age
Ethnicity *(if given)*:	Not provided.
Other Relevant Demographics:	Groups were balanced at baseline.
Anthropometrics:	Groups were balanced at baseline.
Location:	Recruited from Cross Cancer Institute (Edmonton, Alberta, Canada), the Ottawa Hospital Integrated Cancer Program (Ottawa, Ontario, Canada), and the British Columbia Cancer Agency (Vancouver, British Columbia, Canada)
Summary of Results:	• Follow-up assessment for the primary end point was 92.1% • Adherence to supervised exercise was 70.2% • Unadjusted and adjusted mixed-model analyses indicated that aerobic exercise was superior to usual care for improving self-esteem ($p = .015$), aerobic fitness ($p = .006$), and percent body fat (adjusted $p = 0.076$). • Resistance exercise was superior to usual care for improving self-esteem ($p = 0.18$), muscular strength ($p < .001$), lean body mass ($p = .015$), and chemotherapy completion rate ($p = .033$). • Changes in cancer-specific QOL, fatigue, depression, and anxiety favored the exercise groups, but did not reach statistical significance. • Exercise did not cause lymphedema or adverse effects.
Author Conclusion:	In neither aerobic or resistance exercise training was there significant improvements in cancer-specific QOL in breast cancer patients undergoing chemotherapy treatment. However, exercise training did improve self-esteem, physical fitness, body composition, and chemotherapy completion rate without causing the adverse effects of lymphedema or significant adverse effects.
Reviewer Comments:	**Strengths:** • Direct comparison of aerobic and resistance exercise • The largest sample size to date • Well-defined population (only breast cancer patients) • Multi-center recruitment • Supervised exercise • Comprehensive assessment of important end-points with validated measures • Intent-to-treat • Limited loss to follow-up • Use of VO_{2max} for exercise intensity **Limitations:** • 70% adherence rate • 33% recruitment rate • Well-educated, racially homogenous sample • Usual care specifically instructed no exercise programs

Quality Criteria Checklist: Effects of Aerobic and Resistance Exercise in Breast Cancer Patients Receiving Adjuvant Chemotherapy				
Questions	**Yes**	**No**	**Unclear**	**N/A**
Relevance Questions				
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group?	X			
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	X			
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to the dietetics practice?	X			
4. Is the intervention or procedure feasible?	X			
Validitiy Questions				
1. Was the research question clearly stated?	X			
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?				
1.2 Was the outcome(s) (dependent variable(s)) clearly indicated?				
1.3 Were the target population and setting specified?				
2. Was the selection of study subjects/patients free from bias?	X			
2.1 Were inclusion/exclusion critieria specified (e.g. risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?				
2.2 Were criteria applied equally to all study groups?				
2.3 Were health, demographics, and other characteristics of subjects described?				
2.4 Were the subjects/patients a representative sample of the relevant population?				

Questions	Yes	No	Unclear	N/A
3. Were study groups comparable?				
3.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)				
3.2 Were disribution of disease status, prognostic factors, and other factors (e.g. demographics) similar across study groups at baseline?				
3.3 Were concurrent controls used? (Concurrent preferred over historical controls)				
3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	X			
3.5 If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)				
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. 'gold standard')				
4. Was the method of handling widthdrawls described?				
4.1 Were follow-up methods described and the same for all groups?				
4.2 Was the number, characteristics of withdrawls (i.e. dropouts, lost to follow-up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow-up goal for a strong study is 80%)	X			
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?				
4.4 Were reasons for withdrawl similar across groups?				
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?				

Questions	Yes	No	Unclear	N/A
5. Was blinding used to prevent introduction of bias?				
5.1 In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?				
5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)		X		
5.3 In cohort or cross-sectional study, were measurements of outcomes and risk factors blinded?				
5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status?				
5.5 In diagnostic study, were test results blinded to patient history and other test results?				
6. Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?				
6.1 In RCT or other intervention trial, were protocols described for all regimens studied?				
6.2 In observation study, were interventions, study settings, and clinicals/provider described?				
6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	X			
6.4 Was the amount of exposure and, if relevant, subject/patient comliance measured?				
6.5 Were co-interventions (e.g. ancillary treatments, other therapies) described?				
6.6 Were extra or unplanned treatments described?				
6.7 Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?				
6.8 In diagnostic study, were details of test administration and replication sufficient?				

Questions	Yes	No	Unclear	N/A
7. Were outcomes clearly defined and the measurements valid and reliable?				
7.1 Were primary and secondary endpoints described and relevant to the question?				
7.2 Were nutrition measures appropriate to question and outcomes of concern?				
7.3 Was the period of follow-up long enough for important outcome(s) to occur?				
7.4 Was the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	X			
7.5 Was the measurement of effect at an appropriate level of precision?				
7.6 Were other factors accounted for (measured) that could affect outcomes?				
7.7 Were the measurements conducted consistently across groups?				
8. Was the stastical analysis appropriate for the study design and type of outcome indicators?				
8.1 Were statistical analyses adequately described and the results reported appropriately?				
8.2 Were correct statistical tests used and assumptions of test not violated?				
8.3 Were statistics reported with levels of significance and/or confidence intervals?				
8.4 Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	X			
8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g. multivariate analyses)?				
8.6 Was clinical signifiance as well as statistical significance reported?				
8.7 If negative findings, was a power calculation reported to address type 2 error?				

Questions	Yes	No	Unclear	N/A
9. Are conclusions supported by results with biases and limitations taken into consideration?	X			
9.1 Is there a discussion of findings?				
9.2 Are biases and study limitations identified and discussed?				
10. Is bias due to study's funding or sponsorship unlikely?	X			
10.1 Were sources of funding and investigators; affiliations described?				
10.2 Was there no apparent conflict of interest?				

MINUS/NEGATIVE (-)
If most (six or more) of the answers to the above validity questions are "no", the report should be designated with a minus (-) symbol on the Evidence Worksheet.
NEUTRAL (⊘)
If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a (⊘) symbol on the Evidence Worksheet.
PLUS/POSITIVE (+)
If most of the answers to the above validity questions are "yes" (including criteria 2, 3, 6, 7 at at least one additional "yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet)

Citation: Courneya, K., Segal, R., Mackey, J., Gelmon, K., Reid, R., Friedenreich, C., ... McKenzie, D. (2007). Effects of Aerobic and Resistance Exercise in Breast Cancer Patients Receiving Adjuvant Chemotherapy: A Multicenter Randomized Controlled Trial. Journal of Clinical Oncology, 25(28), 4396-4404.

Evidence Worksheet for Primary RESEARCH Article

Citation:	Hsieh, C., Sprod, L., Hydock, D., Carter, S., Hayward, R., & Schneider, C. (2008). Effects of a Supervised Exercise Intervention on Recovery From Treatment Regimens in Breast Cancer Survivors. *Oncology Nursing Forum, 35*(6), 909-915.
Study Design:	Quasiexperimental
Study Class (A,B,C,D):	D
Research Quality Rating:	Ø
Purpose/Population Studied/Practice Studied	
Research Purpose:	To investigate the effects of supervised exercise training on cardiopulmonary function and fatigue in cancer survivors undergoing various clinical treatments.

Inclusion Criteria:	• Breast cancer survivors
	• Undergoing various clinical treatments
	  o Surgery alone
	  o Surgery and Chemotherapy
	  o Surgery and Radiation
	  o Surgery, Chemotherapy, and Radiation

Exclusion Criteria:	Not noted.
Recruitment:	Subjects were chosen from women who were referred by local oncologists to the Rocky Mountain Cancer Rehabilitation Institute (RMCRI) for rehabilitative exercise immediately following treatment for breast cancer. Informed consent and university IRB approved procedures.
Blinding Used:	None.
Description of Study Protocol:	• Trained, certified cancer exercise specialists completed assessments, exercise interventions, and reassessments. • Cancer survivors received comprehensive screening following initial medical examination prior to inclusion to study. • Individual exercise prescriptions following assessment of cardiovascular endurance, pulmonary function, and fatigue. • Interventions developed individually • Supervised exercise sessions, 2-3 days per week for 6 months • Reassessment questionnaire prior to each training session • 60 minute sessions with "whole-body" approach

Intervention:	• Individual exercise prescriptions following assessment of cardiovascular endurance, pulmonary function, and fatigue. • Interventions developed individually • Supervised exercise sessions, 2-3 days per week for 6 months • Reassessment questionnaire prior to each training session o 60 minute sessions with "whole-body" approach o Although individualized interventions, exercise session generally included 10-minute warm-up, 40 minutes aerobic exercise, resistance training and stretching, 10-minute cool-down o Options included: outdoor or treadmill walking, stationary cycling, recumbent stepping, or walking on underwater treadmill + resistance training and flexibility of all major muscle groups
Statistical Analysis:	• Four groups compared using one-way analysis of variance (ANOVA) • Tukey honestly significant difference post-hoc tests • Statistical analysis preformed using SPSS • Significance set at p-value of less than or equal to 0.05
Timing of Measurements:	Pre-test and post-test
Dependent Variables:	• Cardiopulmonary function assessed using Flowmate Spirometer o Systolic blood pressure o Diastolic blood pressure o Resting heart rate o Forced vital capacity o Forced expiratory volume o VO_2max o Treadmill time • Fatigue assessed using Piper Fatigue Scale: o Behavioral fatigue o Affective fatigue o Sensory fatigue o Cognitive and mood fatigue o Total fatigue

Independent Variables	Individualized exercise prescription.
Control Variables:	None. There was no control group/variable in this experiment.
Initial (n):	o 96 breast cancer survivors o 4 groups, based on type of clinical treatment o Surgery alone (n=22) o Surgery and Chemotherapy (n=30) o Surgery and Radiation (n=17) o Surgery, Chemotherapy, and Radiation (n=27)
Final (n):	The article did not discuss any withdrawals/attrition.
Age:	57.9 +/- 10.4 years
Ethnicity *(if given):*	N/A
Other Relevant Demographics	N/A
Anthropometrics:	No significant differences were observed in age, height, and weight between groups.
Location:	Rocky Mountain Cancer Rehabilitation Institute (RMCRI)
Summary of Results:	o Cardiopulmonary function significantly increased in all groups after exercise training ($p < 0.05$). o Breast cancer survivors in the surgery, chemotherapy, and radiation group showed significant reductions in resting heart rate ($p < 0.05$) and concurrent increases on $FVC\%_{pred}$ after the supervised exercise intervention. o The exercise intervention resulted in significant reductions in behavioral fatigue, affective fatigue, sensory fatigue, cognitive and mood fatigue, and total fatigue in the surgery and chemotherapy; surgery and radiation therapy; and surgery, chemotherapy, and radiation therapy groups ($p<0.05$).
Author's Conclusions	
Author Conclusion:	o First study to compare effects of an exercise intervention on cardiopulmonary function and fatigue in breast cancer survivors who received different types of clinical treatments. o Moderate intensity, individualized, prescriptive exercise could alleviate negative side effects of cancer treatment o Studies consistent with previous studies
Reviewer Comments:	Limitations: o Convenience sample o 1 geographic area o No control group o *No specific p-values provided* o *Large-scale individualized exercise prescriptions make it difficult to compare interventions* o *Since no control group, thus no randomization* Strengths: o *Carefully individualized exercise prescriptions* o *Studied multi-levels of treatment* o *Studied many different types of fatigue, rather than just overall fatigue*

Quality Criteria Checklist: Effects of a Supervised Exercise Intervention on Recovery From Treatment Regimens in Breast Cancer Survivors.				
Questions	**Yes**	**No**	**Unclear**	**N/A**
Relevance Questions				
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group?	X			
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	X			
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to the dietetics practice?	X			
4. Is the intervention or procedure feasible?	X			
Validitiy Questions				
1. Was the research question clearly stated?	X			
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?				
1.2 Was the outcome(s) (dependent variable(s)) clearly indicated?				
1.3 Were the target population and setting specified?				
2. Was the selection of study subjects/patients free from bias?	X			
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2.2 Were criteria applied equally to all study groups?				
2.3 Were health, demographics, and other characteristics of subjects described?				
2.4 Were the subjects/patients a representative sample of the relevant population?				

Questions	Yes	No	Unclear	N/A
3. Were study groups comparable?				
3.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)				
3.2 Were disribution of disease status, prognostic factors, and other factors (e.g. demographics) similar across study groups at baseline?				
3.3 Were concurrent controls used? (Concurrent preferred over historical controls)				
3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?		X		
3.5 If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)				
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. 'gold standard')				
4. Was the method of handling widthdrawls described?				
4.1 Were follow-up methods described and the same for all groups?				
4.2 Was the number, characteristics of withdrawls (i.e. dropouts, lost to follow-up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow-up goal for a strong study is 80%)		X		
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?				
4.4 Were reasons for withdrawl similar across groups?				
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?				

Questions	Yes	No	Unclear	N/A
5. Was blinding used to prevent introduction of bias?				
5.1 In intervention study, were subjects, clinicians/practittioners, and investigators blinded to treatment group, as appropriate?				
5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)		X		
5.3 In cohort or cross-sectional study, were measurements of outcomes and risk factors blinded?				
5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status?				
5.5 In diagnostic study, were test results blinded to patient history and other test results?				
6. Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?				
6.1 In RCT or other intervention trial, were protocols described for all regimens studied?				
6.2 In observation study, were interventions, study settings, and clinicals/provider described?				
6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	X			
6.4 Was the amount of exposure and, if relevant, subject/patient comliance measured?				
6.5 Were co-interventions (e.g. ancillary treatments, other therapies) described?				
6.6 Were extra or unplanned treatments described?				
6.7 Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?				
6.8 In diagnostic study, were details of test administration and replication sufficient?				

Questions	Yes	No	Unclear	N/A
7. Were outcomes clearly defined and the measurements valid and reliable?	X			
7.1 Were primary and secondary endpoints described and relevant to the question?				
7.2 Were nutrition measures appropriate to question and outcomes of concern?				
7.3 Was the period of follow-up long enough for important outcome(s) to occur?				
7.4 Was the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?				
7.5 Was the measurement of effect at an appropriate level of precision?				
7.6 Were other factors accounted for (measured) that could affect outcomes?				
7.7 Were the measurements conducted consistently across groups?				
8. Was the stastical analysis appropriate for the study design and type of outcome indicators?	X			
8.1 Were statistical analyses adequately described and the results reported appropriately?				
8.2 Were correct statistical tests used and assumptions of test not violated?				
8.3 Were statistics reported with levels of significance and/or confidence intervals?				
8.4 Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?				
8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g. multivariate analyses)?				
8.6 Was clinical signifiance as well as statistical significance reported?				
8.7 If negative findings, was a power calculation reported to address type 2 error?				

Questions	Yes	No	Unclear	N/A
9. Are conclusions supported by results with biases and limitations taken into consideration?	X			
9.1 Is there a discussion of findings?				
9.2 Are biases and study limitations identified and discussed?				
10. Is bias due to study's funding or sponsorship unlikely?	X			
10.1 Were sources of funding and investigators; affiliations described?				
10.2 Was there no apparent conflict of interest?				

MINUS/NEGATIVE (-)
If most (six or more) of the answers to the above validity questions are "no", the report should be designated with a minus (-) symbol on the Evidence Worksheet.
NEUTRAL (⊘)
If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a (⊘) symbol on the Evidence Worksheet.
PLUS/POSITIVE (+)
If most of the answers to the above validity questions are "yes" (including criteria 2, 3, 6, 7 at at least one additional "yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet)

Citation: Hsieh, C., Sprod, L., Hydock, D., Carter, S., Hayward, R., & Schneider, C. (2008). Effects of a Supervised Exercise Intervention on Recovery From Treatment Regimens in Breast Cancer Survivors. Oncology Nursing Forum, 35(6), 909-915.

Evidence Worksheet for Primary RESEARCH Article

Citation:	Mock, V., Frangakis, C., Davidson, N., Ropka, M., Pickett, M., Poniatowski, B., ... McCorkle, R. (2004). Exercise Manages Fatigue During Breast Cancer Treatment: A Randomized Controlled Trial. *Psycho-Oncology, 14*, 464-477.
Study Design:	Randomized Control Trial
Study Class: (A,B,C,D)	A
Research Quality Rating:	Positive **(+)**
Purpose/Population Studied/Practice Studied	
Research Purpose:	The purpose of the study was to conduct a randomized controlled trial to determine the effects of a home-based walking exercise program on levels of fatigue in women with breast cancer receiving adjuvant cytotoxic chemotherapy or radiation therapy.
Inclusion Criteria:	• Women aged 18-70 years of age • Stage 0-III breast cancer by definitive surgery • Scheduled to receive outpatient radiation therapy or adjuvant chemotherapy
Exclusion Criteria:	• Concurrent major health problems that could affect participation in an exercise program including: obesity, chronic respiratory disease, and cognitive dysfunction. • Those already engaged in active exercise, defined as exercising more than 45 minutes per week.
Recruitment:	Patients were identified from new patient appointment lists at the site clinics between 1998 and 2001 and approached by investigators during their consultation visits prior to initiating adjuvant therapy.
Blinding Used:	Approximately equal numbers of CT and RT patients were randomized to exercise and usual care groups at each study site. Consecutively numbered sealed opaque envelopes containing the computer-generated randomization assignments were prepared at the coordinating center and opened at the site following baseline pretesting for each participant.
Description of Study Protocol:	• The experimental intervention was designed to be consistent with evidence that such programs are effective and to ensure the greatest generalizability of the intervention. • The exercise program was implemented to span the period of time from initiation to cessation of the participant's adjuvant therapy—either six weeks of RT or 3-6 months of CT. • Initial assessments of physical status and fitness level were

	conducted. • Individual exercise programs consistent with American College of Sports Medicine guidelines for ill populations were taught and monitored by oncology nurses. • Exercise participants kept daily diaries of exercise periods including pulse rates, perceived exertion rates, and fatigue levels and the diaries were sent to the coordinating center each week. • Evaluation of the exercise prescription and participant progress were monitored every two weeks by the research team. o If the exercise participant was ill or stopped exercising for more than 3 days, the prescription was adjusted as needed. • Both the intervention and the comparison group received the usual care provided by the outpatient health care team. • Patients in the usual care group were encouraged to maintain current levels of activity, but no exercise prescriptions or formal programs were offered. • Usual care participants also kept daily diaries of fatigue and general physical activity levels. o Usual care participants were called every 2 weeks by the research team as an attentional control and were asked about their cancer treatment experience. o Participants reporting unmanaged symptoms or other clinical problems were referred to their health care provider for treatment.
Intervention:	• The intervention group received a written prescription to walk 5-6 times per week at a moderate pace in the target heart range, as tolerated. o Target heart rate range: approximately 50-70% of maximum heart rate. • The regimen was a brisk 15-minute walk that increased to 30 minutes as training progressed. • The program was detailed in a booklet and a video provided to the patients in the exercise group to ensure standardization across subjects and across all 8 clinical sites. • The Total Score of the Piper Fatigue Scale (PFS), a 22-item ten-point self-report scale, measured fatigue (primary outcome). • The 12-minute Walk Test measured physical functioning and activity levels.
Statistical Analysis:	• Data analysis included both an estimation of the effect of randomization (intention-to-treat), and the effect of actually exercising, namely the efficacy of exercising. o Intention-to-treat measures the potential benefit of assignment to exercise assuming the degree of adherence in the population would be consistent with that observed in the trial. ▪ Estimated by comparing available outcomes by randomized arm, which disregards adherence behavior. ▪ Reported both without adjustment for the baseline covariates using the two sample t-

	test, and with adjustment using multiple linear regression. o The efficacy of exercising measures the potential benefits of actually exercising at a specific level. ▪ Method of *instrumental variables with principle stratification (IV/PS)* • This method is increasingly used in RCT, as well as medical and public health applications to address selective adherence to treatment. • The method compares treatments within certain strata, the *principle strata*, that determine the post-randomization treatment received but that are themselves no affected by randomization. • *Never-taker, always-taker, full-complier, defier* o Power analysis based on 80% power and an alpha of 5% o Effect size of 0.9 as the expected effect of exercise on fatigue based on full adherence. o Sample size of 120 was selected to take into account expected non-adherence as well as attrition and also allow the possibility of comparing randomized arms with different treatments. o All statistical tests are two-sided with a 5% Type I error and confidence intervals have 95% nominal coverage.
Timing of Measurements:	Participants in both groups completed the outcome measures at pretest before the initiation of RT or CT, and at posttest at the end of six weeks of RT or at the last cycle of CT.
Dependent Variables:	**Fatigue** • Primary outcome • Measured by the Total Score of the Piper Fatigue Scale (PFS) • 22-item ten-point self-report scale • Total scores on the PFS of o Less than or equal to 3 = no or mild fatigue o Greater than 3 through 6 = moderate fatigue o Greater than 6 = severe levels of fatigue • Calculated as the difference between the pretest and posttest PFS score • A change of one unit in the fatigue score (e.g. 3-4) represents a clinically significant change in fatigue **Physical Functioning** • Measured by the 12-minutes Walk Test, the Medical Outcomes Study Short Health Form, and by the Physical Activity Questionnaire

Independent Variables:	• The intervention group received a written prescription to walk 5-6 times per week at a moderate pace in the target heart range, as tolerated. o Target heart rate range: approximately 50-70% of maximum heart rate. • The regimen was a brisk 15-minute walk that increased to 30 minutes as training progressed.
Control Variables:	Usual care provided by the outpatient health care team.
Initial Number (n):	• 234 patients were approached for the study, 47 (20%) were regular exercisers and, therefore ineligible. • 66 declined participation • 2 entered but withdrew before randomization • 119 were randomized
Final Number (n):	• Among 119 who were randomized, 11 participants provided no fatigue outcomes and could not be evaluated directly • 108 total
Age:	30-69 with mean age of 52 years
Ethnicity *(if given)*:	82% Caucasian
Other Relevant Demographics:	• 68% partnered • 73% employed • Stage 0: 24% • Stage I: 43% • Stage II: 30% • Stage III: 3% • 58% received RT • 42% received CT
Anthropometrics:	No significant differences among anthropometric data.
Location:	The study was conducted at four university teaching hospitals of National Cancer Institute designated Cancer Centers and four community cancer centers in the eastern United States.
Summary of Results:	Of participants randomized to exercise, 72% adhered to the exercise prescription; 61% of the usual care group adhered. The *intention-to-treat* analysis revealed no group differences in part because of a dilution of treatment effect as 39% of the usual care group exercised and 28% of the exercise group did not. When exercise participation was considered using the data analysis method of *instrumental variables* with *principle stratification*, a clinically important and statistically significant ($p = 0.03$) effect of exercise on pretest-to-posttest change in fatigue levels was demonstrated.
Author's Conclusions	

Author Conclusion:	Adherence to a home‐based moderate‐intensity walking exercise program may effectively mitigate the high levels of fatigue prevalent during cancer treatment.
Reviewer Comments:	**Strengths:** • Randomized Control Trial • Prospective • Patients were treatment naïve and were not exercising regularly at study entry. • Objective physiological measures of exercise tolerance were used in conjunction with self‐report measures of fatigue and other symptoms. • Attentional control • Quality control measures for standardization • Each site was audited after the first 3 subjects were enrolled and annually thereafter for adherence protocol. **Limitations:** • Adherence among participants • Not a double‐blind experiment • Fatigue is a subjective measurement • Potential bias of under‐reporting and over‐reporting • Lack of physiological activity monitor to measure exercise behavior more precisely • Usual care participants did not document physical activity

Quality Criteria Checklist: Exercise Manages Fatigue During Breast Cancer Treatment				
Questions	**Yes**	**No**	**Unclear**	**N/A**
Relevance Questions				
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group?	X			
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	X			
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to the dietetics practice?	X			
4. Is the intervention or procedure feasible?	X			
Validitiy Questions				
1. Was the research question clearly stated?	X			
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?				
1.2 Was the outcome(s) (dependent variable(s)) clearly indicated?				
1.3 Were the target population and setting specified?				
2. Was the selection of study subjects/patients free from bias?	X			
2.1 Were inclusion/exclusion critieria specified (e.g. risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?				
2.2 Were criteria applied equally to all study groups?				
2.3 Were health, demographics, and other characteristics of subjects described?				
2.4 Were the subjects/patients a representative sample of the relevant population?				

Questions	Yes	No	Unclear	N/A
3. Were study groups comparable?				
3.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)				
3.2 Were disribution of disease status, prognostic factors, and other factors (e.g. demographics) similar across study groups at baseline?				
3.3 Were concurrent controls used? (Concurrent preferred over historical controls)				
3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	X			
3.5 If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)				
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. 'gold standard')				
4. Was the method of handling widthdrawls described?				
4.1 Were follow-up methods described and the same for all groups?				
4.2 Was the number, characteristics of withdrawls (i.e. dropouts, lost to follow-up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow-up goal for a strong study is 80%)	X			
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?				
4.4 Were reasons for withdrawl similar across groups?				
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?				

Questions	Yes	No	Unclear	N/A
5. Was blinding used to prevent introduction of bias?				
5.1 In intervention study, were subjects, clinicians/practittioners, and investigators blinded to treatment group, as appropriate?				
5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)		X		
5.3 In cohort or cross-sectional study, were measurements of outcomes and risk factors blinded?				
5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status?				
5.5 In diagnostic study, were test results blinded to patient history and other test results?				
6. Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?				
6.1 In RCT or other intervention trial, were protocols described for all regimens studied?				
6.2 In observation study, were interventions, study settings, and clinicals/provider described?				
6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	X			
6.4 Was the amount of exposure and, if relevant, subject/patient comliance measured?				
6.5 Were co-interventions (e.g. ancillary treatments, other therapies) described?				
6.6 Were extra or unplanned treatments described?				
6.7 Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?				
6.8 In diagnostic study, were details of test administration and replication sufficient?				

Questions	Yes	No	Unclear	N/A
7. Were outcomes clearly defined and the measurements valid and reliable?	X			
7.1 Were primary and secondary endpoints described and relevant to the question?				
7.2 Were nutrition measures appropriate to question and outcomes of concern?				
7.3 Was the period of follow-up long enough for important outcome(s) to occur?				
7.4 Was the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?				
7.5 Was the measurement of effect at an appropriate level of precision?				
7.6 Were other factors accounted for (measured) that could affect outcomes?				
7.7 Were the measurements conducted consistently across groups?				
8. Was the stastical analysis appropriate for the study design and type of outcome indicators?	X			
8.1 Were statistical analyses adequately described and the results reported appropriately?				
8.2 Were correct statistical tests used and assumptions of test not violated?				
8.3 Were statistics reported with levels of significance and/or confidence intervals?				
8.4 Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?				
8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g. multivariate analyses)?				
8.6 Was clinical signifiance as well as statistical significance reported?				
8.7 If negative findings, was a power calculation reported to address type 2 error?				

Questions	Yes	No	Unclear	N/A
9. Are conclusions supported by results with biases and limitations taken into consideration?	X			
9.1 Is there a discussion of findings?				
9.2 Are biases and study limitations identified and discussed?				
10. Is bias due to study's funding or sponsorship unlikely?	X			
10.1 Were sources of funding and investigators; affiliations described?				
10.2 Was there no apparent conflict of interest?				

MINUS/NEGATIVE (-)
If most (six or more) of the answers to the above validity questions are "no", the report should be designated with a minus (-) symbol on the Evidence Worksheet.
NEUTRAL (⊘)
If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a (⊘) symbol on the Evidence Worksheet.
PLUS/POSITIVE (+)
If most of the answers to the above validity questions are "yes" (including criteria 2, 3, 6, 7 at at least one additional "yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet)

Citation: Mock, V., Frangakis, C., Davidson, N., Ropka, M., Pickett, M., Poniatowski, B., ... McCorkle, R. (2004). Exercise Manages Fatigue During Breast Cancer Treatment: A Randomized Controlled Trial. Psycho-Oncology, 14, 464-477.

Evidence Worksheet for Primary Research Article

Citation:	Mock, V., Pickett, M., Ropka, M., Lin, E., Stewart, K., Rhodes, V., ... McCorkle, R. (2001). Fatigue and Quality of Life Outcomes of Exercise During Cancer Treatment. *Cancer Practice, 9*(3), 119-127.
Study Design:	Randomized Control Trial
Study Class (A,B,C,D):	A
Research Quality Rating	Positive **(+)**
Purpose/Population Studied/Practice Studied	
Research Purpose:	Conducted to determine the feasibility of and to explore the effects of a home-based exercise intervention on fatigue, physical functioning, emotional distress, and QOL in women receiving radiation therapy (RT) or adjuvant cytotoxic chemotherapy (CT) after breast cancer surgery.
Inclusion Criteria:	• Recently treated for stage I, II, or IIIa breast cancer by definitive surgery • Scheduled to receive outpatient adjuvant RT or CT
Exclusion Criteria:	• Concurrent major health problem that would contraindicate an exercise program.
Recruitment:	A convenience sample of female subjects was recruited from outpatient cancer treatment sites based on the inclusion criteria and using a number of strategies: • Regular contact with RD and breast cancer clinic staff • Attendance at breast cancer conferences • Study recruitment pamphlets placed in cancer center waiting rooms
Blinding Used:	Eligible consenting subjects were enrolled and randomized to treatment groups using assignments generated by the operations center at the principle investigator's institution, were stored in sealed envelopes for use in sequential order, and were retained at the study sites.
Description of Study Protocol:	The pilot study employed a prospective, controlled, randomized design stratified by cancer treatment of adjuvant CT or RT. Subjects were randomly assigned to the investigational walking exercise intervention or to usual care treatment groups. A stratified design was used to control for potentially confounding variables of length and type of cancer treatment program. Fatigue, physical functioning, emotional distress, and QOL outcomes were evaluated before

	initiation of CT or RT and at the end of treatment by study personnel who received periodic training to maximize consistency across study sites.
Intervention:	• Taught individually to subjects by trained study staff. • Began concurrently with adjuvant CT or RT and continued for the duration of the initial cancer treatment: 6 weeks of RT and 4–6 months of CT. • The program was described in detail in a booklet given to each subject in the intervention group. • The exercise prescription was individualized for subjects based on age, level of physical fitness as determined by the baseline walk test, and type of cancer treatment. • Most exercise prescriptions began at 10–15 minutes per session and 5–6 sessions per week using guidelines developed with an exercise physiologist. • Subjects were advanced to 30 minutes per session, 5–6 daily sessions per week, as their tolerance to exercise and responses to cancer treatment permitted. • Instruction regarding the exercise intervention took place at the clinical site, but the program was implemented by the subjects at home or a setting of their choice. • Adherence to the program was encouraged by suggesting women walk with a partners and record exercise data in a diary to measure progress. • Study staff contacted subjects by phone or during clinic visits every 2 weeks to assess exercise progress and advance exercise prescriptions, monitor for safety, and provide encouragement. • Intervention participants in the exercise group kept diaries on forms especially formatted to record daily exercise activity, pulse rates, perceived exertion, and other comments. These were mailed to study staff weekly.
Statistical Analysis:	• Data analysis for the study was planned as an "intention-to-treat". • Data analysis plan was changed to consider a dose-response perspective in an explanatory cohort compliance model with subjects separated into "high walk" and "low walk" groups to determine the effects of exercise during treatment on study outcomes. • Data management and analysis was performed using appropriate software (SPSS-PC, version 10.0. SPSS. Chicago, IL.)
Timing of Measurements:	Symptoms, physical functioning, and QOL were measured at baseline, mid-treatment and at the end of treatment.
Dependent Variables:	**Fatigue:** • Measured by the modified Piper Fatigue Scale (PFS), a 22-item, 10-point self-report scale that measures overall fatigue and four fatigue dimensions: temporal, severity, affective, and sensory. • The PFS has demonstrated validity and reliability.

	Physical Functioning: • Measured by a 12-minute walk test, the activity level rating scale, and the Medical Outcomes Study Short Health Form (MOS SF-36) physical functioning subscale. **Emotional Distress:** • Measured by the Profile of Moods States (POMS). • The shortened 30-item POMS measures a subject's mental/psychological status by subscales that asses six emotional dimensions. **Quality of Life:** • Measured by the MOS-SF 36, a multi-item scale that focuses on 8 health concepts.

Independent Variables:	• The exercise prescription was individualized for subjects based on age, level of physical fitness as determined by the baseline walk test, and type of cancer treatment. • Most exercise prescriptions began at 10–15 minutes per session and 5–6 sessions per week using guidelines developed with an exercise physiologist. • Subjects were advanced to 30 minutes per session, 5–6 daily sessions per week, as their tolerance to exercise and responses to cancer treatment permitted.
Control Variables:	**Usual Care:** • Consisted of what was considered standard practice in the cancer center outpatient department at each site. • At the time of the study, exercise was not routinely included or emphasized as a part of standard care during cancer treatment. • Subjects recorded fatigue levels and general physical activities as well as voluntary comments in their weekly diaries. • Study staff contacted usual–care participants every 2 weeks to inquire about their responses to treatment.
Initial Number (n):	52 women met the inclusion criteria for study enrollment and signed informed consent forms to participate in the study.
Final Number (n):	48
Age:	• 28–75 years of age • Mean = 48 years
Ethnicity:	Predominantly white (86%)
Other Relevant Demographics:	• Married (70%) • Employed (66%) • Mean years of education, 15 years • No p–values included for demographic data
Anthropometrics:	• Average Body Weight: 156 lb. • Average BMI: 25.66 • No p–values included for anthropometric data
Location:	Five study sites were all university teaching hospital cancer centers in the Eastern United States that had high volumes of patients with breast cancer. The sites were selected to provide diversity in terms of geographic, socioeconomic, and ethnic variables to control for differences in their potential impact on acceptance of or adherence to the home–based walking exercise intervention.
Summary of Results:	**Fatigue:** • Fatigue measured by the fatigue subscale of the POM scale showed a decrease for patient's in the high–walk

	group 5.04 (+/‐ 5.20) to 4.35 (+/‐ 4.54) during treatment, while scored increased for patients in the low‐walk group from 7.18 (+/‐ 4.82) to 9.81 (+/‐ 5.91), p = .00. **Physical Functioning:** • Increase in physical activity in high‐walk group compared to a decrease in the low‐walk group (p = .00). **Emotional Distress:** • Significant differences between the mean post‐test scores for the high‐walk and low‐walk groups (p = .00).
Author's Conclusions	
Author Conclusion:	The results of this study suggest that a home‐based moderate walking program can decrease fatigue and emotional distress while improving physical functioning and QOL during 6 weeks of RT or during 4‐6 months of adjuvant CT.
Reviewer comments:	**Strengths:** • Randomized Controlled Trial • Home‐based moderate walking program is realistic for breast cancer patients undergoing current treatment. • Validated assessment tools • Stratified design to control for potentially confounding variables of length and type of cancer treatment program. **Limitations:** • Convenience sample that may have created a selection bias for those who tend to live a more active lifestyle and would therefore be more inclined to be willing to participate in the study. • Intent‐to‐treat was not the ultimate method of analysis. • Limited sample size. • Some patients came with symptoms from a prior treatment. • Fifty percent of subjects in the usual‐care group were actively exercising during study participation, while 30% of the subjects in the exercise group were not able to maintain a regular exercise program. • Self‐administered intervention • Self‐report measures of outcomes

Quality Criteria Checklist: Fatigue and Quality of Life Outcomes of Exercise During Cancer Treatment				
Questions	**Yes**	**No**	**Unclear**	**N/A**
Relevance Questions				
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group?	X			
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	X			
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to the dietetics practice?	X			
4. Is the intervention or procedure feasible?	X			
Validitiy Questions				
1. Was the research question clearly stated?	X			
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?				
1.2 Was the outcome(s) (dependent variable(s)) clearly indicated?				
1.3 Were the target population and setting specified?				
2. Was the selection of study subjects/patients free from bias?	X			
2.1 Were inclusion/exclusion critieria specified (e.g. risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?				
2.2 Were criteria applied equally to all study groups?				
2.3 Were health, demographics, and other characteristics of subjects described?				
2.4 Were the subjects/patients a representative sample of the relevant population?				

Questions	Yes	No	Unclear	N/A
3. Were study groups comparable?	X			
3.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)				
3.2 Were disribution of disease status, prognostic factors, and other factors (e.g. demographics) similar across study groups at baseline?				
3.3 Were concurrent controls used? (Concurrent preferred over historical controls)				
3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?				
3.5 If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)				
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. 'gold standard')				
4. Was the method of handling widthdrawls described?	X			
4.1 Were follow-up methods described and the same for all groups?				
4.2 Was the number, characteristics of withdrawls (i.e. dropouts, lost to follow-up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow-up goal for a strong study is 80%)				
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?				
4.4 Were reasons for withdrawl similar across groups?				
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?				

Questions	Yes	No	Unclear	N/A
5. Was blinding used to prevent introduction of bias?				
5.1 In intervention study, were subjects, clinicians/practittioners, and investigators blinded to treatment group, as appropriate?				
5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)		X		
5.3 In cohort or cross-sectional study, were measurements of outcomes and risk factors blinded?				
5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status?				
5.5 In diagnostic study, were test results blinded to patient history and other test results?				
6. Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?				
6.1 In RCT or other intervention trial, were protocols described for all regimens studied?				
6.2 In observation study, were interventions, study settings, and clinicals/provider described?				
6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	X			
6.4 Was the amount of exposure and, if relevant, subject/patient comliance measured?				
6.5 Were co-interventions (e.g. ancillary treatments, other therapies) described?				
6.6 Were extra or unplanned treatments described?				
6.7 Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?				
6.8 In diagnostic study, were details of test administration and replication sufficient?				

Questions	Yes	No	Unclear	N/A
7. Were outcomes clearly defined and the measurements valid and reliable?				
7.1 Were primary and secondary endpoints described and relevant to the question?				
7.2 Were nutrition measures appropriate to question and outcomes of concern?				
7.3 Was the period of follow-up long enough for important outcome(s) to occur?				
7.4 Was the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	X			
7.5 Was the measurement of effect at an appropriate level of precision?				
7.6 Were other factors accounted for (measured) that could affect outcomes?				
7.7 Were the measurements conducted consistently across groups?				
8. Was the stastical analysis appropriate for the study design and type of outcome indicators?				
8.1 Were statistical analyses adequately described and the results reported appropriately?				
8.2 Were correct statistical tests used and assumptions of test not violated?				
8.3 Were statistics reported with levels of significance and/or confidence intervals?				
8.4 Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	X			
8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g. multivariate analyses)?				
8.6 Was clinical signifiance as well as statistical significance reported?				
8.7 If negative findings, was a power calculation reported to address type 2 error?				

Questions	Yes	No	Unclear	N/A
9. Are conclusions supported by results with biases and limitations taken into consideration?	X			
9.1 Is there a discussion of findings?				
9.2 Are biases and study limitations identified and discussed?				
10. Is bias due to study's funding or sponsorship unlikely?	X			
10.1 Were sources of funding and investigators; affiliations described?				
10.2 Was there no apparent conflict of interest?				

MINUS/NEGATIVE (-)
If most (six or more) of the answers to the above validity questions are "no", the report should be designated with a minus (-) symbol on the Evidence Worksheet.
NEUTRAL (⊘)
If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a (⊘) symbol on the Evidence Worksheet.
PLUS/POSITIVE (+)
If most of the answers to the above validity questions are "yes" (including criteria 2, 3, 6, 7 at at least one additional "yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet)

Citation: Mock, V., Pickett, M., Ropka, M., Lin, E., Stewart, K., Rhodes, V., ... McCorkle, R. (2001). Fatigue and Quality of Life Outcomes of Exercise During Cancer Treatment. Cancer Practice, 9(3), 119-127.

Evidence Worksheet for Primary RESEARCH Article

Citation:	Mustian, K., Peppone, L., Darling, T., Palesh, O., Heckler, C., & Morrow, G. (2009). A 4-Week Home-Based Aerobic and Resistance Exercise Program During Radiation Therapy: A Pilot Randomized Clinical Trial. *Journal of Community and Supportive Oncology, 7*(5), 158-167.
Study Design:	Randomized, Controlled, Clinical Trial
Study Class (A,B,C,D):	A
Research Quality Rating:	**Positive (+)** +
Purpose/Population Studied/Practice Studied	
Research Purpose:	To conduct an initial test of the feasibility and efficacy of a 4-week, tailored, home-based aerobic (walking) and progressive resistance (therapeutic bands) exercise intervention among breast and prostate cancer patients for improving resistance exercise days (RED), cancer-related fatigue (CRF), aerobic capacity, strength, muscle mass, and quality of life (QOL).
Inclusion Criteria:	1) Primary diagnosis of breast or prostate cancer 2) No distant metastases 3) No recurrent disease 4) No contraindications prohibiting participation in a low-to-moderate intensity walking or resistance exercise program or physical fitness testing, as assessed by patients' radiation oncologist 5) Completion of enrollment and baseline assessments before the end of the first calendar week of radiation treatments 6) At least 30 scheduled radiation treatments (6 weeks) 7) Sedentary lifestyle (no regular exercise or fewer than two exercise sessions per week)
Exclusion Criteria:	If the patient did not meet the above inclusion criteria, a patient would be excluded.
Recruitment:	• Women with breast cancer and men with prostate cancer beginning standard radiation therapy • August 2004 to December 2006 • Physician and nurse referrals to study staff at the University of Rochester James P. Wilmot Cancer Center
Blinding Used:	• Not fully blinded • Condition allocation was concealed from the patient and coordinators until after the completion of the baseline assessments • Study statistician and data managers remained blinded at all times
Description of Study Protocol:	• All patients underwent baseline assessments over 7 days o On-study form, clinical record form, self-report questionnaires, daily diary, pedometer assessment, 6-minute walking test, handgrip dynamometry, and bioelectrical impedance test • Stratified by diagnosis and then randomized to control of radiation therapy alone or the intervention of radiation plus

	exercise program • Patients in control group instructed not to being any new formal physical exercise program; patients did not keep pedometer during intervention period to reduce "exercise contamination" • Daily diaries (both control and intervention) • Assessments at baseline, post-intervention (4-weeks), and 3-month follow-up • Clinical research coordinator, exercise science coordinator, statistician, and data managers
Intervention:	• Home-based aerobic and progressive resistance exercise program • Designed by certified exercise scientist from American College of Sports Medicine • Designed to deliver easily and quickly to patients in busy radiation oncology clinic at beginning of radiation therapy • Implemented concurrently by patients during course of radiation therapy • Single, 45-minute, instructional session • "Exercise kit" with written instructions and materials necessary • **Walking Program:** Moderately intense aerobic exercise, 7 days a week for entire 4 weeks; pedometer given and steps recorded o Instructed to increase total steps by 5%, 10%, 15%, and 20% over baseline • **Resistance Program:** therapeutic resistance band exercise prescription; low to moderately intense progressive resistance exercise, 7 days a week for 4 week period; designed to main muscle strength in upper body o 3 colored bands, representing low and moderate levels of resistance o Coordinator explained proper use of bands and appropriate mechanics o 11 exercises and individually determined number of sets • Home-based patient-selected environment
Statistical Analysis:	• SPSS software • Two-tailed 5% level of significance • Data coded and cleaned by independent data managers using Teleforms scanned into an Access database and visually audited by separate data manager • No outliers of influential data detected • Very little missing data • Calculating descriptive statistics, frequency distributions, means, mean change scores, and standard deviations for the depended variables in the two study arms • Baseline characteristics compared with two-sample t-tests for continuous variables and chi-square tests for categorical variables • ANCOVA with baseline as the covariate used to examine difference in means between exercise group and no-exercise group o DSW, MRE, RED, CRF, strength, muscle mass, and

	QOL
Timing of Measurements:	Assessments at baseline, post-intervention (4-weeks), and 3-month follow-up.
Dependent Variables:	• Aerobic exercise (walking): Daily steps walked (DSW) • Resistance exercise (therapeutic resistance bands): daily minutes of resistance exercise (MRE) and number of resistance exercise days (RED) • Cancer-related fatigue (CRF) • Aerobic capacity: 6-minute walk test • Strength: handgrip dynamometry • Muscle mass: Bioelectrical impedance

Independent Variables:	• Home-based aerobic and progressive resistance exercise program • **Walking Program:** Moderately intense aerobic exercise, 7 days a week for entire 4 weeks; pedometer given and steps recorded o Instructed to increase total steps by 5%, 10%, 15%, and 20% over baseline • **Resistance Program:** therapeutic resistance band exercise prescription; low to moderately intense progressive resistance exercise, 7 days a week for 4 week period; designed to main muscle strength in upper body o 3 colored bands, representing low and moderate levels of resistance o Coordinator explained proper use of bands and appropriate mechanics o 11 exercises and individually determined number of sets
Control Variables:	Patients randomized to the control group were instructed not to begin any new formal physical exercise program and did not keep the pedometer during the study intervention period to avoid "exercise contamination".
Initial (n):	o 120 patients initially screened, 82 potentially eligible o After referral, 61 patients approached o 40 eligible and agreed to participate o Remaining 21 not enrolled because ineligible due to maintaining a regular exercise program or declined o 40 enrolled, 2 did not complete study materials and thus not included in analysis o 38 fully evaluable patients
Final (n):	38
Age:	Not noted.
Ethnicity *(if given)*:	Not noted.
Other Relevant Demographics:	o Women with breast cancer and men with prostate cancer o Demographics reviewed: gender, race, employment status, marital status, education, previous treatment (surgery, chemo, and/or hormone therapy), Karnosfsky performance, age, height, weight, BMI, radiation dose, weekly work hours
Anthropometrics:	Study found no significant differences between the groups at baseline in gender, race, employment status, weekly work hours, marital status, education, previous treatments, performance status, age, height, weight, BMI, radiation dose, DSW, CRF, strength, muscle mass, or QOL. o Significant difference between groups were observed for aerobic capacity with exercise group than no-exercise group at baseline
Location:	Rochester, New York
Summary of Results:	o Participants in the exercise group demonstrated good adherence to the exercise intervention, with significantly more DSW, MRE, and RED at post intervention and 3-month follow-up than controls. o Participants in exercise intervention exhibited significantly high QOL and significantly lower CRF post intervention and at 3-month follow-up than controls. o Results of this pilot study provide positive preliminary evidence that exercise during radiation may be beneficial for cancer patients. o ***No specific p-values provided other than "All values < 0.05"***

Author Conclusion:	Breast cancer and prostate patients undergoing radiation therapy may benefit from individualized, at-home based aerobic and resistance exercise programs to reduce CRF and increase QOL during current treatment and post-treatment periods.
Reviewer Comments:*)*	o **Limitations***:* small size restricts statistical power, heterogenicity of patients, not generalizable to other cancer populations, participants may have been more receptive to exercise, BIA may not be suitable measurement of muscle mass, handgrip tests may not be best measurements of strength, not a full-blinded study, *specific p-values were not provided, authors used "trending toward significant" in their results/discussion, authors discussed results that were not significant eluding they were positively impacted* o **Strengths:** *multiple measurements, aerobic and strength exercise programs, randomized, inclusion criteria, consideration of BIA limitations, realistic approach to providing interventions in busy radiation clinic* o Cannot be generalized to cancer population as a whole

Quality Criteria Checklist: A 4-Week Home-Based Aerobic and Resistance Exercise Program During Radiation Therapy: A Pilot Randomized Clinical Trial.				
Questions	**Yes**	**No**	**Unclear**	**N/A**
Relevance Questions				
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group?	X			
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	X			
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to the dietetics practice?	X			
4. Is the intervention or procedure feasible?	X			
Validitiy Questions				
1. Was the research question clearly stated?	X			
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?				
1.2 Was the outcome(s) (dependent variable(s)) clearly indicated?				
1.3 Were the target population and setting specified?				
2. Was the selection of study subjects/patients free from bias?	X			
2.1 Were inclusion/exclusion critieria specified (e.g. risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?				
2.2 Were criteria applied equally to all study groups?				
2.3 Were health, demographics, and other characteristics of subjects described?				
2.4 Were the subjects/patients a representative sample of the relevant population?				

Questions	Yes	No	Unclear	N/A
3. Were study groups comparable?				
3.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)				
3.2 Were disribution of disease status, prognostic factors, and other factors (e.g. demographics) similar across study groups at baseline?				
3.3 Were concurrent controls used? (Concurrent preferred over historical controls)				
3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	X			
3.5 If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)				
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. 'gold standard')				
4. Was the method of handling widthdrawls described?				
4.1 Were follow-up methods described and the same for all groups?				
4.2 Was the number, characteristics of withdrawls (i.e. dropouts, lost to follow-up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow-up goal for a strong study is 80%)	X			
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?				
4.4 Were reasons for withdrawl similar across groups?				
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?				

Questions	Yes	No	Unclear	N/A
5. Was blinding used to prevent introduction of bias?	X			
5.1 In intervention study, were subjects, clinicians/practittioners, and investigators blinded to treatment group, as appropriate?				
5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)				
5.3 In cohort or cross-sectional study, were measurements of outcomes and risk factors blinded?				
5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status?				
5.5 In diagnostic study, were test results blinded to patient history and other test results?				
6. Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?	X			
6.1 In RCT or other intervention trial, were protocols described for all regimens studied?				
6.2 In observation study, were interventions, study settings, and clinicals/provider described?				
6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?				
6.4 Was the amount of exposure and, if relevant, subject/patient comliance measured?				
6.5 Were co-interventions (e.g. ancillary treatments, other therapies) described?				
6.6 Were extra or unplanned treatments described?				
6.7 Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?				
6.8 In diagnostic study, were details of test administration and replication sufficient?				

Questions	Yes	No	Unclear	N/A
7. Were outcomes clearly defined and the measurements valid and reliable?				
7.1 Were primary and secondary endpoints described and relevant to the question?				
7.2 Were nutrition measures appropriate to question and outcomes of concern?				
7.3 Was the period of follow-up long enough for important outcome(s) to occur?				
7.4 Was the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	X			
7.5 Was the measurement of effect at an appropriate level of precision?				
7.6 Were other factors accounted for (measured) that could affect outcomes?				
7.7 Were the measurements conducted consistently across groups?				
8. Was the stastical analysis appropriate for the study design and type of outcome indicators?				
8.1 Were statistical analyses adequately described and the results reported appropriately?				
8.2 Were correct statistical tests used and assumptions of test not violated?				
8.3 Were statistics reported with levels of significance and/or confidence intervals?				
8.4 Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	X			
8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g. multivariate analyses)?				
8.6 Was clinical signifiance as well as statistical significance reported?				
8.7 If negative findings, was a power calculation reported to address type 2 error?				

Questions	Yes	No	Unclear	N/A
9. Are conclusions supported by results with biases and limitations taken into consideration?	X			
9.1 Is there a discussion of findings?				
9.2 Are biases and study limitations identified and discussed?				
10. Is bias due to study's funding or sponsorship unlikely?	X			
10.1 Were sources of funding and investigators; affiliations described?				
10.2 Was there no apparent conflict of interest?				

MINUS/NEGATIVE (-)
If most (six or more) of the answers to the above validity questions are "no", the report should be designated with a minus (-) symbol on the Evidence Worksheet.
NEUTRAL (⊘)
If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a (⊘) symbol on the Evidence Worksheet.
PLUS/POSITIVE (+)
If most of the answers to the above validity questions are "yes" (including criteria 2, 3, 6, 7 at at least one additional "yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet)

Citation: Mustian, K., Peppone, L., Darling, T., Palesh, O., Heckler, C., & Morrow, G. (2009). A 4-Week Home-Based Aerobic and Resistance Exercise Program During Radiation Therapy: A Pilot Randomized Clinical Trial. Journal of Community and Supportive Oncology, 7(5), 158-167.

Evidence Worksheet for Primary RESEARCH Article

Citation:	Reis, D., Walsh, E., Young-McCaughan, S., & Jones, T. (2013). Effects of Nia Exercise in Women Receiving Radiation Therapy for Breast Cancer. *Oncology Nursing Forum, 40*(5), 374-382.
Study Design:	Randomized Control Trial
Study Class (A,B,C,D):	A
Research Quality Rating:	**NEUTRAL (ø)**
Purpose/Population Studied/Practice Studied	
Research Purpose:	To compare a 12-week nontradiational exercise Nia program practiced at home to usual care on fatigue, quality of life (QOL), aerobic capacity, and shoulder flexibility in women with breast cancer undergoing radiation therapy.
Inclusion Criteria:	All women aged 18 years and older receiving radiation therapy for stage I, II, or III breast cancer.
Exclusion Criteria:	No exclusion criteria noted.
Recruitment:	All women aged 18 years and older receiving radiation therapy for stage I, II, or III breast cancer were invited to participate in the study. Recruitment occurred at Flower Hospital, a community-based hospital in northwest Ohio.
Blinding Used:	There are no notes regarding blinding to either the participants or the researchers.
Description of Study Protocol:	Twenty-two women were randomized to the Nia group and 19 to the usual care group. Those in the Nia group were instructed to practice Nia 20-60 minutes three times per week for 12 weeks. Those in the usual care group were instructed to continue normal activities.
Intervention:	**Intervention Group** • Nia group participants met individually with the principle investigator. • Participants received instructions and demonstration about the Nia techniques and a Nia DVD for home use. • Participants were advised to practice Nia 20-60 minutes at least three times per week for 12 weeks and record their activities in an exercise log. • At 6 and 12 weeks, participants met individually with the principle investigator and discussed variations in movement to enhance Nia practice. **Control Group** • Control group participants also met individually with the principal investigator. • Participants were instructed to maintain their current exercise regimen and record their activities in an exercise log. • At 6 and 12 weeks participants met individually with the principal investigator and discussed topics such as physical, emotional, mental, and spiritual well-being.

Statistical Analysis:	• Descriptive statistics were used to summarize participant characteristics. • Chi-square tests were used with categorical data to evaluate differences between groups. • Repeated-measures analysis of variance (ANOVA) and repeated-measured analysis of covariance were used to assess change over time between the groups.
Timing of Measurements:	Data was collected at baseline, 6 weeks, and 12 weeks.
Dependent Variables:	• **Fatigue and Quality of Life:** Assessed using the *Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale* • **Aerobic Capacity:** Assessed using the *Six-Minute Walk Test (6MWT)* • **Shoulder Flexibility:** Shoulder flexion and shoulder extension were assessed using a *goniometer*.

Independent Variables:	• Nia group participants met individually with the principle investigator. • Participants received instructions and demonstration about the Nia techniques and a Nia DVD for home use. • Participants were advised to practice Nia 20-60 minutes at least three times per week for 12 weeks and record their activities in an exercise log. • At 6 and 12 weeks, participants met individually with the principle investigator and discussed variations in movement to enhance Nia practice.
Control Variables:	Usual care participants who were instructed to maintain their current exercise regimen and record their activities in an exercise log.
Initial (n):	Forty-one women agreed to participate; 22 were randomized to the Nia group and 19 were randomized to the control group.
Final (n):	One woman in the Nia group and two in the control group failed to complete the 12-week assessment.
Age:	Ranged from 34-85 years
Ethnicity:	37 participants were Caucasian, 3 African American, 1 Other
Other Relevant Demographics:	The two groups did not differ statistically in their demographics, although clinical differences appear to exist in age and employment, with the Nia group, on average, five years younger and more likely to be working full time than the control group.
Anthropometrics:	Age and BMI were the only two anthropometrics measured among participants. On average, the Nia group was 5 years younger.
Location:	Flower Hospital, a community-based hospital in northwest Ohio.
Summary of Results:	Controlling for baseline scores, change over time between groups was significantly different for the women who practiced Nia at least 13 times during the 12-week period; those in the Nia intervention reported significantly less fatigue between weeks 6 and 12, as compared to control group ($p = 0.05$). No statistical differences in QOL, aerobic capacity, or shoulder flexibility were found, but trends favoring Nia were identified.
Author's Conclusions	
Author Conclusion:	Nia exercise can help relieve fatigue for women undergoing radiation treatment for breast cancer. Nia may also be beneficial for shoulder mobility and preservation.
Reviewer Comments:	**Strengths:** • Randomized, control trial • Intervention vs. usual care • Assessing a non-traditional exercise method not regularly studied • Outcome measurements assessed with reliable scales **Limitations:** • Exercise logs provided to usual care may have influenced usual care to exercise • Quality of exercise logs entries varied • Not all p-values provided • Fatigue continues to be a subjective measure

Quality Criteria Checklist: Effects of Nia Exercise in Women Receiving Radiation Therapy for Breast Cancer.				
Questions	**Yes**	**No**	**Unclear**	**N/A**
Relevance Questions				
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group?	X			
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	X			
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to the dietetics practice?	X			
4. Is the intervention or procedure feasible?	X			
Validitiy Questions				
1. Was the research question clearly stated?	X			
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?				
1.2 Was the outcome(s) (dependent variable(s)) clearly indicated?				
1.3 Were the target population and setting specified?				
2. Was the selection of study subjects/patients free from bias?	X			
2.1 Were inclusion/exclusion critieria specified (e.g. risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?				
2.2 Were criteria applied equally to all study groups?				
2.3 Were health, demographics, and other characteristics of subjects described?				
2.4 Were the subjects/patients a representative sample of the relevant population?				

Questions	Yes	No	Unclear	N/A
3. Were study groups comparable?	X			
3.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)				
3.2 Were disribution of disease status, prognostic factors, and other factors (e.g. demographics) similar across study groups at baseline?				
3.3 Were concurrent controls used? (Concurrent preferred over historical controls)				
3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?				
3.5 If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)				
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. 'gold standard')				
4. Was the method of handling widthdrawls described?	X			
4.1 Were follow-up methods described and the same for all groups?				
4.2 Was the number, characteristics of withdrawls (i.e. dropouts, lost to follow-up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow-up goal for a strong study is 80%)				
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?				
4.4 Were reasons for withdrawl similar across groups?				
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?				

Questions	Yes	No	Unclear	N/A
5. Was blinding used to prevent introduction of bias?				
5.1 In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?				
5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)		X		
5.3 In cohort or cross-sectional study, were measurements of outcomes and risk factors blinded?				
5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status?				
5.5 In diagnostic study, were test results blinded to patient history and other test results?				
6. Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?				
6.1 In RCT or other intervention trial, were protocols described for all regimens studied?				
6.2 In observation study, were interventions, study settings, and clinicals/provider described?				
6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	X			
6.4 Was the amount of exposure and, if relevant, subject/patient comliance measured?				
6.5 Were co-interventions (e.g. ancillary treatments, other therapies) described?				
6.6 Were extra or unplanned treatments described?				
6.7 Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?				
6.8 In diagnostic study, were details of test administration and replication sufficient?				

Questions	Yes	No	Unclear	N/A
7. Were outcomes clearly defined and the measurements valid and reliable?	X			
7.1 Were primary and secondary endpoints described and relevant to the question?				
7.2 Were nutrition measures appropriate to question and outcomes of concern?				
7.3 Was the period of follow-up long enough for important outcome(s) to occur?				
7.4 Was the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?				
7.5 Was the measurement of effect at an appropriate level of precision?				
7.6 Were other factors accounted for (measured) that could affect outcomes?				
7.7 Were the measurements conducted consistently across groups?				
8. Was the stastical analysis appropriate for the study design and type of outcome indicators?	X			
8.1 Were statistical analyses adequately described and the results reported appropriately?				
8.2 Were correct statistical tests used and assumptions of test not violated?				
8.3 Were statistics reported with levels of significance and/or confidence intervals?				
8.4 Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?				
8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g. multivariate analyses)?				
8.6 Was clinical signifiance as well as statistical significance reported?				
8.7 If negative findings, was a power calculation reported to address type 2 error?				

Questions	Yes	No	Unclear	N/A
9. Are conclusions supported by results with biases and limitations taken into consideration?	X			
9.1 Is there a discussion of findings?				
9.2 Are biases and study limitations identified and discussed?				
10. Is bias due to study's funding or sponsorship unlikely?			X	
10.1 Were sources of funding and investigators; affiliations described?				
10.2 Was there no apparent conflict of interest?				

MINUS/NEGATIVE (-)
If most (six or more) of the answers to the above validity questions are "no", the report should be designated with a minus (-) symbol on the Evidence Worksheet.
NEUTRAL (⊘)
If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a (⊘) symbol on the Evidence Worksheet.
PLUS/POSITIVE (+)
If most of the answers to the above validity questions are "yes" (including criteria 2, 3, 6, 7 at at least one additional "yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet)

Citation: Reis, D., Walsh, E., Young-McCaughan, S., & Jones, T. (2013). Effects of Nia Exercise in Women Receiving Radiation Therapy for Breast Cancer. Oncology Nursing Forum, 40(5), 374-382.

APPENDIX D: OVERVIEW TEMPLATE

Author, Year, Study Design, Class, Rating	Study Purpose	Study Population	Intervention	Outcomes	Conclusions	Limitations
Courneya et al., 2007 *Study Design:* Randomized Controlled Trial *Class:* A *Rating:* +	To evaluate the relative merits of aerobic and resistance exercise in blunting the effects of unfavorable changes in physical functioning, body composition, psychosocial functioning, and quality of life (QOL) in breast cancer patients undergoing chemotherapy.	223 total patients aged 25-78 years; Stage I through IIIA Breast Cancer who were beginning first-line adjuvant chemotherapy	**Aerobic Exercise Training (AET):** Exercise 3 times per week on a cycle ergometer, treadmill, or elliptical beginning at 60% of VO_{2max} for weeks 1 to 6 and progression to 70% during weeks 7 to 12 and 80% beyond week 12. **Resistance Exercise Training (RET):** Exercise 3 times per week performing two sets of eight to 12 repetitions of nine different exercises at 60% and 70% of their estimated one-repetition maximum. **Usual Care:** This group was asked to not initiate an exercise program and was offered a 1-month exercise program after post intervention assessments.	Aerobic exercise was superior to usual care for improving self-esteem ($p = .015$), aerobic fitness ($p = .006$), and percent body fat (adjusted $p = 0.076$). Resistance exercise was superior to usual care for improving self-esteem ($p = 0.18$), muscular strength ($p < .001$), lean body mass ($p = .015$), and chemotherapy completion rate ($p = .033$). Changes in cancer-specific QOL, fatigue, depression, and anxiety favored the exercise groups, but did not reach statistical significance.	In neither aerobic or resistance exercise training was there significant improvements in cancer-specific QOL in breast cancer patients undergoing chemotherapy treatment. However, exercise training did improve self-esteem, physical fitness, body composition, and chemotherapy completion rate without causing the adverse effects of lymphedema or significant adverse effects.	70% adherence rate 33% recruitment rate Well-educated, racially homogenous sample Usual care specifically instructed no exercise programs
Aghill et al., 2007 *Study Design:* Prospective, non-randomized (cohort) *Class:* C	To assess whether an aerobic exercise intervention during a 4-week course of radiotherapy would reduce the incidence and severity of fatigue in cancer patients undergoing RT.	30 total patients, 15 patients in each the control and intervention group Aged between 18 and 65 years Having received at	The training program consisted of daily walking for 20 minutes (or 10 minutes daily for frail patients), which began at the second week and last for 21 days.	At the fourth week, most patients (44%) in the training group had mild fatigue where as 57% of the patients in the comparison group reported severe fatigue ($U = 41$, $P = 0.011$).	Preliminary findings suggest that, similarly to previous research, an exercise program for patients undergoing cancer treatments have positive results. After treatment, rest may be even more ineffective	Small sample size Heterogeneous group of patients Fatigue is a subjective, self-reported measure

Rating: +		least 5 weeks of radiotherapy 5 days/week and 2 Gy/day No previous history of cardiac disease or diabetes At least 3 months of disease duration		Results showed that while severity was unchanged in the training group patients, there was a marked increase in the severity of fatigue in the comparison group patients (median score = 8, z = -1.91, P = 0.039).	in relieving chronic fatigue.	Non-randomized Hospitalization could also be considered limitation as it does not allow for a typical outpatient radiation therapy patient.
Hsieh et al., 2008 *Study Design:* Quasiexperimental *Class:* D *Rating:* Ø	To investigate the effects of supervised exercise training on cardiopulmonary function and fatigue in cancer survivors undergoing various clinical treatments.	Breast cancer survivors undergoing various clinical treatments; 57.9 +/- 10.4 years	Supervised exercise sessions, 2-3 days per week for 6 months. 60-minute sessions with "whole-body" approach. Generally included 10-minute warm-up, 40 minutes aerobic exercise, resistance training and stretching, 10-minute cool-down	Cardiopulmonary function significantly increased in all groups after exercise training ($p < 0.05$). Breast cancer survivors in the surgery, chemotherapy, and radiation group showed significant reductions in resting heart rate ($p < 0.05$) and concurrent increases on $FVC\%_{pred}$ after the supervised exercise intervention. The exercise intervention resulted in significant reductions in behavioral fatigue, affective fatigue, sensory fatigue, cognitive and mood fatigue, and total fatigue in the surgery and chemotherapy; surgery and radiation therapy; and surgery, chemotherapy, and radiation therapy	Moderate intensity, individualized, prescriptive exercise could alleviate negative side effects of cancer treatment	Convenience sample 1 geographic area No control group No specific p-values provided Large-scale individualized exercise prescriptions make it difficult to compare interventions Since no control group, thus no randomization

				groups (p<0.05).		
Reis et al., 2013 *Study Design:* Randomized Controlled Trial *Class:* A *Rating:* ø	To compare a 12-week nontradiational exercise Nia program practiced at home to usual care on fatigue, quality of life (QOL), aerobic capacity, and shoulder flexibility in women with breast cancer undergoing radiation therapy.	All women aged 18 years and older receiving radiation therapy for stage I, II, or III breast cancer.	**Intervention Group** Participants were advised to practice Nia 20-60 minutes at least three times per week for 12 weeks and record their activities in an exercise log. **Control Group** Participants were instructed to maintain their current exercise regimen and record their activities in an exercise log.	Controlling for baseline scores, change over time between groups was significantly different for the women who practiced Nia at least 13 times during the 12-week period; those in the Nia intervention reported significantly less fatigue between weeks 6 and 12, as compared to control group (p = 0.05). No statistical differences in QOL, aerobic capacity, or shoulder flexibility were found, but trends favoring Nia were identified.	Nia exercise can help relieve fatigue for women undergoing radiation treatment for breast cancer. Nia may also be beneficial for shoulder mobility and preservation.	Exercise logs provided to usual care may have influenced usual care to exercise Quality of exercise logs entries varied Not all p-values provided Fatigue continues to be a subjective measure
Mock et al., 2001 *Study Design:* Randomized Controlled Trial *Class:* A *Rating:* +	Conducted to determine the feasibility of and to explore the effects of a home-based exercise intervention on fatigue, physical functioning, emotional distress, and QOL in women receiving radiation therapy (RT) or adjuvant cytotoxic chemotherapy (CT) after breast cancer surgery.	Recently treated for stage I, II, or IIIa breast cancer by definitive surgery Scheduled to receive outpatient adjuvant RT or CT	The exercise prescription was individualized for subjects based on age, level of physical fitness as determined by the baseline walk test, and type of cancer treatment. Most exercise prescriptions began at 10-15 minutes per session and 5-6 sessions per week using guidelines developed with an exercise physiologist. Subjects were advanced to 30 minutes per session, 5-	**Fatigue:** Fatigue measured by the fatigue subscale of the POM scale showed a decrease for patient's in the high-walk group 5.04 (+/- 5.20) to 4.35 (+/- 4.54) during treatment, while scored increased for patients in the low-walk group from 7.18 (+/- 4.82) to 9.81 (+/- 5.91), p = .00. **Physical Functioning:** Increase in physical activity in high-walk group compared to a decrease in the low-walk group (p = .00). **Emotional Distress:**	The results of this study suggest that a home-based moderate walking program can decrease fatigue and emotional distress while improving physical functioning and QOL during 6 weeks of RT or during 4-6 months of adjuvant CT.	Convenience sample that may have created a selection bias for those who tend to live a more active lifestyle and would therefore be more inclined to be willing to participate in the study. Intent-to-treat was not the ultimate method of analysis. Limited sample size. Some patients came with

			6 daily sessions per week, as their tolerance to exercise and responses to cancer treatment permitted.	Significant differences between the mean post-test scores for the high-walk and low-walk groups (p = .00).		symptoms from a prior treatment. Fifty percent of subjects in the usual-care group were actively exercising during study participation, while 30% of the subjects in the exercise group were not able to maintain a regular exercise program. Self-administered intervention Self-report measures of outcomes
Mock et al., 2004 *Study Design:* Randomized Controlled Trial *Class:* A *Rating:* +	The purpose of the study was to conduct a randomized controlled trial to determine the effects of a home-based walking exercise program on levels of fatigue in women with breast cancer receiving adjuvant cytotoxic chemotherapy or radiation therapy.	Women aged 18-70 years of age Stage 0-III breast cancer by definitive surgery Scheduled to receive outpatient radiation therapy or adjuvant chemotherapy	The intervention group received a written prescription to walk 5-6 times per week at a moderate pace in the target heart range, as tolerated. The regimen was a brisk 15-minute walk that increased to 30 minutes as training progressed.	The *intention-to-treat* analysis revealed no group differences in part because of a dilution of treatment effect as 39% of the usual care group exercised and 28% of the exercise group did not. When exercise participation was considered using the data analysis method of *instrumental variables* with *principle stratification*, a clinically important and statistically significant (p = 0.03) effect of exercise on pretest-to-posttest change in fatigue levels	Adherence to a home-based moderate-intensity walking exercise program may effectively mitigate the high levels of fatigue prevalent during cancer treatment.	Adherence among participants Not a double-blind experiment Fatigue is a subjective measurement Potential bias of under-reporting and over-reporting Lack of physiological activity monitor to measure exercise behavior more precisely Usual care

				was demonstrated.		participants did not document physical activity
Mustian et al., 2009 *Study Design:* Randomized Controlled Trial *Class:* A *Rating:* +	To conduct an initial test of the feasibility and efficacy of a 4-week, tailored, home-based aerobic (walking) and progressive resistance (therapeutic bands) exercise intervention among breast and prostate cancer patients for improving resistance exercise days (RED), cancer-related fatigue (CRF), aerobic capacity, strength, muscle mass, and quality of life (QOL).	Primary diagnosis of breast or prostate cancer No distant metastases No recurrent disease No contraindications prohibiting participation in a low-to-moderate intensity walking or resistance exercise program or physical fitness testing, as assessed by patients' radiation oncologist Completion of enrollment and baseline assessments before the end of the first calendar week of radiation treatments At least 30 scheduled radiation treatments (6 weeks)	**Walking Program:** Moderately intense aerobic exercise, 7 days a week for entire 4 weeks; pedometer given and steps recorded **Resistance Program:** therapeutic resistance band exercise prescription; low to moderately intense progressive resistance exercise, 7 days a week for 4 week period; designed to main muscle strength in upper body	Participants in exercise intervention exhibited significantly high QOL and significantly lower CRF post intervention and at 3-month follow-up than controls. Results of this pilot study provide positive preliminary evidence that exercise during radiation may be beneficial for cancer patients.	Breast cancer and prostate patients undergoing radiation therapy may benefit from individualized, at-home based aerobic and resistance exercise programs to reduce CRF and increase QOL during current treatment and post-treatment periods.	Small size restricts statistical power, heterogenicity of patients Not generalizable to other cancer populations Participants may have been more receptive to exercise BIA may not be suitable measurement of muscle mass Handgrip tests may not be best measurements of strength Not a full-blinded study
		Sedentary lifestyle (no regular exercise or fewer than two exercise sessions per week)				

APPENDIX E: QUALITY CRITERIA SUMMARY

Quality Criteria Summary							
Questions	**Courneya et al., 2007**	**Aghili et al., 2007**	**Hsieh et al., 2008**	**Reis et al., 2013**	**Mock et al., 2001**	**Mock et al., 2004**	**Mustian et al., 2009**
Relevance Questions							
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to the dietetics practice?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Is the intervention or procedure feasible?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Validitiy Questions							
1. Was the research question clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?							
1.2 Was the outcome(s) (dependent variable(s)) clearly indicated?							
1.3 Were the target population and setting specified?							
2. Was the selection of study subjects/patients free from bias?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.1 Were inclusion/exclusion critieria specified (e.g. risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?							
2.2 Were criteria applied equally to all study groups?							
2.3 Were health, demographics, and other characteristics of subjects described?							
2.4 Were the subjects/patients a representative sample of the relevant population?							
3. Were study groups comparable?	Yes	Yes	No	Yes	Yes	Yes	Yes
3.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)							
3.2 Were disribution of disease status, prognostic factors, and other factors (e.g. demographics) similar across study groups at baseline?							
3.3 Were concurrent controls used? (Concurrent preferred over historical controls)							
3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?							
3.5 If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)							
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. 'gold standard')							

Questions	Courneya et al., 2007	Aghili et al., 2007	Hsieh et al., 2008	Reis et al., 2013	Mock et al., 2001	Mock et al., 2004	Mustian et al., 2009
4.1 Were follow-up methods described and the same for all groups?	Yes	Unclear	No	Yes	Yes	Yes	Yes
4.2 Was the number, characteristics of withdrawls (i.e. dropouts, lost to follow-up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow-up goal for a strong study is 80%)							
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?							
4.4 Were reasons for withdrawl similar across groups?							
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?							
5. Was blinding used to prevent introduction of bias?	No	No	No	No	No	No	Yes
5.1 In intervention study, were subjects, clinicians/practittioners, and investigators blinded to treatment group, as appropriate?							
5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)							
5.3 In cohort or cross-sectional study, were measurements of outcomes and risk factors blinded?							
5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status?							
5.5 In diagnostic study, were test results blinded to patient history and other test results?							
6. Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6.1 In RCT or other intervention trial, were protocols described for all regimens studied?							
6.2 In observation study, were interventions, study settings, and clinicals/provider described?							
6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?							
6.4 Was the amount of exposure and, if relevant, subject/patient comliance measured?							
6.5 Were co-interventions (e.g. ancillary treatments, other therapies) described?							
6.6 Were extra or unplanned treatments described?							
6.7 Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?							
6.8 In diagnostic study, were details of test administration and replication sufficient?							

Questions	Courneya et al., 2007	Aghili et al., 2007	Hsieh et al., 2008	Reis et al., 2013	Mock et al., 2001	Mock et al., 2004	Mustian et al., 2009
7. Were outcomes clearly defined and the measurements valid and reliable?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7.1 Were primary and secondary endpoints described and relevant to the question?							
7.2 Were nutrition measures appropriate to question and outcomes of concern?							
7.3 Was the period of follow-up long enough for important outcome(s) to occur?							
7.4 Was the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?							
7.5 Was the measurement of effect at an appropriate level of precision?							
7.6 Were other factors accounted for (measured) that could affect outcomes?							
7.7 Were the measurements conducted consistently across groups?							
8. Was the stastical analysis appropriate for the study design and type of outcome indicators?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8.1 Were statistical analyses adequately described and the results reported appropriately?							
8.2 Were correct statistical tests used and assumptions of test not violated?							
8.3 Were statistics reported with levels of significance and/or confidence intervals?							
8.4 Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?							
8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g. multivariate analyses)?							
8.6 Was clinical signifiance as well as statistical significance reported?							
8.7 If negative findings, was a power calculation reported to address type 2 error?							
9. Are conclusions supported by results with biases and limitations taken into consideration?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9.1 Is there a discussion of findings?							
9.2 Are biases and study limitations identified and discussed?							
10. Is bias due to study's funding or sponsorship unlikely?	Yes	No	Yes	Unclear	Yes	Yes	Yes
10.1 Were sources of funding and investigators; affiliations described?							
10.2 Was there no apparent conflict of interest?							