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THE PHYSIOLOGICAL AND PSYCHOLOGICAL EFFECTS OF INDOOR VERSUS OUTDOOR AEROBIC EXERCISE IN FEMALE CANCER SURVIVORS: A LITERATURE REVIEW

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ABSTRACT

THE PHYSIOLOGICAL AND PSYCHOLOGICAL EFFECTS OF EXERCISE IN FEMALE CANCER SURVIVORS: A LITERATURE REVIEW

By

Emily Ferroni

Moderate aerobic exercise is advantageous to physiological and psychological well-being among healthy and diseased populations. Investigating the physiological and psychological effects of indoor and outdoor aerobic training on ROS, antioxidants, QOL, vitamin D, estrogen, kynurenine, cardiovascular disease, obesity, and the immune system within cancer patients and survivors may be imperative to their recovery and survival. Outdoor aerobic exercise within a greenery-rich environment elicits greater positive changes within overall well-being compared to outdoor exercise in an urban setting or indoor exercise. However, both indoor and outdoor aerobic exercise produce benefits in mood state, the immune system, cardiovascular health, bone health, and countering oxidative stress that damages cells. Exercise is able to help counter the psychological, cognitive, and negative physiological effects of cancer treatments. Moderate aerobic exercise helps to decrease depression and tumor proliferation through an increase in kynurenic acid and lower risk of breast cancer by an increased energy expenditure to reduce fat tissue, thus decreasing the production of estrogen in post-menopausal women. Adequate levels of vitamin D are important to combat depression and tumor proliferation as well, which can be controlled through outdoor exercise in the sun or supplementation. Cancer patients and survivors can benefit from engaging in moderate aerobic exercise in both indoor and outdoor environments, however the outdoor environment may provide more benefit psychologically.

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DEDICATIONS

This thesis is dedicated to all of my friends and family who have lost a loved one to cancer, and also to the survivors, who are still fighting.

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TABLE OF CONTENTS

3. CHAPTER THREE
    a. Conclusion…….....92

    b. References……..95

    c. Appendices……...105

CHAPTER ONE

INTRODUCTION

PREVALENCE AND INTRODUCTION

An average of 606,520 Americans is projected to die of cancer-related mortality this year. In 1998, 1.2 million Americans were diagnosed with a form of cancer, the occurrence has now grown in 2020 to an anticipated 1.8 million new cases or more.[1,2] Cancer acts as a barricade within body systems and inhibits proper function. It is a vast group of diseases that account for an uncontrollable growth of abnormal cells that can attack and spread to other tissues in the body. The deoxyribonucleic acid (DNA) breakdown affects the genes that help to normalize a cell's capacity to control their growth, resulting in abnormal development of cells.[1–3] This malignancy in the body negatively affects the physiology of the body systems and quality of life (QOL) of the patient. The disease and treatment induce cardiovascular atrophy and utility, decreased pulmonary function, muscle atrophy, and cachexia. There is a functional decline in patient's physical, psychological, emotional, and social well-being. [4,5]

BREAST CANCER AND BRAIN METASTASIS

In 2020, there will be about 276,480 new cases of invasive breast cancer in the United States, and 42,690 will die from it.[2] Breast cancer is considered to have one of the highest cancer mortality rates among the female population.[2,6] Breast cancer is divided into five main sub-groups, which are described in the definition section: Luminal-A, Luminal-B, HER2-Enriched, Triple-Negative-Basal-Like, and Normal-Like.[6,7] As breast cancer already has a higher mortality rate than most other cancers, the mortality rate is increased due to the prevalence of brain metastases and are related to the HER2 breast cancer and Triple Negative types of breast

cancer. About 10 to 16% of those with the metastatic breast cancer develop brain metastases, which then creates a bleak possible survival clock of four to 18 months with various modes of therapy.[88] The type of breast cancers that metastasize to the brain majority of the time are those that are estrogen receptor negative such as Triple Negative and HER-2 Enriched.[6–8] Luminal A, Luminal B, and Normal-Like are all considered to be estrogen receptor positive.[6–8] Survivors with triple negative breast cancer, and that have a relapse, are said to have an even poorer prognosis of survival than in HER2 positive, which suggests that the subtype plays a role in the overall prognosis of the patient. The Dana Farber Cancer Institute described a risk of brain metastases of 46% from a 116 population of metastatic triple negative breast cancer surivors.[8,9]

PHYSICAL ACTIVITY

Physical activity (PA) is crucial for supporting daily activities, physical functioning, and life itself. It is characterized by bodily movement that is put forth by one's skeletal muscles to create energy expenditure. Exercise is a form of PA that holds a planned, structured, and repetitive nature that elicits improvement in one or more aspects of physical fitness.[10] PA and exercise help to regulate the body systems for proper functioning. Disease can have a major impact on body processes, as well as what a person's activity level may be in a day. Research studies have shown that taking part in PA can help to reduce the risk of cancer as well as to help stabilize the effects of cancer on physiological systems in the body.[10–12]

PA has resulted in decreasing the risk of breast cancer by up to 30-40%, and improves overall health.[12] Performing moderate exercise—using 40% to 59% of maximal oxygen reserve (VO2R)—regularly can be advantageous to one's well-being. However, if the exercise is too intense, or vigorous—such as using 60% to 85% VO2R—it can have damaging effects such as cell damage, muscle impairment, inflammation and oxidative stress on anyone's health, but

particularly those who already have cellular damage and inflammation from cancer.[13,14] Therefore, analyzing different intensities of exercise is important to find which application of exercise intensity may be most beneficial for a cancer survivor's health.

OXIDATIVE STRESS AND ANTIOXIDANTS

Oxidative stress occurs when the equilibrium between the antioxidants and reactive oxidative species (ROS) is disrupted.[15] ROS are unstable molecules that hold oxygen and interact with other molecules in a cell and are made by oxidation during metabolism. These are also known as free radicals.[16] Antioxidants protect cells from the ROS by reducing the damage from the oxygen by inhibiting it to help prevent carcinogensis.[16] Oxidative stress has an impact on carcinogenesis as it influences the damage of DNA from increased ROS production. ROS can cause modifications in the base of DNA by influencing the breaking of strands, which leads to an impairment on DNA protein cross-links.[17]

Oxidative stress that occurs because of an increase in PA or exercise can have positive effects as moderate activity can trigger a beneficial cellular stress response.[11,18] This potentiates an antioxidant defense to counter the stress at a higher capacity in someone who performs moderate aerobic exercise regularly, compared to a sedentary individual, which allows for a cellular defense against oxidative and inflammatory outcomes.[11,18] Antioxidants are categorized by into two groups—enzymatic and non-enzymatic. Non-enzymatic antioxidants include vitamin C, vitamin E, glutathione, and carotenoids such as beta-carotene. Enzymatic antioxidants include superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), glutathione reductase (GR), and catalase (CAT).[15,17]

The enzymatic antioxidants such as SOD, GSH-Px, GR, and CAT have an influence on the development of cancer. [17] For example, SOD serves as a defense mechanism against

superoxide radicals that aid in cancer development. Having higher amounts of enzymatic antioxidants have been demonstrated to help to prevent carcinogenesis.[19] SOD accelerates the alteration of superoxide to form hydrogen peroxide and oxygen when superoxide radicals are present. The superoxide radicals—a mutation in SOD—has been experimentally shown to have an influence with several types of cancer by damaging cells. This is because the antioxidant defense system is unable to protect a cell that is exposed to oxygen because of the defect leading to a superoxide radicals which are a form of ROS.[17] SOD has the potential to breakdown the harmful oxygens within cells which in-turn prevents damage to tissue. The SOD help to eliminate the superoxide radicals and stop the accumulation of oxygen that leads to damage and cellular death.[17] SOD is beneficial as it aids in the protection from superoxide radicals that mutate cells.

Intense exercise produces free radicals from the oxidative stress that can cause cellular damage if there are not enough antioxidants to fight off the free radicals. Moderate exercise is said to induce beneficial oxidative stress that will increase the enzymatic antioxidant defense within the body leading to positive health outcomes.[20] Performing moderate exercise regularly can be advantageous to one's well-being, however if the exercise is too intense it can have a damaging effect producing more ROS than antioxidants can combat. This can lead to cell damage, muscle impairment, inflammation, and oxidative stress.[13] Analyzing the effects of different intensities and modes of exercise is important for the prescription of a beneficial and safe exercise program within cancer survivors.

OBESITY AND CANCER

There are over one billion people across the globe that are overweight or obese, which is a critical risk factor for chronic diseases such as cancer.[21] The recommended body mass index

(BMI) range per the World Cancer Research Fund is a BMI of 18.5 to 24.9 for adults.[22] Approximately 20% of all cancers are initiated by gaining an unhealthy amount of body mass.[23] The mechanisms that stimulate cancer manifestation with the obese population are related to hormonal and metabolic abnormalities. Performing a moderate amount of PA is positively related to decreasing the risk of developing obesity.[23] It has been estimated that breast cancer can be reduced by up to 13,000 cases per year if a healthy weight is maintained. Excess adipose tissue deposited over the abdomen has been linked with pre-menopausal breast cancer.

Overweight women who have gone through menopause have a higher risk of developing breast cancer.[24,25] This may be due to higher estrogen levels in this population, made from an abundance of testosterone converting to estrogen in stored body fat. The higher levels of estrogen have an influence on the development of estrogen receptor positive cancer.[26] A body mass index (BMI) of 35 or higher had a 58% higher risk of developing breast cancer as this was associated with an elevated chance of cancer that is positive for estrogen and progesterone receptors.[27] The relationship between estrogen-progesterone positive tumors has a greater incidence within post-menopausal women who have breast cancer.[28] Regular exercise decreases total and free estradiol levels, therefore those who are overweight or obese can benefit by engaging in PA to help lower the hormone levels. By doing so, the conversion of testosterone within fat tissue may also be lowered from reducing weight, and decreasing overall estradiol.[26,29]

ESTROGEN

The endogenous estrogens, estradiol and estrone, have been associated with a higher chance of breast cancer occurrence when circulating in higher levels within the body after women go through menopause. Both cellular divisional mechanisms and mutations of cells contribute to the formation of cancer from estrogen.[30] Estrogen facilitates the effects of

development, cell changes, and functionality of the mammary gland by fastening to estrogen receptors, such as estrogen receptor-alpha (ER-alpha). ER-alpha acts as a regulator of gene expression by networking with certain DNA arrangements above their target genes. When DNA-binding is altered, ER-alpha affects the gene exression.[31] Estrogen enters into the cell, binds to its' receptor within the nucleus which holds the DNA. The collection of estrogen within the nucleus causes the binding to a response sequence through an activator protein among estrogen-receptor genes that then causes different mRNA levels, protein production, and physiological reaction.[32] One of estrogen's roles in the development of breast cancer originates from the joining of estrogen to the estrogen receptor to encourage the growth of mammary cells. The accumulation of target cells within the tissue, results in a rise of cellular division alongside DNA synthesis. This then causes a higher risk of error during replication of DNA allowing for mutations that negatively impact cell processes such as cellular death, growth, and repairment of DNA.[32]

Participating in daily PA has been suggested to modify estrogen metabolism, by working to move the metabolism to more production of 2-hydroxyestrone (2OHE1). Estrogen metabolism is commenced when estradiol is converted to estrone by the process of oxidation. Once the oxidation is complete, estrone is broken down into two metabolites of 2OHE1 and 16-alpha-hydroxyestrone (16aOHE1). This is performed by hydroxylation so one type of metabolite can be increased, while the other is decreased. The metabolite 16-alpha-hydroxyestrone is considered to be estrogenic, or promoting estrogen, while 2-hydroxyestrone is non-estrogenic. The metabolite of 2OHE1 is considered to have protective effects toward breast cancer development, as well as when the ratio level of 2OHE1 is higher than 16aOHE1. When levels of 16aOHE1 are higher or have a higher ratio level of 16aOHE1 to 2OHE1, breast cancer risk is then amplified.[33]

PA encourages the oxidation of an estrogen to be converted to estrone, which then leads to estrone being broken down and producing a higher amount of non-estrogenic metabolite compared to an estrogenic metabolite.[33]

KYNURENINE PATHWAY AND IMMUNE SYSTEM

The kynurenine pathway is a tumor-stimulating, which breaks tryptophan down into metabolites that can be detrimental or beneficial to health. Cancer cells have higher degradation of tryptophan as it goes through the kynurenine pathway. Indoleamine-2,3-dioxygenase (IDO1) works as the enzyme to metabolize the tryptophan to kynurenine within the pathway indicating an inflammatory response. Tryptophan is an essential amino acid that works as a substrate to create bio-active complexes within the physiological functions of the body. Kynurenine creates immune suppressing actions that can have an negative impact of regulatory T-cells through the process of differentiation, which controls or subdues the immune response.[34,35] The kynurenine pathway creates kynurenines that are involved with inflammation and immune-system reactions, and has been associated with depression, diabetes, and cancer. The fitness level of an individual is related to the absorption of tryptophan through the kynurenine pathway as skeletal muscle is associated with the breakdown of kynurenine. A metabolite of the pathway, kynurenine-aminotransferase enzyme, is expressed more by the skeletal muscle with exercise, which then alters the outlying kynurenine digestion by moving it to the creation of kynurenic acid. This leads to a reduction of kynurenine within the central nervous system resulting in a reduction of depressive symptoms and a decrease in activity of this tumor-stimulating metabolic route .[35,36]

The kynurenine pathway stimulates the destruction of an immune response when there is an infection. The metabolite kynurenine negatively impacts natural killer cells, as it decreases the activity so there is a lack in the control of cancer spreading. It also reduces the role of dendritic

cells so they are not as efficient to activate the T-cells, and prevents the production of the T-cells which can be detrimental to the immune system. In addition to the destruction of key-protectant cells of the immune system, kynurenine can increase the amount of proliferation and traveling capability of cancer cells, as well as help tumors evade immune system surveillance.[35] In breast cancer, among other cancers, the high expression of enzyme indoleamine dioxygenase 1(IDO1) to tryptophan 2,3 dioxygenase (TDO2) and dendritic cells that present antigens, indicates an environment that promotes inflammation.[37] Consequently, there is a reduction of tryptophan that negatively affects T-cells of the immune system, and the deficiency of tryptophan in these cells prevents production of them. The starvation of tryptophan leads to activated T-cells. Regulatory T-cells then mature because of this, creating a suppression of immunity and inflicting an immune-imbalance within the environment that drains lymph nodes to elicit a high chance of metastasis. This phenomenon has been seen among not only breast cancer type with the BrCa gene, but among other cancers.[37] A deficiency of tryptophan not only effects the immune system, but also mental health as low amounts in the brain can result in depression from a lack of serotonin production.[35,38]

VITAMIN D

Vitamin D is best known for its role to regulate calcium homeostasis and the production of bone. It also assists to correct any dysfunction of the immune and muscular systems. Vitamin D originates as 1-25-dihydroxyvitamin D, which is a steroid hormone involved with multiple bodily processes.[39,40] These processes include protecting the body from cancer by stimulating cellular death, generate specialization of a cell, assisting in the reduction of inflammation, and inhibits the growth of cells.[39,40]

Vitamin D in the form of 1-25 dihydroxyvitamin D has a chemoprotective effect to help stop the growth of cancer cells with breast tissues, similar to an antioxidant.[41] When the body has adequate amounts of vitamin D, it can regulate cellular production and function. It can also help to subdue inflammation and decrease the buildup of inflammatory cells in the body.[39] Higher levels of 25-hydroxyvitamin D, a pro-hormonal form of the vitamin, has been associated with a higher survival rate for cancer survivors. The adequate amounts of vitamin D help to hinder the progression of cancer through biological means as it activates molecules used in antioxidant defenses such as glutathione and SOD.[40,41]

Vitamin D is acquired through food and exposure to the sun. When vitamin D stores are inadequate, there is a higher risk of cancer-related mortality and cardiovascular issues. Lower levels of this are linked with advanced breast cancer, and the chance of breast cancer recurrence. Breast cancer survivors who do not meet sufficient levels of vitamin D are at a higher risk of osteoporosis and fractures, especially as treatment of cancer can have adverse effects on the body's skeletal structure. Not only can a low amount of vitamin D have negative effects on bone health, but low levels are also related to obesity.[42] Therefore, a lack of vitamin D can increase health-related risk factors that may negatively impact one's quality of life.

QUALITY OF LIFE

Quality of life (QOL) examines a cancer patient or survivor's physical, functional, psychological, emotional, and social wellbeing. Cancer diagnosis and treatments have a negative impact on the overall QOL of a patient. Although there has been a reduction in cancer mortality rate throughout the years, the treatment of the disease negatively impacts QOL, physical functioning, and body-composition.[43] A few physical effects of the disease and course of treatment include decreased cardiovascular function, reduced strength, a change in weight, and

fatigue. Mental state is also impacted by a decrease in self-esteem, and an increase in anxiety and depression.[4] Evidence continues to support that exercise can increase not only physical fitness capacity and lessen fatigue, but also improve QOL standards in cancer survivors.[44,45] Exercise interventions have shown an effect on the psychological, and emotional well-being impacting anxiety, depression, and mood disturbance.[44,45] The possible effects of a fitness training program include an increase in physical-functional capacity and a decrease in fatigue.[44,45] A training program that is moderate in intensity and frequency may promote positive physiological and psychological adaptations to increase the quality of life in cancer survivors.[44] The best PA for a cancer survivor depends on the type and stage of cancer. Overall QOL has been positively impacted by moderate aerobic exercise while cancer survivors are undergoing treatment and post-treatment.[46]

Cancer induces a high amount of fatigue from the debilitating effect it has on the body. The time of diagnosis is typically when the onset of the fatigue occurs, only to get worse as time passes, and then lasting years past the end of the treatment period. Nausea, pain, depression, and anxiety work alongside fatigue to impact the QOL of the patient. About 81% of patients experience fatigue from the disease and treatment, with 17% to 38% reporting that they experience fatigue at least another six months after treatment.[47] Fatigue often relates to other psychophysiological effects that further implicate themselves into other factors of the quality of life of the patient.[47]

Up to 25% of cancer survivors experience depressive episodes, and up to 50% have restless sleep patterns, this influences a negative effect on psychological and social wellness. Other psychosocial effects include anxiety, cognitive impairment of memory, concentration, and a decline in social activity participation. These factors can be straining on personal relationships

and feelings of motivation.[47] Additionally, psychological and physical impairments have an impact on the quality of life of the cancer patient, and finding a healthy way to recuperate them is crucial to improve the overall well-being of the patient.

CARDIOVASCULAR DISEASE AND CANCER

Cancer survivors have a higher incidence of developing cardiovascular disease because of the toxic effects that chemotherapy and radiation therapy have on the heart. Cardiac muscle may be damaged when undergoing radiation therapy as it is targeted onto the left side of the chest wall.[48,49] Treatment can result in various cardiotoxicity conditions such as left ventricular dysfunction, high blood pressure, arrhythmias, and myocardial ischemia. Along with treatment effects that increase risk of cardiovascular disease, an early onset of menopause may also play a role as there are negative changes in lipid levels and hemostasis issues that can make the risk of cardiovascular incidents more prevalent.The underlying effects of cardiovascular disease can have a negative impact on overall cancer survivorship and quality of life measures. However, cardiovascular disease can be prevented by a healthy diet, an increase in aerobic exercise, and maintaining a healthy weight.[50] By doing so, the total lifetime threat of developing cancer is also noticeably reduced.[50]

AEROBIC EXERCISE

Aerobic exercise that uses large muscle groups to perform movements result in an increased heart rate and energy expenditure. Performing aerobic exercise regularly can lead to enhancements in cardiovascular and skeletal muscle systems which results in increase endurance functioning.[51] An aerobic training program is related to an increase in muscle capillarization and improvement of muscle blood flow.[52]

The environment aerobic exercise takes place in may have a role in exercise adherence, physical and psycho-social benefits. It has been reported that exercise in both indoor and outdoor settings have advantages for the participants. In several studies participants have reported to have more enjoyment and intention of an outdoor walk, versus one in a laboratory environment.[53,54] Seasonal aspects can affect the environment a person decides to work out in. The social environment may also affect this, as some expect to meet friends and new people to a larger extent in indoor settings rather than outdoor. Social interaction may be more prevalent within indoor settings, restorative qualities are more significant in outdoor settings.[53,54] This may be caused by the natural qualities found in the environment such as trees, water, sunshine that enhances vitamin D production, fresh air, and animals.[53,54] Outdoor environments have also been reported to have an improvement on overall mood.[53] Nature may have some of the greatest health benefits for enhancing PA levels by creating the feeling of a reduced rating of perceived exertion, a decrease in stress reduction, restoring psychological fatigue, and also to increase self-esteem within the exerciser.[53]

STATEMENT OF PURPOSE

As the prevalence of cancers continues to rise today, more advancements in medical therapies will be used and developed in order to help control and destroy cancer within the body.[1,42,44,53] Chemotherapy and radiation assist in killing off the cancerous cells that cluster and create malignant tumors, but they can damage other body tissues such as cardiovascular tissue.[50] The disease and treatments can lead to nausea, fatigue, have a negative impact on QOL overall, and increase sedentary behavior which may lead to an unhealthy weight gain, muscular atrophy, and decreased cardiac function.[13,43,45,47,50] A lack of PA or a high of intensity of exercise can have a negative effect on physiological and psychological functions that increase one's risk of

developing cancer or cancer reoccurrence and depression, which all netagively impact QOL.[20] Therefore, this literature review will investigate the physiological effects of indoor and outdoor aerobic training on ROS, antioxidants, quality of life, vitamin D, estrogen, kynurenine, cardiovascular disease, obesity, and the immune system within breast cancer survivors. It will also assess the psychological effects of indoor and outdoor aerobic training to look at changes in QOL outcomes, including overall wellness, fatigue, and mood state.

DEFINITIONS

This review utilizes a large range of terms in relation to disease and health. Therefore, having a section defining these terms was pertinent to understanding the literature.

1. Luminal A: Luminal-A subtype has the best overall prognosis as it is the lowest grade of cancer. This cancer has a slow progression time, and is an estrogen and progesterone receptor positive, HER2 negative, and low levels of the protein Ki-67 that helps to govern how quickly cancer cells grow.[6]

2. Normal-Like: Normal-Like breast cancer subtype comparable Luminal-A in the aspects of being hormone receptor positive, HER2 negative, and also has low levels of the Ki-67 protein. However, this type has a worse prognosis than Luminal-A, but not drastically.[6]

3. Luminal B: Luminal-B cancer is considered to have a marginally poorer prognosis than the A subtype. This type of Luminal also has a positive hormone receptor status, but has HER2 being either positive or negative, with higher levels of the Ki-67 protein compared to Luminal-A.[6]

4. HER-2: Human epidermal growth factor receptor; can be positive or negative.[16]

5. HER-2 Enriched: subtype of breast cancer is a hormone receptor negative, but HER2 positive status. This type of cancer progresses more quickly than both the Luminal subtypes and usually has a poorer diagnosis, however they often have successful outcomes of treatment. Therapies such as trastuzumab, pertuzumab, lapatinib, neratinib, and adotrastuzumab emtansine target the HER2 protein, as this type is HER2 positive.[6]

6. HER-2 Negative: Categorizes cancerous cells that have small amounts of HER-2 protein on their exterior. Within a normal cell HER2 helps to govern the growth of cancer, therefore HER2 negative cells grow slower and are not as likely to metastasize or reoccur.[16]

7. HER-2 Positive: Categorizes cancerous cells with abnormally high amounts of HER-2 protein, which in turn stimulates the growth of cancer cells. They are not as sensitive to hormone therapies, but can still benefit from it.[55]

8. Triple Negative: Basal-like; Is characterized by testing negative for estrogen receptors, progesterone receptors, and HER2. This means that the cancer growth does not occur due to estrogen, progesterone, or HER2 protein. Females that have a prevalence of the BRCA1 gene mutation have a higher risk of developing this type of cancer, as well as those who are younger and of the African American race. An increase in rapid cell development with abnormal DNA sequencing and the amount of genetic abnormal alterations such as the BRCA1 is more highly seen in this subtype.[6,56] This type of cancer isn't treated with hormone therapy (ER negative), or HER-2 therapies like trastuzumab (HER-2 Negative), but is treated with chemotherapy.[16]

9. Stage of Cancer: Describes the location, spread, or metastasis of the cancer.[57]

    a. The tumor is described with a "T" plus a number from zero to four describes size and location of the tumor.[57]
    b. A node is described with a "N" plus one number from zero to three to describe the effect on the lymph nodes.[57]
    c. Metastasis is described by a "M" with either a zero or one; M0 meaning it has not metastasized (or spread) and M1 meaning the cancer has spread.[57]

10. Grade of Cancer: Factor included in determining stage of cancer; describes how cancer cells differ from healthy cells when analyzed under a microscope.[57]

11. Quality of Life: The functionality of an individual in regards to physical, mental, and social states of health. A self-perceived well-being, mood state, and outlook on life.[58]

12. Oxidative Stress: is a condition where the equilibrium between the antioxidants and ROS are upset because of either a reduction of antioxidants or compilation of ROS.[15]

13. Antioxidant: a substance that shields cells from damage due to ROS(ROS). Enzymatic antioxidants breakdown and eliminate ROS by changing oxidative product to hydrogen peroxide and then into water. Non-enzymatic antioxidants interrupt ROS reactions—vitamins C, E, GSH, and carotenoids.[16]

14. Reactive Oxygen Species (ROS): Also termed as Free Radical; unstable molecule formed during cellular metabolism. Build up in cells and cause harm to DNA, lipids, and proteins.[16]

15. Estrogen: Sex hormone produced by the body; develop and regulate female sex characteristics.[16]

16. Kynurenine: metabolite of tryptophan; synthesized by tryptophan dioxygenase and indoleamine 2,3-dioxygenase.[59]

17. Tryptophan: Essential Amino Acid; substrate for bio-active compounds production within physiological roles.[35]

18. Adjuvant Therapy: surgery as the primary line of treatment.[60]

19. Neoadjuvant Therapy: Prior to surgery, the patient undergoes a type of immuno-endocrine or chemotherapy.[60]

CHAPTER TWO

LITERATURE REVIEW

BREAST CANCER AND BRAIN METASTASES

Jin et al. (2018) examined the occurrence of brain metastases, the recurrence of brain metastases, and the outcomes to a relapse of brain metastases.[9] The study used data from a seven year span of 433 patients at a cancer center in Shanghai looking at medical records from January 1, 2010 to December 31, 2016. To be included in the study, patients had to have been diagnosed with Metastatic Triple Negative Breast Cancer (mTNBC). Patients were excluded if both breasts were affected by the cancer, and other malignant types of disease were present within the last five years, with the exception of a removed basal cell skin cancer and stage zero cervical cancer. The median age at the point of diagnosis of the mTNBC was 48 years of age, with 66% of the patients pre-menopausal. Patients were considered diagnosed with brain metastases via the date of the radiological scan. As all data was analyzed, survival analysis and also occurrence of collective brain metastasis was at year one and year two.[9]

The most common behavior of the disease was invasive ductal carcinoma with 97% of the patients experiencing this, and 77% having a grade three occurrence. About 88% of patients started out with a non-metastatic form of breast cancer, but then developed into metastatic cancer later on. A total of 52 patients were diagnosed with stage four Metastatic Triple Negative Breast Cancer at their appointment of first diagnosis. Neoadjuvant—the first step in onset of therapy—chemotherapy, was used in 92% of the patients, with 85% getting anthracycline-containing

enzymes—a type of drug in chemotherapy, considered to be cytotoxic and cardiotoxic—and 70% being administered taxanes and anthracycline neo-adjuvant treatment. The study indicated that after one year of diagnosis, 26% of patients experienced a re-occurrence.[9]

Overall, 29% of the breast cancer patients did develop a brain metastasis, and one-quarter were existent with it at the primary time of diagnosis. The average survival time after the time of diagnosis of the brain metastases was about seven months. It was concluded that breast cancer patients who presented with mTNBC early on had an unfortunate survival rate. Those who had a greater chance of survival with the metastasis were asymptomatic, had few metastases, and had only their first repeated brain metastases, or controlled extracranial metastasis.[9]

As breast cancer is the second most common source of the development of brain metastasis, a data collection study investigated the risk of this in a recently diagnosed human epidermal growth factor receptor-2 (HER2) positive breast cancer patients compared to HER2 negative breast cancer patients.[61] The aim of the selection of the population was to find a recently diagnosed group of breast cancer patients that had the HER2 overexpression occurrence.. The population of patients with no previous cancer, used had HER2 screening, which then accounted for 460 patients considered to have HER2 overexpression. Approximately 44.2% of lymphnode positive patients were HER2-positive, and 42.4% were HER2-negative. All patients who had node-positive or the higher risk lymph node-negative patients were able to receive adjuvant chemotherapy. Hormonal therapy for post-menopausal patients were tamoxifen—a selective estrogen receptor modulator—and also anastrozole— an aromatase inhibitor given to post-menopausal women who had cancer progression even after tamoxifen treatment. All patients were able to receive radiation post-segmental resection the cancer from within the breast tissue. Those who received a mastectomy were able to have chest wall and

regional nodal radiation if node-positive disease was existing or a centralized progressive disease. The study used a tomography or MRI of patients who presented symptoms of brain metastases.[61]

The norm follow-up period with the patients was 3.9 years from the point of diagnosis to either the last follow-up or instance of death. The overall prevalence of recurrence or metastasis was 24.1%, with HER2-positive patients having more prevalence of the disease progression. The patients who had HER2-positive had tumors that were larger in size than the HER2-negative patients by more than two centimeters. They also had a higher grade of cancer. The HER2-negative patients had seven that experienced brain metastasis while the HER2-positive had 27 patients that experienced it. Thirty percent of HER-2 positive patients developed central nervous system metastases as the initial site, and then 70% developed central nervous system metastases that were a consequence to metastatic disease in other locations in the body. A total of 29% of those who were HER2-negative had central nervous system metastases develop as the preliminary location of relapse, and then 71% had this occurring after systemic disease advancement. Conclusively, a five year survival period of those who developed the brain metastasis was 87% for patients who were HER2-negative, and 73% for HER2-positive patients. Those who did not have brain metastasis had a survival rate of 91% for HER2-positive and 97% for HER2-negative. Overall, this study concluded from its results that women with breast cancer who have an overexpression of the HER-2 are at a higher risk for the development of brain metastasis.[61]

The comprehensive review of literature by Rostami et al. (2016) looked at brain metastasis within breast cancer assessed a total of 60,794 patients who had breast cancer, with 14,599 of these patients developing brain metastasis.[62] A time period of one month to about eight

years was indicated from the time of diagnosis of breast cancer to the finding of brain metastasis. The time from the initial finding of brain metastasis to death was a range of one month to 4.58 months. In the studies analyzed, of the 9057 patients had their menopausal status documented, there were 2685 patients who were premenopausal at the time of breast cancer diagnosis and 4186 who were postmenopausal. Sixty-three percent of the patients developed metastasis on the outer portion of the brain before developing brain metastasis intracranially. A relationship between more than one metastasis, having extracranial metastasis, a metastatic tumor at least five centimeters or larger, and presence of triple negative biomarker grade was associated with a briefer survival time period after the development of brain metastasis.[62]

DISCUSSION

Jin et al. (2018) indicated that the survival rate among breast cancer patients who develop metastases, especially those with metastatic triple negative breast cancer patients are unfortunately poor. Those with triple negative breast cancer in this study exhibited 29% development of a brain metastasis within this population. With this occurrence, the average survival time was seven months.[9] Gabos et al. (2006) had similar findings with a recurrence or metastasis development rate of 24.1% within a group of HER2-positive breast cancer patients. Seventy-three percent of patients that developed a brain metastasis among the HER2-positive and 87% that were HER2-negative breast cancer type had a five year survival period. As Gabos et al. (2006) concluded that those with the overexpression of HER2 are at a higher risk of the development of brain metastases, Jin et al. (2018) also indicated the high prevalence of development of brain metastases among their Triple Negative breast cancer population. This suggests that those diagnosed with breast cancer may have an increased risk of brain metastasis compared to others.[9,61] The comprehensive review of literature indicated that about 25% of

subjects—14,599 out of 60, 794—who had breast cancer, later developed a brain metastasis. Average patient age among Jin et al. and Rostami et al. (2016) was 48 years old. Rostami et al. (2016) also had a similar finding to survival time to Jin et al. of less than one year—one to four and a half months—for those who developed the brain metastasis.[9,62] A poorer prognosis is apparent with mTNBC, HER2-positive, and HER2-negative patients. The relationship with survival rate and having various metastases develop, tumor size, and time of reccurrence were associated with a briefer survival period among HER2 and mTNBC patients.[9,61,62] The development of brain metastasis increases the mortality rate among this type of cancer, which in turn makes it one of the most fatal cancers.[8] Finding ways to counter against the initial development of breast cancer to then prevent brain metastasis that may occur with it is important to decrease fatality rate.

PSYCHOLOGICAL & PHYSIOLOGICAL EFFECTS OF INDOOR VS OUTDOOR EXERCISE

Survivors are able to carry out daily activities easier and without as much fatigue when incorporating exercise into their routine.[5] Aerobic training improves metabolic proficiency, as well as increased muscle efficiency, in survivors train throughout a time period. Exercise can help to reverse effects of muscular atrophy as a result of cancer and the treatment process. This allows for an increase cellular metabolism efficiency when creating more energy for the muscles during activity and exercise, as well as to increase antioxidant prevalence to combat the ROS that invade the body to assist in the occurrence of exhaustion. With these improvements in body functioning, the patient or survivor can experience a better QOL and lessen the amount of fatigue experienced.[5]

A study performed among breast cancer patients to compare the effects of aerobic training and a combined aerobic with yoga training, was conducted to assess the effects on functional capacity, muscular strength, fatigue, and QOL within breast cancer survivors.[63] The study had 52 patients who volunteered and were of 20 to 60 years old with a diagnosis of breast cancer in only one breast. The participants were randomly assigned to either the aerobic exercise group, or the aerobic-yoga group, no control group was used. Prior to the start of the training program, functional capacity, muscular strength, QOL, and fatigue was assessed. The interventions for both groups lasted six weeks total, and went three days per week for 30 minutes each day. The subjects exercised at 60% to 70% of their predicted maximum heart rate. Heart rate, blood pressure, and fatigue perceptions were recorded pre-, during, and post- training sessions. The aerobic training had warm-up, exercise, and cool-down sessions. The yoga training had classes lasting one hour, three times a week on the same day that the aerobic training was performed. The results indicated that both groups experienced improvements in functional capacity, muscle strength, QOL, and fatigue, however the combined group of aerobic exercise with yoga sessions had more improvements.[63] Aerobic exercise and yoga helped breast cancer patients to improve functional capacity and QOL measures.[63]

The YMCA offers a Livestrong program to cancer survivors in 478 branches of the YMCA, helping over 37,000 cancer survivors.[64] A study performed within this organization looked at the effects of the exercise program on PA, fitness, QOL, and fatigue in cancer survivor populations. [64] The subjects for the study included individuals with medical clearance who were previously diagnosed with a form of cancer. Baseline measures of weight, height, dual energy x-ray absorptiometry scan, a six-minute walk test to assess maximal oxygen uptake, and blood draws for insulin were taken. Questionnaires on PA levels, quality of life, fatigue, and a safety

survey were administered. A total of 164 participants had a program constructed to their personal criteria based on age, cancer type, and any comorbidities.[64] The mode of exercise, progression of intensity, and duration were modified throughout. The participants followed a 90 minute program at the YMCA with a trainer two times a week, which consisted of a warm-up, aerobic exercise, weight training, and a cool-down, in accordance with American College of Sports Medicine recommendations. The training lasted for 12 weeks, with 24 sessions in total, adherence was 83%. The results of the program indicated significant improvements in maximal oxygen consumption. QOL was improved via the FACT-G questionnaire, and fatigue improved by 7.5% in those who were diagnosed with cancer within the last three and a half years. Insulin and body composition changes were more evident in the exercise group versus the control group. Overall, the Livestrong program was successful in improving PA levels, physical fitness, QOL, and reducing fatigue in cancer survivors.[64]

Indoor or outdoor exercise interventions have been used to determine if one environment favors psychological characteristics such as enjoyment or adherence to exercise. Focht et al. (2009) conducted a studyto see the effect of walking for ten minutes outdoors or in a laboratory setting on affective responses, enjoyment, and adherence for walking in the future for aerobic exercise. The researchers used 35 active female women volunteers who were 20 to 24 years old. Questionnaires were used to report what they did in a usual week, along with how much they exercised. Feelings were assessed using the Feeling Scale, and the Felt Arousal Scale.[65] Affective states were assessed by the Exercise Induced Feeling Inventory measurement scale.[65] Enjoyment was rated on a ten point scale, and "intention" to walk ranged from zero to 100 percent. The participants had to partake in two sessions, one of which was a ten minute treadmill walk in the lab, and the other was a ten minute walk outdoors. All walking was completed at a

self-paced intensity that was “comfortable” but would still elicit good exercise. The Feeling Scale, Felt Arousal Scale, and Exercise Induced Feeling Inventory was assessed at baseline and post-exercise, and heart rate was recorded every minute for the entire walking duration. Ratings of perceived exertion were also recorded. The results showed that walking in both environments did elicit affective responses, but the feeling of pleasure, apparent motivation, revitalization, and optimistic engagement were higher in the outdoor setting.[65]

Another psychological study on exercise environment used two experiments: one looked at social exercise, and the other looked at social exercise in an indoor versus outdoor environment at a moderate intensity. Experiment one utilized a moderate intensity biking protocol for 20 minutes in duration with three different groups: biking alone, biking with a stranger, or biking with a close friend. Experiment two, had four groups: one group walked alone across campus, another walked alone within the university gym on a treadmill, group three walked across campus with a close friend, and group four walked on a treadmill in the university gym with a friend. All walks were of 20 minutes in duration for experiment two. Experiment one results showed that exercising with a friend elicited less of a calm state post-exercise. The second experiment resulted in participants showing the most enjoyment via questionnaire when the walk took place outside. The psychosomatic improvements accompanying exercise may be related to the exercise environment, and have a relationship with the social factors such as exercising with or without a friend.[66]

In 2011, a systematic review was conducted as there was a growing interest in the benefits that might be obtained from nature and time spent outside as a way to re-engage people with nature.[67] The review examined the significance of outdoor green areas in encouraging PA and subsequent mental and physical well-being. The outdoor green environment is defined as

wilderness, urban gardens, countryside, country grounds, forests, and wild-life reserves. The studies reported the effects of exercise outdoors and exercise indoors on physical and mental well-being. All training interventions in the studies were considered to be "short-term" and utilized a single short walk or run in the two different environments on individual occasions.[67] The studies conducted were either a combination of indoor versus outdoor exercise, or used a virtual reality method to provide the environment to the subject through technology. All studies analyzed if the environment had an effect on involvement in PA. There was some evidence that PA in natural environments of the outdoors may elicit further positive effects on measures of psychological well-being that are not found when performing a similar activity inside.[67] The overall results of the review concluded by combining all the interventions results, outdoor green environments had greater results on well-being. The review lacked the evidence needed to base recommendations on indicating a critical need for more research in this area.[67]

Bodin and Hartig (2003) assessed the psychological aspects between running in two different outdoor environments—park versus urban. The participants would alternate between which environment they exercised in over four testing sessions. The study included six males and six females who were of 26 to 46 years old, all were native to the area where running routes were located. The participants were experienced with three or more years of running, and following a run schedule of at least three runs per week prior to the study to be included. The routes were 14 kilometers in total distance, runners were able to run at a relaxed pace and not to exceed 60 minutes. The park route was comprised of dirt and gravel paths through open fields, passing by a lake, and running through a forest shoreline for about two kilometers. They passed by a large manor house and estates, as well as a barbeque spot near the lake. The urban route consisted of sidewalks and streets that varied in the amount of pedestrian and car traffic, as it

could get heavy in the afternoon. They also passed by apartment buildings, and commercial buildings. The pre-testing was conducted before the first session of running in a quiet room where informed consent and the measurement questionnaires for induced feeling, negative mood state, and digit spans were explained. The subjects completed the scales prior and post run, each session. The participants reported great weather on 41 of 48 occasions. The scales used to assess the study measures were: Exercise Induced Feeling Inventory, Negative Mood Scale, Digit Span Test, Digit Span Forward, and Digit Span Backward, and lastly the Symbol Digits Modalities Test.[68] The Digit Span Forward and Backward test asked a subject to repeat a series of numbers forward and backward which increases in length based on last successful series repeated. The Symbol Digits had the subject write a series of numbers that corresponded for symbols. The purpose of the "Digit" tests was to assess the attention of the subject.[68]

Results of the study indicated that running produced changes in emotion and attention while running outside. There were significant changes in anxiety, depression, and anger from the pre-run to post-run testing. Focus attention actually declined during the run. Larger emotional benefits were exhibited by the the runs in the park versus the urban setting. Limitations to this study included an urban setting as it wasn't as "city-like" as it could have been to really compare it to a park setting. The runners had reported lower levels of anxiety or depressive state before beginning their run, therefore giving a weakened state for a restorative effect. The aspect of focus attention could have decreased as runners tend to focus on physiological states in the body, and ratings of exertion, rather than the running environment. The measures that were utilized were only taken at one timepoint after the run, not throughout the day post-run. Another limitation was a smaller sample size of runners.[68]

The assessment of mood alteration following an exercise intervention was used within an elderly population of females. This study can be used to make inference within a breast cancer population as they experience negative mood state from treatment and exercise can possibly help to improve this.[47] The purpose was to look at the effects of a 12-week program on states of feeling post exercise, and to find the minimum amount of sessions needed to reach improvement.[69] Subjects were 55 healthy females who were 60 to 75 years old as the subjects, located in northern Greece and lived in a public care home. These subjects had been sedentary, which was defined as not engaged in PA for at least six months, prior to the training intervention. The intervention included three groups and one control group—Group A participated three times a week, Group B twice a week, and Group C was once a week, sessions lasting 45 minutes. The training consisted of indoor and outdoor recreational leisure activities and calisthenic exercises. The calisthenic exercises focused on improving flexibility, strength, and coordination in an effort to reinforce self-esteem and self-confidence.[69] There was a recreational component which included games to focus on agility, balance, and muscular dexterity. The program overall was composed of a five minute warm up, a 15 minute aerobic session of walking or aerobic exercises, 10 minutes of upper and lower body conditioning, and another 10 minutes of recreational activities, with a five minute cool-down. An Exercise-induced Feeling Inventory was taken as a pre-and post-test. The results showed an improvement of mood in elderly females who participated in the exercise, as a positive mood was increased versus the control group. Those who performed the activity two to three times weekly had significant improvement in positive engagement, revitalization, and tranquility, and reduced physical exhaustion.[69]

Forest bathing (Shinrin-yoku) has been shown to have a positive effect on relaxation of the body and mind. Park et al. (2010) reviewed studies that conducted experiments in 24 forest

areas in Japan, within a male population, to assess the physiological effects of forest bathing and a study that dealt with the affiliation between the psychological effects of Shinrin-yoku and environmental influences. Physiological measures taken included pulse rate, blood pressure, heart rate variability, parasympathetic nervous involvement, sympathetic nervous involvement, cortisol levels via saliva, and immunoglobulin concentrations via saliva. Psychological response was assessed via Profile of Mood States questionnaire. The study took note of temperature, humidity, heat, and wind for environmental factors each testing session. The participants were given a preview of the areas in the city and forest during pre-testing, along with physiological measures and independent feelings. Randomization of subjects allowed for two groups, a cross-analysis of environments was used so both groups experienced city and forest settings. The groups would view the opposing sites on opposite days, a total of two days for the intervention. Measurements of physiological measures were taken before breakfast, and then sent to their corresponding site for that day—forest or city. Upon arrival at the specified site, participants would walk around for about 15 minutes, and then sit for approximately 15 minutes as well. The second measurement was taken prior to the walking portion, and after the walking portion for the third measurement. The fourth and fifth measurements were taken prior to the "sitting to view" and preceding this as well. Walking intensity was assessed with an activity monitor, and there was no difference in the intensity between walking in the forest versus walking in the city.[70]

The results across the 24 different forest areas concluded that cortisol levels were lower preceding the forest area intervention versus the city. The decrease was two-percent more after walking versus just viewing. The average heart rate and blood pressure was considerably lower in the forest setting post-viewing compared to the city setting. Parasympathetic nervous activity involvement was significantly increased with the natural forest environment—the

parasympathetic nervous activity is enhanced when one feels relaxed, therefore showing the forest is a more relaxing environment versus a city as surroundings. Sympathetic nervous system activity involvement—measured by ratios of high and low frequencies of the heart rate—was decreased when in the forest as this activity increases when stress is apparent. Therefore, the natural environment of the wooded area allows for a more relaxing environment versus a city setting. Looking at the psychological measurement via the Profile of Mood Scale, the forest environment elicited lower scores in tension and depression compared to the city setting. Fatigue and confusion scores were also lower post-forest viewing as well. Conclusions of the study indicate that forest bathing can effectively relax the human body, and the forest area has positive psychological responses of the human mind.[70]

Xiang et al. (2012) conducted a study on forest bathing, investigating the effects of Shinrin-yoku on oxidative stress, inflammation, immunity, and cardiovascular health in healthy subjects. The intervention was conducted in a broad-leaved evergreen woodland area, and also a city for a comparison group. Pre-testing was conducted the day before the experiment started, a blood draw was collected in the morning prior to eating. The subjects were given identical single rooms and meals during the process. Randomization was used to divide the subjects into a forest group versus city group. During the protocol subjects walked a designated course for about one and a half hours at a relaxed pace, allowing for a 10 minute rest during the walk. Once the first walk was completed, they had lunch in the "resting room" and then walked another designated course for one and half hours, with another 10 minute rest during. The participants stayed at the intervention site for a total of two days. The findings of the study indicated a reduction in inflammation in subjects that were in the forest setting versus those in the city. The air pollution in the city may induce oxidative stress and lead to cellular damage. The study indicated lower

levels of lipid peroxidation within the forest group compared to the urban, revealing that forest bathing can reduce lipid peroxidation. Forest bathing may be advantageous to reducing oxidative stress in humans, thus those who live in urban settings should visit the forest environment to reduce inflammatory actions and oxidative stress to help improve overall health. Forest bathing was shown to have positive effects on human health that may aid cancer survivors to decrease risk of pathological conditions through the improvement of oxidative stress.[71]

Experiences in nature can help to reduce stress. A decrease in cortisol concentrations was noted in an urban nature experience study. An increase in cortisol is associated with weight gain, muscle weakness, and negative changes in mood leading to a decrease in the overall QOL.[72] The study of eight weeks in an urban-living population used a natural environment to assess whether being outdoors three times a week for at least ten minutes or more has an effect on cortisol levels. The subjects' nature experience could be sitting or walking in an outdoor setting for at least three times a week. The results showed that the time spent in nature did reduce stress via a salivary measurement of cortisol. The subjects had the greatest benefit when they spent at least 20 to 30 minutes outside. This study showed a reduction in stress measured physiologically rather than subjectively, indicating that time in the outdoors has a positive effect on health via reduction in stress.[72]

Mackay and Neill (2010) collected data from participants who were already participating in an outdoor exercise program of different modes of aerobic exercise---biking, running, boxercise, and walking. They utilized a questionnaire to assess state anxiety and predictor variables such as duration, intensity, and naturalness pre-and post-exercise. The participants completed the questionnaire before and after the exercise session within the intervention. The duration of the exercise session was measured at the start of the exercise and at the end of the

session on the post-testing questionnaire. The data collection study showed that green exercise reduced the subject's state anxiety through the involvement of exercise outdoors in areas with a high amount of greenery. This study strengthened past research conducted as exercise in a "green" environment led to a great enhancement in self-esteem and a reduction in negative mood change.[73]

DISCUSSION

Exercise elicits a positive effect on overall QOL, mental health, and also physiological functionality.[52,53,63] Within both indoor and outdoor environments, these positive effects are prominent. Indoor exercise training such as aerobic exercise, and aerobic exercise with yoga combined has shown improvements in strength, QOL, functional ability, and decreased fatigue within a breast cancer population according to Vardar et al. (2015).[63] However, the combined exercise protocol exhibited greater improvements compared to just aerobic exercise alone.[63] Cancer patients and survivors from a study at the YMCA also elicited similar improvements in physiological function, QOL, and fatigue after a combined program of aerobic and weight training. The combination of endurance exercise and strength training, or yoga which also helps to strengthen musculature, in both studies of Vardar et al. (2015) and Irwin et al. (2008), indicated that a balanced exercise program would help to improve mental, emotional, and physical health, thus all factors of QOL.[63,64]

The study by Focht et al. in 2009 showed that an active female population had feelings of pleasure, apparent motivation, revitalization, and optimistic engagement when exercising in both an indoor and outdoor environment. Although when the participants walked outside, they had greater positive affective responses versus when they walked indoors.[65] The social environment affected the psychosomatic capacity of individuals during exercise as well. Plante et al. (2007)

demonstrated that when you exercise with a partner, more motivation and excitement is apparent during and post-exercise. Exercise environment also played a role as the subjects had the most enjoyment when they exercised outside.[66] The shift in psychosomatic states due to social environment may be associated with a motivational factor. Exercising with a friend may push you to work harder and be more motivated to complete the workout. This then may lead to a more "excited" state when done rather than feeling a calming sense of being. More enjoyment in the outdoor environment during exercise may be related to time spent in nature, and the effects of nature on psychosomatic states.[68]

Matsouka et al. (2005) demonstrated positive mood state improvement in those who participated in the recreational exercise and activity two to three times per week. The subjects were outdoors and indoors using calisthenics and games to improve strength, flexibility, coordination, and self-esteem and confidence. The games aided in balance, agility, and dexterity. Positive engagement, revitalization, tranquility, and reduced physical exhaustion were apparent after the 45 minutes sessions, two to three times a week over the course of the 12 weeks.[69] Like Plante et al. (2007), this study also demonstrated the effect of a social environment on the quality of life and psyche of an individual. Matsouka et al. (2005), used socialization through recreational activity, and Plante et al. (2007) used it through exercise, both demonstrating a respectable adherence rate and mood state.[66,69]

Thompson et al. (2011) had inconclusive recommendations for their review study because of a lack of significant results from the analysis of the studies, however overall, natural environments did produce positive effects on the well-being of subjects analyzed.[67] Bodin & Hartig (2003) demonstrated that an outdoor environment for running is conducive to positive changes in mental health such as anxiety, depression, and hostility. Those that ran in the park had

greater psychological improvements in emotional states compared to those who ran in a more city-like community. This difference can be attributed to time spent in nature as it has restorative qualities.[53,68] Mackay and Neill (2010) also attributed the affect state and self-esteem measures to the participation of exercise in a "green" setting. The high amount of greenery helps for the mind to utilize the restorative natural effects, giving results on anxiety similar to Bodin & Hartig (2003).[68,73]

Forest bathing was shown to have a positive effect on the body and mind within studies conducted by Park et al. (2010), and Xiang et al. (2012). Both studies exhibited an improvement in physiological mechanisms as lower cortisol levels were shown, as well as reduced inflammation, lipid peroxidation, and plasma endothelin-one levels. In those who were walking, it was apparent that this exercise among the forest had a greater role in the improvements.[70,71] The psychological benefits were demonstrated in both Park et al. (2010), and Hunter et al. (2019) after having an experience in nature. Both of these studies exhibited decreases in cortisol, which indicates decreased stress. Those who had the greatest benefit from their time spent in nature, and reduction of stress, spent at least 20 to 30 minutes walking or sitting.[70,72] All three studies exhibited that time in nature, exercising, being active, or sitting, resulted in positive effects within the psychological and physiological system of the body.[70–72]

AEROBIC EXERCISE EFFECTS ON OXIDATIVE STRESS & ANTIOXIDANTS

Moderate exercise is beneficial to the body by increasing enzymatic antioxidant defense to help counter oxidative stress in the body that leads to cellular damage and inflammation.[20] ROS accumulate when exercise increases substrate activity due to more energy being utilized for muscular activity. This then results in more consumption of oxygen in order for the aerobic oxidative pathway to convert substrate into ATP for use. This then influences the body's

antioxidant defense system to provide appropriate levels of protection.[11,18] With more oxygen consumption at a molecular level and metabolic pathways being triggered during and post-exercise, ROS accumulation can occur.[74] Performing moderate aerobic exercise for 30 minutes regularly can help to alleviate oxidative damage done to the DNA by increasing the number of antioxidants present.[11] Campbell et al (2010) concluded that participating in aerobic exercise for one year can help to reduce oxidative stress markers found in the urine. The antioxidants can then take away or mend the damaged molecules before a build-up can occur and result in a changed cell metabolism and cell damage.[75,76] Research suggests regular aerobic exercise has a positive effect on oxidative stress with aerobic training.[75]

Intense exercise produces free radicals from the oxidative stress that can cause cellular damage if there are not enough antioxidants to fight off the free radicals. Moderate exercise is said to induce beneficial oxidative stress that will increase the antioxidant defense within the body leading to positive health outcomes. Too high of an intensity (such as above 60% of maximum heart rate) is detrimental to cells because of an imbalance created between ROS and antioxidants, which alters the body's defense mechanism.[20]

Environmental factors play a role in oxidative stress as well. Stressors from the environment can cause metabolic changes that may increase ROS production and decrease antioxidant production. Exposure to pollutants in the air can cause an increased lipid peroxidation, DNA oxidation and decrease in antioxidants as a defense mechanism leading to cardiovascular disease, inflammation in the body, and promotion of apoptosis of healthy cells, which can then lead to cancerous changes. Free radicals are introduced to our system from the exogenous pollutants, and we cannot emit them from our body, which then generates a ROS assembly.[77] Air pollutants initiate ROS production through biological relations and responses of

the immune system. Hydroxide and the ozone layer of the atmosphere react with antioxidants and a surface-active agent to form resultant natural oxidants. The redox-active factors of iron and copper irons within the air can activate and maintain catalytic reaction sequences that produce ROS.[78] Free radicals found in air pollution are more detrimental to the body compared to tobacco smoke. Exercising and spending time in an environment that has a decreased concentration of air pollution could be advantageous to one's overall well-being.[77]

As one performs moderate aerobic training over time, the resting level of hydrogen peroxide produced by mitochondria decreases. In animal models an increase in SOD and glutathione peroxidase is seen in exercising, but not sedentary animals. This increase in enzymatic antioxidants may be responsible for decreased protein oxidation within the exercising animals. As exercise increases oxidative stress, it may have a long term effect that can counteract the damaging effects by enhancing the enzymatic antioxidant activity and decreasing the oxidant production, which may ameliorate chronic diseases, such as cancer.[79]

Sixteen weeks of an aerobic exercise program showed a response to oxidative stress from biological markers such as enzymatic antioxidants.[80] The researchers wanted to assess the effect on the aerobic training program on antioxidant enzyme activity in an acute bout and long-term over the 16-week period.[80] The intervention used 17 sedentary healthy individuals and sedentary was defined as no regular PA for more then two hours per week for the last three months. The participants performed an incremental cycling ergometer test with maximal oxygen uptake, minute ventilation, and respiratory exchange ratio being measured during the test. During the exercise training intervention period, the subjects completed an individual-supervised protocol of aerobic training, four days a week for 30 minutes. This eventually increased to five days a week for 50 minutes and continued at this frequency-duration for the remainder of the training

protocol. The subjects exercised at 65-80% of their VO2 max. Blood samples were taken before each session of exercise, immediately after, and then post exercise at the 30, 60, 120 minute mark, and 24 hours after. The results of the antioxidant enzymatic activity increased after both an acute bout of exercise and regular exercise.[80]

Twelve weeks of moderate intensity aerobic training was found to decrease levels of pro-inflammatory cytokines, and thiobarbituric acid-reactive substances—a byproduct of lipid peroxidation—with an increase in interleukin-10, which is an anti-inflammatory cytokine, and total thiol content.[81] This demonstrates the positive effects of exercise on oxidative stress and inflammatory biological markers in females diagnosed with metabolic syndrome. This study utilized 30 non-physically active women who were considered to be middle-aged, and had the condition of metabolic syndrome.[81] The women underwent 12 weeks, 3 days per week of aerobic training lasting 30 to 60 minutes on the treadmill at 50-70% of their heart rate reserve. Intensity of the training progressed throughout the weeks. Plasma assays were used to measure oxidative damage through oxidative protein products, and cytokine levels were assessed via enzyme-linked immunosorbent assays.[81]

Oxidative stress markers of thiobarbituric acid-reactive substance decreased after the 12 weeks of training, as well as inflammatory cytokine levels.[81] This study therefore exhibits positive effects of aerobic training on women with insulin resistance syndrome in regards to oxidative stress and inflammatory factors causing cellular damage through mutations and weakness.[81] As this was beneficial to this population, it can also be assumed to be beneficial to breast cancer survivors because of the factors similar within both populations. The immune system of a breast cancer patient is compromised from the treatment and disease as the immune function of a person with metabolic syndrome is as well.[81,83] Obesity is a risk factor for

metabolic syndrome and breast cancer, this also plays a role on immune system function as well. These factors together can make the assumption through similar characteristics, that this exercise program can be beneficial not only to people with metabolic syndrome, but also breast cancer survivors.[81,83,84]

ROS are considered a form of oxidative stress. Intense exercise can raise the levels of ROS from the increased oxygen consumption which leads to the formation of superoxide anions, a form of ROS. Certain red blood cells, such as erythrocytes, contain antioxidant enzymes such as SOD, glutathione peroxidase, and catalase, which are defensive against oxidative stress.[85] Aerobic exercise helps the red blood cells to counter the ROS by the antioxidants they contain, as well as upregulating the production of them in the blood cell.[85] Miyazaki et l. (2001) investigated whether high intensity aerobic training reduced exercise-related oxidative stress in red blood cells—either by the role of antioxidants or by the neutrophil oxidant production among a population of sedentary, healthy males.[85] Pre-testing included an incremental cycle ergometer test to measure a baseline of performance for the exercise training sessions. The training program was at 80% of a subject's maximal heart rate for 60 minutes each session. Five sessions were conducted per week over a 12 week time period. Blood samples were collected pre-and post-exercise session to measure enzyme antioxidants by the process of hemolyzation of erythrocytes. After the twelve weeks of training concluded, there was an increase in maximal oxygen consumption which showed an increase in aerobic capacity.[85]

The endurance training increased antioxidant function in the red blood cells as well, and decreased the function of neutrophils within oxygen production post-intense exercise. Erythrocytes contain antioxidant enzymes such as SOD and glutathione peroxidase, as well an non-enzymatic antioxidants, which then help to maintain a higher antioxidant capacity within the

cell.[85] Therefore, a 12 week aerobic training program may be beneficial to upregulate the antioxidant defense mechanisms within the red blood cells, to increase protection against oxidative stress.[85] Although this study was conducted on males and not females or breast cancer survivors, it may still be useful to connect the information to the breast cancer population. Breast cancer survivors are often sedentary like the population in this study.[83] When looking at the effects of a sedentary population, a sedentary breast cancer patient may benefit from the moderate exercise protocol performed in this study as the sedentary males did.

As obesity is prevalent among breast cancer survivors, the population in the study by Roh and So (2017) can be used to make inferences about the effects of this protocol on breast cancer subjects.[27,83,86,87] A non-obese versus obese population was studied through aerobic exercise training over an eight week period. Subjects were considered to be healthy and obese, or healthy and non-obese qualification. The subjects in this were not taking any medication, and were asked not to make any dietary modifications during the duration of the study. Pre-testing of the subjects included anthropometric measures of: height, weight, BMI, percentage of fat, resting blood pressure, resting heart rate, and maximal oxygen consumption via the treadmill Bruce Protocol.[87] Blood collection occurred at pre-and post-testing, measuring for antioxidants, neurotrophic factors, and blood brain barrier function using an ELISA kit for analyzation. The exercise training program was three days a week, consisting of a ten minute warm up, 40 minutes of treadmill exercise, and 10 minutes of a cool-down period. The intensity was measured by heart rate of 70% heart rate reserve. The conclusion of the study resulted in a significant reduction of weight, body fat, and BMI within the obese group, and and an increased maximal oxygen uptake. The non-obese subject group did not have any significant change in maximal oxygen uptake.[87] The baseline measures of ROS was much higher in the obese group compared to the non-obese

group, as well as the obese group having lower levels of SOD at baseline. Post-training results showed that ROS decreased and SOD increased to improve antioxidant balance. The study also concluded a rise in levels of neurotrophic factors post-training in the obese group compared to the non-obese group. This indicates that a decrease in ROS and increase in SOD are associated with decreased oxidative stress and improved antioxidant function from exercise can have a beneficial effect on certain neurotrophic factor levels. The study found that obese people had reduced levels of neurotrophic factors and more occurrences with blood brain barrier dysfunction. Regular cardiorespiratory endurance exercise has a positive effect on antioxidant and ROS balance, which the disease obesity may negatively impact. This positive alteration in balance can benefit neurotrophic factor levels, and limit blood brain barrier dysfunction.[87]

A study performed in a cancer patient population focused on investigating the effect of a ten week exercise program within cardiorespiratory fitness, strength, and plasma markers of oxidation of protein, DNA, and antioxidant capacity via enzyme linked immunoassays. The intervention split subjects into three groups: a cancer exercise group, cancer control group, and healthy control group. The healthy control group had a single blood draw taken at baseline testing, and the cancer groups had a blood draw at baseline and post-testing. A maximal exercise test was conducted at pre- and post-testing on the treadmill, and the participants continued until exhaustion to determine a peak maximal oxygen consumption. Blood pressure, heart rate, and rating of perceived exertion was taken at every stage of the test. Muscular strength was assessed pre-and post-testing as well, utilizing a lat pull-down, shoulder press, chest press, seated row, leg press, leg extension, and leg curl exercises. The exercise intervention took place over ten weeks, three days a week, for one hour. An exercise specialist developed an individualized program for each patient, and supervised the exercise sessions. The sessions consisted of a warm-up, aerobic

exercise, resistance training, and a cool down period. Heart rate and blood pressure were measured pre-and post exercise, and heart rate and rating of perceived exertion were monitore. The aerobic exercise was offered indoors and outdoors, and was dependent on the goal of the participant—walking, stationary cycling, or recumbent stepping.The goal of the program was to increase speed weekly, but keeping the heart rate below 75% of heart rate reserve. Subjects had an increase in muscular strength, cardiorespiratory endurance, and antioxidant volume. The control group did have an increase in antioxidant capacity, however there was more of an increase in the exercise group. The decrease in protein carbonyls was also larger in the exercise versus control group. There was a decrease in oxidation of protein and DNA as well, therefore exhibiting that low to moderate exercise was beneficial in the role of physical fitness and balancing oxidative stress and antioxidants as a protection mechanism.[86]

DISCUSSION

Antioxidants combat the effects of oxidative stress that damages cells of the body, eventually leading to diseased states. An aerobic exercise program has been shown to increase the production of antioxidants in those exercising at an intensity of 65%-80% of their maximal oxygen uptake or maximal heart rate for 30 to 60 minutes.[80] Antioxidant enzymatic levels increased after acute exercise, as well as an increase in the endogenous antioxidant activity after exercising regularly. Over the course of 12 to 16 weeks utilizing moderate to high intensity aerobic exercise, antioxidant activity and defense mechanisms were shown to be upregulated among healthy participants partaking in the exercise.[80,85] Repka and Hayward (2016) demonstrated a decrease in oxidative stress markers and an increase in antioxidants with the cancer population after ten weeks of training, three days a week for 60 minutes. There was no

indication if antioxidants or oxidative stress were different between the different environments. This could be because the environment varied session to session based on subject preference.[86]

Aerobic exercise not only showed an upregulation of antioxidants, but also elicited a positive effect on antioxidant to oxidant ratio to create a balance.[87] This could be due to an upregulation of enzymatic antioxidant production or a reduction in markers of oxidative stress. Obesity and metabolic syndrome populations were positively affected by aerobic exercise alongside the healthy, and cancer populations. Like the other trials specified, at least two months of aerobic training occurring three to five times a week at a moderate intensity for 30 to 60 minutes helped to improve physiological stress.[80,81,85,86] Decreased levels of oxidative stress such as thiobarbituric acid-reactive substance and inflammatory cytokine levels occur with moderate aerobic exercise.[81] By decreasing these levels of stress markers, a more equal relationship can occur between the antioxidants and oxidative stress.[81]

EFFECTS OF AEROBIC EXERCISE ON THE IMMUNE SYSTEM

Moderate exercise is beneficial in regulating the immune system through its role in decreasing chronic inflammation and upregulating defensive immune cells when they are needed. Schmidt et al. (2018) sought to compare the effects of aerobic and strength training exercise on the immune system within the breast cancer patients who were undergoing chemotherapy.[84] Twelve weeks of training took place to compare a resistance, endurance and usual care group. Eighty-one patients were split into groups randomly. The resistance and endurance sessions were completed twice a week on Monday and Wednesdays, with chemotherapy treatment being given on Thursday. The sessions were 60 minutes in duration, and supervised. The resistance training utilized machines for lower body and upper body exercises. The endurance training used an indoor bike, and was 45 minutes in duration, which included the

warm-up and cool-down. After 12 weeks, the amount of CD3 T-lymphocytes (T-cells) were decreased in both the resistance and aerobic group. However, the aerobic group had a significant decrease in CD3 T-cells compared to a non-significant decrease in the resistance group. Natural killer cells decreased slightly in the resistance group, while the endurance group had a significant decrease. From the data described, the exercise conditions did not have a role on the inducement of immunosuppression from the cancer treatment.

A review article discussed the effect of PA on the immune system in cancer survivors. Six studies were utilized, and investigated the effects of subjects undergoing treatment, or post-treatment. Two studies investigated the effects during treatment, while four investigated the cancer survivors. All of the studies utilized followed the recommendations for physical exercise among cancer survivors—which set of recommendations used was not stated. The range of frequency of the exercise was three to ten times per week for 30 to 60 minutes of duration. The shortest studied analyzed was two week, and the longest study analyzed was 29 weeks. Five of the six studies had the subjects exercise at 60% to 80% of maximum heart rate, the other study did not state this information. Most exercise was on a stationary bike, while some used a combination of walking and resistance training, with range of motion exercises as well. Blood samples from the studies were collected to assess: natural killer cell levels, cytolytic activity, neutrophils, leukocytes—lymphocyte, monocyte, and granulocyte—T cells, and/or B cells. The results of the studies indicated that exercise was advantageous to the immune system functionality. Enhancements in natural killer cell cytolytic activity, monocyte utility, and amount of granulocytes were considered to be statistically significant.[88]

A randomized controlled trial of exercise and blood immune function within a population of post-menopausal breast cancer survivors was conducted to investigate the effects of exercise

on immune function. An exercise training group engaged in aerobic exercise three times per week for a total of 15 weeks. The exercise was performed on a recumbent bike, at an intensity of 70% to 75% of maximum oxygen consumption. The first three weeks the participants started at 15 minutes of exercise and increased by five minutes every week until the end of the study. The control group was asked not to take part in any type of structured exercise. The principal termination point of the study was if and when there was a change in natural killer cell cytotoxic activity within secluded exterior blood single-nuclear cells. The subjects had blood collected after at least 48 hours of an exercise-fasting period and after a 12 hour food-fast. Blood was collected pre-intervention and post-intervention. The results showed that exercise improved natural killer cell cytotoxic activity. The increased natural killer cytotoxic activity in breast cancer survivors who are post-menopausal is beneficial for immune function.[89]

DISCUSSION

Schmidt et al. (2018) demonstrated that aerobic training had a positive effect on the immune system in breast cancer patients.[84] The CD3 T-cells and Natural Killer cells were significantly decreased in the aerobic group.[84] The decrease in CD3 T-cells and NK cells suggest that there is less inflammation occurring, as the immune system is not as activated as when higher levels of inflammation are present. However, low levels of NK cells can be detrimental to health as they are one defense mechanism employed to defeat cancerous cells.[90] Antioxidants produced by aerobic exercise also help to reduce levels of inflammation in the body, the combination of an increase in antioxidants such as SOD and a decrease in pro-inflammatory immune factors help to decrease oxidative stress in the body and protect it from cell mutation.[84,86] Fairey et al. (2002) also described the effects of exercise among cancer survivors and the results showed that aerobic exercise was advantageous to immune system function.[88]

Natural killer cell protective activity, monocyte utility, and level of granulocytes to fight off infections, were all enhanced.[88] Another study by Fairey et al. (2005), produced results demonstrating that again, that aerobic exercise improved immune system in breast cancer survivors. Natural killer cells cytotoxic activity, which aid in destruction of tumorigenic cells, was improved post-training intervention.[89] This improvement in cytotoxic activity may be more important than an increase in the number of immune cells due to the immunosurveillance and destruction of cancerous cells from NK cells.

AEROBIC EXERCISE EFFECTS ON ESTROGEN AND KYNURENINE

ESTROGEN

Overweight women who have gone through menopause have a higher risk of developing breast cancer.[24,25] Estrogen levels are higher in overweight and post-menopausal females because of the testosterone being converted to estrogen within fat tissue. The higher levels of estrogen have an influence on the development of estrogen receptor positive cancer.[26] As regular exercise decreases total and free estradiol levels, those who are overweight or obese can benefit through PA to help lower these. By doing so the conversion of testosterone within fat tissue may also be lowered from reducing weight, and decreasing overall estradiol.[26,29]

As high body mass index readings have been related to breast cancer, as well as other cancers, there is also a link with elevated levels of sex steroids from weight gain that is implicated in the growth of cancer. Sex hormones play a role in breast cancer tumor cell growth and facilitate the effect of obesity on cancer. As estrogen levels are increased in the obese population, it is said to play a cellular divisional role, regulates the communication of enzymes acting on insulin receptors in breast tissue, prompt free radical DNA destruction, and cellular genetic mutation, thus promoting the formation of cancerous cells. Possible factors leading to the

development of cancer in the obese population include: body mass index, unhealthy weight gain, visceral fat, a sedentary lifestyle, sex hormones such as estrogen, and oxidative stress. Moderate aerobic exercise can help to counter the effects of these factors within the body.[24,25,28] As the state of being overweight and/or obese have a direct impact on most cancer types, it is suggested that losing weight can decrease risk of development of cancer. By increasing exercise, such as aerobic exercise, and avoiding weight gain before and after cancer diagnosis, there can be physical and mental benefits.[23] The investigation of aerobic exercise, estrogen, and obesity is still ongoing.

A non-significant decreased risk of breast cancer in females is associated with increased levels of 2-hydroxyestrone.[33] Campbell et al. (2007) conducted a study to establish the effects of a 12 week training program focusing on aerobic exercise on estrogen metabolites within a population of sedentary and/or recreationally active women.[33] The women were Caucasian, took part in less than 20 minutes of intense exercise at least three times per week over the past six months, were 20-35 years of age and premenopausal. They reported regular menstrual cycles, had a body mass index of 18 to 29.9, and had not been on birth control for the past six months. They did not have an endocrine condition, were not using medications to alter hormonal status, and were able to participate in the aerobic exercise program with no indications of a musculoskeletal condition. A total of 32 females that fit the criteria volunteered for the study, and all completed the trial.[33]

Anthropometric measures were taken at baseline, mid-point, and end-point of the study. Body mass, height, waist to hip circumference measures, and a dual energy x-ray absorptiometry was taken to assess body composition. Aerobic fitness was also assessed by a maximal oxygen consumption test on a stationary bike that increased the resistance by 30 watts in 2 minute

intervals until a respiratory exchange ratio was achieved of 1.0. Once this was achieved, resistance was raised by 30 watts every minute until exhaustion or a drop in cadence below 60 repetitions per minute occurred. The participants were asked to keep a record of their diet for three days during their first and fourth menstrual cycle during the study. Data for one menstrual cycle was also recorded. As a final assessment measurement, the participants took the Godin Leisure Time Exercise Questionnaire to assess their PA.[33]

The participants were randomly assigned to an intervention group or control group. Those selected for the intervention group began the exercise training during the first five days of their cycle. The training was 12 weeks in duration, individualized, supervised, and aimed to increase their maximal oxygen consumption.[33] The exercise program divided the weeks into different blocks of training. Weeks one through four had three sessions per week that consisted of 20 minutes to 40 minutes on a stationary bike. Weeks five through eight had four sessions per week, with two consisting of 30 to 45 minutes on the stationary bike, and then had two additional interval sessions completed. Interval one allowed the participants to pedal at a higher power output for ten minutes, pedal easy for ten minutes, and then began interval two. Interval two required the participant to pedal hard for 30 seconds and easy for 30 seconds, with a power output matching one that elicited maximal oxygen consumption from their graded exercise test in pre-assessment session. Weeks nine through 12 consisted of four sessions a week with two aerobic sessions of 30 to 45 minutes, and two interval sessions. The interval sessions were updated based on the mid-point aerobic test results. Interval one stayed the same as weeks five through eight, while interval two consisted of two minutes of pedaling at a power output that corresponded to the new amount of maximal oxygen consumption. Interval two had two minutes

of pedaling with three minutes of easy pedaling, for four times per session. The control group sustained their usual activity throughout the duration of the study.[33]

Urine samples were used to analyze estrogen metabolites of 2-hydroxyestrone and 16-alpha-hydroxyestrone. Samples were collected after a ten hour fast, excluding water, between six-thirty in the morning and eleven o'clock in the morning. This was done between days 20 and 22 of the menstrual cycle, for four menstrual cycles in a row throughout the study. The participants were also asked not to participate in any exercise for at least 24 hours prior to getting a urine sample taken. Samples of saliva were also taken to assess the average amount of midluteal progesterone at baseline and fourth menstrual cycle being measured. The participants drooled into a tube on day 19, 21, and 22 of their cycles. Enzyme-linked immunosorbent assay was used to measure the estrogen metabolites, while a competitive enzyme immunoassay was used to measure the progesterone level in the saliva.[33]

There was an average of 91% adherence rate to exercise sessions, with an adherence range of adherence of 64% to 100%.[33] The control group did not report any changes in the amount of exercise or activity from baseline measurement. The results of the aerobic program within the intervention group indicated an increase in maximal oxygen consumption by 4.6 mL.kg.min, which is a 14% increase, and the control group decreased by three percent.[33] The aerobic exercise did not have a significant effect on body weight, body mass index, waist to hip circumference or ratio. Both groups did not indicate significant changes in dietary intake or macronutrient amounts, and there was no difference between both groups pertaining to the amount of soy intake. At baseline there was no initial difference in between groups with levels of estrogen metabolites. After the training, it was indicated that there was no effect on the amount of 2-hydroxyestrone and 16-alpha-hydroxyestrone or ratio level of 2-hydroxyestrone to 16-alpha-

hydroxyestrone. An improvement in maximal oxygen consumption was not connected with alterations in amount of estrogen metabolites.[33] There was a positive relationship found with an increase in overall lean body mass and the ratio of 2-hydroxyestrone to 16-alpha-hydroxyestrone. Overall, the study concluded that there were significant improvements within body composition and aerobic capacity in a premenopausal female population.[33] There were not any significant changes from the urinary analysis of the estrogen metabolite levels which are suggested biomarkers of breast cancer risk. However, a positive relationship was seen with a rise in lean body mass and greater levels of 2OHE1 to 16aOHE1 ratio.[33]

As high endogenous estrogen levels are considered to be related to an increase in breast cancer risk, a study sought to examine if aerobic exercise had an influence on circulating estradiol and estrone levels within the body in cancer free females. Friedenreich et al. (2010) examined females of 50 to 74 years of age, and were postmenopausal for at least 24 months prior ot the study. They had no preceding cancer diagnosis with the exception of nonmelanotic skin cancer, and no major comorbidities. The participants were considered sedentary based off of not participating in more than 90 minutes of activity per week, or having a maximal oxygen uptake of less than 34.5 mL.kg.min. The participant was also able to undergo non-restricted PA, had normal levels of fasting lipids, TSH, and ALT, had a body mass index of 22 to 40, and were not taking any medication or exogenous hormone that could potentially influence estrogen metabolism and/or breast tissue development. Breast density was also measured, and to be included they must have a density greater than a zero level.[91]

A total of 160 participants were placed randomly in the exercise group, and 159 were placed in the control. Both groups had similar demographics, body composition, and sex hormone concentration at baseline assessment. Baseline measures and post-study measures

consisted of a dietary intake assessment from the past year via a United States National Cancer Institute's Diet History Questionnaire (124 item). Level of physical fitness was also assessed using the modified Balke Treadmill Protocol, to estimate maximal oxygen uptake from a submaximal intensity. Blood collection was taken at baseline, month six, and month 12 once the participants were randomly assigned. Blood was drawn after at least a ten hour fast.[91]

The intervention included a monitored program that was at least 45 minutes of aerobic exercise per day for five days a week over the course of 12 months at an intensity of 70% to 80% of their heart rate reserve. Three of the sessions per week were in a facility setting with trainers, and all other sessions were considered to be home-based. The intervention gradually increased intensity over the course of the first three months. The program started out with three sessions a week of 15 to 20 minutes in duration at 50% to 60% of their heart rate reserve, until the final prescription was set at the end of the third month. From week 12, the intervention included a monitored program that was at least 45 minutes of aerobic exercise per day for five days a week over the course of 12 months at an intensity of 70% to 80% of their heart rate reserve. Submaximal tests were performed at weeks 12, 24, 36, and 48 to assess progress and adjust exercise prescription to avoid a plateau. Heart rate monitors were worn, and the participants documented their activities in weekly exercise logs. The type of activity, duration, average heart rate, and rating of perceived exertion was recorded.[91]

Walking on a treadmill was the most common activity for the facility based exercise, while walking at home was the most common for home-based. The average amount of sessions per week was 3.6 sessions for an average of 178.4 minutes per week. The estimated heart rate maximum was an average of 80.1%. The control group had ten-percent of their participants increase their recreational activity by more than 20 metabolic equivalent hours per week. After

the 12 month training period was up, the exercise group had a larger decrease in estradiol over the control group, however there was no change in estrone between the two groups. Devotion to exercise was not reliably related to decreases or increases in the estrodiol or estrone concentrations. Although, exercisers who regularly performed 150 minutes to 225 minutes of aerobic exercise per week had a decrease of 18% in estradiol concentrations versus the control group. With an adjustment made for a change in the weight of participants post-intervention, the intervention effect persisted to be significant for estradiol and free-estradiol. The study concluded that the 12 month intervention did yield a decrease in estradiol and free estradiol levels. There was not a statistically significant difference between the control and exercise group even though there were reductions within the exercise group larger than that of the control group. Adhering with the exercise program resulted in greater reduction of estradiol concentrations, which in turn is related to a decreased risk of breast cancer.[91]

Yoon et al., (2018) conducted a study that looked at the effects of different exercise training methods such as aerobic and resistance with a control on estrogen levels within the postmenopausal obese women.[92] The combination of being in a post-menopausal state while being obese is linked to breast cancer. Having higher amounts of estradiol and estrone are linked to breast cancer. After menopause, the body creates estrogen from adipose tissue, linking the higher amounts of estrogen in the blood to the increased risk of breast cancer.[30] Therefore, this study may be beneficial to make connections to the breast cancer population as obesity and post-menopause are linked with a risk of breast cancer.[8,27,30] All interventions took place over a 12-week period, three times per week for one hour. Height, weight, body mass index, waist circumference, fat percentage, blood pressure, maximal oxygen uptake, maximal and relative strength, and blood samples were taken at pre-testing. Blood was taken after a ten hour fasting

period, and estrogen was analyzed by radioimmunoassay at pre and post testing. The aerobic exercise group conducted their sessions on a treadmill utilizing different speeds and inclines at 60% to 80% of their heart rate reserve. After the twelve months, the blood samples indicated that there were no changes in estrogen levels.[92]

As PA may have a role in lowering the endogenous estrogen hormone levels to induce a reduction in risk of breast cancer, Matthews et al. (2018) sought to investigate effects of exercise and cardiorespiratory health on the metabolism of estrogen in a group of post-menopausal females. Females included in the study were of the following characteristics: age 50 to 74 years old, post-menopausal for 24 months, a body mass index of 22 to 40, and considered sedentary, which is defined as having a maximal oxygen uptake of less than 34.5 mL.kg.min or taking part in less than 90 to 120 minutes per week. The participants were also not using menopausal hormone therapy. The women were placed randomly into an exercise group or a control group. The exercise group consisted of 153 participants and a control group of 154. The exercise period was 12 weeks, with a goal to participate in exercise at least five days per week for 45 minutes a day at an intensity of 70% to 80% of their individual heart rate reserve. Testing took place at baseline, six months, and one year marks to track progress and results. The blood samples were taken at baseline and at the one year mark.[93]

Subject characteristics were as follows: 61 years of age, average body mass index of 29, and 91% of the study population of Caucasian. Baseline testing indicated that characteristics, estrogen, estrogen metabolites, or metabolic pathway concentrations were not different in the two groups. The exercise group had an average exercise time of 178 minutes per week over a years time, and developed a cardiorespiratory fitness level of 13% higher than the control group. The overall estradiol level was decreased by ten percent in the exercise group, but there were not

any significant effects on levels of 2-hydroxyestrone, 4-hydroxyestrone, 16-alpha-hydroxyestrone, or two of the metabolite pathway estrogen ratio. As the participants cardiorespiratory fitness improved, there were decreased levels of 2-pathway estrogen metabolites. This is an unpredictable indication of reduced breast cancer risk. The study did not indicate a protective effect due to the down-regulation of estrogen metabolism, but did suggest that exercise has a shielding effect on post-menopausal risk of breast cancer by a decrease in estradiol.[93]

F2-Isoprostanes—oxidative stress markers—are associated with DNA damage caused from oxidative stress within cellular mechanisms. Identification of this has been associated as a marker for the risk of breast cancer. A study examined the effect of aerobic exercise on F2-isprostane, endogenous estrogen metabolites, and body composition in healthy females with a normal menstrual cycle. This study may be useful to make inference to with breast cancer survivors as many are sedentary.[94] The oxidative stress marker being assessed with the study is also important as oxidative stress can damage cells and lead to carcinogenesis. Endogenous hormones such as estrogens are related to breast cancer, as high amounts of estrogen have a link to higher risk of breast cancer.[30,83,86]

Sedentary women of ages 18 to 25 were used in the study. Sedentary was defined as two or less moderate exercise sessions per week for the last six months. The females had a menstrual cycle that lasted for 25 to 32 days, had undamaged ovaries and uterus, and also had a body mass index of 18 to 40. Those who took a hormonal contraceptive method in the past year, had gynecologic issues, were pregnant, or had medical conditions that kept them from exercising, were not included in the study. A total of 15 women were included in the study. The study used pre-testing and post-testing measures to assess body composition via dual-energy x-ray, a fitness

assessment on the treadmill using a graded exercise test that went until 80% of their predicted heart rate maximum was reached, surveys to analyze caloric intake and antioxidants, and a urine sample for endogenous estrogen metabolites and F2-isoprostane.[94]

The training for participants lasted about 15 weeks to allow for three to four menstrual cycles to occur. The subjects all started the exercise on day 11 of their cycle and ended on day five of their cycle over the course of three to four menstrual cycles. The five training sessions per week included a warm-up, cool-down, stretching, and 30 minutes on the treadmill or elliptical. The intensity for weeks one through five was 70% to 75%, weeks six through ten was 75% to 80%, and week eleven through the end was 80% to 85% of their maximum heart rate. The average heart rate was collected by a Polar heart rate monitor. Participants encountered a face-to-face session at least once a week with a staff-member. The results of the intervention indicated that levels of F2-isoprostanes—markers of oxidative stress—were reduced by 33.8% after 15 weeks of aerobic exercise. This indicates oxidative stress was being altered to a balanced state through the exercise. However, the endogenous hormones did not indicate a significant change.[94]

KYNURENINE

Vigorous exercise can create a brief reduction within the immune system function of the body. Tryptophan is metabolized through the kynurenine pathway when the immune system is activated. A study by Strasser et al. (2016) analyzed the effect of a vigorous endurance exercise on biomarkers of the immune stimulation and breakdown of tryptophan and kynurenine within athletes.[38] The study encompassed 30 healthy athletes of both male and female gender to undergo an exhaustive endurance test. Although the testing was performed in athletes, the outcomes of the testing may be beneficial to make inference within a breast cancer population. The participants were given a uniform breakfast two hours before performing the exercise test.

All participants were tested to assure they were qualified by a fitness test that consisted of an incremental cycling test until the athlete hit exhaustion and stopped. The athletes that were qualified then performed a 20-minute maximal test on a cycle ergometer. The participant had 20 minutes rest between the qualifier and the test. The subjects pedaled at 100 repetitions per minute to then produce a peak power output 70%. This power output was determined in the qualifying test. A blood sample was collected before the exercise test and no more than five minutes after the test was complete.[38]

The results showed that the males exhibited a higher average power output throughout the 20 minute exhaustive test. They also had a higher body mass index compared to the female athletes. The females had a lower kynurenine level than the males. Indoleamine 2,3 dioxygenases (IDO1) was involved which then enhanced the breakdown of tryptophan and kynurenine production after exhaustive physical exercise.[38] The relationship between neopterin—a marker of immune system activation—and the kynurenine and tryptophan suggest that the IDO1 prompts the breakdown of tryptophan. As there were low levels of tryptophan reported after exhaustive exercise, it was suggested that this may reduce the amount to the brain that then decreases the availability of the tryptophan for the creation of serotonin.[38] The ratio of kynurenine to tryptophan was increased after the exhaustive exercise, as the breakdown of tryptophan produces kynurenine. Therefore, it was also suggested that the metabolism of tryptophan via the kynurenine pathway into kynurenine metabolites may alter the mood of the individual.[38] As breast cancer causes anxiety and depression among many survivors and patients, tryptophan levels in association with the kynurenine pathway are evident within this population as well. Exhaustive exercise impacts a reduction of tryptophan which in turn can lead to a lack of

serotonin production and lead to a negative mood state. This high intentisty of exercise then affects the quality of life of an individual.[35,38]

Mudry et al., (2016) examined the effect of aerobic exercise on the kynurenine metabolism, which reported that kynurenine concentration in the plasma was positively related to body mass index. This implies that high levels of kynurenine could potentially have a role in the depression of the obese population.[95] Many breast cancer survivors experience an unhealthy weight gain leading to overweightness or obesity from sedentary behaviors during treatment and experience depressive symptoms from the treatment as well.[27,47] Therefore this study can be used to make interpretations about the effect of aerobic exercise on the breakdown of kynurenine in the body in regards to the breast cancer population.[27,38,47]

Mudry et al., (2016) used a protocol involving baseline collection anthropometric measures and body fat analysis, reference measurements, and blood samples.[95] Maximal oxygen uptake was also assesed using a test on a cycle ergometer maintaining 85% of the subject's maximum heart rate for 30 minutes. Immediately after the test was complete, samples were collected again, and once more during the recovery three hours later.[95] Skeletal muscle and plasma were collected from men with a normal glucose tolerance at rest, after the exercise protocol, and during the recovery period. Aerobic exercise had an effect on the concentrations of tryptophan, kynurenine, and kynurenic acid. The exercise reduced the plasma levels of kynurenine and tryptophan in subjects with normal glucose acceptance. The kynurenic acid increased in response to the acute exercise which then supports the theory that exercise is involved in the breakdown of kynurenine.[95] It was suggested that exercise induces the activation of tryptophan, kynurenine, and kynurenic acid in human subjects, which is similar to mouse models, therefore exercise increases kynurenic acid without affecting the tryptophan or

kynurenine. [95] The decrease in the kynurenine levels, and increase in kynurenic acid levels, may describe the neuro-protective effect of exercise within the deterrence and management of depression.[95]

Schlittler et al. (2016) conducted a study to see if aerobic exercise increases the skeletal muscle kynurenine aminotransferase (KAT) and plasma kynurenic acid within aerobically-trained athletes (two experimental groups) and aerobically-untrained recreational athletes (control group).[96] The aerobically trained athletes were going to be cycling in a 150 kilometer time trial, and others were running a half marathon. Skeletal muscle and blood plasma was collected in both groups at rest, and also after exercise in the experimental groups. The blood was collected post-cyling at the one, five, and 24 hour mark, as well as one week later. Average heart rate or intensity of the exercise was not specified in this study. The aerobically trained subjects in the cycling group had an increase in kynurenic acid by 63% one hour post cycling, this returned to baseline after 24 hours. The half marathon subjects had an increase of 125% of kynurenic acid a half hour post race.[96] The results of the showed that endurance exercise causes a temporary increase in kynurenic acid, and those who perform regular aerobic training have a higher expression of kynurenine aminotransferase than those who do not perform aerobic exercise.[92] Although the subjects were recreational athletes, the results may help to encourage breast cancer survivors to develop a long-term aerobic program. Increasing kynurenic acid and kynurenine aminotrasferase, which have been shown to be neuroprotective and fight depression.[35,96]

DISCUSSION

Estrogen metabolites are significant markers of breast cancer risk. Estrogen levels are elevated in overweight, post-menopausal women because testosterone is converted to estrogen

within the fat tissue.[33] Campbell et al. (2007) study's results on estrogen metabolites did not show a significant alteration on the levels or ratio of 2-hydroxyestrone or 16-alpha-hydroxyestrone. However, those with greater lean mass composition were associated with increased levels of the 2OHE1 and 16aOHE1 ratio.[33] These results suggest that a leaner body composition is beneficial to reducing the risk of cancer by having lower levels of estrogen metabolites.[33] Aerobic exercise can aid in weight-loss, via energy expenditure, to create a leaner body composition, which in turn may benefit women by having these lower levels of 2OHE1 and 16aOHE1.[33]

Similarly to Campbell et al. (2007), Yoon et al. (2018) did not see alteration in estrogen levels after aerobic exercise.[92] Friedenreich et al. (2010) demonstrated a decrease in estradiol in women who performed aerobic exercised 150 to 225 minutes a week over their controls. When data was adjusted for weight reduction after the intervention, the results showed a significant change in the estradiol and free-estradiol.[91] Estrogen metabolites were evaluated based on levels of estrogens—estradiol, estrone, estriol. The estrogen metabolites of 2OHE1 and 16aOHE1 are beneficial in reducing the risk of breast cancer with an increase within the ratio of the two. However, higher levels of endogenous estrogen are considered to be high risk.[33,91] The association between leanness and adequate ratio-levels of 2-OHE1 and 16aOHE1 may suggest that keeping a healthy body composition can aid in the reduced risk of breast cancer by having improved estrogen metabolite ratios. Perhaps the lower levels of estradiol post-exercise are related to the breakdown of the estrogen into metabolites and a higher ratio aids in prevention.

Matthews et al. (2018), showed a 10% decrease in estradiol with exercise, thus aiding in the reduction of risk of breast cancer, but did not see any significant alterations in estrogen metabolites. Although there was a shielding effect present from a decrease in the estradiol, a

physiological “protective” effect was not apparent from the estrogen metabolism of the metabolites, possibly because the 2OHE1:16OHE1 ratio was not increased significantly.[93] When comparing the effect of aerobic exercise on endogenous estrogen to F2-isopranes, there were no significant changes seen in the estrogen levels, but there was a decrease in the F2-isopranes which are associated with oxidative stress. Although aerobic exercise was not consistent with alterations in estrogen levels for breast cancer, it does provide a decrease in oxidative stress.[94]

However, it is important to consider what happens if estrogen levels are too low, as neurological complications may become apparent. Women who have too low of levels of estrogen may experience negative effects on mental health, due to the interaction within the kynurenine pathway.[97] The amount of estrogen within the body is suggested to have an effect on how much kynurenic acid is able to be produced because of its inhibitory effect on kynurenine aminotransferase. Estrogen helps to control the actions of kynurenine aminotransferase so it doesn’t over produce kynurenic acid, which can then lead to metal illness that can effect quality of life.[97] Although too high of levels may increase breast cancer risk, too low of levels can inflict issues among the mental health. Moderate aerobic exercise may help to induce positive changes for both.[75,93,97]

Not many studies are conclusive on the effects of aerobic exercise on the kynurenine pathway in the body. Tryptophan is broken down into kynurenine or kynurenic acid by the kynurenine pathway, dependent upon the mechanism.[35] Moderate exercise induces the onset of a positive response of the kynurenine pathway by producing kynurenic acid.[35,38]

Strasser et al. (2016) demonstrated that exhaustive exercise was shown to lower levels of tryptophan after exhaustive exercise because of an upregulated immune activation response.[38] The enzymes that are responsible for the breakdown of tryptophan are found within immune

cells. The induction of these enzymes occur when immune cells such as macrophages and IDO1 are activated, such as from the exhaustive exercise.[38] By doing so there is a lack of availability to create serotonin from the tryptophan, creating a higher ratio level of kynurenine to tryptophan. The increase in kynurenine within the kynurenine to tryptophan ratio can lead to a negative mood state inducing depressive symptoms.[35,38,59] Mudry et al. (2016) indicated that a decrease in kynurenine levels, which would then increase kynurenic acid levels, may be effective in the deterrence of depression by providing a neuroprotective effect.[95] Kynurenine-aminotransferase expression within skeletal muscle during an exercise session aids in the production of kynurenic acid by altering the kynurenine metabolism process. This in turn leads to a decrease in kynurenine and decreases activity of tumor stimulation and positively affects an individual's mood.[35] Likewise, Schlittler et al.(2016) indicated an increase in kynurenic acid and kynurenine aminotransferase, which have neuroprotective effects and can help reduce depression.[96] An increase in the kynurenic acid can be influenced by the availability of tryptophan that is no longer bound to albumin—a blood plasma protein. This occurs through exercise because free fatty acids attach to albumin pushing the tryptophan off, which increases the amount of tryptophan in the blood. This increase in tryptophan may influence the increased amount within the kynurenine pathway to be metabolized into kynurenic acid.[96] Through these mechanisms, a breast cancer survivor can benefit by combatting depressive symptoms because of the protective effect of the kynurenic acid and the decrease of kynurenine.

Moderate aerobic exercise seems to have a beneficial effect on depressive state, mood, and physiological function compared to exhaustive aerobic exercise.[35] This may be because throughout exhaustive exercise, the amino acid tryptophan is being broken down in the kynurenine pathway much more quickly than someone performing moderate exercise. As

moderate exercise stimulates the breakdown of kynurenine within the pathway into kynurenic acid, the immune system is positively affected.[35] The more kynurenine there is in the body, the more negatively it impacts NK cells from performing their role and controlling tumorigenic cells from spreading.[35] By creating more kynurenic acid and decreasing kynurenine, the body is positively impacted by enhancing mood state through the reduction of depressive symptoms, and also increasing the role of NK cells to protect from cancerous cells proliferation and traveling through the body.[35] Control of the kynurenine pathway to keep levels of tryptophan and kynurenic acid at adequate levels allows for T-cell activation to participate in an immune response. When the body is deficient from tryptophan it stops the production and activates the current T-cells leading to the maturation of Regulatory T-cells and creating a suppression of immune response which then alters the balance of the immune environment.[37] This imbalance can inflict a higher risk of metastasis, which can be detrimental to the health of a cancer patient.[37] Moderate exercise can help to regulate the kynurenine pathway in regards to psychological and physiological health. [35]

AEROBIC EXERCISE EFFECTS ON CARDIOVASCULAR DISEASE & OBESITY

A lack of PA is accountable for 12.2% of heart attacks after accounting for other cardiovascular diseases in the general population. Only 17.6% of women meet the American Heart Association (AHA) guidelines of 150 minutes of moderate exercise per week. Studies have shown that conforming to the AHA guidelines is connected with a reduced breast cancer risk for active women versus sedentary women, as well as, a reduced risk of cardiovascular disease because of the appropriate amounts of PA being performed. By changing sedentary behavior to a more active lifestyle, this can aid in breast cancer prevention.[50] Cardiovascular disease risk is drastically increased when one has a BMI of 25 to 30, which is a condition of overweightness

and an increased risk of obesity (BMI > 30). Obesity is a risk factor for both cardiovascular disease and breast cancer. Women with breast cancer tend to gain weight from the treatment and disease itself, which also leads to a more sedentary lifestyle. Cardiorespiratory function—the capacity of the circulatory and respiratory systems to allocate oxygen to skeletal muscles during continuous PA—is enhanced in breast cancer survivors who exercise regularly, which also results in a better quality of life. Exercise can help to control weight gain along side a healthy diet, and also positively impact breast cancer progression.[50]

Cardiovascular disease may be implicated in the breast cancer population as a cause of death post-treatment.[48] A follow-up study was performed using the Long Island Breast Cancer Study Project subjects to assess whether the cause of death was because of cardiovascular disease in the breast cancer survivors. The survivors were age matched to each other and the control group, who were women who did not have, or ever had, breast cancer.[48] The cancer survivor subjects were first diagnosed between 1996 and 1997, with non-invasive and invasive breast cancer—subtype was not specified. The study then used the National Death Index to determine the status of the participants up to 2009, and death from any cause was considered.[48] The results of the study showed that the overall risk factors associated with cardiovascular disease was marginally higher in women with breast cancer compared to their cancer-free controls. Cardiovascular disease related-death was shown to have a sharp increase after the five year mark in breast cancer survivors, and was higher after seven years of follow up in long-term breast cancer survivors versus those females without breast cancer.[48] The cardiovascular disease mortality frequency was prominent in the breast cancer survivors who had received chemotherapy as primary treatment for their initial diagnosis of breast cancer. The study noted that the elevated risk of cardiovascular disease in breast cancer survivors was not evident until

several years post-diagnosis. Breast cancer treatments, such as chemotherapy and radiation, have toxic effects on the heart muscle and tissue. Breast cancer survivors who underwent long term treatment, were at increased risk of cardiovascular disease mortality several years after diagnosis, compared to the the non-breast cancer population.[48]

Substances found in chemotherapy have negative effects on the heart leading to acute and long-term cardiac impediments.[49] As some issues are apparent during the treatment period, some have an effect by decreasing the left ventricular ejection fraction and increasing complications associated with congestive heart failure. As mechanisms of cardiac dysfunction from chemotherapy are not fully clarified, ROS and cardiac cell death may play a large role.[49] ROS might be continually produced as a result of drugs within cardiac cells, which may demonstrate a late onset of cardiovascular damage leading to cardiovascular diseases. Radiation therapy was also reported to have negative implications on heart health, and when combined with chemotherapy, there was an increased risk of heart failure as compared to patients who only received the radiation.[49] Patients undergoing therapies for cancer are subjected to multiple cardiovascular assaults, which when paired with lifestyle choices can leave the patient with a greater risk of cardiovascular disease development. Cancer therapy effects can be countered through healthy lifestyle behaviors such as exercise, and pharmacological cardiovascular disease medications. Angiotensin converting enzyme (ACE) inhibitors and exercise can have beneficial effects to fight against ROS through their function as antioxidant mechanisms.[49] It can be surmised that a decrease in oxidative stress by ROS may have a protective outcome against cardiac muscle toxicity from treatment. The varying severity of cardiovascular injury and cancer treatment relationship is prevalent among the breast cancer population.[49] The consequence of the

"multiple hit" of treatment and lifestyle factors are important to manage in women with early breast cancer to reduce the risk of cardiovascular disease through cardiac injury.[49]

Cardiovascular disease risk escalates about five to seven years after the primary diagnosis of breast cancer. The extent to which cardiovascular risk factors and cardiovascular disease are present in the life of a patient before the initial diagnosis of breast cancer, and onset of treatment affects the degree of susceptibility for negative effects on the heart. This portrays the multiple-hit scheme—criterion cardiovascular risk elements, diagnosis, decreased cardiovascular reserve which is affected by modifiable risk factors (an indirect effect) and adjuvant therapy (a direct effect), which then leads to a potential degree of cardiovascular disease. A case study performed in Sweden and Denmark showed a linear correlation with one-Gy dose amount of radiation and increased the risk of cardiovascular events, which was 7.4%. There was an elevated risk of cardiovascular disease after radiation for up to the five years. The high risk from radiation treatment combined with a greater amount of cardiovascular risk factors associates with a higher risk of cardiovascular trauma.[98]

Other risk factors include chronic inflammation, which is associated with cardiovascular disease and breast cancer via oxidative stress. However, PA has been shown to reduce the risk of both diseases through balancing out the oxidative stress within the body with antioxidant defense mechanisms creating a modifiable risk factor. Genetics are non-modifiable risk factors. For example, the breast cancer gene one and two are not only involved in breast cancer, but also with cardiovascular disease, as they affect the protection of cardiac function leading to more damage. Modifiable and non-modifiable risk factors have been shown to intertwine to affect both diseases, creating a conducive environment for the disease to progress under certain circumstances.[98]

Cardiovascular health has an influence on the outcomes in cancer patients as survivorship is altered through effects of cardiovascular disease. Managing comorbid conditions can affect the overall prognosis of a patient or survivor. By modification of lifestyle factors such as diet, exercise, weight management, controlling blood pressure, and keeping a healthy lipid count, minimizing these cardiovascular risk factors can also help to reduce the risk of cancer over a life period. Being physically inactive accounts for 12.2% of heart attacks, and as 82.4% of American females do not meet PA guidelines, sedentary behavior causes cardiovascular problems in the United States population. Sedentary behavior has been related to a higher breast density, as this is an independent risk factor of breast cancer. Studies have regularly shown that moderate-vigorous exercise can decrease the risk of breast cancer, and also supports a healthy cardiovascular system. As breast cancer and its treatment can contribute to weight gain and decrease in PA, overweightness and obesity can occur. Both are risk factors for cancer and cardiovascular disease, however regular PA can help to counter this. The American Heart Association recommends 30 minutes or more five days a week for heart health, and this can also improve pulmonary function in breast cancer, therefore improving physical and mental overall QOL.[50]

As cardiovascular disease is the leading cause of death in women with non-metastatic breast cancer, a study investigated the effects of exercise and risk of a cardiovascular event. Those who have history of breast cancer may be at a further risk of cardiovascular events because of the toxic effects that cancer therapies have on the body and heart tissue. Jones et al., (2016) looked specifically at whether exercise was an independent predictor of cardiovascular events, if a dose relationship exists, and if there is a relationship between exercise and cardiovascular endpoints based off of the initial cardiovascular risk and type of therapy used.

Subjects were females with nonmetastatic breast cancer, and exercise was assessed at the time of enrollment using an activity frequency questionnaire to evaluate PA, recreational, and non-recreational activity. The primary "end-point" was indicated by the first occurrence of coronary artery disease, heart failure, valve abnormality, arrhythmia, stroke, or cardiovascular disease related death, which occurred after the study enrollment. The study found that exposure to exercise after diagnosis was related to reductions of cardiovascular disease traumas or death in women with early stage breast cancer. Exercise was connected to a decrease in heart failure and coronary artery disease. The reduction in heart failure is especially important for breast cancer patients as the chemotherapy that has doxorubicin can cause damage leading to a cardiovascular event. A 23% decreased risk of cardiovascular disease was associated with patients who met the exercise guidelines. Overall, the study concluded that exercise is related to a substantial decrease in the occurrence of cardiovascular events, the principal cause of early morbidity and mortality within non-metastatic breast cancer patients.[99]

Cardiovascular competes with breast cancer as the primary cause of death in older breast cancer patients.[100] The effects of comorbid conditions in the breast cancer explicit mortality versus other causes of mortality and also the prominent cause of death within the breast cancer survivor population was investigated.[100] Comorbid conditions, associated with all causes of death considered in the study were previous cancer, cardiovascular disease, chronic obstructive pulmonary disease, and diabetes. A total of 63,566 women, 66 years of age or older, were used in the study, and classified from the Surveillance, Epidemiology, and End Results-Medicare database. Medicare files were investigated for diagnostic and codes that were directly related to comorbidities and treatments, including any forms of cancer treatment. The women were followed for about nine years and 48.7% were alive around the time of the follow-up period.

Breast cancer specific mortality was highly affected by comorbidities at the point of diagnosis as well as stage of the tumor, grade of the tumor, the status of the estrogen receptor, and age. Other causes such as age and comorbidities at the point of diagnosis had a large effect on overall mortality not necessarily related to breast cancer. Breast cancer survivors were found to be significantly affected by comorbid conditions when looking at total mortality and breast-cancer specific mortality.[100]

Chaudhary et al, (2010) examined aerobic exercise in obese sedentary to see the effects on their cardiovascular fitness. Blood pressure, heart rate, cholesterol, high density lipoprotein, triglycerides, and anthropometric measures were evaluated as the cardiac variables within the study. Participants were 35 to 45 years old. Heart rate was monitored by a Polar Heart Rate Monitor chest strap and wrist monitor throughout the exercise sessions. Aerobic exercise intervention took place three days a week for six weeks, or via exhaustion status of the subjects. The aerobic exercise sessions consisted of a warm-up with stretching and low-intensity exercises, followed by aerobic exercise that kept with 60% to 70% of maximum heart rate, and a cool down session of ten minutes. The control group did not partake in any exercise training but were asked to follow a certain diet.[101]

The results of the study indicated that aerobic exercise reduced cholesterol and low density lipoprotein levels, while high density lipoprotein levels were significantly increased and triglyceride levels lowered within the aerobic group compared to the control group. The exercise group showed a decrease in body weight, BMI, and fat percentage, and also a decrease in systolic and diastolic blood pressure. Overall, aerobic training was deemed to be beneficial to improve cardiovascular fitness via cardiac variables to help with prevention of cardiovascular disease in an obese population.[101] The breast cancer population relates to this as treatment and

sedentary behavior from consequences of treatment can have negative effects on cardiac tissue. By performing the aerobic exercise they are able to strengthen the heart tissue and allow the cardiorespiratory system to function more efficiently, help to reduce risk factors.[27,48,101]

Dieli et a al., (2018) analyzed the effects of a combined aerobic and resistance exercise program over the course of a 16 week period on metabolic syndrome—a group of conditions that increase your risk of heart disease, stroke, and diabetes. Metabolic syndrome was assessed via modified scores of waist circumference, blood pressure, high density lipoprotein levels, triglyceride levels, and glucose levels—all of which are conditions that make up metabolic syndrome.[83] The participants in the study included breast cancer survivors who were considered sedentary and also overweight or obese. Sedentary was defined as less than 60 minutes of exercise over a seven day period. The state of being overweight or obese was categorized by a body mass index of 25 or more, body fat of 30% or more, or a waist line of 88 centimeters or more. Participants were within six months post-treatment for breast cancer of stages zero to three. Subjects were excluded if they smoked, or a normal weight. A dual-energy X-ray absorptiometry was used to assess body fat, fat-free mass, and skeletal mass. PA levels were assessed by a questionnaire, and a three day dietary record was completed at pre-test, post-test, and follow-up of three months. Regular diet was asked to be maintained throughout the intervention process. Maximal oxygen uptake was also assessed using a one-stage submaximal treadmill exercise test at baseline and post-intervention time.[83]

The 16-week exercise intervention followed the American College of Sports Medicine and also the American Cancer Society exercise recommendations for cancer survivors. Subjects were randomly assigned to exercise or the usual care groups. The participants performed 150 minutes of aerobic exercise, and two to three days of weight training per week. Each week on

day one and three, a combined session of weight training and aerobic activity was performed for about 80 minutes, and on day two, aerobic exercise was about 50 minutes. Sessions were supervised and conducted in a one-on-one format with the subject and supervisor. Those who were placed in the usual care group logged and kept up their current PA routine over the 16 week study, and wore an accelerometer each day. At the conclusion of the study there were significant improvements, on obesity associated with a low lean muscle mass, and various circulating biomarkers. These improvements were maintained at the three month follow-up among the sedentary, overweight-obese breast cancer survivor population. The study's results indicated that a structured exercise program early on after post-treatment has a positive impact on survivorship. They included resistance exercise to produce an influence on lean mass and glucose metabolism. Aerobic exercise was included to help decrease waist circumference, fasting glucose, triglycerides and increase high density lipoproteins, but combining weight training and aerobic activity helped to improve metabolic syndrome and supports functional improvements in strength after the breast cancer treatment period. The study's findings reinforced the inclusion of supervised clinical exercise programs for breast cancer survivors receiving treatment, or those who have survived it.[83]

Wewege et al. (2017) conducted a systematic review and meta-analysis to look at the value of high intensity interval training and moderate intensity continuous training on body weight and composition within healthy, overweight or obese adults. The study examined both randomized controlled trials and matched controlled trial designs. Within these studies, participants were all healthy overweight (>25 BMI) or healthy obese (>30 BMI) subjects who were 18 to 45 years old. Four or more weeks of training took place with subjects being allocated to high intensity interval training groups or a matched group for comparison that performed

moderate intensity continuous training. The high intensity protocols encompassed intervals of up to four minutes in duration at 85% or greater maximum heart rate or 80% of their maximal aerobic capacity. Moderate intensity continuous training utilized 60% to 75% of maximal heart rate or 50-65% maximal aerobic capacity. Outcome measures looked at pre-testing and post-testing values of body mass and body composition including measures of: fat mass, lean mass, regional fat measures, body weight, body mass index, and circumference measures of the waist. The review concluded that high intensity interval training and moderate intensity continuous training both helped to improve body fat measures and waist circumference measures in the healthy overweight or obese adult population of the interventions.[102]

DISCUSSION

Cardiovascular health has an influence on the outcomes within cancer patients and survivors. Survivorship can be altered through the damages of cardiovascular disease. It may be of higher risk among those who undergo breast cancer treatment. Chemotherapy and radiation have toxic effect on the heart muscle and tissue.[48,49,98] In a recent study, survivors had a 7.4% increase in a cardiovascular events after the average dose of radiation. This may be due to the toxicity it has on the heart muscle therefore breaking down the tissue and altering its functionality.[98] A 23% decreased risk was found in breast cancer patients after participating in more exercise and activity utilizing exercise guidelines.[99] Exercising after the diagnosis of breast cancer was associated with a reduction in heart failure for those receiving chemotherapy.[99] Aerobic training also results in decreased cholesterol, low density lipoproteins, and triglyceride levels which have an effect on heart function.[101] By improving these variables, cardiac function is strengthened as the heart can pump blood throughout the body more effectively. A healthier heart is then apparent with the cardiovascular risk factors decreased.

When an individual is obese, more stress is put on the heart and potentially narrowed arteries. The American Heart Association's 2018 study, aerobic exercise reduced variables contributing to heart disease such as a larger waist, fasting glucose, and triglycerides, in obese breast cancer patients.[83] By improving these factors, and considering the effects of cancer treatment on the heart, it can be implied that these have a protective effect on the heart to fight against damages. Wewege et al. (2017) study's results within a healthy obese population, aerobic exercise—moderate and vigorous—both elicited improvements in body composition measures.[102] By reducing the body weight and levels of fat, this relieves stress on the heart, helping to prevent further damage from being done.

AEROBIC TRAINING AND SUPPLEMENTATION OF VITAMIN D

Breast cancer treatment can lead to bone loss, up to 80% of survivors have been diagnosed with osteoporosis or osteopenia. Peppone et al., (2018) tried to determine the practicality and tolerability of giving breast cancer survivors receiving hormone replacement therapy, a high-dose of calcitriol weekly, to determine the effect of this in combination with an exercise program on bone metabolism biomarkers. Participants who were eligible for the study were diagnosed with stage 0-III breast cancer within the last five years. This time frame was chosen as this is when patients are at greatest risk of bone loss due to hormonal therapy. The cancer had to be hormone receptor positive, and patients were actively obtaining hormone therapy.[103]

Participants were randomly placed into four groups: Group One; a weekly high-dose of calcitriol, Group Two; at-home exercise, Group Three; combination of calcitriol and exercise, and Group Four; control group that took a multivitamin with 400 IU of vitamin D and 200 mg of calcium. At baseline testing measures, subjects experienced lab tests, questionnaires, and a

fitness test. Blood draws were taken to assess serum concentrations of calcitriol, calcium, and bone metabolism biomarkers. After 12 weeks of the intervention, the same measures were taken for comparison of the baseline.[103]

Group one received one dose of 45 micrograms of calcitriol weekly and performed no exercise. Group two received an individualized exercise program that encompassed both aerobic exercise and resistance training. The aerobic exercise involved walking at 60% to 70% heart rate reserve every day for the 12 week period, the duration of the aerobic exercise was not specified. They also were asked to increase their daily step count until a maximum of 12,000 steps were reached per day while maintaining the aerobic exercise portion. The resistance training portion took place three days per week and focused on upper and lower limb muscle strength. Resistance bands were used, and subjects had an individually prescribed number of sets that encompassed seven to ten repetitions. Group three received the 45 micrograms of the calcitriol and the exercise program, while group four was the control and took the multivitamin. After the 12 weeks of the intervention was completed, elevated amounts of bone formation was indicated in the high-dose calcitriol group, which aided in increasing bone mineral density. The high amount of calcitriol and the amount of exercise was well tolerated within the groups that received it. Calcitriol significantly increased the remodeling of the bone, while exercise alone did not, which may have been because of the adherence rate to the program.[103]

Ninety-six vitamin D-deficient female subjects aged 70 or older, volunteered to be part of a study to investigate the effects of an exercise program and the supplementation of vitamin D on fitness levels over the course of nine months.[104] A higher breast cancer risk is associated with low levels of vitamin D. The subjects of this study may not have breast cancer, however they are female and vitamin D deficient.[105,106] The deficiency of vitamin D among the female participants

can be used to make inference to a population with breast cancer patients as many are deficient as well.

Participants were able to be included if they were able to perform the exercise training, had a mental state of over 20, and were not taking any of the following supplements: calcium, vitamin D, estrogens, steroids, and other drugs that could inhibit the breakdown of vitamin D in the body. Those who volunteered were given the information and informed consent, as well as had a blood draw taken in the morning to assess the level of 25(OH) vitamin D. The participants were placed into one of four groups: training-calcium, training-calcium-vitaminD, no training-with calcium, and no training-with vitamin D. Pre-testing and post-testing measures included body composition, bone mineral density, hand grip strength, isometric strength of the quadriceps, endurance measured via distance, general fitness, a body sway for balance, and a fasting blood sample.[104]

The participants who were placed in the training groups attended two sessions a week for an hour and a half of strength, balance, and endurance exercise. The strength training protocol was as follows: three intensities of chair stands, modified squats, chair step-ups, and six sets of arm pulls. The subjects used resistance bands for intensity, and performed three sets of ten repetitions. Balance exercises included tandem walking with varying difficulties added in, and balance on soft surfaces. The endurance training was incorporated before the resistance training and after, in 15 minute periods. They were asked to walk without stopping at a comfortable fast pace without becoming completely out of breath.[104]

Each month the subjects checked in and brought any leftover pills to the clinic. They were replenished new ones for the month at the time of the visit. The participants in the calcium alone and calcium-vitamin D group had a high compliance rate taking the pills at 92%, with a

standard deviation of three. The end of the study results concluded that the training increased muscle strength among the participants and the calcium-vitamin D group also had developments in bone mass. The supplementation of calcium-vitamin D improved bone density within the femoral bone, and functional capacity with and without the exercise regimen. Improved balance, walking pattern, and muscle strength was also indicated.[104] Overall, increasing vitamin D and partaking in exercise is beneficial to improving physical function and strength among those who are vitamin D deficient.

Almstedt et al. (2016) investigated the effect of 26 weeks of a combination of aerobic and resistance training on the bone mineral density on 18 women who were cancer survivors. The average age was 63 years of age, and subjects were not currently receiving chemotherapy or outpatient radiation. Weight, height, body mass index, PA level, nutritional status, and bone mineral density were measured pre- and post intervention. No control group was reported, and the 18 subjects all participated in the exercise intervention. The exercise program took place three days a week for an hour a day over a 32 week period—26 weeks of training was performed, however they followed the academic calendar as school breaks and holidays needed to be accounted for making it a total of 32 weeks. The sessions were all supervised and included 20 minutes of cardiorespiratory exercise, 25 minutes of a resistance training circuit, and 15 minutes of core exercises with stretching. The endurance exercise included walking, however if weather persisted it was moved to an indoor setting on the elliptical or bike at a heart rate of 35% to 80% of their heart rate reserved that gradually increased over time. The circuit training utilized eight upper body movements and eight lower body movements using body weight, resistance bands, and free-weights. There were no set amount of repetitions and sets, however 12 to 15 was the average among most of the participants.[107]

The results of this study indicated that there were significant enhancements in bone mineral density throughout the whole body. Lean body mass was also increased, however fat mass was maintained and not lost. Overall, the combined training regimen positively impacted this group of female cancer survivors in terms of increasing bone mineral density as a countermeasure of helping to prevent bone loss from past treatment.[107]

DISCUSSION

Supplementation of calcitriol, calcium & vitamin D, and also exercise by itself has been demonstrated at improving bone health among cancer subjects and the elderly. [103,104,107] Bone mineral density and formation was improved in all studies analyzed in this review. In three studies, (Peppone et al. 2018, Bunout et al., 2006, and Almstedt et al., 2016) a protocol of either supplementation alone or combined with exercise, or exercise alone was utilized. In all instances, bone health was improved.[103,104,107] Almstedt et al. (2016) conducted the exercise over the course of 32 weeks. Resistance training and aerobic training were performed by all participants, which resulted in significant increases in bone mineral density throughout the whole body in cancer subjects.[107] In Bunout et al., (2006) study, subjects utilized supplementation and exercise, it was demonstrated again that there were enhancements in bone density in the exercise group, as well as in the supplementation groups.[104] However, Peppone et al. (2018) concluded that the supplementation significantly increased bone formation, while the exercise alone group did not. This could have been because of the adherence rate to the program.[103] As all three studies showed enhancements in bone health, those who are undergoing cancer treatment, were cancer survivors, or others in danger of bone loss may benefit greatly from a combination of exercise and supplementation of calcitriol, calcium, and vitamin D combined. However, supplementation

may not be necessary as Almstedt et al. (2016) demonstrated that exercise alone can improve bone health.[103,104,107]

EFFECTS OF VITAMIN D ON BREAST CANCER AND FUNCTION

Vitamin D assists in keeping a healthy bone metabolism, immune function, and cellular function. Studies have suggested that low levels of vitamin D may be linked with a progressive stage of breast cancer. Shi et al. (2014) investigated the levels of 25-hydroxyvitamin D to assess vitamin D status in patients after diagnosis, as well as links between the level of vitamin, lifestyle influences, and tumor characteristics. Subjects of the study included breast cancer patients of 22 to 77 years old from China. The sample was taken from the years 1996 to 1998, with 1,044 cases, and also 2002 to 2005 with 896 cases. Levels of 25-hydroxyvitamin D were measured no more than six months after the initial diagnosis of breast cancer. Questionnaires were used to collect socio-demographics, nutrition analysis, PA levels, any smoking habits, amount of alcohol consumed, history of cancer within their family, and also a thorough medical history. Access was granted to medical charts in order to collect data on the cancer diagnosis, metastasis stage progress, and estrogen and progesterone receptor position. Information was gathered about their PA levels for about ten years pre-diagnosis, looking at the duration, length of participation in a sport or exercise, and estimation of total daily energy expenditure was calculated based on their answers. Non-exercise activities were also assessed and calculated for an estimated total daily energy expenditure.[42]

The study defined vitamin D deficiency as being less than 30 nmol/L, insufficiency as 30 to 50 nmol/L, and sufficiency as over 50 nmol/L. The results indicated that 23.2% had 25-hydroxyvitamin D deficiency and 48.4% had insufficiency. Those that were more physically active (such as using a bike for transportation), did not smoke, and were in a healthy body mass

index classification were associated with sufficient levels of vitamin D. Vitamin D deficiency was associated with a higher body mass index, a smoking habit, and those who were less physically active. The study's findings supported that vitamin D levels should be monitored in the cancer patient and survivor population, as well as taking actions to improve vitamin D status may be beneficial to breast cancer survivors.[42]

In 2007, total consumption of calcium and vitamin D were assessed from both supplements and food sources relative to risk of breast cancer within a pre-menopausal and post-menopausal population of women. A total of 10,578 pre-menopausal and 20,909 post-menopausal women who did not have cancer or cardiovascular disease were used in the study and filled out a questionnaire about medical history and lifestyle choices over the past year. The questionnaire included information regarding the use of a calcium supplement, multivitamins, and food items. Duration of use, dosages, serving sizes, and amount of servings were assessed within the responses as well. Questionnaires were given at the first and second, six month mark, and then every year after that as part of the follow up protocol. Within these questionnaires, participants reported if they had been diagnosed with breast cancer. Over the course of the ten year follow-up period, 276 pre-menopausal women were diagnosed, and 743 post-menopausal women were diagnosed with breast cancer. The study concluded that women with higher consumption of calcium and vitamin D were at a lower risk of breast cancer, especially those premenopausal women with aggressive tumors.[108]

Hines et al. (2010) conducted a review of literature on vitamin D and breast cancer on the relationship of vitamin D and breast cancer survivors. One study indicated that women who had cancer had lower levels of 25-hydroxyvitamin D compared to the control group. Those that had about 53 nmol/L had a 50% reduced risk of developing breast cancer than those whose serum

levels were lower than 13 nmol/L. Another study revealed that vitamin D may have an important job in intiating an immune system response. A very powerful activating factor of macrophages (Gc: vitamin D3 binding protein--Gc macrophage activating factor) was looked at with its effect on metastatic breast cancer patients. The study treated the patients every week with the Gc macrophage over the course of five months. Over time, their levels of the Gc protein increased, and there were no recurrences of breast cancer reported for at least four years. Therefore, this study suggested that vitamin D could have a crucial role within the immune system by initiating an immune response to attack cancer cells. Overall, this review indicated that vitamin D may help to positively impact events at a cellular level within the overall projection and survival of cancer. The study also reported that in many studies reviewed, there was a high occurrence of vitamin D deficiency in the breast cancer populations examined. Being vitamin D deficient (less than 30 nmol/L) may worsen the effects of cancer treatment such as weakening bones, increased depression, and fatigue.[109]

In 2019, Robsahm et al., performed a study to examine the relationship of cancer fatality and serum levels of 25-hydroxyvitamin D. Pre-diagnosis, time of diagnosis, and changes within levels of pre-diagnostic and diagnostic serums were assessed. Subjects donated samples between 1973 and 2004, and those who developed cancer gave a second sample at the point they were diagnosed. Of the second samples that were given, 202 of them were from patients diagnosed with breast cancer. The serum 25-hydroxyvitamin D levels were assessed with a radioimmunoassay to then compare pre-diagnosis and diagnosis samples. The study concluded that serum levels of 25-hydroxyvitamin D, that were less than 46 nmol/L at the time of diagnosis and pre-diagnosis, had a greater mortality compared to those with higher levels in different cancer cases. Survivors had a higher level of 25-hydroxyvitamin D closer to diagnosis. These

findings suggest that there is an association between higher vitamin D levels and a decreased cancer case morality within not only breast cancer cases, but other cancers as well.[40]

A secondary analysis of breast cancer survivors conducted in 2019 comparing those who sought naturopathic (553 patients) and non-naturopathic (360 patients) oncologists to supplement their treatment, examined the role of vitamin D. The analysis looked at the number of breast cancer patients who supplemented with vitamin D during their course of treatment, the levels of the supplement consumed, and also the effects of the vitamin D use. A questionnaire was given to assess supplement use and health related quality of life, and patients gave consent to release medical records for data collection. The analysis reported that supplementing with vitamin D is common during cancer treatment. Those who were not deficient with blood levels of vitamin D and taking a vitamin D supplement were associated with better health related quality of life. Elevated levels of vitamin D supplement use at the half year mark were associated with a decreased degree of deficiency. However it is unclear how vitamin D levels of 30 nmol/L is associated with health related QOL, but it was found that slight positive developments took place in health related QOL in patients with a naturopathic physician.[106]

Even those that are typically sufficient in vitamin D may experience lower amounts of it in the body during seasons lacking sun. This can be detrimental to the healthy and deficient populations. Aydin et al. (2019) investigated the effects of seasonal changes on indoor and outdoor sports with associated vitamin D levels in athletes.[54] As getting enough vitamin D is important among breast cancer survivors, this study can be used to make inference to the effects of different seasonal environments effects on vitamin D concentrations. This then can help guide what to do in seasons and environments with less sunlight to make vitamin D endongenously. Vitamin D measurements of athletes from a variety of sports within different seasons was

assessed to look at if the production of vitamin D is effected according to environment or season. Five hundred and fifty-five participants ages five to 52 years old, took part in the study from September 2014 to February 2015. The participants were free from any malignancy, diabetes, cardiovascular disorder, thyroid or parathyroid dysfunction, and joint disease. Non-fasted blood samples were taken from participants in the morning, and they had not participated in exercise for 24 hours prior to the collection. This collection was taken at pre-and post-testing. Indoor and outdoor sports were assessed in this study, the winter season was shown to have a negative impact on vitamin D levels. It was found that the latitude the countries were located in played a large role, those in the 37th parallel north did not receive as much adequate sunlight during the winter months (November to February). This was assumed to lead to a decrease in production of vitamin D in this time of the seasons. It was concluded that athletes should increase their vitamin D levels during the winter months to help maintain best performance outcomes. Therefore, this study shows that winter months have a negative impact on vitamin D levels, and supplementation may be needed to keep an adequate amount in the blood.[54]

DISCUSSION

A higher consumption of vitamin D and calcium have been associated with a lower risk of breast cancer in pre-menopausal women.[108] Hines et al. (2010), revealed that women with breast cancer had lower levels of 25-hydroxyvitamin than those who did not. Breast cancer survivors who had sufficient vitamin D levels are at a lower risk than those who were insufficient. Part of this could be because vitamin D sufficiency has beneficial effects on the immune system. Cancer survivors need as treatment and the disease compromises their immune system.[109] Vitamin D has shown to have a role in activating macrophages to protect the immune system, this allows the body to fight against infection.[109] Vitamin D3 binding protein influenced

a lower recurrence rate in metastatic breast cancer patients when they were treated with it over the course of five months. This could have a role in attacking cancer cells to prevent the proliferation and recurrence of carcinogenesis.[109] Robsahm et al. (2019), demonstrated that there was a decrease in mortality among those who had higher levels of 25-hydroxyvitamin D close to the diagnosis of their breast cancer.[40] Risk fatality and reoccurrence seem to be associated with levels of 25-hydroxyvitamin D, with higher levels eliciting beneficial effect. This may be because of the role vitamin D has on activation of an immune response to protect against foreign invaders[40,109] Increased risk of mortality and recurrence rate are not the only health factors related to levels of vitamin D, a better QOL is also effected and enhanced when blood levels of vitamin D are sufficient. Deficiency in vitamin D can lead to depression, musculo-skeletal pain, fatigue, and being more prone to sickness and infection.[106] Environment and season have an influence on levels of vitamin D. Those who live in areas with long winters and little sunlight may be at a higher risk for deficiency.[54] Breast cancer survivors should take advantage of summer months and perform as much PA and moderate exercise as they can outside to obtain vitamin D from sunlight and also to have the restorative effects of nature to combat depression and decrease risk of cancer.[54,70,105] During winter months, or in areas with less sunlight, supplementation with vitamin D may be beneficial to keep up levels, especially if diet is not adequate. This may benefit the immune system and mental-emotional well-being.[54,70]

The suggestion that vitamin D plays a role aiding in the protection of the immune system and lowering the risk of breast cancer may be because it helps to fight against the damage cells leading to disease. Vitamin D's protection against the repercussions of cancer on the body, when combined with calcium, is important for musculoskeletal strength. As treatment weakens the individual, supplementation with these can help to restore bone mineral density and rebuild bone

itself. Having sufficient amounts of vitamin D in the body system can help to combat depression and fatigue, both factors that negatively impact QOL and greatly affect cancer survivors.[104,107,109]

PSYCHOLOGICAL QOL OUTCOMES WITH CANCER AND TREATMENT

Being diagnosed with breast cancer is extremely taxing on emotional, social, and physical health. Tojal and Costa (2015) investigated if signs of depression were prevalent in women with breast cancer. Looking at the relationship of depressive signs, demographic, clinical variables, and the association of mental alteration to cancer with signs of depression were the key measures. A total of 150 portuguese women diagnosed with breast cancer agreed to participate in the study. About 85% of the participants had been diagnosed with cancer in the past 18 months, and approximately 14% had been diagnosed for 19 or more months. The age range for the subjects varied from 20 to 79 years of age, with half of the participants in a marital relationship, 72% having a high school diploma, and about 28% graduating university. The subjects answered questionnaires while they were being hospitalized for treatment for breast cancer. A socio-demographic questionnaire was used, as well as the Mini Mental Adjustment to Cancer Scale, and Beck of Depression Inventory. The Beck Depressive Inventory used a scale indicating that a score a less than 13 was not indicative of depressive symptoms, between 13 and 19 displayed some, and a score of 20 or more was categorized as clinically significant.[110]

The study's analyses to assess if the occurrence of depressive indicators within a breast cancer population, as well as assessing the relationship between the depressive indicators and mental alteration concluded that there was a high occurrence of depressive symptoms within this population of women. Over 50% of the participants in the study fell into the clinically significant depressive indicators, and less than one-fifth of the study had no depressive symptoms indicated. In this study, those with a lower level of schooling, and those that are married or living with a

significant other were at a higher risk of developing signs of depression. The relationship between mentally adjusting to the diagnosis and depressive indicators was significant. The women who decided to receive treatment to fight the disease and kept a positive mindset, had less prevalence of depression. Tojal and Costa (2015) concluded that those diagnosed may benefit from stress management, psycho-social support, and positive thinking may elevate coping abilities with the disease.[110]

The cognitive function of breast cancer survivors is a priority post-treatment in an effort to keep a high QOL. Cognitive function was assessed in a total of 107 women in a study with breast cancer patients (three years post-diagnosis) and healthy-matched controls to assess the if post-menopausal women treated with adjuvant tamoxifen experienced change in their cognitive abilities. Eligibility criteria for breast cancer subjects was as follows: female, underwent surgery with or without radiotherapy and adjuvant tamoxifen or women who only had surgery with or without radiotherapy. The adjuvant tamoxifen users had to have been treated with this for at least one year with no change in endocrine therapy. Exclusion criteria included the following: received adjuvant chemotherapy, diagnosed with a psychiatric disorder or central nervous system disorder that affects cognitive function, or had signs of dementia. The healthy controls had the same exclusion criteria with an additional inclusion factor which was having no history of breast cancer.[111]

The study's assessment took place at the home of the subject or at the Cancer Institute in the Netherlands. In depth information about medical history and background was provided from the subjects throughout a systematized interview. It took about two hours to fill out the questionnaires and neuropsychological exams in a specified order. Those who underwent adjuvant tamoxifen treatment scored worse on verbal memory compared to those who had only

undergone surgery or radiotherapy, and also with the control group. The study concluded that post-menopausal breast cancer patients who were treated with selected estrogen receptor modulators were at a higher risk of cognitive deterioration. Verbal function such as verbal articulacy and memory was at a high risk of decline for those being treated with tamoxifen.[111]

Heidari and Ghodusi (2015) investigated whether there was a relationship between appreciating the body, hope, and mental health in females who had a mastectomy because of a breast cancer diagnosis. One hundred breast cancer patients who underwent a mastectomy took part in the study. Over 50% of the subjects were age 50 to 70 years old, 71% were of marital status, 32% graduated high school, 33% indicated a past abortion, and 17% had experienced cancer in other organs as well. The following tools were used to assess the variables: Body Esteem Scale, Herth Hope Index, and Symptom Checklist 25 mental health survey. The results indicated a low level of body self-image esteem, and the relationship between body image, hope, and mental health was considered to be linear. Therefore, alongside treatment, the study suggests that mental-emotional support may play a crucial role after the invasive surgery.[112] Other mental support systems such as activities improving overall psychological status may be beneficial as well.

Fong et al. (2017) investigated that the path and degree of transformation in attribute and amount of social support, as well as the degree of these variables effecting a transformation in emotional well-being throughout the first year after breast cancer treatment. A total of 201 women aged 28 to 79 years old, who completed chemotherapy, radiation, or both for their initial breast cancer therapy less than five months before the start were studied. About 75% of the subjects had stage I or II cancer, and the diagnosis was less than a year before the start of the study. Participants signed a consent form and were asked to complete questionnaires at the start,

and every three months over the course of one year for the duration of the study. The social support questionnaire investigated listening and emotion support, task challenge, tangible assistance, and the understanding of breast cancer. Emotional well-being was described by signs of depression, stress, and positive and negative affect. The analysis of the questionnaires concluded that total social support decreased over a one year time period, but the quality of support given, stayed the same. The decline in amount of social support was related to an increase in depression, stress, and negative affect. Results of this study indicated that post-treatment, breast cancer survivors should have an abundant, high-quality, social support system.[113]

Triple negative breast cancer patients have a poorer prognosis than a non-triple negative breast cancer patients because of the occurrence of metastasis of the cancer. Watkins et al. (2017) investigated differences in coping mechanisms among women with different types of breast cancer.[114] The subjects of the study were African American, as women with triple negative breast cancer are commonly found in this population. The aim of the pilot study sought to determine any psychological distress, symptomatic, and coping capacity differences, as well as coping abilities, and spiritual well-being within the non-triple negative, and triple negative breast cancer patients. Thirty African American women over the age of 18, who were scheduled to receive any type of chemotherapy combination were used in the study. The only exclusion criteria included any type of mental confusion, or if they were not able to complete the questionnaire via instructions. The study utilized several survey instruments to analyze their variables. The Hospital Anxiety and Depression Scale was used to identify depression and anxiety signs. The Pain-O-Meter was used to assess the intensity of the pain the patient experienced. The European Organization for Research and Treatment of Cancer Quality of Life

Questionnaire-Core 30 assessed cognitive function, emotional function, nausea, fatigue, and vomiting. Coping capacity was assessed via the Sense of Coherence questionnaire, and Coping Strategies Questionnaire was used to evaluate coping strategies. Any type of religious coping mechanisms was surveyed via the Brief Religious Coping Inventory, and the Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being analyzed spiritual well-being.[114]

Before the start of their initial chemotherapy care, the subjects completed a demographic survey. Patients then completed the questionnaires at the start of chemotherapy, mid-point, and at the completion of chemotherapy. The surveys were completed and turned in within one week of completion. The study found that patients who did not have triple negative breast cancer experienced a higher intensity of pain, nausea/vomiting, better emotional functioning, lower cognitive functioning, and used more spiritual-religious tactics such as prayer, hope, and self-statements. The triple negative group results gave a lower capacity of coping score and was related to psychological pain at mid-point Both groups had an increase of optimistic religious coping. The study concluded that women with triple negative breast cancer and non-triple negative breast cancer may benefit from receiving a comprehensive psychological care program in order to decrease mental-emotional stress, and increase coping mechanisms.[114]

A mastectomy can take away a patient's sense of femininity and create a traumatic psychological occurrence. Berhili et al. (2019) conducted a study to assess if a radical mastectomy has an effect on psychological distress within breast cancer patients. The aim was to establish any factors that produce a psychological distress within breast cancer patients. The type of procedure and the onset of anxiety and depression were the outcomes of interest. Patients in Morocco who were 45 years old or younger, with a localized cancer, and either had a radical mastectomy or conservative surgery, and a suggestion for adjuvant chemotherapy, were used as

subjects. Those who had a locally advanced, or metastatic form of breast cancer were not used, as well as anyone who had more than a third round of adjuvant chemotherapy in order to avoid any side effects of the therapy on a patients' mental state. With this criteria, 122 female breast cancer patients underwent the study. Data of socio-demographic and clinical respects were collected from the subjects. A Hospital Anxiety and Depression Scale was used to look at psychological standing, which then formed a regression within analysis to establish the level of psychological distress. Conclusively, the study determined that the type of procedure the patient undergoes surgically is a large determinant of psychological status in. The social factors in the lives of a patient were also a determinant. The Hospital Anxiety and Depression Scale gave a result of 33.6% having a score indicating psychological distress within the patient's life from the surgery. Within that 33.6% was a total of 41 patients, with 31 of those patients having undergone the radical mastectomy. The patients that underwent the mastectomy had a higher risk of developing psychological distress than those who had a more conservative surgical approach. The results concluded that efforts need to be made to improve psychological screening screening in third world countries, so breast cancer survivors living and being treated there have options for life-saving conservative approaches.[115]

Negative feelings occur after a woman has a mastectomy performed, such as unpleasantness, anger, guilt, or sadness, also known as negative affect. A recent study sought to investigate how various characteristics of post-surgery body image predicts negative affect six months after mastectomy in breast cancer patients. Three-hundred and ten breast cancer patients who received a mastectomy, between the age of 20 to 70 years old, were subjects. They were without a psychiatric illness, did not have a family history of any disorders, without any diseases except for breast cancer, and they were not undergoing any chemotherapy during the collection

period. They also had no history of drug abuse, and were able to read and understand the surveys given. The Hamilton Anxiety Scale, Hamilton Depression Scale, Body Image After Breast Cancer Questionnaire, and the Negative Affect Subscale of the Positive and Negative Affect Schedule were used as tools of measurement. They were administered, two weeks post-mastectomy. Two weeks after the baseline administration, 32 subjects selected at random were given the assessment again. Six months after the baseline assessment was given, 251 subjects completed the Negative Affect subscale. Vulnerability and body image were the two aspects that had an effect on the negative affect among patients that underwent breast removal.[116] Negativity affect body image therefore negative affects a patient's overall quality of life.

Breast cancer in non-developed countries is higher than in developed countries. In Ghana, breast cancer is a very common form of cancer that is primarily diagnosed within the advanced stages of the disease process. A 2019 study investigated if cancer-specific managing tactics had a significant impact on the quality of life in the women of Ghana, who were living with breast cancer. A total of 205 breast cancer patients were used in the study, the age of the subjects ranged from 20 to 80 years old. Inclusion criteria included: being diagnosed with breast cancer for the first time in their life, and for a period of six months or longer, and also receiving treatment for breast cancer only. The study collected measures of demographics, mental health, and a functional evaluation. The Mini Mental Adjustment to Cancer questionnaire evaluated the ways they coped with the disease, assessing the adjustment to their illness. The Functional Assessment of Cancer Therapy—Breast Cancer, evaluated the quality of life within the subjects with measures of emotional, social & family, physical, and functional well-being. Other breast cancer related concerns were also appraised within this questionnaire.[117]

The results of the demographics questionnaire revealed that 139 participants indicated being currently married, 125 were employed, 99 had a monthly income less than 500 in Ghana Currency which amounts to about $113 US dollars. The type of patient care that was the highest reported indicated 84 subjects undergoing surgery, chemotherapy, and radiotherapy, with the next highest mode of care being chemotherapy only. The average period of disease duration from the point of diagnosis was over two and a half years.[117]

The results of the questionnaires indicated a positive relationship to the point of diagnosis with emotional and functional well-being within the realm of QOL. The duration of the disease affected the relationship with QOL measures, more than the age of the patient at diagnosis, the researchers reasoned that this could potentially be due to acceptance of the disease over time compared to those who are freshly diagnosed and haven't had as much time to cope with it. This then indicates those who have had the disease longer have a decreased level of anxiety compared to those with a fresh diagnosis of breast cancer, however, this finding does contradict other studies. Noteworthy negative associations were detected with helplessness-hopelessness and four of the QOL realms, but not within the social and family well-being realm. Anxiety was negatively associated with all realms of QOL measures, while fighting attitude was positively related to the emotional and function well-being realms. The cognitive evasion was positively associated with functional welfare, and fatalism was positively connected with all the realms of the QOL measured. These findings were in support of previous findings in other studies that discussed coping mechanisms on QOL. Coping strategies used have a major impact on the QOLwithin the women of Ghana living with breast cancer, which highlights the necessity to confront the psychosocial issues amid breast cancer patients. The relationship between the subjects and their belief of fate indicated religious beliefs may have been responsible for positive

outcomes of realms within QOL, therefore the sociocultural aspects in the life of breast cancer survivors should receive further investigation.[117]

Velikova et al. (2018) performed a substudy from the SUPREMO trial looked at the effects of using radiotherapy and a mastectomy as therapy for breast cancer as it wasn't clear on the outcomes of the two combined on the mental-emotional aspects for the patients.[118] As receiving radiation therapy after a mastectomy is considered to be a superior method of treatment to decrease the reccurrence of the disease and chance of death, it still causes symptoms that interfere with daily living of those treated. The study conducted aimed to investigate the effects of radiotherapy after a mastectomy procedure on QOL outcomes such as: comprehensive QOL, exhaustion, physical function, symptoms of the chest, shoulder, and arm (ie: feelings associated), body image, anxiety and depression.[118] These were investigated at one, two, five, and ten years post-treatment. This study examined the 2 year results. Women over the age of 18 with breast cancer and the following qualifications were eligible for the study: had a unilateral mastectomy, had intermediate risk of breast cancer, had an axillary lymph node dissection, and were able to have surgery, radiation or both. Those who had a concurrent malignancy, ductal carcinoma in situ, breast cancer in both breasts, were pregnant at the time of radiation treatments, or male were excluded. [118]

The women were randomly put into either the post-operative chest-wall radiation or no chest-wall radiation.[118] Those who were receiving chest-wall radiation received it after they received chemotherapy, if the chemotherapy was part of their treatment plan. The following doses were considered to be equivalent to each other for the course of the treatment: two, 25 Gy doses daily for five weeks; two, 20 Gy doses daily for four weeks; and two, 15 Gy doses daily for three weeks. The researcher also gathered data to assess cardiovascular factors, radiation

exposure to the heart and lungs, systemic therapies, and any type of reconstructive surgery. The QOL was assessed via the European Organization for Research and Treatment of Cancer (EORTC), body image was assessed by the Body Image Scale, Anxiety and Depression were assessed using The Hospital Anxiety and Depression Scale, and the EQ-5D-3L was used to look at health status according to mobility, self-care, daily activity, pain or discomfort, and anxiety and depression. The examination found that those who had post-mastectomy radiation treatment were related to a worse self-reported chest-wall symptoms of pain, swelling, sensitivity, and skin problems compared to those who did not have radiation done. However, it was reported that these symptoms did get better as time went on.[118]

DISCUSSION

Being diagnosed with breast cancer takes a toll on emotional, social, and physical health. In Tojal and Costa's (2015) study, 50% of the subjects were considered to have clinically significant depressive markers according to the surveys they answered during treatment.[110] Issues with cognitive function are associated with cancer treatment, especially those who are being treated with estrogen receptor modulators. Verbal articulacy and memory were at a high risk of deterioration from tamoxifen treatment.[111] It was suggested that estrogen has a role to establish the balance of kynurenic acid in the brain. If there are too low of levels of kynurenic acid then a risk of depression or a mental disorder may be apparent.[97] The low levels of kynurenic acid (a tryptophan metabolite) indicate a potential tryptophan deficiency, and in combination with low levels of estrogen, serotonin production is reduced even more, which in turn can lead to depression.[97,111]

Patients who were treated by mastectomy indicated poor levels of body-image, hope and mental health.[112] Support is critical for those undergoing all types of treatment, however Fong et

al. (2017) reported that support declines after a one year time period. Due to this decline, an increase among depression, stress, and negative mood was apparent in the breast cancer patients.[113] A mastectomy takes away a piece of femininity from the patient leading to traumatic psychological distress.[115] Different types of cancer seem to produce more negative affects compared than others. Triple negative cancer patients reported a lower capacity of a coping score that was related to psychological pain than those without triple negative cancer.[114] Those who have a type of breast cancer with a poorer prognosis than other types, seem to experience and have less coping mechanisms for the psychological pain. Attributing this lower capacity of coping to a lower hope score and negative affect state as well, a support system is crucial to try to keep spirits up. The treatment type also plays a role in the psychological pain of the patient, those who had a mastectomy versus a more conservative approach had a superior risk of developing psychological distress.[115] In conclusion, the diagnosis and treatment of cancer has been shown to have a psychological and physical toll on patients.

CHAPTER THREE

CONCLUSION

In conclusion, moderate aerobic exercise—performing at 40% to 59% of maximum heart rate—can be beneficial to cancer survivors in regards to physiological and psychological well-being.[52,53,63] Exercise environment has an effect on mood state among aerobic exercisers, although both indoor and outdoor settings elicit positive effects, compared to no exercise. Outdoor environments stimulated greater positive affective responses when walking than indoor environments.[65] Running in the outdoor environment produced positive changes among anxiety, depressive symptoms, and hostility. Performing aerobic exercise in an environment rich in greenery can invoke positive changes in physiological and psychological states.[70–72] Moderate aerobic exercise upregulates the production of antioxidants which in turn helps to create a balance of antioxidant to ROS ratio.[87] These upregulations fight the repercussions of oxidative stress that can damage cells and lead to cancerous mutations of organelles.[17,87] Aerobic exercise can also help to reduce the risk of cardiovascular disease and improve health in obese individuals by lowering inflammation implicated from oxidative stress, lowering triglycerides, fasting glucose, and helping with weight loss. As cancer treatment effects the heart tissue by weakening it, it is important to strengthen the muscle through aerobic exercise.[83,102]

The role that aerobic exercise has on estrogens and estrogen metabolites should be investigated more as alterations in estrogen levels were not consistent among the literature.[94] However, it is important to consider that higher amounts of body fat are related to high estrogen

levels as testosterone is converted within the adipose tissue to estrogen, which then increases risk of breast cancer.[119] Performing exercise can help to decrease body fat through an increased energy expenditure, which in-turn can aid in inhibiting the conversion of testosterone to estrogen, and reduce risk of breast cancer.[94,119]

The kynurenine pathway can be controlled and elicit positive outcomes when moderate exercise is performed. It activates the production of kynurenic acid through the metabolism of kynurenine because of the expression of enzyme kynurenine-aminotransferase in working skeletal muscle. The exercise causes free fatty acids to attach to albumin, the tryptophan is pushed off the albumin into the bood, which inturn increases tryptophan levels within the blood. This is then metabolized into kynurenic acid, which decreases the activity of tumor stimulation and enhances positive mood state.[35,38,59] The immune system is also improved through moderate aerobic exercise as inflammatory factors are improved and different immune cells are upregulated, such as NK cells, which aid in tumorigenic cells termination.[89] Vitamin D helps to activate macrophages, which helps the immune system of the cancer survivor to fight off disease. Cancer survivors should make sure they have adequate levels of this either from getting enough vitamin D from the outdoors, or if they are deficient from diet or seasonal aspects, they should consider supplementing. Performing aerobic exercise and supplementing with vitamin D has shown benefits to improving bone mineral density among cancer patients and survivors, this is critical to health as treatment can have a negative impact on the bone mineral density.[103,104,107]

As being diagnosed with cancer takes a toll on emotional, social, and physical health, it is important to find ways to help elicit positive outcomes to counter the negative effects of treatment.[110] Aerobic exercise has been shown to improve physiological function, reduce risk factors for the development of cancer, and enhance positive mood states. An individual's mood

state may be further affected depending on their exercise environment. When looking at the effects of indoor versus outdoor exercise, the psychological state was improved more in the outdoor-greenery environment compared to an indoor setting.[70–72] Although studies on the effects of indoor versus outdoor exercise on estrogen, kynurenine, and vitamin D among breast cancer survivors is not well studied, it may be beneficial to investigate this through interventions in the future. Overall, moderate aerobic exercise elicited positive effects on physical and mental health.

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APPENDICES

APPENDIX A

From: **Janelle Taylor** jantaylo@nmu.edu
Subject: Modification Approval: HS19-1047
Date: October 17, 2019 at 9:55 AM
To: Emily Ferroni eferroni@nmu.edu, Elizabeth Wuorinen ewuorine@nmu.edu
Cc: Derek Anderson dereande@nmu.edu, Lisa Schade Eckert leckert@nmu.edu

JT

MEMORANDUM

TO: Emily Ferroni
School of Health and Human Performance

CC: Elizabeth Wuorinen
School of Health and Human Performance

FROM: Lisa Eckert
Dean of Graduate Education and Research

DATE: October 17, 2019

RE: Modification to HS19-1047
Original IRB Approval Date: 5/30/2019
Modification Approval Date: 10/17/2019
"The Physiological and Psychological Effects of Indoor Versus Outdoor Aerobic Exercise in Female Cancer Survivors"

Your modifications to the project "The Physiological and Psychological Effects of Indoor Versus Outdoor Aerobic Exercise in Female Cancer Survivors" have been approved under the administrative review process. Please include your proposal number (HS19-1047) on all research materials and on any correspondence regarding this project.

Any additional personnel changes or revisions to your approved research plan must be approved by the IRB prior to implementation. Unless specified otherwise, all previous requirements included in your original approval notice remain in effect.

If you have any questions, please contact the IRB at hsrr@nmu.edu.

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