Physiological Factors Impacting Fitness in Breast Cancer Survivors

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

FIGURE PAGE

LIST OF ABBREVIATIONS

ATP	Adenosine triphosphate
BMI	Body Mass Index
CO	Cardiac Output
CO_2	Carbon Dioxide
CRF	Cardiorespiratory Fitness
CVD	Cardiovascular Disease
DNA	Deoxyribonucleic Acid
eNOS	Endothelial Nitric Oxide Synthase
FEV1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
Hb	Total Hemoglobin
HbO2	Oxygenated Hemoglobin
HR	Heart Rate
HER2	Human Epidermal Growth Factor Receptor 2
HHb	Deoxygenated Hemoglobin
LVEF	Left Ventricular Ejection Fraction
MET	Metabolic Equivalent
MVV	Maximum Voluntary Ventilation
NIRS	Near-Infrared Spectroscopy
O_2	Oxygen
OUES	Oxygen Uptake Efficiency Slope
SV	Stroke Volume

TOI	Tissue Oxygenation Index
V_E	Minute Ventilation
V_E/VCO_2	Ventilation/Carbon Dioxide Production

Chapter I

A. Introduction to the Problem

Breast cancer is the most common type of cancer in the United Sates, with nearly 1 in every 8 women developing invasive breast cancer over the course of her lifetime (57). According to 2019 United States estimates, 316,700 new cases will be diagnosed among women and 41,760 women will die from breast cancer per year (57). In addition, breast cancer survivors are at increased risk of cardiovascular disease (CVD), in part, due to the side effects of cancer therapies (144). The importance of exercise in improving mortality rates and decreasing CVD has been extensively documented in the literature; however, breast cancer survivors tend to have much lower (~22%) cardiorespiratory fitness (CRF) compared to age-matched healthy individuals (25, 113, 161). This is very critical since CRF is a major predictor of all-cause mortality and CVD in the general population (222), but also a major predictor of morbidity and mortality in breast cancer survivors (113).

CRF is explained by cardiac, pulmonary, and/or skeletal muscle factors and previous research has shown cancer treatments could affect these physiologic factors. First, cardiac function can be affected by drugs used in chemotherapies for breast cancer survivors that induce cardiomyocyte injury (147), and eventually impair contractility of the heart. As a result, stroke volume and cardiac output during exercise can be lower, thus potentially lower CRF as well. Second, pulmonary function can be weakened by chemotherapy, but also by radiation therapy, another common therapy in breast cancer survivors, causing decreased lung perfusion and inspiratory capacity (92, 132, 205). Therefore, pulmonary function might be impaired during peak exercise in breast cancer survivors compared to a healthy control group. Third, skeletal

muscle function could be altered by cancer treatments. For example, doxorubicin, a drug used in chemotherapies, alters mitochondrial integrity and function via increased oxidative stress (212), which can lead to significant alterations in glycolysis and fatty acid oxidation (108). Therefore, chemotherapies may cause impairment in muscle function during exercise leading to early fatigue (212) and low CRF. Taken together, cardiac, pulmonary, and skeletal muscle dysfunction caused by cancer treatments likely have a negative effect on CRF in breast cancer survivors; however, this is still unclear given these physiological factors have been understudied in this population, in particular during acute exercise.

Initially, reduced aerobic capacity in breast cancer survivors was mainly attributed to cardiotoxicity caused by certain cancer therapies (153, 227); however, recent studies have shown impaired CRF does exist in breast cancer survivors with normal left ventricular ejection fraction, suggesting that other components may also contribute to impaired oxygen transportation and utilization (25). Additionally, previous studies have evaluated cardiac (153) and pulmonary function (132) in breast cancer survivors under resting conditions, which may not reveal abnormalities. An acute stressor (37), like exercise, has been recommended as a better indicator of cardiac dysfunction, as well as other physiological systems of the body (e.g. pulmonary). Several studies have previously examined cardiac function in breast cancer survivors during exercise and reported conflicting results (12, 75, 115, 123).Therefore, it follows other factors could impair peak oxygen uptake (VO_{2peak}), the gold standard measure of CRF. Moreover, only one study (155) evaluated pulmonary function at peak exercise in breast cancer survivors, and reported lower inspiratory capacity compared to a control group. This suggests pulmonary abnormalities may also physiologically impact CRF in this population. However, no study has examined all major physiologic factors during exercise among breast cancer survivors.

Therefore, the overall aim of our study was to determine what physiological factors limit CRF in breast cancer survivors. We tested this with three specific hypotheses. The first hypothesis was to determine if breast cancer survivors would have an attenuated increase in **cardiac output** (using heart rate and stroke volume) at peak cycling exercise compared to healthy controls. The second hypothesis was to evaluate if breast cancer survivors would have attenuated markers of **pulmonary function** (using oxygen uptake efficiency slope (OUES) and ventilation/carbon dioxide production (V_E/VCO_2 slope)) at peak cycling exercise compared to healthy controls. The third hypothesis was to determine if breast cancer survivors would have attenuated **muscle oxygenation** (using oxygenated and deoxygenated hemoglobin) at peak cycling exercise compared to healthy controls.

B. Significance and Relevance of the Research

Approximately one in every eight women develops breast cancer over the course of her lifetime (57). In 2001, the overall economic burden of breast cancer in the U.S. was $15–20 billion (172). In 2016, there were an estimated 3,477,866 breast cancer survivors in the U.S. (103), with the estimates of lifetime per-patient costs of breast cancer ranging from $20,000 to $100,000 (27). Given that breast cancer survivors are at increased risk of CVD (144), and that CRF is a major predictor of CVD (222), identifying physiological factors that impact CRF in this population is very crucial. Although previous studies have reported low CRF in breast cancer survivors (25, 113, 161), the exact physiologic factors are not well delineated at this time in the literature.

This proposed study will examine three potential contributors to lower CRF in breast cancer survivors: a) cardiac, b) pulmonary, and c) skeletal muscle function. The findings of our study will help us to better understand what limits fitness in breast cancer survivors. Thus, the

results of our study will help us in developing more appropriate lifestyle, exercise guidelines and behavioral interventions to improve or prevent reductions in CRF in this population. As a result, this study will provide important information in reducing all-cause and CVD mortality in breast cancer survivors.

Chapter II: Literature Review

A. Breast Cancer Epidemiology

Global health data have reported high breast cancer incidence rates, and also forecast continued high incidence rates (46). According to epidemiological studies, there are more than 400,000 breast cancer deaths and one million breast cancer diagnosis every year (46). It is estimated there are approximately 3 million breast cancer survivors in the United States (52), and the annual incidence of breast cancer worldwide will reach 3.2 million by 2050 (102). Interestingly, an epidemiological study reported that low- and middle-income countries had experienced a drastic increase in the incidence of breast cancer and almost 75% of women were diagnosed with stage III-V breast cancer, as a result of unavailable resources for routine screening (46). In contrast, approximately 70% of newly diagnosed breast cancer cases were in stages 0 and I in North America (46). Even if resources for routine screening are available in developed countries compared to developing countries, incidence rates are higher, with North America having 92 cases per 100,000 (149).

As a result of the high incidence rates of breast cancer, the cost of breast cancer care is inevitably very high as well. The substantial economic burden of breast cancer is due to the high direct, but also high indirect, medical costs of this disease (27, 201, 225). In 2010, the costs across all cancer survivors in the United States were $124.5 billion dollars, with the highest costs specifically for breast cancer at $16.5 billion (225). With regards to indirect costs, almost $3.13 billion is annually estimated for losses associated with time spent receiving medical care, morbidity costs, and mortality costs (172). Interestingly, the total cost for cancer care is estimated to approach $172.8 billion dollars in 2020 (a 39% increase from 2010), whereby

survival, costs and decreasing incidence (225). Therefore, the economic cost of breast cancer care contributes to the total burden of this disease and will progressively increase in the following years.

Along with the high incident rates and medical costs, breast cancer has high mortality rates as well. Even if therapeutic and diagnostic methods have improved survivorship over the last decade, approximately 41,760 deaths were expected in the United States by the end of 2019 (57). In 2012, breast cancer was the most common cause of death in less developed countries, the second cause of death in western societies, and the fifth leading cause of cancer death in worldwide, with approximately 324,000 deaths/year worldwide (149). Moreover, breast cancer has been documented as the second leading cause of cancer-specific death (15.4% of all deaths) in developed countries after lung cancer (71). Although new therapeutic methods have improved breast cancer care, mortality rates in European Union countries are expected to increase by the end of 2020, based on a research that evaluated changes in the time trends of breast cancer mortality rates during the period 2000–2010 (39).

A significant contributor to high mortality rates in this disease is the fact that breast cancer survivors tend to have additional clinical conditions before or after cancer treatment. Breast cancer patients have a high prevalence of different comorbidities, such as hypertension (22%), chronic obstructive pulmonary disease (20%), rheumatologic disease (19%), and diabetes mellitus (17%) (188). Interestingly, CVD is not only the most common comorbidity in this disease (prevalence of 34%) (188), but it is also the leading cause of death (15.9%) in older females with breast cancer (160). Breast cancer survivors are at increased risk of CVD and the reason for that is complex and multifactorial (32, 33).

B. Why is CVD High in Breast Cancer Survivors?

Even if advances in technology have improved cancer therapies and survival rates, CVD in breast cancer survivors remains a significant concern. A big part of this problem is the multiple factors that contribute to increased risk of CVD in breast cancer patients. Earlier (101, 114, 116), as well as recent studies (120, 144), have reported different reasons for direct and indirect adverse effects on cardiovascular function in this population. Three very common factors are: a) low fitness, b) cancer therapies, and c) lifestyle factors (**Figure 1**).

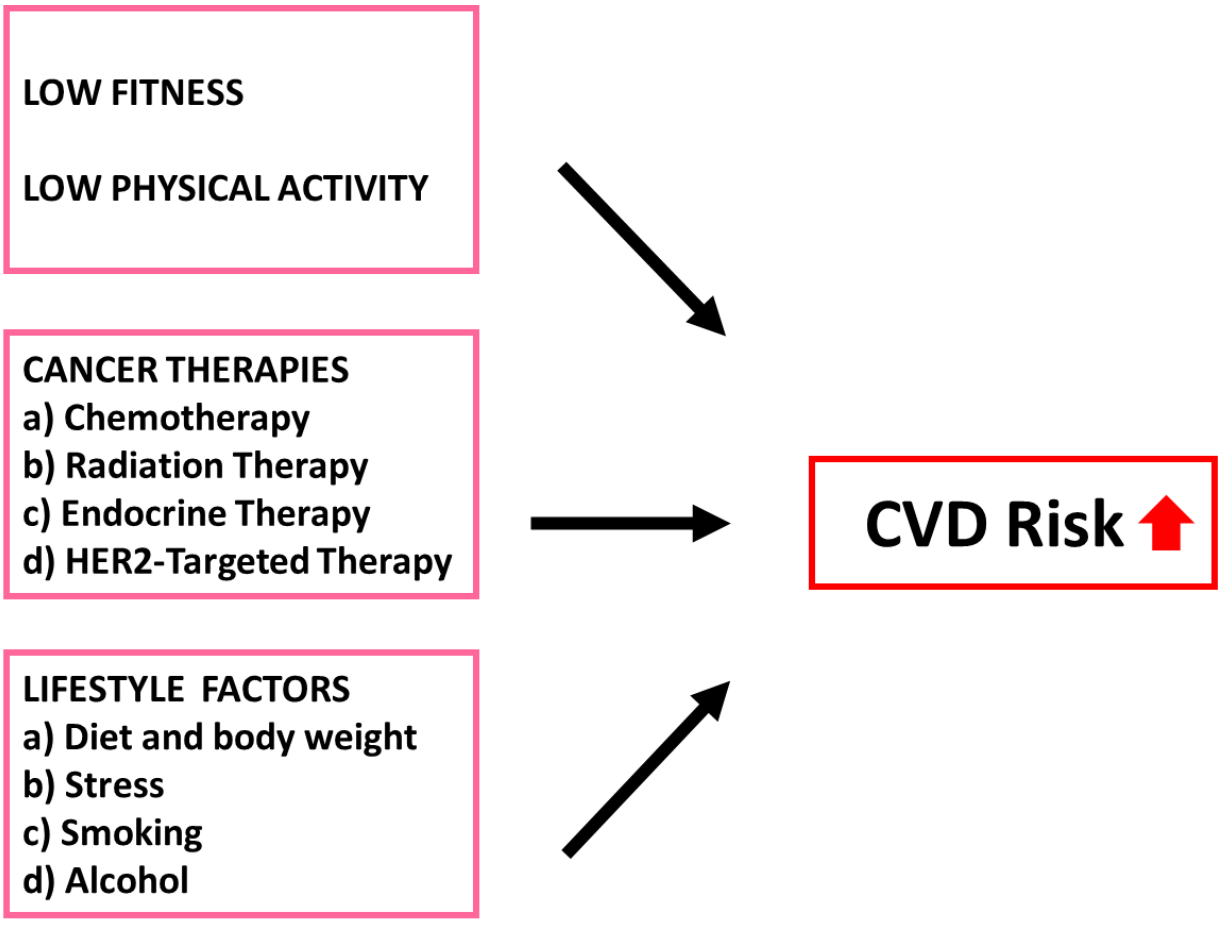

Figure 1. Why is CVD High in Breast Cancer Survivors?
Three main factors that make breast cancer survivors more susceptible to CVD: a) low fitness, b) cancer therapies, and c) lifestyle factors.

i) Fitness is low in breast cancer survivors and contributes to high CVD risk

Exercise and physical activity are recommended to prevent CVD. Physical fitness may be a crucial factor to avoid CVD in breast cancer survivors, since CRF is a major predictor of CVD in the general population (222) and improves survival rates in cancer survivors. For example, healthy females who later developed breast cancer with CRF values below 28 ml/kg/min at baseline had a nearly 3 fold increase in breast cancer deaths compared to females with higher CRF at baseline (162). Moreover, lower CRF in breast cancer survivors may result in shorter survival (113). A study with stage IV breast cancer patients reported that median survival after diagnosis was 16 months for those reporting CRF ≤ 1.09 L/min compared with 36 months for those with CRF > 1.09 L/min) (113). Even if previous research has shown the importance of CRF in this population, breast cancer survivors tend to have 22% lower VO_{2peak} compared to an aged-matched healthy group (113). Additionally, almost one-third of breast cancer survivors have VO_{2peak} below the required for functional independence (15.4 mL/kg/min) (5). Collectively, achieving and/or maintaining higher CRF in breast cancer patients is of critical concern and may improve survivorship rates and lower one's risk for CVD; but unfortunately, CRF in breast cancer survivors has been reported to be substantially lower compared to healthy individuals.

Another important component of healthy lifestyle is physical activity. Low physical activity is linked with higher lifetime risk of CVD (126). Physical activity may indirectly reduce the risk of CVD via reduced or maintained body weight, reduced blood pressure, as well as prevention of dyslipidemia and glucose intolerance (152). Furthermore, potential direct mechanisms include improved endothelial function (86), reduced systemic inflammation (68), decreased plasma viscosity (124), lower estrone/estradiol levels (36), and reduced oxidative stress (129). Interestingly, a longitudinal study supports that breast cancer survivors tend to

drastically decrease their physical activity levels reporting 50% reduction (from 18.8 to 9.2 metabolic equivalent (MET)-hours/wk) 12 months post diagnosis (133). An observational study showed that breast cancer survivors who engaged in more than 3 MET-hours/wk (equivalent to walking at 2-2.9mph (3.2-4.7kmh) for 1 hour) of physical activity had lower adjusted relative risk of death from breast cancer compared to a group with less than 3 MET-hours/wk of physical activity (100). Additionally, a recent meta-analysis reported that women engaging in moderate or vigorous physical activity (≥150 min/wk activities associated with sweating) reduced their lifetime risk of breast cancer by 9% compared to inactive women (167). Taken together, achieving higher levels of physical activity in breast cancer patients may improve survivorship rates and CVD risk.

ii) Breast cancer treatments directly increase CVD risk in breast cancer survivors

It is widely documented that breast cancer treatments, such as chemotherapy, radiation therapy, endocrine therapy, and targeted therapies, can increase CVD risk (**Figure 1**), by affecting function and/or structure of the heart and arteries (120, 144). Some of the most common side effects of cancer treatments are left ventricular dysfunction, hypertension, heart failure, cardiac arrhythmias, myocardial ischemia and pericarditis (144). Interestingly, each cancer therapy can result in cardiovascular toxicity via different pathophysiological mechanisms.

First, drugs used in chemotherapies have been reported to directly affect cardiac function. Common anthracycline agents, such as doxorubicin and epirubicin, damage the deoxyribonucleic acid (DNA) in cancer cells, but they can also result in left ventricular dysfunction by affecting the function of DNA in cardiac cells (131, 143, 144). When anthracyclines interact with DNA, topoisomerase IIβ progression can be inhibited (143). Inhibition of this enzyme leads to disruption of DNA replication and therefore to cardiomyocyte cell death (131, 143). Another

potential mechanism is that anthracyclines generate excessive oxidative stress when combined with ferric iron, or interact with cytochrome c in the mitochondrial respiratory chain (35), which eventually contributes to DNA damage and cardiomyocyte death (182). An additional proposed mechanism includes sarcomere degradation via downregulation of transcriptional factors (such as GATA4), which suppresses synthesis of myofilament proteins (such as titin), and decrease of cardiac progenitor cells (79).

Interestingly, the higher cumulative dose of anthracyclines chemotherapy results in higher risk of heart failure, with an increase of up to 48% risk at a cumulative dose of 700 mg/m^2 (144). Additionally, patients that received anthracycline chemotherapies had 60% more likelihood for cardiac arrhythmias compared to patients without (95). Similarly, a systematic review reported that anthracycline chemotherapies are related to atrial fibrillation, evaluating different studies that reported a range of 2-10% (84). Moreover, 9% of patients decreased more than 10 percentage points and below 50% of left ventricular ejection fraction (LVEF) within the first five years of survivorship (28). Therefore, previous research supports that anthracycline therapies may contribute to cardiac dysfunction and the development of certain arrhythmias.

Along with the side effects on cardiac function, anthracyclines may also negatively affect arterial function by impairing the endothelial cells, smooth muscle cells (89) , platelet function (139) and increasing arterial aortic stiffness (31). An animal study showed that only 4 weeks of doxorubicin administration (5 mg/kg per week) contributes to thrombus formation via increasing platelet activation (139). Studies that evaluated the short-term (up to 6 months) effect of anthracycline therapy in cancer patients revealed a drastic and negative effect on arterial function (31, 61, 226). Within only four months, patients that received anthracycline, almost doubled the pulse wave velocity (from 6.9 m/s to 13.5 m/s), a marker of arterial stiffness (31). Additionally,

patients that received a low to moderate dose of doxorubicin (50 to 375 mg/m^2) increased pulse wave velocity by 50% (from 6.7 m/s to 10.1 m/s) 6 months after cancer therapy (61), providing further evidence for increased arterial stiffness with this therapy. Nevertheless, the previous findings have been reported only in short-term studies. Interestingly, a study in breast cancer survivors who were 6.5 years post therapy compared to an age-, (body mass index) BMI-, and activity level-matched control group reported no differences in pulse wave velocity and flow-mediated dilation (a marker of endothelial function) (123), suggesting that anthracycline chemotherapies may not impair arterial function in the long-term. Taken together, anthracyclines appear to have a drastic and negative effect on arterial function in the short-term; however, further research is required to evaluate the long-term effect.

Non-anthracyclines chemotherapies (alkylating agents, taxanes, antimetabolite drugs) may also contribute to cardiovascular adverse effects. Cancer patients receiving alkylating agents (cisplatin and cyclophosphamide) developed cardiac abnormalities, such as bradycardia (1), supraventricular tachycardia (88) and atrial fibrillation (84). Moreover, taxanes (paclitaxel) can contribute to apoptosis of cardiac cells by disrupting mitosis (189). Previous research using taxanes reported bradycardia (29% of patients had heart rate below 40 bpm) (177), or other arrythmias (asymptomatic left bundle-branch block and ventricular tachycardia) (177). Last, antimetabolite drugs (5-fluorouracil and capecitabine) cannot only contribute to DNA damage and cardiomyocyte death (196), but also to coronary artery dysfunction by inducing arterial vasocontractions (200).

Second, radiation therapies, which is a common localized therapy in breast cancer survivors, can affect cardiovascular function via inflammation, cardiomyocyte injury, fibrosis and oxidative stress (144). This is supported by animals studies that documented ionizing

radiation: 1) increased reactive oxygen species in the heart (7), 2) caused microvascular endothelial damage, which followed with thrombus formation, and capillary loss in the heart (130), and 3) promoted atherosclerosis and fibrosis in the arterial walls of the coronary and carotid arteries (13). Human subjects research has also demonstrated an increased rate of ischemic heart disease by 7.4% for each increase of 1 Gray unit of ionizing radiation therapy in women with breast cancer (51). Additionally, human subjects research showed chest radiotherapy as a significant predictor of cardiotoxicity in patients who received anthracyclines (137). Systematic review papers have widely documented the increased risk of cardiac disease in cancer patients receiving radiation therapy (29, 111), with an aggregate incidence rate of 10% and 30% by five to ten years post therapy, respectively (29). Patients received thoracic radiation therapy also demonstrated signs of autonomic dysfunction, with resting heart rate over 80 beats/min and abnormal heart rate recovery post exercise (83). Even if radiation therapies have been improved to reduce cardiovascular toxicities (modern techniques, higher radiation beam energy, improved delivery of radiation), studies from the last 10 years still report high risk of CVD mortality risk (hazard ratio = 1.30) (204), increased risk of heart failure with preserved ejection fraction (180), increased arterial stiffness (209), and cardiac perfusion defects (142, 228). Taken together, radiation therapies can increase CVD risk via multiple ways.

Third, endocrine therapies (tamoxifen and aromatase inhibitors) reduce cancer recurrence, but they can also result in cardiovascular function side effects. Tamoxifen is a hormonal agent, which is commonly used in premenopausal breast cancer survivors, and attaches to the hormone receptor in the cancer cell (76). As a result, estrogen cannot attach to the cancer cells and this stops or decelerates the growth of the cancer cells (76). Tamoxifen has beneficial effects on vascular function; however, it also has prothrombogenic effects by potentially

affecting platelet levels, as well as antithrombin III and fibrinogen (138) that can lead to pulmonary dysfunction, stroke and deep vein thrombosis (69). Interestingly, a recent meta-analysis reported no CVD events in patients receiving tamoxifen for more than 5 years, but high risk (odds ratio:1.73) for thrombosis in veins and pulmonary arteries (50). Moreover, aromatase inhibitors (anastrozole, letrozole, and exemestane), which are commonly used in postmenopausal breast cancer patients, inhibit the aromatase enzyme and reduce estrogen levels (21). Aromatase inhibitors can also lead to arterial dysfunction. Breast cancer patients with aromatase inhibitors may have higher arterial stiffness than breast cancer patients with tamoxifen (154, 226), and higher possibilities for cardiac events (69). Collectively, commonly used endocrine therapies contribute to increase CVD risk.

Lastly, targeted therapies can also affect cardiovascular function. About 20-25% of breast cancer survivors are human epidermal growth factor receptor 2 (HER2) positive (191, 192). This tyrosine kinase receptor mediates critical signaling pathways and promotes tumor growth (191, 192). Trastuzumab and pertuzumab are two common antibodies used in breast cancer survivors, which bind to HER2 and inhibit tumor development and substantially improve survivorship in HER2 positive cancer patients (148). However, HER2 expression also plays a crucial role in the regulation and survival of cardiomyocytes, and any disruption of this tyrosine kinase receptor may cause cardiac side effects (156). Therefore, inhibition of HER2 with trastuzumab or pertuzumab can result in different cardiomyopathies (47, 181). This is supported by clinical studies showing that breast cancer patients treated with trastuzumab had a higher risk of developing heart failure (risk ratio = 5.11) and left ventricular ejection decline (risk ratio = 1.83), compared to breast cancer patients not treated with trastuzumab (148). Additionally, an epidemiological study with 9,535 patients reported that older breast cancer survivors (≥66 yrs)

receiving HER2 therapy had higher rates of heart failure (29.4%) compared to those without (18.9%) (33). Consequently, targeted therapies may also affect cardiovascular function and CVD in breast cancer survivors.

Table 1. Cancer Treatments and Potential Cardiovascular Consequences

Cancer Treatments	Action in Breast Cancer Treatment	Cardiovascular Consequences
Anthracyclines	- DNA damage in cardiac cells - Generate excessive oxidative stress - Protein synthesis suppression	Thrombus formation, increased aortic stiffness, left ventricular dysfunction, heart failure, atrial fibrillation, impaired endothelial cells, impaired smooth muscle cells
Taxanes	- Contribute to apoptosis of cardiac cells by disrupting mitosis	Asymptomatic left bundle-branch block, ventricular tachycardia, bradycardia,
Alkylating agents	- DNA damage in cardiac cells	Bradycardia, supraventricular tachycardia, atrial fibrillation
Antimetabolite drugs	- DNA damage in cardiac cells - Arterial vasocontractions	ventricular tachycardia, arterial vasocontractions and in the coronary arteries
Radiation Therapies	- Oxidative stress - Inflammation - Cardiomyocyte injury - Fibrosis	Heart failure, atherosclerosis and fibrosis of the coronary and carotid arteries, pericardial disease, coronary artery disease, valvular heart disease, autonomic dysfunction, arterial stiffness, cardiac perfusion defects
Tamoxifen	- blocks estrogen from attaching to the receptor of the cell	Pulmonary dysfunction, stroke, deep vein thrombosis
Aromatase inhibitors (anastrozole, letrozole, and exemestane)	- inhibit the aromatase enzyme and reduce estrogen levels	Cardiac failure, ischemic heart disease, arterial stiffness
Targeted therapies (trastuzumab and pertuzumab)	- Binds to HER2 and inhibit growth	Heart failure, reduced left ventricular ejection fraction

To summarize, all four common breast cancer treatments (chemotherapy, radiation therapy, endocrine therapy, targeted therapies,) have contributed to increased survival rates in

breast cancer survivors, but also appear to play an important role in augmenting higher CVD risk in this population, via functional and/or structural changes within the cardiovascular system. Along with other risk factors, such as low fitness and poor lifestyle habits, CVD risk in breast cancer survivors can become substantially high.

iii) Other Risk factors contributing to CVD risk in breast cancer survivors

In addition to CRF and the negative effects from cancer treatments, other lifestyle factors also importantly contribute to CVD risk in breast cancer survivors. Some of the most common are a) diet and body weight, b) stress, c) smoking and d) alcohol consumption.

Consumption of healthy food and a proper diet are beneficial in preventing CVD (135). However, breast cancer patients before and during cancer treatments have been shown to not consume appropriate nutrients and engage in an unhealthy diet that includes abstaining from fruits, vegetables, whole grains and fish, while consuming larger portions of red meat and high-fat products (30, 49, 127). Interestingly, breast cancer patients who gained weight during chemotherapy reported decreased enjoyment of food, changes in taste, and exhibited increased an selection of unhealthy food (127). Not surprisingly, women with breast cancer during and after cancer treatments have a tendency to lose lean mass (213), and increase weight, BMI, and waist circumference (49), which also increases the risk for cardiovascular implications (169). In addition to this, adjuvant cancer treatments have been reported to be independently associated to weight gain in breast cancer survivors studies (82, 175). Therefore, an unhealthy diet and weight gain also contribute to higher CVD risk in breast cancer survivors.

Another lifestyle factor that contributes to CVD is stress. Research shows that acute and chronic stress can lead to cardiac dysfunction and cardiomyopathies (59). Acute stress can lead to a decrease of left ventricular ejection fraction (41), and chronic stress almost doubles the risk

of myocardial infarction and ischemia (59) Inevitably, cancer patients deal with high levels of psychological stress during the cancer treatments, which frequently persists after treatment completion (3). Almost 50% of breast cancer survivors experience depression and/or anxiety within the first year of diagnosis, and a high percentage (almost 15%) still experience the same after four years (24). Therefore, stress plays a crucial role in CVD risk in breast cancer survivors.

Smoking is a popular lifestyle factor, which negatively affects cardiovascular function. It is an independent risk factor of CVD and smoking cessation has been proven an effective strategy to decrease cardiovascular events and mortality (150). Additionally, an epidemiological study has shown a positive correlation between smoking and breast cancer risk (45). Interestingly, a high percentage of breast cancer survivors (32%) were smokers in a prospective study, and only a 7% of them quit smoking after diagnosis (15). Moreover, female smokers have double the risk (hazard ratio=2.01) of dying from breast cancer and almost four times higher risk from other causes (hazard ratio=3.84) compared to non-smokers (19). Taken together, it is not surprising smoking plays a pivotal role in CVD risk in breast cancer survivors.

Lastly, alcohol consumption has an interesting role in CVD risk in breast cancer survivors. Light to moderate alcohol consumption (5-14g/d) seems to have a positive effect and lower the risk of stroke (112), ischemic heart disease (176), and coronary heart disease (105) in general population. However, higher alcohol drinking (>30g/d) did not reveal beneficial effects on cardiovascular function and was associated with higher rates of hypertension in the general population (105). Additionally, alcohol drinking increased breast cancer risk (134, 187). An epidemiological study reported a 82% increase in breast cancer risk when young women consume two or more alcoholic drinks per day compared to non-alcoholic drinkers (14). A potential explanation for this relates to estrogen levels. High consumption of alcohol may lead to

elevated estrogen levels, which may interact with the estrogen receptors in the mammary epithelial cells and promote carcinogenesis (134). Moreover, the Nurses' Health Study has clearly demonstrated that higher alcohol consumption is correlated with higher breast cancer risk (relative risk=1.07 per 10 g/d increase of alcohol) (34). Interestingly, the type of alcoholic beverage seems to play an important role in breast cancer risk. Studies support a positive association between mammographic density, a marker of breast cancer risk, and white wine and/or beer, and an inverse association between mammographic density and red wine (74, 208). Collectively, studies in general population suggest that light to moderate alcohol consumption may have a cardioprotective effect, but high alcohol consumption should be avoided in breast cancer survivors to prevent cancer recurrence.

Taken together, lifestyle factors such as diet, body weight, stress, smoking and alcohol play a crucial role in preventing CVD and cancer recurrence in breast cancer survivors. Therefore, appropriate lifestyle modification should be recommended in women with breast cancer during and after the completion of cancer treatments.

C. Why Exercise is the Solution to CVD - Chronic Cardiovascular Adaptation to Exercise

As discussed in the previous section of this chapter, there are major concerns regarding the high risk of CVD in breast cancer survivors. Many oncologic strategies and preventative therapies have been proposed to face this problem, including exercise (144). Previous literature has extensively documented that aerobic exercise improves mortality rates and decreases CVD (73, 222). This is primarily achieved through chronic adaptations in the cardiovascular system: i) cardiac, ii) vascular and iii) hemostatic adaptations.

i) Cardiac adaptations to aerobic exercise

Aerobic exercise improves cardiovascular function in part by altering the morphology and function of the heart. This is achieved by inducing beneficial adaptations to cardiac dimensions and hemodynamic variables (blood volume, cardiac output, stroke volume, and heart rate). These exercise adaptations have been extensively reviewed in the literature.

First, aerobic exercise alters cardiac structure through changes in left ventricular end-diastolic diameter and wall thickness. Chronic aerobic exercise increases venous return and stroke volume and both will lead to increased left ventricular end-diastolic diameter (42, 168). Moreover, repeated contractions during long-term aerobic exercise lead to increased wall thickness of the heart (168, 184, 215), and coupled together with increased left ventricular end-diastolic diameter that characterizes the athlete's heart. These are the two common characteristics of left ventricular hypertrophy in endurance athletes, which should not be confused with left ventricular hypertrophy in pathological conditions. The main difference between the athlete's heart and pathological conditions is that while there is increased wall thickness in chronic conditions, this is not typically associated with an increase in left ventricular end-diastolic diameter, which is seen in the athlete's heart (193). This is why only exercise-induced cardiac hypertrophy has a beneficial effect on cardiac function (193). Aerobic exercise proportionally increases left ventricular end-diastolic diameter and wall thickness, which maintains the relative wall thickness (ratio of wall thickness to diameter), thus contributing to improved cardiac function (42, 184).

Second, blood volume increases with chronic aerobic exercise training by increasing plasma and red blood cell volumes. A review paper reported that endurance athletes can have up to 25% larger blood volume compared to sedentary individuals, which is largely explained by increased plasma volume (43). Aerobic exercise increases plasma volume via increasing total

plasma protein and/or sodium in the body and therefore increasing water retention (43, 44). Additionally, red blood cells can also contribute to higher blood volume, but not as much as plasma volume. Studies have reported up to 25% higher total hemoglobin and red blood cell mass in endurance athletes compared to sedentary individuals, and this percentage can be ever higher if we take into account the higher body mass of the athletes (90, 185). Taken together, exercise can increase plasma volume and red blood cells and in turn total blood volume.

Third, chronic aerobic exercise results in beneficial adaptations in other hemodynamic variables as well, such as improved cardiac output and stroke volume during exercise and reduced resting heart rate. Resting cardiac output remains the same after chronic aerobic exercise by decreasing resting heart rate and increasing stroke volume (179); however, maximal cardiac output during exercise increases as a consequence of higher stroke volume (87, 179). A research study in highly trained cyclists reported a 39% difference (24 ml/m^2) in maximal stoke volume index between the aerobically trained and age-matched non-trained group (179). Additionally, a systematic review that included 13 studies, showed maximal cardiac output can increase up to 3.6 L/min (average increase was ≈ 2 L/min) after chronic aerobic exercise (151). Resting and maximal stroke volume increases with aerobic training as a result of changes in left ventricular diameter and hemodynamics. Specifically, higher blood volume contributes to greater venous return (125). The last, in turn, increases left ventricular end-diastolic volume and consequently stroke volume (220). This is also supported by studies showing that endurance athletes have higher maximal stroke volumes compared to sedentary individuals, reporting higher ventricular filling (lusitropic effect) and emptying rate (positive inotropic effect) during exercise (70, 81). Compared to sedentary individuals, endurance athletes have a lower heart rate at a given absolute submaximal intensity, but higher stroke volume, as a result of higher ventricular filling and

emptying rate (70, 81). Last, aerobic exercise leads to a decrease of resting heart rate with no change at maximal exercise. A potential mechanism for the reduction in resting heart rate is the increase of cardiac vagal tone (190, 194). Collectively, aerobic exercise improves cardiac function via altering stoke volume, heart rate and cardiac output.

ii) Vascular adaptations to exercise

Aerobic exercise training contributes to beneficial vascular adaptations. Adaptations such as vascular remodeling and improved vasodilatory capacity contribute to improved blood pressure, muscle and coronary blood flow.

Chronic aerobic exercise results in vascular remodeling, with a) larger arterial diameter, b) angiogenesis, and c) increased tortuosity of capillaries. First, aerobic exercise can increase the arterial diameter when repeated exposure to increased blood flow and shear stress initiate the stimulus of growth in arteries (60) and collateral blood vessels (136). This, in turn, has a beneficial effect on blood flow by reducing vascular resistance (56). Second, aerobically active individuals are able to grow new capillaries (angiogenesis) (16, 170). This can happen when exercise stimulus initiates the upregulation of vascular endothelial growth factor, and other growth factors (16, 170). As a result, more capillaries will improve oxygen extraction to the muscles by providing greater surface area for exchange and a shorter distance between muscles and capillaries (16). Third, aerobic exercise may also help in creating more tortuous capillaries (32). Instead of growing parallel to muscle fibers, an exercise stimulus might promote new sprouts that loop around the muscle fibers (32). This will also contribute to a greater surface area, and therefore greater oxygen extraction to the muscles. Therefore, larger arterial diameter, more capillaries and more capillary tortuosity caused by aerobic exercise training helps to promote improved vascular function in trained individuals.

Along with vascular remodeling, aerobic exercise can improve vasodilatory capacity as well. Numerous studies have reported that aerobic training increases (38, 146) or prevents age-related decline (58) in endothelium-dependent vasodilatory capacity. The main proposed mechanism of this phenomenon is that aerobic exercise increases nitric oxide availability, a molecule with a crucial role in endothelium-dependent vasodilation (94). Exercise is known to increase the activity of endothelial nitric oxide synthase (eNOS), an enzyme which catalyzes nitric oxide synthesis, and thus increases bioavailability of nitric oxide (85). Additionally, aerobic exercise training reduces oxidative stress by increasing antioxidant enzymes, such superoxide dismutase (63, 164). This enzyme leads to fast dismutation of superoxide to hydrogen peroxide and oxygen, and thus avoiding reaction with nitric oxide to form peroxynitrite (164, 173). Excessive production of peroxynitrite inhibits eNOS production and thus nitric oxide bioavailability (158). Last, aerobic exercise may increase vasodilation via other substances as well, such as increased synthesis of prostacyclin or endothelial hyperpolarizing factor, as well as other potent vasodilators (224). Collectively, aerobic exercise increases the availability of many different molecules that contribute to enhanced vasodilatory capacity.

Vascular remodeling and improved vasodilatory capacity with chronic aerobic exercise training improves blood pressure, as well as muscle and coronary blood flow. Exercise has been shown to decrease systolic and diastolic blood pressure in healthy (118) or hypertensive individuals (163). This happens as a result of vascular remodeling and improved vasodilatory capacity that in turn reduces total peripheral resistance, a determinant of mean arterial pressure (163). Moreover, studies have shown that maximal muscle blood flow is higher in aerobically active individuals compared to sedentary ones (171, 174). Reduced vascular resistance contributes to increased blood flow, since resistance is inversely related to blood flow (171, 174).

Last, there is evidence that vascular adaptations enhance coronary blood flow as a result of larger diameters (22) and improved vasodilation of the coronary vessels (157). Exercise improves coronary blood flow by reducing diastolic blood pressure as well (23). Hence, aerobic exercise training improves blood pressure and flow via vascular remodeling and improved vasodilatory capacity.

Aerobic exercise training also improves blood pressure and blood flow with beneficial adaptations on autonomic function as well. Aerobic exercise training improves baroreceptor activity, which contributes to improved autonomic function. Increased sympathetic nerve activity contributes to higher total peripheral resistance, which in turn increases blood pressure. Baroreceptors in the aortic arch and carotid artery can sense changes in blood pressure and respond accordingly to keep blood pressure at desired levels. A 6-month aerobic training period resulted a 26% increase of baroreflex sensitivity (from 10.6 to 12.9 msec/mmHg) and that was mainly attributed to neural adaptations (55). A longitudinal study showed that 4 months of aerobic training in hypertensives improved blood pressure via improving muscle sympathetic nerve activity and baroreflex sensitivity (128). Therefore, aerobic exercise-induced adaptations on autonomic function via improved sympathetic nerve activity and baroreceptor sensitivity can also improve blood flow and blood pressure.

To sum up, aerobic exercise produces larger diameter in arteries, higher number of capillaries, and increased tortuosity of capillaries. Along with improved vasodilatory capacity and autonomic function, all those vascular adaptations contribute to improved blood pressure, muscle and coronary blood flow. The last, in turn, plays a crucial role in CVD prevention.

iii) Hemostatic adaptations to exercise

A third exercise-induced adaptation that improves cardiovascular function is hemostatic alterations. Aerobic exercise training can positively affect coagulation and fibrinolytic properties, as well as platelet function. These hemostatic adaptations play a critical role in helping to prevent CVD.

Aerobic exercise can reduce activity of important proteins involved in coagulation control: thrombin, prothrombin, partial thromboplastin, coagulation Factor VII, tissue plasminogen activator, plasminogen activator inhibitor. Even if several training studies have reported no exercise effect on some of these proteins (65, 210), some cross-sectional studies report lower fibrinogen levels in trained individuals compared to sedentary (223). Interestingly, cardiac patients exhibited reduced coagulation activity (longer activated partial thromboplastin time, decreased coagulation Factor VII activity and fibrinogen levels) after a month of aerobic training (202). Therefore, aerobic exercise may play a vital role in controlling coagulation and reducing the risk for thrombosis.

Exercise does not only prevent thrombus formation by reducing coagulation cascade activity, but also by enhancing fibrinolysis. Aerobically active individuals are reported to have greater activity of tissue plasminogen activator following a bout of aerobic exercise than sedentary individuals (197, 203). Additionally, several other studies showed that aerobically trained individuals had greater release of tissue plasminogen activator and reduced plasminogen activator inhibitor-1 at rest compared to sedentary individuals (53, 203). Thus, aerobic exercise may lead to increased fibrinolytic activity, which in turn contributes to the prevention of thrombus formation.

Last, it is very important to clarify the chronic aerobic exercise effect on platelet function. Even if acute strenuous exercise increases platelet adhesion and aggregation (26, 67, 217),

chronic aerobic exercise, in contrast, contributes to reduced platelet adhesion and aggregation (218, 219). Potential mechanisms are the following: a) exercise increases nitric oxide and prostacyclin that impede platelet aggregation (140), and b) exercise decreases oxidized low-density lipoproteins that increases platelet activation (48). Interestingly, exercise improves platelet function at rest but also in response to an acute stress, such as exercise (218, 219). The last is also significant since acute strenuous exercise increases the risk for cardiac events (11). In other words, exercise-induced improvement in platelet function contributes to cardiovascular protection and prevention of cardiac sudden deaths.

iv) Lung and Muscle function adaptations

As discussed earlier, aerobic exercise can directly improve cardiovascular function through cardiac, vascular and hemostatic adaptations. Increased attention has also been given to lung (216) and muscle (198) adaptations that can indirectly prevent CVD.

Chronic aerobic exercise contributes to improved lung function. Exercise can improve respiratory indices such as the oxygen uptake efficiency slope (OUES) (54, 211). This respiratory marker is derived during incremental exercise testing and depicts the increase of oxygen uptake compared to the increase in minute ventilation (V_E) (8). It is calculated as the slope of the linear regression between oxygen uptake and logarithmic transformation of V_E (8). This marker is more prevalent in research because it offers an objective way to estimate cardiopulmonary functional reserve and is correlated with VO_{2peak}. Moreover, it can be used in disease populations as well, due to the fact that it does not require maximal effort and it can be calculated during submaximal exercise. Interestingly, aerobic training has been documented to improve OUES in different disease populations, such individuals with coronary artery disease (54) and chronic heart failure (211).

Previous literature has shown that chronic aerobic exercise can improve other respiratory indices as well, such as maximum voluntary ventilation (MVV) forced expiratory volume in one second (FEV1), and forced vital capacity (FVC) (6, 78, 110). Specifically, obese young individuals were able to improve MVV (+0.6 l/min) after 24 weeks of aerobic training (6). Additionally, a cross-sectional analysis reported that active individuals (≥11 flights (a flight was equal to 10 steps) of stairs per day) had 90 ml higher FEV1 than sedentary controls (110). The same is supported by a longitudinal study showing an increase of 50 ml in FEV1 and 70 ml in FVC in a group maintained high physical activity (≥ 4 hours per week of light activity or 2-4 hours of vigorous activity per week) for 19 months (78). Sedentary individuals in the same study reported a decline of 30 ml in FEV1 and 20 ml in FVC (78). These respiratory improvements stem largely from respiratory muscle strengthening, as a result of chronic exercise (6, 78, 110). Taken together, aerobic exercise and physical activity have been related to better pulmonary function in the previous literature.

As for muscle function, aerobic exercise has a beneficial effect via morphologic and metabolic adaptations. First, endurance training improves muscle function as a result of increased number of capillaries per fiber. A cross-sectional study reported that aerobically trained individuals had a higher capillary per fiber ratio (2.49 vs 1.77), number of capillaries around each fiber (5.87 vs 4.43), and number of capillaries per mm^2 (821 vs 585) compared to sedentary individuals (107). This crucial adaptation will lead to greater diffusion of oxygen in the muscles during exercise. Second, aerobic exercise increases the size and function of the mitochondria (98, 145). A training study reported a 55% increase of mitochondrial volume density following 6 weeks of endurance training (145). In the same study, subjects were able to improve oxidative capacity by increasing citrate synthase activity (+44%), an enzyme that

catalyzes the first reaction in the Krebs cycle (145). Therefore, aerobic exercise does not only improve muscle function by morphologic adaptations, but also by improving metabolic function.

Chronic aerobic exercise improves metabolic function by improving substrate utilization and enzymatic activity. Aerobic exercise has been proven to have a beneficial effect on glycogen (99). Aerobically trained individuals do not only increase the amount of glycogen storage in the muscles (93, 165), but also the ability to preserve glycogen during a prolonged exercise (91) (as a result of greater fat oxidation with chronic aerobic exercise (97)). Additionally, aerobic training can increase hexokinase activity, which is the first enzyme that catalyzes the glycolytic pathway(9). Along with glycolytic enzymes improvements, aerobic exercise improves enzymatic activity in different mitochondrial functions such as the Krebs cycle, respiratory chain, and fatty acid oxidation (99). A follow-up study evaluating long duration aerobic training reported a 30% increase in citrate synthase within only 3 weeks (183). In the same study, the participants exhibited a 50% increase of 3-hydroxyacyl-CoA-dehydrogenase activity, an enzyme that is involved in fatty acid metabolism, after 8 weeks of training (183). Another follow-up study reported 6 weeks of aerobic training increased enzymatic activity between 46-61% in electron transport chain complexes I–IV (77). Taken together, aerobic exercise not only changes the morphology, but also improves substrate utilization and capacity within skeletal muscles. All these, in turn, improve muscle oxygenation and oxygen utilization in the muscles.

This is also supported by studies that directly evaluated the effect of aerobic exercise on muscle oxygenation. These studies non-invasively assessed skeletal muscle oxygen consumption using near-infrared spectroscopy (NIRS). NIRS initializes light-emitting diodes and operates at wavelengths (~700–900 nm) that can penetrate biological tissues (10). As a result, the light can be absorbed by molecules that contain heme, such as hemoglobin. If oxygen is bound on heme,

the light absorption is different. Detecting different light absorption values, the device can estimate deoxygenated and oxygenated, and total hemoglobin (**Figure 2).** Then, tissue oxygenation (TOI) is calculated as TOI = $[HbO_2]/ ([HbO_2] + [HHb]) \times 100$. Due to its non-invasive function, the application of NIRS has increased exponentially in recent exercise studies (**Figure 3**) (10). As such, a 16 week endurance training study reported a 48% increase of muscle oxygenation at rest (117). In the same study, VO_{2peak} was positively correlated with muscle oxygenation at rest (r = 0.63) (117). Another study reported that aerobically trained individuals had two times faster muscle oxygen recovery, another way to evaluate muscle function, of the vastus lateralis following maximal twitch contractions compared to untrained individuals (20). Therefore, aerobic exercise training can also improve muscle function by increasing muscle oxygenation.

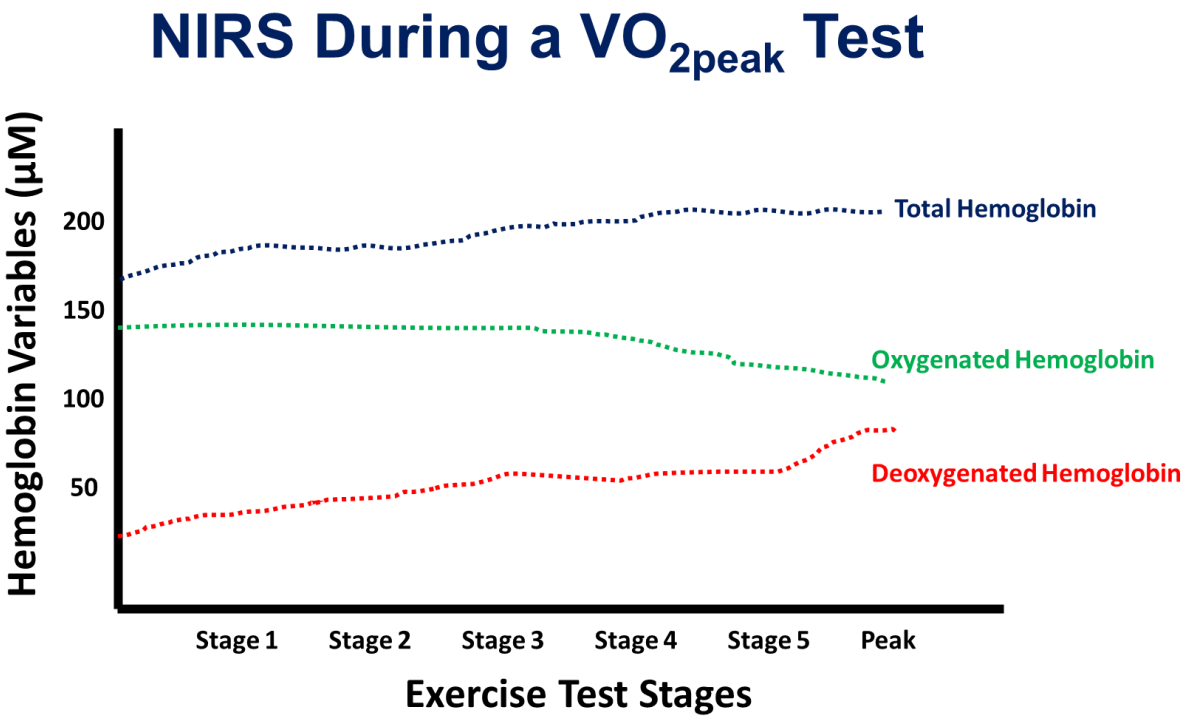

Figure 2. Deoxygenated, oxygenated, and total hemoglobin concentrations during a VO2peak Test

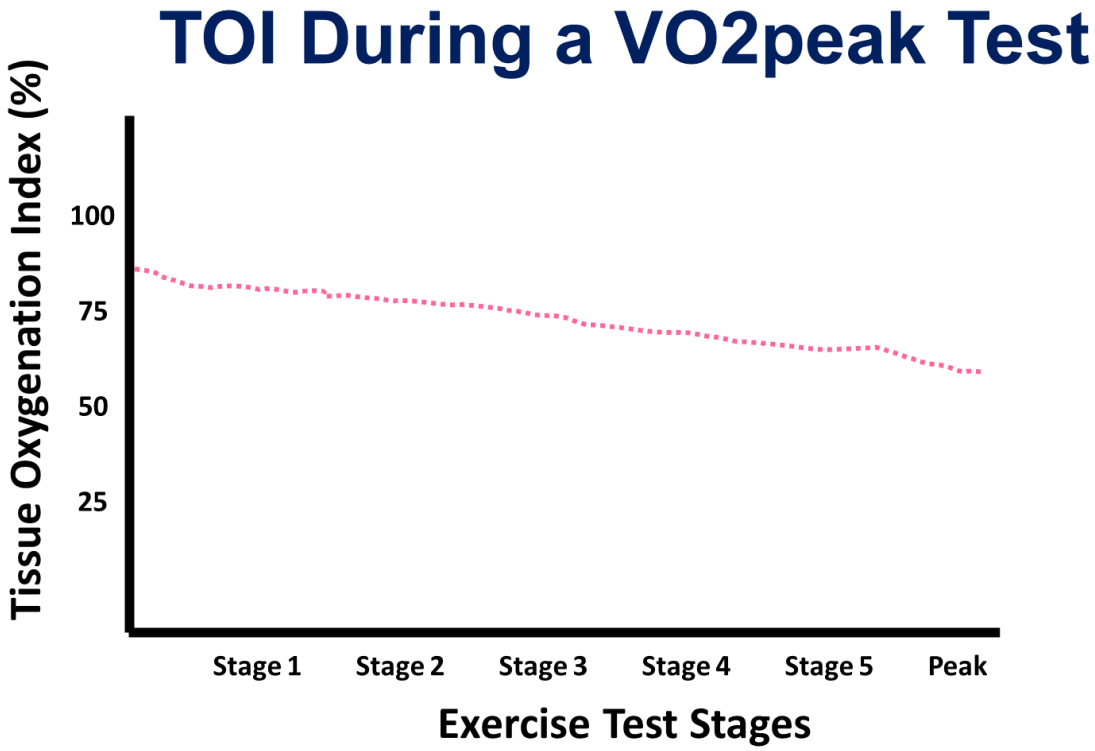

Figure 3. Tissue oxygenation index during a VO2peak Test

D. Why is CRF Low in Breast Cancer Survivors?

i) Wasserman's physiological factors - how CRF is explained by the heart, lungs, and muscles.

CRF depicts the capacity of oxygen transport and utilization in the body and can reveal abnormalities in cardiovascular, pulmonary and/or skeletal muscle function. According to Wasserman's physiological representation of gas transport (221) (**Figure 4**), these three systems interact during exercise to meet the increased metabolic demands of the contracting muscles. Therefore, the coordination and proper function of the heart, lungs and muscles contribute to higher CRF.

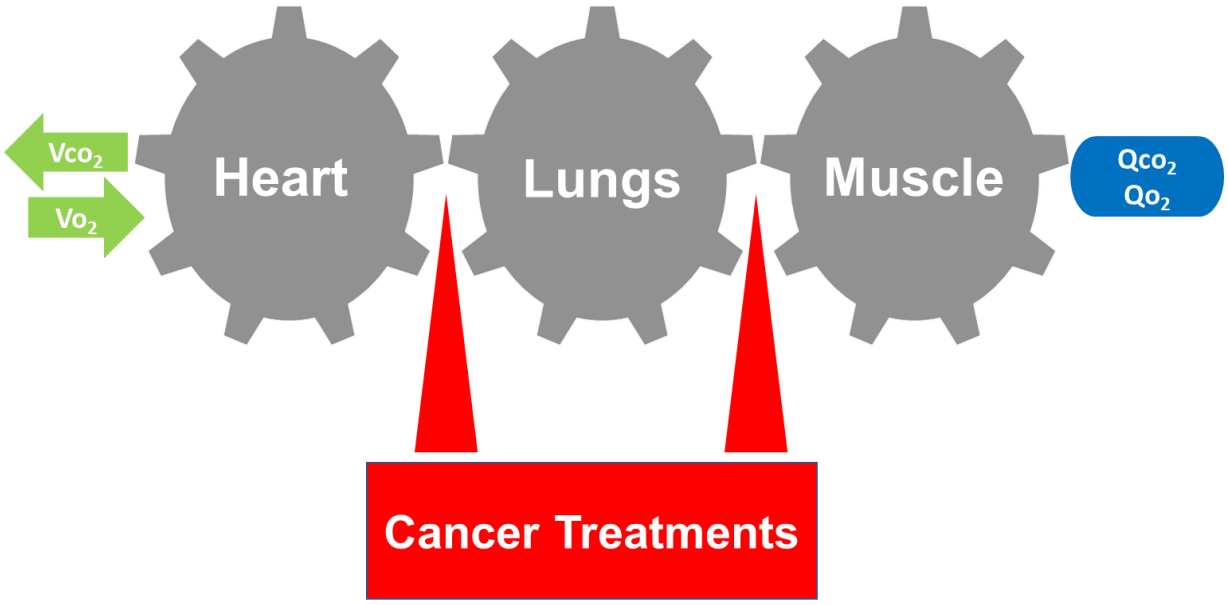

Figure 4. Wasserman's physiological factors
The heart, lungs and muscles accordingly interact during exercise to meet the increased metabolic demands of the contracting muscles. Adapted from *Wasserman et al. Principles of Exercise Testing and Interpretation: Pathophysiology and Clinical Applications. Lippincott Williams &Wilkins. 2012.*

During a physiological stress, such as aerobic exercise, there is an increased need for O_2. When this occurs, it is crucial to increase oxygen supply and, in turn, efficiently distribute oxygen within the body. The heart responds to exercise demands by increasing heart rate and stroke volume, and therefore increasing blood flow to the pulmonary and systemic circuits. Thus, O_2 availability for the muscles drastically increases during physical activity. The lungs concomitantly respond to exercise by increasing the ventilatory rate and volumes, which increases the rate of oxygen diffusion to the pulmonary circulation. Hence, a higher amount of oxygenated blood is delivered to the heart before being redistributed to the various organs via the systemic circuit. Muscles respond to aerobic exercise by increasing O_2 extraction from the circulating blood in an effort to meet increased demand for ATP via oxidative phosphorylation and mitochondrial respiration. Taken together, the heart, lungs and muscles respond in an

intricate manner with significant cross-talk in an effort to meet increased metabolic demand associated with aerobic exercise.

Higher CRF reflects the proper function between these three gears and has the potential to reveal abnormalities within these three physiological systems (221). In individuals with normal CRF, cardiac output increases at an adequate rate to meet the muscle O_2 requirements during aerobic exercise. However, individuals with cardiac dysfunction have limited ability to increase cardiac output during exercise, resulting low CRF (121). Therefore, the heart might be a potential contributor to low CRF commonly observed in breast cancer since cancer treatments can result in cardiovascular dysfunction. Importantly, cancer treatments in breast cancer may also affect the lung and muscle function. Thus, any physiological factor (heart, lungs, muscles) can contribute to low CRF in breast cancer survivors, but this is not well delineated at this time in the literature.

ii) Cancer treatments cannot only affect cardiac, but also lung and muscle function.

Breast cancer therapies not only lead to cardiovascular dysfunction, but also contribute to impaired lung function via decreased lung perfusion and inspiratory capacity (9–11, 107) . An early follow up study in breast cancer survivors showed a larger decrease in alveolar volume with a higher dose of radiation therapy (0.9% reduction per Gray unit during the first 3 months, and 0.4% reduction at 18 months post radiation therapy) (205). Moreover, studies in breast cancer survivors have shown a reduction in diffusing capacity for carbon monoxide at three (1.1% per Gray unit) (205), nine (92), and 18 months post-radiation therapy (205). The diffusing capacity of the lung for carbon monoxide is the gold standard test for assessing diffusing capacity, and at the end of a tidal breath participants maximally inhale a mixture of air containing carbon monoxide (0.3% is typical) and hold their breaths for 10 sec. Then,

participants exhale, and the difference in carbon monoxide levels between the inhaled and exhaled samples are used to determine the amount of carbon monoxide diffused from the alveoli to the blood. Carbon monoxide is used in this test because hemoglobin has an incredibly high affinity for this gas over oxygen (i.e. 200-250 times greater). Spirometry values have also been negatively affected by breast cancer treatments (chemotherapy and radiation therapy) with declines between 4-8% for FEV1 and FVC (92).

Unfortunately, pulmonary dysfunction in breast cancer patients is supported by recent papers as well, evaluating more modern techniques of radiation therapies Interestingly, a follow-up study in breast cancer survivors reported a 1.8% reduction in FVC and FEV1 6 months post radiation therapy, but both variables fully recovered seven years after radiation therapy (109). Conversely, breast cancer survivors had between a 3-5% reduction in ventilation, perfusion and diffusing capacity for carbon monoxide two years post cancer therapy, and all three remained significantly reduced even after 7 years of survivorship (109). Collectively, early and recent research support that pulmonary function can be weakened by chemotherapy and radiation therapy in breast cancer survivors.

Along with heart and lung function, cancer therapies could negatively affect muscle function as well. Chemotherapies alter mitochondrial integrity and function via increased oxidative stress (212), which can cause alterations in glycolysis and fatty acid oxidation (108). Animal studies showed that doxorubicin caused muscle weakening in the soleus by decreasing twitch force, rate of force, fatigues rate, and fractional shortening in a dose-dependent manner within only five days of exposure (89, 106). These studies recommended that doxorubicin-induced muscle dysfunction might be related to morphological (199), enzymatic (195) calcium release (229), and contractile (212) alterations. Another study in the extensor digitorum longus of

mice reported a dose-dependent effect of doxorubicin on muscle relaxation time (more than +100% with 175mM doxorubicin) and maximal force (-20% with 175mM doxorubicin) after 1 hour exposure (212). In a cross-sectional human study, breast cancer survivors following chemotherapy had lower strength (12–16% lower for shoulder, 25% lower for knee flexors/extensors) compared to healthy controls (122). Moreover, breast cancer survivors reported muscle fatigue (-91 meters in the 12-minute walk test) 6 months post chemotherapy treatment (186). This is also supported by studies in different cancer types, where patients received doxorubicin developed muscle weakness and fatigue 1-5 years post chemotherapy (66, 207, 214). Taken together, breast cancer patients are at increased risk to develop muscle dysfunction and fatigue following the cancer treatments and aerobic exercise might be an effective strategy to prevent these negative consequences in the muscle

iii) Heart, lung and muscle function limit CRF in breast cancer survivors.

Numerous studies support that breast cancer survivors have overall much lower CRF (~22% lower) compared to healthy individuals. First, in 2007, a study reported that postmenopausal breast cancer patients who received chemotherapies and endocrine therapies had a 19% lower VO_{2peak} compared to age-matched healthy controls (115). Jones et al. (113) also demonstrated a 27% reduction in VO_{2peak} among breast cancer survivors compared to age- and sex-predicted sedentary values, measured on average 21 month post-cancer diagnosis. Additionally, a meta-analysis including 27 different studies documented a 17% lower VO_{2peak} in breast cancer patients prior to adjuvant therapy suggesting that the cancer pathology itself may also contribute to lower VO_{2peak}, and a 25 % lower VO_{2peak} in breast cancer patients after adjuvant therapy compared to healthy sedentary women (161). The previous findings suggest that VO_{2peak} in breast cancer survivors tends to decrease even more after the completion of

adjuvant therapies, such as chemotherapy and/or radiation therapy after the primary surgery. Moreover, Beaudry et al. (12) reported that breast cancer patients prior to adjuvant chemotherapy had a 29% lower VO_{2peak} compared to age- and sex-matched controls. A longitudinal study showed a 16% and 7% reduction in VO_{2peak} among untrained and trained breast cancer survivors, respectively, 16 months post-anthracycline chemotherapies (75). It is clear that breast cancer survivors have reduced CRF levels as a whole compared to their age-mated sedentary peers following therapy, ranging from 17 to 29%. Yet, no study has thoroughly evaluated mechanisms for this phenomenon.

Low CRF among breast cancer survivors is likely explained by multiple factors such as cardiac, pulmonary, and/or skeletal muscle function. As we previously discussed (Chapter II, Bii), cardiac function can be affected by various cancer treatments. Therefore, cardiac output during exercise can be impaired and eventually VO_{2peak}. Additionally, pulmonary function can be weakened by chemotherapy and radiation therapy in breast cancer survivors (Chapter II, Dii). This will ultimately impair pulmonary gas exchange, lung perfusion, and inspiratory capacity, which limit oxygen transport and VO_{2peak}. Lastly, skeletal muscle function may be altered by cancer treatments (Chapter II, Diii). Reduced muscle capillary density, calcium release, and enzymatic activity in mitochondria, cause impairment in oxygen transport and use in the skeletal muscles during exercise. Taken together, cardiac, pulmonary, and skeletal muscle dysfunction caused by cancer treatments likely have a negative effect on CRF in breast cancer survivors; however, given these physiologic factors have been understudied in this population, in particular during exercise, in relation to CRF.

Initially, studies targeted cardiac function to explain reduced CRF given the cardiotoxicity caused by cancer therapies. However, Burnett et al. (25) showed that impaired

CRF does exist in breast cancer survivors with normal left ventricular ejection fraction, suggesting that other components also contribute to impaired oxygen transportation and utilization, or that resting heart function measurements are not adequate to reveal abnormalities in breast cancer survivors. Another important consideration is that many previous studies have evaluated cardiac and pulmonary function in breast cancer survivors under resting conditions, which is not always enough to reveal abnormalities. Especially in breast cancer survivors, resting cardiac imaging has been inadequate to detect early subclinical detection of cardiac abnormalities, suggesting measurements during times of greater cardiac stress (37), such as exercise, would be more informative.

Previous studies have attempted to evaluate physiological factors in breast cancer survivors during peak or submaximal exercise. A cross-sectional study examined cardiac function in breast cancer survivors during peak exercise and reported an 11% lower peak cardiac output (1.3 L/min less) in breast cancer survivor group. Unfortunately, the statistical approach of this paper did not examine differences in the change of cardiac output and heart rate (baseline – peak) compared to the control group (115). According to the authors interpretation, the difference in peak cardiac output was driven by differences in peak stroke volume (11% or 8 ml difference), but there were no differences in the change of stroke volume between the two groups (17). Beaudry et al. (12) reported approximately 30% lower cardiac index, as a result of reduced stroke volume, and ventricular end diastolic volume during peak exercise in breast cancer patients compared to controls; however, this study recruited patients before adjuvant chemotherapy and the results do not include potential side effects of heart function after the cancer therapies. A longitudinal study in breast cancer survivors reported a 14% reduction in peak stroke volume and approximately 8% in left ventricular ejection fraction, with no changes

in heart rate 12 months post-chemotherapies, suggesting that cardiac contractility affects VO_{2peak} in this population (75). Interestingly, a cross-sectional study with similar VO_{2peak} between breast cancer survivors and controls, reported no differences in stroke volume, heart rate and cardiac output at rest and submaximal exercise (75% of the subject's maximal work rate), but ejection fraction was reduced at submaximal level in breast cancer survivors (123). Taken together, the previous studies have shown contrasting results in various cardiac function variables (cardiac output, stroke volume, heart rate, ejection fraction, and end diastolic volume) in breast cancer survivors.

A cross-sectional study evaluated pulmonary function during peak exercise in breast cancer survivors reporting a 11% lower inspiratory capacity (240 ml less) compared to a control group, suggesting that pulmonary abnormalities may also physiologically impact CRF in this population (155). Lastly, only one study evaluated muscle function during exercise in breast cancer survivors reporting no differences in tissue oxygenation compared to controls; however, tissue oxygenation was evaluated at submaximal level (up to the ventilatory threshold) during cycling exercise. Taken together, the physiological factor affecting CRF in breast cancer survivors are still unclear and no study has examined all physiologic factors in one study, especially at peak exercise. This is important because evaluating all the potential factors during peak exercise will allow for a more thorough examination of the physiological factors affecting cardiorespiratory fitness in breast cancer survivors.

E. Summary

Breast cancer is the most common type of cancer in the United States, with nearly a quarter million new cases diagnosed each year and approximately 40,000 women will die from breast cancer per year (57). Moreover, breast cancer survivors are at increased risk of

cardiovascular disease (CVD), in part, due to the side effects of cancer therapies (144). Aerobic exercise has been recommended as an effective way to improve mortality rates and decrease CVD, but breast cancer survivors tend to have lower cardiorespiratory fitness (CRF) compared to age-matched healthy individuals (25, 113, 161). This shows the importance of the problem since CRF is a major predictor of all-cause mortality and CVD in the general population (222), but also a major predictor of morbidity and mortality in breast cancer survivors (113).

As CRF involves the integration of several physiological systems, low CRF in breast cancer survivors may be related to alterations in a) cardiac, b) pulmonary and c) skeletal muscle function. It is well established that cancer treatments negatively affect cardiac function, via impairing contractility of the heart (147) that eventually may impair stroke volume and O_2 availability during peak exercise. Additionally, pulmonary function can be weakened by chemotherapy and radiation therapy and therefore breast cancer survivors may have decreased lung perfusion and inspiratory capacity (9–11, 107). Moreover, skeletal muscle function could be altered by cancer treatments (89, 106, 212), which in tun may cause muscle function impairments during exercise leading to early fatigue and low CRF. Taken together, cardiac, pulmonary, and skeletal muscle factors might have a negative effect on CRF in breast cancer survivors; however, this is still unclear given these physiological factors have been understudied in this population, in particular at peak exercise.

Due to the lack of information regarding this crucial topic, the overall aim of our study is to determine what physiological factors limit CRF in breast cancer survivors. We expect this study to elucidate if cardiac, pulmonary and muscle function are the limiting factors at peak exercise in breast cancer survivors compared to a control group. We expect that the results of this

study will help future investigations in order to determine how CRF can be improved in BCS and eventually reduce risk of CVD.

F. Specific Aim

The overall aim of our study was to determine what physiological factors limit CRF in breast cancer survivors. We tested this with three specific hypotheses**:**

Hypothesis 1: To determine if breast cancer survivors would have an attenuated increase in cardiac output (using heart rate and stroke volume) at peak cycling exercise compared to healthy controls.

Hypothesis 2: To evaluate if breast cancer survivors would have attenuated markers of pulmonary function (using oxygen uptake efficiency slope (OUES) and ventilation/carbon dioxide production (VE/VCO2 slope)) at peak cycling exercise compared to healthy controls.

Hypothesis 3: To determine if breast cancer survivors would have attenuated muscle oxygenation (using oxygenated and deoxygenated hemoglobin) at peak cycling exercise compared to healthy controls.

Chapter III: Physiological Factors Impacting Fitness in Breast Cancer Survivors

A. Abstract

Breast cancer is the most common type of cancer in the United States, and breast cancer survivors have a high prevalence of cardiovascular disease (CVD) and reduced cardiorespiratory fitness. Cardiorespiratory fitness is a major predictor of CVD and all-cause mortality in the general population, and an important predictor of survival in breast cancer survivors. However, the physiological factors that contribute to reduced cardiorespiratory fitness in breast cancer survivors have not been completely elucidated yet. The purpose of this study was to evaluate what primary physiological factors (cardiac, pulmonary, and muscle function) contribute to reduced cardiorespiratory fitness in breast cancer survivors. To examine this, 23 breast cancer survivors (50 ± 9 yrs; 25.5 ± 2.9 kg/m^2), and 23 age-BMI matched controls (49 ± 9 yrs; 25.7 ± 4.6 kg/m^2), underwent a cycling exercise test and variables of cardiac, pulmonary and muscle function were evaluated at baseline and at peak exercise. Cardiac hemodynamics (stroke volume (SV), heart rate (HR), cardiac output (CO) were evaluated and calculated using ultrasonography. Pulmonary function was evaluated using the oxygen uptake efficiency slope (OUES) and ventilation to carbon dioxide production slope (V_E/VCO_2 slope)) during the peak cycling exercise test. Muscle oxygenation variables (oxygenated (HbO_2), deoxygenated (HHb) and total hemoglobin (Hb), and tissue oxygenation index (TOI)) were measured non-invasively with near-infrared spectroscopy (NIRS). Breast cancer survivors had similar $VO_{2peak,}$ OUES, V_E/VCO_2 slope values compared to the control group. All the hemodynamic variables (HR, SV, SVindex, CO, COindex) increased at peak exercise compared to baseline ($p<0.001$). Group effects were detected for HR and SVindex, with breast cancer survivors having higher HR and lower SVindex ($p<0.05$) values, but both groups had the same cardiac hemodynamic responses from baseline to

peak exercise. TOI decreased at peak exercise compared to baseline (Table 7 $p<0.001$), and Hb and HHb increased at peak exercise compared baseline (Table 7, $p<0.001$), and both groups responded the same from baseline to peak exercise. The results of our study suggest that breast cancer survivors do not exhibit differences in cardiac, pulmonary, and muscle function at peak exercise compared to controls, at least when they have similar cardiorespiratory fitness.

B. Introduction

Breast cancer is the most common type of cancer in the U.S., with approximately one in every eight women developing breast cancer in their life (57). Breast cancer survivors have a 13% higher possibility to develop cardiovascular disease (CVD) compared to controls (5), in part, due to the side effects of cancer therapies (3). Breast cancer survivors have 1.9 times higher CVD death risk than women without breast cancer after at least 7 years of cancer diagnosis (80). Additionally, CVD is the leading cause of death in post-menopausal breast cancer survivors (160, 166). Cardiorespiratory fitness is a major predictor of CVD and all-cause mortality in the general population (222), and is also an important predictor of survival in breast cancer survivors (113); however, breast cancer survivors tend to have lower cardiorespiratory fitness compared to age-matched healthy individuals (between 17% - 29% difference) (25, 113, 115, 161).

Reduced cardiorespiratory fitness in breast cancer survivors may be a side effect of cancer treatments on some of cardiorespiratory fitness's key contributors: cardiac, pulmonary, and skeletal muscle function. First, cardiac function can be impaired by different cancer therapies, such as chemotherapies (131, 143), radiation therapies (51, 180, 228), hormonal therapies (69) and human epidermal growth factor receptor 2 (HER2) therapies (33, 148). Therefore, stroke volume and cardiac output during exercise can be lower, and in turn this lowers cardiorespiratory fitness in breast cancer survivors. Additionally, pulmonary function can be weakened by radiation and chemotherapy, leading to decreased lung perfusion and inspiratory capacity (9–11, 107), which can impact cardiorespiratory fitness. Lastly, breast cancer patients are at increased risk to develop skeletal muscle dysfunction due to chemotherapies (212). Consequently, breast cancer survivors may not be able to increase O_2 extraction from the blood during the increased ATP demands in the muscles throughout a cardiorespiratory fitness test.

Taken together, cardiac, pulmonary, and skeletal muscle dysfunction caused by cancer treatments likely have a negative effect on cardiorespiratory fitness in breast cancer survivors; however, this is still unclear given these physiologic factors have been understudied in this population, in particular during peak exercise. Evaluating the potential factors during peak exercise will allow for a more thorough examination of the physiological factors affecting cardiorespiratory fitness in breast cancer survivors. To our knowledge, this is the first study that aims to evaluate all three potential contributors to cardiorespiratory fitness at peak exercise in breast cancer survivors.

The purpose of this study was to evaluate what physiological factors (cardiac, pulmonary, and muscle function) limit cardiorespiratory fitness in breast cancer survivors. We hypothesized that compared to healthy controls, breast cancer survivors would have attenuated increases in cardiac output, decreased markers of pulmonary function (using oxygen uptake efficiency slope (OUES) and ventilation to carbon dioxide production slope (V_E/VCO_2 slope), and attenuated muscle oxygenation (measuring oxygenated and deoxygenated hemoglobin) during peak cycling exercise test.

C. Methods

Participants

Fifty-one volunteers were recruited for this study. Three participants were excluded after the screening process and two participants were excluded from the data analysis as they did not achieve the peak exercise criteria. Twenty-three female breast cancer survivors, and 23 age- and BMI-matched healthy females completed this study. Participants were free of cardiovascular, metabolic, respiratory, or inflammatory autoimmune disease. All participants were non-smokers

and had no contraindication to exercise or any orthopedic limitation to cycling. Participants were fasted at least 4 hours before the study visit. The study visits were conducted either morning or afternoon. Additionally, they abstained from alcohol or caffeine for 12 hours and exercise for at least 24 hours before the visit to the laboratory. Over- the -counter medications were not allowed for 7 days prior to each study visit. The breast cancer survivor group was treated with chemotherapy and/or radiation therapy for a minimum of 3 months, and up to 15 years prior to enrollment. Participants that reported at least ≥150 minutes of moderate activity per week using the Paffenbarger Physical Activity Questionnaire (159), were categorized as physically active. Participants provided written informed consent before the study visit and the study was approved by the Institutional Review Board of the University of Illinois at Chicago

Study Design

After completing the consenting process, participants were screened for inclusion with the following procedures: health history questionnaire, resting blood pressure measurements, body mass index determination (BMI), and pulmonary function testing. Participants were excluded from the study if they had one of the following: a) blood pressure greater than 159/100 mmHg or more than two antihypertensive medications (beta blockers were not allowed for this study), b) BMI over 35 kg/m^2, and c) predicted forced expiratory volume in one second (FEV1) <80%. Participants who passed all the screening measurements, next completed a waist circumference and body composition assessment. Following this, participants were placed in a seated position for at least 10 min before the baseline seated measurements of stroke volume (SV), heart rate (HR), and muscle oxygenation, as this position will offer appropriate comparison with the measurement at peak exercise. After the baseline seated measurements, participants underwent a peak cardiorespiratory exercise test on an upright cycle ergometer.

Body Composition

Body composition was assessed using a dual energy X-ray absorptiometry device (DEXA) (GE Lunar iDXA, GE Healthcare, Madison, WI, USA), which was calibrated prior to each participant . Total leg fat mass was obtained from the DEXA body composition report in order to control the effect of leg adipose tissue on muscle oxygenation measurements. The depth of the adipose tissue on the right vastus lateralis was measured with Doppler ultrasound (ProSound α7, Hitachi-Aloka, Tokyo, Japan). Waist circumference was measured to the nearest mm using Seca 201 retractable tape measure at the level of the umbilicus.

Cardiorespiratory Capacity

Cardiorespiratory capacity was measured on an upright cycle ergometer (Excaliber Sport, Lode, The Netherlands) using a metabolic cart (TrueOne 2400, Parvo Medics, Sandy, UT, USA). The tests started at 20-30 W and increased 20-30 W every 3 min until volitional exhaustion. The initial intensity and progression (20 or 30 W) for each participant were selected based on the reported physical activity and age of the participants. VO_{2peak} was averaged using 15-sec epochs, and the highest value obtained during the last stage was used. Three out of four criteria had to be satisfied for achieving VO_{2peak} (respiratory exchange ratio ≥1.10, peak heart rate within 10 bpm of age-predicted maximum, peak rating of perceived exertion ≥17, volitional exhaustion – defined as falling below 60 rpm despite verbal encouragement). The participants had HR, blood pressure and rating of perceived exertion measurements made at the end of each stage. The breast cancer survivors who met higher risk stratification criteria, based on ACSM guidelines (2), were prepped with electrodes for a 12-lead electrocardiogram (Quinton Q-Stress, Cardiac Science, Bothell, WA) and monitored by a physician during the peak exercise test.

Cardiac Function Measurements

Aortic diameter was measured at the leaflets of the aortic valve with a high-fidelity ultrasound (ProSound α7, Hitachi-Aloka, Tokyo, Japan) using 2.5- to 5.0-MHz phased-array probe in the parasternal long-axis view, while the participant was in the supine position. Aortic diameter was also measured in seated position, but the quality of the ultrasound images was not appropriate due to scar tissue formation and reconstruction amongst the breast cancer participants, hence supine aortic diameter values were used in the SV calculations. Because diameter was assessed at the leaflets and not the proximal junction, the diameters should be very stable between the supine and upright positions. Doppler echocardiography was used to measure aortic blood flow velocity where a pedoff probe in the supersternal notch as previously described (178) at baseline and during the last 30 seconds of each stage of the cardiorespiratory test. SV was calculated as $SV = \pi \times (LVOT^2/2) \times VTI$, where LVOT = left ventricular outflow tract diameter and VTI = subvalvular velocity time integral (104). This method has been previously validated and recommended for noninvasive SV measurements (18, 104). Cardiac output was calculated as SV multiplied by HR.

Pulmonary Function Measurements

The outcomes used to evaluate pulmonary function from the peak exercise tests were the OUES and V_E/VCO_2 slope. OUES is determined using Baba's method and equation: $VO^2 = a \times \log10\ V_E + b$, where a = OUES (8). OUES is estimated by the slope of the linear regression between the logarithm of V_E and VO_2 and represents the rate of increase in VO_2 in response to a given ventilation. Higher OUES values corresponds to more efficient oxygen uptake by the participant and it integrates cardiovascular, musculoskeletal, and pulmonary function, but it is mainly affected by pulmonary function (96). OUES has been validated in other

disease populations, such as multiple sclerosis (64) and patients with coronary artery disease (40). The V_E/VCO_2 slope was based on Wasserman's equation (221) by plotting V_E (L/min) as a function of VCO_2 (L/min) over the total duration of the maximal test. This variable is a measure of ventilatory efficiency, which expresses the matching of ventilation and perfusion within the pulmonary system (221). The V_E/VCO_2 slope has been shown to be a powerful predictor for mortality and hospitalization in certain populations, such as heart failure patients (4).

Muscle oxygenation

Muscle oxygenation was measured non-invasively with near-infrared spectroscopy (NIRS) (OxiplexTS, ISS Inc., Champaign, IL), and measures oxygenated (HbO_2), deoxygenated (HHb) and total hemoglobin (Hb) and muscle tissue oxygenation index (TOI). TOI is determined from the equation: TOI = [HbO2]/ ([HbO2] + [HHb]) x 100. The NIRS probe was placed on the right vastus lateralis, 10-15 cm from the right knee joint, and supported with a cohesive bandage for the measurements at baseline and during the cardiopulmonary exercise test. The cohesive bandage kept the NIRS probe stable in the same location during the exercise test. Ultrasonography was used to measure the depth of the muscle and control for adipose tissue thickness. NIRS data were recorded at 2 Hz and averaged into 30 sec bins for the off-line analyses. Baseline TOI, HbO_2, HHb, and Hb were calculated off-line using a two-min average recording. Peak TOI, HbO_2, HHb, and Hb were calculated off-line using the last 30 sec of the exercise test.

Statistics

To address how we calculated the present sample size, a priori power analyses. were conducted after calculating mean change values and standard deviations from α previous study

(115), using a power of 0.80 and a = 0.05. An a priori analysis using change in cardiac output between baseline and peak exercise (effect size = 0.86) resulted in a sample size of 46 participants (n= 23 per group). Using previous data (62) with muscle oxygenation during submaximal exercise in breast cancer survivors, an a priori power analyses (effect size = 0.93) resulted in a sample size of 40 participants (n= 20 per group). Using the preliminary data in OUES from our pilot study in breast cancer survivors, an a priori analysis (effect size = 1.09) resulted in 30 participants (n=15 per group).

Statistical analyses were performed using SPSS version 24.0 (IBM Corporation, Armonk, NY) and an *a priori* level set at $p<0.05$. Normal distribution was assessed via histograms, Q-Q plots, and Shapiro-Wilk tests. Independent *t*-tests were conducted to compare descriptive characteristics and pulmonary variables. A Chi-Square test was conducted to evaluate differences in physical activity between breast cancer survivors and controls. Independent *t*-tests were also conducted to evaluate if differences exist between breast cancer survivors and controls in baseline values of cardiac hemodynamics and muscle oxygenation, in case the need to covary for group differences were needed. A group (breast cancer survivors, controls) by time (baseline, peak exercise) repeated measures ANOVA was used to evaluate group differences in cardiac hemodynamic and muscle oxygenation variables. *Post hoc* analyses were conducted using a Bonferroni correction when a significant time or group effect were detected. Change values of cardiac hemodynamics and muscle oxygenation variables were estimated by calculating the difference between baseline and peak values.

D. Results

Descriptive Characteristics and Baseline Pulmonary Variables

Descriptive characteristics and baseline pulmonary variables are presented in **Table 2**. There were no differences in anthropometric measurements between the breast cancer survivors and control group. Additionally, there were no differences in aortic diameter between the two groups. Moreover, there were no differences in baseline pulmonary variables evaluated by FVC, FVC % predicted, FEV1, and FEV1 % predicted.

Cardiac Hemodynamics at Baseline and at Peak Exercise

There were no differences in baseline values of HR, CO, COindex and SV (**Table 5**). However, breast cancer survivors had lower baseline SVindex compared to the control group (**Table 5**, $p<0.05$). Non-normally distributed variables (ΔCOindex, HR,SV,SVindex) were log transformed to meet the assumptions of parametric analyses. Reciprocal transformation was conducted for COindex to meet assumptions of parametric analyses. All the hemodynamic variables (HR, SV, SVindex, CO, COindex) increased at peak exercise compared to baseline (**Table 5**, $p<0.001$). Group effects were detected for HR and SVindex, with breast cancer survivors having higher HR and lower SVindex (**Table 5**, $p<0.05$). There were no group by time interactions (**Table 5**) or differences in change values (**Table 6**) for these cardiac hemodynamic variables. The pattern of COindex (**Figure 5**) and SVindex (**Figure 6**) response during the first five stages of the cycling exercise test were similar. Stage 6 and stage 7 were excluded from the SVindex and COindex figures, because 85% or more of the participants did not achieve those stages.

Cardiopulmonary Variables at Peak Exercise

Breast cancer survivors were not different from the control group in absolute or relative VO_{2peak}, V_E/VCO_2 slope, OUES, V_E, or the respiratory exchange ratio (**Table 7**)

Muscle Oxygenation at Baseline and at Peak Exercise

TOI decreased at peak compared to baseline (**Table 8** $p<0.001$), and Total hemoglobin and HHb increased at peak compared baseline (**Table 8**, $p<0.001$). There were no group effect or time by group interactions for TOI, total hemoglobin, HHb and HbO2, as well as no differences in the change values (**Table 9**). Total hemoglobin, HbO2, and HHb were log transformed to meet the assumptions of parametric analyses. Reciprocal and square root transformation were conducted for TOI and Δ HHb respectively, to meet the assumptions of parametric analyses.

E. Discussion

Our main findings were that breast cancer survivors do not differ in terms of the variables we used to assess cardiac, pulmonary, or muscle function, when compared to an age-matched control group. While not anticipated and in contrast to previous work (115, 119, 161), breast cancer survivors did not exhibit lower absolute or relative VO_{2peak} compared to the control group. To our knowledge, this is the first study to evaluate all three primary physiological factors (cardiac, pulmonary, and muscle) that contribute to cardiorespiratory fitness during peak exercise in breast cancer survivors.

Cardiac Hemodynamic Variables at Baseline

The baseline comparisons in our study showed that breast cancer survivors had a lower SVindex compared to the control group. This is in accordance with previous work demonstrating that breast cancer survivors tend to have lower resting SV (115), and resting SVindex values (12) compared to controls. The reduced resting SVindex in breast cancer survivors may reflect the reduced cardiac contractility, impaired diastolic function or reduced left ventricular end-diastolic volume, as a side effect of the cancer therapies. In contrast, some studies did not observe

differences in resting SV (119, 123) between breast cancer survivors and controls. Differences between these studies and the current study may be related to variances in study designs. For instance, Khouri et al. (119) did not age match their groups (6 yr difference) as we did, and Koelwyn et al. (123) had a longer time period post cancer therapy compared to our groups (6.5 yrs vs. 3 yrs, respectively). It may take a longer time period to recover from cardiac damage that chemotherapies may impose.

We report no differences in baseline HR in our cohort, while previous studies in breast cancer survivors have shown a discrepancy in resting HR, with some reporting resting HR 16-20% higher compared to controls (115, 119), and others reporting no differences (12, 123). Interestingly, the studies that reported higher baseline HR in breast cancer survivors, also report reduced VO_{2peak} compared to the control group (115, 119), suggesting autonomic dysfunction may play a role in diminished aerobic reserves. It is difficult to determine which branch of the autonomic nervous system may contribute to higher HRs in these studies, as it could be reduced parasympathetic function and/or increased sympathetic modulation. In contrast, our study and Koelwyn et al. (123) demonstrate no group differences in resting HR coupled with no differences in VO_{2peak}. While we did not specifically assess cardiac autonomic function in this study, we believe our two groups are not different in this regard given similar resting HR values, which may help explain the lack of difference in aerobic fitness between them as well.

We report no differences in baseline CO and COindex between breast cancer survivors and the control group at rest, as well as during the exercise test. Even if there is a discrepancy in baseline HR and SV between different studies as we described previously, baseline CO in breast cancer survivors was not different than controls in the other studies as well (115, 119, 123). This

suggests that breast cancer survivors can preserve or rescue resting CO post-cancer therapies via SV and/or HR, as previously described above.

Cardiac Hemodynamic Variables at Peak Exercise

The results of our study showed no differences in cardiac hemodynamic variables between breast cancer survivors and controls in response to the cycling exercise test. As we would expect, all the cardiac hemodynamic variables (HR, SV, SVindex, CO, COindex) increased at peak exercise compared to baseline, but the two groups did not exhibit differences in change values for these cardiac hemodynamic variables. Similarly, the pattern of COindex (**Figure 5**) and SVindex (**Figure 6**) response during exercise were the same between breast cancer survivors and controls, which likely contributes to the similar VO_{2peak} between groups. In contrast to our results, Beaudry et al. (12) reported at 30% lower VO_{2peak} between breast cancers survivors prior to therapy compared to a control group, which was explained in part by a reduced cardiac index of~ 30% at peak exercise in breast cancer survivors. Using cardiac MRI data conducted during supine exercise the cardiac index reductions are explained by lower SV and not HR during exercise. Reduced SV in this study (12) was explained by reduced end-diastolic volume and not ejection fraction, suggesting that breast cancer survivors may be predisposed to diastolic dysfunction before undergoing chemotherapies. While body size may have played a role, it is important to note that body surface area was similar between the two groups (12). Interestingly, 45% of the variance in VO_{2peak} in this study (12) was explained by cardiac output, suggesting that other factors such as pulmonary function, muscle blood flow and oxygenation may also contribute to limited VO_{2peak} in breast cancer survivors prior to chemotherapy. Beaudry et al. (12) is one of the first studies to contribute to the understanding of whether exercise intolerance and factors associated with it may predispose women to breast cancer.

Additionally, breast cancer survivors have demonstrated a 14 % reduction in peak SV (cardiac MRI while supine cycling) between their pre and post-chemotherapy period (12 months), regardless if they followed an exercise training program or not following the cancer therapies (75), suggesting that other factors, such as pulmonary and/or muscle function may have contributed to the reduction in VO2peak, with more decrements possible in the untrained group. The discrepancy between our results and these two previous studies (12, 75) may relate to differences in the time post chemotherapy and/or radiation therapy, since participants in our study were near 3 yrs since their respective cancer treatments. Another important difference is our breast cancer survivors did not have a reduced VO_{2peak} compared to the control group. Moreover, in our study we excluded participants with comorbidities, which is not clarified in the previous two studies (12, 75). Collectively, time after cancer therapy and comorbidities may have an effect in SV in breast cancer survivors.

Importantly, our results are supported by a cross-sectional study, where there were no differences in stroke volume changes from baseline to peak cycling exercise between breast cancer survivors and a control group (115). Moreover, Koelwyn et al. (123) showed no differences in the change of HR, SV and CO between baseline and 75% of the subject's maximal work rate. With no group differences observed in these cardiac hemodynamic variables with exercise, it is not surprising that aerobic capacity was similar between the groups as well (123). This suggests that preventing or rescuing reduction in VO_{2peak} after cancer therapies in breast cancer survivors, potentially with aerobic exercise, can prevent cardiac hemodynamic dysfunctions during exercise. Eleven breast cancer survivors in our study were engaged in moderate to vigorous aerobic activity for at least 150 min per week, and this might contribute to the similar VO_{2peak} compared to the control group. Importantly, the average time post-cancer

therapies in our study and others (115, 123) were more than 3 years, suggesting that cardiac hemodynamic impairments due to cancer treatments may recover after a period, but it is difficult to ascertain in our study as almost half of our breast cancer survivors were also very active. Future work would need to be conducted to fully examine this concept. Taken together, our results suggest that cardiac hemodynamics during exercise are rescued or maintained in breast cancer survivors, at least 3 years after the completion of their cancer therapies and when VO_{2peak} is rescued or maintained post-cancer therapies.

Pulmonary variables

We observed no differences between groups in baseline measurements of FVC and FEV1, as well as percent predicted FVC and FEV1. In contrast, follow-up studies in breast cancer survivors have shown a decline in spirometry values, such as FVC and FEV1; however, this may be associated with the short-time period post-cancer therapy in these studies (3-9 mo follow-up) (92, 205). Our data are in accordance with previous work, reporting no differences in FVC and FEV1, where mean time after therapy was at least 33 months (109, 155). Therefore, acute pulmonary function in breast cancer survivors due to chemotherapies and radiation therapies, may recover or is maintained 3 yrs post- cancer treatments. The fact that breast cancer survivors had no differences in FVC and FEV1 compared to the control group suggests that ventilatory mechanics are not impaired among breast cancer survivors, and assessing these parameters after exercise would be a next step to further evaluate pulmonary function.

In response to peak aerobic exercise, we report no differences in our main pulmonary variables (V_E/VCO_2 slope, OUES, V_E, and the respiratory exchange ratio) between the breast cancer survivors and control groups. This suggests that breast cancer survivors did not exhibit any ventilatory inefficiency, and they were able to effectively modulate $V_{E,}$ while the metabolic

and anaerobic production of VCO_2 were increasing during the exercise test. Additionally, it suggests that breast cancer could efficiently diffuse oxygen from the lungs into circulation, extract O_2 by the muscles, and transport CO_2 back to the lungs. In accordance with O'Donnell's (155) study, breast cancer survivors had similar V_E/VCO_2 slopes compared to controls, suggesting that breast cancer survivors did not exhibit ventilatory inefficiency during the exercise tests. In contrast to our study, breast cancer survivors in O'Donnell's (155)study had lower V_E and inspiratory capacity at peak exercise, compared to controls. Lower inspiratory capacity during exercise is related to inspiratory muscle weakness, which is also a side effect of radiation and chemotherapy. Potential factors for this discrepancy in V_E at peak exercise between our study and O'Donnell's (155) might be the differences in age (50 vs 61yrs) of the breast cancer participants. Moreover, 50% percent of the breast cancer participants in O'Donnell's (155) study were defined as physically active (exercised regularly at least twice per week), but no information is provided on the type or intensity of exercise. In our study, active participants were defined differently (at least 150 minutes of moderate activity per week), with 11 breast cancer survivors reporting 150 min of moderate or vigorous aerobic activity.

To our knowledge, previous studies have not evaluated OUES in breast cancer survivors. Previous studies in other populations with impaired pulmonary and/or cardiac function have shown lower OUES compared to controls (64, 141). However, breast cancer survivors in our study did not exhibit lower OUES, suggesting proper delivery and extraction of oxygen during the cycling test. The similar pulmonary variables in our study could, in part, be explained by the physical activity status of the breast cancer survivors, as 11 of them were engaged in moderate to vigorous aerobic activity for at least 150 min per week. Therefore, our results suggest that breast

cancer survivors in our study were able to rescue or maintain pulmonary function, potentially due to their rescued or maintained fitness level or the time post-cancer therapy.

Muscle Oxygenation

Interestingly, our study showed no differences in baseline tissue oxygenation between the two groups as well. This would not be anticipated based on previous animal and human work (186, 195, 199, 229), reporting that chemotherapies lead to muscle dysfunction and muscle fatigue via morphological (199), enzymatic (195) calcium release (229), and contractile alterations (212). Even before or during chemotherapy, cancer patients tend to have reduced (≈ 20%) muscle fiber cross-sectional area, suggesting that cancer is associated with reduced muscle function and thus exercise intolerance, before completion of the cancer therapies (206). Moreover, we observed that breast cancer survivors had similar muscle oxygenation responses at peak exercise, compared to the control group.

Similar to previous work (62), TOI decreased at peak compared to baseline, and total hemoglobin and HHb increased at peak compared baseline, as a result of increased need for O_2. Previous work has shown that HHb and TOI increases during exercise reflecting higher muscle microvascular O_2 extraction (17, 72). Additionally, total hemoglobin is expected to increase as well, as local blood flow is increased in the leg muscles during cycling exercise. Previous literature in muscle oxygenation in breast cancer survivors at peak exercise has been very limited. A previous cross-sectional study reported reduced exercise response of TOI, total hemoglobin and HHb in cancer survivors compared to controls (62), suggesting impairment in O_2 delivery and extraction during exercise. However, it is difficult to compare to our study due to two differences: a) Ederer et al. (62) evaluated tissue oxygenation at submaximal levels (up to the ventilatory threshold) during cycling exercise, b) the sample size was very small (only 8

subjects) including different types cancer patients (7 female and 1 male cancer patient). In our study, the similar exercise responses between groups in TOI, HHb and Hb suggests that breast cancer survivors did not exhibit any impairment in delivering and extracting O_2 into the muscles at peak exercise. Thus, breast cancer survivors may have rescued or preserved muscle function, when they have similar aerobic capacities compared to non-breast cancer survivors individuals

Limitations

Our study has some limitations that should be considered. First, this is a cross-sectional study and therefore we cannot distinguish if the cardiac, pulmonary and muscle function variables in this study were rescued or maintained after the cancer therapies. Second, this study aimed to measure stroke volume during the last completed stage of the cycling test; however, the quality of measurements in 26% of the participants were not ideal, thus "peak" SV data presented here stems from the 2nd to last stage of exercise. Third, aortic diameter was obtained in the supine position, but exercise cardiac hemodynamics were obtained in the seated exercise position, and this may provide some artifact of the data. Aortic diameter may differ between supine and seated position, as previous literature has shown that hemodynamic variables can also differ between the two positions due to different hydrostatic pressures. However, because of similar diameters in the supine position, we believe differences, if any, would be minimal in the upright position. Forth, the cancer treatment plans of the participants varied, and the inclusion criterion was chemotherapy and/or radiation therapy. As a result, 7 participants (30% of breast cancer survivors) had underwent only radiation therapies, and therefore had likely avoided any potential cardiovascular impairments due to a chemotherapy regimen. However, this is common in this population and we aimed for results that are relatable to the general breast cancer population. Fifth, the NIRS probe was attached on a specific spot on the right vastus lateralis,

and this would not allow to examine physiological differences in the whole muscle. Sixth, our study design did not control for physical activity, and the inclusion of 11 aerobically well-trained breast cancer survivors likely affected the VO_{2peak} in this group. Seventh, the time post-cancer therapy had a large range in our study (from 3 months to 15 years), and the variables of our study might be differentially affected varying times after therapies. Last, this study did not evaluate local blood flow in the right leg, which might be another contributor to cardiorespiratory fitness in breast cancer survivors. Future work is still required to evaluate all three primary physiological factors (cardiac, pulmonary, and muscle) during exercise in breast cancer survivors, when VO_{2peak} is different compared to the control group.

F. Conclusions

We aimed to examine what physiological factors affect cardiorespiratory fitness in breast cancer survivors by evaluating cardiac, pulmonary and muscle variables at peak cycling exercise. The results of our study suggest that breast cancer survivors with rescued or maintained cardiorespiratory fitness do not exhibit differences in cardiac, pulmonary, and muscle function at peak exercise compared to controls. These results depict the importance of preserving or rescuing cardiorespiratory fitness after cancer treatments, and health practitioners should focus the rehabilitation methods on this direction in breast cancer survivors. Future studies are required to evaluate physiological factors in breast cancer survivors and control for physical activity after the completion of cancer therapies.

Table 2. Descriptive characteristics

	BCS (n=23)	**Control (n=23)**	**p-value**
Age (yrs)	50±9	49±9	0.735
Height (cm)	165.3±6.1	163.2±5.4	0.224
Weight (kg)	69.6±9.1	68.6±14.1	0.438
BMI (kg/m^2)	25.5±2.9	25.7±4.6	0.796
Waist Circumference (cm)	86.5±7.5	84.3±13.8	0.502
Body Surface Area (m^2)	1.78±0.14	1.76±0.20	0.567
Total Body Fat (%)	37.9±6.7	33.9±7.6	0.064
Right Leg Adipose Tissue Depth (cm)	1.01±0.29	0.92±0.27	0.271
Total Leg Fat Mass (kg)	9.2±2.2	8.2±2.4	0.138
Aortic Diameter (cm)	1.94±0.15	1.97±0.14	0.525
FVC (L)	3.44±0.64	3.33±0.55	0.526
FVC predicted (%)	97±13	101±12	0.298
FEV1 (L)	2.75±0.46	2.63±0.49	0.381
FEV1 predicted (%)	97±10	99±12	0.532
SBP (mmHg)	116±11	117±13	0.905
DBP (mmHg)	74±8	74±9	0.946
MAP (mmHg)	88±8	88±10	0.991
Physical Activity*	(11/23)	(20/23)	**<0.05**
African American (n/total)	(3/23)	(7/23)	
Caucasian (n/total)	(16/23)	(11/23)	
Asian (n/total)	(1/23)	(5/23)	
Hispanic (n/total)	(2/23)	(0/23)	

Data are mean ± SD.
BCS, breast cancer survivors
BMI, body mass index
FVC, Forced Vital Capacity
FEV1, Forced Expiratory Volume in One Second
SBP, systolic blood pressure
DBP, diastolic blood pressure
MAP, mean arterial pressure.
* Reported >150 minutes of moderate activity per week.

Table 3. Cancer Therapies

	BCS (n=23)
Time since last chemotherapy/radiation (months)	35±34
Chemotherapy	16/23
Radiation Therapy	19/23
Hormonal Therapy	21/23
Ovarian Suppression Therapy	5/23

Table 4. Medications

	BCS (n=23)	Control (n=23)
Angiotensin Receptor Blockers	-	4/23
Angiotensin-converting enzyme inhibitors	1/23	-
Calcium Channel Blocker	1/23	1/23
Diuretics	-	1/23
Statins	2/23	2/23
Thyroid Medication	2/23	5/23
Anticholinergics/Antimuscarinics	1/23	-
Sedative-Hypnotics	1/23	-
Anticonvulsants	1/23	1/23
Tetracycline Antibiotics	1/23	-
Proton-pump Inhibitors	1/23	1/23
Calcitonin Gene-related Peptide Antagonist	-	1/23
Laxatives	-	1/23
Allergy Pills	5/23	1/23
Anxiety-Depression Pills	2/23	1/23

Table 5. Cardiac hemodynamic variables at baseline and at peak exercise

	Group	Baseline	Peak	Time	Group	Interaction
Heart Rate (bpm)	BCS	68±9	175±10	**<0.001**	**<0.05**	0.565
	Control	64±9	168±13			
Cardiac Output (L/m)	BCS	3.41±0.71	11.95±3.07	**<0.001**	0.296	0.352
	Control	3.60±0.84	12.85±2.89			
Cardiac Output Index ($L/min/m^2$)	BCS	1.92±0.43	6.71±1.74	**<0.001**	0.178	0.474
	Control	2.06±0.48	7.31±1.34			
Stroke Volume (ml)	BCS	51±11	68±17	**<0.001**	0.072	0.904
	Control	57±11	77±17			
Stroke Volume Index (ml/m^2)	BCS	28.6±7.0[#]	38.4±9.8	**<0.001**	**<0.05**	0.904
	Control	32.4±6.1	43.5±7.5			

Data are mean ± SD.
BCS, breast cancer survivors.
All data presented are raw values.
Log transformation statistics are presented for heart rate, stroke volume, stroke volume index.
Reciprocal transformation statistics are presented for cardiac output index.
[#]Indepedent t-test for baseline stroke volume index indicted significant differences between breast cancer survivors and controls ($p<0.05$).

Table 6. Cardiac hemodynamic variables: Change values

	BCS (n=23)	Control (n=23)	p-value
Δ Heart Rate (bpm)	107±14	105±12	0.526
Δ Cardiac Output (L/m)	8.54±2.78	9.25±2.33	0.352
Δ Cardiac Output Index (L/min/m^2)	4.79±1.57	5.25±1.07	0.136
Δ Stroke Volume (ml)	17.7±11.9	20.0±10.4	0.497
Δ Stroke Volume Index (ml/m^2)	9.8±6.6	11.1±5.1	0.468

Data are mean ± SD.
BCS, breast cancer survivors.
All data presented are raw values
Log transformation statistics are presented for Δ Cardiac Output Index.

Table 7. Pulmonary variables at peak exercise

	BCS (n=23)	Control (n=23)	p-value
Absolute VO_{2peak} (L/min)	1.8±0.4	1.9±0.3	0.399
Relative VO_{2peak} (ml/kg/min)	26.6±7.0	28.4±6.0	0.338
VCO_{2peak} (L/min)	2.0±0.5	2.1±0.3	0.346
Ventilation (L/min)	74.8±17.9	77.9±12.5	0.502
Respiratory Exchange Ratio	1.11±0.06	1.11±0.07	0.712
Rating of Perceived Exertion	19±1	19±1	0.504
V_E/VCO_2 Slope	35.9±5.7	35.0±3.8	0.545
OUES	1693±393	1831±380	0.231

Data are mean ± SD.
BCS, breast cancer survivors
VO_{2peak}, peak oxygen uptake
VCO_{2peak}, Peak carbon dioxide production
FEO_2, fraction of oxygen in expired air
$FECO_2$, fraction of carbon dioxide in expired air
V_E/VCO_2 Slope, Slope of ventilation vs carbon dioxide production
OUES, oxygen uptake efficiency slope

Table 8. Muscle oxygenation at baseline and at peak exercise

	Group	Baseline	Peak	Time	Group	Interaction
TOI (%)	BCS	69.0±4.3	64.0±4.2	**<0.001**	0.749	0.375
	Control	70.3±5.3	64.0±6.0			
Total Hemoglobin (μM)	BCS	128±52	144±63	**<0.001**	0.367	0.943
	Control	148±69	165±75			
HbO_2 (μM)	BCS	89±39	93±44	0.299	0.375	0.629
	Control	106±51	107±52			
HHb (μM)	BCS	39±14	51±19	**<0.001**	0.462	0.213
	Control	43±19	58±26			

Data are mean ± SD.
BCS, breast cancer survivors
TOI, tissue oxygenation index
HbO_2, oxygenated hemoglobin
HHb, deoxygenated hemoglobin
Reciprocal transformation for TOI
Log transformation for total, HbO_2, and HHb.
All data presented are raw values.
Log transformation statistics are presented for total hemoglobin, HbO_2, and HHb.
Reciprocal transformation statistics are presented for TOI.

Table 9. Muscle oxygenation - Change values

	BCS (n=23)	Control (n=23)	p-value
Δ TOI (%)	-5.0±4.7	-6.3±3.9	0.334
Δ Total Hemoglobin (μM)	16±17	17±16	0.938
Δ HbO_2 (μM)	4.2±13.4	1.6±11.6	0.491
Δ HHb (μM)	12.1±7.0	15.0±9.2	0.299

Data are mean ± SD.
BCS, breast cancer survivors
TOI, tissue oxygenation index
HbO2, oxygenated hemoglobin
HHb, deoxygenated hemoglobin.
All data presented are raw values.
Square root transformation statistics are presented for Δ HHb.

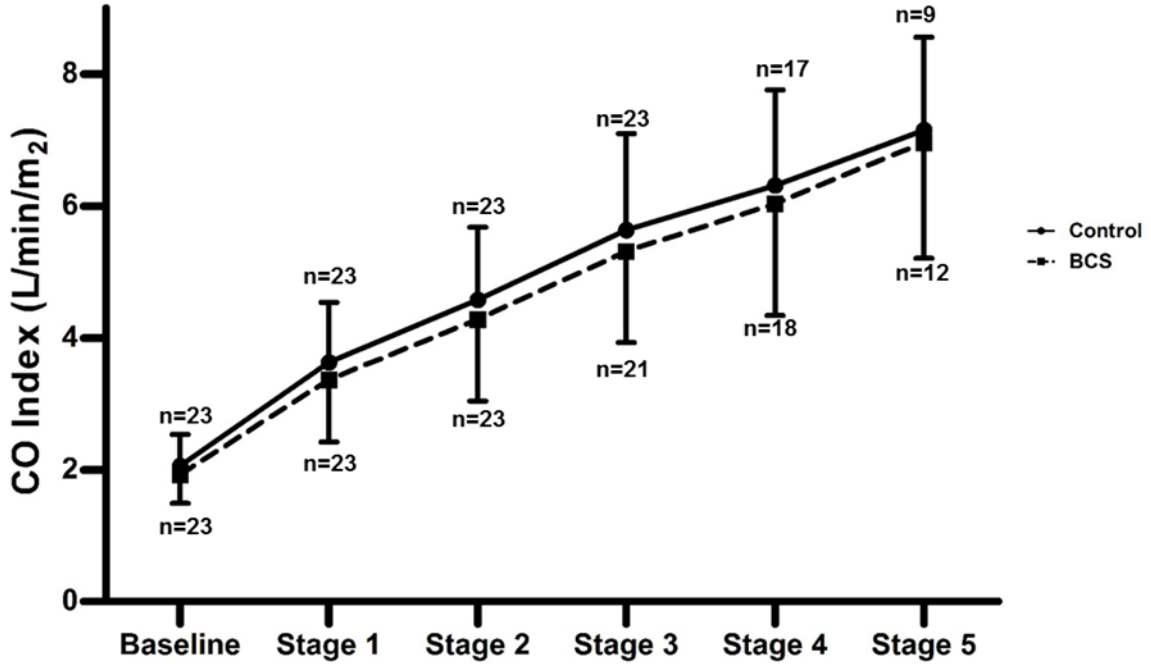

Figure 5. Cardiac output index responses during the cycling exercise test in breast cancer survivors and controls. BCS, breast cancer survivors; COIndex, cardiac output index. Data are mean ± SD.

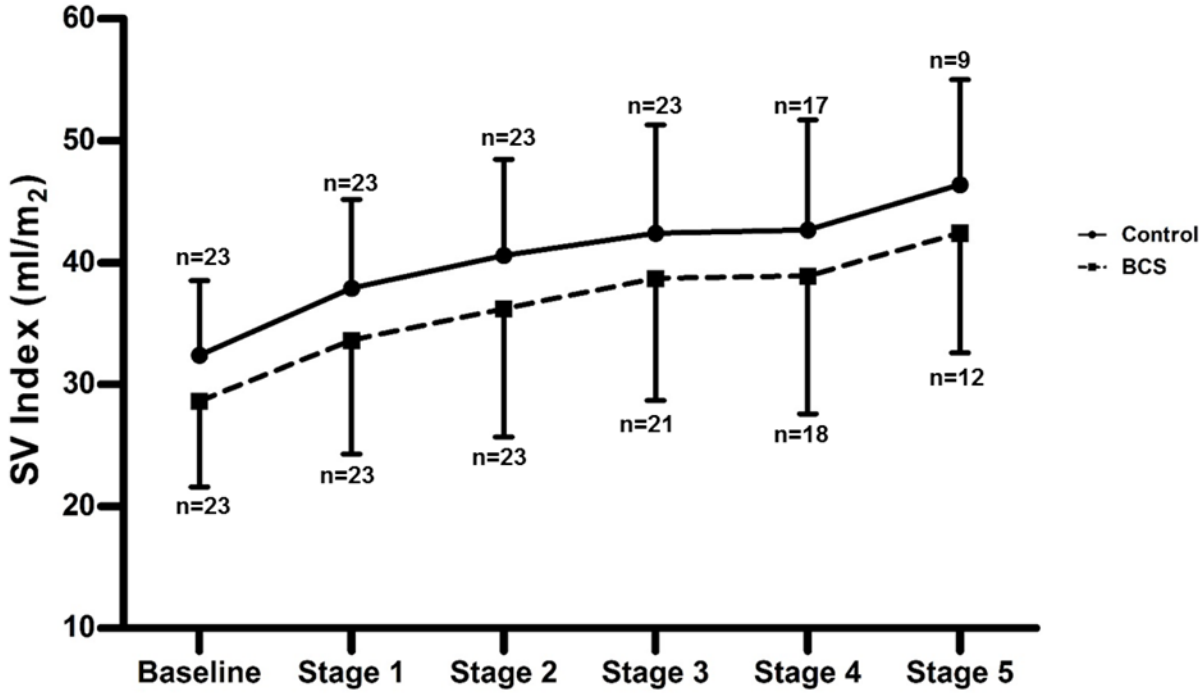

Figure 6. Stroke volume index responses during the cycling exercise test in breast cancer survivors and controls. BCS, breast cancer survivors; SV Index, stroke volume index. Data are mean ± SD.

Chapter IV: Summary of Results and Future Directions

Breast cancer survivors did not exhibit differences in $VO_{2peak,}$ nor cardiac, pulmonary or muscle function variables from baseline to peak exercise, compared to the control group. The results of our study suggest that breast cancer survivors can either rescue or preserve cardiac, pulmonary and muscle function following cancer therapies, when they exhibit similar aerobic fitness levels as their peers. Therefore, health practitioners should aim in preserving or improving VO_{2peak} in breast cancer survivors. To our knowledge, this is the first study that evaluated all three main physiological contributors (cardiac, pulmonary, and muscle) related to cardiorespiratory fitness, during peak cycling exercise.

In contrast to the previous literature, breast cancer survivors did not exhibit reduced cardiorespiratory fitness compared to the control group. Therefore, it was not surprising that the two groups had the same cardiac, pulmonary and muscle responses to peak exercise. The similar cardiorespiratory fitness between the two groups might be explained by the physical activity levels reported in 11 of the breast cancer survivors, who were engaged in moderate or vigorous aerobic exercise at least 150 min per week. Therefore, future studies should evaluate the same factors between physically active and non-physically active breast cancer survivors.

This study evaluated different variables related to pulmonary, cardiac and muscle function; however, our research is somewhat limited in that a comprehensive evaluation was not performed to assess more sophisticated aspects of these physiological factors. First, futures studies should evaluate other components of cardiac function, such as end diastolic volume and left ventricular ejection fraction at exercise that can be informative in regards to both diastolic and systolic function of the heart. Second, our study examined pulmonary variables related to

ventilatory mechanics. Future studies should also test diffusing capacity, and alveolar volume to examine potential limitations in oxygen transport from the lungs into the blood. A pre/post spirometry bronchodilator challenge could also be useful in rounding out the pulmonary picture. Third, our study evaluated muscle function via NIRS that assess muscle oxygenation levels. Future studies should aim in performing muscle biopsies, as this method can elucidate potential differences in morphological and biochemical characteristics of the muscles. Additionally, future studies are important to examine the same topic by evaluating local blood flow in the legs, which might be another contributor to cardiorespiratory fitness in breast cancer survivors.

This is a cross -sectional study that aimed to evaluate physiological factors in breast cancer survivors after cancer therapies with a range of 3 mo to 15 yrs. This study design cannot evaluate what factors may affect cardiorespiratory fitness during or before the period of the cancer treatments, and future longitudinal studies conducted before and after the completion of cancer therapies could thoroughly evaluate changes of cardiac, pulmonary and muscle function in the years following the cancer treatments. Moreover, future studies in this topic should aim to recruit breast cancer survivors with the same cancer treatment regimen; however, this is very challenging since the type (chemotherapy, radiation therapy, hormonal therapy, HER2 targeted therapy), frequency and doses of the cancer therapies vary substantially in this population.

The results of this study depict the importance of maintaining VO_{2peak} post-cancer treatments, and future studies should aim to identify effective methods to achieve this, as previous literature suggests that breast cancer survivors tend to have reduced $VO_{2peak.}$ This will not only help breast cancer survivors to improve their cardiorespiratory fitness, but also avoid cardiovascular disease, which is the main cause of death in this population.

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Chapter VI: Curriculum Vitae

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2015-Present	Ph.D. Candidate, Kinesiology and Nutrition University of Illinois at Chicago, Chicago, IL Advisor: Tracy Baynard, PhD
2011-2013	Master of Science in Exercise Science Northeastern Illinois University, Chicago, IL
2001-2006	Bachelor's degree, Physical Education and Sports Science Aristotle University of Thessaloniki

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TEACHING EXPERIENCE:

2015-Present	Department of Kinesiology & Nutrition, *Exercise Assessment and Programming, KN 345*, Graduate Teaching Assistant. 2 Laboratory sections, Enrollment: 20 students/section, University of Illinois at Chicago, IL
2010-2013	Athena Greek Academy - Chicago, Illinois. Taught Greek language and Greek folk dances in elementary Greek school
2003-2016	Taught Greek dances (Thessaloniki – flame of dance, Athens – Cultural Association, Chicago – Athena Greek Academy)

Invited Lectures

- Aerobic Exercise Testing. Presented to Exercise Assessment and Programming, KN 345, (every semester from Fall 2016 until present)
- Aerobic Exercise Programing. Presented to Exercise Assessment and Programming, KN 345, (every semester from Fall 2016 until present)
- Body Composition Measurements. Presented to Exercise Assessment and Programming, KN 345, Summer 2016
- Benefits of Physical Activity. Presented to Exercise Assessment and Programming, KN 345, Fall 2016
- Pre-participation Risk Screening in Physical Activity. Presented to Exercise Assessment and Programming, KN 345 Fall 2016

- Statistics in Kinesiology. Presented to Exercise Assessment and Programming, KN 345, Fall 2016
- Pre-exercise Health Evaluations. Presented to Exercise Assessment and Programming, KN 345, Fall 2016
- Does Fitness Matter? Exercise after Cancer Treatment. Presented to Gilda's cancer patient support center (11-6-18) and Cancer Wellness Center in Northbrook (1-24-19)
- Exercise Recommendations in Cancer Patients. Presented to Cancer Wellness Center in Northbrook (8619)
- Eating Well and Moving More. Presented to Cancer Wellness Center in Northbrook (10-17-19)
- Walk Away from Cancer and Cardiovascular Disease – The Importance of Physical Activity in Cancer Survivors. Presented to Cancer Wellness Center in Northbrook (1-24-19) and Kellogg Cancer Center in Evanston (8-5-19)
- Reviewing and Interpreting Research Papers. Presented to Exercise Assessment and Programming, KN 345, Summer 2020.

PROFESSIONAL EXPERIENCE:

University of Illinois at Chicago **Chicago, IL**
Research Assistant 2015- Present

Assisted in cardiovascular and exercise research projects in the Integrative Physiology Laboratory. Collected and analyzed data in human subjects. Conducted cardiovascular measurements in human subjects with a primary focus upon arterial, micro-vascular and cardiac function. Recruited subjects for participation in research studies.

United Rehab Providers **Chicago, IL**
Physical Therapy Assistant 2013

Supervised injury patients perform their prescribed exercise regiments

Health Clubs (Formula Health Club, Xsport Health Center) **Chicago, IL**
Group Exercise Instructor 2012-2013

Led group exercise classes in dance flow and in total body conditioning

Fitness & Wellness Center at Northeastern Illinois University **Chicago, IL**
Group Exercise Instructor 2011-2013

Led group exercise classes in dance flow and in total body conditioning

Pacific Labyrinth Health Club **Athens, Greece**
Personal Trainer 2007-2010

Personal trainer, body building and conditioning. Designed personal training programs for both groups and individuals for fat burning, body sculpting and circuit training programs

Health Club Stadium **Athens, Greece**
Power Lift Instructor 2007-2009
Created and trained clients in personal fitness programs for improved sport performance or power lifting programs with special emphasis on vibration training for speedy results

Health Clubs (Holmes Place, Palestra Active, Human, Let's Go) **Athens, Greece**
Group Exercise Instruct 2007-2010
Led classes in specialized aerobic and circuit training programs for weight loss and improved coordination, conditioning, and fitness in a positive team atmosphere.

MANUSCRIPT PUBLICATIONS – PUBLISHED

1. Rosenberg AJ, Schroeder EC, **Grigoriadis G**, Wee SO, Bunsawat K, Heffernan KS, Fernhall B, Baynard T. Aging reduces cerebral hemodynamic regulation following an acute hypertensive stimulus. *J Appl Physiol 128: 1186 –1195, 2020. First published April 2, 2020; doi:10.1152/japplphysiol.00137.2019*
2. Hibner BA, Hilgenkamp TIM, Schroeder EC, Motl RW, Bollaert R, Griffith G, **Grigoriadis G**, Baynard T, Fernhall B. Physical activity and aerobic capacity are associated with walking performance in multiple sclerosis. Physical Activity and Peak Oxygen Consumption are Associated with Walking in Multiple Sclerosis *Multiple Sclerosis and Related Disorders – 2020 Jan 9;40:101941*
3. **Grigoriadis G**, Rosenberg AJ, Lefferts WK, Wee SO, Schroeder EC, Baynard T. Similar effects of acute resistance exercise on carotid stiffness in males and females. *Int J Sports Med. 2020 Jan 5.* DOI https://doi.org/10.1055/a-1044-2321
4. Hilgenkamp TIM, Schroeder EC, Wee SO, **Grigoriadis G**, Rosenberg AJ, Baynard T, Fernhall B. Altered Central Hemodynamics in Individuals with Down syndrome. *Artery Research – Vol. 25(3); December (2019), pp. 107–112*
5. Bunsawat K, **Grigoriadis G**, Schroeder EC, Rosenberg AJ, Rader MM, Fadel PJ, Clifford PS, Fernhall B, Baynard T. Preserved ability to blunt sympathetically-mediated vasoconstriction in exercising skeletal muscle of young obese humans. *Physiol Rep, 7 (8), 2019, e14068*

MANUSCRIPTS PUBLICATIONS – IN REVIEW

1. Lefferts WK, Rosenberg AJ, Schroeder EC, **Grigoriadis G**, Sandroff B, Motl R, Baynard T. Effects of acute aerobic exercise on cerebrovascular hemodynamics and cognitive function in individuals with multiple sclerosis. In Revision: Submitted to "Int J MS Care"
2. Schroeder EC, Rosenberg AJ, **Grigoriadis G**, Wee SO, Horn GP, Smith DL, Fernhall B. Hemodynamic responses to different training environments in firefighters and instructors. Submitted to "European Journal of Applied Physiology"
3. Bunsawat K, **Grigoriadis G**, Wee SO, Fadel PJ, Clifford PS, Fernhall B, Baynard T. Obese adults do not exhibit impaired post-exercise arterial hemodynamics. Submitted to "Medicine Sciences Sports & Exercise"

MANUSCRIPTS PUBLICATIONS – IN PREPARATION

1. Wee SO, Schroeder EC, **Grigoriadis G**, Rosenberg AJ, Baynard T, Fernhall B. Effect of a Single Bout of Aerobic Exercise on Cerebral Blood Flow in Individuals with Down Syndrome.
2. **Grigoriadis G**, Sherman S, Schroeder EC, Lima N, Hibner BA, Baynard T. Physiological Factors Impacting Fitness in Breast Cancer Survivors.

REFEREED SCIENTIFIC ABSTRACTS: ORAL PRESENTATIONS

1. **Grigoriadis G**, Rosenberg AJ, Wee SO, Schroeder EC, Bunsawat K, Griffith G, Baynard T. sex differences in carotid strain following resistance exercise. *North American Artery Conference, Chicago 2017 *Best Abstract Award*
2. **Grigoriadis G**, Rosenberg AJ, Wee SO, Schroeder EC, Griffith G, Fernhall B, Baynard T. No sex differences in arterial stiffness and hemodynamics response to resistance exercise in older individuals. *American College Sports Medicine, Minneapolis 2018 – Thematic Poster Presentation*
3. **Grigoriadis G,** Rosenberg AJ, Wee SO, Schroeder EC, Bunsawat K, Fernhall B, Baynard T. sex differences in the influence of leg strength on arterial stiffness. *American College Sports Medicine, Denver 2017 – Thematic Poster Presentation*

REFEREED SCIENTIFIC ABSTRACTS: POSTER PRESENTATIONS

1. Lima NS, Rosenberg AJ, Schroeder EC, Lefferts WK, Sherman SR, **Grigoriadis G**, Baynard T. Increased cerebral blood velocity during acute resistance exercise is similar between young and older adults. *Experimental Biology, San Diego 2020.*

2. Sherman SR, Rosenberg AJ, Schroeder EC, Lefferts WK, Lima NS, **Grigoriadis G**, Baynard T. No sex differences in cerebral blood velocity responses during resistance exercise. *Experimental Biology, San Diego 2020.*
3. Burton LC, Wee SO, Schroeder EC, **Grigoriadis G**, Fernhall B, Hilgenkamp TIM. Oxygen pulse is reduced in individuals with down syndrome. *American College of Sports Medicine, San Francisco 2020.*
4. **Grigoriadis G**, Hibner BA, Schroeder EC, Rosenberg AJ, Griffith G, Sardeli AV, Danciu OC, Fernhall B, Baynard T. Acute effect of aerobic exercise on arterial stiffness in breast cancer survivors: preliminary results. *American College of Sports Medicine, Orlando 2019.*
5. **Grigoriadis G**, Hibner BA, Schroeder EC, Rosenberg AJ, Danciu OC, Fernhall B, Baynard T. Breast cancer survivors improved forearm blood flow following a single bout of aerobic exercise: Preliminary results. *Experimental Biology, Orlando 2019.*
6. **Grigoriadis G**, Hibner BA, Schroeder EC, Rosenberg AJ, Danciu OC, Fernhall B, Baynard T. Similar effects of acute aerobic exercise on hemodynamics in breast cancer survivors: Preliminary results. *North American Artery, Iowa 2019.*
7. Lima NS, Rosenberg AJ, **Grigoriadis G**, Schroeder EC, Lefferts WK, Baynard T. Visceral adiposity is associated with lower cerebral blood velocity in older adults. *American College of Sports Medicine, Orlando 2019.*
8. Wee SO, Schroeder, **Grigoriadis G**, Alexander AJ, Kanokwan B, Baynard T, Fernhall B. Vascular response to submaximal intensity aerobic exercise in individuals with down syndrome. *American College of Sports Medicine, Orlando 2019.*
9. Hilgenkamp TIM, Wee SO, **Grigoriadis G**, Schroeder EC, Baynard T, Fernhall B. Central hemodynamic response to lower body negative pressure in individuals with down syndrome. *Artery International Conference, Hungary - Budapest 2019.*
10. Ando A, Baynard T, Carmona-Powell E, **Grigoriadis G**, McMillan N, Ansari S, Caldwell J, Dabbas W, Chen J, Fernhall B, Ricardo AC. Resistance exercise training in chronic kidney disease: a randomized pilot trial. *American Society of Nephrology – Annual Meeting 2019.*
11. **Grigoriadis G**, Rosenberg AJ, Wee SO, Schroeder EC, Griffith G, Baynard T. Sleep quality is associated with cerebrovascular function in individuals with multiple sclerosis. *Artery International Conference, Guimaraes, Portugal 2018.*
12. **Grigoriadis G**, Rosenberg AJ, Wee SO, Schroeder EC, Griffith G, Baynard T. Sleep quality is associated with cerebrovascular function in individuals with multiple sclerosis. *North American Artery Conference, Chicago 2018.*
13. **Grigoriadis G**, Rosenberg AJ, Wee SO, Schroeder EC, Griffith G, Baynard T. Acute effect of aerobic exercise on carotid strain in individuals with multiple sclerosis. *Experimental Biology, San Diego 2018, CA.*
14. Rosenberg AJ, Schroeder EC, **Grigoriadis G**, Wee SO, Griffith G, Fernhall B, Baynard T. The influence of aging on central artery stiffness and cerebral vascular function following an acute bout of leg extension/flexion exercise. *Experimental Biology, San Diego 2018, CA.*
15. Schroeder EC, Rosenberg AJ, **Grigoriadis G**, Wee SO, Fernhall B, Baynard T. Differences in autonomic recovery following maximal resistance exercise in young and older adults. *Experimental Biology, San Diego 2018, CA.*

16. Wee SO, Schroeder EC, **Grigoriadis G**, Bunsawat K, Rosenberg AJ, Griffith G, Baynard T, Fernhall B.
cerebral blood flow characteristics responses following acute aerobic exercise in individuals with and without Down syndrome. *Experimental Biology 2018 , San Diego, CA*
17. Bunsawat K, **Grigoriadis G**, Wee SO, Griffith G, Fernhall b, Baynard T. Cardiac Autonomic Modulation Following Acute Aerobic Exercise in Young Obese Adults. *American college of Sports Medicine, 2018, Minneapolis.*
18. Griffith G, Rosenberg AJ, **Grigoriadis G**, Bunsawat K, Wee SO, Schroeder EC, Saed B, Baynard T. Cardiometabolic Prediction Equations Overestimate cardiorespiratory fitness for treadmill and cycle ergometry in multiple sclerosis patients. *American college of Sports Medicine, 2018, Minneapolis.*
19. Wee SO, Schroeder EC, **Grigoriadis G**, Rosenberg AJ, Kanokwan B, Garett G, Baynard T, Fernhall B, Effects of acute aerobic exercise on cognitive function in individuals with Down syndrome. *2018 American College of Sports Medicine Southwest Chapter. Long Beach, CA.*
20. **Grigoriadis G**, Rosenberg AJ, Wee SO, Schroeder EC, Hilgenkamp TIM, Griffith G, Baynard T. Effects of aerobic capacity on arterial stiffness in individuals with multiple sclerosis. *Experimental Biology, Chicago, 2017.*
21. Griffith G, Hilgenkamp TIM, Rosenberg AJ, **Grigoriadis G**, Bunsawat K, Wee SO, Schroeder EC, Saed BM, Baynard T. Treadmill vs. cycle ergometry graded exercise test responses in multiple sclerosis patients. *American College of Sports Medicine Annual meeting, Denver 2017, CO.*
22. Rosenberg AJ, Wee SO, Schroeder EC, Bunsawat K, **Grigoriadis G**, Griffith G, Fernhall B, Baynard T. Effect of Acute Resistance Exercise on arterial hemodynamics and cerebral blood flow dynamics: does sex matter? *Artery International Conference, Pisa, Italy 2017.*
23. Rosenberg AJ, Wee SO, Schroeder EC, **Grigoriadis G**, Bunsawat K, Griffith G, Baynard T. Effect of age on cerebral blood flow dynamics following acute resistance exercise. *2017 American Physiological Society Conference: Cardiovascular Aging, New Frontiers and Old Friends.*
24. Rosenberg AJ, Wee SO, Schroeder EC, Bunsawat K, **Grigoriadis G**, Saed BM, Fernhall B, Baynard T. Effect of sex on arterial hemodynamics and cerebral blood flow dynamics following acute resistance exercise. *American College of Sports Medicine, Denver, 2017.*
25. Bunsawat K, **Grigoriadis G,** Griffith G, Wee SO, Schroeder EC, Fernhall B, Baynard T. Muscle blood flow responses to dynamic handgrip exercise in young obese adults. *American College of Sports Medicine, Denver, 2017.*
26. Bunsawat K, **Grigoriadis G**, Wee SO, Griffith G, Brown MD, Phillips SA, Fadel PJ, Clifford PS, Fernhall B, Baynard T. No evidence of impaired functional sympatholysis in young obese adults. *Experimental Biology, Chicago, 2017.*
27. Rosenberg AJ, Wee SO, Schroeder EC, **Grigoriadis G**, Bunsawat K, Hilgenkamp TIM, Griffith G, Baynard T. The effects of acute aerobic exercise on cerebral blood flow and cognition in persons with multiple sclerosis. *Experimental Biology, Chicago, IL. Abstract: 2017.*

28. Rosenberg AJ, Wee SO, Schroeder EC, **Grigoriadis G**, Bunsawat K, Griffith G, Baynard T. Effect of age on carotid artery circumferential strain following acute maximal resitance exercise. *North American Artery Conference, Chicago 2017.*
29. **Grigoriadis G**, Bunsawat K, Fernhall B, Baynard T. Blood pressure variability and baroreceptor sensitivity in normotensive obese in response to aerobic exercise. *Artery Research, Volume 16, December 2016, Page 93-94.*
30. **Grigoriadis G**, Wee SO, Griffith G, Rosenberg AJ, Bunsawat K, Fernhall B, Baynard T. Blood pressure and wave separation analysis: lower body negative pressure in individuals with Down syndrome. *Med Sci Sports Exerc.* 48(5 Suppl 1): 840, May 2016.
31. **Grigoriadis G**, Bunsawat K, Hilgenkamp TI, Baynard T. Females have altered hemodynamics during exercise recovery with caffeine consumption. *FASEB J. April 2016; 30(1): LB744.*
32. Bunsawat K, **Grigoriadis G,** Fernhall B, Baynard T. Sympathetic vasoconstrictor response to lower body negative pressure in young obese adults: the preliminary finding. *Artery Research, Volume 16, December 2016, Page 67. Presented at Artery International Conference, Copenhagen, Denmark 2016.* 33. Bunsawat K, **Grigoriadis G**, Fernhall B, Baynard T. Central Hemodynamics and Arterial Stiffness in Young Obese Adults: the Preliminary Finding. *Artery Research, Volume 16, December 2016, Page 91.*
34. Rosenberg AJ, Wee SO, Schroeder E, Bunsawat K, **Grigoriadis G**, Fernhall, B, Baynard T. Effect of acute isokinetic resistance exercise on systemic arterial hemodynamics and cerebral blood flow dynamics: is there a mismatch? *Artery Research, Volume 16, December 2016, Pages 101-102*

PROFESIONAL MEMBERSHIPS:

1. **American Heart Association Member** 2017 – 2018
2. **American Physiological Society Member** 2016 – 2019
3. **American College of Sports Medicine (ACSM) Member** 2015 – Present
4. **Midwest Chapter American College of Sports Medicine Member** 2015 – Present

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RECOGNITIONS/AWARDS:

1. **The 2017 North American Artery Annual Meeting (Chicago) Best Abstract Award Recipient** (May 2017 – $200 USD)
2. **Graduate Student Council's Travel Award, University of Illinois at Chicago, IL** (September 2019, November 2018, May 2017, April 2016 - Total $1,100 USD)
3. **Graduate College Student Presenters Award, University of Illinois at Chicago, IL** (September 2019, November 2018, November 2017, Total $600 USD)
4. **Health Professional Student Council Travel Grant Application, University of Illinois at Chicago, IL (**November 2019, September 2018, September 2017, October 2016, Total $1,200 USD)

5. **Gerondelis Foundation Graduate Scholarship (**October 2012 - $5,000 USD)
6. **Voluntary Participation Diploma – Olympic Games ATHENS 2004** (Participation at the Folk Dances Team)
7. **Distinctions at Team Sports**
   1st Place at the District High School Soccer Competition (1998 – 1999)
   1st Place at the Domestic Soccer Championship D.P.E.S. (2004)
   1st Place at B Soccer Category of Argolida (1999 – 2000)
   Member of Championship handball Team of East Peloponnese
8. **Dance Group Participation**
   Olympic Games Dancing Team, ATHENS 2004
   Cultural Association of Tolo.
   Laboratory of Greek Dances, Nafplion
   Charilaou Cultural Association, Thessaloniki
9. **Trained in Kung-Fu - Blue Belt Holder**
10. **Greek Conservatory – Nauplio Branch (**Six-year Studies of Classical Guitar, Intermediate Level)

SPECIALIZED TRAINING:

1. **Studio One, (Fitness School, Athens, Greece)** Aerobic Elite Choreography Diploma
2. **North Academy of Fitness, (Fitness School, Thessaloniki, Greece)** Aerobics Instructor Diploma
3. **YMCA (Thessaloniki, Greece)** Water safety and Lifeguard Diploma
4. **A.F. Studies (Gymnastics School, Athens, Greece)**
   Vibrating Exercise Training Certification

PROFESSIONAL TRAINING:

1.American College of Sports Medicine
ACSM/ACS Certified Cancer Exercise Trainer (2017 – Present)
2.American College of Sports Medicine
ACSM Certified Personal Trainer (2019 – Present)
3.American Red Cross
Adult and Pediatric First Aid/CPR/AED Certified (2011 – Present)

COMMUNITY SERVICE:

1. **Cancer Wellness Center – Northbrook**
   Assist in development of exercise programs in cancer survivors (October 2018 Present). - Invited guest speaker
2. **Kellogg Cancer Center in Evanston**
   Assist in development of exercise programs in cancer survivors. - Invited guest speaker:
3. **Recovery on Water for Breast Cancer Survivors**
   Assist in measuring body composition in breast cancer survivors.
4. **Cancer Support Group – Gilda's Chicago**
   Invited guest speaker
5. **St. George Greek Orthodox Church**
   Invited guest speaker: "Cardiovascular disease in Breast Cancer Survivors". (October 15th, 2017)
6. **National Hellenic Museum in Chicago.** Assisted in organizing social events.