

EXERCISE TO PREVENT ANTHRACYCLINE-BASED CARDIOTOXICITY IN
INDIVIDUALS WITH BREAST OR HEMATOLOGICAL CANCERS

by

Stefan D Heinze-Milne

Submitted in partial fulfilment of the requirements
for the degree of Master of Science

at

Dalhousie University

Halifax, Nova Scotia

June 2018

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ABSTRACT

Anthracyclines (ACs) are a powerful anti-cancer drug used to treat a wide range of cancers, including those of the breast and blood. It is well established that ACs can lead to cardiac dysfunction and heart failure well within the desired dosing range used to treat these cancers. Current management tools such as dexrazoxane and heart failure medications are in question and often do not fully treat the cardiotoxicity. However, there is strong preclinical evidence to suggest aerobic exercise therapy (AET) can be used as an alternative or complimentary therapy to prevent AC-mediated cardiotoxicity. Before investing in a large clinical trial, the feasibility of performing AET with AC-treated cancer patients must be known. Specifically, the feasibility of conducting it within the researcher's geographical area (Halifax, Nova Scotia (NS), a smaller Canadian metropolis). Therefore, the purpose of this study was to examine the feasibility of a 12-week individualized AET intervention to mitigate AC-mediated cardiotoxicity and adverse patient outcomes in Halifax, NS. The primary study objective was to examine the intervention's feasibility, including recruitment, adherence, retention, and safety. Secondary study objectives evaluated cardiorespiratory fitness, biomarkers of cardiotoxicity, and self-reported functional and fatigue questionnaires. Overall, the intervention was deemed feasible after comparing to similar studies that were in other geographical areas. The feasibility statistics for the present study were within the range of comparator studies. No changes were found in secondary outcome measures, suggesting that AET could have prevented a detrimental change in these measures. In conclusion, a 12-week aerobic exercise intervention in cancer patients with breast or hematological cancers is feasible in Halifax, NS.

LIST OF ABBREVIATIONS USED

ACs	Anthracyclines
ACE	Angiotensin converting enzyme
AET	Aerobic exercise therapy
BAD	Bcl-2-associated death promotor
BAX	Bcl-2-associated X protein
Bcl-2	B-cell lymphoma 2 protein
BMI	Body mass index
BNIP1	Bcl-2 interacting protein 1
BP	Blood pressure
CPC	Cardiac progenitor cell
CRP	C-reactive protein
CVD	Cardiovascular disease
EXACT	EXercise to prevent Anthracycline-based CardioToxicity
FACT	Functional assessment of cancer therapy
FDA	Food and Drug Administration
HR	Heart rate
HRR	Heart rate reserve
IL-	Interleukin- (i.e., Interleukin-6)
LVEF	Left-ventricular ejection fraction
METs	Metabolic equivalents
NT-pro-BNP	N-terminal pro brain natriuretic peptide
ROS	Reactive oxygen species
TNF- α	Tumor necrosis factor alpha

ACKNOWLEDGEMENTS

Foremost I wish to extend my sincere gratitude to my supervisor, Dr. Scott Grandy. Your mentorship has helped me grow as a young investigator, and I appreciated all your guidance and trust. I look forward to continue working with and learning from you in the coming years.

I am grateful to all others that helped and/or inspired me thus far, including my committee, other faculty, and my peers. I especially wish to mention the participants in this study. They helped me better understand the place of clinical research in this world and the importance of a human connection.

I wish to thank Dalhousie University, particularly all faculty/administrators in the kinesiology department. I thoroughly enjoyed my undergraduate and graduate experience with the school, which was possible through their hard work and dedication.

Lastly, I am grateful for the funding received from Dalhousie University, the Nova Scotia Health Research Foundation, the Heart and Stroke Foundation, and the Canadian Institutes of Health Research.

CHAPTER 1: INTRODUCTION

Introduction to Anthracyclines and their Cardiotoxicity

Our ability to treat cancer is steadily improving due to advances in cancer therapy. Many survivors have been treated with a class of anti-cancer drugs called anthracyclines (ACs), which were introduced in the 1960s.¹ ACs are used to treat many cancers, including breast and hematological cancers, and have become a fundamental component to many treatment regimes.¹ Although a highly effective anti-neoplastic therapy that treats cancers, ACs are known to be toxic to the heart during therapy. This increases the risk of cardiovascular disease (CVD) post-therapy.^{1,2} CVD is perhaps the greatest medical concern amongst cancer survivors, often accounting for more disease related deaths than the original cancer diagnosis.^{3,4}

As AC-related cardiotoxicity during and after treatment is of such great concern, it is necessary to understand how to manage it. Cardiotoxicity can occur during or after therapy, and ranges in severity from asymptomatic ventricular dysfunction through to symptomatic heart failure.⁵ Left-ventricular ejection fraction (LVEF) decline is usually the first sign of AC-mediated cardiotoxicity to develop.⁶ The most important determinant of AC toxicity is the cumulative dose, defined as the total lifetime amount of ACs the individual was treated with. This is positively associated with increased risk for cardiovascular complications.^{7,8} For instance, the estimated prevalence of heart failure at cumulative doses of doxorubicin (an AC) at 400, 550, and 700 mg/m² was 5, 26, and 48%, respectively.⁹ This cumulative dose risk often limits the use of the drug to treat cancer.¹⁰ It is important to note that there does not appear to be a universally safe dosage

for AC administration, as doses as low as 100 mg/m² have reportedly caused cardiotoxicity.¹¹

Cardiotoxicity can manifest through two general and related types of cardiac damage:¹ Type I refers to cardiotoxicity from myocardial cell death, which can predispose cancer survivors to CVD and cardiomyopathies after therapy. Type II is a reversible condition that is caused by cardiomyocyte dysfunction rather than cell death. How ACs induce cardiotoxicity is not completely understood, although it is represented by both Type 1 cardiotoxicity (cell death) as well as Type 2 (cellular dysfunction). There are two dominating hypotheses for AC-mediated cardiotoxicity the first is the Reactive Oxygen Species (ROS) hypothesis. This theorizes that the molecular structure of ACs contribute to the production of ROS in the cell, leading to myocardial death and dysfunction through oxidative damage, inflammation, and mitochondrial dysfunction.¹²⁻¹⁵ The second theory is the Topoisomerase 2b hypothesis, which posits that ACs disrupt the enzyme's ability to function, which then inhibits DNA replication, repair, and gene expression.¹⁶ In short, the two hypotheses describe mitochondrial and bioenergetic problems, increased ROS production, inflammation, and alterations in gene handling, eventually causing myocardial dysfunction and cellular apoptosis.

This cardiotoxicity forces physicians into a difficult decision between the anti-cancer properties of ACs and their negative implications of cardiotoxicity. Indeed, this limits the therapeutic use of ACs in practice, and presents a problem for oncologists.¹⁷ Therefore, finding ways to minimize cardiotoxicity while still using ACs is a research goal. Various pharmacologic methods have been somewhat successful in managing or preventing left ventricular dysfunction from ACs, which primarily rely on heart failure

treatment strategies.¹⁸ These strategies include the use of beta blockers and angiotensin-converting enzyme (ACE) inhibitors.¹⁹ Other management strategies include PEGylation (altering the drug's molecular profile) and using the cardioprotective drug dexrazoxane.²⁰⁻²² However, neither method fully ameliorates AC cardiotoxicity and there are issues surrounding dexrazoxane's use. Dexrazoxane is currently under review for its use with ACs due to its association with bone marrow suppression (myelosuppression) and concerns regarding its potential to reduce their anti-neoplastic ability.^{18,23} Additionally, dexrazoxane is only approved by the U.S. Food and Drug Administration (FDA) for use in patients* with a cumulative AC dose of >300 mg/m², which may be a higher dose than when cardiotoxicity first presents.²³

Although management strategies exist, the continued presence of cardiotoxicity in patients treated with ACs has led to a renewed interest in alternative or complementary approaches. A suggested alternative or complementary therapy to manage AC-induced cardiotoxicity is aerobic exercise.⁶ Aerobic exercise therapy (AET) before or during AC-administration has been shown to decrease AC-mediated cardiotoxicity (i.e., preserving LVEF) in animal models.^{6,24} However, research regarding AET in humans to mitigate AC-mediated cardiotoxicity is sparse. To date, one mechanistically driven clinical trial has been reported by Kirkham et al.²⁵ Their study investigated the effects of aerobic exercise 24-hours before receiving AC-therapy over several treatments. They found that exercise improved common symptoms associated with ACs, although their results regarding markers of cardiotoxicity were inconclusive. An ongoing trial, the TITAN

* In this document, the term "cancer patient" refers to cancer survivors being actively treated for cancer. Where applicable, the term "cancer survivor" is used to connote survivors not on active cancer therapy.

study, is investigating the effect of exercise on AC-induced cardiotoxicity via blood borne markers.²⁶ However, that is the extent of current mechanistically-driven research into the area. Lastly, the OptiTrain trial found that high-intensity interval training preserved cardiorespiratory fitness in patients receiving ACs but did not measure indicators of cardiotoxicity, such as echocardiography or blood borne markers. Therefore, although there have been several trials investigating aerobic exercise during cancer therapy (including ACs) to improve various associated symptoms, there is extremely little known regarding the use of AET to manage AC-mediated cardiotoxicity from a physiologic standpoint (i.e., prognostic cardiotoxic measurements). Thus, more research is needed to determine if AET can be used as a prescribed therapy for AC-mediated cardiotoxicity.

To determine the efficacy of AET to prevent AC-mediated cardiotoxicity, randomized clinical trials need to be performed. Prior to investing in a large clinical trial the safety and feasibility of conducting such a trial should be known. Currently, the feasibility of conducting a clinical trial in the proposed study area (Halifax, NS) is unknown. However, reviewing related studies and guidelines can provide an estimate for feasibility and safety. Regarding safety, AET is considered safe for cancer patients that are screened and properly prescribed exercise.^{27,28} Aerobic exercise is often recommended to the cancer patient population, because it can improve cardiovascular fitness, quality of life, and reduce cancer-related fatigue.²⁷ Regarding feasibility, published trials throughout the world using AET and cancer patients suggest that it is possible to recruit participants and retain the majority throughout the study.²⁹⁻³¹ Such trials have also shown relatively high adherence rates (66-85%) to aerobic exercise

interventions with very low adverse event rates, as per a review of aerobic exercise interventions with cancer patients.²⁹ Therefore, evidence suggests that performing an aerobic exercise intervention in cancer patients is safe and feasible in research centers outside of Halifax, NS.

In summary, ACs present significant cardiotoxic risk during and, perhaps more importantly, after treatment. The current pharmacologic treatment methods are moderately effective at managing AC-mediated cardiotoxicity. Current research surrounding AET as an alternative or complimentary therapy to reduce AC-mediated cardiotoxicity has been very promising but almost solely been conducted in rodent models. Early clinical trials have begun, and more research is needed to determine the protective role of AET against AC-mediated cardiotoxicity.²⁴ The safety and feasibility of performing AET in a cancer patient population receiving ACs does not raise concerns based on past research and guidelines.^{27,29} However, prior to investing effort and resources into a large clinical trial in Halifax, NS, its local feasibility needs to be assessed.

Therefore, the purpose of this study was to determine the feasibility and potential efficacy of a 12-week individualized AET program to mitigate cardiotoxicity and adverse patient outcomes associated with AC-based therapy. The primary study objective was to determine if a 12-week individualized AET was feasible by assessing program recruitment, retention, adherence, and safety and comparing them to similar exercise interventions with cancer patients. The secondary study objectives examined the potential efficacy of AET to prevent changes in cardiorespiratory fitness, biomarkers associated with cardiotoxicity, and patient-reported quality of life. It was hypothesized that an AET

program for cancer patients would be safe and feasible.^{29,32} Additionally, it was hypothesized that the AET would improve overall levels of aerobic fitness, bloodborne biomarkers of cardiotoxicity, and patient-reported quality of life. No formal hypotheses were given for cardiac biomarkers due to the novel nature of the research in this population.

CHAPTER 2: REVIEW OF LITERATURE

Anthracyclines as an anti-neoplastic therapy

Having entered clinical trials in the 1960s, ACs have become a mainstay drug to treat a wide variety of cancers due to their powerful ability to combat neoplastic growth. The first AC was synthesized from the soil bacterium *Streptomyces peucetius* and was named daunorubicin. A derivative of daunorubicin named doxorubicin closely followed, and since then more ACs have been synthesized.¹ They are useful in treating most cancers, including hematological and breast cancers.¹ However, as was discovered early in their history, the use of ACs to treat cancer is limited primarily by their cardiotoxic effects. Thus, the management and prevention of cardiotoxicity is important to cancer patients and survivors treated with ACs.

Anthracycline cardiotoxicity management and aerobic exercise therapy

The management of AC-mediated cardiotoxicity is important, because of the cardiotoxic risks during and particularly long after treatment. Cancer survivors treated with ACs are at risk for potentially deadly cardiomyopathies later in life. An exponential rise in heart failure is observed between 300-700 mg/m² total cumulative doses of doxorubicin (with similar profiles for other ACs), although the risk of cardiotoxicity is present at any dose.^{7,8,11,33,34} In addition, some cancer patients would benefit from treatment beyond these dosages, however they cannot receive them due to cardiotoxicity.³⁵ There are known risk factors that predispose patients to AC-mediated cardiotoxicity, which include pre-existing hypertension or CVD, being treated with other cardiotoxic drugs, older age, being female, mediastinal radiation, and lifestyle factors (i.e., high physical inactivity levels).^{1,11,36} Currently the only FDA approved drug to combat this cardiotoxicity is

dexrazoxane, and is only used when the cumulative dose is greater than 300 mg/m² due to concerns surrounding the drug and myelosuppression.^{18,23} Additionally, AC-mediated cardiotoxicity is commonly managed using pharmacologic strategies for heart failure (e.g., beta blockers, statins, angiotensin receptor blockers, and ACE inhibitors).¹⁹ Altering the pharmacokinetics of ACs by attaching polyethylene glycol (PEGylation) has also reduced cardiotoxicity.^{20,21} However, these management strategies are not perfect, as many patients still present with cardiotoxicity during and after chemotherapy despite prophylactic management (e.g., dexrazoxane).^{19,37} Therefore, better management strategies are warranted to treat AC-mediated cardiotoxicity.

Aerobic exercise has been suggested as an alternative or complimentary therapy to manage this cardiotoxicity.^{6,24,38} Early investigations into the use of aerobic exercise to reduce markers of AC-mediated cardiotoxicity have begun and will be discussed further in the chapter.^{25,26} They are based on premises from preclinical research suggesting that AET can prevent cardiotoxicity. Specifically, AET aims to combat Type I (cell death) and Type II (dysfunction) AC-mediated cardiotoxicity through a variety of mechanisms, including: 1) reduced ROS production and subsequent cellular apoptosis,³⁹⁻⁴² 2) improved resistance to ROS and inflammation,^{39,42-45} 3) improved mitochondrial function,^{39,41,43} 4) increased cardiac progenitor cell (CPC) proliferation,^{6,46-48} 5) increased myocardial AC clearance,⁴⁹ and 6) preserving cardiac function.⁴⁹⁻⁵¹ It is important to note that although these are presented separately, there is much overlap between these mechanisms. The following section defines them individually for clarity, although the reader is encouraged to view all six sections holistically.

How aerobic exercise mitigates anthracycline cardiotoxicity (sections 1-6)

1) Reduced ROS production and cellular apoptosis

At the cellular level, mitochondrial dysfunction leading to ROS production and pro-apoptotic signalling is a key factor leading to AC-mediated myocardial cell death. This partially explains why the heart is so susceptible to AC-mediated toxicity, as the heart muscle is mitochondrion-rich. ROS production theoretically begins at complex I of the electron transport chain in the mitochondrion (NADH dehydrogenase), where ACs are converted into a semi-quinone free radical, which then catalyzes the production of ROSs inside of the cell.^{52,53} Additional ROS production from ACs may occur from iron redox cycling within the cell.⁵⁴ Crucial to AC-mediated toxicity and cell death, increased ROS production leads to increased oxidative stress and impaired calcium handling.⁵⁵ This can directly affect mitochondria and lead to increased mitochondrial membrane permeability.⁵⁶ This in turn leads to the release of several pro-apoptotic factors, including cytochrome c and the apoptosis-inducing factor.⁵⁷ In addition to or alongside mitochondrial dysfunction, other pro-apoptotic mechanisms have been associated with ACs. These include the activation of several caspases,^{39,58} an increased ratio of Bax:Bcl-2 proteins,^{39,59} overexpression of tumor suppressor protein 53 (p53),⁶⁰ increased BAD (Bcl-2-associated death promoter) levels⁵⁹, and terminal deoxynucleotidyl transferase (TUNEL)-positive nuclei,⁵⁹ which are all associated with increased apoptosis.

The effects of AET on mitochondrial function and pro-apoptotic signalling during AC treatment has been previously studied in animal models. The results suggest that AET helps to reverse AC-mediated pro-apoptotic signalling. Acute bouts of aerobic exercise prior to AC treatment in rats have been shown to maintain mitochondrial function and

maintained mitochondrial membrane impermeability.⁶¹ In addition, Bcl-2 and Bcl-2 interacting protein (BNIP1) expressions, both markers of apoptosis, were lower in rats that performed AET for two weeks after AC administration versus sedentary rats.⁶² Caspase 9 activation and the Bax:Bcl-2 ratio were decreased in pre-trained mice following AC-administration.³⁹ Lastly, p53 expression decreased during AC administration following 21 days of voluntary exercise in rats.⁴⁰ The decrease in p53 was indicative of reduced cell death, and did not decrease in the group that did not exercise.⁴⁰ These results all suggest that AET reduces pro-apoptotic signalling in response to AC-administration, thus lowering Type I cardiotoxicity.

2) Improved resistance to ROS and inflammation

The increased development of ROS is central to many AC-induced cardiotoxic mechanisms.^{6,63} High levels of ROS directly lead to DNA damage and inflammatory cytokine release contributing to myocardial dysfunction and death.^{13,14} Specifically, the cytokine interleukin-1 β (IL-1 β) has been implicated in inflammatory pathways, triggering the systemic rise of tumor necrosis factor- α (TNF- α) and IL-6.^{15,64,65} As ROS induce an inflammatory response, it is important to consider how AET affects ROS management. AET is known to provide cardioprotection against non-AC mediated ROS production through enhancing antioxidant capacity and increasing heat shock protein (HSP) expression.^{66,67} HSPs aid in cardioprotection by lessening ROS-mediated cellular injury (i.e., protein denaturation and damage),^{67,68} while antioxidants like glutathione help to remove excess ROS.^{41,67} It appears that exercise can provide cardioprotection against AC-induced ROS production by these same mechanisms. AET prior to AC administration in mice has been shown to decrease ROS production, oxidative damage,

and increase antioxidants (i.e., glutathione) in the heart after AC-therapy.^{39,69} A similar study in rats found a decreased ROS production and oxidative damage due to therapy when exercise was performed prior to AC treatment.⁴³ Superoxide dismutase, an enzyme that turns the ROS superoxide (O_2^-) into oxygen (O_2), increased due to aerobic exercise prior to AC administration in rats, indicating an increased antioxidant capacity.⁴⁴

Regarding HSPs, the proteins that stop protein degradation and damage, aerobic exercise prior to AC administration in mice resulted in HSP60 increases after therapy.⁶⁹ Similarly, both voluntary and structured (5x per week, 20 minutes per day, at a low intensity) exercise in rats 8-12 weeks prior to AC administration resulted in significantly increased HSP72 levels after therapy.^{70,71} The same effect has occurred when aerobic exercise was performed along with AC administration, which showed a beneficial change in levels of HSP70 in a rat model.⁴⁵ These increases in HSP expression due to exercise may be one mechanism by which AET protects against AC-mediated cardiotoxicity. In summary, AET can help to improve resistance to ROS by upregulating the production of anti-oxidants and HSPs.

The ROSs produced from AC-therapy lead to increased levels of inflammation in the heart. Along with myocardial inflammation, AC-treatment also raises systemic inflammation levels.¹⁵ Of note, systemic inflammatory markers can serve as indicators of AC-mediated myocardial dysfunction.⁷²⁻⁷⁴ Systemic inflammation is also associated with several disease pathologies, including CVD.⁷⁵ Thus, finding ways to increase protection against systemic inflammation may help to manage AC-mediated cardiotoxicity and cardiovascular disease risk. AET is well documented to reduce chronic low grade systemic inflammation in humans.^{75,76} This decrease in systemic inflammation leads to an

improved CVD risk profile. It has also been demonstrated in non-AC models that AET can lead to improved inflammatory profiles and cardiac function during various induced-CVDs in animal models.^{77,78} To summarize, AET may play an important role in managing ROS in the myocardium by improving antioxidant capacity and HSP production. In turn, this improves cardiovascular function and reduces systemic inflammation, thus lowering CVD risk. Speculatively, AET may decrease systemic inflammation independent of ROS regulation while on AC therapy, although this area has only been researched in healthy non-AC models.

3) Improved mitochondrial function

Mitochondrial dysfunction in the myocardium is central to AC-mediated cardiotoxicity.⁴¹ When exposed to ACs, mitochondria experience decreased respiratory endpoints (markers of mitochondrial function),^{39,61,79} reduced mitochondrial antioxidant capacity,^{39,80} and impaired mitochondrial electron transport chain (ETC) complex activity,^{81,82} which can all lead to myocardial dysfunction and apoptosis.^{39,41,58} Thus, finding therapies that reverse these effects of ACs on mitochondria may be beneficial in preventing AC-mediated cardiotoxicity. AET is hypothesized to positively change all these toxicity measures. Firstly, structured AET in mice and rats prior to AC therapy led to increases in several respiratory endpoints.^{39,61,83} These included longer training protocols, such as four weeks of 60- to 90-minutes of moderate intensity exercise per day,³⁹ or shorter protocols such as a one-time 60-minute bout of moderate intensity exercise 24-hours prior to AC-administration.⁶¹ Similar animal model study designs found AET to improve mitochondrial antioxidant capacity (via upregulations of enzymes^{39,83} and antioxidants³⁹) and mitochondrial ETC complex activity.⁶¹ Additionally,

AET in rats showed a decrease in mitochondrial permeability transition pore formation after AC treatment, which is another mitochondrial toxicity that leads to dysfunction and possibly apoptosis.⁶¹ These results suggest that AET may mitigate AC-induced cardiotoxicity by reversing dysfunctional effects on mitochondria

4) Improving CPC proliferation

CPCs, otherwise known as cardiac stem cells, are known to be present in the adult human heart and can give rise to new myofilaments and endothelial cells.⁸⁴ ACs and ROS are known to impair CPC proliferation and function through the death or deactivation (senescence) of these cells.⁸⁵⁻⁸⁹ This AC-mediated damage leads to impaired myofilament regeneration, eventually leading to myocardial dysfunction via Type I cardiotoxicity.⁸⁸ No significant amount of research has been done yet regarding CPC proliferation after exercise and AC-administration. However, evidence indicates that AET can increase CPC proliferation in non-AC models to repair and adapt to physiologic stress within the heart.^{46,90-92} Thus, AET may be cardioprotective against Type I AC-mediated cardiotoxicity by increasing CPC proliferation.

5) Increased myocardial anthracycline clearance

AET may not only possess the power to combat AC-mediated toxicity, but also to reduce the amount of time that drug remains in the myocardium. AET prior to AC administration in rats led to reduced AC accumulation within the myocardium.⁴⁹ Of note, the reduced AC accumulation was associated with preserved cardiac function. This indicates that AET can lessen the total time ACs are present in the myocardium, effectively lowering the amount of oxidative damage incurred.

Because total cumulative dose is a primary risk factor for AC-mediated cardiotoxicity,¹⁰ increased clearance of ACs from the heart could have significant benefits in reducing cardiotoxicity and CVD risk later in life. However, this idea is speculative, and more research is needed to substantiate the longitudinal effects.

6) Preserved cardiovascular function

Preclinical work has also demonstrated that AET can preserve cardiovascular function after AC-administration. For example, rats that voluntarily exercised for 11-weeks demonstrated that exercise preserved cardiovascular function (fractional shortening of the left ventricle and ejection velocity from the aortic and mitral valves) after AC-administration compared with a control group.⁹³ Similarly, after 10-weeks of either structured treadmill running or voluntary wheel running prior to AC-administration, rats that performed either type of exercise showed significant preservation of stroke volume and ejection velocity compared to sedentary counterparts.⁴⁹ The same 10-week protocol also showed that exercise preserved myosin heavy chain expression, which positively associated with preserved cardiovascular function.⁴⁸ Cardioprotection may even occur after very small amounts of AET. As little as five days of aerobic exercise (voluntary wheel running performed by rats) before AC-administration significantly preserved markers of cardiovascular health in rats (left ventricular fractional shortening and developed ventricular pressure) compared to sedentary controls.⁹⁴

AET also preserved cardiac function during AC-administration. When juvenile rats were exercised or sedentary and given an AC for 7 days, the exercised rats showed a preserved ejection fraction and ejection velocity when compared to the sedentary group.⁵¹

Thus, AET may help to preserve cardiovascular function in cancer patients receiving ACs.

Based on the potential impact of AET on identified mechanisms underlying AC-mediated cardiotoxicity there is more than enough evidence to suggest that AET could be used to reduce the risk of cardiotoxicity in cancer survivors.

Aerobic exercise to mitigate anthracycline cardiotoxicity: Preclinical to clinical

It is clear that AET helps to manage or prevent AC-mediated cardiotoxicity in animal models. The previous six sections identified several mechanisms by which AET can accomplish this. It is important to mention here that AET has been shown to maintain the anti-tumor ability of ACs in preclinical research,⁹³ which should not be of concern moving forward. In addition, performing regular aerobic exercise is recommended for all cancer patients and survivors due to its innumerable health benefits.^{27,28} Based on this information, it is unsurprising that structured AET as a method of preventative and rehabilitative care in cancer patients and survivors is currently being researched, with promising results.^{32,38} There are currently very few mechanistically-driven clinical trials regarding AET and AC-mediated cardiotoxicity that have been conducted. Kirkham et al.²⁵ investigated the effects of a bout of aerobic exercise 24-hours prior to AC-treatment and found that the exercise had several positive effects on the cardiovascular system and psychological well being. However, they reported no change in cardiac troponin, a subclinical marker of cardiotoxicity. Another related trial, the OptiTrain study, found that 16-weeks of high intensity aerobic interval training plus aerobic exercise or resistance

training prevented the decline in cardiorespiratory fitness while on ACs, although no mechanistic measurements were taken.⁹⁵ Lastly, the ongoing TITAN trial will add to this body of research by assessing the impact of structured and self-directed aerobic and resistance exercise on systemic cardiac troponin levels. More research measuring cardiotoxicity is needed to determine if AET can prevent AC-mediated cardiac damage.

The lack of clinical trials investigating the effects of AET to prevent AC-mediated cardiotoxicity means that more studies are necessary. Knowing the safety and feasibility of conducting an aerobic exercise intervention in the proposed geographical area is important to know before investing time and resources into a trial. The safety and feasibility of conducting an aerobic exercise intervention with cancer patients in Halifax, NS, is currently not known. Examining relevant literature can help answer these unknowns to a certain extent. As such, a brief review of the feasibility and safety of performing aerobic exercise interventions in cancer patients was reviewed and discussed hereafter:

Safety of aerobic exercise therapy in cancer patients

Firstly, published guidelines state that exercise is safe for people during and after cancer therapy, provided there is proper screening and prescription.^{27,28,96} Furthermore, aerobic exercise testing is a safe, non-invasive method of assessing cardiopulmonary fitness of cancer patients and survivors.⁹⁷ Therefore, there do not appear to be significant risks in implementing an AET intervention in a cancer population, provided that there is adequate screening for exercise contraindications and sensible prescription.

Feasibility of aerobic exercise therapy in cancer patients

It may be a concern that cancer patients receiving chemotherapy would be too fatigued to participate in regular structured aerobic exercise. However, evidence shows that structured exercise therapy in a cancer patient population is a viable intervention. Several studies have shown relatively high adherence rates (range: 66-85% adherence) with low adverse event rates to 4-12+ week exercise interventions in cancer patients.^{31,98-103} Of note, most of the patients involved in these trials were receiving chemotherapy during the exercise sessions. Thus, this evidence indicates that performing AET with cancer patients during chemotherapy is a feasible intervention. However, the feasibility statistics specific to a structured 12-week AET program in cancer patients receiving ACs in a smaller Canadian metropolis such as Halifax are not known. Thus, determining them is the primary objective of this study.

Summary of literature and proposed research question

ACs are an effective anti-cancer therapy commonly used to treat a variety of cancers, including those of the breast and blood. They are also well known to be cardiotoxic, leading to impaired cardiovascular function during therapy and increased risk for CVD post-therapy. Current management strategies cannot fully manage this cardiotoxicity, and complimentary or alternative strategies need to be researched. Strong preclinical evidence suggests AET can fulfill this need and has revealed many pathways of cardioprotection. However, there is very little clinical data regarding the use of AET as an alternative or complimentary therapy to reduce AC-mediated cardiotoxicity. Thus, the next logical step forward is to perform clinical trials. The present study sought to investigate this and was hereafter called the “EXACT” study, in reference to the study’s title “EXercise to prevent Anthracycline-based CardioToxicity”. The research question addressed by the EXACT

study was: What is the feasibility and potential efficacy of a 12-week individualized AET program to mitigate cardiac toxicity and patient outcomes associated with AC-based therapy in Halifax, NS? Based on related studies, it was hypothesized that AET in this population would be safe and recruiting would be feasible. Specifically, feasibility was assessed by comparing the EXACT study's statistics to those from other research centers. If the EXACT study's values were within the range of clinical exercise trials of similar design in other research centers, the intervention was deemed feasible in that way. This would demonstrate that Halifax is non-inferior to other recruitment centers investigating aerobic exercise interventions with cancer patients.

CHAPTER 3: METHODOLOGY

Purpose, objectives, and outcomes

The purpose of the EXACT study was to examine the feasibility and potential efficacy of a 12-week individualized AET intervention to mitigate AC-mediated cardiotoxicity and adverse patient outcomes in Halifax, NS. This was to inform investigators whether a larger trial is possible within their geographical location. The primary study objective was to examine the feasibility of an individualized 12-week AET intervention by assessing 1) recruitment, 2) program adherence, 3) program retention, and 4) safety. Secondary study objectives were to explore the effects of an AET intervention on biological markers of cardiotoxicity as well as patient centered outcomes (see “Data collection” section for a detailed description of measures). AET was hypothesized to be a safe and feasible intervention for cancer patients based on relevant literature described above in the literature review. The primary means of determining feasibility were to compare feasibility statistics to similar published trials. It was hypothesized that AET could prevent the decline in secondary outcome measures, including cardiorespiratory fitness and cancer-related fatigue. No formal hypotheses were stated for markers of systemic inflammation, due to the lack of relevant literature.

Study design and participant recruitment

The study protocol was created using the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement.¹⁰⁴ This was a single-armed prospective feasibility study using a 12-week AET intervention. The intervention was tailored to the participant’s fitness level and ranged from light to vigorous intensity and 20-45 minutes

per session (Figure 1, methods). Participants were identified and screened for eligibility by their medical oncologist or hematologist during a routine visit to the Queen Elizabeth II Health Sciences Center (QEII HSC) in Halifax, Nova Scotia, Canada. If eligible and medically approved for study participation, patients were asked by a medical staff member if they may be contacted by a research coordinator to discuss the study. The research coordinator then provided patients with a detailed overview of the study (Appendix A) followed by informed consent (Appendix B) if the patient wished to enroll. The number of participants screened and contacted were recorded and used to assess recruitment feasibility. Consenting participants then underwent additional cardiovascular risk and fitness assessments, including a cardiopulmonary exercise stress test.¹⁰¹ Baseline anthropometric, quality of life, and blood samples were taken prior to the beginning of the AET intervention. Following this, participants began an individualized 12-week AET intervention. Pending completion, participants repeated the baseline measurements (i.e., anthropometrics, quality of life, etc.) and cardiopulmonary stress test. This study was ethically approved by the Nova Scotia Health Authority Research Ethics Board (REB file: NSHA ROMEO file #: 1019999) and was a registered trial at ClinicalTrials.gov (# NCT02471053). A feasibility study protocol has previously been published for the EXACT study.¹⁰⁵

Strategies to optimize participant recruitment were employed, including on-site face-to-face recruitment and physician endorsements of the study. In addition, strategies to improve participant adherence and retention were used. These included group-based, individually tailored exercise training sessions, personalized performance feedback from the study's personal trainer, follow-ups regarding missed sessions, the ability to make up

missed sessions, and scheduling flexibility. All exercise sessions were performed in a fitness centre located near to the hospital.

Participant profile

The proposed study sought to recruit 20 participants receiving AC therapy for either a primary breast or hematological cancer at the QEII HSC. These two types of cancers were chosen due to the high use of ACs to treat them and because of the investigators' personal contacts within the healthcare system. Study measurements pre- and post-study were completed at an affiliated center nearby the cancer clinics. Participants were identified based on the following inclusion/exclusion criteria (continued on the next page):

Inclusion

- Between the ages of 18 and 70 at enrollment
- Were within 8-weeks of receiving first dose of an AC-based chemotherapy regimen for a primary, non-metastatic HER2-negative breast cancer, or hematological malignancy
- Were scheduled to receive a minimum dose of 100 mg/m² of doxorubicin (or equivalent)
- Underwent a pre-treatment cardiopulmonary stress test
- Were willing to participate in a twice-weekly 12-week community-based AET intervention
- Had consent from their medical oncologist / hematologist to

Exclusion

- Significant cognitive limitations, assessed by the signing physician
- Significant cardiovascular disease (e.g., myocardial infarction, cerebrovascular disease, peripheral vascular disease, congestive heart failure, or cardiomyopathy) or any known contraindication to exercise
- A previous history of cancer
- Known bone metastases

participate in this study

Exercise intervention

The AET intervention was designed using a published framework for designing exercise programs for cancer patients.²⁹ The intervention was 12-weeks in duration, because AET interventions of similar length have been shown to produce positive changes in aerobic fitness. The 12-week AET intervention was performed in conjunction with standard oncologic care, which included radiation and/or surgery alongside chemotherapy including but not limited to AC-treatment. Participants were asked to complete two exercise sessions per week on non-consecutive days. They were also asked to engage in physical activity outside of the supervised sessions in an attempt to reach 150 minutes of moderate-vigorous activity per week. It was thought that two supervised exercise sessions per week would be a suitable frequency to assess feasibility and be sufficient to promote fitness gains in addition to non-supervised activity. As outlined in Figure 1, supervised sessions ranged in intensity from 35-85% heart rate reserve (HRR) and in training volume by 20-45 minutes per session. HRR was calculated as:

$$\textit{Equation 1: } HRR = HR_{resting} + (HR_{peak} - HR_{resting})(\textit{intensity quotient})$$

Where HRR = heart rate reserve; HR = heart rate; $HR_{resting}$ = resting heart rate while standing; HR_{peak} = peak heart rate achieved during the cardiopulmonary stress test; Intensity quotient = intensity percentage converted to a number between 0 and 1 (i.e., 35% would be 0.35).

The non-linear approach was based on foundational principles of exercise training including: individualization, specificity, progressive overload, and recovery and has been

used by other AET interventions for cancer patients.^{29,106,107} The peak heart rate (HR) achieved during the participant's cardiopulmonary stress test was used to generate the intensity prescription, rather than using a generic age-predicted maximum that could result in under- or over-prescription.²⁹ Exercise was performed on a treadmill. Exercise sessions began with a 5-minute warm-up activity, followed by the 20- to 45-minute exercise session, and ended with a 10-minute cool-down period. HRs were measured during the sessions by a wrist-worn HR monitor (Polar A360 from Polar Electro Canada Inc., QC). The AET protocol was designed with periods of progressive overload and periods of rest and active recovery to minimize excessive fatigue or injury risk. Fatigue and injuries were assessed on an individual basis, with serious events being disseminated to all study investigators and the research ethics board to determine any further action or trial modification.

Data collection

Sample size

We aimed to recruit as many individuals as possible into the study over a 12-month period. This preliminary data can be used to inform future power analysis for a larger randomized clinical trial. In addition, the recruitment statistics found from this feasibility study can help to determine the number of collaborating centers required to reach significant patient recruitment in future trials. Currently it is difficult to predict required sample sizes for secondary variables regarding cardiotoxicity. This is because it is not well known how aerobic exercise can change cardiotoxic measures and, more importantly, how much change is required to be clinically relevant. Future studies

investigating the efficacy of AET to prevent cardiotoxicity will need to base sample size calculations on expected changes reported in exercise trials assessing if and by how much AET can prevent AC-mediated cardiotoxicity (i.e., via cardiac imaging).

Primary outcome measures and program monitoring

The primary outcome measures of this feasibility study were: recruitment, adherence, retention, and safety (see Data analysis for calculations and descriptions). An investigators meeting was held every three months to review and discuss any minor adverse events (i.e., muscle stiffness or activity-related fatigue) and/or how to improve recruitment. As there was no control and no repeated measures, there were no stopping guidelines for the trial.

Secondary outcome measures

General participant information: Participant's height, weight, body mass index (BMI), and waist circumference were measured using standard procedures.¹⁰⁶ Sex, age, smoking habits, and cancer type were collected through a combination of self-reporting and participant-consenting reviews of their medical record.

Cardiopulmonary fitness: Cardiopulmonary stress tests determined the peak aerobic fitness achieved, measured in metabolic equivalents (METs). The MET values were calculated by the stress test system (General Electric) to estimate workload. It also established whether participants exhibited any adverse clinical cardiovascular symptoms (i.e., chest pain). They were performed according to the American Heart Association's guidelines.¹⁰⁷ Participants completed either a Bruce treadmill or a Ramp treadmill protocol, during which they had a standard 12-lead ECG recording. ECG recording pre-, during, and post-exercise were recorded.¹⁰⁷ Blood pressure was recorded prior to

exercise, as well as during testing (at the end of every stage), and after exercise, by an automated blood pressure cuff. All tests were performed by a certified technician and supervised by a cardiologist. Upon completion of the stress test the ECG tracings were reviewed by a cardiologist to identify any undiagnosed CVD or contraindications to exercise. The participant's resting HR, measured prior to the intervention while standing, and their peak HR achieved during the test were used to calculate HRR for the exercise intervention.

It is important to mention that performing cardiopulmonary stress tests is a very safe tool to measure aerobic fitness. Only 2-5 people per 100 000 experiences serious or life-threatening complications during a maximal symptom-limited exercise test, according to the American Thoracic Society/American College of Chest Physicians.¹⁰⁸ More specific to cancer patients, a review of clinical cancer trials using aerobic stress tests found that adverse events were found in less than 15% of evaluated studies with no mortality.¹⁰⁹ Furthermore, a systematic review found that only 1% of cancer patients experienced an adverse event during exercise testing.⁹⁷ Thus, cardiopulmonary exercise testing should be regarded as a safe measurement tool used to assess aerobic fitness in cancer patients.

Cardiac biomarkers: Blood samples were collected from the participants within 7 days prior to starting and finishing the exercise intervention. Samples of 200 μ L were collected in a microtainer using a fingerprick blood draw and centrifuged for 15 minutes at 9391 Gs to extract the serum. Serum levels of IL-1 β , IL-6, and TNF- α were quantified due to their potential mechanistic relevance to AC-mediated cardiotoxicity.^{15,65,72} Blood samples for testing systemic inflammation were stored at -20 °C until analyzed.

Inflammatory markers of the blood's serum were measured using a BioPlex Pro human cytokine immunoassay via a Bio-Rad MAGPIX Suspension Array System as per Bio-Rad's instructions.

Patient-reported measures: Cancer-related fatigue and disease-specific quality of life were measured pre- and post-intervention using the Functional Assessment of Cancer Therapy (FACT) tools. These are valid and reliable assessment tools for cancer populations for assessing cancer- and therapy-specific changes in quality of life.¹¹⁰⁻¹¹⁴ These included the FACT-G (general measures), FACT-B (breast-cancer specific), FACT-Lym (lymphoma specific), and FACIT-Fatigue (chronic illness-related fatigue) questionnaires. These were administered during the pre- and post-intervention assessments prior to conducting the cardiopulmonary stress test.

Data analysis and management

De-identified data were entered into SPSS 24. Basic descriptive statistics were generated to describe the study population and outcomes. Feasibility rates for recruitment, adherence, and retention were calculated as follows using Microsoft Excel:

$$\text{Recruitment} = \frac{\# \text{ consented participants}}{\# \text{ eligible to participate}}$$

$$\text{Adherence} = \frac{\# \text{ exercise sessions attended}}{\# \text{ scheduled exercise sessions (24)}}$$

$$\text{Retention} = \frac{\# \text{ participants that completed baseline testing}}{\# \text{ participants that completed post intervention testing}}$$

Safety was assessed by tracking the number of adverse events that occur throughout the intervention.

Reasons for non-participation and leaving the study were recorded and discussed. Secondary outcome measures (i.e., cardiopulmonary fitness) were assessed pre- and post-intervention using descriptive statistics and a dependent t-test. Exploratory correlational analysis was used to examine the relationship between program adherence and cardiovascular fitness.

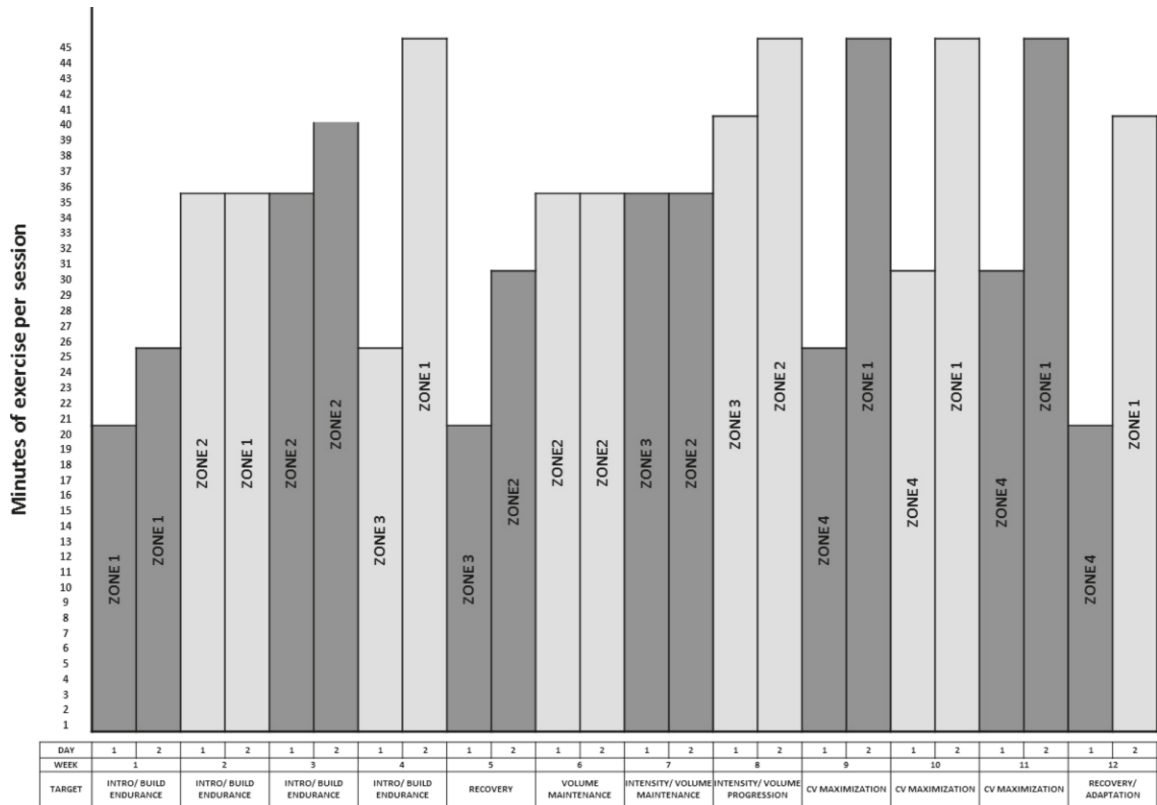


Figure 1: 12-week progressive aerobic exercise intervention. Zone 1: 35-45% Heart rate reserve (HRR); Zone 2: 45-55% HRR; Zone 3: 55-70% HRR; & Zone 4: 70-85% HRR. Adapted from Keats et al.¹⁰⁵

CHAPTER 4: RESULTS

Primary outcome measures

Recruitment: A total of 169 cancer patients were screened for eligibility over the 12-month recruiting period; 115 were breast and 54 were hematological cancer patients (Figures 2 & 3). Of those that were screened, 29% of patients met the eligibility criteria. Regarding each cancer type, 24% of the total breast cancer patients and 39% of the total hematological cancer patients were eligible. The most common reasons for exclusion were: not being within 8-weeks of beginning treatment (46% of total excluded) or being above the age cut-off (45% of total excluded). A further 14% of the total number of patients screened were ineligible due to having metastatic cancer. This left a total of 49 eligible patients (28 breast and 21 hematological cancer). This number dropped to 44 as five patients (two breast and three hematological cancer) were not given medical clearance. Fifteen of these 44 eligible patients consented to participate. Thus, 30% of the eligible patients were recruited. Notably, of the 29 patients that did not consent, 23 did not participate in the study due to travel distance/inconvenience. Twelve of the 23 were not contacted by the research assistant because they lived too far from the intervention site (i.e., a 1-2+ hour commute). A further 11 personally declined once contacted due to travel distance or inconvenience.

Participant characteristics: Seven females with breast cancer and three males with hematological cancer completed the study. One participant was a current smoker and another four were past smokers. Participants began the aerobic exercise intervention on average 8.4 weeks after beginning cancer treatment. The 12-week aerobic exercise

intervention had no effect on waist circumference, body mass, or BMI pre- to post-intervention (Table 1). However, there were changes in weight on an individual basis (data not shown). Weight change ranged from gaining six kilograms to losing 10. Six participants gained an average of 3.55 kg over the course of the intervention. The four participants that lost weight lost an average of 5.00 kg throughout the intervention. The same patterns were found for waist circumference measures and BMI.

Retention: As previously stated, 10 of the 15 consenting participants completed the study. Therefore, our retention statistic was 67%. Of the five participants that withdrew, one withdrew before baseline testing, and four participants did so after the study began. Of the four that withdrew during the intervention, two withdrew due to distance/inconvenience of commuting and the third left for job-related reasons. The fourth participant completed the intervention but was unable to attend follow-up testing and therefore was not included in secondary outcome analysis.

Adherence: The intervention consisted of 24 sessions over 12 consecutive weeks (2 sessions per week). The average number of sessions attended by all participants was 17.5 ± 7.1 , which represented an adherence statistic of $72.9 \pm 30.0\%$. The number of sessions attended per participant ranged from 2-24 sessions (8- 100%; Figure 4). One participant (P9) attended the first two sessions and did not attend any further until the follow-up session due to fatigue. Removing them from analysis yielded an average adherence of 19.2 ± 4.8 sessions ($80.0 \pm 20.0\%$; range: 54-100%).

Safety: No exercise-related adverse events occurred. In addition, no participants were excluded due to cardiovascular concerns. Common non-exercise related complications

that impacted session adherence were chemotherapy-related fatigue and symptoms of peripheral neuropathy.

Secondary outcome measures

Cardiovascular outcomes: Fitness levels were examined by comparing peak METs achieved during the aerobic stress tests pre- and post-intervention. Examination of individual aerobic responses showed that peak MET scores increased or decreased on an individual basis (Figure 5A), although group averages showed no difference pre- to post-intervention (Figure 5B). Four participants increased their peak workload by +1 MET post-intervention, four decreased by at least -1 MET, and one changed very little. It was thought that session attendance may have partially predicted the changes. However, a linear regression showed no association between peak MET changes pre- and post-intervention and total number of sessions attended (Figure 5C; $R^2 = 0.06$). Notably, there were no issues with protocol adherence within the study (i.e., participants were able to complete the exercise prescribed to them). Resting systolic and diastolic blood pressures were unchanged pre- and post-intervention (Figure 7A & B). Lastly, resting HR did not change pre-post intervention (Figure 8).

Functional Assessment of Cancer Therapy tools: No significant differences were observed pre-post intervention in the total FACT-G scores (Figure 8) or individual components of the FACT-G (Physical, Emotional, Social, and Functional well-being; Figure 9). When comparing within cancer groups using breast or hematological cancer-specific questionnaires, no differences were observed for either cancer (Figure 10). Lastly, there was no significant change in measured cancer-related fatigue (Figure 11).

Systemic inflammation: No significant changes were observed pre-post intervention for systemic markers of inflammation that have been associated with AC-mediated cardiotoxicity. These included serum concentrations of IL-1 β (Figure 12A), IL-6 (Figure 12B), and TNF- α (Figure 12C).

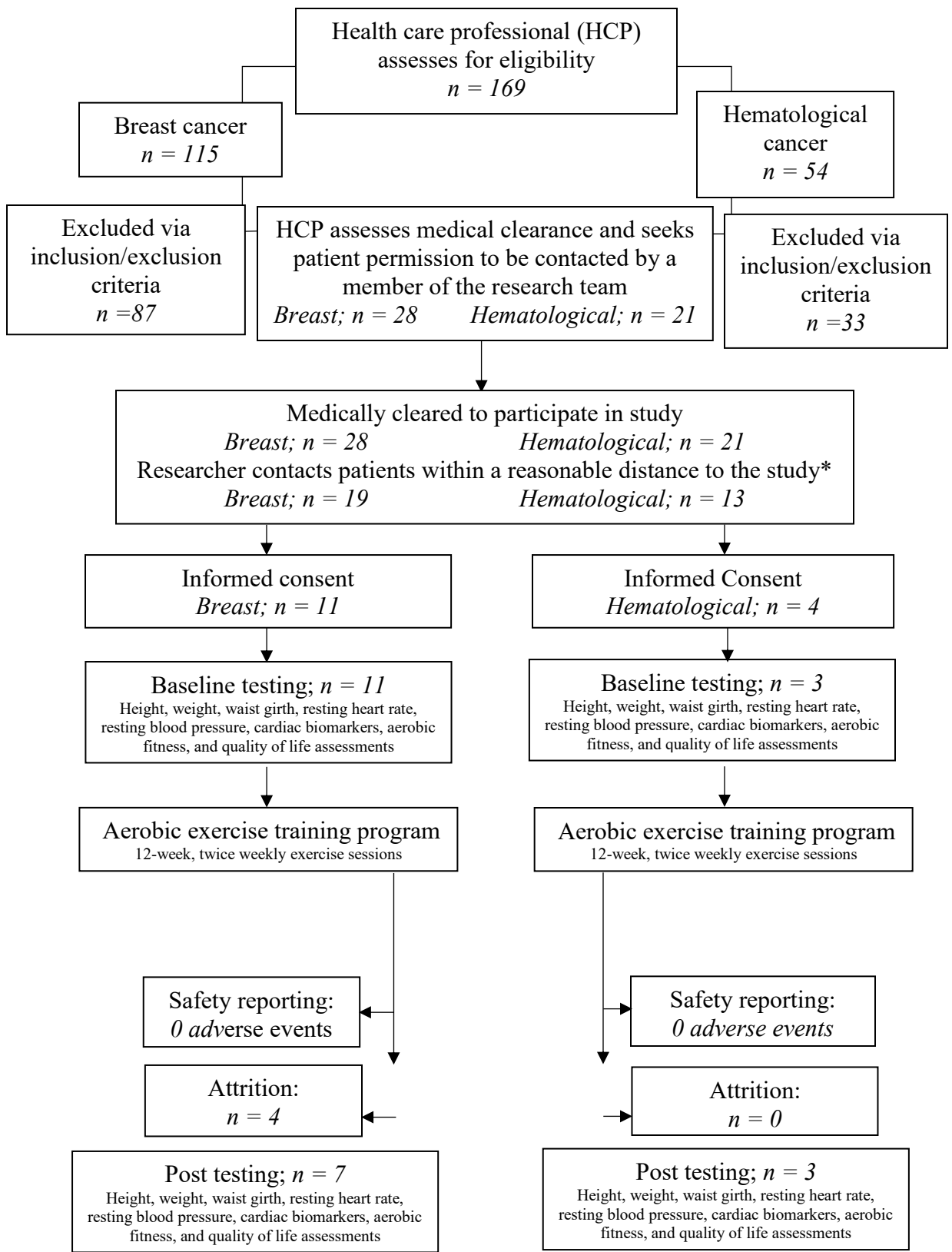


Figure 2: EXACT study flowchart for breast and hematological cancer patients. *Note: A reasonable distance was loosely defined as within 1-2+ hour commute to the intervention site.

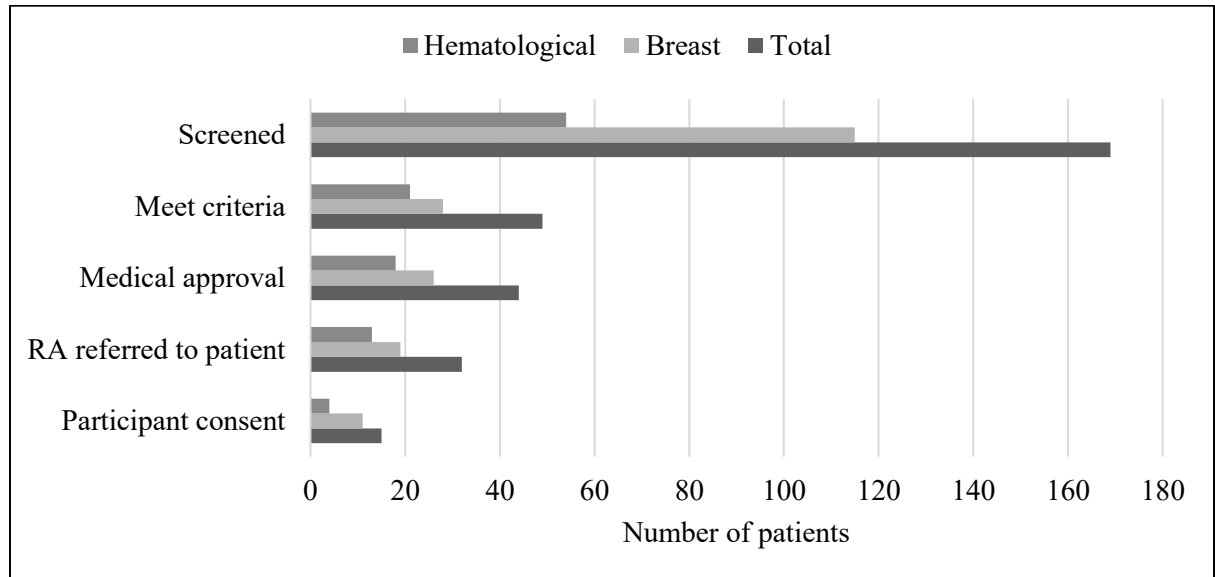


Figure 3: EXACT study graphic for screening and recruitment for hematological, breast, and all cancer patients. RA = research assistant.

Table 1: Participant characteristics and time entering exercise intervention from treatment start date (mean±SD) for breast and hematological cancer participants. WC = Waist circumference; BMI = Body mass index; M = Male; F = Female. Pre-post values were non-significant ($p>0.05$). * denotes n-1; one individual's treatment history records were unclear.

	Breast (n=7)		Hematological (n=3)		All (n=10)	
Age (years)	55.0±6.5		37.7±17.8		49.8±13.0	
Sex (M/F)	0/7		3/0		3/7	
Height (cm)	162.6±5.7		175.2±4.6		166.4±8.0	
	<i>Pre</i>	<i>Post</i>	<i>Pre</i>	<i>Post</i>	<i>Pre</i>	<i>Post</i>
Weight (kg)	79.1±12.55	81.0±13.1	88.7±23.1	84.8±19.6	82.0±15.7	82.1±14.3
BMI (kg/m ²)	29.8±3.0	30.4±3.1	29.2±9.2	27.8±7.6	29.6±4.5	29.6±5.0
WC (cm)	96.8±8.3	96.4±9.0	96.7±24	97.3±18.4	96.8±13.2	96.65±11.4
Current smoker	1		0		1	
Past smoker	3		1		4	
Time from treatment start	8.0±5.1		9.6±5.8*		8.4±5.1*	

date to beginning
of exercise
program (weeks)

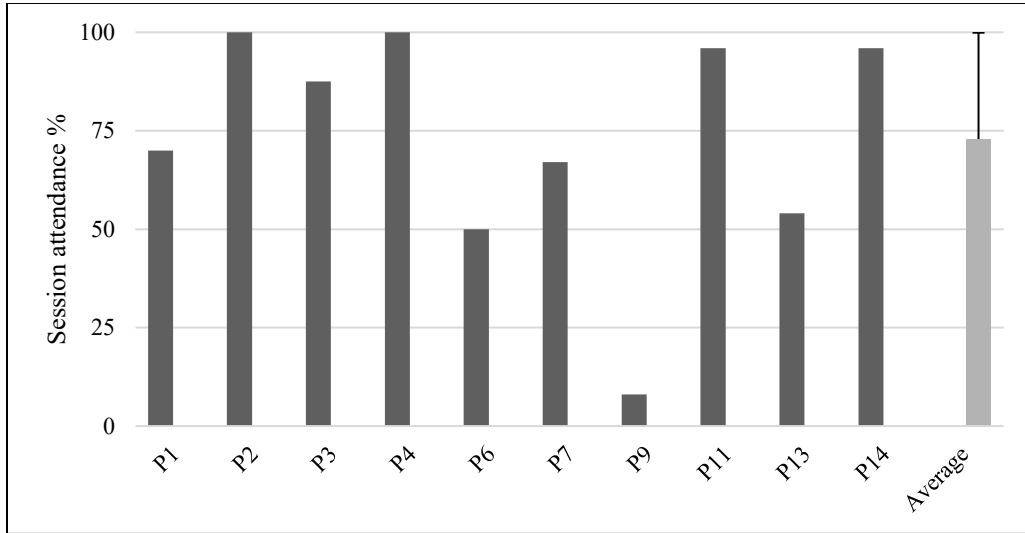


Figure 4: Session adherence for individual participants presented as a percentage of total sessions attended. P stands for Participant and their number denotes their order of recruitment. The error bar with the Average is presented as standard deviation.

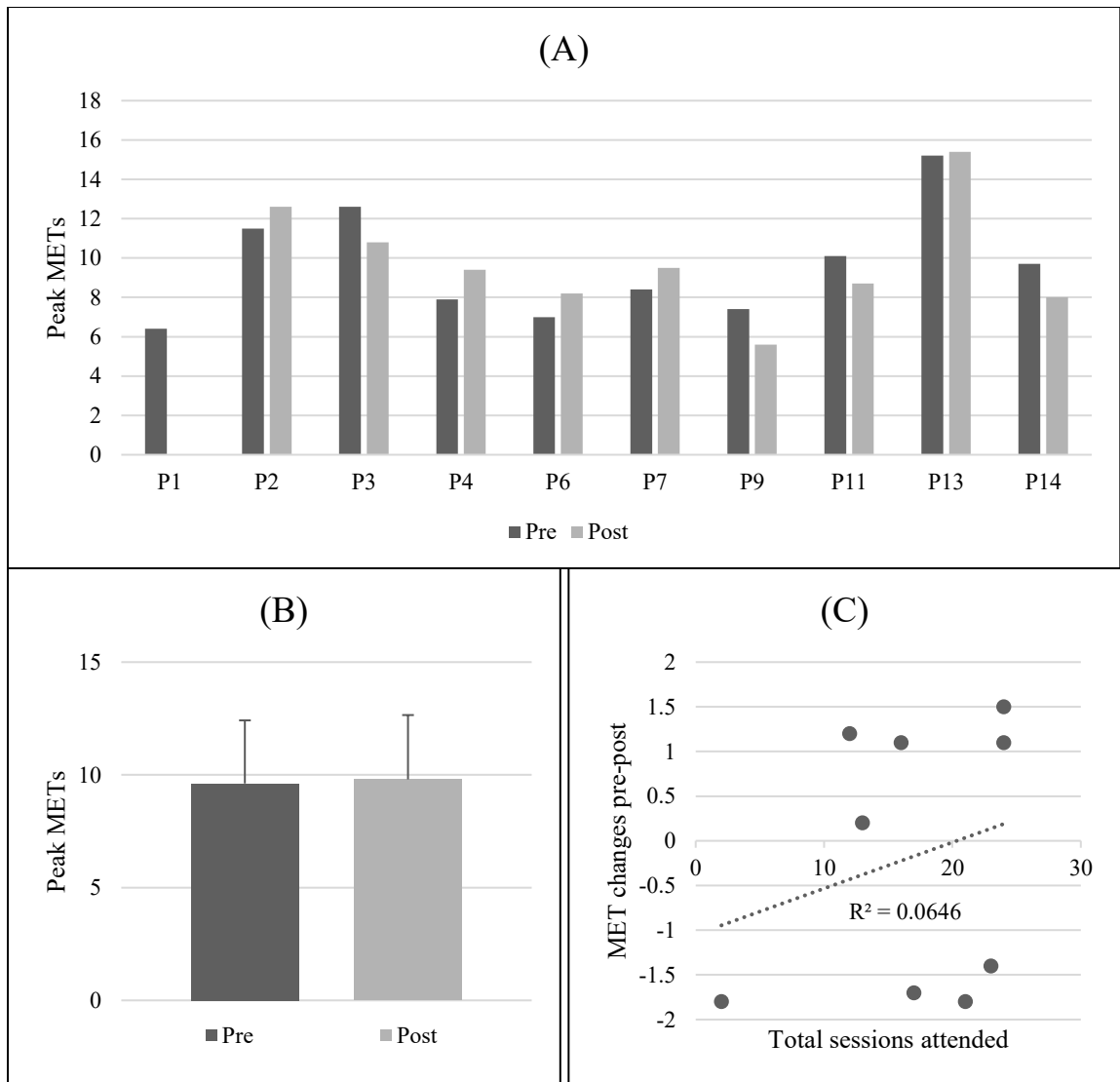


Figure 5: Peak metabolic equivalents (METs; 3.5ml O₂/kg/min) achieved during a submaximal ramped aerobic treadmill-based stress test (P = participant and their number denotes the order of recruitment). (A): Individual peak MET scores pre- and post-intervention for the 9 participants that completed pre- and post-intervention testing. (B): Peak MET score (mean±SD) pre- and post-intervention for all participants (p>0.05). NOTE: P1 was unable to complete their post-intervention stress test. (C): Regression analysis of absolute peak MET changes pre-post intervention (n=9). R² = 0.06.

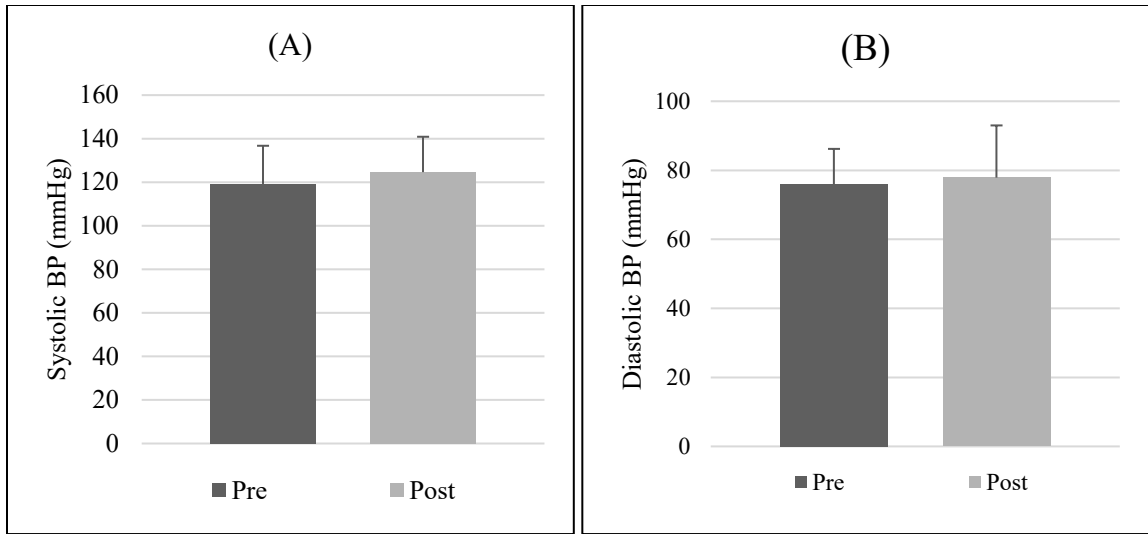


Figure 6: Resting blood pressure (BP) readings of all participants pre- and post-intervention (mean±SD; n=10). (A): Resting systolic BP values ($p>0.05$). (B): Resting diastolic BP values ($p>0.05$).

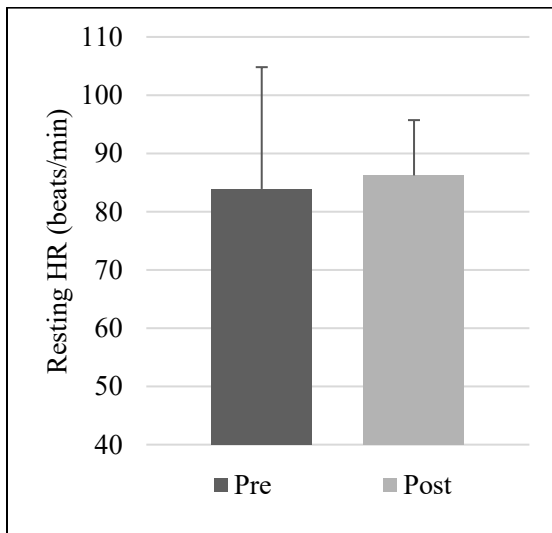


Figure 7: Resting heart rate (HR; mean±SD) pre- and post-intervention for all participants (n=10; $p>0.05$).

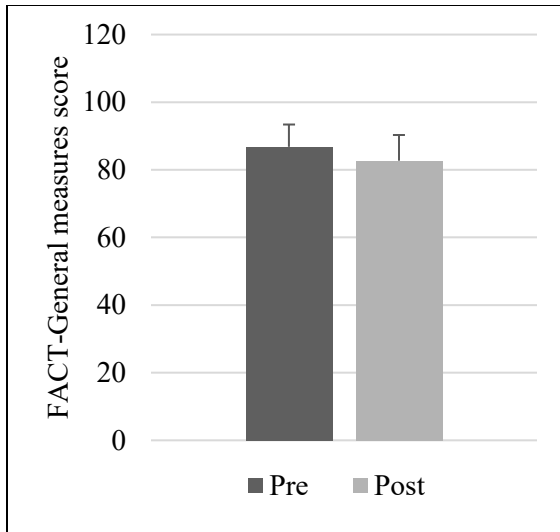


Figure 8: FACT-G (General Measures) scores (mean±SD) pre- and post-intervention for all participants (n=10; p>0.05).

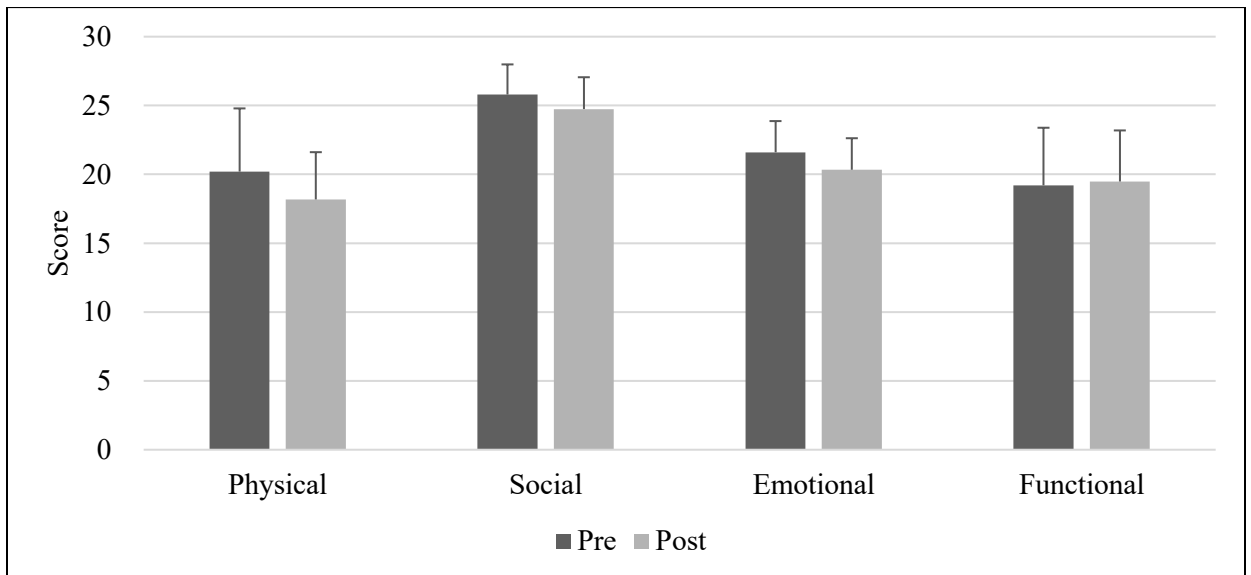


Figure 9: FACT-G (General Measures) scores for each of its four constituents (mean±SD) pre- and post-intervention for all participants (n=10; p>0.05 for all)

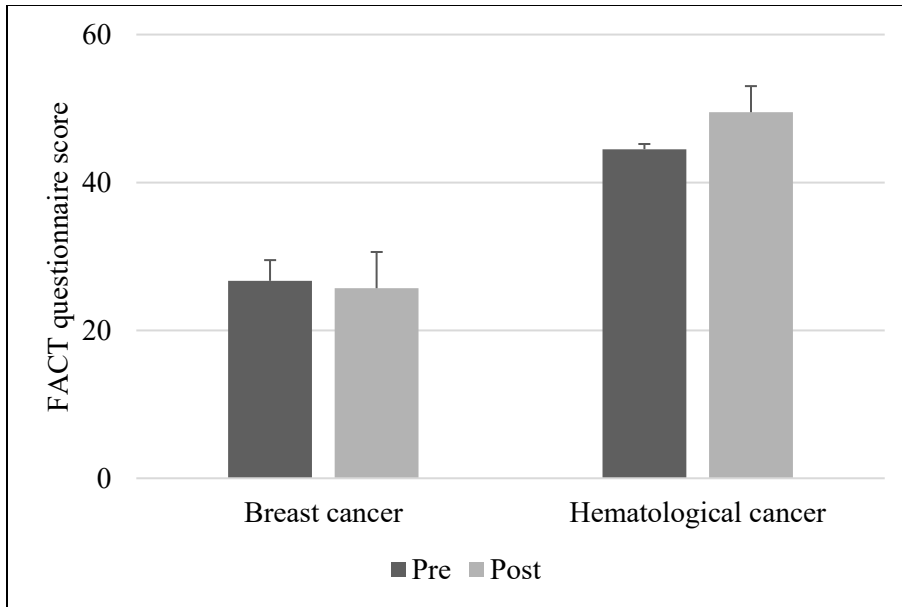


Figure 10: FACT questionnaire scores (mean±SD) for breast cancer-specific functional assessment questions (FACT-B; n=7; p>0.05) and hematological cancer-specific functional assessment questions (FACT-Lym; n=3; p>0.05). NOTE: FACT-B and FACT-Lym have different questions and are thus non-comparable.

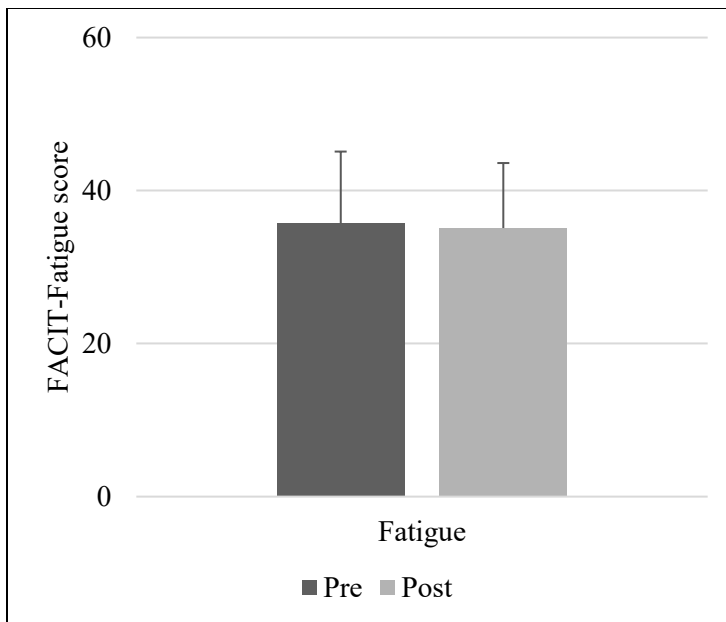


Figure 11: FACIT-Fatigue (for chronic-illness-related fatigue) questionnaire scores (mean±SD) for all participants (n=10; p>0.05).

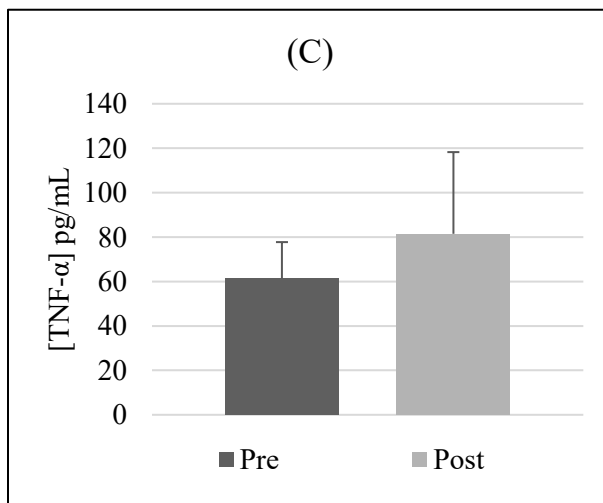
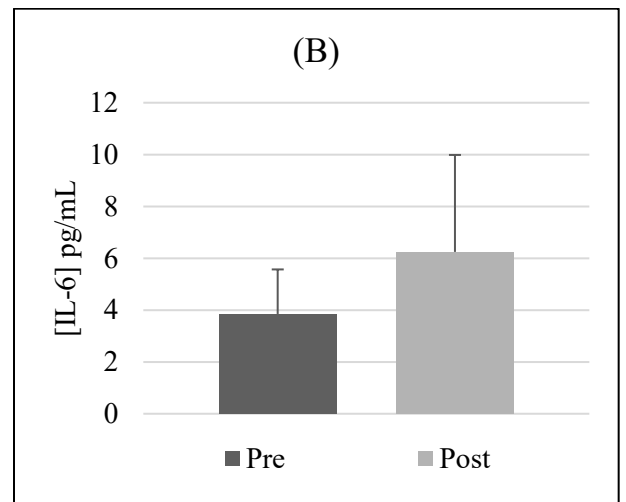
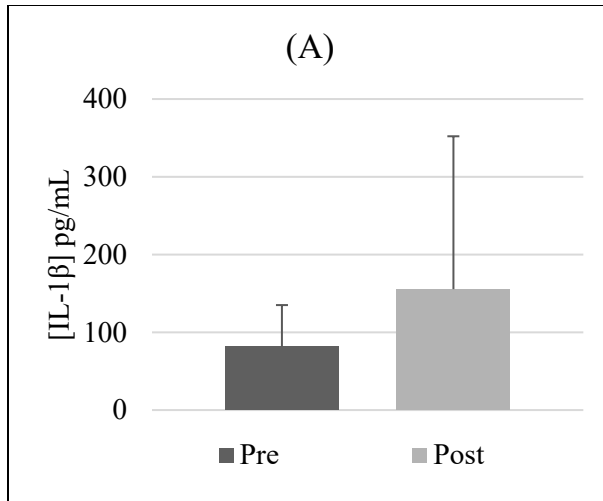


Figure 12: Systemic inflammatory markers pre-post intervention for all participants (means±SD; n=10). (A): Interleukin-1 β (IL-1 β ; p>0.05). (B): Interleukin-6 (IL-6; p>0.05). (C): Tumor necrosis factor- α (TNF- α ; p>0.05).

CHAPTER 5: DISCUSSION

General findings: Before committing to a large clinical trial in a smaller city such as Halifax, the feasibility of an aerobic exercise intervention must be known. Thus, this study primarily sought to determine the feasibility of a 12-week aerobic exercise intervention in breast and hematological cancer patients taking ACs. Overall, the intervention was deemed feasible based on comparisons to other similar trials. Of note, the largest barrier to recruiting eligible participants was travel distance to the intervention site. In addition to feasibility, secondary outcome measures sought to evaluate the efficacy of an aerobic exercise intervention to prevent cardiotoxicity associated with AC-administration. There were no significant changes between pre- and post-intervention measurements of any secondary outcome variable. Notably, there were no decreases in cardiorespiratory fitness and self-reported functional and fatigue questionnaires. Based on previous literature these values were expected to decline.^{95,101} Speculatively, AET may have helped prevent these declines. However, larger sample sizes and a control group are needed before any conclusions can be made. In summary, this study shows that an aerobic exercise intervention for breast and hematological cancer patients is feasible in Halifax, NS, and that further investigation examining its efficacy to prevent cardiotoxicity from ACs is warranted.

Before comparing the EXACT study to others, it is important to mention the variation in relevant literature. Some studies are very relatable, such as Kirkham et al.²⁵ and their bouts of aerobic exercise 24-hours prior to AC-therapy. However, there is ultimately little literature regarding the use of AET to mitigate cardiotoxic risks in

humans mechanistically. Many of the other interventions use a mix of therapies and exercise types. These studies are still worth discussing, although the reader is encouraged to keep these differences in mind when interpreting the comparisons. For example, some exercise studies only had a fraction of patients on ACs. This makes comparisons for cardiovascular measures difficult since cardiotoxicity can manifest differently (or barely at all) for other therapies. Additionally, comparing feasibility measures for exercise interventions are often not direct, because interventions range in frequency, intensity, duration, and exercise modality. This would naturally affect the willingness of participants to join and adhere. Some studies use very similar designs to the EXACT study (i.e., non-linear progressive aerobic exercise) and others use linear aerobic exercise models and/or home-based exercise interventions. These studies were often similar in total duration, session intensity, and session duration. However, certain differences existed between them. Notably, these other interventions all utilized cycle ergometers for their exercise modality.

The EXACT study will now be placed within the context of the literature, however it is acknowledged that the natural variability in cancer, cancer therapies, and exercise interventions make the comparisons indirect. The author has attempted to explain relevant differences from the EXACT study where appropriate.

Recruitment: Our recruitment statistic (30%) is within the range of other aerobic exercise trials with cancer patients. Five clinical trials in cancer patients using a similar exercise intervention/design to the EXACT study (progressive non-linear supervised aerobic exercise during chemotherapy) yielded an average recruitment statistic of 45% (range: 25-67%).^{31,98,100-102} These studies were notably similar to the EXACT study in session

duration and intensity, and overall program length, which makes them useful for comparison.

The most similar study to the EXACT trial was done by Hornsby et al.¹⁰², which randomized stage II-III breast cancer patients on ACs to a standard of care group or standard of care plus AET (cycle ergometry). Their recruitment statistic was 67%, which was much higher than the EXACT study. One reason it could be so much higher was because a large percentage of individuals (677 of 1445 patients screened) were excluded before eligibility screening occurred. This makes it difficult to accurately calculate a recruitment statistic for this study, as some of the 677 may have been deemed eligible (although eventually not recruited, just as in the EXACT study). Thus, their recruitment statistic may have been lower if the screening protocol was equal to the EXACT study's. It is also worth noting that this study was performed in Durham, NC, which has an estimated population of ~650 000. The EXACT study was performed in a slightly smaller area (Halifax), which has an estimated population of ~400 000. The discrepancy in screening numbers (169 for EXACT and 1445 for Hornsby et al.) can be explained by surrounding town and city population numbers. Including Hornsby et al., five studies were comparable in duration to the EXACT study. Four ranged from 12- to 14-weeks,^{31,100-102} and one had a 6-week intervention.⁹⁸ Four studies use cycle ergometry, which was different than the treadmills used for the EXACT study. Cancer models ranged from hematological,¹⁰¹ lung cancer,^{31,98} or a mix.¹⁰⁰ Differences aside, these are still highly comparable studies to the EXACT study based on their duration and exercise intervention. They showed that the EXACT study's recruitment statistic was within the range of similar studies (25-67%).^{31,98,100-102}

Another way to compare recruitment is to examine the average number of participants recruited to the exercise intervention per year. The EXACT study recruited 15 patients in its one-year of recruiting. Five comparable trials recruited an average of 18.5 participants per year.^{31,98,100-102} These values, along with the recruitment statistics, indicate that the number of cancer patients recruited into the EXACT study is similar to other clinical trials. Importantly, these trials were published as randomized controlled trials and not feasibility studies, which furthers the argument that a trial in Halifax is feasible.

As with the EXACT study, travel distance to the intervention site and study inconvenience seem to be the largest issues with recruitment in this type of research. One or both were cited in the top three reasons for non-consent for all five of the aforementioned studies.^{31,98,100-102} This means that one way to engage a larger patient population in exercise is increasing accessibility. This is not new information, as accessibility has been well-established in non-cancer models to be a barrier to physical activity.¹¹⁵ It does however reinforce this notion in a arguably more vulnerable population of cancer patients on cardiotoxic therapies.

A note on home-based therapies: Improving recruitment for future exercise interventions with cancer patients is important. Provided that most non-consenting eligible patients did not participate due to travel distance/inconvenience, finding ways to remove those issues can help. When thinking of ways to increase the accessibility of an intervention, home-based programs are often thought of. Home-based exercise interventions attempt to remove the issues of travel distance and inconvenience from a study design to allow more participants to join. There have been successful home-based exercise interventions for

cancer patients in the past. For example, Pinto et al.¹¹⁶ found that exercise counseling and weekly activity tips for breast cancer patients increased their physical fitness and measures of psychological well-being. Their recruitment statistic was 70%, which was higher than any of the previously mentioned supervised aerobic exercise interventions (range: 25-67%).^{31,98,100-102} Mock et al.¹¹⁷ and Schwartz et al.¹¹⁸ found similar results, citing that a home-based exercise intervention helped to improve physical function (via a 12-minute walk test) and markers of psychological well-being. These results sound promising, although studying the effects of a home-based intervention in a randomized and controlled way can prove challenging. For example, a study completed by Courneya et al.¹¹⁹ completed a home-based exercise intervention with colorectal cancer patients to improve their quality of life and cardiovascular capacity. No significant differences were observed pre- and post-intervention, which was primarily explained by the fact that 52% of their control group exercised during the study period. While this issue is welcomed by exercise activists, it highlights a challenge that researchers will experience if using this study design. As a final note on home-based exercise interventions, a review by Galvão & Newton¹²⁰ interestingly suggested that very few studies examining exercise interventions in cancer patients compared multiple exercise interventions. Thus, the EXACT study could expand by incorporating multiple streams of exercise interventions, whereby patients are offered either home-based or supervised aerobic exercise prescriptions. This could help to increase recruitment by offering two modalities of the same intervention (and appealing to more people). Furthermore, comparing different home-based or supervised interventions to themselves and each other (i.e, comparing two

home-based interventions, or comparing equivalent home-based interventions to supervised ones) could help bridge that gap in the literature.

Retention: The retention statistic in the EXACT study (67%) is within the range of comparable studies, albeit below average. Four clinical trials using progressive non-linear supervised aerobic exercise and a similar intervention duration to the EXACT study had a retention statistic range of 65 to 100% and a mean of $89\pm 16\%$.^{31,98,100,102} Six other studies using linear supervised aerobic exercise interventions had a very similar range of 69 to 95% retention with a mean of $84\pm 9\%$.^{25,121-125} Interestingly, the EXACT study lost most of its participants to travel/inconvenience (4 of the 5 withdrawals), which does not appear to be the norm for other studies of similar design. For example, Noble et al.¹²¹ had 117 of their 557 participants withdraw due mainly to personal reasons (35%) or medical reasons not associated with the exercise intervention (23%), while only 8% left due to travelling barriers. This is in stark contrast to the EXACT study, which lost 80% of withdrawals due to travel distance/inconvenience (although the sample size differs greatly from Noble et al.). Additional reasons for withdrawal in other studies involving exercise interventions with cancer patients include surgical complications,⁹⁸ chemotherapy toxicity,^{31,101,123} and death.^{98,125-127} Although these were not witnessed in the EXACT study, it is possible they could occur in a larger future trial.

Adherence: Session adherence for the EXACT study was nearly identical to other aerobic exercise interventions with cancer patients. After removing a participant from analysis that only attended the first two sessions, adherence for the EXACT study was $80.0\pm 20.0\%$. The average adherence for five similar (non-linear progressive aerobic exercise) interventions with cancer patients was $80.4\pm 5.5\%$ (range: 72-85%).^{31,98,100-102}

This roughly matches the adherence rates for other broadly similar exercise interventions in cancer patients (linear aerobic exercise).^{25,122-125} The reasons for non-adherence are not commonly presented in relevant literature, which may be because they are either 1) difficult to track, and/or 2) reflected in the withdrawal reasons. Anecdotally, participants commonly declined to attend exercise sessions due to chemotherapy-related fatigue or personal scheduling conflicts. These were commonly reported measures in another study that did mention them, although without any statistics.¹²¹ For the EXACT study, patients that could not attend were offered alternative times to attend. These sessions outside of regular hours were attended often. Noble et al.¹²¹ also provided their participants the opportunity to extend their total number of weeks to reach the full number of sessions. This strategy in combination with a flexibility to re-schedule could help to increase session adherence. Notably, although the intervention was set-up to allow several patients to exercise concurrently, the study's rolling recruitment and scheduling difficulties meant that participants often exercised singularly with the study's trainer. Multiple participants attending the same session was less common than single participant sessions. It is unknown if this altered the adherence significantly. Regardless, the EXACT study's adherence levels were well within the expected range.

Safety: No adverse effects associated with exercise occurred during the duration of the study. This is largely congruent with other studies using a non-linear aerobic exercise intervention.^{31,98,100-102} For example, no adverse events were seen in two studies that exercised participants 3x per week on cycle ergometers.^{31,100} Other studies report adverse events, although they are not cause for concern. These include two cases of systolic hypotension and one case of unexplained leg pain, both of which quickly

recovered after exercise.^{98,102} These events occurred in very similar interventions to the EXACT study. Another similar intervention reported that three participants had joint problems (i.e., knee or back).¹⁰¹ This caused one participant to leave, while the other two successfully completed alternative exercise programs. When combining all studies (including EXACT), a total of three one-time non-serious adverse events and three joint-related issues with exercise within a combined number of 247 cancer patients.^{31,98,100-102} This means that 2.5% of the total populations were reported to have any incidence of an adverse event. In context to cancer, three people died during these interventions from non-exercise related reasons (presumably cancer).

Compared to exercise interventions in other diseased populations with high morbidity/mortality, the prevalence of exercise-associated adverse events is very similar. For example, pulmonary arterial hypertension disease is characterized by low exercise capacity, high morbidity/mortality, and cardiovascular/respiratory/muscular dysfunction.¹²⁸ A systematic review looked at the number of adverse events associated with exercise interventions in patients with pulmonary arterial hypertension. It found that of all 482 participants included in their analysis, 3.3% had exercise-associated adverse events.¹²⁸ This number is similar to those seen in AET interventions for cancer patients and indicates that the risks seen in cancer patients are similar to those observed in other chronic conditions. Altogether, the risks of AET in the EXACT study were in line with similar trials with cancer patients, and these were akin to exercise-associated adverse event rates in other at-risk diseased populations.

Cardiorespiratory fitness and measures: Although the EXACT study was primarily a feasibility study, cardiorespiratory fitness and function were of interest given the

detrimental effects of ACs on cardiac health. Previous studies similar to the EXACT protocol that performed AET with cancer patients (many of whom received ACs) found that exercise significantly increased exercise capacity (relative VO_{2peak}) and/or workload (in Watts).^{31,98-102} The ability of AET to increase aerobic capacity post-cancer therapy (including those that received ACs) is also known.^{129,130} Thus, it was reasonable to posit the EXACT study could elicit the same effects. However, the exercise sessions did not increase cardiorespiratory fitness levels. Peak METs achieved (an indicator of workload) after the intervention were not statistically different on average (Figure 5A). Importantly, although fitness levels did not increase, they also did not decline. Mijwel et al.⁹⁵ found that aerobic capacity declined during usual care for breast cancer patients on ACs or taxanes (both cardiotoxic), but aerobic and/or resistance training plus high-intensity interval training prevented this decline. Therefore, the EXACT intervention may have stopped a decline in aerobic capacity for its participants, although future trials with a control are necessary to confirm this.

When analyzing individual fitness changes, four participants increased from baseline and four decreased, while one individual barely changed at all. A decline in peak METs in an individual was always possible. For example, AC treatment has been linked with declines in aerobic capacity.^{102,131,132} These increases or decreases were thought to correlate with session adherence (i.e., the more sessions attended, the more fitness gained). Oddly, the increases or decreases in peak METs achieved after the intervention did not correlate with session adherence (Figure 5C). This lack of relationship between session adherence and aerobic capacity is confounding after examining six similar studies suggesting AET for cancer patients improves aerobic fitness.^{31,98-102} One possible reason

for this discrepancy is that not all participants in those studies were receiving ACs (i.e., some were pre-operation lung cancer patients). Another possible explanation is that the participants in the EXACT study received less overload stimulus to their cardiovascular system than in related studies using a non-linear AET approach. Four comparable studies that saw fitness gains exercised participants three times per week,^{31,100,119} and the other two exercised them five times per week.^{98,99} Using a typical adherence rate (i.e., 80%), this would increase total exercise sessions over a 12-week period from approximately 19 sessions for the EXACT study (2x week) to 29 (3x per week) or even 48 (5x per week) sessions. That is a difference of an extra 10 or 29 exercise sessions, respectively, compared to a 12-week intervention. In terms of exercise minutes per week, assuming the average exercise session were 30 minutes, that would equal an extra 288 or 864 minutes per week more than the EXACT study for 3x and 5x per week, respectively. These extra exercise sessions arguably provide more overload stimulus to the cardiovascular system and could therefore elicit a greater response.

Alternative influences on aerobic capacity could include, but are not limited to, patient-specific therapy-associated fatigue and/or performance-altering medications. Additionally, it is not well known how quickly aerobic capacity regenerates post-AC therapy in human adults. Some patients may have recovered from the acute AC-mediated cardiotoxicity prior to their post-intervention stress test. Altogether, the lack of change in aerobic capacity for the EXACT study is not congruent with the results of similar studies that indicate an improvement. This may be because participants in the EXACT study did not receive as much overload stimulus to their cardiovascular system as other studies provided.

Functional Assessment of Cancer Therapy (FACT) tools: The FACT questionnaires sought to evaluate the impact of the AET intervention on participants' quality of life, physical function, and fatigue. Aerobic exercise could be expected to improve quality of life and physical function while decreasing fatigue in cancer patients.^{101,133} Overall, the FACT questionnaires showed no change in any of the recorded measurements. This suggests the intervention did not significantly alter cancer- or therapy-associated changes in quality of life, function, or fatigue, including: general well-being (FACT-G; including physical, social, emotional, and functional), breast or hematological cancer-related issues (FACT-B & FACT-Lym), or chronic illness-related fatigue (FACIT-Fatigue). There is supporting and non-supporting evidence from the relevant literature. For example, non-significant changes in both the FACT-B and -G were published in a very similar exercise intervention to the EXACT study in breast cancer patients.¹⁰² FACT-B and -G levels also remained unchanged after Segal et al.¹³³ completed a 26-week supervised exercise intervention with breast cancer patients. It is worth noting that Segal et al.¹³³ found an increase in physical functioning with Medical Outcomes Survey Short Form-36, which could be roughly compared to the Functional well-being section of the FACT-G questionnaire.

In contrast, other studies do indicate a beneficial effect of exercise on well-being. A combined analysis of three studies in breast cancer patients (including the previously mentioned trial by Segal et al.¹³³ that found no statistical difference) suggest that exercise improves general (FACT-G) and/or breast-cancer specific well-being (FACT-B),^{119,133,134} as per a systematic review by McNeely et al.¹³⁵ Another way to analyze the FACT-G and -B questionnaires is to break them down into their individual constituents (as was done in

Figure 9). Hornsby et al.¹⁰² broke down the FACT-G this way when evaluating their exercise intervention with breast cancer patients receiving ACs. Unlike the EXACT study, they found significant improvements pre-post intervention for the social and emotional well-being sections. However, the functional and physical sections were non-significant, similar to the EXACT study. The discrepancies in results for the interventions with breast cancer patients could be due to numerous personal and medical reasons, as well as intervention-specific differences.

Regarding hematological patients, a combined resistance and aerobic exercise program for lymphoma survivors found that it improved FACT-Lym scores, which was contrary to what the EXACT study found.¹³⁶ This difference could have been attributable to the participant characteristics (i.e., the EXACT study recruited patients, whereas the other intervention recruited survivors) or the modality (only aerobic versus aerobic + resistance). Another study that completed an exercise intervention similar to the EXACT study in 122 lymphoma patients found that their 12-week non-linear aerobic exercise intervention significantly improved the scores for the FACT-An (for anemia) questionnaire (which includes the FACT-G) but did not report any differences in the lymphoma-specific questions (FACT-Lym).¹⁰¹ The FACT-An questionnaire was used because of the prevalence of anemia in the study population, and consists of different (although similar in nature) questions than the FACT-Lym. It is noteworthy that the FACT-An improved with exercise but the FACT-Lym (for lymphoma) remained unchanged. This indicates that future exercise interventions with lymphoma patients should take advantage of both questionnaires to better isolate what quality of life aspects the intervention is targeting.

The non-significant changes in the FACIT-Fatigue scores (for chronic-illness related fatigue) in the EXACT study also add to a mixed body of results. One relevant and comparable to the EXACT study is a trial by Hornsby et al.,¹⁰² which agreed with the EXACT study by reporting no changes to FACIT-Fatigue scores post-exercise. However, a larger trial by Courneya et al.¹⁰¹ reported that fatigue levels decreased. Interestingly, both of these trials used a 12-week cycle ergometer intervention that had patients exercise 3x per week at similar intensities. This highlights the level of variability when measuring qualities such as fatigue. Furthermore, low starting levels of fatigue could have masked any potential effect exercise had on reducing fatigue. AET also could have prevented a rise in fatigue levels, although future trials with a control arm are needed to confirm.

Lastly, it is important to mention larger analyses on physical function and fatigue involving exercise interventions and cancer patients. These do not reflect the non-linear aerobic exercise approach used by the EXACT study directly but are broadly similar in that they use AET in a cancer population. A systematic review and meta-analysis of exercise interventions for cancer patients analysed 4 studies involving self-reported functionality and determined exercise has a small to moderate effect on its improvement.¹³⁷ Regarding fatigue, a Cochrane meta-analysis reviewing 28 studies concluded that exercise reduced fatigue better than control groups.¹³⁸ Furthermore, a meta-analysis by McNeely et al.¹³⁵ found that exercise was beneficial versus a control for all evaluated studies (n=6), although the effect was removed when only assessing studies using exercise adjuvant to therapy (n=4). Thus, exercise interventions can aid in improving cancer-related function and fatigue. However, their efficacy appears to vary, which is likely due to factors outside of the intervention. These could include the type

and stage of cancer, the kind of therapy used to treat it, and the current lifestyle of the patient.¹³⁹

Systemic inflammation and biomarkers of cardiotoxicity: There is a lack of comparable evidence regarding the use of exercise to reduce systemic levels of IL-1 β , TNF- α , and IL-6. However, these cytokines have been mechanistically implicated in AC-mediated cardiotoxicity and thus were worth discussing. Their serum concentrations have been reported in non-exercise-based studies treating cancer patients with ACs. For instance, although rises in IL-1 β have been mechanistically implicated in AC-mediated cardiotoxicity in a preclinical study,¹⁵ it did not increase or correlate as a functional marker of cardiotoxicity (via strain rate changes) in humans.⁷² This is in agreement with the EXACT study, which saw no increase from baseline values (although the exercise intervention is a confounding variable). It is important to mention the EXACT study did not measure functional cardiotoxicity (i.e., echocardiography) and therefore is limited while interpreting cytokine changes. A similar story to IL-1 β is found with TNF- α . Guo et al.⁶⁴ reported that TNF- α production in cardiac cell models related to AC-mediated inflammation. However, human studies have not shown any systemic increase in TNF- α levels with AC-treatment.^{65,72,73} Although TNF- α levels may increase at local sites of toxicity, it does not seem to be sensitive enough to be a reliable predictive biomarker.

Serum IL-6 is a more relevant biomarker than IL-1 β and TNF- α since it is associated with cardiotoxicity in humans.^{65,72} One study looking at epirubicin (an AC) cardiotoxicity in humans reported a significant increase of IL-6 at a 200 mg/m² but did not find a difference at 0, 300, or 400 mg/m².⁷³ These levels of IL-6 correlated with changes in myocardial strain rate, which is a marker of cardiotoxicity.⁷³ The lack of

significant changes in IL-6 at 300 and 400 mg/m² could be attributed to a smaller sample size. A larger follow-up study by several of the same authors reported significant IL-6 increases at all concentrations.⁶⁵ However, Mercurio et al.⁷² similarly reported higher IL-6 values at 200 mg/m² of epirubicin but not at 0, 300, or 400 mg/m². In addition to IL-6, they measured soluble IL-6 receptor levels, which were significantly increased at 200, 300, and 400 mg/m² of epirubicin. Intriguingly, IL-6 significantly correlated with a functional measure of cardiotoxicity (strain rate changes), while the soluble IL-6 receptor did not. This indicates that IL-6 measures alone may not be specific enough on their own to evaluate cardiotoxicity, and further models incorporating its receptor may prove more efficacious. The EXACT study saw a minor increasing trend in IL-6, although it was far less dramatic than the trends witnessed in the other studies.^{65,72,73} Thus, exercise may have helped to attenuate a rise in systemic IL-6 levels, which has not been previously examined. Further investigation with randomized controlled trials is needed to confirm this, along with functional measurements of cardiotoxicity (i.e., strain rate changes).

Unfortunately, cardiac troponin, was not measured in the EXACT study. This is the most commonly reported predictive biomarker when investigating AC-mediated cardiotoxicity.^{37,74} This was not tested due to logistical reasons and should be rectified in a future and larger trial. The other biomarkers, NT-proBNP and CRP, have also been reported predictors of cardiotoxicity. However, CRP's usefulness is questionable and NT-proBNP may not be time-sensitive enough for measuring general cardiotoxicity.¹⁴⁰⁻¹⁴² Therefore, future and larger studies based on the EXACT protocol should focus on examining cardiac troponins as a biomarker for cardiotoxicity and consider not examining NT-proBNP and CRP.

Regarding exercise and biomarkers, Kirkham et al.²⁵ had cancer patients perform a 30-minute bout of aerobic exercise 24-hours prior to four AC-therapy sessions. They found that the exercise was not successful in reducing cardiac troponin levels, and both the exercise and control group saw significant increases in its systemic concentration. Thus, it will be interesting to witness how cardiac troponin reacts to further exercise trials. Perhaps alternative biomarkers will be better predictors of exercise-specific protection. During comparisons it should be remembered that the EXACT study did not tightly control AC dosing relative to exercise schedules (participants were simply within 8-weeks of beginning their regimen). Doing so would theoretically lower the inherent variability with the data and would be more congruent with other studies correlating biomarkers to cardiotoxicity.

Limitations: The limitations of this study can be divided into two categories: feasibility-related limitations and efficacy-related limitations. Regarding feasibility, the study's main limitation was that it did not recruit age/sex/cancer/etc. matched controls, and thus the feasibility of doing so is unknown. Efficacy-related limitations include a lack of matched controls for comparison, not recording the most relevant prognostic biomarker (cardiac troponin), and not evaluating cardiac function (i.e., via echocardiography). A future study based on this design should attempt to rectify these points to better evaluate the ability of AET to prevent AC-mediated cardiotoxicity.

Other ongoing and related trials: Apart from the trials mentioned already, the author believes it is important to acknowledge other ongoing and related trials that have investigated the effects of exercise on AC-mediated cardiotoxicity and health measures. Perhaps the most relevant study is currently ongoing, called the TITAN trial. The study

looks to evaluate the effects of a multidisciplinary team approach to prevent cardiotoxicity from ACs and another cardiotoxic chemotherapy.²⁶ The intervention provides exercise prescription and counseling (along with other care supporters such as pharmacists) to patients receiving ACs to compare to usual care. Cardiotoxicity measures include a cardiac computed tomography scan, echocardiography, systemic high sensitivity cardiac troponin levels, and systemic BNP levels. They anticipate recruiting 40 participants to the intervention and 40 into their control arm. According to ClinicalTrials.gov, their estimated completion date was May 2018.

Another highly-related study to the research area is the OptiTrain trial.^{30,95} This trial sought to investigate the use of high-intensity interval training in combination with moderate-intensity aerobic training or resistance training in cancer patients, all compared to standard care. In total 240 women with breast cancer receiving ACs or taxanes (other cardiotoxic agents) were randomized into the three groups. Their outcomes assessed many different variables, including cardiorespiratory fitness, muscle strength, pain thresholds, physical characteristics, and hemoglobin levels, and cancer-related fatigue.^{30,95} Their results were promising and suggested that aerobic exercise can prevent the decline of cardiorespiratory fitness and improve cancer-related fatigue. Unfortunately, this trial appears to lack mechanistic measurements of cardiotoxicity. Thus far two peer-reviewed articles have been published from the trial.^{30,95} It is uncertain if other measurements of cardiotoxic variables have yet to be published.

CHAPTER 6: CONCLUSION

As outlined in the introduction, the case has been made to use AET in an attempt to prevent or reduce AC-mediated cardiotoxicity. Currently very few trials have moved the investigation into humans. The EXACT study sought to evaluate how feasible this type of intervention was in a smaller metropolis such as Halifax, Nova Scotia. Breast and hematological cancer patients receiving ACs were recruited and feasibility statistics were assessed. Based on comparisons to similar study designs in other areas in North America, this exercise intervention study used for breast and hematological cancer patients receiving ACs is feasible. Specific comparisons included recruitment, retention, and adherence. All variables for the EXACT study were within the range of similar study designs and were often just below the average rates. Safety was not a concern and no exercise-related adverse events were reported. With this knowledge, a larger trial can be designed to evaluate the efficacy of using AET to mitigate AC-related cardiotoxicity.

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APPENDIX A - PARTICIPANT'S BROCHURE



EXACT study

EXercise to prevent Anthracycline-based Cardio-Toxicity

WHAT WE KNOW

Exercise or physical activity can be safe and beneficial at all stages of the cancer continuum from prevention, through treatment, into survivorship.

HOW COULD BEING ACTIVE HELP ME?

Being active throughout the cancer journey can...

- Help with coping & decrease emotional distress
- Improve sleep quality
- Improve immune function
- Decrease treatment-related fatigue
- Improve fitness & overall quality of life

IS NOW THE RIGHT TIME?

- Only you can decide if this program is right for you.
- The mode of exercise in the EXACT study is walking or jogging on a treadmill.
- An exercise specialist will accompany you throughout each session and make sure the intensity is adjusted to your current fitness level and fatigue/energy level that day.

WHAT WE STILL NEED TO LEARN ABOUT

Exercise is known to improve heart health but we do not know what the benefits are when heart damage is due to chemotherapy side effects.

WHAT IS BEING RESEARCHED?

The doctors and researchers involved in this study are interested in the following question:

- Can a 12-week exercise program help protect the heart against cardiotoxicity (heart damage) in patients receiving AC chemotherapy?

HOW TO LEARN MORE

If you are interested in learning more about the EXACT study, speak to your oncologist or contact the research coordinator:
Ashley Zahavich, RN
902-473-6825 ashley.zahavich@nshealth.ca

NSHA REB File #: 1019999
February 9, 2016 - Version 1



APPENDIX B - PARTICIPANT'S INFORMED CONSENT

Informed Consent Form Clinical Trial

STUDY TITLE: Exercise to prevent AnthraCycline Cardio-Toxicity: EXACT Study

CLINICAL STUDY REGISTRATION NUMBER: NCT02471053

PRINCIPAL INVESTIGATOR: Dr. Miroslaw Rajda,
Division of Cardiology, Department of
Medicine 902-473-8913

Dr. Miroslaw Rajda

STUDY SPONSOR:

FUNDER: Capital Health Research Fund
Beatrice Hunter Cancer Research Institute

Introduction

You have been invited to take part in a research study. A research study is a way of gathering information on a treatment, procedure or medical device or to answer a question about something that is not well understood. Taking part in this study is voluntary. It is up to you to decide whether to be in the study or not. Before you decide, you need to understand what the study is for, what risks you might take and what benefits you might receive. This consent form explains the study.

Feel free to discuss it with your friends and family, or your family doctor. However, if you wish to participate in the study, you must enroll within the first eight weeks of receiving your first chemotherapy treatment.

Please ask a member of the research team to clarify anything you do not understand or would like to know more about. Make sure all your questions are answered to your satisfaction before deciding whether to participate in this research study.

The researchers will:

Discuss the study with you;

Answer your questions;

Be available during the study to deal with problems and answer questions.

You are being asked to consider participating in this study because you have been diagnosed with a primary breast or hematological cancer and you are currently or are about to receive a cancer drug known to be harmful to your heart.

If you decide not to take part or if you leave the study early, your usual health care will not be affected.

2. Why is this study being conducted?

With improvements in cancer treatments, more people diagnosed with cancer are becoming long-term survivors. However, studies have shown that the damage caused by the treatments responsible for this success can lead to other health problems. One of the most concerning problems associated with a cancer drug known as anthracyclines (type of chemotherapy) is its damaging effect on the heart.

Aerobic exercise (e.g., riding a bike, walking, or swimming) has been shown to be very safe and beneficial for those with cancer. Cancer patients and survivors are often encouraged to increase their levels of physical activity to help improve their fitness, health, and overall quality of life. While exercise has been shown to be beneficial for individuals receiving cancer treatments, very little is known about how exercise may protect the heart of those receiving anthracyclines. This study will serve as a pilot project to examine feasibility and logistics before a large-scale trial is conducted. The purpose is also to gather preliminary information about the potential heart protective benefits of a 12-week aerobic exercise program for cancer patients receiving chemotherapy.

3. What Is Being Tested?

Research studies have shown that performing aerobic exercise before or during anthracycline therapy helps to maintain heart function as well as prevent damage to heart. However, these research studies have been conducted primarily in animals and it is not clear whether exercise has the same protective effects in humans. This study will explore the potential benefits of exercise on heart health in patients receiving anthracycline therapy.

4. How Long Will I Be In The Study?

This is a 14-week long study. If you decide to participate you will be invited to attend a 12-week, twice weekly aerobic (e.g., walking, cycling) training program. Each training session is expected to last 60 minutes to allow time for warm up and cool down (total of 24 training sessions). In addition to the exercise program, you will also be asked to complete two testing sessions. The first will take place about one week before starting the exercise training. The second will take place following the completion of the 12-week program. Each assessment will take approximately 60-90 minutes to complete. Your total time commitment would be about 26-27 hours.

To help us better understand the long-term impact of cancer treatment and the potential benefits of physical activity and exercise over time, we will also ask your permission to follow your health for up to 25 years. Much of this follow-up will be done “behind the scenes” by accessing your hospital records and other health databases. You may also be contacted in the future to provide additional information on your health and lifestyle behaviors (e.g., physical activity) or to return to our assessment center to provide additional health data (e.g., blood samples, fitness assessments, heart scans). *You do not need to agree to be followed for this period of time to be eligible to participate in this study.* Also, if you agree to be followed, you do not have to take part in any additional assessment (e.g., fitness tests) activities. Participating in any future assessments will be your choice.

5. How Many People Will Take Part In This Study?

It is anticipated that about 15-20 people will participate in this study throughout the Halifax region at the QEII.

6. How Is The Study Being Done?

Adult breast and hematological cancer patients will be recruited primarily from the QEII Cancer Clinics. Following physician approval, you will meet with a trained research assistant to review the study information and informed consent. If you agree to take part, you will be asked to sign this consent form and...

Complete a baseline (pre-exercise training) assessment;

Attend a 12-week, twice weekly aerobic (e.g., walking) exercise training program; and

Complete a post training assessment.

Over the course of the three month study, you will be asked to return to the QEII for 26 visits.

7. What Will Happen If I Take Part In This Study?

If you agree to take part in the study, you will be asked to complete the following:

BASELINE ASSESSMENT

During the baseline assessment you will be asked to complete a survey and provide some basic information about yourself (e.g., age, sex, occupation, household income, lifestyle behaviors, quality of life, etc.). It will take you approximately 20-25 minutes to complete the survey. You may skip any questions that you are uncomfortable answering. We will also measure your height, weight, and waist size. You will also be asked to complete an exercise stress test and provide a blood sample (about 1 tablespoon of blood). The exercise stress test is described in more detail below. The blood sample will be drawn by a trained research nurse. The collection of the blood sample and completion of the stress test is necessary for study participation. Blood samples will be taken to Dr. Scott Grandy's secure research lab (Dalhousie University) where it will be stored in a secured freezer until it is analyzed at the end of the study.

Exercise Stress Test

The exercise stress test will be supervised by a cardiologist. Prior to beginning the test, electrocardiograph (ECG) or heart monitoring stickers will be placed on your chest (a private room will be available for the application the stickers). The electrode stickers will then be attached to cables which link to an ECG machine (allowing us to monitor your heart while exercising). You will then be asked to perform a graded exercise test by walking on a treadmill. You will begin at a very slow pace. The speed and incline (slope) of the treadmill will increase every three minutes until you feel that you are no longer able to continue. If you feel unwell during the test, you will be asked to tell the doctor and technician at once. The test will be stopped if you feel severe chest pain or become very tired or short of breath.

12 WEEK EXERCISE PROGRAM

The aerobic exercise training program will be developed and supervised by a member of the research team. The intensity (i.e., how hard you will work) of the exercise program will be determined by an assessment of your current fitness level and abilities. To ensure

that you are not working too hard, we will provide you with a heart rate monitor (worn around your chest or wrist) so that we can monitor how hard you are exercising. Before starting any exercise, we will calculate your safe training heart rate using the information collected during your baseline exercise stress test.

The 12-week exercise program will consist of a warm up activity, 45 minutes of light-to-vigorous intensity exercise (e.g., walking on a treadmill, stationary cycle), and a cool down activity (e.g., light stretching). With warm up and cool down activities, each session will last about 60 minutes. We will document your attendance, training heart rate, and perceived exertion (e.g., how hard you feel you are working) at each session. Participation is voluntary, but you will be encouraged to attend as many of your assigned sessions as possible.

POST TRAINING ASSESSMENT

Following the completion of the exercise program, you will be asked to complete a final survey assessing your lifestyle behaviors and overall quality of life. We will repeat the measures of weight and waist girth. You will also be asked to complete another exercise stress test and provide a final blood sample.

OPTIONAL FOLLOW-UP

If you agree, we will follow your health for up to 25 years. The bulk of this follow-up will be done “behind the scenes” by accessing your hospital records and other health databases. However, you may also be contacted in the future to provide additional information on your health and lifestyle behaviors (e.g., physical activity) or to return to our assessment center to provide additional health data (e.g., blood samples, fitness assessments, heart scans). You may indicate your consent for long-term follow-up on the signature page.

ADDITIONAL RESPONSIBILITIES

Throughout your participation in the study, it is important that you tell the research team about any new treatment therapies, drugs or medicines you are taking or wish to take. You must also tell the research team about anything unusual that is happening with your health. This includes any medical problems that seem to be getting worse. If you have to see another doctor or have to go to a hospital, you should let the doctors know that you are in a research study. You should also tell your own doctor as quickly as possible, for your safety.

NOTE: You may decide not to take part in any of these activities and to stop participating in the study at any time by contacting the research team.

8. Are There Risks To The Study?

As with any physical activity program or study there are some risks. To give you the most complete information available, we have listed the *possible* risks, which may appear alarming. We do not want to alarm you but we do want to make sure that you have had a chance to think about all the risks carefully before you choose to participate. Please also be aware that there may be risks in participating in this study that we do not know about yet.

Physical activity studies have shown that a very common side-effect of training for both with and without cancer is mild fatigue, shortness of breath, increased body temperature, muscle soreness and/or stiffness. These symptoms will vary depending on your level of fitness. For example, if you have not exercised for a long time, it is likely that you will experience greater muscle stiffness at the beginning of the program than at the end. We will monitor your training very closely to ensure that you are not doing too much and increase your risk of experiencing unnecessary fatigue or muscle soreness. In the event that you experience an injury during training, the research staff are all trained in CPR and first aid and will be able to provide emergency care. We will also ask you to report any injuries or illnesses that occur during the time of the study.

Exercise stress testing has been shown to be a safe procedure with the risk of a serious adverse event occurring (e.g., life threatening complication) is very rare (i.e., less than 5 per 100,000 tests). Given that many cancer patients receive treatments that may impact exercise tolerance, the risk of an adverse event may be elevated. A cardiologist will be present for all testing and we will closely monitor your response to the test to maximize your safety.

In addition to the exercise program, you will be asked to complete two surveys (one at each assessment) and provide two blood samples. These surveys will ask you questions about your lifestyle behaviors and overall quality of life. If you are uncomfortable in responding to any of these questions you can leave them blank or you are free to withdraw from the study at any time without penalty. There is a possibility of pain, bruising, swelling or infection related to giving blood. These discomforts are minimal and brief.

To protect your information, we will not keep your name or other information that may identify you with the sample; only a code number. Files that link your name to the code

number will be kept in a secure place. Although no one can absolutely guarantee confidentiality, using a code number makes the chance much smaller that someone other than the research staff or other authorized groups or persons (discussed later in the consent form) will ever be able to link your name to your sample or to any test results.

The effects or discomforts of tests/procedures that are part of this study but are also part of your normal clinical care (e.g., heart scan, additional blood tests) will be reviewed by your treating physician. In order to ensure your safety, a copy of this consent form, outlining the study details and contact information, will be sent to your primary physician.

You will be told about any new information that might reasonably affect your willingness to continue to participate in this study as soon as the information becomes available to the research team.

9. Are There Benefits Of Participating In This Study?

You may or may not benefit directly from participating in this study. However, possible benefits include improved fitness and quality of life. Your participation may or may not help other people with cancer receiving treatment in the future.

10. Are There Other Choices?

You are free to seek other opinions or choices if you wish. You do not have to participate in this trial to begin an exercise program or to become more physically active. You may choose to speak with your physician, oncologist, or a qualified fitness expert about physical activity.

11. What Happens at the End of the Study?

If you would like a summary of the results, please notify the research team and a summary will be mailed or emailed to you upon completion of the study. Should you be interested in learning more about the physical activity options in your area, we encourage you to speak to your physician, oncologist, or a certified fitness professional.

12. What Are My Responsibilities?

As a study participant you will be expected to:

Read and sign the consent form;

Follow the directions of the research team;

Attend the 12 week, biweekly exercise program;

Complete the fitness assessments and study surveys at the beginning and end of the study;

Maintain an activity log book to help keep track how many aerobic activity sessions you complete over the duration of the study;

Report any problems that you experience that you think might be related to participating in the study; and

Report any changes to your health during the time of the study (even those occurring outside of the study).

13. Can My Participation in this Study End Early?

The Nova Scotia Health Authority Research Ethics Board, study sponsors, and the principal investigator have the right to stop patient recruitment or cancel the study at any time.

The principal investigator may decide to remove you from this study without your consent for any of the following reasons:

There is new information that shows being in this study is not in your best interest;

You are experiencing side-effects that are harmful to your health or well-being;

You are not following the directions of the Principal Investigator or research team;

The Principle Investigator, Nova Scotia Health Authority Research Ethics Board, or study sponsors decides to stop the study.

If you are withdrawn from this study, a member of the research team will discuss the reasons with you and plans will be made for your continued care outside of the study.

You can also choose to end your participation at any time. If you choose to withdraw from this study by providing notice to the research team, your decision will have no effect on your current or future medical treatment and healthcare.

If you withdraw your consent, the information about you, including all completed assessments (e.g., exercise stress test, questionnaires, blood samples) that were collected

before you left the study will still be used. No new information about you will be collected (and no further testing of your blood samples will be done without your permission). If you wish to withdraw from the study, please inform the study staff.

14. What About New Information?

It is possible that new information may become available while you are in the study that might affect your health, welfare, or willingness to stay in the study and you will be asked whether you wish to continue taking part in the study or not.

15. Will It Cost Me Anything?

Compensation

Participating in this study will involve several additional visits to the QEII and may result in added transportation and parking costs. Unfortunately, we are not able to reimburse you for these costs.

Research Related Injury

If you become ill or injured as a direct result of participating in this study, necessary medical treatment will be available at no additional cost to you. Your signature on this form only indicates that you have understood to your satisfaction the information regarding your participation in the study and agree to participate in the study. In no way does this waive your legal rights nor release the principal investigator, the research team, the study sponsor or involved institutions from their legal and professional responsibilities.

16. What About My Privacy and Confidentiality?

Protecting your privacy is an important part of this study and every effort to protect your privacy will be made. However, complete privacy cannot be guaranteed. For example, the principal investigator may be required by law to allow access to research records. Also, as your physician/oncologist has reviewed your medical history to ensure your fit with this study he/she will be aware that you are taking part in the study. Finally, as you may be exercising with other cancer patients, other study participants will know you are involved.

If the results of this study are presented to the public, nobody will be able to tell that you were in the study.

If you decide to participate in this study, the research team will collect personal health information from you and your health record. The research team will collect and use

only the information they need for this study and to judge the safety and usefulness of the study.

“Personal health information” is health information about you that could identify you because it includes information such as your;

Name,

Information from the study surveys;

New and existing medical records; or

The types, dates and results of various tests and procedures.

Access to Records

Other people may need to look at your personal health information to check that the information collected for the study is correct and to make sure the study followed the required laws and guidelines. These people might include:

The study sponsors and its representatives and partner companies as per the title page of this consent form; and

The Nova Scotia Health Authority Research Ethics Board and people working for or with the Nova Scotia Health Authority Research Ethics Board because they oversee the ethical conduct of research studies at the QEII in Halifax.

These people will view your study records at this institution and will not take identifying information away with them.

Use of Your Study Information

To protect your information, we will not keep your name or other information that may identify you with any of the study measurements; only a code number. Files that link your name to the code number will be kept separately from any of the measurements, samples or other information about you. Although no one can absolutely guarantee confidentiality, using a code number makes the chance much smaller that someone other than the research staff or other authorized groups or persons will ever be able to link your name to your sample or to any test results.

Information collected for this study will be kept for 7 years. Information will be stored in a databank at Dalhousie University and at Nova Scotia Health Authority in Halifax. Information may be shared with other researchers for the purposes of health research. Any study data about you that is sent outside of the Nova Scotia Health Authority will have a code and will not contain your name or address, or any information that directly identifies you.

The REB and people working for or with the REB may also contact you personally for quality assurance purposes.

Your Access to Records

You may ask the study researchers to see the information that has been collected about you.

17. Declaration of Financial Interest?

The Capital Health Research Fund and the Beatrice Hunter Cancer Research Institute are reimbursing the principal investigator and/or the principal investigator's institution to conduct this study. The amount of payment is sufficient to cover the costs of conducting the study.

18. What About Questions or Problems?

For further information about the study you may call the principal investigator who is the person in charge of this study. You may also contact the research coordinator.

The principal investigator is Miroslaw Rajda.

Telephone: 902-473-8913

Your research coordinator is Ashley Zahavich.

Telephone: 902-473-6825

E-mail: ashley.zahavich@nshealth.ca

If you experience any symptoms or possible side effects or other medical problems, please let the principal investigator or research coordinator know immediately.

In the case of a medical emergency, please call 9-1-1 or go to the nearest emergency department.

19. What Are My Rights?

You have the right to all information that could help you make a decision about participating in this study. You also have the right to ask questions about this study and your rights as a research participant, and to have them answered to your satisfaction before you make any decision. You also have the right to ask questions and to receive answers throughout this study. You have the right to withdraw your consent at any time.

If you have any questions about your rights as a research participant, contact Patient Relations at (902) 473-2133 or healthcareexperience@nshealth.ca

If you are calling us long distance (NS, NB and PEI), please use our toll free number 1-855-799-0990.

In the next part you will be asked if you agree (consent) to join this study. If the answer is “yes”, please sign the form.

20. Consent Form Signature Page

I have reviewed all of the information in this consent form related to the study called:

Exercise to prevent AnthraCycline Cardio-Toxicity: EXACT Study

I have been given the opportunity to discuss this study. All of my questions have been answered to my satisfaction.

I authorize access to my personal health information, and research study data as explained in this form.

This signature on this consent form means that I agree to take part in this study. I understand that I am free to withdraw at any time without affecting my future care.

I **agree** to permit the researchers to follow my health (through review of health records) over the next 25 years.

I **do not agree** to permit the researchers to follow my health (through review of health records) over the next 25 years.

I **agree** to permit the researchers to re-contact me to consider participation in future related research studies. (If yes, please provide contact information: _____)

I **do not agree** to permit the researchers to re-contact me to consider participation in future related research studies.

/ ____ / ____
Signature of Participant Name (Printed) Year Month Day*

/ ____ / ____
Signature of Person Conducting
Consent Discussion Name (Printed) Year Month Day*

/ ____ / ____
Signature of Investigator Name (Printed) Year Month Day*

***Note: Please fill in the dates personally**

**I will be given a signed copy of this consent form.
Thank you for your time and patience!**