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Award Number: W81XWH-06-1-0336

TITLE: THE EFFECTS OF EXERCISE TRAINING ON TUMOR VASCULARITY AND RESPONSE TO NEOADJUVANT THERAPY IN OPERABLE BREAST CANCER: A PHASE I-II STUDY (IDEA AWARD)

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The Effects of Exercise Training on Tumor Vascularity and Response to Neoadjuvant Therapy in Operable Breast Cancer: A Phase I-II Study

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**14. ABSTRACT**

To explore the effects of exercise training on tumor vascularity and response to neoadjuvant therapy in operable breast cancer in a phase I-II randomized design. Method: Using a two-armed, prospective, randomized design, potential participants will be identified and screened for eligibility via medical record review of patients scheduled for their primary neoadjuvant chemotherapy treatment consultation at DUMC. Following the successful completion of all baseline assessments participants will be randomly assigned to an exercise or control group. Participants assigned to combined exercise training and chemotherapy will perform an individualized exercise training program consisting of three cycle ergometry sessions per week at approximately 60-80% of VO2peak on nonconsecutive days for the duration of neoadjuvant chemotherapy (approximately 12 weeks). Most Significant Research Finding During Reporting Period: As per our statement of work, human ethnical approval was obtained (Task 1); all exercise testing / training procedures and clinical protocols were clarified (Task 2), and data collection has been initiated (Task 3). To date, all 3 patients in phase I of the study have been enrolled and no dose-limiting toxicities have been identified with acceptable exercise adherence (>60%), thus phase II has been initiated.

**15. SUBJECT TERMS**
breast cancer, neoadjuvant therapy, exercise training, tumor response, tumor vascularity

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## Table of Contents

**Page**

## INTRODUCTION

**Background:** Neoadjuvant or adjuvant chemotherapy for women with locally advanced carcinoma of the breast is now accepted as an effective treatment modality to improve relative risk of recurrence and death by up to 30%. Unfortunately, most solid tumors are resistant to chemotherapy as a result of poorly developed vascular systems. As such, strategies that normalize the tumor vasculature - eliminating inefficient blood vessels to improve overall global blood flow, may improve therapy effectiveness and inhibit the metastatic potential of cancer cells by limiting shedding of cancer cells into the circulation. One intervention that may favorably modulate the tumor vasculature is exercise training.

**Specific Aims:** The primary aim of phase I of this study is to establish whether combining endurance exercise training with chemotherapy leads to unacceptable exercise adherence rates or unusually high DLTs. In absence of these effects, the specific aims of phase II will be to explore the effects of combining endurance exercise training with chemotherapy versus chemotherapy alone in 23 patients with locally advanced breast cancer on (i) tumor physiology (blood flow, MVD), (ii) systemic response (circulating VEGF and EPCs, endothelial function and exercise capacity) and (iii) tumor response (pathologic and clinical response).

**Hypotheses:** In phase I, we hypothesize that patients receiving combined endurance exercise training with chemotherapy will achieve acceptable exercise adherence rates (>70% of total number of planned sessions) and normal dose limiting toxicities (DLTs). In phase II, we hypothesize that patients assigned to receive combined endurance exercise training with chemotherapy will have (i) significantly lower blood flow, mircovessel density (MVD), (ii) serial increases in circulating levels of endothelial progenitor cells (EPCs) and vascular endothelial growth factor (VEGF), (iii) increased pathologic and clinical tumor response and (iv) increased exercise capacity and endothelial function than patients assigned to chemotherapy alone.

**Study Design:** Using a two-armed, prospective, randomized design, potential participants will be identified and screened for eligibility via medical record review of patients scheduled for their primary neoadjuvant chemotherapy treatment consultation at DUMC. Following the successful completion of all baseline assessments participants will be randomly assigned to an exercise or control group. Participants assigned to combined exercise training and chemotherapy will perform an individualized exercise training program consisting of three cycle ergometry sessions per week at approximately 60-80% of $VO_{2peak}$ on nonconsecutive days for the duration of neoadjuvant chemotherapy (approximately 12 weeks).

**BODY**

The following section describes the research accomplishments achieved to date associated with each tasks outlined in the approved statement of work.

**Task 1: Gain Human Ethnical Approval (Months 0-3)**

Please find below a detailed history of our process of obtaining human ethical approval for the present investigation. *Please note, at Duke University Medical Center, there is a two-tiered system to obtain ethical approval to conduct clinical investigations among individuals diagnosed with cancer. Prior to submission to the Institutional Regulatory Board (IRB), all clinical protocols have to be submitted and approved by the Duke Comprehensive Cancer Center (DCCC) Cancer Protocol Committee (CPC).

Table 1. Detailed History

| Date | Description |
|---|---|
| October 2005 (specific date not known) | Received notification from the US Department of Defense that this proposal was funded |
| October 10, 2005 | Protocol submitted to the CPC |
| February 02, 2006 | CPC comments received. Protocol modifications required |
| February 03, 2006 | Protocol re-submitted to the CPC |
| **February 15, 2006** | **Protocol approved by the CPC** |
| March 16, 2006 | Protocol submitted to Duke IRB |
| **April 1, 2006** | **Received notification from the DOD that the award is fully executed** |
| April 10, 2006 | Preliminary comments received from IRB reviewer |
| April 12, 2006 | Revised protocol submitted to the IRB |
| April 13, 2006 | Revised protocol reviewed at April 13th IRB meeting |
| April 18, 2006 | Received notification from IRB that protocol had been deferred requiring further modifications |
| April 21, 2006 | Revised protocol submitted to the IRB |
| **May 15, 2006** | **Protocol approved by the IRB** |
| May 16, 2006 | Approved Duke IRB protocol submitted to the DOD for internal review |

| Date | Description |
|---|---|
| July 12, 2006 | Participated in the HSRRB meeting (via conference call) |
| August 4, 2006 | Received notification that further protocol modifications were required based on the HSRRB July 12 meeting |
| August 8, 2006 | Received notification that further protocol modifications were required based on the HSRRB July 12 meeting |
| August 16, 2006 | Revised protocol submitted to the DOD modified based on the HSRRB's recommendations |
| August 31, 2006 | Protocol revisions and informed consent found to be acceptable by the DOD |
| **October 12, 2006** | **Final approval from DOD** |
| October 12, 2006 | Revised protocol submitted to the Duke IRB to gain approval for the changes made by the DOD |
| **November 11, 2006** | **Modified protocol approved by the IRB** |
| December 19, 2006 | 1st patient enrolled |
| January 9, 2007 | Protocol amendment submitted to the Duke IRB. Protocol was amended to reflect change in practice regarding neoadjuvant chemotherapy (from 24 to a 12 week schedule). See Appendix A for revised study consent. |
| February 6, 2007 | Amended protocol approved by the Duke IRB |
| March 14, 2007 | 2nd patient enrolled |
| March 21, 2007 | 3rd patient enrolled |

As demonstrated, attainment of human ethical approval for the present investigation was a long and complex process. Based on the date of full study execution (April 1, 2006) and our 'statement of work', full human ethical approval was anticipated by July 1, 2006. However, full approval was not obtained until October 12, 2006, approximately 4 months behind schedule.

**Task 2: Clarification on Exercise Testing/Training Protocol and Clinical Study Procedures (Months 4-6)**

In the statement of work, we anticipated that two months would be required to order equipment and supplies and overview full study procedures. Again, based on the date of study execution, Task 2 should have been completed by August 31 (2 months following IRB approval). However, due to the prolonged time required to obtain IRB approval, we did not begin Task 2 until October 12. Task 2, including several 'pre-study

commencement meeting' with study co-investigators and the Duke Breast Tumor Group, Task 2 was completed on schedule on December 12, 2006.

**Task 3: Data Collection**

Based on our original statement of work and study execution date, we anticipated initiating data collection on September 1, 2006. However, as described, study enrollment was actually initiated 4 months after this date (December 12, 2006). As per our statement of work, locally advanced breast cancer patients are to be enrolled into the study on a continual basis until the desired number of patients (i.e., 23) is achieved for phase I (i.e., 3) and phase II (i.e., 20). Approximately ~400 newly diagnosed breast cancer patients are treated at DCCC every year and ~15% will be eligible for neoadjuvant chemotherapy. Approximately, 35% of these cases will reside with the Durham area (n=21) and based on our prior trials, we expect to recruit ~50% of these patients, yielding an estimated sample size of 11 patients/year (0.9 patients/month). As such, we anticipate it will take ~24 months to recruit the desired number of patients. To date, we have successfully recruited 3 patients over a period of 4 months (recruitment rate of 0.75 patients/month), which is slightly lower than our original anticipatory accrual rate. It is important to note, however, that during this initial recruitment period we were forced to submit and gain IRB approval on an amended protocol which took approximately one month (see Table 1). As such, we are currently recruiting subjects as anticipated and we are very confident that all subjects will be accrued within the 24 month 'data collection' period. Detailed information on subject accrual to date is provided herein. The study flow is presented in Figure 1. To date, a total of 17 patients have been screened for study eligibility. Of these, 6 met inclusion criteria (6/17 = 35%) and 3 agreed to participate, a participation rate of 50%. Reasons for non-eligibility were receiving neoadjuvant endocrine therapy (n=5), receiving adjuvant therapy (n=3), physician non-approval (n=1), receiving dose-dense neoadjuvant chemotherapy (n=1), and presence of metastatic disease (n=1). The 3 patients that met inclusion criteria are currently pending (i.e., had biopsy and awaiting primary treatment consultation to determine whether appropriate for neoadjuvant chemotherapy). Detailed information on the 3 patients enrolled in the study are provided in Table 2.

**Figure 1. Study Flow**

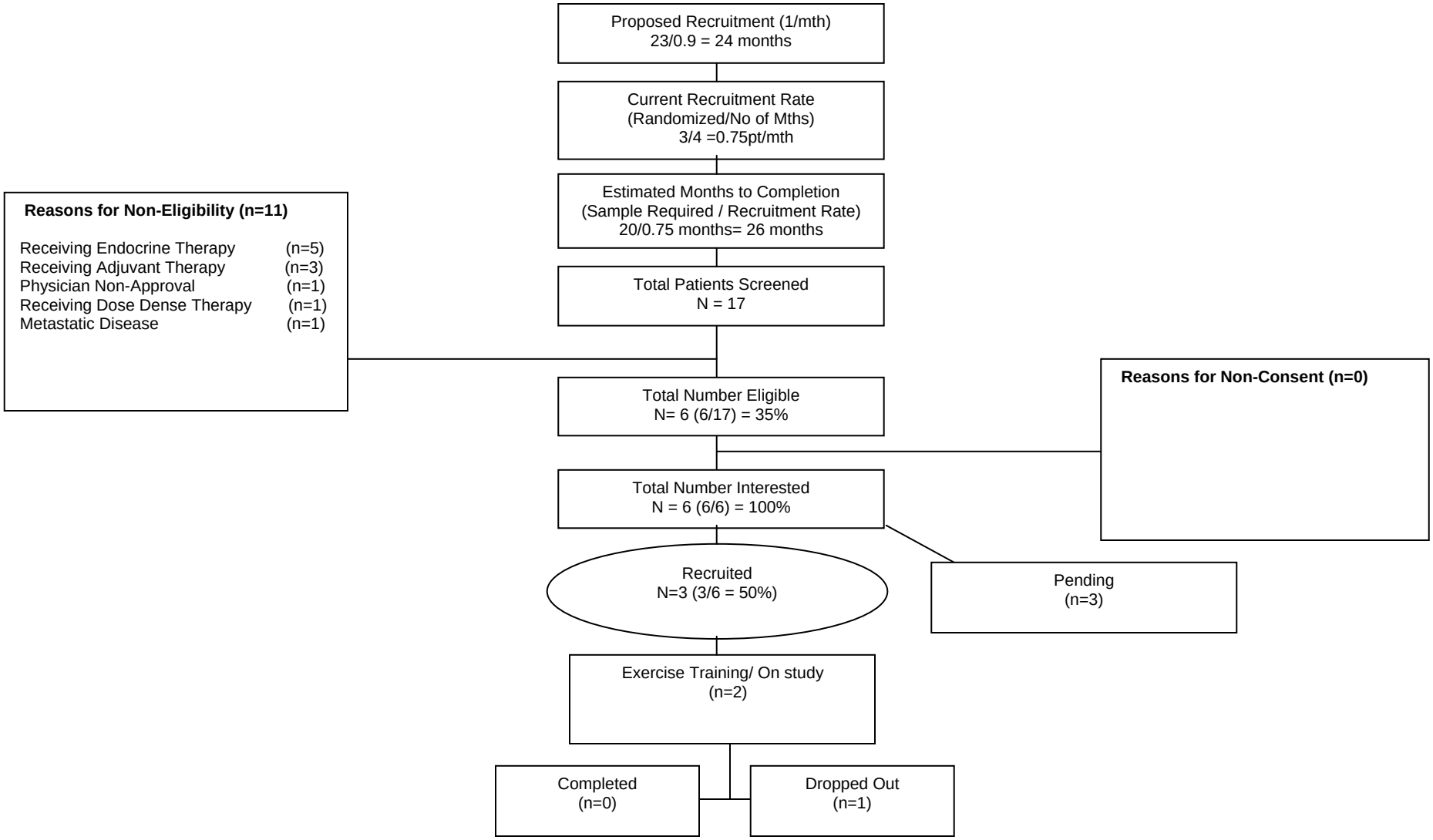

**Table 2. Summary Information on Study Participants***

| Patient ID | Baseline Exercise Capacity (mL.kg.min) | Midpoint Exercise Capacity | Follow-up Exercise Capacity | Number of Planned Sessions | Number Attended (%) | Status |
|---|---|---|---|---|---|---|
| 001* | 8.0 | - | - | 24 | 11 (46%) | Dropped Out |
| 006 | 14.5 | - | - | 6 | 5 (83%) | Week 2 completed |
| 009 | 8.7 | - | - | 6 | 5 (83%) | Week 2 completed |
| Mean±SD | 10.4 | | | | 58% | |

*Data regarding other study outcomes (e.g., baseline tumor vascularity, endothelial function, etc) will be analyzed in one batch to maximize reliability and validity and thus are not presented in this annual report.

As illustrated in Table 2, of the 3 patients recruited to study phase I, one patient dropped out due time commitments. However, during study participation, the patient experienced no dose-limiting toxicities and study drop put was not related to exercise training. Until study drop out, subject 001 adherence rate was 100%. However, the patients overall adherence rate was 46% (total number of planned sessions / total number of sessions attended). The remaining two patients are currently 'on trial' starting week 3. Adherence rate of both patients is currently 83%. Clearly, both patients have not experienced any dose-limiting toxicities. The overall adherence for all patients is currently 58%, which we anticipate will increase as the 'on-trial' patients progress through the trial. Based on the current information, it appears that exercise training is a safe and feasible intervention for women undergoing neoadjuvant chemotherapy for operable breast cancer. As such, we anticipate launching study phase II in the next 2 weeks (i.e., once both 'on-trial' patients have completed 6 weeks of exercise training). As described, phase II will follow the identical study procedures as phase I, except following the successful completion of baseline assessments participants will be randomly assigned to combined exercise training with neoadjuvant chemotherapy or neoadjuvant chemotherapy alone.

**KEY RESEARCH ACCOMPLISHMENTS**

- No key research accomplishments as the present time due to the preliminary stages of the present proposal

**REPORTABLE OUTCOMES**

- Based on the infrastructure provided for by this award/proposal, we have applied for supplemental funds from the American Cancer Society to add cutting-edge imaging technology to evaluate the effects of exercise training on chemotherapy-induced cardiac dysfunction.

## CONCLUSION

***"So what, who cares?"***

The American Cancer Society recently published guidelines recommending that all cancer patients be encouraged to exercise during chemotherapy. These recommendations are primarily based on the promising preliminary evidence of the effects of exercise on maintaining or enhancing QoL. As such, studies investigating the potential interaction between exercise and chemotherapy efficacy are essential to the interpretation and acceptance of exercise as a modifier of QoL.[1]

To date however, only one study, to our knowledge, has investigated the potential interaction between exercise therapy and concurrent breast cancer therapy. Our laboratory recently completed a preclinical study (funded by the DAMD BCRP) that examined the effects of endurance exercise training on the antitumor efficacy of doxorubicin in human breast cancer xenografts. Human breast cancer cells were transplanted into female mice and then randomly assigned to one of four groups (n=21/group). (i) control, (ii) exercise only, (iii) doxorubicin only, or (iv) exercise + doxorubicin. Exercise groups performed progressive treadmill running up to 18m/min at 0% grade for 45mins, 5 days/wk for 8 weeks. There was no significant difference between doxorubicin only and exercise + doxorubicin groups suggesting that moderate intensity exercise does not significantly influence doxorubicin-induced tumor growth delay.[2] Against this background, the present study will provide insight into the interaction between exercise training and chemotherapy efficacy, and candidate mechanisms that may underlie this relationship. Such studies are essential to fully understand the safety and application of exercise as a supportive intervention in cancer control.

Our preliminary results indicate it appears that exercise training is a safe and feasible intervention for women undergoing neoadjuvant chemotherapy for operable breast cancer. We are excited to proceed to study phase II.

## REFERENCES


**1.** Brown JK, Byers T, Doyle C, et al. Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. *CA Cancer J Clin.* Sep-Oct 2003;53(5):268-291.

**2.** Jones LW, Eves ND, Courneya KS, et al. Effects of exercise training on antitumor efficacy of doxorubicin in MDA-MB-231 breast cancer xenografts. *Clin Cancer Res.* Sep 15 2005;11(18):6695-6698.

**APPENDIX (Appendix A – Updated Consent Form)**

You are being asked to take part in this research study because you have been diagnosed with operable early-stage breast cancer and have opted to undergo chemotherapy before your surgery. Research studies include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

The study is being conducted at Duke University Health System (DUHS) by Dr. Lee Jones and members of the Breast Cancer Program at Duke. Dr. Jones and DUHS are receiving funding from the US Department of Defense Breast Cancer Research Program (DOD BCRP) to support this research.

**WHO WILL BE MY DOCTOR ON THIS STUDY?**

If you decide to participate, your regular medical oncologist will be your doctor for the study. He or she will be in contact with you while you are in the study and afterwards, if needed.

**WHY IS THIS STUDY BEING DONE?**

The purpose of this study is to assess how your tumor will respond when endurance exercise training is combined with your chemotherapy when given before surgery (neoadjuvant). Previous research in persons without cancer have shown that exercise training can improve delivery of blood to different tissues in the body. Therefore, we want to determine that exercise training during chemotherapy (which is delivered through the blood stream) will increase the delivery of chemotherapy to the tumor. No study has tested this question and this is the reason for this study.

**HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?**

Approximately 23 people will take part in this study at DUHS.

**WHAT IS INVOLVED IN THE STUDY?**

If you agree to be in this study, you will be asked to sign this consent form. Below is a detailed description of tests and procedures that are standard of care and those that are solely related to participation in this research study.

Standard of Care

The following tests and procedures will be performed to determine if you are eligible for chemotherapy before your surgery:

- Physical exam and medical history
- Vital signs (blood pressure, heart rate
- Height
- Weight

- Blood pregnancy test
- Review Incisional biopsy results
- Review clinical tumor measurements results

If you are eligible for chemotherapy, these tests and procedures will be repeated after you have completed four cycles of chemotherapy. Your physician will provide more specific details on these test and procedures.

Research-Study

The following tests and procedures also will be performed to determine if you are eligible for participation in this research study:

- Cardiopulmonary Exercise Test
- PET (Positron Emission Tomography) Imaging
- Research blood draw
- Peripheral endothelial function
- Echocardiograph
- A lifestyle questionnaire

A detailed description of these tests and procedures are provided below:

Cardiopulmonary Exercise Test

The purpose of this test is to assess the functional capacity (fitness level) of the entire cardiovascular system sometimes called a stress test. The test involves pedaling on a stationary bicycle at a constant speed while the intensity of pedaling is increased every minute (feels like you are pedaling up a steeper and steeper hill). The test is stopped when you cannot pedal at the desired speed or you become too tired to pedal. To accurately measure your fitness level, we will measure all the gases that come in and out of your mouth during exercise. We do this by asking you to wear a mouthpiece (similar to a snorkel used in deep sea diving) which is connected to a tube which transports all gases into a machine where it is analyzed. The exercise test will go to exhaustion and will last approximately 8 to 12 minutes. As a safety precaution, during the test we also will monitor your heart using a 12-lead EKG. Ten EKG electrodes (sticky pads) are placed at specific locations on your body so that we can monitor the response of your heart to exercise.

PET Imaging

This is a special technique that is used to image your tumor. This test requires you to wear a hospital gown and lie quietly while an external scanner images your tumor. This test takes approximately 45-60 minutes.

Research Blood Draw

The purpose of this blood draw is to measure circulating stem cells in your blood that may be associated with exercise training. The amount of blood drawn is approximately 5 teaspoons.

Peripheral Endothelial Function

This test uses ultrasound to assess the blood flow in your arm. This test will take approximately 30-45 minutes to complete. This assessment requires you to lie quietly while a blood pressure cuff is inflated around your upper arm. After five minutes, the blood pressure cuff is deflated and we measure the blood flow in your arm using ultrasound equipment. We then repeat the test using nitrolingual spray (spray that people who have had heart attacks use) at a dose of 400μg. We will ask you to push your tongue to the roof of your mouth and the doctor will spray nitrolinglyercine under your tongue. The nitroglyercine spray acts as a vasodilator (it makes the arteries expand) which is another method to assess blood flow in your arm.

Echocardiograph

The echocardiograph is a cardiac ultrasound that will require you to lay on your back or side in a quiet room for approximately 30 minutes while an ultrasound technologist takes several pictures of your heart by gently placing a rounded probe at several points on your chest. The test will allow the physician who reads the ultrasound to evaluate the structure and function of your heart muscle and valves and to see if, and how, these parameters change with regular exercise training. The test is not painful and there is no radiation exposure or other risks associated with it.

A Lifestyle Questionnaire

The lifestyle questionnaire will ask you questions about how you are feeling and your exercise history.

If you are eligible for this study, all standard care and research-related tests will be repeated after you have completed 4 cycles of chemotherapy (approximately 12 weeks); research blood draws will be provided every two weeks. A cycle is equal to 21 days. Every 21 days, or each cycle, you will receive doxorubicin and cyclophosphamide (standard chemotherapy for your type of tumor). You will receive information about side-effects and risks of chemotherapy, biopsy, and diagnostic tests from members of your cancer treatment team.

Following the successful completion of all initial tests and procedures (as described above), you will be randomly assigned (like flipping a coin) to one of the following two groups:

**(1) Chemotherapy Combined with Exercise Training:** You will be given a customized and supervised exercise training program that will last the duration of your chemotherapy treatment (approximately 3 months). The exercise program will consist of cycling on a stationary bike and will be tailored to your individual fitness level. The exercise program will consist of three exercise sessions a week that are approximately 45-60 minutes in duration. All exercise sessions will take place at Duke Center for Living free of charge.

**OR**

**(2) Chemotherapy Alone:** If you are assigned to the chemotherapy alone group, you will be asked not to change your current exercise levels. This group is very important because it helps us understand whether the exercise is or is not helpful.

Prior to your third cycle of chemotherapy, you will have a second biopsy of your tumor and a breast ultrasound. This is a research related procedure and will be paid for by the study.

Approximately 21 days after you have finished your four cycles of chemotherapy, you will be reassessed by your doctors to determine whether you will proceed to surgery or have further chemotherapy prior to surgery.

The first three patients who take part in this study will all receive the exercise training program. We are doing this because we want to make sure the exercise program is appropriate for subjects with breast cancer during chemotherapy before enrolling all subjects to this study.

**HOW LONG WILL I BE IN THIS STUDY?**

You will be in this study for approximately 3 months (the length of your chemotherapy treatment). You can choose to stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to your cancer doctor first.

**WHAT ARE THE RISKS OF THIS STUDY?**

Cardiopulmonary Exercise Test Risks

There is some possible risk involved if you choose to participate in this study. Some risk is associated with a physical fitness assessment. During and after the assessment, it is possible to experience symptoms such as abnormal blood pressure, fainting, light-headedness, muscle cramps, nausea, and in very rare circumstances (1 per 20,000 in testing facilities), heart rhythm disturbances or heart attack. While serious risk to healthy participants is very unlikely, it is important that you are made aware of these risks before deciding whether to join this study. Your physical fitness assessment will be monitored by a doctor with EKG monitoring. If any heart problems are detected on the EKG, you will be referred to a heart specialist.

Imaging Scans Risk

If you take part in this research, your tumor will be imaged with a special technique called a PET or body water scan. This technique uses radiation and a radioactive substance will be injected. To give you an idea about how much radiation you will get, we will make a comparison with an every-day situation. Everyone receives a small amount of unavoidable radiation each year. Some of this radiation comes from space and some from naturally-occurring radioactive forms of water and minerals. This research gives your body the equivalent of about 10 extra months' worth of this natural radiation. The radiation dose we have discussed is what you will receive from this study only and does not include any exposure you may have received or will receive from other tests.

Endothelial Function Test Risks

There may be some discomfort and a feeling of tightness when a blood pressure cuff is inflated on the arm for 5 minutes. Nitroglycerin spray (at a dose of 400μg may cause a sensation of flushing and some individuals experience a mild headache or dizziness for a short while afterwards. Your endothelial function test (including dose of nitrolingual spray) will be monitored by a trained vascular doctor.

Echocardiograph

There are no known risks of cardiac ultrasound tests.

Blood Draw Risks

Risks associated with drawing blood from your arm include minimal discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

Lifestyle Questionnaire Risks

Finally, some of the questions in the questionnaires will be asking you to recall your cancer experience which may be stressful. If you or the study coordinator feel that your level of stress or worry is increasing significantly as a result of your participation in the study, we will ask that you stop your participation. You will then be referred to an appropriate counseling professional in your area.
There also may be other side effects that are unknown at this time.

**FOR WOMEN OF CHILDBEARING POTENTIAL**

The standard therapy you will receive for your breast cancer exposes the unborn child to significant risks. In addition, this study involves procedures that could harm the unborn child. Therefore, pregnant women will be excluded from this study. If you are a woman of childbearing potential and have not had a blood pregnancy test in the past 3 days a blood pregnancy test will be done (using 1 teaspoon of blood drawn from a vein by needle stick). It must be negative before you can enter this study. If sexually active, you must agree to use appropriate contraceptive measures for the duration of the study. Medically acceptable contraceptives include: (1) surgical sterilization, (2) barrier methods (such as a condom or diaphragm) used with spermicide, or (3) an intrauterine device (IUD) that does not contain progesterone. If you do become pregnant during this study, you must inform your doctor immediately.

**ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?**

If you agree to take part in this study, there may or may not be direct medical benefit to you for participating in this study. However, it is hoped that what is learned in this study may benefit other breast cancer patients in the future. Finally, results of this study will be available to you following its completion.

**ARE THERE ALTERNATIVES TO PARTICIPATION IN THIS STUDY?**

Instead of being in this study, you have the following alternatives:

- Standard chemotherapy without exercise
- Taking part in another research study

**WILL MY INFORMATION BE KEPT PRIVATE?**

Study records that identify you will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except when required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of Duke University Health System (DUHS). For records disclosed outside of DUHS, you will be assigned a unique code number. The key to the code will be kept in a locked file in Dr. Lee Jones' office at Duke University Medical Center.

The study results will be retained in your research record for at least six years or until after the study is completed, whichever is longer. At that time either the research information not already in your medical record will be destroyed or information identifying you will be removed from such study results at DUHS. Any research information in your medical record will be kept indefinitely.

In addition, your study records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives of the Duke University Health System Institutional Review Board and Duke University Cancer Protocol Committee.

Finally, representatives of the U.S. Army Medical Research and Materiel Command are eligible to review research records as a part of their responsibility to protect human subjects in research.

If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by the federal privacy regulations.

**WHAT ARE THE COSTS?**

There will be no additional costs to you as a result of being in this study (physical fitness tests, exercise training, research blood draws, etc.). However, routine medical care for your condition (care you would have received whether or not you were in this study such as chemotherapy costs etc.) will be charged to you or your insurance company. You may wish to contact your insurance company to discuss this further.

**WHAT ABOUT COMPENSATION?**

You will be reimbursed (in the form of a $20 gift certificate) for each assessment you attend for your expenses related to your participation (gas and time). The total amount you may receive is $100 (five assessments over the course of your treatment).

**WHAT ABOUT RESEARCH RELATED INJURIES?**

Immediate necessary medical care is available at Duke University Medical Center in the event that you are injured as a result of your participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., or your Duke physicians to provide monetary compensation or free medical care to you in the event of a study-related injury.

If you are hurt or get sick because of this research study, you can receive medical care at an Army hospital or clinic free of charge. You will only be treated for injuries that are directly caused by the research study. The Army will not pay for your transportation to and from the hospital or clinic. If you have questions about this medical care, talk to the principal investigator for this study (Dr. Lee Jones, 919.668.6791). If you pay out-of-pocket for medical care elsewhere for injuries caused by this research study, contact the principal investigator. If the issue cannot be resolved, contact the U.S. Army Medical Research and Materiel Command (USAMRMC) Office of the Staff Judge Advocate (legal office) at 301-619-7663/2221.

**WHAT ABOUT MY RIGHTS TO DECLINE PARTICPATION OR WITHDRAW FROM THE STUDY?**

You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes other than data needed to keep track of your withdrawal. All data that have already been collected for study purposes will be retained by Dr. Lee Jones.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at Duke. If you do decide to withdraw from this study, we ask that you notify Dr. Lee Jones at (919) 668-6791 or (919) 451-3706 after hours and on weekends and holiday.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Your doctor may decide to take you off this study if your condition gets worse, you have serious side effects, or your study doctor determines that it is no longer in your best interest to continue. The principal investigator (Dr. Lee Jones), Department of Surgery or regulatory agencies may stop this study at anytime without your consent. If this occurs, you will be notified and your study doctor will discuss other options with you.

**WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?**

For questions about the study or a research-related injury, contact Dr. Lee Jones at (919) 668-6791 during regular business hours and at (919) 451-3706 after hours and on weekends and holidays. For questions about your rights as a research participant, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

**STATEMENT OF CONSENT**

> "The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have additional questions. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed copy of this consent form."

_____ _____

Signature of Subject Date

_____ _____

Signature of Person Obtaining Consent Date

## SUPPORTING DATA

Not applicable