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PRINCIPAL INVESTIGATOR:	Lucile Adams-Campbell, Ph.D. Lombardi Comprehensive Cancer Center Brett Lewis, M.D., Ph.D. Hackensack University Medical Center
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A Randomized Controlled Trial of Exercise to Reduce Cancer Related Fatigue in Women Undergoing Radiation Treatment for Breast Cancer

Brett Lewis, M.D., Ph.D. (HUMC)
Loren Godfrey, M.D. (HUMC)
Deena Graham, M.D. (HUMC)
Donna McNamara, M.D. (HUMC)
Stan Waintraub, M.D. (HUMC)

Lucile Adams-Campbell, Ph.D. (LCCC)
Claudine Isaacs, M.D. (LCCC)
Chiranjeev Dash, M.D., Ph.D. (LCCC)

b. ABSTRACT

Cancer related fatigue (CRF) is a common and debilitating side effect of radiotherapy in breast cancer patients. Physical activity interventions can attenuate CRF. The proposed study is a randomized, controlled trial (RCT) of exercise of structured moderate-intensity exercise intervention, delivered concurrently with radiotherapy, to reduce CRF and improve health-related quality of life among breast cancer patients. Eighty women with breast cancer scheduled to receive radiation therapy at HUMC will be randomized to one of the two trial arms: 1) a facility-based aerobic exercise utilizing a portable stationary pedal exerciser; or 2) a control group. Intervention arm participants will exercise at the hospital either before or after their radiation treatment. Assessments will be conducted at baseline, 4 weeks into radiation course, and at 4-week follow-up visit. The outcome variables are CRF, biomarkers of inflammation, and health-related quality of life. The study will provide preliminary evidence on whether a short-term moderate-intensity exercise intervention might be effective in reducing CRF in women undergoing radiotherapy for breast cancer, and whether this effect is mediated by inflammation.

c. Specific Aims

The specific aims of this study are: (1) to test the efficacy of a structured, moderate intensity exercise intervention delivered concurrently with radiation therapy (RT) in reducing CRF among breast cancer patients; (2) to provide pilot data on the acceptability and adherence of the exercise intervention on women receiving treatment; and (3) to determine the impact of exercise on serum inflammation markers among women undergoing RT.

d. Background

Radiation therapy (RT) is frequently used in the treatment of early stage breast cancer.[1] Adjuvant RT combined with partial mastectomy or lumpectomy is associated with better outcomes in early stage breast cancer as compared to surgery alone.[2,3] RT delivered through conventional external beam radiotherapy or more targeted alternatives like intensity modulated RT (IMRT), is a well-established treatment modality for clinically localized cancer.[4,5] However, RT has side effects associated with decreases in physical functioning and quality of life.

Cancer related fatigue (CRF), defined as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning", is one of the most debilitating side effects of RT.[6-9] Nearly all breast cancer patients report fatigue as a consequence of treatment,[10,11] and RT-related fatigue is reported in up to 80% of patients.[1,6-8,12,13] Fatigue can limit a patient's ability to care for herself and can decrease her quality of life.[10,14] The severity of its occurrence may also impact treatment continuity.[10,11]

The etiology of RT-CRF is poorly understood. [14-17] Radiation exposure initiates a programmed response of normal tissue towards tissue remodeling, of which inflammation is an important component.[18-20] Inflammation has been hypothesized as a potential cause of treatment-related fatigue[14] as inflammatory markers such as cytokines have been positively associated with increases in fatigue during radiation treatment. [15,21,22] Although biological correlates of fatigue such as cytokine expression have been identified,[14] elevations in individual cytokines are not consistently associated with fatigue and do not fully explain the occurrence of fatigue in patients who are treated with RT. [23]

Several studies have found that physical activity may be an effective intervention to enhance QOL in cancer survivors. [24-26] Physical activity has been reported to decrease fatigue, anxiety, and depression[27-31], and to improve sleep among healthy adults[30,31]. More than one third of the decline in functional capacity experienced by cancer patients can be attributed to prolonged physical inactivity[32]. Prolonged physical inactivity and sedentary lifestyle can lead to rapid losses in fitness, energy, and physical functioning[33]. Decreased physical activity may also worsen complaints of cancer related fatigue[25]. Aerobic exercise training has been found to significantly lower levels of fatigue in patients undergoing RT; however, the mechanism underlying this positive effect is unclear[7,11,34-36]. Despite the uncertainty about the precise contributions of diverse mechanistic pathways and the timing of introducing an exercise regimen, enough evidence exists of the potential utility of increased exercise to warrant further controlled intervention studies.

e. Methods, including statistical analysis

Study Design

This RCT targets women with breast cancer stages 0-IIIA scheduled to receive RT (no T4, N3, or M1 disease). After obtaining written informed consent, participants are randomized either to a structured moderate-intensity aerobic training exercise regimen concurrent with radiotherapy or to a control group. Endpoints are assessed at baseline, 4 weeks into the radiation course, and at the 4-week follow-up visit. In order to minimize loss to follow up, visits coincide with radiation appointments. Participants in the structured exercise group are instructed to use portable stationary pedal exercisers to achieve an exercise goal of 75 minutes/week of moderate-intensity exercise. All exercise sessions are supervised and conducted in the RT facility while patients are waiting for their RT or after their RT. Radiation therapy is typically administered on a five-times-weekly schedule, amounting to 15 minutes of exercise per weekday. Control group participants are asked to maintain their normal physical activity levels.

Eligibility Criteria

Eligibility for the study includes the following parameters: (1) women between the ages of 18 and 75 years; (2) histologically confirmed non-metastatic carcinoma of the breast (*in situ* disease or invasive); (3) radiation therapy naïve; (4) sedentary activity level at baseline, as defined by less than 60 minutes per week of modest physical activity based on 7-day physical activity recall questionnaire (5) ambulatory; (6) negative serum pregnancy test and not planning to become pregnant in the next three months; and (7) able to provide meaningful consent. Patients must have been deemed by their medical oncologist or internist that they "may participate in [this] exercise trial." The exclusion criteria include the following: (1) younger than 18 or older than 75 years; (2) no histological confirmation of breast cancer; (3) prior breast, chest, or pelvic radiotherapy; (4) concurrent chemotherapy; (5) distant metastases; (6) physical limitations that contraindicate participation in low to moderate intensity exercise; (7) positive pregnancy test; (8) currently engaged in moderate to vigorous physical activity; and (9) psychiatric disorder which would render the participant unable to provide informed consent. Prior to randomization, participants are required to complete a physical activity readiness questionnaire (PAR-Q) that includes questions regarding physical and medical conditions that would preclude safe participation in an exercise program.

Recruitment

Women with breast cancer stages 0-IIIA, who are scheduled to receive radiation therapy, will be recruited from the Department of Radiation Oncology at Hackensack University Medical Center (HUMC) and screened for eligibility by a study coordinator. Study coordinators will complete, in-person, the eligibility checklist (Appendix A) to confirm eligibility. The study coordinators will obtain informed consent (Appendix B), complete baseline and follow-up assessments, including demographic and treatment history, and will make study assignment as below, under "Randomization".

Randomization
Participants will be randomly assigned to structured moderate-intensity aerobic exercise program or to the control group using a block randomization scheme. The study biostatistician (Kepher Makambi, Ph.D.) will generate the computer-based randomization sequence. The intervention assignment is placed in opaque envelopes and delivered to the study coordinator. After completing baseline assessments, eligible participants will be assigned to study arm by a study coordinator who will open the next one of the sequentially-numbered, sealed envelopes.

Intervention
Arm 1: Exercise Intervention Arm
Participants randomized to the exercise intervention will be required to exercise before or after each radiation treatment session, on a five-treatment per week schedule. No special accomodations will be made to open the clinic on weather days or on extra days in the event of machine failure or patient unavailability. The exercise intervention will be administered at the radiation treatment facility in a room allocated for the study. The exercise prescription consists of aerobic training utilizing the portable stationary pedal exerciser (Pedlar) which contains two cycling pedals mounted to a stationary block that allows patients to exercise while sitting. Pedal tension is adjusted to provide desired resistance. Exercise intensity is self-rated by participants, instructed that moderate intensity goal will "make you breathe somewhat harder than normal". Participants may move and position the device to permit comfortable use while sitting in a chair. Participants are required to perform 15 minutes/day of aerobic exercise using the Pedlar device on radiation treatment days; during a standard radiation course, this will typically yield 75 minutes/week of aerobic time. Ten Pedlar devices have been approved for purchase for HUMC Department of Radiation Oncology through the Development Grant. Participants will record their activity on a daily basis on an exercise log (Appendix H).

Arm 2: Control Arm
Control group participants will be told to maintain their current daily activities and exercise habits for the duration of their treatment.

Study retention and adherence
All participants in the study undergo RT as scheduled by their physician. The exercise intervention does not interfere with dose or timeline of RT. No specific requirements are made herein regarding prone or supine positioning, utilization of standard fractionation or hypofractionation, use of cardiac blocking or for utilization or omission of boost phase of radiation. These treatment decisions are completely at the discretion of the treating radiation oncologist. Adherence to the exercise intervention is achieved by offering participants flexibility in scheduling daily exercise, either before or after radiation treatment. Adherence is recorded in daily participation logs. Logs document participant identification, date, and length of time utilizing the Pedlar device. Participant retention efforts include a $20 gift card incentive at baseline and one follow-up visit.

Assessments
Three assessments: at baseline, at 4-weeks into radiation course and at 4-week follow-up visit, will be assessed (see Table 1 below).

Table 1: Baseline and Follow-up Assessments

Assessment	Screening	Baseline (T0)	4 weeks (T1)	Follow-up visit (T2)
Eligibility (Appendix A)	X			
Informed Consent (Appendix B)	X			
Demographics (Appendix C)	X			
Medical history (Appendix C)	X			
Medications (from MD Consultation Note)	X			
Cancer and Treatment Summary (Appendix D)	X			
Performance Status	X			
Physical activity readiness questionnaire (Appendix C)	X			
Physical activity recall questionnaire (Appendix E)	X			
Blood tests for hematology (Appendix F)		X		
Vital signs and anthropometrics (Appendix G)		X	X	X
FACIT-Fatigue (in Appendix C)		X	X	X
FACT-B HRQOL (in Appendix C)		X	X	X
Inflammation biomarkers (Appendix F)		X	X	X
Adverse events assessments			X	X
Radiation Treatment Summary (by Treating MD)				X

Outcomes

Primary outcomes

CRF will be determined using the Functional Assessment of Chronic Illness Therapy (FACIT-Fatigue) survey instrument. The FACIT is a 13-item subscale developed to identify a finite set of concerns specific to fatigue. The responses to the 13 items on the FACIT-Fatigue questionnaire are each measured on a 4-point likert scale, with score ranging from 0 to 52. The FACIT-Fatigue scale has been validated in patients with cancer and showed excellent internal consistency and reliability. The following biomarkers of inflammation will be assessed at the Hackensack UMC: (1) High sensitivity CRP (hsCRP) - Serum hsCRP will be measured on the Vitros 5,1 FS Chemistry platform via an immunoassay with a reportable range of 0.10 -15.00 mg/L, and intra- and inter-assay CVs of 1.8-4.0%. (2) Serum fibrinogen and (3) Ferritin will be measured using standardized clinical protocols. All assays have intra- and inter-assays coefficient of variations <10%. We will collect CBC data at each blood draw for correlative and explorative purposes.

Secondary Outcomes

Cancer-related healthcare quality of life (HRQOL) among participants in the study will be measured using the Functional Assessment of Cancer Therapy (FACT) system questionnaires. The HRQOL measures four different domains (physical well-being, functional well-being, emotional well-being, and social/family well-being). FACT-B is a breast cancer specific module that will be used to reflect patients' concerns; moreover, they are reliable, reproducible, and have been validated in numerous studies. Higher scores on the FACT questionnaires reflect higher QOL. Post hoc analysis will be performed to associate RT treatment parameters against differences in outcomes, including utilizing the following pre-specified parameters: heart V5, lung V20, utilization of supraclavicular field (yes/no), utilization of supraclavicular field with axillary coverage (yes/no). These will potentially be hypothesis-generating and no Bonferroni corrections will be applied.

Sample size Considerations
In this study participants are randomized into two groups: a structured exercise intervention group and a usual care control group. It is expected that there will be two levels of fatigue measurements: at baseline and after the exercise intervention. Our sample size calculation is based on analysis of covariance (ANCOVA) comparing mean fatigue score differences between the two intervention arms at the end of intervention, adjusting for baseline. In our exercise intervention study (Dash et al, unpublished data, mean fatigue scores of 42.53 (SD=9.35) and 37.12 (SD=9.42) were reported for the intervention and control arms, respectively. In the same study, the correlation coefficient between baseline and after intervention fatigue scores was calculated as 0.64. With the above guidelines and a level of significance of α=0.05 (two-sided), we will use randomize 40 women/arm to obtain statistical significance between the arms with 90% power for the overall ANCOVA F-ratio.

Statistical analysis
Baseline characteristics will be compared between the two intervention groups using two-sample t-test or Wilcoxon rank-sum test depending on whether the t-test assumptions are satisfied or not. Suitably transformed variables will be used when necessary. Categorical variables will be compared between the two groups using chi-square tests or Fisher's exact test. The major analytical tool for addressing the specific aims of this study is linear mixed modeling for repeated measures. Study endpoints will be measured three times in each participant in the study, and it is expected that measures on the same individual will be correlated. We will also examine whether the variance of repeated measures changes over time. An appropriate correlation structure will be selected depending on whether there is a trend of variance with time or not. For each outcome measure of interest, a linear mixed repeated measures model will be fit to evaluate the main effects of time, study group, and group-by-time interaction. Known confounders and other covariates will be included in the linear mixed models if their individual bivariate associations with both the group variable and outcome are significant at 10% level.

We hypothesize that participants in the intervention group will have lower average fatigue scores compared to the usual care group after the intervention. For Aim 1 and Aim 3, "change scores" will be defined as the difference between baseline score and 4 week, (end of radiation treatment) score. Change scores will be compared between the two groups using t-test or Wilcoxon rank-sum test. An ANCOVA model will be utilized to assess group differences in change scores adjusting for covariates including age. We hypothesize that participants in the structured exercise intervention group will have lower levels of fatigue (Aim 1) and lower levels of inflammatory biomarkers (Aim 3) compared to baseline at follow-up visits as compared to the usual care control group. We hypothesize that there will be at least partial normalization of both the fatigue levels reported and the inflammatory biomarkers to baseline by the 4-week follow-up visit. Linear mixed models as described above will be used to compare fatigue scores and inflammatory biomarkers levels over time across the study groups. For Aim 2, we will report rates of acceptability and adherence at baseline and end of intervention. We will use the binomial test to compare acceptance and adherence rates between the two intervention arms. Baseline and end of intervention acceptability levels evaluated using the Wilcoxon sign-rank test or McNemar's test (or generalized McNemar's test) for numerical and categorized outcomes, respectively.

A Graduate Research Assistant (GRA) will assist with data collection for the survey data. The GRA will collect log data of the women exercising using the Pedlar device. There is an hourly reimbursement for GRA labor without incentive. This has been approved via the Development Grant.

f. Significance
This study will contribute to the literature on the role of concurrent radiation treatment and moderate-intensity exercise in reducing cancer-related fatigue and improving HRQOL among breast cancer patients undergoing.

This study will also provide pilot data on the correlation of inflammatory markers with exercise-related changes in fatigue and other HRQOL measures in breast cancer patients undergoing RT. The strengths of this study include the use of an “in-office” easy to use exercise intervention that reduces participant burden, the timing of exercise inception that coincides with RT inception, and use of biomarkers.

g. Future Plans

It is our intent to seek external federal funding in the area of symptom management utilizing exercise interventions. Data from this study will be combined with a similar pilot study conducted at Georgetown MedStar Washington Hospital Center among 30 African-American breast cancer survivors undergoing radiation therapy. The combined data will result in a stronger and substantive preliminary data to support a larger and more definitive trial on exercise interventions to reduce fatigue and improve quality of life among breast cancer survivors undergoing radiation therapy. The pilot data on biomarkers of inflammation will also allow us to propose innovative biomarker endpoints for the exercise intervention in an effort to elucidate pathways associated with CRF and lower HRQOL among radiation therapy patients.

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