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An Exercise Trial to Reduce Cancer Related Fatigue in African American Breast Cancer Patients Undergoing Radiation Therapy: Design, Rationale, and Methods

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Abstract

Background—Cancer related fatigue (CRF) is a common and debilitating side-effect of radiotherapy in breast cancer patients. Physical activity interventions can attenuate CRF but evidence in African-American women with breast cancer is lacking.

Methods/Design—The “Pedlar” Study is a prospective, 8-week structured moderate-intensity exercise intervention, delivered concurrently with radiotherapy, to reduce CRF and improve health-related quality of life among African American breast cancer patients. Forty African American women with breast cancer scheduled to receive radiation therapy at MedStar Washington Hospital Center will be randomized to one of the two trial arms: 1) a facility-based aerobic exercise utilizing a portable stationary pedal exerciser; and 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, and 8 weeks. The outcome variables are CRF, biomarkers of inflammation, and health-related quality of life.

Discussion—The Pedlar Study will provide preliminary evidence on whether a short-term moderate-intensity exercise intervention might be effective in reducing CRF in African American women undergoing radiotherapy for breast cancer, and whether this effect is mediated by inflammation.

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Keywords

breast cancer; radiotherapy; clinical trial; physical activity; African-American

Introduction

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 limits patients’ ability to care for themselves and decreases their quality of life.^{10,14} The severity of its occurrence may also impact treatment continuity.^{10,11}

However, 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 fatigue¹⁴ 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 (PA) may be an effective intervention to enhance QOL in cancer survivors.^{24–26} PA 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 inactivity³². Prolonged physical inactivity and sedentary lifestyle can lead to rapid losses in fitness, energy, and physical functioning³³. Decreased physical activity may also worsen complaints of cancer related fatigue²⁵. 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}

Previous studies suggest that RT-CRF peaks as early as two to four weeks from the start of treatment and persists beyond treatment at static levels^{8,12,16,36,37}. PA intervention studies in patients undergoing RT are usually 12 or 24 week interventions and do not measure fatigue levels soon after the initiation of RT. It is also not clear whether starting PA concurrent with RT might be more efficacious than starting PA after the completion of RT.

PA intervention studies in patients undergoing RT have mostly been done in White populations and there is no evidence on the efficacy of PA among African American patients undergoing RT.^{38–41} Despite 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, especially among African Americans. Consequently, we designed an exercise study, using a stationary pedal exerciser, i.e., the “Pedlar Study”, to test the efficacy of a structured moderate-intensity PA intervention, in reducing CRF among African American patients undergoing RT for breast cancer.

Objective

The primary objective of the Pedlar Study is to test the efficacy of a 8-week structured moderate-intensity PA intervention, delivered concurrently with RT, in reducing CRF among African American breast cancer patients. This study is also designed to provide pilot data on the acceptability and adherence of PA interventions in African Americans with breast cancer; and the correlation of serum inflammation markers with fatigue and PA.

Methods

Study Design

The Pedlar RCT targets African-American women with breast cancer stages 0–3A scheduled to receive RT. After obtaining written informed consent, participants are randomized to either a structured, moderate-intensity aerobic training exercise regimen concurrent with radiotherapy or a control group. Endpoints are assessed at baseline, 4 weeks, and 8 weeks (study completion). In order to minimize loss to follow up, visits coincide with RT/medical 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. This goal was based on physiologic and adherence rationales. The American College of Sports Medicine’s exercise guidelines for cancer survivors recommend 150 min/week of moderate-intensity or 75 min/week of vigorous intensity endurance exercise with prescriptions following intensity recommendations for healthy participants.⁴² However, definitions of moderate- and high-intensity exercise are unclear among cancer survivors and recent evidence suggests that, in breast cancer survivors, intensity prescriptions for healthy adults might result in too intense training dependent on the definition used. This is important because the heart rate reserve and maximal oxygen capacity is reduced in breast cancer survivors due to chemotherapy and radiation therapy.⁴³ We decided to use a 75-minute moderate intensity regimen for this study to reduce risks of injury and to enhance adherence to the protocol by coinciding the exercise sessions with participant waiting time for radiation therapy which averages 20–25 minutes at our center. All exercise sessions are supervised and conducted in the RT facility while patients are waiting for their RT or after their RT. Control group participants are asked to maintain their normal physical activities. A schema of the study is presented in Figure 1. This study was approved by the Georgetown University Institutional Review Board.

Theoretical Framework

This study is guided by the Theory of Planned Behavior, which proposes that behavioral intentions are proximal determinants of individual behavior.⁴⁴ Behavioral intentions are influenced by attitudes (positive or negative perspectives of physical activity behaviors), subjective norms (perceived social pressure regarding exercise and diet), and perceived control (confidence and control of one's exercise performance and dietary habits). This framework is relevant to this study because : 1) it demonstrates robust performance in physical activity interventions; 2) it highlights perceived control that African-American women may have regarding physical activity barriers, including specific barriers and opportunities; 3) it has been utilized to address physical activity in minorities.⁴⁵ The study also includes aspects of the broader model of the Ecological Framework Neighborhood (e.g. the safety and availability of affordable or free exercise locations) that may impact physical activity behaviors.

Eligibility Criteria

Eligibility for the study includes the following parameters: (1) African-American women; (2) between the ages of 18 and 75 years; (3) histologically confirmed non-metastatic carcinoma of the breast; (4) radiation therapy naïve; (5) sedentary as defined by less than 60 minutes per week of modest physical activity based on 7-day physical activity recall questionnaire (6) ambulatory; (7) negative serum pregnancy test and not planning to be pregnant in the next three months; (8) able to provide meaningful consent. 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; (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

African-American women with breast cancer stages 0–3A scheduled to receive radiation therapy are recruited from the Medstar Washington Hospital Center's Cancer Institute, an urban community hospital. Breast cancer patients interested in the study are screened for trial eligibility at radiation oncology consultation and prior to the initiation of radiation therapy by a study coordinator. Study coordinators, with the assistance of a nurse practitioner, complete in-person eligibility checklists to confirm eligibility. Thereafter, study coordinators obtain informed consent, following which participants complete baseline assessments, including demographic and treatment history, and are randomized into one of two study groups.

Randomization

Participants are randomly assigned, in a 1:1 ratio, to an 8-week structured moderate-intensity aerobic exercise program or control group using a block (n=4) randomization scheme. The study biostatistician has generated the computer-based randomization sequence. The intervention assignment is placed in opaque envelopes and delivered to the trial coordinator. After completing baseline assessments, eligible participants are randomized to the study either by the nurse practitioner or research study coordinator who open the sequentially-numbered, sealed envelopes.

Intervention

Arm 1: Facility-based Exercise Intervention Arm—Participants randomized to the exercise group are required to exercise 5 days/week for 8 weeks coinciding with radiation treatment sessions. The exercise intervention is administered at the radiation treatment facility in a room allocated for research purposes. 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 can be adjusted to provide desired resistance. Participants can also move the equipment so they can use it conveniently while sitting in any chair. Participants are required to maintain a goal of 75 minutes/week of aerobic exercise by using the PEDLAR; that is, 15 min/day for 5 days/week.

Arm 2: Control group—Control group participants are required to maintain their current daily activities and exercise habits for the duration of the study (8 weeks).

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. In fact, 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 by the participants and supervised weekly by study staff. Logs document participant identification, date, and length of time utilizing the PEDLAR. Participant retention efforts include gift card incentives for baseline and follow-up visits.

Assessments

Three assessments, one at baseline and two follow-up assessments at 4 and 8-weeks are conducted in this trial. Assessments at baseline include individual measurements of demographic, lifestyle, medical history, physical activity, readiness for physical activity, cancer-related fatigue, quality of life measures and anthropometric variables. Assessments also include blood pressure, resting heart rate, and blood samples for biomarker analysis.

At the midpoint and conclusion of the study, and radiation treatment, participants provide information on fatigue and quality of life. Additionally, vital signs, anthropometric measurements, and a blood sample are collected.

Outcomes

Primary outcomes

1. **Fatigue:** CRF is determined using the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) survey instrument.⁴⁶ 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. Thus, the total score ranges from 0 to 52. THE FACIT-Fatigue scale has been validated in patients with cancer and showed excellent internal consistency and reliability.⁴⁶

Secondary Outcomes

1. **Health-Related Quality of Life:** Cancer-related healthcare quality of life (HRQOL) among participants in the study is measured using the Functional Assessment of Cancer Therapy (FACT) system questionnaires. The Functional Assessment of Cancer Therapy – General (FACT-G) questionnaire is a widely used HRQOL instrument.⁴⁷ It measures HRQOL in four different domains (physical well-being, functional well-being, emotional well-being, and social/family well-being). The Functional Assessment of Cancer Therapy – Breast cancer specific (FACT-B) module was added to this questionnaire. The questionnaires were developed 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.
2. **Process Feasibility:** Acceptability and satisfaction with the exercise intervention program among participants in the intervention group is measured by administering a process outcomes questionnaire.
3. **Biomarkers**
 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%.

 Other Biomarkers: Serum levels of inflammation biomarkers (IL-1B, IL-6, TNF- α and TGF-B) will be measured using X-MAP, bead-based (multiplex) assays from Millipore, on the BioRad Bioplex platform at MedStar Research Laboratories. Serum fibrinogen and ferritin will be measured using standardized clinical protocols. All assays have intra- and inter-assays coefficient of variations <10%.

Sample size

In this study participants are randomized into two groups: an 8-week structured exercise intervention group and a usual care control group. It is expected that there will be two levels of weight measurements: at baseline (T0) and after the exercise intervention (assumed to be 8 weeks – T1 for the power analysis). Therefore, our sample size calculation is based on an analysis of variance (ANOVA) comparing mean change from baseline in FACIT fatigue scores (change scores) between the two groups. Table one presents sample sizes for selected

values of effect size (difference in change scores), with the standard deviation of the change scores assumed to be 5.8, a two-tailed level of significance of 0.05, and no adjustment for multiple testing (based on a previous exercise intervention trial on fatigue by Segal et al.)³⁵ Based on the table above, we will require a sample size of 20 participants per group to provide 80% power to detect a difference in change scores of 6 points (standard deviation=5.8). The power calculation above was for the primary objective. Data generated from this study will be used to inform power and sample size calculations for the secondary and exploratory objectives in future studies.

Statistical analysis

Baseline characteristics will be compared among the two intervention groups using analysis of variance (ANOVA) or Kruskal-Wallis tests depending on whether the ANOVA assumptions are satisfied or not. Suitably transformed variables will be used when necessary. Categorical variables will be compared using chi-square tests or Fisher's exact test, when necessary. The major analytical tool for addressing the specific aims of this study is mixed linear 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; treating baseline scores for outcomes as covariates. Known confounders and other covariates will be included in the linear models if their individual bivariate associations with both the group variable and outcome are significant at 10% level. Covariates of interest include demographics (age, education status), lifestyle factors (tobacco use history, alcohol intake, physical activity), and medical history (comorbidities, breast cancer stage at diagnosis, type of surgery, estrogen, progesterone and Her2 receptor status, menopausal status at diagnosis, and chemotherapy).

We hypothesize that participants in the intervention group will have greater reductions in fatigue and increases in HRQOL from the baseline as compared to the usual care group at the 8-week follow-up. For this aim, "change scores" will be defined as the difference between baseline score and 8-week follow-up score. We also hypothesize that participants in the exercise intervention group will have lower levels of inflammatory biomarkers compared to baseline at 4- and 8-week follow-up visits as compared to the control group. Linear mixed models as described above will be used to compare changes in inflammatory biomarkers over time across the study groups.

Summary

The Pedlar Study will contribute to the literature on the role of concomitant, moderate-intensity exercise in reducing cancer-related fatigue and improving HRQOL among African American breast cancer patients undergoing RT. 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 focusing on an underserved population that bears a high burden of breast cancer

morbidity, use of an “in-office” exercise intervention that reduces participant burden, the timing of exercise inception that coincides with RT inception, and use of biomarkers. Limitations of our study include a small sample size necessitating confirmation of study findings in a subsequent large scale study especially for the biomarker and quality of life outcomes, an exercise intervention that is lower than the dose recommended by exercise guidelines for survivors, and use of a seated Pedlar exercise machine that only exercises the lower limbs without involvement of all the core muscles.

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Figure 1.