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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.



## 1. 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 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 (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

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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].

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.

## 2. Objective

The primary objective of the Pedlar Study is to test the efficacy of an 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.

## 3. Methods

### 3.1. 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 min/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 are reduced in breast cancer survivors due to chemotherapy and radiation therapy [43]. We decided to use a 75-min 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 min 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 Fig. 1. This study was approved by the Georgetown University Institutional Review Board.

### 3.2. 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.

### 3.3. 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 min 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.

### 3.4. 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.

### 3.5. 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,