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An exercise trial targeting African-American women with metabolic syndrome and at high risk for breast cancer: Rationale, design, and methods

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ABSTRACT

Background: Metabolic syndrome and obesity are known risk factors for breast cancers. Exercise interventions can potentially modify circulating biomarkers of breast cancer risk but evidence in African-Americans and women with metabolic syndrome is lacking.
Methods/design: The Focused Intervention on Exercise to Reduce CancEr (FIERCE) trial is a prospective, 6-month, 3-arm, randomized controlled trial to examine the effect of exercise on obesity, metabolic syndrome components, and breast cancer biomarkers among African-American women at high risk of breast cancer. Two hundred-forty inactive women with metabolic syndrome and absolute risk of breast cancer ≥1.40 will be randomized to one of the three trial arms: 1) a supervised, facility-based exercise arm; 2) a home-based exercise arm; and 3) a control group that maintains physical activity levels through the course of the trial. Assessments will be conducted at baseline, 3 months, and 6 months. The primary outcome variables are anthropometric indicators of obesity, metabolic syndrome components, and inflammatory, insulin-pathway, and hormonal biomarkers of breast cancer risk.
Discussion: The FIERCE trial will provide evidence on whether a short-term exercise intervention might be effective in reducing breast cancer risk among African-American women with comorbidities and high breast cancer risk — a group traditionally under-represented in non-therapeutic breast cancer trials.
Clinical Trial Registration Number: NCT02103140.

1. Introduction

Breast cancer is the most common cancer among African American women [1]. Although incidence of breast cancer is lower among African Americans, mortality from breast cancer is greater in African American women compared to White women at all ages [1]. Disparities in socio-economic status and access to health insurance, preventive care and high-quality cancer treatments, and presence of comorbidities and aggressive breast cancer subtypes in African Americans are the major drivers of this mortality difference [1]. These observations highlight the need for primary prevention approaches for breast cancer, especially among high-risk women.

Although risk factors for breast cancer are similar among postmenopausal White and African American women, the prevalence of risk factors is different in the two populations. African American women have higher prevalence of certain metabolic syndrome components, such as abdominal obesity and hypertension, and are more likely to be metabolically unhealthy than White females [2]. This is particularly important because metabolic syndrome is associated with a 17% increase in breast cancer risk [3–5] and breast cancer recurrence [6].

Obesity, a major component of the metabolic syndrome, and the lack of ovarian hormones interact to contribute adversely to the risk of postmenopausal breast cancer [7]. Estradiol is the major circulating estrogen in premenopausal women. The role of estradiol in several important metabolic functions including abdominal obesity, insulin sensitivity, lipid transport, blood pressure, and inflammation is well established and provides a link between estrogen levels and metabolic syndrome in postmenopausal women [8]. Estrogen depletion in menopause results in decreases in insulin sensitivity, glucose uptake, and glucose metabolism, leading to reductions in cellular metabolism and total energy expenditure [9]. Reductions in energy expenditure combined with premenopausal obesity and a poor lifestyle, characterized by lack of physical activity and unhealthy diet, promote postmenopausal weight

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gain and obesity [10]. Abdominal obesity can result in tissue hypoxia leading to inflammation by promoting macrophage recruitment and secretion of inflammatory cytokines such as IL-6, IL-1β, PGE2, and TNFα. In addition, breakdown of large lipid droplets in obese women could lead to activation of inflammatory signaling pathways such as NFκB activation. The release of inflammatory cytokines and activation of the inflammatory signaling pathways leads to increased aromatase gene expression that results in extragonadal estrogen production from androgen/testosterone in the surrounding tissues [11]. Local extragonadal estrogen production together with low SHBG makes estrogen readily available to breast cells. Higher circulating levels of estrone and estradiol in obese postmenopausal women have been shown to be mitogens that stimulate cell proliferation and can lead to breast cancer by activation of several signaling pathways [12,13]. Higher testosterone levels have been associated with breast cancer risk because they can be converted to estrone and estradiol in the breast tissue and can also act directly by binding to the androgen receptor in the breast [14,15].

Further, abdominal obesity and lack of estrogen in menopause result in an insulin resistant state with compensatory hyperinsulinemia, characterized by high circulating levels of insulin and IGF-1 [16,17]. Insulin may have a mitotic effect via IGF-1 receptor affinity or by a direct effect on DNA proliferation [18,19]. In addition, leptin production from adipocytes is increased in obese women and studies show a positive correlation between increasing leptin levels and the risk for postmenopausal breast cancer [20]. High levels of circulating IGF-1, insulin, and leptin may help promote the development and growth of breast cancer cells in postmenopausal women.

Physical activity can independently alter circulating cytokine and adipokine levels, insulin resistance, circulating insulin levels, sex hormones, and growth factors (i.e., insulin, IGF-1, IGF binding proteins) [21,22]. Physical activity reduces adiposity thereby lowering estrogen levels, and also reduces insulin levels, which results in higher sex hormone-binding globulin (SHBG) that decreases estradiol bioavailability [23,24]. Exercise training also reduces testosterone levels and bioavailability by reducing adiposity and insulin levels [23,25]. Exercise training improves insulin sensitivity independent of body weight or body composition changes, although concomitant weight loss results in even greater improvements [26].

Despite uncertainly about the precise contributions of these pathways in breast cancer causation, enough evidence exists of the potential utility of increased physical activity and weight reduction in breast cancer prevention to warrant further controlled intervention studies, particularly in groups underrepresented in clinical trials, such as African-Americans and women with comorbidities. Consequently, we designed the Focused Intervention on Exercise to Reduce CancEr (FIERCE) trial to determine the effect of exercise on breast cancer biomarkers among African-American women at high risk of breast cancer.

2. Objectives

The primary objective of the FIERCE trial is to determine the effects of a 6-month supervised facility-based exercise intervention and a 6-month unsupervised home-based exercise intervention on obesity, MetS components, and breast cancer-related biomarkers, compared to a control group among postmenopausal African-American women with MetS who are at increased risk of breast cancer. The secondary objective is to determine the effects of supervised facility-based and unsupervised home-based exercise on cardiorespiratory fitness, body composition, and quality of life.

3. Methods

3.1. Study design

This RCT targets postmenopausal African-American women with MetS who are also at increased risk of breast cancer. After obtaining written informed consent, participants are randomized either to a supervised facility-based exercise group, a home-based exercise group, or a control group. Endpoints are assessed at baseline, 3 months, and 6 months (study completion). In order to minimize loss to follow-up, participants in the control group are offered the opportunity to exercise at the facility once they have completed the study. Participants in the facility-based exercise group follow an individualized exercise program and are supervised during their exercise sessions by a clinical exercise physiologist. Participants in the home-based exercise group are given pedometers and asked to meet and maintain a goal of 10,000 steps per day. Control group participants are asked to maintain their normal daily 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 [27–29]. It postulates that an individual's behavioral intention is the most proximal determinant of their behavior. Attitudes (e.g., positive or negative evaluation of physical activity behaviors), subjective norms (perceived social pressures regarding exercise/diet), and perceived control (confidence and control over performing exercise/diet) are postulated to independently influence behavioral intention [30]. We selected this framework because: 1) it has demonstrated robust performance in physical activity interventions; 2) this model highlights perceived control that includes specific barriers and opportunities that African-American women may have regarding physical activity behaviors; and, 3) this model has been used to address physical activity in minorities [31–33].

3.3. Eligibility criteria

The criteria for eligibility for this study include the following: (1) African-American women; (2) between the ages of 45 and 65 years; (3) postmenopausal (last menstrual period ≥12 months); (4) waist circumference >35 in. (88 cm); (5) 5-year individual invasive breast cancer risk ≥1.66% using the "CARE" model. We used the CARE model to project absolute risk of breast cancer because it has been shown to perform better among African American women as compared to the Gail model [34,35]. The CARE model uses data on current age, race, age at menarche, number of first degree relatives with breast cancer, number of breast biopsies, and atypical hyperplasia on biopsy to determine breast cancer risk [35]; (6) at least two of the following: elevated fasting glucose (≥100 mg/dL), reduced HDL cholesterol (<50 mg/dL), or elevated triglycerides (≥150 mg/dL), and elevated blood pressure (≥130/85 mm Hg); (7) have a cell phone with text messaging capabilities; (8) able to read and speak English; (9) reside in close proximity to or have access to Georgetown-Lombardi Cancer Center's Office of Minority Health and Health Disparities Research (OMH); (9) able to provide meaningful consent (i.e., women with severe cognitive impairment will be excluded); (10) no physical limitations that prevent exercising; and (11) can provide evidence of medical clearance by healthcare provider, if required. The exclusion criteria include the following: (1) premenopausal; (2) history of cancer, except non-melanoma skin cancer; (3) diabetes or use of anti-diabetic medications (including insulin); (4) currently exercising regularly (at least two times per week of at least 20 min of moderate or vigorous activity); (5) current enrollment in another physical activity and/or dietary clinical trial or on diet/weight loss program; and (6) inability to commit to the intervention schedule. Prior to randomization, all participants are required to complete a physical activity readiness medical examination (PARmed-X). The PARmed-X is a 4-page form that is filled out by the study nurse practitioner. The PARmed-X includes questions regarding physical and medical conditions that may preclude safe participation in an exercise program. If a non-contraindicated condition for exercise is present, participants are