Published in final edited form as:

Contemp Clin Trials. 2015 July ; 43: 33–38. doi:10.1016/j.cct.2015.04.015.

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, 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.

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There are no conflicts of interest to disclose.

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Keywords

clinical trial; physical activity; breast cancer; metabolic syndrome; African-American; randomized controlled trial

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 are 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 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-1 β , PGE2, and TNF α . In addition, breakdown of large lipid droplets in obese women could lead to activation of inflammatory signaling pathways such as NF κ B 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 uncertainty 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.

Objectives

The primary objectives of the FIERCE trial are 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. Secondary objectives are to determine the effects of supervised facility-based and unsupervised home-based exercise on cardiorespiratory fitness, body composition, and quality of life.

Methods

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 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 (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).

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 inches (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 ($\geq 130/85$ mmHg); (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 minutes 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 required to have a signed authorization and medical clearance from their healthcare provider prior to randomization.

Recruitment

Participants are recruited from the predominantly African-American communities in the DC metropolitan area via OMH's community recruiter and community outreach coordinator. Recruitment is conducted using multiple approaches including study flyers and postcards, advertisements in the local media and faith-based newsletters, and presentations by study team members in the community at town hall meetings. The recruiters post study flyers and actively provide information on the study at local churches, businesses, physician offices, and neighborhood centers (e.g., recreation centers and libraries). In addition, recruiters also attend health fairs and other health-related events in the area targeted at minority women to provide information on the FIERCE study to potential participants.

Interested participants call the study coordinator and are screened for eligibility via telephone. Participants eligible on the telephone screening are invited for a second-round of in-person screening at the OMH where informed consent is obtained. After confirming eligibility, participants complete baseline assessments and are randomized into one of the three study groups.

Randomization

Participants are randomly assigned, in a 1:1:1 ratio, to supervised facility-based exercise, home-based exercise, or control group using a block randomization scheme. The computer-based randomization sequence is generated by the study biostatistician. The intervention allocation is printed and placed in opaque envelopes by the OMH secretary who then seals and delivers them to the trial coordinator. After completing baseline assessments eligible participants are randomized to the study by the trial coordinator by opening the sequentially-numbered, sealed envelopes.

Intervention

Arm 1: Supervised Facility-Based Exercise Intervention Arm—Participants randomized to the exercise group are required to meet and maintain a goal of 150 min/wk of moderate intensity exercise for 6 months. The exercise intervention is conducted at the exercise facility in OMH located in the community. Heart rate and rating of perceived exertion (RPE) are used to define moderate intensity. Polar heart rate monitors are used throughout the study in order to monitor and record heart rate. Participants are also taught how to use the heart rate monitors and RPE in order to determine the appropriate moderate exercise intensity during the intervention. Participants exercise for the prescribed duration at a heart rate in the range of 45-65% of their VO_{2max} , as determined during baseline testing, and with an RPE in the range of 11-14 on the 20-point RPE scale (36).

The exercise prescription consists of three days per week of supervised physical activity using treadmills and/or exercise bikes. Exercise duration is increased gradually from 75 min/wk to 150 min/wk by week 4, using American College of Sports Medicine guidelines for progression in obese/overweight, low-risk individuals (37). Thereafter, women maintain 150 minutes or more of moderate-intensity physical activity per week. Participants are provided with daily exercise diaries to record exercise adherence and activity. The post-randomization week number (1 to 24), the date of the exercise session, the type of physical activity (mode), total minutes of physical activity (duration), heart rate, and RPE (intensity) are recorded by the supervising exercise physiologist at each exercise session in an adherence form

Arm 2: Home-Based Exercise Intervention—Participants randomized to this intervention arm are required to meet and maintain a goal of 10,000 steps per day as measured by a pedometer. At Week 1, participants are required to meet a goal of 5000 steps per day. Each week thereafter, the required number of steps is increased by 500 steps until 10,000 steps per day are reached. An Omron digital pedometer with a 7-day memory is provided to all participants randomized to the home-based exercise group. Participants are encouraged to meet their exercise goal through moderate-intensity activities such as, walking or slow jogging. Participants are also provided with an “exercise training log” – an adherence form to record their pedometer reading at the end of each day, as well as, the type and duration of exercise activities. Participants randomized to this arm are provided a 12-week adherence log at the time of the baseline visit to record adherence to intervention for weeks 1 to 12, and another 12-week log at the time of the first follow-up visit to record adherence to intervention for weeks 13 to 24. Participants are requested to turn in the adherence logs during their follow-up visits. In addition, participants in this arm receive text messages once a week to promote and reinforce exercise adherence. All text messages are sent via Google Voice, which allows specifications of text message content, delivery options, and carrier/receiver information, as well as the capability to send text messages to individuals or groups of users at a particular time of day on a regular basis.

Arm 3: Control Group—Control group participants are asked to maintain their current daily activities and exercise habits for the duration of the study (6 months). In addition, these participants receive weekly text messages on general health topics and healthy lifestyle information, such as “Be tobacco free! Tips on how to quit www.smokefree.gov” and “Stay healthy year-round. Get a flu shot”. After the end of the study control group participants are offered the chance to exercise at the OMH facility for 6 months.

Study retention and adherence

The following steps have been taken to retain participants in the study and increase adherence to the intervention: (1) participants randomized to the supervised facility-based intervention arm have a choice of exercising at one of the two community-based exercise centers based on their convenience; (2) the exercise sessions can be scheduled as early as 8 am in the morning or 5:30 pm in the evening and even during the usual office lunch hours; (3) the cost of transportation and parking is reimbursed to participants who come in for the exercise sessions or follow-up visits; (4) Home-based and control group participants receive

weekly texts to retain interest in the study and to remind them of upcoming follow-up visits; and, finally (5) participants receive \$25 grocery gift cards as incentives for their baseline and follow-up visits.

Assessments

Three assessments, one at baseline and two follow-up assessments at 3 and 6-months, are conducted in this RCT. Assessments include individual measurements of demographic, socioeconomic, medical history, physical activity, diet, cardiorespiratory fitness, body composition, and anthropometric variables. Assessments also include blood pressure and resting heart rate. Fasting blood samples for biomarker assessments at baseline are drawn in the morning on a day when the participants have not undergone any significant exercise for the preceding 3 days. During follow-up visits, blood samples are drawn in the fasting state in the morning 16-24 hours after the most recent exercise session for those participants randomized to the intervention arms.

Outcomes

Primary Outcomes

Obesity: Anthropometric measures of height, weight, and waist and hip circumference are collected. Weight is measured using a beam balance scale while participants are wearing light clothing and no shoes, and recorded to the nearest 1/2 pound. Height is measured using a stadiometer. Participants stand erect against the board, without shoes, and look straight ahead. Height is read to the nearest 1/4 inch. BMI is calculated based on height and weight. Waist circumference, measured at the level of the navel with a measuring tape, and waist-to-hip ratio (WHR) are used to assess abdominal/central obesity.

Biomarkers—A fasting finger stick sample of blood (35 μ l) is assessed for immediate analysis of fasting glucose by reflectance photometry using the Cholestech-LDX[®] System (Cholestech Corp, Hayward, CA).

Lipid Panel: Serum lipids are analyzed on the Ortho Clinical Diagnostics Vitros 5,1 FS Chemistry Systems platform using a multilayered, enzymatic, slide method. Intra- and inter-assay CVs are 1.5-1.8% for total cholesterol, 2.9-3.0% for HDL-cholesterol, 0.9-1.4% for triglycerides, and 1.8-3.7% for calculated LDL. Direct LDL-cholesterol is run as a reflex test when triglycerides are >350.

Screening Insulin: Assays are performed on the Siemens Advia Centaur XP platform with a reference range of 3.0–25.0 μ IU/ml and CV <10%.

High sensitivity CRP (hsCRP): Serum hsCRP is 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%.

Breast Cancer Risk Biomarkers: Serum levels of IL-6, TNF α , Adiponectin, Leptin, C-peptide, Insulin, IGF-1 and IGFBP-3 are measured using X-MAP, bead-based (multiplex) assays from Millipore, on the BioRad Bioplex platform. Hormones, including estrone,

estradiol, testosterone, androstenedione, as well as SHBG are all assayed by specific ELISA using commercially available reagents with inter-assay CVs <10%.

Secondary Outcomes

Cardiorespiratory Fitness: Exercise tolerance and cardiovascular fitness are assessed by measuring maximal oxygen consumption (VO_{2max}). The Bruce treadmill protocol is used to determine VO_{2max} using a ParvoMedics TrueOne 2400 metabolic cart (Sandy, UT). This involves a 5-minute warm-up followed by increases in treadmill speed and grades every 3-minutes until volitional exhaustion. VO_{2max} was determined using the following criteria: (1) a respiratory exchange ratio (RER) ≥ 1.1 ; (2) a maximal HR within 10 bpm of the age-predicted maximum ($220 - \text{age}$); or (3) volitional fatigue. This protocol is also used to determine heart rate reserve (HRR). HRR is defined as increased heart rate as a result of increased activity. HRR values lower than or equal to 85% are considered to be normal (38).

DEXA Scan: A dual-energy X-ray absorptiometry (DXA, Hologic Discovery A, Waltham, MA) is used to assess regional and whole body lean mass (appendicular skeletal muscle mass) and fat mass at baseline and 6-month follow-up.

Health-Related Quality of Life: The SF-36[®] self-report instrument designed to measure multidimensional quality of life is used (39). The SF-36 measures eight health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health. Scores are on a continuous scale and a higher score denotes higher quality of life.

Other covariates—Physical activity is assessed using the International Physical Activity Questionnaire (IPAQ). The IPAQ is a structured interview that measures a person's time spent engaging in physical activity over a 7-day period (40). The usual dietary intake, micronutrients, dietary patterns and alcohol consumption are assessed using the Block 2005 Food Frequency Questionnaires (FFQ) (41), which includes 110 food items commonly consumed by African-Americans.

Sample size

We based our sample size calculations on the effect of exercise on the hormones including estrone, estradiol and SHBG, for the three intervention arms. We adopted a between-group repeated measure model assuming a modest correlation of 0.40 between the four repeated measurements of hormone levels. With an effect size of 0.1 (10% difference between the intervention and control group), a total sample size of 240 (80/arm) is needed to detect a significant effect of exercise on hormone levels, at 0.05 level of significance and power of 0.80 and assuming a dropout rate of 20%, for the overall between-group analysis of variance (ANOVA) F-test. Using estimates from McTiernan et al. (2004), an effect size of 0.1 for our model translates to about 2.8 pg/ml, 1.1 pg/ml, and 3.0 nmol/l of estrone, estradiol, and SHBG, respectively (42). Therefore, for this study, a sample size of 80 per group will accord

us ample power to detect differences in waist circumference and hormone levels among the three intervention groups after accounting for a 20% dropout rate.

Statistical analysis

The main intervention effects on change in obesity (weight, waist circumference, and BMI), MetS components (fasting glucose, triglycerides, high-density lipoprotein, hypertension, abdominal obesity), and breast cancer-related biomarkers (inflammation, sex hormones, adipokines, and insulin pathway markers) will be determined based on the following comparisons using the 'intent-to-treat' principle: (a) supervised facility-based exercise group compared to control group, and (b) home-based exercise group compared to control group. Numerical baseline characteristics will be compared among the three groups using ANOVA or Kruskal-Wallis tests depending on whether or not the ANOVA assumptions are satisfied. Categorical variables will be compared using chi-square tests. The major analytical tool for addressing the specific aims of this study is mixed linear modeling for repeated measures, which has been advocated by many authors (43-45). For most outcomes in this study, each individual will be measured three times, and it is expected that measures on the same individual are correlated. It is also expected that variances of repeated measures change with time (45). An appropriate correlation structure will be selected depending on whether or not there is a trend of variance with time. For each numerical outcome measure of interest, a linear mixed, repeated measures model will be fit to evaluate the main effects of time, 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 the 10% level. We will also conduct these analyses for secondary outcomes of the trial: cardiorespiratory fitness, body composition based on DEXA, and quality of life based on the SF-36 measures. No adjustment for multiple comparisons will be made for the analyses.

Summary

The present clinical trial will contribute to the literature on the role of exercise in breast cancer prevention among high-risk women with respect to a focus on under-represented minority women, who have co-morbidities and are commonly excluded. The strengths of this study include the use of biomarkers and biological correlates for different carcinogenic pathways. The limitations of the study include generalizability, as is the case for many intervention trials. Women enrolling in this type of study may not be representative of women in general because of their intentions, the incentives, intensive monitoring, and other factors.

Presently, we do not definitively know the reasons for the high breast cancer mortality rate among Black women. Their increased likelihood to be physically inactive and overweight / obese may contribute to this disparity. Limited research has focused on improving energy balance in minority and underserved communities, particularly Black women. This will be the first study to assess the feasibility of intervening on MetS as a risk factor for post-menopausal breast cancer in African-American women.

Acknowledgments

This study is supported by grants from NIH NIMHD (1P60MD006920-01)

The Georgetown Lombardi Comprehensive Cancer Center Biostatistics & Bioinformatics Shared

Resource is partially supported by NIH/NCI grant P30 CA051008 and GHUCCTS grant UL1TR000101.

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Figure 1. Study flow