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Recruitment strategies, design, and participant characteristics in a trial of weight-loss and metformin in breast cancer survivors

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ABSTRACT

Weight loss and metformin are hypothesized to improve breast cancer outcomes; however the joint impacts of these treatments have not been investigated.

Reach for Health is a randomized trial using a 2 × 2 factorial design to investigate the effects of weight loss and metformin on biomarkers associated with breast cancer prognosis among overweight/obese postmenopausal breast cancer survivors. This paper describes the trial recruitment strategies, design, and baseline sample characteristics.

Participants were randomized in equal numbers to (1) placebo, (2) metformin, (3) weight loss intervention and placebo, or (4) weight-loss intervention and metformin. The lifestyle intervention was a personalized, telephone-based program targeting a 7% weight-loss in the intervention arm. The metformin dose was 1500 mg/day. The duration of the intervention was 6 months. Main outcomes were biomarkers representing 3 metabolic systems putatively related to breast cancer mortality: glucoregulation, inflammation, and sex hormones.

Between August 2011 and May 2015, we randomized 333 breast cancer survivors. Mass mailings from the California Cancer Registry were the most successful recruitment strategy with over 25,000 letters sent at a cost of $191 per randomized participant. At baseline, higher levels of obesity were significantly associated with worse sleep disturbance and impairment scores, lower levels of physical activity and higher levels of sedentary behavior, hypertension, hypercholesterolemia, and lower quality of life ($p < 0.05$ for all). These results illustrate the health burden of obesity.

Results of this trial will provide mechanistic data on biological pathways and circulating biomarkers associated with lifestyle and pharmacologic interventions to improve breast cancer prognosis.

1. Background

The National Cancer Institute estimates that approximately 3 million women with a history of breast cancer were alive in 2012 [1]. Excess adiposity is an established risk factor for postmenopausal breast cancer mortality and has reached epidemic proportions with over 70% of US women aged 40–59 classified as overweight or obese [2]. A twin epidemic is type 2 diabetes mellitus, which is increasing at an alarming rate. The number of Americans with diagnosed diabetes is projected to increase 165%, from 11 million in 2000 (prevalence of 4.0%) to 29 million in 2050 (prevalence of 7.2%), with even larger increases in older women [3]. Numerous studies have shown that diabetes has a negative impact on breast cancer prognosis [4–7]. Given the large numbers of breast cancer survivors, the high prevalence of excess adiposity, and increasing trends in diabetes; research on interventions to improve breast cancer outcomes via weight management and/or improved blood sugar regulation is of considerable public health importance.

Obesity and diabetes share biological mechanisms for their associations with breast cancer prognosis, including a direct effect of insulin on breast cancer cell proliferation, increased extraglandular estrogen production and bioavailability, inflammation, and activation of the AMP-activated protein kinase (AMPK) pathway [8]. Weight loss appears to have favorable effects on these biological pathways, including improvements in insulin resistance and sex hormone concentrations [9,10] and is generally recommended to breast cancer survivors who are overweight or obese [11]. However, there are no prospective randomized trial data regarding its efficacy to improve breast cancer prognosis [12]. Recently, an antidiabetic agent called metformin has been

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hypothesized to improve breast cancer outcomes [13–16]. Metformin has been shown to significantly reduce insulin and testosterone concentrations among non-diabetic breast cancer patients [17], and appears to have insulin-independent direct effects on tumor cells that are mediated by activation of AMPK with downstream inhibition of mTOR [18]. Several epidemiologic studies have found an association of metformin with improved cancer prognosis [13], although the data are not consistent [19]. In view of this evidence, the National Cancer Institute of Canada initiated a Phase III randomized trial of metformin in early stage breast cancer survivors with results expected after 2017 [20]. Specifically, this trial is designed to compare the effects of metformin vs placebo in addition to standard adjuvant therapy on disease-free survival among patients with early-stage breast cancer. An important ancillary question concerns whether weight loss could be an alternative, or valuable addition, to this pharmacologic intervention.

Reach for Health is a 6-month randomized trial designed to investigate the effects of weight loss and metformin on sex hormones and glucoregulatory and inflammation biomarkers associated with breast cancer recurrence and mortality [21–23]. We hypothesize that in overweight/obese postmenopausal breast cancer survivors, weight loss and metformin will reduce circulating concentrations of biomarkers associated with increased risk of breast cancer mortality, and that the combination of these interventions will have an additive effect on biomarker profiles. The purpose of this article is to describe the recruitment strategies, design, and baseline sample characteristics of the Reach for Health trial.

2. Methods

2.1. Research design

2.1.1. Overview of Reach for Health

Reach for Health is a project within the UC San Diego Transdisciplinary Research in Energetics and Cancer (TREC) program project (1U54CA155435-01; PI, Patterson) [21]. The objective of our TREC Center is to enhance knowledge regarding insulin resistance and inflammation underlying the association of energetics with breast cancer carcinogenesis, from the cell to the community.

Reach for Health is a randomized trial using a 2×2 factorial design to compare the degree to which weight loss, metformin, or both, influence biomarkers associated with increased breast cancer mortality. Eligible participants were overweight or obese women with a history of early-stage postmenopausal breast cancer. Women were randomized in equal numbers to (1) placebo, (2) metformin, (3) weight-loss intervention and placebo, or (4) weight-loss intervention and metformin. Main outcomes of this trial are changes in circulating biomarkers associated with breast cancer mortality ascertained from fasting blood samples collected at baseline and 6-month follow-up. Specifically, we plan to test the impacts of these interventions on changes in glucoregulatory markers (fasting insulin and glucose), inflammation (C-reactive protein), and sex hormones (estrogen). An exploratory outcome of great interest is the impact of these interventions on mild cognitive impairment as assessed using NeuroTrax computerized testing [24]. The UCSD institutional review board approved study procedures and all participants provided written informed consent. We also formed an independent Data Safety and Monitoring Board that met annually.

2.1.2. Participant screening and eligibility

Preliminary eligibility was assessed via a telephone interview. Eligible participants were overweight or obese breast cancer survivors (BMI ≥ 25 kg/m^2) [25] diagnosed with primary operable breast carcinoma (Stage IA–IIIC) within the past 10 years, postmenopausal at the time of breast cancer diagnosis, and not scheduled for or currently undergoing chemotherapy or radiotherapy. Women who recently completed primary treatment for breast cancer were required to wait at least 1-month before being enrolled in the trial. Women taking adjuvant therapy (e.g., aromatase inhibitors) had to be willing and able to remain on treatment for the 6-month intervention period to prevent confounding of endogenous hormones or other biomarker concentrations. All study materials, and the dietary intervention, were available in English and Spanish.

Women were excluded if they had been diagnosed with an additional primary or recurrent invasive cancer within the last 10 years or had serious medical conditions such as renal insufficiency, liver impairment, or congestive heart failure. Participants were also excluded if they were diabetic, using hormone replacement therapy, or had a condition that would interfere with participation in the trial.

2.1.3. Pre-randomization screening assessments

Women who appeared eligible based on the telephone interview were invited to a screening visit to verify eligibility and identify women who might have difficulty completing the protocol. Screening assessments included an in-person interview to explain the trial, written informed consent for pre-randomization procedures, physical measurements (height, weight, pulse, blood, pressure), and a review of their pathology report to verify the initial breast cancer diagnosis and treatment (e.g., stage, grade, anti-estrogen use). Participants provided a fasting blood draw to ensure that they were not diabetic and had normal kidney and liver function to minimize the risk of lactic acidosis, which is a rare but serious side effect of metformin.

After successful completion of the screening visit, participants were asked to complete an online baseline questionnaire and were given an accelerometer and GPS tracking device to wear for 7 days and return at the next (i.e., baseline) visit. Participants received 2 reminder phone calls from the study team during the scheduled wear period.

2.1.4. Baseline clinic visit and randomization procedures

At the baseline visit, written informed consent for participation in Reach for Health was obtained, online questionnaires and a computerized cognition test were completed, and physical measurements and a fasting blood specimen were collected. Accelerometers were checked for adequate wear time (10 h on at least 5 days). Using a computer program, participants were randomized to 1 of the 4 study groups using a random permuted-block design that included strata for stage at diagnosis (Stage I vs. Stages II and III) and BMI (<30.0 kg/m^2 vs. ≥30.0 kg/m^2), which is known to influence biomarker concentrations. All study personnel were blinded to the medication group assignment (metformin vs. placebo).

2.1.5. 6-month clinic visit

All baseline assessments were repeated, including anthropometric measures, online questionnaires, cognitive function test, accelerometer and GPS, and fasting blood draw.

2.2. Intervention groups

2.2.1. Medication groups: metformin vs. placebo

We received a waiver from the FDA to provide metformin to non-diabetic women who met our eligibility criteria. At the baseline visit, participants received randomly assigned, blinded medication (metformin or placebo). The study physician provided a prescription for the medication. To minimize potential gastrointestinal symptoms, participants were instructed to begin taking the pills at a low dose (one 500 mg metformin tablet [or one placebo pill] at dinner). If no gastrointestinal distress was experienced at 1 week, the dose was increased to 2 pills at dinner (1000 mg metformin [or two placebos]). At 1 month, the dose was increased to 1 pill in the morning and 2 pills at dinner (1500 mg metformin) for the remainder of the intervention. If side effects arose, participants were instructed to notify study personnel who were trained in providing strategies for managing gastrointestinal symptoms. In some cases, the study physician spoke to the participants regarding management of symptoms. If a participant was unable to