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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.

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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.

Keywords

Breast cancer; weight loss; metformin; survivorship; trial

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 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 in 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.

METHODS

Research Design

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.

Participant screening and eligibility—Preliminary eligibility was assessed via a telephone interview. Eligible participants were overweight or obese breast cancer survivors (BMI ≥ 25 kg/m²)²⁵ diagnosed with primary operable breast carcinoma (Stage IA-IIIIC) 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.

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.

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 hours 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 ($<30.0 \text{ kg/m}^2$ 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).

6-month Clinic Visit—All baseline assessments were repeated, including anthropometric measures, online questionnaires, cognitive function test, accelerometer and GPS, and fasting blood draw.

Intervention Groups

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 remain

on the dose of 1500 mg (or 3 pills), she was allowed to reduce her dose to 1000 mg (or 2 pills). Women who stopped taking medication because of side effects were encouraged to remain in the study and complete follow-up assessments. It is possible that women who reported experiencing side effects could have become unblinded as to their medication (metformin versus placebo), which is a limitation of drug trials. However, it seems unlikely that patients who believed that they knew their treatment assignment could intentionally or unintentionally bias the objective study outcome: changes in biomarker concentrations.

Adherence to study medication was assessed by structured telephone interviews conducted post-randomization at 2 weeks, 1 month, and 3 months. Counselors were blinded to the randomization allocation of participants (i.e., metformin or placebo). During these scheduled pill adherence calls, counselors queried participants about adverse events in a nondirective manner. Participants were asked to return all empty, partially empty, or full pill bottles at the final clinic visit. To assess adherence, study staff determined the amount of unused medication.

Weight-Loss Intervention vs. Comparison Group—In addition to receiving pills, each participant was randomly assigned to a telephone-based weight-loss intervention or the comparison group. Participants were given an individual goal of 10% weight loss in order to achieve the study goal of 7% weight loss for the intervention arm.

Experienced and trained lifestyle coaches from the UC San Diego Moores Cancer Center's Diet and Physical Activity Shared Resource delivered the telephone-based intervention. Participants remained with the same coach throughout the 6-month intervention to facilitate development of rapport continuity of care. The counseling protocol consisted of 12 motivational interviewing calls over the 6-month intervention period. The intervention followed a stepwise, phased approach using strategies outlined by social cognitive theory²⁶ that focused on (a) establishing a series of short-term goals and (b) reviewing performance on these goals in a way that builds self-efficacy. The intervention consisted of a highly supportive initial phase with weekly calls followed by a gradual transition to monthly calls. The intervention focused on portion control, number of food group servings per day, and healthy eating. Early monitoring of weight loss suggested that we were not meeting our intervention goal and therefore the weight loss intervention was intensified with a stronger focus on counting calories. Participants were given a personalized calorie goal based on their starting weight to support a 500 to 1000 kcal reduced calorie diet.²⁷ Participants were also instructed to self-monitor their caloric intake using paper logs or online tools like myfitnesspal.com.²⁸ Throughout the intervention, counselors encouraged participants to report difficulties or challenges and adjust dietary or physical activity targets to help participants achieve short-term goals and build self-efficacy. Women in the weight-loss intervention group received print materials on diet and physical activity and reference material to aid in self-assessment of food intake.

The physical activity goal was 300 minutes/week of moderate-intensity activity. Participants were encouraged to select activities that they enjoy and suit their lifestyle (e.g., brisk walking, swimming, stationary bike). Pedometers were provided to encourage increasing daily steps and self-monitoring.

Women randomized to the comparison group received US Dietary Guidelines for Americans, 2010.²⁹ As noted above, all participants received 3 pill adherence calls. Therefore, similar to women in the weight loss intervention, women in the comparison group were regularly contacted by study staff during the 6-month intervention period.

Measurements

Physical Measurements—Anthropometric measures were taken in duplicate at the baseline and final (6-month) clinic visits. Height was measured without shoes at the screening visit using a stadiometer. Weight was measured without shoes using a bariatric digital scale and waist was measured along the midaxillary line using a flexible, non-stretchable measuring tape.

Physical Activity & Sedentary Behavior—Physical activity and sedentary behavior were objectively assessed at baseline and 6-months with 7 days of a hip-worn accelerometer: the ActiGraph GT3X+ (ActiGraph, Pensacola, FL) collected on 3 axes at 30 hertz. The ActiGraph measures movement and intensity of activity and has been validated against heart rate telemetry³⁰ and total energy expenditure.^{31,32} Non-wear time was classified using Choi's algorithm of 90 consecutive zero counts on the x-axis.³³ Sufficient wear time was defined as 5 days with 600 minutes of wear time; or 3,000 minutes (50 hours) across 4 days. Participants with incomplete accelerometer data were asked to re-wear the device for the number of days needed plus one. To be considered valid data, the device re-wear had to occur within 2 weeks of when clinical measurements and blood specimens were collected. Data were processed in Actilife 6.11 and aggregated to the minute level. The low frequency extension was applied. Moderate to vigorous physical activity was classified at counts per minute above 1951, and sedentary behavior below 100 counts per minute.^{34,35}

Self-reported physical activity was assessed with the Global Physical Activity Questionnaire (GPAQ) at baseline and 6-months.³⁶ The GPAQ calculates metabolic equivalents (METs) to express the intensity of self-reported physical activities. The GPAQ has good reliability (Kappa=0.67 to 0.73; Spearman's rho=0.67 to 0.81) and has been validated with the International Physical Activity Questionnaire in the general population,³⁷ and against objective accelerometer measures in population sub-groups.³⁸

Sedentary behavior was self-reported via a 19-item questionnaire adapted from the Sedentary Behavior Questionnaire,³⁹ which assesses the amount of time spent in common behavior domains (e.g., sitting while watching television, reading) on weekdays as well as on weekends. Response options are none, 15 minutes or less, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, or 6 hours or more. For total sedentary behavior, hours per day for each item were summed separately for weekday and weekend days.

Since accelerometers are known to misclassify transportation modes such as cycling and riding in a vehicle, GPS data was also collected. A Qstarz BT1000X GPS device was deployed on the same hip worn belt as the accelerometer. X,Y coordinates were collected every 15 seconds.

Sleep—Sleep impairment and disturbance were assessed using 8-item short forms available through the Patient-Reported Outcomes Measurement Information System (PROMIS™), which is part of a National Institutes of Health Roadmap initiative for measuring patient-reported outcomes.⁴⁰ Respondents rated aspects of their sleep over the past 7 days on 5-point scales. Items assessing sleep-related disturbance or impairment were scored 1 to 5 with 1 for the lowest category (i.e., *not at all*) and 5 for the highest category (i.e., *very much*). Responses to these items were summed to create an overall score, with higher scores indicating greater levels of sleep disturbance and impairment. Sleep duration was assessed at each time point with a single-item: “On average, how many hours of sleep do you get per night?”.

Quality of Life—Quality of life was assessed at baseline and 6-months using the Short Form Health Survey (SF-36).⁴¹ The SF-36 provides physical health and mental health summary scores that range from 0 to 100, with higher scores corresponding to better quality of life. The questionnaire has been used in diverse populations, including women with breast cancer,⁴² and has shown to be reliable (Cronbach’s $\alpha=0.75$ to 0.91)⁴³ with good construct validity.⁴⁴

Cognitive Functioning—Cognitive functioning was assessed at the clinic visit using a 45-minute computerized testing battery designed to sample a range of cognitive domains (NeuroTrax).²⁴ Validation studies have shown the computerized tests to be comparable to traditional neuropsychological tests in their ability to differentiate cognitively healthy individuals from those with mild cognitive impairment.²⁴ The computerized tests are adaptive, such that the level of difficulty is based on performance of the individual being assessed. Cognitive domain index scores were computed from individual test scores. Specifically, information processing speed was assessed using low- and medium-load stages of Staged Information Processing Speed test; memory was assessed using Verbal and Non-verbal Memory tests; and executive function was assessed by the Stroop Interference test, Go-NoGo Response Inhibition test, and the Catch Game.²⁴

Additional Measures—Other information collected at baseline included self-reported current smoking status and smoking history, alcohol consumption within the past 3 months, weight history, medication and supplement use, psychosocial measures, and medical co-morbidities. The original study proposal included resources for obtaining 24-hour recall data from participants at baseline and follow-up. However, the budget was reduced by almost 24%, which required numerous changes to the protocol. Rather than reduce the sample size and risk inadequate power, we elected to eliminate dietary assessment because (1) dietary intake was not an outcome of the trial and (2) adherence to the weight loss protocol could be objectively assessed by changes in weight.

Study Outcomes: Biomarkers

Serum and plasma, buffy coat, and red blood cell samples were obtained from 30 ml whole blood specimen collected at baseline and final clinic appointments. Samples were centrifuged for 10 minutes and stored in 1.0-ml aliquots at -80 degrees Celsius.

The main candidate biologic mechanisms linking adiposity and cancer risk are (1) glucoregulatory markers, (2) endogenous sex hormones, and (3) chronic systemic inflammation.⁴⁵⁻⁵¹ The specific biomarkers of breast cancer risk and prognosis most strongly supported by the literature are fasting insulin and glucose (or homeostasis model assessment-estimated insulin resistance [HOMA-IR]), bioavailable estradiol, and high-sensitivity C-reactive protein (CRP). Individually, these 3 biomarkers have each been associated with an approximate 2-fold increased risk of incident or recurrent breast cancer.⁵²⁻⁵⁵

Statistical Issues

Data Analysis Plan—We will compare the 4 treatment arms on demographic, tumor, and lifestyle characteristics to test if randomization achieved balance across groups on key covariates. Biomarkers will be transformed as needed to better approximate Gaussian distributions. We will use repeated measures mixed models⁵⁶ to compare biomarker changes between study arms. We will use the F test from a multivariate mixed model^{57,58} as an omnibus test to assess group effects across the three biomarkers, namely HOMA-IR, CRP and bioavailable estrogen. Mixed models will include subject-specific intercepts; fixed effects will be included for time (baseline, 6 months), treatment, and treatment*time interactions. We will compare main effects of the 2 treatments (e.g., metformin vs placebo and weight loss vs control) and test for an interaction between the metformin and weight loss interventions.

Sample Size and Study Power: This study aimed to enroll 340 women. We allowed for a drop-out rate of 6% based on 6-month adherence data reported in previous dietary interventions in breast cancer survivors⁵⁹ and weight loss intervention among overweight and obese women.⁶⁰ Therefore, we expected 320 women to complete the study (80 women per group). We based our a priori sample size calculations on the effect of weight loss and metformin on biomarkers associated with breast cancer mortality. The first set of power computations used PASS 2008 (NCSS Statistical Software). With 80 participants per arm, there would be 90% power to detect a main effect of a standardized mean difference in changes (i.e., effect size) in biomarker levels of 0.37, for a 2-sided t-test with $\alpha=0.05$. For example, a sample size of 80 per group would yield 90% power to detect a mean reduction in insulin concentration of 11.5 pmol/L when comparing the metformin vs no metformin arms, assuming a baseline standard deviation (SD) of 31.1 pmol/L.⁵³ These calculations assumed correlations of 0.5 between baseline and 6 month biomarker values, similar to values observed in our previous breast cancer trial (personal communication, JP Pierce). Finally, a linear trend in intervention effects (e.g., Metformin+Lifestyle > Lifestyle > Metformin > Placebo) would yield 90% power to detect an effect size of 0.21 with 80 participants in each of the 4 arms. As a second set of power calculations, we simulated multivariate data for a trial with 3 biomarker outcomes with intercorrelations among the markers ranging from 0 to 0.5. Based on the F-test from a multivariate mixed model, with 320 total participants, we have 84% power to detect a main effect-size of 0.37 for a single marker with negligible intervention effects on the other two. Considering another scenario, if the intervention had a small effect-size of 0.25 on each marker, power is 80%. Thus, under

a variety of plausible assumptions, our study was well powered to detect meaningful main effects of changes in biomarker concentrations between the intervention and control groups.

RESULTS

Recruitment

From August 2011 through May 2015, we enrolled 253 women from San Diego County and 80 women from outlying counties (e.g., Orange and Riverside). We were able to enroll women from relatively distant locations because the weight loss intervention was telephone administered and therefore participants were not required to drive to a centralized location to receive group or individual face-to-face counseling. As shown in the Consort diagram (Figure 1), 2122 women were screened by telephone, 368 (17%) attended a screening visit, and 333 women (90%) were randomized. Primary reasons for not entering the trial were ineligibility ($n=1186$) or declined participation ($n=503$). Major reasons for ineligibility were BMI $<25 \text{ kg/m}^2$ (21%), diagnosed >10 years ago (14%), not being postmenopausal (13%), and taking insulin or other diabetic drugs (13%). Major reasons women gave for declining to participate were telephone contact difficulty (22%), unwilling to take medication (15%), not interested (10%), and too busy (10%). Only 3 participants were ineligible based on results of the bloodwork collected at the screening visit. These women were advised to follow-up with their primary care physician.

Recruiting breast cancer survivors is a time-intensive, expensive, and challenging endeavor. Table 1 gives an overview of the strategies used to recruit survivors living in the San Diego area. We originally focused on physician referrals and community outreach, including distributing study brochures at breast cancer support groups and other events attracting large numbers of breast cancer survivors (e.g., Susan G. Komen walks) as well as mass media approaches (e.g., Facebook). We also posted study flyers at hospitals and oncology clinics throughout the San Diego area. For the physician referrals, we met regularly with the Moores Cancer Center team of breast cancer oncologists, surgeons, radiologists, and social workers to communicate the study objectives, patient eligibility criteria, and recruitment goals. We altered the Epic electronic medical records so that physicians could easily refer patients to the trial coordinator via a “single click”. Nonetheless, after over a year of recruitment, it became clear that these approaches were inadequate to meet our goal of randomizing 10 women per month.

Our second recruitment strategy was focused on mailings to breast cancer survivors on the California Cancer Registry who were 50-80 years old, diagnosed with Stage I through III breast cancer in the past 10 years, and lived in San Diego, Riverside, Orange, or Imperial County. These large mailing lists were augmented by smaller, more targeted lists obtained from UC San Diego patient registries. Women who received recruitment letters from the California Cancer Registry were asked to contact us if they believed that they were eligible and were interested in learning more about the trial. Registry-based recruitment mailings exceeded 25,000 letters that were hand-stamped and hand-signed with the help of faculty, student and staff volunteers who had completed the appropriate training regarding the protection of human subjects in research.⁶¹

As shown in Table 1, of the 2122 initial contacts with potential participants, the largest proportion were from the California Cancer Registry mailings (52%), followed by community outreach (20%). Among the 333 women randomized to the study, mailings to women on registry lists resulted in the randomization of 215 (65%) study participants and other recruitment methods ranged from 24-35 women randomized (7-11%). Physician referrals and flyers were the most efficient strategies and yielded the highest percentage of screened women who were eligible and subsequently randomized (22% and 31% respectively). Cancer registries were critical for meeting our recruitment goal, but had an extremely low yield (less than 1% of mailings resulted in a randomization).

We estimate that the registry-based recruitment approach cost \$41,000, consisting of costs for supplies (paper, envelopes, stamps), printing charges, and fees to the California Cancer Registry. In addition there were costs associated with obtaining permissions to mail through the California Cancer Registry as well as personnel costs for managing the bulk mailing lists and preparing annual reports. While physician referrals and community-based recruitment were less expensive in terms of materials (estimated \$5,000), they required considerable staff time and the total yield was lower and less predictable than the registry lists. Overall, material costs ranged from \$0 per person for physician referrals to \$191 per person for registry mailings. These cost estimates do not include personnel time, which is a limitation these data. Nonetheless, we believe that these data on recruitment costs can be useful to investigators conducting studies in cancer survivors.

Sample Characteristics

As shown in Table 2, randomization balanced participants' personal and breast cancer characteristics with no statistically significant differences by group assignment. Participants in the study were a mean age of 63 years (SD=6.9) and predominantly non-Hispanic white (84%). This was a well-educated sample of women, with over 90% having some college education. The average time between breast cancer diagnosis and enrollment was 2.7 years (SD=2.0). Almost half of participants were diagnosed with Stage I cancer (48%) and most had ER+/PR+ tumors (70.3%).

Table 3 gives the associations of baseline adiposity with participant characteristics, thereby illustrating the burden of obesity as well as the importance of randomization for eliminating confounding. Specifically, higher levels of adiposity were statistically 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).

DISCUSSION

The Reach for Health randomized trial was designed to examine the individual and combined effects of weight loss and metformin on biomarkers associated with breast cancer mortality. A Phase III Randomized Trial of Metformin Versus Placebo on Recurrence and Survival in Early Stage Breast Cancer ($n=3,649$) is underway, with results expected in 2017.²⁰ The Reach for Health trial will address an important ancillary question concerning whether weight loss could be an alternative, or valuable addition, to this pharmacologic

intervention. To our knowledge, no study has assessed the joint impacts of these interventions in the context of breast cancer survival.

Participant recruitment is critical if clinical and translational research is to meet its promise of improving health. Although no comprehensive data are available across US academic health centers, discontinuation of clinical trials appears to be common with poor recruitment being the most frequently reported reason.⁶² Trial discontinuation has ethical implications, because participants consent on the premise of contributing to new medical knowledge.⁶³ In addition, under-enrolled studies waste scarce resources and do not contribute to scientific or clinical knowledge. An analysis conducted at Oregon Health & Science University (OHSU) found that one-third of all studies terminated between 2005 and 2009 at OHSU had low enrollment and these low-enrolling studies cost the institution almost \$1 million annually.⁶⁴ We found that an intensive population-based approach to recruitment using the California Cancer Registry was the most successful approach, largely because the study team is able to control the pace of recruitment efforts and is not dependent on physician referrals or personnel-intensive in-person recruitment strategies, such as attending support groups and community events. Despite the overall effectiveness of this approach, we had less than a 1 percent response rate to cancer registry mailings, which is lower than rates reported in previous randomized intervention trials in cancer survivors.⁶⁵ For example, the Reach out to ENhance Wellness trial of a home-based multi-behavior intervention among cancer survivors reported an 11% response rate using a similar registry-based recruitment strategy.⁶⁵ However, comparing response rates is difficult because trials vary considerably regarding type of cancer survivor, eligibility criteria, specific recruitment methods, and degree of participant burden. For example, our participants had to be willing to take a drug, come to multiple clinic visits, and donate blood samples. In addition, the California Cancer Registry does not allow follow-up letters of invitation or telephone recruitment of women on registry lists. All of these aforementioned factors are likely to reduce participation rates in a trial. These findings offer several cautionary conclusions about large-scale studies of cancer survivors: (1) considerable planning and resources should be invested in determining the feasibility and costs associated with participant recruitment, (2) recruitment needs to be carefully monitored and new approaches initiated if monthly randomization goals are not being met, and (3) multiple strategies for recruitment are likely to be needed because mass media approaches are not practical for these relatively rare populations. Finally, it is notable that despite this population-based recruitment strategy, women enrolled in the study were highly educated with over 90% having attended some college. We do not believe that education levels are likely to be associated with the objective outcome: changes in biomarker concentrations. Therefore the results of this study should be widely generalizable to breast cancer survivors. Nonetheless it is clear that the recruitment strategies used here are insufficiently targeted if the study objective is to enroll a low socioeconomic sample or a specific race or ethnic group.

As noted above, Reach for Health is part of the UC San Diego Transdisciplinary Research in Energetics and Cancer (TREC) center initiative to examine the role of insulin resistance and inflammation in breast cancer risk (1U54CA155435-01; PI, Patterson). UC San Diego has 4 major projects funded by this initiative in addition to numerous small-scale pilot studies.^{21,66} Many of these projects complement or build on one another, thereby leveraging recruitment

and assessments to further the knowledge that can be gained. For example, an interrelated project in the UC San Diego TREC Center captured sophisticated, objective measures of physical activity on our study participants at baseline and follow-up. The goal of this project is to improve the assessment of physical activity energy expenditure by applying novel computational techniques to accelerometer and GPS device data (PI: Jacqueline Kerr).²¹ The GPS data will be used to study the impact of built environment on weight and other health outcomes. While the project on physical activity emphasized insulin resistance as the primary outcome, merging of the two datasets (Reach for Health and the physical activity database) will permit investigation of the impacts of physical activity on sex hormones and inflammation as well as peripheral questions related to cognition and sleep. Similarly, neuropsychological testing was added to the study protocol to examine the effect of weight loss, with and without metformin, on cognitive functioning among breast cancer survivors. In this time of limited research funding and reduced budgets, transdisciplinary studies that leverage the costs of recruitment and intervention implementation can result in efficient and exciting research opportunities.

In summary, the Reach for Health randomized trial will provide important mechanistic information on weight loss versus metformin in relation to biomarkers associated with breast cancer prognosis, thereby potentially offering a lifestyle option to breast cancer survivors who prefer not to take a pharmacologic agent. Information gained from this trial, combined with the novel objective physical activity data and in-depth cognitive tests, will provide a rich dataset that will permit multiple, diverse investigations of breast cancer survivorship. If weight loss and metformin do not change the targeted biomarkers, information will still be gained as this would indicate that the hypothesized associations of weight loss and metformin on breast cancer prognosis do not act through these biological systems. Results of this study will support the development of future clinical trials to improve breast cancer outcomes.

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Figure 1. Reach for Health CONSORT Diagram

Table 1
Overweight/Obese Breast Cancer Survivors Screened and Randomized into the Reach for Health Trial and Estimated Costs by Recruitment Method

Recruitment Method	Women Screened by Recruitment Method N (% of 2122)	Women Randomized by Recruitment Method N (% of 333)	Success Rate: Randomized/ Screened N (%)	Estimated Total Costs ¹	Cost Per Participant Enrolled ¹
Physician Referral	117 (5.4%)	26 (7.8%)	26/117 (22.2%)	\$0	\$0
Community Outreach	423 (19.9%)	33 (9.9%)	33/423 (7.8%)	\$5,028	\$152
Flyer	114 (5.4%)	35 (10.5%)	35/114 (30.7%)	\$337	\$10
Registry-Based Mailings	1105 (52.1%)	215 (64.6%)	215/1105 (19.5%)	\$41,150	\$191
Other ²	363 (17.1%)	24 (7.2%)	24/363 (6.6%)	NA	NA

¹ Estimated costs do not include personnel time; only direct costs are reported.

² Other recruitment methods include, Craigslist, Facebook, ResearchMatch, referral from study participants, NCI Website, and referral from other UC San Diego research studies.

Table 2
Baseline Characteristics of Overweight/Obese Post-menopausal Breast Cancer Survivors Enrolled in the Reach for Health Randomized Trial

	Group A ^{1a}	Group B ^{1a}	Group C ^{1b}	Group D ^{1b}	Total	p-value ²
Randomization	N=83	N=83	N=84	N=83	N=333	
Age, mean years (SD)	62.7 (7.1)	63.4 (6.8)	62.6 (6.3)	63.6 (7.4)	63.1 (6.9)	0.7
Education, N (%)						
College grad	20 (24.1%)	10 (12.1%)	16 (19.1%)	21 (25.3%)	67 (20.1%)	0.16
Grad school	28 (33.7%)	26 (31.3%)	28 (33.3%)	22 (26.5%)	104 (31.2%)	
High school or less	6 (7.2%)	11 (13.3%)	3 (3.6%)	10 (12.1%)	30 (9.0%)	
Some college	29 (34.9%)	36 (43.4%)	37 (44.1%)	30 (36.1%)	132 (39.6%)	
Time since diagnosis, years (SD)	2.5 (1.9)	3.1 (2.3)	2.7 (1.9)	2.6 (1.8)	2.7 (2.0)	0.27
Race, N (%)						
White	70 (84.3%)	68 (81.9%)	70 (83.3%)	70 (84.3%)	278 (83.5%)	0.62
Black or African-American	3 (3.6%)	2 (2.4%)	5 (6.0%)	2 (2.4%)	12 (3.6%)	
Asian	3 (3.6%)	0 (0%)	1 (1.2%)	2 (2.4%)	6 (1.8%)	
Mixed race or other race	7 (8.4%)	13 (15.7%)	8 (9.5%)	9 (10.8%)	37 (11.1%)	
Ethnicity, N (%)						
Non-Hispanic	73 (88.0%)	71 (85.5%)	80 (95.2%)	71 (85.5%)	295 (88.6%)	0.12
Hispanic	10 (12.1%)	12 (14.5%)	4 (4.8%)	12 (14.5%)	38 (11.4%)	
Cancer Stage, N (%)						
Stage I	41 (49.4%)	40 (48.2%)	40 (47.6%)	40 (48.2%)	161 (48.4%)	0.96
Stage II	30 (36.1%)	31 (37.4%)	28 (33.3%)	27 (32.5%)	116 (34.8%)	
Stage III	12 (14.5%)	12 (14.5%)	16 (19.1%)	16 (19.3%)	56 (16.8%)	
Estrogen receptor (ER)/Progesterone receptor (PR) status, N (%)						
ER-/PR-	14 (16.9%)	8 (9.6%)	14 (16.7%)	8 (9.6%)	44 (13.2%)	0.45
ER-/PR+	2 (2.4%)	1 (1.2%)	0 (0%)	2 (2.4%)	5 (1.5%)	
ER+/PR-	12 (14.5%)	9 (10.8%)	5 (6.0%)	7 (8.4%)	33 (9.9%)	
ER+/PR+	51 (61.5%)	59 (71.1%)	60 (71.4%)	64 (77.1%)	234 (70.3%)	
ER+/PR Missing	4 (4.8%)	5 (6.0%)	5 (6.0%)	2 (2.4%)	16 (4.5%)	
Missing	0 (0%)	1 (1.2%)	0 (0%)	0 (0%)	1 (0.3%)	

^{1a}Weight-loss Intervention;

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$I/h_{\text{Control Arm}}$;

² p-values based on ANOVAs for continuous and Fisher-test (exact or simulated) for categorical variables.

Table 3
Baseline Characteristics of Overweight/Obese Post-menopausal Breast Cancer Survivors Enrolled in the Reach for Health Randomized Trial by Body Mass Index

Body Mass Index	Total				p-value
	25-26.9 kg/m ²	27-29.9 kg/m ²	30-34.9 kg/m ²	35 kg/m ²	
N	68	92	107	66	333
Alcohol Intake, N (%)					
Yes	53 (77.9%)	65 (70.7%)	70 (65.4%)	37 (56.1%)	225 (67.6%) 0.05 ^{3a}
Smoking, N (%)					
Never	40 (58.8%)	53 (57.6%)	59 (55.1%)	32 (48.5%)	184 (55.3%) 0.62 ^{3a}
Previous ^I	28 (41.2%)	39 (42.4%)	48 (44.9%)	34 (51.5%)	149 (44.7%)
Sleep², Mean (SD)					
Disturbance Score	49.9 (8.8)	48.1 (8.5)	52.8 (7.6)	50.7 (9.9)	50.5 (8.8) <0.01 ^{3b}
Impairment Score	46.2 (8.3)	44.9 (9.4)	48.1 (8.8)	48.5 (8.9)	46.9 (9.0) 0.03 ^{3b}
Physical Activity, Median (Q1-Q3)					
MET ⁴ hours per week (self-report)	27.5 (8.0-56.0)	19.0 (7.8-41.5)	16.0 (0.5-45.3)	5.0 (0.0-23.3)	16.0 (2.7-42.0) <0.001 ^{3c}
MVPA (1952+ CPM) min per day (objective) [*]	19.5 (11.8-35.9)	17.3 (5.7-29.9)	14.1 (5.1-26.6)	9.2 (4.9-19.4)	15.1 (6.0-26.6) <0.001 ^{3c}
Sedentary Behavior, Median (Q1-Q3)					
Hours per day (self-report)	10.0 (7.5-12.0)	10.1 (7.0-11.8)	10.7 (8.5-14.7)	10.9 (8.3-13.2)	10.4 (7.7-13.1) 0.04 ^{3c}
Hours per day (<100 CPM) (objective) [*]	8.5 (7.6-9.1)	8.5 (7.1-9.6)	8.4 (7.6-9.4)	8.9 (7.3-10.2)	8.5 (7.4-9.6) 0.57 ^{3c}
Medical Conditions, N (%)					
High Blood Pressure	19 (27.9%)	42 (45.7%)	60 (56.1%)	45 (68.2%)	166 (49.9%) <0.001 ^{3a}
High Cholesterol	26 (38.2%)	47 (51.1%)	52 (48.6%)	39 (59.1%)	164 (49.3%) 0.05 ^{3a}
Depression	26 (38.2%)	32 (34.8%)	47 (43.9%)	31 (47.0%)	136 (40.8%) 0.36 ^{3a}
Quality of Life², Mean (SD)					
Physical Health	70.2 (17.6)	71.2 (16.3)	64.7 (18.9)	57.4 (19.5)	66.2 (18.7) <0.001 ^{3b}
Mental Health	74.3 (19.3)	78.5 (16.5)	71.3 (18.8)	69.6 (17.9)	73.6 (18.4) 0.01 ^{3b}

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¹ Current smoking was < 2% and therefore combined with previous smoking

² Score was normalized

^{3a} Chisq-test

^{3b} ANOVA F-test

^{3c} Kruskal-Wallis test

⁴ Metabolic Equivalent Task Units

* Analyses did not adjust for wear time as there were no differences between the groups.