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Effects of a walking intervention using mobile technology and interactive voice response on serum adipokines among postmenopausal women at increased breast cancer risk

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Abstract

Practical methods to reduce the risk of obesity-related breast cancer among high-risk subgroups are lacking. Few studies have investigated the effects of exercise on circulating adipokines, which have been shown to be associated with obesity and breast cancer. The aim of this study was to examine the effects of a walking intervention on serum adiponectin, leptin and the adiponectin-to-leptin ratio (A/L). Seventy-one overweight and obese postmenopausal women at increased risk of developing breast cancer were stratified by BMI (25-30 kg/m^2 or >30 kg/m^2) and randomized to a 12-week, 2-arm walking intervention administered through interactive voice response (IVR) and mobile devices. The intervention arms were: IVR + coach and IVR + no coach condition. Pre-post changes in serum adiponectin, leptin and the A/L ratio were examined using mixed regression models, with ratio estimates (and 95% confidence intervals [CI]) corresponding to post-intervention adipokine concentrations relative to pre-intervention concentrations. While post-intervention effects included statistically significant improvements in anthropometric measures, the observed decreases in adiponectin and leptin (Ratio=0.86, 95% CI 0.74-1.01 and Ratio=0.94, 95% CI 0.87-1.01, respectively) and increase in A/L (Ratio=1.09, 95% CI 0.94-1.26) were not significant. Thus, these findings do not support significant effects of the walking intervention on circulating adipokines among overweight and obese postmenopausal women. Additional studies are essential to determine the most effective and practical lifestyle interventions that can promote beneficial modification of serum adipokine concentrations, which may prove useful for obesity-related breast cancer prevention.

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Conflict of interest

The authors declare that they have no conflict of interest.

Keywords

physical activity; intervention; adipokines; adiponectin; leptin; postmenopausal women

Introduction

Consistent observational epidemiologic evidence suggests that regular, moderate-intensity physical activity provides many health benefits including weight loss and maintenance, improved insulin sensitivity, and improved lipid profile [1-3]. Prospective studies suggest that women who lose weight and maintain the weight loss experience a 10-30% reduction in breast cancer risk [1, 4, 5]. Alterations in hormone signaling, including the obesity-related adipokines, adiponectin and leptin, may play an important role in the biologic mechanisms that mediate the association of obesity, sedentary lifestyle, and weight loss with breast cancer risk [2, 6-8].

Some epidemiological studies, have shown increased plasma leptin [8-10] and decreased adiponectin [7, 11, 12] concentrations to be associated with increased breast cancer risk among postmenopausal women. However, few studies have investigated the effects of physical activity on circulating adipokine levels and how these changes could translate into practical modalities for breast cancer prevention in postmenopausal women [2, 13-16]. Additionally, these studies differ in design and study sample characteristics, yielding inconsistent data, particularly related to intervention effects on circulating adiponectin concentrations. Given that few modifiable risk factors have been identified for breast cancer, the public health need and possible benefit for clarification on the nature of the associations between obesity and breast cancer is very high [17, 18].

The purpose of the present study was to determine if a walking intervention that utilized mobile technology with interactive voice response (IVR) and personal coaching could improve serum adipokine profiles in overweight and obese postmenopausal women at increased risk of developing breast cancer.

Methods

Study recruitment

As described elsewhere [19], overweight and obese (BMI 25-40 kg/m^2) postmenopausal women (*i.e.*, age >55 years or no menstruation for 12 months if ≤55 years; women who had their ovaries removed were also considered postmenopausal) were recruited for study participation between January 2008 and March 2009 through radio and television advertisements and newsletters mailed to faculty and staff at the Ohio State University (OSU). Inclusion criteria included: medical clearance for participation in physical activity from primary care physician, BMI between 25 and 40 kg/m^2, postmenopausal, willingness to participate in 12-week wellness program, access to mobile phone during the 12-week intervention period, and ability to read and speak English without assistance and provide consent. Women were excluded from study participation if they were: previously diagnosed with breast cancer, taking hormone replacement therapy or Tamoxifen or Raloxifene (within 3 months of study enrollment), enrolled in a weight management program (*e.g.*, Weight Watchers), engaged in regular physical activity (at least ≥30 minutes per day), age >75 years and unable to complete a one-mile walk. The study was approved by the Ohio State University Institutional Review Board and all participants provided written informed consent prior to enrollment in the study.

Measures

All eligible women interested in participating were scheduled for an initial visit (Visit 1) with a research staff member. At Visit 1, study requirements were explained, questions were answered, written informed consent and HIPAA authorization were obtained, and a one-mile walk test was administered. Upon successful completion of the test, participants were officially enrolled in the study and scheduled Visit 2 with the research staff. During Visit 2, participants measured height, weight, waist and hip circumferences, resting pulse rate and resting blood pressure, and collected blood specimens to measure serum adipokine levels. An interviewer-administered questionnaire (as previously described [19]) was also completed during this visit. All measures collected during Visit 2 (baseline) were also collected post-intervention.

Randomization and intervention content

Following the collection of baseline measures, participants were stratified by BMI and randomized to one of two intervention arms: (1) Interactive Voice Response (IVR) + coach condition or (2) IVR + no-coach condition, which have been previously described in detail [19]. All participants were instructed on the use of the pedometer and the IVR component of the intervention. The IVR system was developed using SALT (Speech Application Language Tags) and was run on a Microsoft Speech Server.

Biospecimen collection and laboratory analyses

Serum specimens were used to measure changes in biochemical endpoints including adiponectin and leptin concentrations. Serum adiponectin and leptin were determined using the Human Leptin Quantikine and Human Adiponectin/Acrp30 Quantikine ELISA kits (R&D Systems, Minneapolis, MN) according to manufacturer's instructions. Samples were assayed blindly, in duplicate, random order. Each batch included replicates, commercial controls, and blinded serum controls to assess laboratory variation. The coefficients of variation (CVs) for the serum assays were 9.18% and 6.31% for leptin and adiponectin, respectively. Assay sensitivity was <7.8 pg/mL for leptin and 0.08 ng/mL for adiponectin. No samples were below the limits of detection.

Data analyses

Linear mixed models (LMMs) were used to examine changes in adiponectin, leptin and the adiponectin-to-leptin ratio (A/L). LMMs are an established method for performing intent-to-treat analyses in randomized trials; LMMs can accommodate data with incomplete follow-up (*i.e.*, missing post-test data), thereby including all subject randomized in the analysis [20]. The LMMs we used contained fixed effects for time (pre, post) and an unstructured covariance matrix for the residual errors. We did not include treatment condition (coach/no coach) in our models because the coach intervention was not utilized, as previously reported [19]. To be included in the analysis, post-test measures had to be completed within 30 days after the end of the intervention. Adiponectin, leptin and the A/L ratio were natural log-transformed to produce residuals which were approximately normally distributed. The Kenward-Roger method for computing degrees of freedom [21] was used in performing all hypothesis tests. In secondary analyses, we fit LMMs in which participant's weight, BMI, and waist circumference at baseline were interacted with time to determine if these factors affected changes in adiponectin, leptin or the A/L ratio.

Results

Participants

As previously reported [19], of the 259 women screened, 85 were deemed eligible for study participation. Of these, 71 women enrolled in the study and were stratified by BMI (25-30 kg/m^2 and >30 kg/m^2), with 37% and 63% in the lower and higher BMI groups, respectively. Among the 71 women who were randomized, 35 were allocated to the IVR + coach condition and 36 to the IVR + no coach condition. The mean age of participants was 57 years and mean BMI was 31.5 kg/m^2. The majority of participants were white (n=66; 93%), and many were married (n=50; 70%), college educated (n=53; 75%) and reported household incomes greater than $75,000 (n=39; 55%).

Effects of intervention on serum adipokine concentrations

After randomization, nine participants (12.7%) withdrew from the study due to injury or other reasons (unrelated to the intervention) and 23 participants (32.4%) did not complete the post-intervention assessments within 30 days of the end of the intervention period. Withdrawal and retention rates did not differ by intervention arm. Throughout the course of the intervention period, participants completed 66% and 51% of the calls to and from the IVR system, respectively. Completion of these calls did not differ by intervention arm (*P*-values = 0.68 and 0.90, respectively).

Following the intervention, we observed significant decreases in weight (-0.93 kg, standard error (SE) =0.31, BMI (-0.28 kg/m^2, SE=0.11) and waist circumference (-1.33 cm, SE=0.58) overall, with no differences by intervention group [19]. However, these anthropometric improvements did not translate into significant changes in adipokine concentrations. There was a 14% decrease in serum adiponectin (Ratio=0.86, 95% CI 0.74-1.01), 6% decrease in serum leptin (Ratio=0.94, 95% CI 0.87-1.01), and 9% increase in the A/L ratio (Ratio=1.09, 95% CI 0.94-1.26) from baseline to the end of the study (Table 1). We hypothesized that there would be larger mean changes in adipokine concentrations among women who were obese at baseline and had higher weight and/or waist circumference, however we observed no statistically significant adipokine change differences by BMI, body weight or waist circumference (data not shown).

Discussion

There are currently no practical modes of preventing breast cancer or reducing risk among postmenopausal women who may be at increased risk of developing the disease. Attractive strategies include lifestyle modifications, specifically increasing PA. In this study, we hypothesized that a walking intervention could beneficially modify serum adipokine concentrations and thus, could prove to be a useful strategy for preventing obesity-related breast cancer among high-risk, overweight and obese postmenopausal women. Contrary to our hypotheses, our findings demonstrated that while anthropometrics improved following a 12-week walking program utilizing mobile technology and personal coaching, there were non-significant changes in serum adipokine concentrations.

While many studies have shown that serum leptin concentrations decrease following weight loss [14, 22-36], the relationship between serum adiponectin concentrations and weight loss is less clear, although some studies indicate that adiponectin concentrations increase following weight loss [24-26, 29, 36-42]. Similarly, the effect of exercise on serum adipokines is also unclear. Few previous studies have examined these relationships among postmenopausal women [2, 13-16]. Abbenhardt *et al.*'s recent study [13] of a year-long randomized-controlled trial of a combined diet and exercise intervention observed

significant reductions in leptin and increases in adiponectin. Their findings [13] supported a dose-dependent effect of weight loss on adipokine concentrations, and also showed that while diet- or exercise-induced weight loss could beneficially modify adipokine concentrations, the strongest effects were observed for the combination of diet *and* exercise [13]. Another study [2] examining the effects of a year-long aerobic exercise intervention also observed no significant change in adiponectin, and significant improvements in leptin (reduction) and the A/L ratio (increase). Findings from Ryan *et al.* [16] also reported similar findings. Following a 6-month weight loss program involving exercise, no change in plasma adiponectin was observed, while there were significant reductions in leptin [16]. Similarly, Riesco *et al.* [15] found that a 6-month mixed training exercise intervention (with or without the addition of dietary isoflavones) resulted in decreased leptin and no significant change in adiponectin among overweight to morbidly obese women. A 14-week weight loss trial [14], which examined the combined effects of diet and exercise on adipokine concentrations, demonstrated significant reductions in plasma leptin concentrations and a non-significant increase in plasma adiponectin. In our short-term (12-weeks) exercise intervention, we observed statistically non-significant decreases in both adiponectin and leptin, and an increase in the A/L ratio. Of note, the greatest improvements in serum adipokine concentrations tend to be observed in studies where a weight loss of ≥10% is achieved [43].

There are no clear explanations for why serum adiponectin concentrations would decrease following short-term exercise-induced weight loss, however two other studies of postmenopausal women also reported non-significant decreases in adiponectin following lifestyle interventions [15, 16]. It may be that longer duration of exercise is necessary for more substantial weight loss, which could translate into an increase in adiponectin [44]. Additionally, it is possible that interventions combining both diet and exercise, particularly for longer durations and varying intensities, are necessary to more effectively increase adiponectin concentrations [13, 16, 38, 44], as there is evidence that exercise alone is insufficient to induce weight loss that is substantial enough to yield significant increases in serum adiponectin concentrations [43]. Further studies are required to clarify these associations.

This study had both strengths and limitations. First, the randomized nature of the intervention and the use of mobile technology for delivery of some components of the intervention strengthened the study. Interactive health tools have proliferated in recent years, together with a growing trend toward empowering patients to take a more active role in their health [45]. This study is unique because it demonstrates that mobile technology for health interventions can be integrated into translational research studies. Secondly, the examination of intervention effects on biomarkers related to obesity, in addition to effects on weight loss, was also a strength. Additionally, the use of highly reproducible immunoassays to assess our primary outcomes strengthened the study. One major limitation was the small sample of mostly white women, which may have contributed to the lack of significant intervention effects on serum adipokine concentrations despite significant improvements in anthropometric measures. Relatedly, the lack of diversity among study participants may limit the generalizability of our findings. Additional limitations included the fairly high withdrawal rate, lack of completion of post-intervention assessments in a timely manner by many participants, low completion rates of calls to and from the IVR system, and the lack of a non-exercise control arm.

In summary, our data and data from other studies of postmenopausal women may support the concept that long-term (≥12 months) interventions have superior effects on improvements in adipokine concentrations, given that they tend to promote larger losses of body weight. These studies have consistently demonstrated substantial reductions in leptin concentrations as a result of diet- and/or exercise-induced weight loss. Although findings for

adiponectin have been somewhat inconsistent, some studies have supported increases in adiponectin concentrations as a result of diet- and/or exercise-induced weight loss. Furthermore, studies support the combination of both improving diet and increasing exercise as a means for maintaining weight loss and improved adipokine profiles. Therefore, it is plausible that lifestyle interventions that promote these modifications in adipokine concentrations would be beneficial and associated with reduced breast cancer risk.

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Table 1

Intent-to-treat analysis of intervention effects on serum adipokine concentrations

Biomarker	*Pre-intervention* Geometric Mean (95% CI)	*Post-intervention* Geometric Mean (95% CI)	*Post-pre change* Ratio (95% CI)	*P*[a]
Adiponectin (μg/mL)	13.72 (11.89-15.82)	12.86 (11.02-15.02)	0.86 (0.74-1.01)	0.07
Leptin (ng/mL)	35.26 (30.46-40.81)	30.47 (25.01-37.12)	0.94 (0.87-1.01)	0.09
A/L ratio	0.39 (0.31-0.49)	0.42 (0.33-0.55)	1.09 (0.94-1.26)	0.27

[a]Serum adiponectin and leptin concentrations were not normally distributed and therefore were natural log transformed for normality; back transformed data (geometric means and 95% CIs) are presented for ease of interpretation.