Research Article

Cancer Prevention Research

Dietary Weight Loss, Exercise, and Oxidative Stress in Postmenopausal Women: A Randomized Controlled Trial

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Abstract

Oxidative stress, a potential mechanism linking obesity and cancer, results from an imbalance between activation/inactivation of reactive oxygen species, byproducts of cellular metabolism. In a randomized controlled trial, we investigated effects of diet and/or exercise on biomarkers of oxidative stress. A total of 439 overweight/obese [body mass index (BMI) > 25 kg/m^2] postmenopausal women, ages 50 of 75 years, were randomized to 12 months of (i) reduced-calorie weight loss diet ("diet"; $n = 118$); (ii) moderate-to-vigorous intensity aerobic exercise ("exercise"; $n = 117$); (iii) combined diet and exercise intervention ("diet + exercise"; $n = 117$); or (iv) control ($n = 87$). Outcomes were circulating markers of oxidative stress, including fluorescent oxidation products (FOP), F_2-isoprostanes, and oxidized low-density lipoprotein (LDL). On average, participants were 57.9 years, with a BMI of 30.9 kg/m^2. F_2-isprostanes were significantly reduced in the diet (−22.7%, $P = 0.0002$) and diet + exercise (−23.5%, $P < 0.0001$) arms versus controls (−2.99%) and nonsignificantly reduced in the exercise arm (−14.5%, $P = 0.01$). Participants randomized to the diet and diet + exercise arms had significant increases in levels of FOP [control −5.81%; diet +14.77% ($P = 0.0001$); diet + exercise +17.45%, ($P = 0.0001$)]. In secondary analyses, increasing weight loss was statistically significantly associated with linear trends of greater reductions in oxidized LDL and in F_2-isoprostanes and increases in FOP. Compared with controls, exercise participants whose maximal oxygen consumption increased had significant decreases in levels of F_2-isoprostanes and in oxidized LDL and increases in FOP. Dietary weight loss, with or without exercise, significantly reduced some markers of oxidative stress in postmenopausal women. *Cancer Prev Res; 9(11); 835–43. ©2016 AACR.*

Introduction

An estimated 25% of cancers are due to obesity and sedentary lifestyles (1). Low-grade chronic inflammation is a hallmark of obesity and has been implicated in the etiology of cancer via a number of processes, possibly mediated by alterations in levels of adipokines, cytokines, and release of reactive oxygen species (ROS) from a number of sources, including infiltrating macrophages (2). ROS, byproducts of cellular metabolism, can act as signaling molecules (3), which at low-to-moderate concentrations are essential in a number of physiologic processes (4, 5). At higher levels, imbalances between ROS production and inactivation lead to oxidative stress. Evidence from animal models and cell lines support the role of oxidative stress and ROS in cancer initiation and promotion (6, 7), via inactivation of tumor suppressors (8), increasing expression of proinflammatory cytokines (9) and inducing signaling pathways (10). Oxidative stress also causes peroxidation of lipids and proteins and is a source of DNA damage (11).

Oxidative stress can be assessed via circulating levels of its byproducts. Levels of lipid peroxidation have been widely used as an indicator of ROS-mediated damage to cell membranes, and oxidized low-density lipoprotein (ox-LDL) is a circulating global marker of oxidative stress. F_2-isoprostanes are a complex family of isomeric F_2-prostaglandin–like compounds derived from free radical–catalyzed nonenzymatic peroxidation of arachidonic acid (12). Finally, fluorescent oxidation products (FOP) result from oxidation of a variety of sources, including DNA proteins and lipids (13,14).

Studies have reported conflicting associations between oxidative stress biomarkers and risk of breast and other cancers in women. In the Long Island Breast Cancer Project case–control study, there was a statistically significant trend in breast cancer risk with increasing quartiles of urinary 15-F(2t)-isoprostanes (15). A nested case–control study from the Shanghai Women's Health Study reported that levels of F_2-isoprostanes were significantly associated with increased risk of breast cancer, but only among women with a body mass index (BMI) $\geq$29 kg/m^2 (16).

For other cancers, a case–control study reported a 2-fold increase in risk of lung cancer for men in the second and third tertiles of urinary 15-F(2t)-isoprostane, but not in women (17). Positive associations were also reported between increasing urinary levels of F_2-isoprostanes and gastric cancer (18), and incident colorectal adenomas in one study (19), but not in another (20). There are limited data on associations between ox-LDL or FOP

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Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

Clinical Trial registration: Clinicaltrials.gov identifier NCT00470119.

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doi: 10.1158/1940-6207.CAPR-16-0163

and cancer risk. Increased levels of ox-LDL are associated with risk of colorectal cancer (21) and FOPs with increased risk for incident colorectal adenomas (19).

Mixed associations with premenopausal breast cancer risk were seen in a nested case–control analysis of the Nurses' Health Study. Three FOPs were measured in a subset of participants from a case–control study of premenopausal breast cancer patients nested in the Nurses' Health study: There was no association with one FOP, and a trend toward an inverse association with breast cancer risk was observed for the other two (22).

Markers of oxidative stress are higher in obese individuals, and are associated with presence of the metabolic syndrome, and diabetes (23–25), both associated with cancer risk (26, 27). Two cross-sectional studies reported correlations between BMI, waist circumference, and increased serum F_2-isoprostane levels (3, 28, 29). There are few data on the role of weight loss or physical activity on markers of oxidative stress, and studies tend to be small and of short duration (30–33). Although we and others have found that exercise can lower markers of oxidative stress (34–36), to our knowledge, no previous studies have assessed the effect of amount of weight loss on oxidative stress measures.

The purpose of this study was to examine, in a randomized controlled clinical trial (RCT), effects of 12-month dietary weight loss and moderate-to-vigorous exercise programs, alone and in combination, on circulating markers of oxidative stress (ox-LDL, plasma F_2-isoprostane, and FOP) in 439 overweight/obese postmenopausal women. Secondary aims were to assess dose–response effects of weight loss and exercise, the latter measured by change in cardiorespiratory fitness (VO_2max).

Materials and Methods

This study is ancillary to the NEW study, a 12-month RCT testing the effects of caloric restriction and/or exercise versus control on circulating sex steroid hormones and other biomarkers in healthy overweight/obese postmenopausal women. The study was performed with the approval of the FHCRC Institutional Review Board according to an assurance filed with and approved by the U.S. Department of Health and Human Services. Written informed consent was obtained from each participant.

Study population

The study is described in detail elsewhere (37). Briefly, 439 postmenopausal, overweight/obese (BMI $\geq$ 25 kg/m^2), sedentary women, ages 50 to 75 years, not taking hormonal therapy, were enrolled between 2005 and 2008 and randomly assigned to a reduced-calorie dietary modification intervention (n = 118), moderate-to-vigorous intensity aerobic exercise intervention (n = 117), combined diet and exercise intervention (n = 117), or control (n = 87). Exclusion criteria were $\geq$100 minutes per week of moderate physical activity, diabetes/other serious medical condition(s), >2 alcoholic drinks per day, current smoker, participation in another structured weight loss program, and contraindications, such as, abnormal exercise tolerance test, or inability to attend sessions. Permuted block randomization was used to achieve a proportionally smaller control group, stratified according to BMI ($\geq$/<30 kg/m^2) and race/ethnicity.

Interventions

The dietary intervention was a modification of the Diabetes Prevention Program and LookAHEAD lifestyle behavior change programs with goals of 1,200 to 2,000 kcal/day, <30% daily calories from fat, 10% weight loss by 6 months, and weight maintenance thereafter. Participants had at least two individual meetings with a dietician, followed by weekly group meetings for 6 months; thereafter, they attended monthly, with biweekly phone/e-mail contact. Intervention adherence was defined by the percentage of in-person nutrition session attendance, by tertiles.

Exercise intervention goals were 45 minutes of moderate-to-vigorous [$\geq$4 metabolic equivalents (MET)] intensity exercise at a target heart rate of 70% to 85% observed maximum 5 days per week by week 7. Participants attended three facility-based supervised sessions per week and exercised 2 days per week at home. They recorded exercise mode, duration, peak heartrate and perceived exertion at each session. Activities of $\geq$4 METs (38) counted toward the prescribed target.

Controls were asked not to change their diet or exercise habits and were offered four weight loss classes and 8 weeks of exercise training at study completion.

Covariates

All study measures were obtained and analyzed by trained personnel blinded to participants' randomization status at baseline and 12 months at study completion. Height, weight, and BMI were measured as described previously (37). Body composition was measured by DXA (dual-energy X-ray absorptiometry) whole-body scanner (GE Lunar). Cardiorespiratory fitness (VO_2max; mL/kg/minute) was assessed using a maximal graded treadmill test according to a modified branching protocol. Questionnaire data included demographics, medical history, dietary intake, supplement use, and physical activity patterns. Medication use known to affect inflammatory markers, including systemic corticosteroids, ACE (angiotensin-converting enzyme) inhibitors, statins, or nonsteroidal anti-inflammatories (39), was coded as use/nonuse at baseline and 12 months.

Blood specimen collection and processing

Participants refrained from alcohol (48 hours), vigorous exercise, or NSAID use (24 hours) prior to fasting venous blood collection (50 mL) at baseline and 12 months. Blood was processed within one hour and stored at −70°C.

Assays

Oxidative stress assays were performed at the Advanced Research and Diagnostic Laboratory, University of Minnesota (Minneapolis, MN). FOPs were measured using a spectrofluorometer at an excitation/emission wavelength of 360/380 nm from plasma extracted by ethanol–ether and fluorescence measured as relative fluorescent intensity units/mL (FI/mL) of plasma (40). Ox-LDL was measured from serum samples by ELISA (Mercodia). Plasma F_2-isoprostanes were prepurified using thin-layer chromatography. Samples were excluded if the purification step failed and assessed using QC standards; in total, 33 samples were excluded (Fig. 1). F_2-isoprostane levels were assayed by GC/MS using an Agilent 6890 Series GC and an Agilent 5973N Mass Selective Detector as described previously, with modifications (41, 42).

QA samples were included in each assay to assess coefficients of variation (CV). Participant's baseline and 12-month samples were included in the same batch; paired samples were randomly placed across batches. Inter- and intra-assay CVs for the analytes were

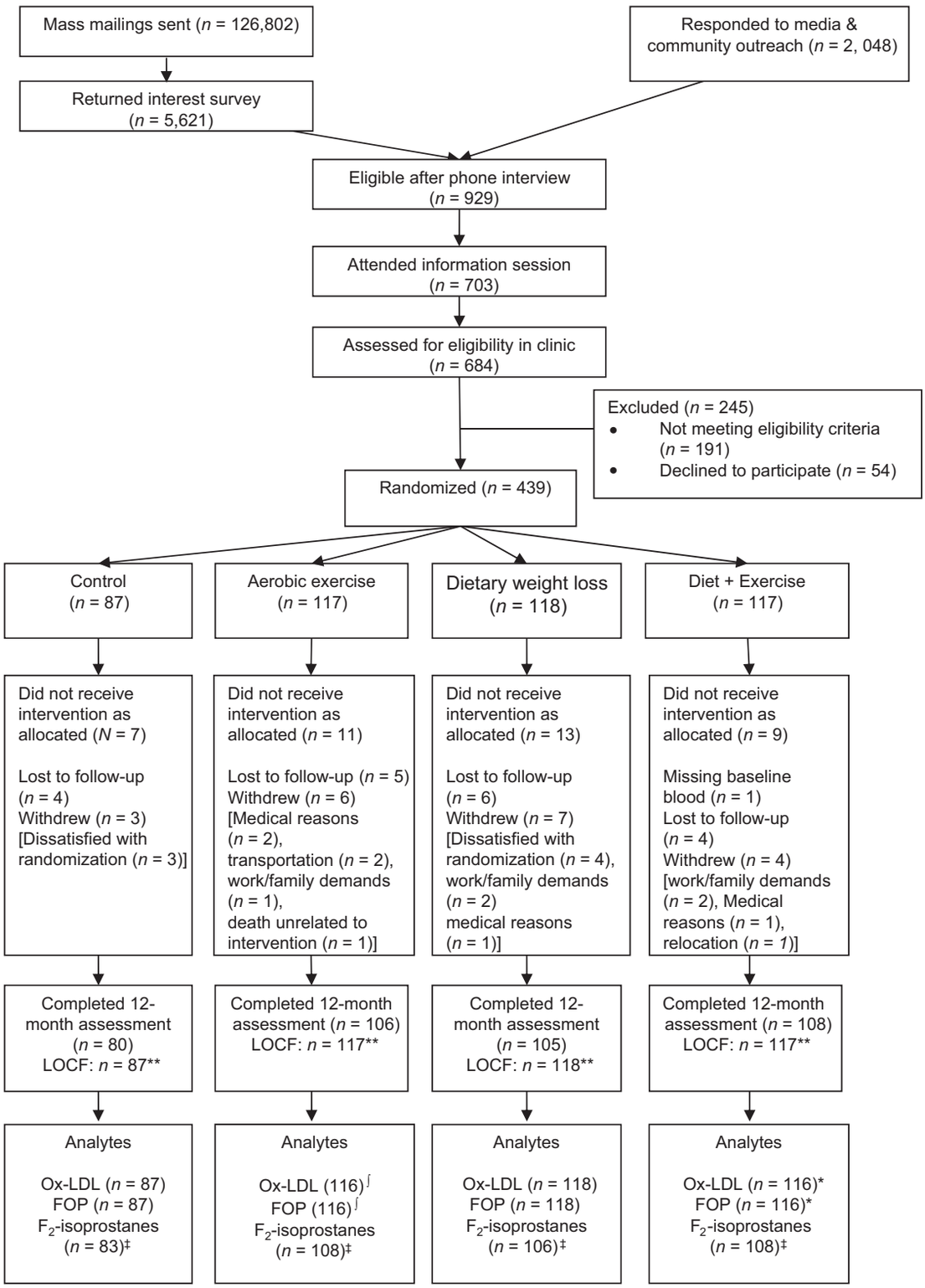

Figure 1.

CONSORT diagram of the Nutrition and Exercise for Women trial. *, missing baseline blood sample ($n = 1$); ∫, missing 12-month blood sample; ‡, Omitted 33 analytes from the F_2-isoprostanes assay, as they failed assay quality control ($n = 4$, control arm; $n = 9$ exercise arm; $n = 12$ diet arm; $n = 8$ diet + exercise arm); **, LOCF: Missing data at 12 months were imputed using the method last observation carried forward.

6.62% and 4.42% (FOP), 27.3% and 22.76% (ox-LDL), and 31.1% and 29.4% (F_2-isoprostane).

Statistical analyses

Logarithmic transformations were applied to outcome variables to improve normality of the distribution. Descriptive data are presented as geometric means (95% confidence intervals). Mean changes in analytes from baseline to 12 months, stratified by arm, were computed. Intervention effects on variables were examined on the basis of assigned treatment at randomization, regardless of adherence or study retention (i.e., intent-to-treat). Mean 12-month changes in intervention arms were compared with controls using the generalized estimating equations modification of linear regression to account for intraindividual correlation over time. Intervention effects are presented as both absolute and relative change. Bonferroni correction was adjusted for multiple comparisons (two-sided $\alpha = 0.05/6 = 0.008$ for 6 comparisons) for the primary analysis. Analyses were adjusted for baseline age, race/ethnicity, BMI, and NSAID/statin use. We used the method of last observation carried forward (LOCF) to deal with missing data at 12 months. In preplanned analyses, we examined changes in analytes in each intervention arm in subgroups of participants by (i) weight loss (no change/gained weight; lost >0%–<5% of baseline weight; lost >5% of baseline weight); (ii) change in VO_2max stratified by tertiles. Analyses stratified by changes in body fat stratified by tertiles, and dietary adherence assessed by percentage of support groups attended (tertiles) were also performed (Supplementary Tables S1 and S2). Participants with missing 12-month weight, VO_2max, or body-fat data were classified as "no change" (LOCF). For these subgroup analyses, $P < 0.05$ was considered significant.

Results

Baseline characteristics of participants are presented in Table 1. On average, participants were 57.9 years, with a BMI of 30.9 kg/m^2, and were predominantly non-Hispanic White (84.9%). At 12 months, 399 women (91%) returned for clinical measures and blood draws (Fig. 1). One participant randomized to the diet + exercise arm was missing a baseline blood sample (Fig. 1); and three 12-month samples were missing from the exercise ($n = 2$) and diet arms ($n = 1$). As described above, a total of 33 samples were excluded from the F_2-isoprostane assay for failing QC inclusion criteria.

Weight, body composition, and other inflammation-related biomarker changes were previously reported. Participants in the diet arm lost a mean of −8.5% of their baseline weight ($P < 0.0001$), those in the exercise arm, −2.4% ($P = 0.03$), and those in the diet + exercise arm, −10.8% ($P < 0.0001$), all compared with −0.8% decrease among controls (37). Adherence to the diet and aerobic exercise interventions was excellent. Estimated relative fat intake (% total kcal/day) decreased by 18% and 20% in the diet and diet + exercise arm respectively; women in both arms attended an average of 86% of behavior change sessions. By 12 months, women randomized to exercise and diet + exercise arms achieved an average of 80% and 85%, respectively, of the target 225 minutes per week aerobic exercise and significantly increased average pedometer steps per day (exercise, 42% increase; diet + exercise, 58% increase) and VO_2max (exercise 9% increase; diet + exercise, 7% increase), compared with baseline.

In fully adjusted models, participants randomized to the diet + exercise intervention nonsignificantly reduced levels of ox-LDL (−7.49%; $P = 0.03$) compared with controls (+2.25%) at 12 months (Table 2). Participants randomized to the diet and the diet + exercise arms had significant increases in levels of FOP [control, −5.81%; diet, +14.77% ($P = 0.0001$); diet + exercise, +17.45% ($P = 0.0001$)]. F_2-Isprostanes were significantly reduced in the diet (−22.7%, $P = 0.0002$) and diet + exercise (−23.5%, $P < 0.0001$) arms compared with controls (−2.99%). Exercise reduced levels of F_2-Isprostanes, but this was not significant after Bonferroni correction (−14.5%, $P = 0.01$).

Participants randomized to the diet + exercise arm who lost ≥5% of their baseline body weight had significantly greater reductions in levels of ox-LDL (−8.7%, $P = 0.02$) compared with controls (+2%); there was a statistically significant overall trend of decreasing levels of ox-LDL with increasing weight loss ($P_{trend} = 0.02$; Table 3). In all three intervention arms, there was a statistically significant linear association between increasing levels of weight loss and reductions in F_2-isoprostanes [$P_{trend} < 0.0001$ (diet); $P_{trend} = 0.0002$ (exercise); $P_{trend} < 0.0001$ (diet + exercise)]. In contrast, there was a significant trend between increasing levels of weight loss and increases in FOP compared with controls in the diet + exercise arm ($P_{trend} < 0.0001$) and in the diet arm ($P_{trend} < 0.0001$), but not in the exercise arm ($P_{trend} = 0.93$). Among participants who were randomized to exercise intervention arms (exercise and diet + exercise), those who increased their VO_2max had significant decreases in levels of F_2-isoprostanes compared with controls (Table 4) in both exercise ($P_{trend} = 0.003$) and diet + exercise ($P_{trend} = 0.0006$) arms. Participants randomized to the diet + exercise arm had statistically significant increases in FOP levels with increasing VO_2max ($P_{trend} = 0.0002$), but not for those participants randomized to the exercise arm. Participants who increased their VO_2max by 3.5% to 14.3% above baseline in the diet + exercise arm had a marginally significant decrease in ox-LDL compared with controls (−11.0% vs. +2.0%, respectively, $P = 0.05$). We compared changes in tertiles of percent body fat change versus controls across the three intervention arms (Supplementary Table S1). Increasing levels of fat loss were statistically significantly associated with decreasing levels of ox-LDL in the diet + exercise arms only ($P_{trend} = 0.006$). There were no consistent associations for changes in ox-LDL by fat loss in the diet or exercise arms. FOPs were significantly increased in the diet and diet + exercise arms with increasing levels of fat loss [$P_{trend} < 0.0001$ (diet) and $P_{trend} = 0.0001$ (diet + exercise)] compared with controls, but not in the exercise arm. F_2-isoprostanes levels significantly decreased with increasing fat loss in each of the three arms compared with controls: [$P_{trend} < 0.0001$ (diet); $P_{trend} = 0.002$ (exercise); $P_{trend} < 0.0001$ (diet + exercise)]. Finally, in participants receiving the dietary intervention, increased adherence as measured by attendance at the support groups, stratified by tertiles, was associated with significant reductions in ox-LDL (diet + exercise $P_{trend} = 0.03$), increases in FOP in both diet and diet + exercise arms $P_{trend} = 0.0001$ and $P_{trend} = 0.0007$, respectively), and reductions in F_2-isprostanes ($P_{trend} = 0.0003$, $P_{trend} < 0.0001$, respectively; Supplementary Table S2). Repeating the analyses using only available data (i.e., missing data were not imputed) did not meaningfully affect any of the fndings. Exclusion of outliers (values >99th percentile) had no effect on results for any analyte (data not shown).

Table 1. Baseline characteristics of randomized participants

	Control ($n = 87$) Mean (SD)	Diet ($n = 118$) Mean (SD)	Exercise ($n = 117$) Mean (SD)	Diet + Exercise ($n = 117$) Mean (SD)	All participants ($n = 438$)[a]
Age (years)	57.4 (4.4)	58.1 (6.0)	58.1 (5.0)	58.0 (4.5)	57.9 (5.0)
BMI (kg/m^2)	30.7 (3.9)	31.1 (3.9)	30.7 (3.7)	31.0 (4.3)	30.9 (4.0)
Waist circumference (cm)	94.83 (10.2)	94.61 (10.2)	95.05 (10.1)	93.71 (9.9)	94.5 (10.1)
VO_2max (kg/mL/min)	23.1 (4.1)	22.7 (3.8)	22.5 (4.1)	23.6 (4.1)	22.9 (4.03
Usual physical activity (min/wk)	23.8 (41.2)	33.6 (45.5)	37.7 (43.7)	32.4 (42.9)	32.4 (43.6)
Total calories (kcal/d)	1988 (669)	1884 (661)	1986 (589)	1894 (638)	1935 (637.9)
	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Race/ethnicity					
Non-Hispanic White	74 (85.1)	101 (85.6)	98 (83.8)	100 (85.4)	372 (84.9)
African American	6 (6.9)	9 (7.6)	15 (12.8)	5 (4.3)	35 (8.0)
Hispanic/Latino	3 (3.4)	2 (1.7)	2 (1.7)	5 (4.3)	12 (2.7)
Other	4 (4.6)	6 (5.1)	2 (1.7)	7 (6.0)	19 (4.3)
Education					
College graduate and above	59 (67.8)	76 (64.4)	70 (59.8)	81 (69.8)	286 (65.3)
Medication use					
Statins	19 (21.8)	10 (8.5)	19 (16.2)	25 (21.6)	73 (16.7)
NSAID	26 (29.9)	51 (43.2)	36 (30.8)	44 (37.9)	157 (35.8)
Smoker (ever)	32 (36.8)	55 (46.6)	47 (40.2)	47 (40.5)	181 (41.3)
Analytes	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Ox-LDL (U/L)	104.9 (40.45) *n*=87	112.4 (36.40) *n*=118	111.3 (46.20) *n*=116	105.9 (32.89) *n*=116	108.9 (39.20) *n*=437
FOP (FI milliunits/mL)	64.03 (175.9) *n*=87	45.71 (99.28) *n*=118	81.35 (217.6) *n*=116	47.41 (73.53) *n*=116	59.27 (151.3) *n*=437
F_2-isprostane (pg/mL)	62.93 (31.09) *n*=83	64.91 (32.77) *n*=106	67.79 (32.32) *n*=108	61.47 (28.75) *n*=108	64.36 (31.26) *n*=405

[a]Differences in the final number of analytes are due to the following:
Omitted 33 analytes from the F2-isoprostanes assay, as they failed assay quality control ($n = 4$ control arm; $n = 9$ exercise arm; $n = 12$ diet arm; $n = 8$ diet + exercise arm); one participant randomized to the diet + exercise arm was missing a baseline blood sample ($n = 1$); two participants randomized to the diet arm and to the exercise arm were missing a 12-month serum sample ($n = 2$). Finally, one participant randomized to the exercise arm was missing a 12-month plasma sample ($n = 1$).

Discussion

Women randomized to a 12-month dietary weight loss program, with or without exercise, significantly reduced levels of F_2-isoprostanes and ox-LDL compared with controls. In contrast, FOPs increased in women randomized to either diet or diet + exercise arms. Further analyses showed that higher levels of weight loss were associated with greater reductions in F_2-isoprostanes and ox-LDL and to greater increases in FOP. Levels of F_2-isoprostanes were significantly reduced in participants who increased their VO_2max in the exercise and diet + exercise arms, suggesting that exercise may have effects on F_2-isoprostanes independent of adiposity changes.

A variety of uncontrolled small studies reported significantly reduced levels of oxidative stress after bariatric surgery–induced weight loss (30, 43) or moderate-intensity exercise interventions in women (31, 32, 44). A 12-week dietary intervention among

Table 2. Change in levels of circulating levels of oxidative stress biomarkers, by intervention arm, using LOCF

		Time points				Change		P[a]	
		Baseline		12 Month		Absolute	Relative change		
Biomarker	**Study arm**	***n***	**GM (95% CI)**	***n***	**GM (95% CI)**	**change[b] (%)**	**12MΔ (I-C)[c]**	**Unadjusted**	**Adjusted[d]**
Oxidized LDL (U/L)	Control	87	97.22 (89.33–105.8)	87	99.41 (91.97–107.4)	2.19 (2.25)	—	—	—
	Diet	118	106.5 (100.3–113.1)	118	100.2 (94.11–106.7)	−6.32 (−5.93)	−8.51	0.08	0.09
	Exercise	116	102.6 (95.32–110.5)	116	101.3 (94.63–108.4)	−1.33 (−1.29)	−3.52	0.47	0.60
	Diet+Ex	116	100.9 (95.22–106.8)	116	93.31 (87.88–99.08)	−7.56 (−7.49)	−9.75	0.03	0.03
FOP[e] (FI milliunits/mL)	Control	87	39.7 (35.1–44.9)	87	37.4 (35.0–39.9)	−2.31 (−5.81)	—	—	—
	Diet	118	36.2 (33.6–39.1)	118	41.6 (38.6–44.9)	5.35 (14.77)	0.01	0.0002	0.0001
	Exercise	116	44.3 (38.8–50.6)	116	42.2 (37.1–48.0)	−2.1 (−4.70)	0.00	0.86	0.85
	Diet + Ex	116	39.3 (36.3–42.6)	116	46.2 (42.0–50.8)	6.9 (17.45)	0.01	0.0001	0.0001
F2-Isoprostane (pg/mL)	Control	83	56.23 (50.71–62.36)	83	54.55 (49.15–60.54)	−1.68 (−2.99)	—	—	—
	Diet	106	57.41 (52.06–63.31)	106	44.37 (39.26–50.14)	−13.0 (−22.7)	−11.4	0.0004	0.0002
	Exercise	108	60.49 (55.07–66.45)	108	51.71 (46.56–57.4)	−8.78 (−14.5)	−7.10	0.03	0.01
	Diet + Ex	108	54.10 (48.67–60.13)	108	41.38 (37.31–45.89)	−12.7 (−23.5)	−11.0	<0.0000	<0.0000

Abbreviations: CI, confidence interval; GM, geometric mean.
[a]P for comparing the 12-month changes versus control group. $P < 0.008$ is considered significant due to multiple comparisons (Bonferroni correction).
[b]Change at 12-month from baseline.
[c]Relative difference of absolute change at 12 months from baseline between intervention and control arms.
[d]GEE model adjusted for age, baseline BMI (<30 kg/m^2, ≥30 kg/m^2) and race/ethnicity, and NSAID and statin use.
[e]Absolute and relative changes appear as zero due to rounding.

Table 3. Change in levels of analytes stratified by percent weight loss compared with controls, by randomization arm, where missing data on weight were imputed using LOCF

Analyte and weight change categories[a]	Diet						Exercise						Diet + Exercise					
	Baseline		12 months		Abs. change		Baseline		12 months		Abs. change		Baseline		12 months		Abs. change	
	n	GM (95% CI)	*n*	GM (95% CI)	(%)[b]	*P*[c]	*n*	GM (95% CI)	*n*	GM (95% CI)	(%)[b]	*P*[c]	*n*	GM (95% CI)	*n*	GM (95% CI)	(%)[b]	*P*[c]
Oxidized LDL (U/L)																		
Control	87	97.22 (89.33–105.8)	87	99.41 (91.97–107.4)	2.19 (2.3)	—	87	97.22 (89.33–105.8)	87	99.41 (91.97–107.4)	2.19 (2.3)	—	87	97.22 (89.33–105.8)	87	99.41 (91.97–107.4)	2.19 (2.3)	—
No change/gained weight	23	112.0 (98.38–127.6)	23	107.6 (94.24–122.9)	−4.41 (−3.9)	0.26	41	106.4 (96.28–117.6)	41	109.1 (98.19–121.2)	2.67 (2.5)	0.78	12	106.2 (89.22–126.3)	12	108.8 (88.56–133.8)	2.70 (2.5)	0.93
Lost <5%	19	103.3 (88.90–120.0)	19	97.35 (80.90–117.1)	−5.93 (−5.7)	0.28	46	104.7 (91.52–119.7)	46	99.22 (88.98–110.6)	−5.43 (−5.2)	0.43	14	116.5 (98.72–137.5)	14	107.4 (89.56–128.7)	−9.16 (−7.9)	0.21
Lost ≥5%	76	105.7 (97.93–114.1)	76	98.77 (91.52–106.6)	−6.95 (−6.6)	0.08	29	94.51 (81.43–109.7)	29	94.26 (81.38–109.2)	−0.25 (−0.3)	0.92	90	97.96 (91.80–104.5)	90	89.44 (83.83–95.43)	−8.52 (−8.7)	0.02
P_{trend}[d]				0.06						0.62						0.02		
FOP (FI milliunits/mL)																		
Control	87	39.7 (35.1–44.9)	87	37.4 (35.0–39.9)	−2.3 (−5.8)	—	87	39.7 (35.1–44.9)	87	37.4 (35.0–39.9)	−2.3 (−5.8)	—	87	39.7 (35.1–44.9)	87	37.4 (35.1–39.9)	−2.3 (−5.8)	—
No change/gained weight	23	41.5 (30.2–57.1)	23	42.7 (31.3–58.4)	1.2 (2.9)	0.15	41	46.3 (35.1–61.1)	41	43.9 (33.1–58.4)	−2.3 (−5.1)	0.90	12	37.6 (33.0–42.8)	12	38.6 (33.2–44.9)	1.0 (2.7)	0.12
Lost <5%	19	35.3 (31.5–39.5)	19	36.8 (32.8–41.2)	1.5 (4.2)	0.05	46	43.2 (35.6–52.3)	46	40.8 (33.7–49.5)	−2.3 (−5.4)	0.98	14	32.7 (28.1–38.1)	14	38.0 (35.2–41.1)	5.3 (16.3)	0.003
Lost ≥5%	76	35.0 (32.8–37.4)	76	42.6 (39.9–45.4)	7.5 (21.5)	<0.0001	29	43.4 (35.5–53.0)	29	42.0 (37.0–47.7)	−1.3 (−3.1)	0.88	90	40.7 (36.9–44.9)	90	48.7 (43.3–54.8)	8.0 (19.7)	0.0001
P_{trend}[d]				<0.0001						0.93						<0.0001		
F2-Isoprostanes (pg/mL)																		
Control	83	56.23 (50.71–62.36)	83	54.55 (49.15–60.54)	−1.68 (−3.0)	—	83	56.23 (50.71–62.36)	83	54.55 (49.15–60.54)	−1.68 (−3.0)	—	83	56.23 (50.71–62.36)	83	54.55 (49.15–60.54)	−1.68 (−3.0)	—
No change/gained weight	19	66.94 (55.02–81.45)	19	57.39 (36.49–90.26)	−9.55 (−14.3)	0.54	39	62.35 (54.88–70.85)	39	59.28 (52.16–67.36)	−3.08 (−4.9)	0.60	9	62.87 (45.25–87.35)	9	68.38 (47.21–99.04)	5.508 (8.8)	0.06
Lost <5%	16	56.17 (43.95–71.80)	16	47.43 (38.00–59.19)	−8.75 (−15.6)	0.15	42	60.80 (51.51–71.77)	42	50.80 (42.06–61.35)	−10.0 (−16.5)	0.05	13	59.90 (47.15–76.10)	13	56.69 (40.90–78.57)	−3.22 (−5.4)	0.72
Lost ≥5%	71	55.36 (48.89–62.69)	71	40.80 (36.00–46.23)	−14.6 (−26.3)	<0.0001	27	57.44 (46.73–70.61)	27	43.64 (34.80–54.72)	−13.8 (−24.0)	0.0002	86	52.44 (46.37–59.32)	86	37.44 (33.72–41.57)	−15.0 (−28.6)	<0.0001
P_{trend}[d]				<0.0001						0.0002						<0.0001		

Abbreviations: CI, confidence interval; GM, geometric mean.

[a]Change at 12 months from baseline.

[b]Analyses stratified by weight loss percentage and using all available data (participants randomized to intervention arms with missing 12-month weight were classified as having no change/gained).

[c]*P* value obtained from GEE model comparing the difference in change of the biomarkers from baseline to 12-month in intervention group versus control within strata of percent weight loss, adjusted for age, baseline BMI (<30 kg/m^2, ≥30 kg/m^2), race/ethnicity (White, Black, and others), NSAID use, and statins use.

[d]*P* value obtained from GEE model testing the linear trend in the change of the biomarkers from baseline to 12-month from control through all levels of percent weight loss, adjusted for age, baseline BMI (<30 kg/m^2, ≥30 kg/m^2), race/ethnicity (White, Black, and others), NSAID use, and statins use.

Table 4. Change in levels of analytes by tertiles of percent change in VO_2max levels (mL/kg/min), compared with controls

Analyte and change in VO_{2max}, stratified by tertiles	Exercise only						Diet + Exercise					
	Baseline		12 months		Abs. change		Baseline		12 months		Abs. change	
	n	GM (95% CI)	*n*	GM (95% CI)	(%)[a]	*P*[b]	*n*	GM (95% CI)	*n*	GM (95% CI)	(%)[a]	*P*[b]
Oxidized LDL (U/L)												
Control	87	97.22 (89.33–105.8)	87	99.41 (91.97–107.4)	2.19 (2.3)	—	87	97.22 (89.33–105.8)	87	99.41 (91.97–107.4)	2.19 (2.3)	—
Increased <3.5%	47	107.1 (95.28–120.4)	47	110.2 (99.89–121.6)	3.10 (2.9)	0.49	53	98.91 (91.64–106.8)	53	93.92 (86.31–102.2)	−5.00 (−5.1)	0.12
Increased ≥3.5%–14.3%	36	99.33 (87.75–112.4)	36	92.14 (80.41–105.6)	−7.19 (−7.2)	0.19	32	111.0 (100.0–123.1)	32	98.77 (88.97–109.7)	−12.2 (−11.0)	0.05
Increased ≥14.3%	33	100.0 (86.28–116.0)	33	99.59 (88.45–112.1)	−0.43 (−0.4)	0.84	31	94.52 (82.98–107.7)	31	87.03 (76.16–99.44)	−7.50 (−7.9)	0.11
P_{trend}[c]				0.49						0.04		
FOP (FI milliunits/mL)												
Control	87	39.7 (35.1–44.9)	87	37.4 (35.0–39.9)	−2.3 (−5.8)	—	87	37.7 (35.10–44.9)	87	37.4 (35.0–39.9)	−2.3 (−5.8)	—
Increased <3.5%	47	40.2 (33.8.0–47.8)	47	36.0 (32.6–39.8)	−4.2 (−10.5)	0.57	53	40.8 (35.2–47.3)	53	48.3 (40.1–58.1)	7.4 (18.2)	0.002
Increased ≥3.5%–14.3%	36	51.1 (37.2–70.4)	36	54.9 (37.8–79.7)	3.7 (7.3)	0.22	32	40.9 (36.5–45.8)	32	48.2 (42.1-55.2)	7.3 (17.9)	0.0004
Increased ≥14.3%	33	43.5 (35.9–52.6)	33	39.8 (35.9–44.0)	−3.7 (−8.5)	0.69	31	35.4 (31.6–39.7)	31	41.0 (38.0–44.2)	5.6 (15.7)	0.001
P_{trend}[c]				0.84						0.0002		
F_2-Isoprostanes (pg/mL)												
Control	83	56.23 (50.71–62.36)	83	54.55 (49.15–60.54)	−1.68 (−3.0)	—	83	56.23 (50.71–62.36)	83	54.55 (49.15–60.54)	−1.68 (−3.0)	—
Increased <3.5%	45	67.56 (59.35–76.90)	45	62.27 (55.17–70.27)	−5.29 (−7.8)	0.13	49	53.12 (44.22–63.81)	49	40.22 (34.14–47.38)	−12.9 (−24.3)	0.002
Increased ≥3.5%–14.3%	34	57.09 (48.18–67.64)	34	51.29 (43.81–60.05)	−5.80 (−10.2)	0.30	28	55.27 (46.38–65.87)	28	44.76 (36.01–55.64)	−10.5 (−19.0)	0.03
Increased ≥14.3%	29	54.54 (44.64–66.65)	29	39.13 (30.10–50.85)	−15.4 (−28.3)	0.001	31	54.62 (46.10–64.72)	31	40.32 (34.36–47.31)	−14.3 (−26.2)	0.002
P_{trend}[c]				0.003						0.0006		

[a]change at 12 months from baseline.

[b]*P* value obtained from GEE model comparing the difference in change of the biomarkers from baseline to 12 months in intervention group versus control within tertiles of percent change in VO_2max.

[c]*P*-value obtained from GEE model testing the linear trend in the change of the biomarkers from baseline to 12 months from control through all tertiles of percent change in VO_2max. All models adjusted for age, baseline BMI (<30 kg/m^2, ≥30 kg/m^2), race/ethnicity (White, Black, and others), NSAID use, and statins use.

20 women found that F_2-isoprostane decreased by 32% among women who lost ≥5kg of bodyweight (45). However, another 12-week weight loss intervention produced no change in F_2-isoprostanes versus controls in 42 individuals with metabolic syndrome (46). Fifty-six overweight healthy individuals randomized to a dietary weight loss intervention with an average 10.4% weight loss in the intervention arm, significantly reduced ox-LDL versus controls (47). Significant reductions in ox-LDL were observed in overweight women with abnormal metabolic profiles who underwent a 12-week dietary intervention; there were no reductions among women who were overweight but metabolically healthy (48).

In 318 sedentary premenopausal women randomized to 4 months of 150 minutes per week of aerobic exercise versus control, F_2-isoprostanes were significantly reduced only in women who were in the highest quartile of plasma F_2-isoprostanes at baseline (36). We previously reported significant reductions in F_2-isoprostane levels, which decreased linearly with gain in VO_2 max relative to controls among 173 overweight postmenopausal women in a year-long exercise RCT (34). However, exercise had no effect on levels in 55 individuals with diabetes, randomized to a low-fat diet, exercise, (30 minutes/day, 50%–65% VO_2max, 3 days/week), a combination, or to a control arm for 8 weeks (49).

F_2-isopostanes are formed by free radical–induced peroxidation of arachidonic acid in both skeletal muscle and plasma. These data support reductions of levels of this marker of oxidative stress via weight loss. In addition, of the analytes measured, only F_2 -isoprostane levels were significantly altered in participants randomized to the exercise intervention or in participants who increased their VO_2max. Exercise is known to promote ROS production in contracting muscle, and there has been concern about the effects of this oxidative stress both at a cellular and tissue level (50). However, our data demonstrate that moderate-to-vigorous physical activity, associated with increases in VO_2max, significantly decreased circulating levels of markers of oxidative stress, compared with controls.

The increase in levels of FOP in the diet and diet + exercise arm is surprising. In a case–control study of individuals with colon rectal adenomatous polyps, CRP and F_2-isoprostanes were inversely associated with an oxidative balance score calculated by combining pro- and antioxidant factors, but there was an unexpected positive association with FOP (19).

Strengths of our study include (i) the RCT design allowing us to test the independent and combined effects of dietary weight loss and exercise on markers of oxidative stress; (ii) use of a number of measures associated with oxidative stress, which measure lipid peroxidation (ox-LDL), F_2-isoprostanes, and oxidation from several sources (FOP); (iii) the long-term intervention with excellent study retention and intervention adherence; and (iv) a large sample size that provided excellent power and the ability to examine dose response of change in outcomes with change in weight and VO_2max.

Limitations include (i) the relatively homogenous study population, which may limit generalizability; and (ii) a selection of global markers of oxidative stress, which limits our ability to determine the exact components of the oxidative stress "profile" affected by the intervention..

In conclusion, a dietary weight loss intervention significantly reduced F_2-isoprostanes and ox-LDL, and increased FOP, while an exercise intervention significantly reduced F_2-isoprostanes. These results suggest further mechanisms through which obesity and sedentary lifestyles could increase risk of several cancers and support testing weight loss and exercise interventions as cancer prevention methods.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: C. Duggan, C.-Y. Wang, A. McTiernan
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C. Duggan, K.L. Campbell, K. Foster-Schubert, M.D. Gross, A. McTiernan
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C. Duggan, J. de Dieu Tapsoba, C.-Y. Wang, K.L. Campbell, M.D. Gross
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Grant Support

This work was supported by grants from the NCI at the NIH (R01 CA105204-01A1 and U54-CA116847 AMcT; to C. Duggan, C.-Y Wang, K.L. Campbell, and K. Foster-Schubert; R01 CA161131-01A1; to A. McTiernan, C. Duggan, C.-Y. Wang, and M.D. Gross) and grants from the Breast Cancer Research Foundation (to A. McTiernan, C. Duggan, C.-Y. Wang, and J. de Dieu Tapsoba,).

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Received June 16, 2016; accepted August 2, 2016; published online November 1, 2016.

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Cancer Prev Res 2016;9:835-843.