

Long-term Diet and Biomarker Changes after a Short-term Intervention among Hispanic Breast Cancer Survivors: The *iCocinar Para Su Salud!* Randomized Controlled Trial

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Abstract

Background: Among Hispanic breast cancer survivors, we examined the long-term effects of a short-term culturally based dietary intervention on increasing fruits/vegetables (F/V), decreasing fat, and changing biomarkers associated with breast cancer recurrence risk.

Methods: Spanish-speaking women ($n = 70$) with a history of stage 0–III breast cancer who completed treatment were randomized to *iCocinar Para Su Salud!* ($n = 34$), a culturally based 9-session program (24 hours over 12 weeks, including nutrition education, cooking classes, and food-shopping field trips), or a control group ($n = 36$, written dietary recommendations for breast cancer survivors). Diet recalls, fasting blood, and anthropometric measures were collected at baseline, 6, and 12 months. We report changes between groups at 12 months in dietary intake and biomarkers using 2-sample Wilcoxon t tests and generalized estimating equation (GEE) models.

Results: At 12 months, the intervention group compared with the control group reported higher increases in mean daily F/V servings (total: +2.0 vs. –0.4; $P < 0.01$), and nonsignificant decreases in the percentage of calories from fat (–2.2% vs. –1.1%; $P = 0.69$) and weight (–2.6 kg vs. –1.5 kg; $P = 0.56$). Compared with controls, participants in the intervention group had higher increases in plasma lutein (+20.4% vs. –11.5%; $P < 0.01$), and borderline significant increases in global DNA methylation (+0.8% vs. –0.5%; $P = 0.06$).

Conclusions: The short-term *iCocinar Para Su Salud!* program was effective at increasing long-term F/V intake in Hispanic breast cancer survivors and changed biomarkers associated with breast cancer recurrence risk.

Impact: It is possible for short-term behavioral interventions to have long-term effects on behaviors and biomarkers in minority cancer patient populations. Results can inform future study designs. *Cancer Epidemiol Biomarkers Prev*; 25(11); 1491–502. ©2016 AACR.

Introduction

There are approximately 3.1 million breast cancer survivors in the United States today and over 230,000 women were newly diagnosed in 2015 (1). Scientific, clinical, and patient advocacy communities continue to have considerable interest in under-

standing whether postdiagnosis lifestyle behaviors affect breast cancer outcomes (2–5). It has been hypothesized that a diet high in fruits and vegetables and low in energy dense foods, engagement in regular physical activity, and achieving and maintaining a healthy body weight will be associated with better breast cancer outcomes. The proposed mechanism is that these behaviors results in favorable inflammatory, hormonal, metabolic, and DNA methylation changes that result in decreased tumor progression, decreased recurrence risk, and benefit other health outcomes (i.e., cardiovascular disease and diabetes). The American Cancer Society, the American Institute of Cancer Research, and the American College of Sports Medicine have all issued guidelines in support of these behaviors largely based on observational data. Despite these guidelines, few breast cancer survivors meet the recommendations (6). In addition, few programs among cancer survivors have demonstrated health behavior changes and maintenance of these changes, while also showing measurable effects on biomarkers associated with cancer risk and recurrence (7, 8).

To date, the majority of the major behavioral intervention trials among breast cancer patient populations have predominantly

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included non-Hispanic white women (9–13). Hispanic breast cancer survivors are a growing population of cancer survivors with a clear health disparity. Although Hispanic women have a lower incidence of breast cancer compared to non-Hispanic whites, they are more likely to be diagnosed at later stages and are more likely to be diagnosed with larger and hormone receptor–negative tumors, both of which are more difficult to treat (14). Currently available data conflict on whether Hispanic women have worse prognosis after controlling for these factors (15–18). The role of postdiagnosis lifestyle factors in this population has not been evaluated. Hispanics in the United States have higher rates of obesity and sedentary behavior, and are less likely to meet physical activity guidelines (19). In addition, Hispanic subgroups do not have uniform dietary patterns (20). For example, compared with non-Hispanic white populations, Mexican Americans have higher intake of fruits and vegetables, whereas Dominicans have much lower rates.

With the growing number and longevity of cancer survivors, there is a need for effective behavioral interventions that both address the risk of cancer recurrence and secondary cancers, as well as the risk of other chronic disease. Studies on maintaining behavioral change over time among noncancer populations, mostly focused on weight loss, show that improvements are seldom maintained long term (21–24). Among the several diet and physical activity interventions conducted among cancer survivors (7), few resulted in maintenance of long-term behavioral change (25–28).

There are limited data on effective dietary interventions among minority cancer patient populations. To address this gap, *iCocinar Para Su Salud!* (Cook For Your Health!) was designed as a randomized controlled trial to examine the effect of a 9-session, culturally based dietary intervention on change in fruit/vegetable and fat intake among Hispanic breast cancer survivors. Primary objectives of the study were changes at 6 months in daily servings of fruits/vegetables intake, percent energy from fat, and anthropometric measures and have been previously reported (29). Here, we report data on secondary, long-term outcomes, including change at 12 months in daily fruit/vegetable intake, percent energy from fat, anthropometric measures, plasma carotenoids, metabolic biomarkers, inflammatory biomarkers, and DNA methylation.

Materials and Methods

Study description

Details on the study design of *iCocinar Para Su Salud!* (Cook For Your Health!) have been previously published (29, 30). Briefly, investigators from Columbia University partnered with the New York City–based nonprofit organization Cook For Your Life (31) to develop and test the effects of a culturally and theory-based dietary intervention on achieving and maintaining dietary recommendations for cancer survivors among Hispanic breast cancer survivors. Nine classes (four nutrition roundtables, two food-shopping trips, and three cooking lessons) were conducted over 24 hours of class time over a 12-week period. The curriculum was tailored to Hispanic women by developing recipes based on traditional Latin American cuisine and incorporating the neighborhood food environment into behavioral recommendations regarding food shopping, cooking, and eating out. All study staff were bilingual and study materials and assessments were in Spanish.

Study participants

A description of study participants has been previously published (29). Briefly, between April 7, 2011, and March 30, 2012, 70 women were randomized into the intervention ($n = 34$) and control ($n = 36$) arms. Target participants were Spanish-speaking women with a history of stage 0–III breast cancer (≥ 3 months posttreatment, including surgery, radiation or chemotherapy; current hormonal therapy allowed) and no evidence of metastatic disease. Additional eligibility criteria included: age ≥ 21 years; Hispanic descent and fluent in Spanish; no uncontrolled diabetes mellitus, defined as hemoglobin A1C $>7\%$; no uncontrolled comorbidities (e.g., hypertension); currently a nonsmoker (given the low likelihood of current smokers to engage in healthy lifestyle behaviors); average intake of <5 servings of fruits/vegetables per day as assessed by the Block Fruit/Vegetable/Fiber Screener (32); access to functional home or cell phone; and not currently active in a dietary change program. Women were screened and recruited from the Columbia University Medical Center (CUMC) Breast Oncology Clinic. A detailed screening interview was conducted to assess eligibility. The study was approved by institutional review boards of the participating institutions (ClinicalTrials.gov NCT01414062). All participants provided written informed consent.

Randomization and data collection

Once participants completed the screening questionnaire, eligible participants were contacted and scheduled for a baseline clinic visit two weeks before the dietary intervention program start date. Clinic visits took place at the Irving Center for Clinical and Translational Research at CUMC. Clinic visits included the following procedures: assessment of anthropometric measures (standing height, weight, waist, and hip circumference); fasting blood collection for biomarker analysis; and a detailed questionnaire on health behaviors and psychosocial constructs. Baseline dietary intake was assessed using three 24-hour recall assessments (1 in-person and 2 telephone-based recalls) using the multiple pass approach (33) with the Nutrition Data System for Research (NDSR) developed by the University of Minnesota (one in-person during the baseline clinic visit, two by phone).

Upon completion of baseline data collection, participants were randomly assigned to the intervention group: the 9-session *iCocinar Para Su Salud!* program, or a control group, which received standard of care written dietary recommendations for cancer survivors (29). Randomization used a permuted block design and stratified at enrollment based on menopausal status and current use of hormonal therapy. Classes were conducted in small groups of 4 to 12 participants.

Follow-up clinic visits were scheduled at 6 and 12 months after the initial clinic visit and included anthropometric measures, fasting blood draw, interviewer-administered questionnaires, and 24-hour dietary recalls (1 in-person and 2 telephone-based recalls).

Laboratory methods

Serum carotenoids and retinol concentrations. Samples were analyzed in batches using HPLC methods that allow for the simultaneous determination of serum β -carotene, α -carotene, lycopene, β -cryptoxanthin, zeaxanthin, and all-*trans* retinol (34–36). The lower limits of detection for retinol, α -carotene, β -carotene, lycopene, β -cryptoxanthin and zeaxanthin are,

respectively, 0.1, 10, 12, 8, 6, and 2 ng/mL for serum. The detection limits for these nutrients are very low and hence these compounds can be detected and quantified in extracts of human serum. The assay variability for assays performed on the same day is between 3% and 6%; and for assays performed on different days the variability is between 5% to 8% (37).

Metabolic markers. Serum samples were analyzed in batches for metabolic tests, including fasting insulin and fasting glucose. Serum insulin concentration was measured with the use of a Roche Diagnostics Elecsys 2010 automated analyzer and an Elecsys 1010/2010 insulin kit (no. 2017547). Serum glucose was measured on the COBAS INTEGRA 400 plus system (Roche Diagnostics). Insulin resistance was calculated using the homeostasis model assessment (HOMA) index (38).

Markers of inflammation. Serum samples were batch analyzed for markers of inflammation. Interleukins (IL1 α , IL6, IL8, and IL10), granulocyte macrophage colony-stimulating factor (GM-CSF), and TNF α were measured using a Luminex high sensitivity bead-based multiplex assay (EMD Millipore). High sensitivity C-reactive protein (CRPhg) was measured on the COBAS INTEGRA 400 plus system (Roche Diagnostics).

Global DNA methylation. White blood cells (WBC) were batch analyzed at the completion of the study. Genomic DNA was extracted from the total WBC fraction by a standard salting out procedure. Following the manufacturer's protocol, aliquots of DNA (500 ng) were bisulfite-treated with the EZ DNA methylation kit (Zymo Research) and resuspended in 20 μ L of distilled water and stored at -20° C until use. Pyrosequencing for Long Interspersed Nuclear Element 1 (LINE-1) methylation levels was performed using PCR and sequencing primers (39). Pyrosequencing was conducted using a PyroMark Q24 instrument (Qiagen) with subsequent quantitation of methylation levels determined with PyroMark Q24 1.010 software. Three CpG sites were included in the analysis. Each set of amplifications included bisulfite-converted CpGenome universal methylated, unmethylated, and nontemplate controls.

Statistical analyses

Our *a priori* hypothesis to test was whether the *iCocinar Para Su Salud!* program increased daily servings of fruits/vegetables and decreased fat as a percentage of daily calories for the intervention group compared with the control group at 12 months. Comparisons between the absolute and percentage of change in dietary, anthropometric, metabolic and inflammation outcomes from baseline to 12 months between groups were performed using 2-sample Wilcoxon signed-rank tests. Statistical tests used $\alpha = 0.05$ and 2-sided *P* values. Differences in the changes in these outcomes over 12 months were estimated using generalized estimating equation (GEE) models by fitting an interaction term between randomization arm and time, adjusting for menopausal status and use of hormonal therapy. In secondary analyses, we estimated percent changes in anthropometric measures, metabolic markers, inflammatory markers and global DNA methylation associated with every 10% increase in dietary factors using a GEE model, adjusted for the baseline value of the predictor of interest, randomization arm and stratification. All analyses were performed using R (40). The GEE models were fit using the R "gee" package (41).

Results

Subject characteristics

A description of participant characteristics has been previously published (29). Briefly, at baseline, participants reported an intake of less than 4 servings of fruits/vegetables per day. There were no statistically significant differences between the intervention and control groups in demographic and clinical characteristics, including age, acculturation, education, income, use of government sponsored food programs, health literacy, stage of breast cancer diagnosis, time since diagnosis or body mass index (BMI). At baseline, participants were on average age 56.6 years (SD 9.7 years). All women self-identified as Hispanic and self-reported low levels of acculturation. Sixty percent of women reported a high school education or less, 40% reported working full-time or part-time, and 62.9% reported an annual household income of \leq \$15,000. Approximately one quarter of participants had been diagnosed with ductal carcinoma *in situ* and one-third had stage I tumors. Mean time since diagnosis was 3.4 years (range, 0.3 to 15.6 years). Mean BMI of study participants was 30.9 (SD 6.0; data not shown). At month 6, 61 women (87%) were retained ($n = 30$, intervention; $n = 31$, control), and at month 12, 58 women (83%) were retained ($n = 29$, intervention; $n = 29$, control). The main reasons for loss to follow-up included withdrawal from study, leaving the country, and family disapproval.

Change in dietary intake of fruits/vegetables

Change in fruit/vegetable intake at 3 and 6 months has been previously reported (29). At 12 months, participants who received the 9-session *Cocinar Para Su Salud!* intervention compared with participants in the control arm maintained significant increases from baseline in mean daily servings of total fruits/vegetables (+2 vs. -0.4 ; $P < 0.01$); total daily servings of vegetables (+1.6 vs. -0.2 ; $P < 0.01$); targeted fruits/vegetables excluding juices, fried vegetables, potatoes and legumes (+2.3 vs. -0.1 ; $P < 0.01$), and targeted vegetables (+1.6 vs. $+0.1$; $P < 0.01$). Furthermore, at 12 months, participants in the intervention arm compared with the control arm maintained significantly higher intake from baseline of individual fruits/vegetables: citrus fruit (+0.1 vs. -0.2 ; $P = 0.01$); dark-green vegetables (+0.5 vs. -0.1 ; $P < 0.01$); and percentage of change in deep-yellow vegetables (+249.1% vs. -75.1 %; $P = 0.02$; Table 1).

Change in dietary intake of fat

Change in the percentage of kcal from fat, saturated fat, mono-unsaturated fat, polyunsaturated fat and trans fats at 3 and 6 months has been previously reported (29). Although participants in the intervention arm maintained a decrease in the percentage of calories from fat and saturated fat from baseline to 12 months, the difference compared to the controls was no longer statistically significant (Table 2).

Change in anthropometric measures

Change in weight, BMI, waist circumference, hip circumference, and waist-to-hip ratio at 3 and 6 months has been previously reported (29). At 12 months, participants in the intervention arm maintained a numerical, but not statistically significant difference compared to the controls in percent weight change (-3.1 % vs. -1.6 %; $P = 0.50$); BMI change (-2.8 % vs. -1.6 %; $P = 0.59$); and waist circumference ($+0.1$ % vs. $+0.4$ %; $P = 0.89$; Table 3).

Table 1. Change in dietary intake of fruits and vegetables at 12 months

	Group	Baseline (BL)				12 months									
		N	Mean	SD	P	N	Mean	SD	P	Absolute Δ from BL ^c			Percent Δ from BL ^c		
										Mean	SD	P	Mean	SD	P
Total fruit and vegetables ^a															
Daily fruits and vegetables servings															
	Intervention	34	4.8	2.8	0.12	29	6.8	2.2	0.10	2.0	3.5	<0.01	114.7	199.5	<0.01
	Control	36	5.8	2.8		29	5.8	2.3		-0.4	2.5		6.2	63.1	
Fruits					0.43				0.93			0.42			0.15
	Intervention	34	2.2	2.2		29	2.7	1.5		0.4	2.7		218.1	689.2	
	Control	36	2.6	2.0		29	2.8	1.9		-0.2	2.1		17.2	83.0	
Vegetables					0.13				0.01			<0.01			0.14
	Intervention	34	2.5	1.8		29	4.1	1.4		1.6	2.2		496.2	1491.6	
	Control	36	3.2	1.8		29	3.0	1.5		-0.2	2.5		74.8	240.7	
Restricted total ^b															
Daily fruits and vegetables servings					0.37				<0.01			<0.01			0.01
	Intervention	34	3.4	2.2		29	5.8	1.9		2.3	2.9		184.4	312.8	
	Control	36	3.9	2.2		29	3.9	1.8		-0.1	1.9		20.1	77.0	
Fruits					0.31				0.22			0.08			0.18
	Intervention	34	1.4	1.6		29	2.3	1.3		0.7	2.2		598.4	2123.0	
	Control	36	1.8	1.4		29	1.8	1.6		-0.2	1.6		-9.0	59.0	
Vegetables					0.78				<0.01			<0.01			0.40
	Intervention	34	2.0	1.5		29	3.5	1.4		1.6	2.3		543.7	1418.6	
	Control	36	2.1	1.5		29	2.1	0.9		0.1	1.7		264.8	1026.8	
Fruit subcategories															
Citrus juice					0.54				0.39			0.40			0.35
	Intervention	34	0.4	1.2		29	0.3	0.5		-0.1	1.2		101.3	392.7	
	Control	36	0.3	0.6		29	0.4	0.8		0.1	0.6		-40.1	76.1	
Fruit juice excluding citrus					0.49				0.20			0.05			0.24
	Intervention	34	0.2	0.4		29	0.1	0.4		-0.1	0.6		8170.7	17768.8	
	Control	36	0.1	0.4		29	0.3	0.7		0.3	0.7		77.8	307.9	
Citrus fruit					0.02				0.28			0.01			0.62
	Intervention	34	0.0	0.1		29	0.1	0.3		0.1	0.3		-75.6	42.3	
	Control	36	0.2	0.5		29	0.1	0.2		-0.2	0.6		-46.1	134.9	
Fruit, excluding citrus					0.89				0.28			0.31			0.15
	Intervention	34	1.4	1.5		29	2.1	1.3		0.6	2.2		163.9	467.9	
	Control	36	1.4	1.3		29	1.7	1.6		0.1	1.6		11.9	84.2	
Avocado and similar					0.03				0.91			0.13			0.49
	Intervention	34	0.0	0.2		29	0.1	0.2		0.0	0.2		-23.8	68.9	
	Control	36	0.2	0.3		29	0.1	0.1		-0.1	0.3		-72.3	50.3	
Fried fruits					0.26				0.13			0.58			0.22
	Intervention	34	0.2	0.5		29	0.0	0.3		-0.2	0.7		-100.0	0.0	
	Control	36	0.5	1.1		29	0.2	0.5		-0.3	1.2		-80.5	41.2	
Vegetable subcategories															
Dark green					0.31				<0.01			<0.01			0.78
	Intervention	34	0.1	0.2		29	0.6	0.6		0.5	0.6		313.9	360.5	
	Control	36	0.2	0.3		29	0.1	0.2		-0.1	0.4		407.3	1060.0	
Deep yellow					0.37				0.56			0.96			0.02
	Intervention	34	0.1	0.2		29	0.3	0.3		0.1	0.4		249.1	566.9	
	Control	36	0.2	0.4		29	0.3	0.6		0.1	0.6		-75.1	40.8	
Tomato					0.47				0.02			0.15			0.22
	Intervention	34	0.3	0.4		29	0.5	0.4		0.1	0.5		641.0	2444.0	
	Control	36	0.3	0.4		29	0.2	0.3		0.0	0.4		33.7	195.4	
White potatoes					0.05				0.16			0.12			0.74
	Intervention	34	0.3	0.6		29	0.2	0.2		-0.2	0.6		-51.6	75.0	
	Control	36	0.8	1.1		29	0.3	0.4		-0.5	1.1		-62.1	92.9	
Other starchy vegetables					0.27				0.01			0.40			0.33
	Intervention	34	0.2	0.3		29	0.1	0.2		0.0	0.4		485.2	1445.7	
	Control	36	0.3	0.4		29	0.4	0.5		0.1	0.7		1748.4	5788.3	
Legumes (cooked dried beans)					0.60				0.75			0.49			0.39
	Intervention	34	0.5	0.6		29	0.9	0.8		0.4	0.9		17.0	142.8	
	Control	36	0.6	0.8		29	0.9	0.6		0.2	0.9		69.4	204.9	
Other vegetables					0.74				<0.01			0.06			0.35
	Intervention	34	0.9	0.8		29	1.3	0.9		0.5	1.4		274.6	474.9	
	Control	36	0.8	0.7		29	0.6	0.4		-0.1	0.9		164.3	372.6	

^aServing counts for both fruits and vegetables were compiled using the University of Minnesota Nutrition Data System for Research (NDSR) Nutrition Coordinating Center (NCC) food group serving count system.

^bServing counts reported here exclude juices, potatoes, fried vegetables and legumes.

^cMean absolute and percent changes are based on individual-level data.

Table 2. Changes in dietary fat intake at 12 months

	Group	Baseline (BL)				12 months														
		N	Mean	SD	P	Absolute Δ from BL ^a				Percent Δ from BL ^a										
						N	Mean	SD	P	Mean	SD	P	P							
Daily total caloric intake (kcal)					0.76					0.07					0.35				0.28	
	Intervention	34	1577.6	403.4		29	1440.5	440.2												
	Control	36	1608.1	423.6		29	1640.4	390.9												
Fat consumption																				
Total fat, % of daily total calories					0.43					0.89					0.69				0.29	
	Intervention	34	28.5	6.4		29	26.2	8.0												
	Control	36	27.0	8.9		29	25.9	6.9												
Saturated, % of daily total calories					0.29					0.56					0.31				0.10	
	Intervention	34	9.9	3.2		29	8.8	3.4												
	Control	36	8.9	4.0		29	9.3	3.0												
Monounsaturated, % of daily total calories					0.45					0.11					0.50				0.72	
	Intervention	34	10.9	3.4		29	11.4	4.1												
	Control	36	10.2	4.2		29	9.9	3.1												
Polyunsaturated, % of daily total calories					0.68					0.89					0.93				0.87	
	Intervention	34	5.2	1.7		29	4.7	1.4												
	Control	36	5.4	2.1		29	4.8	1.7												
Trans fats, % of daily total calories					0.53					0.67					0.72				0.33	
	Intervention	34	0.8	0.4		29	0.7	0.4												
	Control	36	0.8	0.8		29	0.7	0.5												
Energy density (kcal/grams)					0.65					0.04					0.29				0.24	
	Intervention	34	0.8	0.2		29	0.6	0.2												
	Control	36	0.8	0.2		29	0.7	0.1												

^aMean absolute and percentage of changes are based on individual-level data.

Change in biomarkers: carotenoids and retinol, metabolic markers, markers of inflammation, DNA methylation

Carotenoids and retinol. At 6 months, participants in the intervention arm achieved significant percent change from baseline in plasma lutein (+13.8% vs. -9.7%; $P < 0.01$); and α -carotene (+33.5% vs. +3.1%; $P = 0.04$) compared with controls. At 12 months, participants in the intervention arm maintained a significant trend in differences compared with the controls in plasma lutein (+20.4% vs. -11.5%; $P < 0.01$; Table 4).

Metabolic markers. At 6 months, participants in the intervention had a non-significantly greater increase in fasting glucose, insulin, and HOMA-IR compared to controls. At 12 months, there was no significant difference in metabolic changes (Table 4).

Markers of inflammation. At 6 months, the intervention group had nonsignificant greater decreases in IL1 α , IL6, IL10, TNF α , and

CRPhs compared with the controls. At 12 months, the level of inflammatory markers increased in both groups, but the intervention group had non-significant lower increases in GM-CSF, IL-6, IL-8, and TNF- α compared with controls (Table 4).

DNA methylation. At 6 months, participants in the intervention arm achieved a non-significant increase from baseline in global DNA methylation (+0.9% vs. +0.5%; $P = 0.56$); and maintained a borderline significant increase at 12 months (+0.8% vs. -0.5%; $P = 0.06$) compared with the controls (Table 4).

GEE analyses of group differences in change from baseline to 6 and 12 months

At 6 months, compared with the controls, participants in the intervention arm achieved greater increases in daily servings of fruits/vegetables (+2.4; $P < 0.01$); vegetables (+1.5; $P < 0.01$); targeted fruits/vegetables (+2.3; $P < 0.01$); targeted fruits (+1.1;

Table 3. Changes in anthropometric measures at 12 months

	Group	Baseline				12 months														
		N	Mean	SD	P	Absolute Δ from BL ^a				Percentage Δ from BL ^a										
						N	Mean	SD	P	Mean	SD	P	P							
Weight (kg)					0.55										0.56				0.50	
	Intervention	34	75.7	17.2		29	74.2	17.8												
	Control	36	78.2	16.1		29	78.1	15.9												
BMI (kg/m ²)					0.78										0.52				0.59	
	Intervention	32	30.7	6.5		29	29.9	6.6												
	Control	36	31.1	5.6		29	31.6	5.8												
Waist circumference (cm)					0.31										0.64				0.89	
	Intervention	33	94.3	14.2		23	92.8	12.4												
	Control	35	97.7	13.3		26	100.3	13.0												
Hip circumference (cm)					0.34										0.49				0.55	
	Intervention	33	108.8	14.3		23	108.7	13.8												
	Control	35	112.2	15.1		26	112.7	12.6												
Waist-to-hip ratio					0.27										0.41				0.38	
	Intervention	26	0.9	0.1		33	0.9	0.1												
	Control	25	0.9	0.1		35	0.9	0.1												

^aMean absolute and percentage of changes are based on individual-level data.

Table 4. Changes in biomarkers at 12 months

	Group	Baseline				12 months									
		N	Mean	SD	P	N	Mean	SD	P	Absolute Δ from BL ^a			Percentage Δ from BL ^a		
										Mean	SD	P	Mean	SD	P
Plasma carotenoids															
Total carotenoids ($\mu\text{g/L}$)															
	Intervention	34	642.8	287.8	0.48	22	742.1	222.6	0.96				0.76		
	Control	33	702.5	390.2		25	736.0	522.2		46.4	295.3		15.8	34.0	0.24
Lutein ($\mu\text{g/L}$)															
	Intervention	34	109.5	51.0	0.26	22	132.3	48.9	0.06	21.0	266.6		3.3	37.1	<0.01
	Control	33	125.5	64.0		25	105.3	47.2				<0.01			
Lycopene ($\mu\text{g/L}$)															
	Intervention	34	226.6	98.2	0.96	22	253.6	138.2	0.14	15.2	41.6		20.4	37.8	0.08
	Control	33	225.3	107.6		25	198.3	107.3		-21.3	45.0		-11.5	24.2	
α -Carotene ($\mu\text{g/L}$)															
	Intervention	34	79.8	52.8	0.48	22	102.4	86.9	0.57	17.8	103.2		16.2	42.1	0.08
	Control	33	95.7	117.5		25	125.6	180.6		-20.1	60.9		-5.6	39.1	
β -Carotene ($\mu\text{g/L}$)															
	Intervention	34	117.3	181.3	0.54	22	132.8	92.2	0.32	15.4	62.6		23.7	44.8	0.92
	Control	33	147.5	215.3		25	200.4	318.3		24.9	88.8		21.4	104.3	
β -Cryptoxanthin ($\mu\text{g/L}$)															
	Intervention	34	109.6	28.5	0.87	22	121.0	28.2	0.06	-6.6	179.1		1387.7	6234.1	0.17
	Control	33	147.5	215.3		25	200.4	318.3		40.6	153.6		39.7	144.6	
Retinol ($\mu\text{g/L}$)															
	Intervention	34	108.5	23.9	0.12	22	121.0	28.2	0.10	4.6	22.0		5.7	19.6	0.15
	Control	33	108.5	23.9		25	106.4	22.3		-3.1	15.6		-1.4	14.8	
Metabolic markers															
Glucose (mg/dL)															
	Intervention	34	102.8	23.9	0.33	23	99.1	16.8	0.05	-1.0	12.3		-0.1	10.0	0.26
	Control	33	108.6	24.9		25	117.0	39.9		6.2	25.2		4.9	19.1	
Insulin (mIU/L)															
	Intervention	32	17.0	13.2	0.72	22	15.1	7.9	0.57	-1.5	9.2		10.0	50.1	0.82
	Control	33	18.4	18.5		24	16.5	9.5		0.5	6.8		6.8	40.3	
HOMA-IR															
	Intervention	32	4.8	5.1	0.71	22	3.7	2.0	0.12	-0.6	3.1		12.6	53.7	0.93
	Control	33	5.3	6.9		24	5.0	3.7		0.5	2.6		14.0	50.7	
Markers of inflammation															
GM-CSF (pg/mL)															
	Intervention	34	0.9	2.6	0.38	23	1.0	2.9	0.37	0.5	2.0		14.5	54.3	0.59
	Control	33	0.5	1.1		25	0.5	1.1		0.1	0.7		49.7	311.4	
IL1 α (pg/mL)															
	Intervention	34	0.2	0.4	0.34	23	0.4	1.0	0.28	0.1	1.0		22.5	123.3	0.67
	Control	33	0.2	0.1		25	0.2	0.1		0.0	0.1		10.0	60.7	
IL6 (pg/mL)															
	Intervention	34	10.3	30.1	0.84	23	8.3	18.9	0.54	2.1	10.1		3.8	55.5	0.84
	Control	33	12.0	39.1		25	16.6	64.3		3.8	20.3		7.4	63.8	
IL8 (pg/mL)															
	Intervention	34	8.3	7.6	0.74	23	7.2	5.5	0.84	0.1	3.5		3.9	47.6	0.45
	Control	33	7.8	4.5		25	7.5	3.9		0.5	3.4		15.6	58.0	
IL10 (pg/mL)															
	Intervention	34	16.5	19.2	0.63	23	25.0	61.2	0.64	6.9	42.4		30.9	140.3	0.51
	Control	33	19.2	27.0		25	18.2	30.1		1.3	8.9		9.7	64.2	
TNF α (pg/mL)															
	Intervention	34	12.5	7.7	0.92	23	11.7	7.3	0.92	-0.5	6.1		2.3	63.1	0.90
	Control	33	12.3	5.5		25	11.9	4.5		0.2	2.6		4.2	24.5	
CRPhs (mg/L)															
	Intervention	34	4.4	8.3	0.67	23	4.0	7.6	0.78	0.2	5.0		9.7	76.0	0.62
	Control	33	3.7	3.5		25	3.5	3.0		-0.2	1.6		0.7	42.6	
DNA Methylation															
LINE-1															
	Intervention	32	69.5	2.6	0.59	23	69.9	2.2	0.59	0.8	2.3		1.2	3.5	0.06
	Control	32	69.9	3.2		24	69.5	2.7		-0.5	2.5		-0.7	3.8	

Abbreviations: HOMA-IR, homeostasis model of assessment of insulin resistance; CRPhs, high sensitivity C-reactive protein; LINE-1, long interspersed nucleotide element 1.

^aMean absolute and percentage of changes are based on individual-level data.

$P = 0.01$); and targeted vegetables (+1.2; $P = 0.01$). Participants in the intervention arm had greater increases compared to the controls in intake of the following fruits/vegetables: avocado and

similar (+0.1; $P = 0.03$); dark-green vegetables (+0.6; $P < 0.01$); deep-yellow vegetables (+0.3; $P = 0.01$). In addition, participants in the intervention arm achieved a greater decrease in daily total

caloric intake (-388.4 kcal; $P < 0.01$) and a greater increase in plasma lutein ($+33.9$ $\mu\text{g/L}$; $P < 0.01$) compared with the controls (Table 5).

At 12 months, compared with the controls, participants in the intervention arm maintained greater increases in daily servings of fruits/vegetables ($+2.1$; $P = 0.01$); vegetables ($+1.7$; $P < 0.01$); targeted fruits/vegetables ($+2.5$; $P < 0.01$); and targeted vegetables ($+1.7$; $P < 0.01$), dark-green vegetables ($+0.6$; $P < 0.01$), and lutein ($+69.4$ $\mu\text{g/L}$; $P < 0.01$; Table 5).

Association between changes in diet and changes in anthropometric, metabolic, inflammation, and DNA methylation markers

We conducted hypothesis generating secondary analyses to understand how the changes in dietary components were associated with changes in cancer-related biomarkers. Figure 1 shows a heat map style figure indicating associations between dietary components and changes in anthropometric, metabolic, inflammatory and DNA methylation markers. We found that increases in fruit/vegetable intake was generally associated with beneficial changes in anthropometric, metabolic, inflammation and DNA methylation markers, whereas increases in fat intake were associated with worsening of these biomarkers. In addition, increases in both lutein and retinol were associated with beneficial changes in inflammatory markers. However, the increase in retinol was associated with unfavorable changes in some anthropometric outcomes (weight, BMI and waist circumference; $P < 0.05$, data not shown).

Discussion

The 9-session (24 hours over 12 weeks) *iCocinar Para Su Salud!* culturally based dietary intervention successfully increased the combined intake of fruits/vegetables among urban Hispanic breast cancer survivors, the majority of whom were of low socioeconomic status, and the dietary changes persisted at 12 months. The intervention focused on teaching women how to achieve and maintain the dietary composition guidelines set forth by the AICR and ACS (3, 4). At 12 months, women in the intervention group consumed more daily servings of fruits/vegetables than women in the control group and, more importantly, they consumed more dark-green and deep-yellow vegetables. These self-reported results were confirmed by measured increases in plasma carotenoids, specifically lutein, a marker of green leafy vegetable intake. At 3 months, there was a decrease in the daily percentage of calories from fat in the intervention group compared with the control group, but this difference did not persist at 12 months, partially because the control group also changed their diet.

Among the several diet and physical activity interventions that have been conducted among cancer survivors, few resulted in maintenance of long-term behavioral change (25–28). Two large dietary interventions among breast cancer survivors were effective in long-term maintenance of dietary changes. Participants in the Women's Intervention Nutrition Study (WINS) intervention were successful in maintaining significantly lower intake of dietary fat at 5 years and participants in the Women's Healthy Eating and Living (WHEL) study reported significant increases in fruit and vegetable intake and decreases in dietary fat intake at 6 years (12, 42). However, both interventions were long, intensive, and individualized, and included maintenance follow-up contacts

throughout the duration of the studies, making it difficult to determine if observed dietary changes would be sustainable once behavior changes are no longer reinforced. In contrast, the *iCocinar Para Su Salud!* short-term intervention was successful in promoting long-term increases in fruit and vegetable intake with minimal reinforcement.

The U.S. Hispanic population is heterogeneous and consists of both new immigrants and resident Hispanics. Previous findings have demonstrated that minorities are less likely to adhere to prevention programs or participate in clinical trials compared with non-Hispanic whites (43–46). Important barriers, including language, family support, and work constraints have been identified as potential barriers to adherence in minority populations (47–51). As such, there is a need for culturally based dietary interventions and studies examining behavioral change specifically among minority breast cancer survivors, including Hispanics (52–54). Our study was unique in that it used a hands-on approach to address specific barriers related to Hispanics. All intervention procedures were conducted entirely in Spanish, minimizing potential barriers related to language. In addition, lessons and other program procedures were conducted in small group settings, making it easier for women to be willing to participate and providing women with peer support.

Although our results showed that participants in the intervention arm had trends toward more favorable changes in biomarkers of interest compared with the control group, only the changes in lutein showed a statistically significant difference at 12 months. Obviously, in order for a behavioral intervention to affect cancer recurrence and survival outcomes, it is likely that long-term changes are needed in biomarkers along the carcinogenesis pathways. The fact that we did not observe long-term changes in many of the biomarkers could result from the intervention not being intensive enough. The lack of statistical significance may be also due to limited power to detect a difference, as sample size was determined on the basis of dietary changes not change in biomarkers. Because most biomarkers have a smaller mean:SE ratio compared with fruit/vegetable intake, a larger sample size would likely be needed to detect statistically significant differences in biomarkers.

We did observe a trend toward increased DNA methylation levels in the intervention but not the control arm. A growing body of literature suggests that high fruit/vegetable intake may be associated with high DNA methylation of LINE-1 (55–57). In addition, increased LINE-1 DNA methylation is associated with decreased genomic instability and less frequent nucleic acid sequence changes or chromosomal rearrangements (58, 59), which are important biological mechanisms underlying the cancer development and progression. Our findings support the hypothesis that higher fruit/vegetable intake may increase DNA methylation. However, the magnitude and duration of change in DNA methylation needed to affect cancer endpoints is unknown.

Unexpectedly, our hypothesis-generating analyses show that anthropometric measures were associated with circulating concentrations of retinol, indicating that as the subjects became leaner their circulating levels of retinol decreased. This is an intriguing observation because of the recent identification of retinol-binding protein (RBP4) as an adipokine, as well as RBP4's association with breast cancer (60–62). RBP4 secreted from the liver is the sole transport protein for retinol in the blood, with

Table 5. GEE estimates of the difference in changes from baseline to 6 and 12 months between randomization groups

	6 months		12 months	
	β^c	P^d	β^c	P^d
Total fruit and vegetables ^a				
Daily fruits and vegetables servings	2.40	<0.01	2.09	0.01
Fruits	0.82	0.12	0.28	0.66
Vegetables	1.54	<0.01	1.74	<0.01
Restricted total ^b				
Daily fruits and vegetables servings	2.29	<0.01	2.45	<0.01
Fruits	1.12	0.01	0.69	0.17
Vegetables	1.16	0.01	1.74	<0.01
Fruit subcategories				
Citrus juice	-0.27	0.24	-0.19	0.42
Fruit juice excluding citrus	-0.18	0.18	-0.27	0.12
Citrus fruit	0.14	0.18	0.17	0.11
Fruit, excluding citrus	0.87	0.05	0.48	0.33
Avocado and similar	0.12	0.03	0.04	0.57
Fried fruits	0.17	0.46	0.08	0.73
Vegetable subcategories				
Dark green	0.63	<0.01	0.59	<0.01
Deep yellow	0.34	0.01	0.02	0.89
Tomato	0.04	0.68	0.20	0.09
White potatoes	0.36	0.10	0.28	0.18
Other starchy vegetables	0.12	0.23	-0.12	0.38
Legumes (cooked dried beans)	-0.37	0.19	0.35	0.13
Other vegetables	0.52	0.06	0.58	0.05
Daily total caloric intake (kcal)	-388.41	<0.01	-25.56	0.85
Fat consumption				
Total fat, % of daily total calories	-3.79	0.10	-2.99	0.23
Saturated, % of daily total calories	-1.59	0.12	-1.37	0.18
Monounsaturated, % of daily total calories	-1.15	0.32	-0.26	0.84
Polyunsaturated, % of daily total calories	-1.10	0.09	-0.22	0.71
Trans fats, % of daily total calories	-0.14	0.44	-0.04	0.82
Energy density (kcal/grams)	-0.17	<0.01	-0.05	0.41
Anthropometric measures				
Weight (kg)	-0.99	0.49	-2.64	0.29
BMI (kg/m ²)	-0.82	0.26	-1.08	0.48
Waist circumference (cm)	-2.67	0.10	-0.21	0.88
Hip circumference (cm)	0.86	0.71	1.31	0.40
Waist-to-hip ratio	-0.02	0.30	-0.02	0.28
Plasma retinol and carotenoids				
Retinol ($\mu\text{g/L}$)	-4.33	0.82	8.56	0.76
Lutein ($\mu\text{g/L}$)	33.92	<0.01	69.37	<0.01
Lycopene ($\mu\text{g/L}$)	18.85	0.53	32.81	0.11
α -Carotene ($\mu\text{g/L}$)	10.39	0.69	6.07	0.84
β -Carotene ($\mu\text{g/L}$)	-1.06	0.98	-48.76	0.33
β -Cryptoxanthin ($\mu\text{g/L}$)	4.97	0.34	6.82	0.19
Total carotenoids ($\mu\text{g/L}$)	69.50	0.30	19.11	0.80
Metabolic markers				
Glucose (mg/dL)	-3.22	0.51	-9.12	0.22
Insulin (mIU/L)	3.47	0.43	0.53	0.88
HOMA-IR	0.75	0.63	-0.58	0.68
Markers of inflammation				
GM-CSF (pg/mL)	-0.18	0.62	0.27	0.69
IL1 α (pg/mL)	-0.04	0.49	0.26	0.36
IL6 (pg/mL)	-1.69	0.76	-12.53	0.38
IL8 (pg/mL)	0.46	0.75	0.66	0.66
IL10 (pg/mL)	5.87	0.42	32.82	0.32
TNF α (pg/mL)	-1.12	0.35	-0.18	0.93
CRPhs (mg/L)	-0.10	0.96	-0.29	0.87
DNA Methylation				
LINE-1	0.36	0.55	1.11	0.09

Abbreviations: HOMA-IR, homeostasis model of assessment of insulin resistance; CRPhs, high sensitive C-reactive protein; LINE-1, long interspersed nucleotide element 1.

^aServing counts for both fruits and vegetables were compiled using the University of Minnesota Nutrition Data System for Research (NDSR) Nutrition Coordinating Center (NCC) food group serving count system.

^bServing counts reported here exclude juices, potatoes, fried vegetables, and legumes.

^c β coefficients were group differences in the changes from baseline to 6- or 12-month, adjusted for stratification.

^d95% CIs and *P* values were calculated using the robust SE from a GEE model.

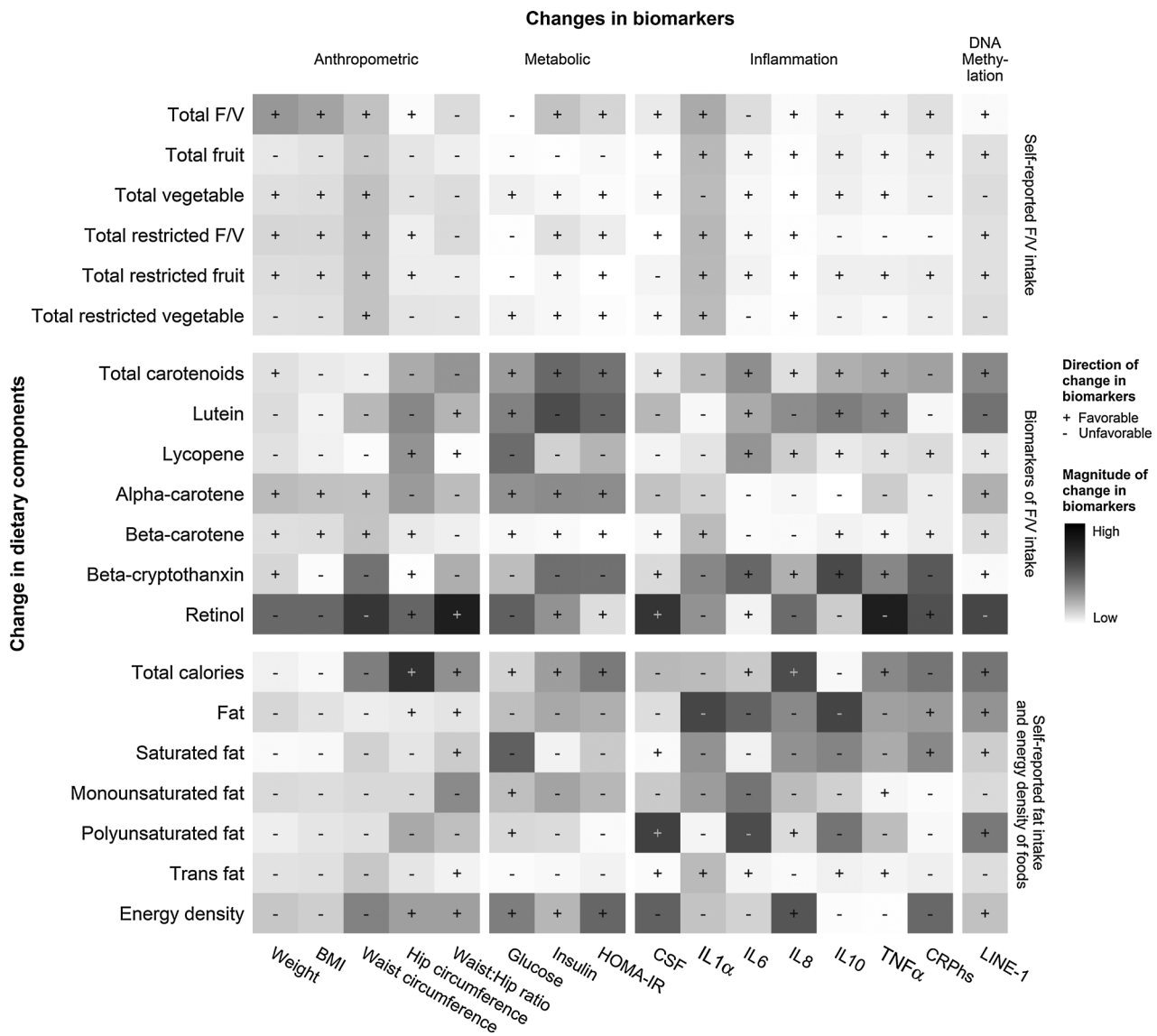


Figure 1. Heatmap of associations between changes in dietary components and changes in anthropometric, metabolic, inflammatory, and DNA methylation markers. Each pixel represents the percentage of change in cancer-related biomarkers on the x-axis associated with every 10% change in dietary factors on the y-axis, adjusted for the baseline value of the dietary factor of interest, randomization arm, and stratification. These estimated changes in cancer-related biomarkers were labeled as "+" if the change is in a favorable direction that reflects improvements in biomarkers, or "-" if otherwise. The darkness of color represents the magnitude of the percentage of changes in cancer-related biomarkers. Our results showed that increases in fruit/vegetable intake were generally beneficial as measured by these cancer-related biomarkers, whereas increases in dietary fat generally led to unfavorable changes.

circulating levels of retinol tightly correlating with circulating RBP4 levels (63, 64). Adipose tissue also synthesizes and secretes RBP4, with Yang and colleagues (60) subsequently proposing that this RBP4 was an adipokine, providing a link between increased adiposity, insulin resistance and type 2 diabetes mellitus (65). Although we did not measure RBP4 directly, we speculate that the association between decreasing levels of circulating retinol and anthropometric indicators of adiposity (i.e., body weight, BMI, and waist circumference) are reflective of decreased circulating RBP4 levels. As reviewed by Frey (66), some follow-up studies have confirmed the link between increased circulating levels of RBP4 and insulin resistance, whereas others have not seen a

significant effect. The majority of these follow-up studies only reported circulating RBP4 levels and did not measure retinol, thus, our data is of particular interest because we show a correlation between circulating retinol levels and indicators of adiposity. Although we did not observe a significant association between retinol and the measured metabolic parameters (glucose, insulin, and HOMA-IR), it is possible that the slight decrease in body weight and associated decrease in circulating retinol levels may be beneficial and reflect an improvement in insulin sensitivity. Further research with a focus on these parameters is required to definitively establish a link between markers of adiposity and insulin resistance, and circulating levels of RBP4 and retinol in this

population. Our data also show that serum retinol levels are significantly associated with waist circumference, but not hip circumference. This observation is consistent with the fact that RBP4 is expressed at a higher level in visceral adipose tissue vs. subcutaneous adipose tissue, and is therefore a marker of intra-abdominal fat mass (67). Similarly, Lee and colleagues (68) demonstrated that serum RBP4 levels are correlated with visceral adiposity but not subcutaneous fat area in women. Thus, the significant association we observed between retinol and waist circumference, but not hip circumference, is consistent with the literature regarding the known expression pattern of RBP4 in these different adipose tissue depots, and the link between visceral adiposity and circulating RBP4.

Although this intervention did not actively examine dietary change in relation to cancer-related outcomes, our results are unique as there are scant data on behavioral change among Hispanic breast cancer survivors. Strengths of this study include its rigorous, randomized controlled design and the use of three, separate 24-hour dietary recalls. One limitation of this study is that the brief Block fruit/vegetable/fiber questionnaire was used to assess fruit/vegetable intake before enrollment and may have resulted in an underrepresentation of intake at screening, as the baseline assessments using the 24-hour recalls reported higher intake. In addition, because this study was conducted specifically among Hispanic cancer survivors in an urban environment it is likely that results are not generalizable to other populations of cancer survivors.

Using a theory-based, culturally tailored curriculum design, the *iCocinar Para Su Salud!* study was successful in improving fruit and vegetable intake, but not total fat intake, among a group of Hispanic breast cancer survivors and maintaining them at 12 months with minimal reinforcement. Such an intervention may be beneficial in other disease types where fruit/vegetable intake is important (i.e., colorectal cancer). However, the intervention had modest but provocative effects on biomarkers of interest. Dietary changes that address well-established risk factors for primary and secondary cancers, such as inadequate nutrition and obesity, are likely to help cancer survivors reduce their risk and improve their overall health. Our research can inform future community-based dietary interventions aiming to promote long-term behavioral change among Hispanics. Future studies can examine how best to promote and implement changes in other behaviors,

including other dietary components, physical activity, and weight management.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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