

Metabolic Syndrome and Mammographic Density in Mexican Women

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Abstract

Metabolic syndrome has been associated with an increased risk of breast cancer; however, little is known about the association between metabolic syndrome and percent mammographic density, a strong predictor of breast cancer. We analyzed cross-sectional data from 789 premenopausal and 322 postmenopausal women in the Mexican Teacher's Cohort (ESMaestras). Metabolic syndrome was defined according to the harmonized definition. We measured percent density on mammograms using a computer-assisted thresholding method. Multivariable linear regression was used to estimate the association between density and metabolic syndrome, as well as its components by state (Jalisco, Veracruz) and menopausal status (premenopausal, postmenopausal). Among premenopausal women in Jalisco, women with metabolic syndrome had higher percent density than those without after adjusting for potential confounders including BMI [difference = 4.76; 95% confidence interval (CI), 1.72–7.81]. Among the metabolic syndrome components, only low high-density lipoprotein levels (<50 mg/dL) were associated with significantly higher percent density among premenopausal women in Jalisco (difference = 4.62; 95% CI, 1.73–7.52). Metabolic syndrome was not associated with percent density among premenopausal women in Veracruz (difference = –2.91; 95% CI, –7.19 to 1.38), nor among postmenopausal women in either state. Metabolic syndrome was associated with higher percent density among premenopausal women in Jalisco, Mexico, but was not associated with percent density among premenopausal women in Veracruz, Mexico, or among postmenopausal women in either Jalisco or Veracruz. These findings provide some support for a possible role of metabolic syndrome in mammographic density among premenopausal women; however, results were inconsistent across states and require further confirmation in larger studies. *Cancer Prev Res*; 6(7); 701–10. ©2013 AACR.

Introduction

Percent mammographic density, the percentage of dense area of the breast on a mammogram, is a strong breast cancer risk factor (1). Fat is radiolucent and appears dark on a mammogram, whereas epithelial and stromal tissue in the breast is radiodense and appears light. Women with more than 75% dense tissue on a mammogram have 4 to 6 times

the risk of developing breast cancer compared with women with little to no dense tissue (1). Researchers have hypothesized that mammographic density reflects cumulative exposure to hormones and growth factors, which also have been associated with metabolic syndrome and its components (2, 3).

Metabolic syndrome is a cluster of interrelated metabolic risk factors including abdominal obesity, high blood pressure, hyperglycemia, and dyslipidemia. While metabolic syndrome is known to predict risk of cardiovascular disease and type 2 diabetes, recent evidence suggests that metabolic syndrome may be involved in breast carcinogenesis. In a recent analysis of 2 case-control studies, postmenopausal women with metabolic syndrome had a 75% higher risk of breast cancer than women without the syndrome (4). A small nested case-control study among postmenopausal women in the ORDET cohort also observed an increased risk of breast cancer among women with metabolic syndrome (5). However, at least 2 studies have not observed an association between metabolic syndrome and breast cancer risk (6, 7) and 1 study on metabolic syndrome and percent

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mammographic density in premenopausal women did not observe an association (8). To date, no studies have examined the association between metabolic syndrome and percent mammographic density among postmenopausal women.

Metabolic syndrome is an increasingly prevalent public health issue in Mexico with more than 40% of Mexican women estimated to have the condition (9). In addition, rates of breast cancer incidence and mortality are rapidly increasing among Mexican women (10). However, little is known about the association between metabolic syndrome and breast cancer risk in this population. Therefore, we examined the association between metabolic syndrome and its individual components with mammographic density among pre- and postmenopausal women in the Mexican Teacher's Cohort study (ESMaestras).

Materials and Methods

Study population

The ESMaestras cohort has been described in detail previously (11). Briefly, ESMaestras was formed when 28,345 female teachers ages 35 years and older in the Mexican states of Jalisco and Veracruz replied to a baseline questionnaire in 2006. In 2007, a subsample of 2,084 ESMaestras teachers participated in a clinical evaluation that included an interview, anthropometry, phlebotomy, and mammography conducted on the same day. For this analysis, 1,488 participants had laboratory, anthropometry, and breast density measurements available. We excluded 230 women with insufficient information on metabolic syndrome components as well as 67 women with unknown menopausal status at the time of their mammogram. We further excluded an additional 80 postmenopausal women who were using postmenopausal hormones (PMH) at the time of their mammogram due to the known impact of hormone use on mammographic density (12). Our final analytic sample was composed of 789 premenopausal and 322 postmenopausal women. Informed consent was obtained from all participants and the study was approved by the human research committee at the National Institute of Public Health in Mexico.

Metabolic syndrome

We used the harmonized definition of metabolic syndrome in our analysis (13). The unified criteria define metabolic syndrome as having 3 or more of the following components: waist circumference ≥ 88 cm, triglyceride levels ≥ 150 mg/dL, high-density lipoprotein (HDL) cholesterol levels < 50 mg/dL, systolic blood pressure (SBP) > 130 mmHg or diastolic blood pressure (DBP) > 85 mmHg, and glucose levels ≥ 100 mg/dL. While the harmonized definition recommends a cutoff value of 80 cm for "ethnic Central and South American" women, there is debate as to whether this is a valid cutoff value for women residing in Mexico (14, 15). Therefore, high

waist circumference was defined as ≥ 88 cm in our primary analysis and was defined as ≥ 80 cm in sensitivity analyses.

Participants underwent anthropometry measurements by previously trained personnel and provided fasting blood samples that were used to determine metabolic syndrome status. Participants were asked to not eat after midnight the night before the clinical evaluation and blood was collected between 8 and 9 AM on the morning of the evaluation. Study personnel conducted weight and height measurements using an electronic digital scale (Tanita Corp.) to the nearest 0.1 kg and a wall stadiometer (Seca Corp.) to the nearest millimeter. Waist circumference was measured in supine position at the umbilicus level using a fiberglass measuring tape (Seca Corp.) registered to the nearest millimeter. Sitting blood pressure measurements were taken twice, 5 minutes apart, using a digital blood pressure monitor (Omron Corp.). We used the average of the 2 measurements when available.

Trained nurses conducted phlebotomy. Samples were centrifuged and aliquoted into cryotubes and kept in liquid nitrogen at -70°C until stored at -70°C in ultrafreezers. Triglyceride, HDL cholesterol, and glucose were measured on fasting plasma blood samples at the Endocrinology and Metabolism Laboratory at the National Institute of Nutrition and Medical Sciences using standard assays. We used the automatized glucose oxidase method to measure glucose. Triglycerides and HDLs were measured using enzymatic hydrolysis in an automatic analyzer with a tungsten lamp (Prestige 24i, Tokyo Boeki Medical System LTD). The interassay coefficients of variation (CV) were 2.3% for glucose, 5.7% for triglycerides, and 5.3% for HDL cholesterol.

Mammographic density

A radiology technician conducted mammography using the Giotto Image M (Internazionale Medico Scientifica) in Jalisco and the Hologic Lorad M-III (Hologic) in Veracruz. Mammograms were developed using the Agfa CP1000 (Agfa-Gevaert Group) developer. Craniocaudal and mediolateral oblique views were taken on each breast. Mammograms from the 2 states were combined, and an Astra 2400S scanner (Umax) was used to digitize the mammograms. A single observer outlined the edge of the breast as well as the dense area of the breast on the craniocaudal view of the left breast using Mamgr, a computer-assisted program based on previously reported mammographic density assessment methods and developed at the Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine (16). This thresholding software measures total area as well as total dense area on a mammogram. We subsequently calculated percent density by dividing the dense area by the total area as well as nondense area by subtracting the dense area from the total area. The Mamgr observer was blinded to metabolic syndrome status. In a reliability study of 100 ESMaestras mammograms, the intraclass correlation coefficient (ICC) between density

measurements evaluated using the Mamgr software versus the Cumulus program developed at the University of Toronto by the same reader was 0.87. In 108 duplicate mammograms, the intra-observer ICC was 0.84.

Covariate data

From the 2006 self-administered questionnaire, we obtained information on age at menarche, parity, age at first birth, family history of breast cancer, personal history of benign breast disease (BBD), hormonal contraceptive use, smoking status, alcohol consumption, and age at menopause (among postmenopausal women). Age was calculated on the basis of the date of the clinical visit, and body mass index (BMI) was calculated on the basis of measured height and weight during the clinical visit or the 2006 questionnaire if clinical data were unavailable. Socioeconomic status (SES) was based on whether the participant had the following items as reported on the 2006 questionnaire: telephone, mobile telephone, car, computer, vacuum cleaner, microwave oven, and internet access (low SES, ≤ 3 items; medium SES, 4–5 items; high SES, 6+ items; ref. 17).

Statistical analysis

Linear regression was used to estimate the relationship between the presence of metabolic syndrome, as well as the individual components of metabolic syndrome, and percent mammographic density. Multivariable models were adjusted for age, age at menarche, parity, age at first birth, family history of breast cancer, personal history of BBD, hormonal contraceptive use, smoking status, alcohol consumption, age at menopause (among postmenopausal women), and SES. In a separate multivariable model, we additionally included BMI. We included indicator variables for missing values when necessary. *A priori*, separate analyses were conducted for pre- and postmenopausal women. In addition, as the average percent density as well as prevalence of metabolic syndrome varied by state, all analyses presented also are stratified by state. In secondary analyses, we modeled dense area and nondense area of the breast as outcomes. In addition, we assessed whether the association between metabolic syndrome and mammographic density in pre- and postmenopausal women varied by state (Veracruz, Jalisco), age (less than or greater than the median), BMI (less than or greater than the median), and parity (nulliparous, parous). We conducted likelihood ratio tests comparing multivariate models with and without multiplicative interaction terms to determine whether the associations varied significantly by these factors. Finally, we conducted a sensitivity analysis excluding women with self-reported diabetes. All analyses were conducted using SAS version 9.2 (SAS Institute).

Results

Forty percent of premenopausal and 51% of postmenopausal women not on PMH in Jalisco were classified as

having metabolic syndrome. In contrast, 21% of premenopausal women and 39% of postmenopausal women not on PMH were classified as having metabolic syndrome among women in Veracruz. On average, women in Jalisco had 5-percentage point higher percent mammographic density than women in Veracruz, after adjusting for age, BMI, and other predictors of mammographic density. In addition, the distribution of lifestyle and reproductive characteristics varied by state. Premenopausal women in Jalisco were slightly older and more likely to be nulliparous than premenopausal women in Veracruz. In addition, postmenopausal women in Jalisco had more children than those in Veracruz. As expected, BMI was significantly higher in women with metabolic syndrome among both premenopausal and postmenopausal women in Jalisco and Veracruz (Table 1). In addition, women with metabolic syndrome tended to be older than women without metabolic syndrome.

Among premenopausal women in Jalisco, there was no difference in percent mammographic density between women who had metabolic syndrome compared with those who did not in the age-adjusted model [difference = 2.06; 95% confidence interval (CI), -0.64 to 4.76]; however, there was an inverse association among premenopausal women in Veracruz (difference = -5.28 ; 95% CI, -9.10 to -1.45 ; Table 2). These estimates did not substantially change in multivariate models excluding BMI (difference in Jalisco = 2.63 ; 95% CI, -0.18 to 5.44 ; difference in Veracruz = -5.84 ; 95% CI, -9.86 to -1.82). When we further adjusted for BMI, metabolic syndrome was significantly associated with an approximate 5-percentage point greater percent mammographic density (difference = 4.76 ; 95% CI, 1.72 – 7.81) among premenopausal women in Jalisco but was not significantly associated among premenopausal women in Veracruz (difference = -2.91 ; 95% CI, -7.19 to 1.38). These estimates were similar when we considered abdominal obesity to be a waist circumference of 80 cm or greater (difference in Jalisco = 4.79 ; 95% CI, 1.89 – 7.68 ; difference in Veracruz = -0.69 ; 95% CI, -4.50 to 3.13). In secondary analyses of absolute measures of mammographic density, metabolic syndrome was significantly associated with higher dense area (difference in cm^2 = 6.28 ; 95% CI, 0.49 – 12.07) in the fully adjusted model among premenopausal women in Jalisco (Supplementary Table S1). There was no significant association between metabolic syndrome and dense area among premenopausal women in Veracruz or nondense area among premenopausal women in either state after adjustment for BMI and other covariates (Supplementary Tables S1 and S2). Of the individual components, low HDL cholesterol was significantly associated with higher percent mammographic density among premenopausal women in Jalisco (difference = 4.62 ; 95% CI, 1.73 – 7.52) after adjustment for covariates including BMI (Table 2). Low HDL cholesterol also was significantly associated with higher dense area (difference in cm^2 = 5.54 ; 95% CI, 0.01 – 11.07) as well as lower nondense area (difference in cm^2 = -6.58 ; 95% CI, -12.03 to -1.12) in fully adjusted models (Supplementary

Table 1. Characteristics of the study population by presence of metabolic syndrome stratified by menopausal status and state (ESMaestras, 2006)

	Premenopausal				Postmenopausal			
	Jalisco		Veracruz		Jalisco		Veracruz	
	No metabolic syndrome (n = 300)	Metabolic syndrome (n = 196)	No metabolic syndrome (n = 232)	Metabolic syndrome (n = 61)	No metabolic syndrome (n = 69)	Metabolic syndrome (n = 73)	No metabolic syndrome (n = 110)	Metabolic syndrome (n = 70)
Mean (IQR)								
Age at mammogram	42.9 (39.9–45.4)	44.9 (41.2–47.8)	42.8 (40.4–45.6)	42.8 (40.5–44.5)	53.1 (50.1–55.2)	54.2 (50.0–57.4)	52.6 (48.9–56.0)	54.4 (51.6–57.1)
BMI at mammogram	26.3 (23.0–28.7)	30.5 (27.4–33.2)	27.5 (24.3–30.4)	32.1 (29.3–35.4)	26.7 (23.7–29.3)	31.1 (27.7–35.1)	28.6 (25.6–31.3)	31.8 (28.1–34.5)
Percent density	39.2 (29.9–49.3)	40.2 (29.0–50.4)	34.2 (24.0–44.5)	29.0 (18.6–37.2)	33.1 (24.6–41.3)	29.9 (20.9–41.4)	27.2 (16.7–35.4)	23.2 (14.5–29.7)
n (%)								
Age at menarche, y								
<12	70 (23.7)	43 (22.1)	56 (24.1)	14 (23.3)	12 (17.7)	23 (31.9)	28 (26.2)	30 (29.0)
12	81 (27.5)	49 (25.3)	65 (28.0)	13 (21.7)	16 (23.5)	15 (20.8)	26 (24.3)	21 (30.4)
13	65 (22.0)	52 (26.8)	51 (22.0)	19 (31.7)	13 (19.1)	12 (16.7)	23 (21.5)	9 (13.0)
14+	79 (26.8)	50 (25.8)	60 (25.9)	14 (23.3)	27 (39.7)	22 (30.6)	30 (28.0)	19 (27.6)
Parity								
Nulliparous	50 (17.4)	22 (11.8)	18 (8.2)	4 (6.8)	9 (13.4)	10 (14.5)	16 (14.8)	6 (8.6)
1	35 (12.2)	13 (7.0)	42 (19.2)	17 (28.8)	8 (12.0)	9 (13.0)	14 (13.0)	11 (15.7)
2	83 (28.8)	54 (29.0)	105 (48.0)	24 (40.7)	12 (17.9)	14 (20.3)	47 (43.5)	23 (32.9)
3	87 (30.2)	64 (34.4)	47 (21.4)	11 (18.6)	24 (35.8)	16 (23.2)	25 (23.2)	22 (31.4)
4+	33 (11.5)	33 (17.7)	7 (3.2)	3 (5.1)	14 (20.9)	20 (29.0)	6 (5.5)	8 (11.4)
Age at first birth (parous)								
<20	21 (9.0)	16 (10.0)	21 (10.5)	4 (7.6)	7 (12.1)	5 (8.8)	10 (11.1)	6 (9.4)
20–24	98 (42.2)	63 (39.4)	81 (40.7)	18 (34.0)	16 (27.6)	22 (38.6)	37 (41.1)	25 (39.0)
25–29	79 (34.1)	68 (42.5)	68 (34.2)	19 (35.8)	26 (44.8)	18 (31.6)	29 (32.2)	22 (34.4)
30+	34 (14.7)	13 (8.1)	29 (14.6)	12 (22.6)	9 (15.5)	12 (21.0)	14 (15.6)	11 (17.2)
Family history of breast cancer	18 (6.0)	9 (4.6)	8 (3.5)	3 (4.9)	8 (11.6)	2 (2.7)	12 (10.9)	3 (4.3)
History of BBD	40 (13.3)	31 (15.8)	36 (15.5)	5 (8.2)	5 (7.3)	6 (8.2)	20 (18.2)	5 (7.1)
Hormonal contraceptives								
Never	145 (50.5)	93 (48.4)	104 (46.6)	32 (54.3)	38 (56.7)	38 (52.8)	50 (48.1)	26 (38.2)
Ever, <5 y	62 (21.6)	56 (29.2)	63 (28.3)	14 (23.7)	16 (23.9)	16 (22.2)	20 (19.2)	21 (30.9)
Ever, 5+ y	68 (23.7)	36 (18.8)	48 (21.5)	11 (18.6)	13 (19.4)	16 (22.2)	28 (26.9)	18 (26.5)
Ever, unknown duration	12 (4.2)	7 (3.6)	8 (3.6)	2 (3.4)	0 (0.0)	2 (2.8)	6 (5.8)	3 (4.4)
Smoking status								
Never	204 (75.3)	117 (67.6)	138 (65.7)	35 (66.0)	47 (74.6)	49 (75.4)	62 (72.1)	40 (69.0)
Past	35 (12.9)	39 (22.6)	41 (19.5)	10 (18.9)	3 (4.8)	4 (6.2)	9 (10.5)	11 (19.0)
Current	32 (11.8)	17 (9.8)	31 (14.8)	8 (15.1)	13 (20.6)	12 (18.4)	15 (17.4)	7 (12.0)

(Continued on the following page)

Table 1. Characteristics of the study population by presence of metabolic syndrome stratified by menopausal status and state (ESMaestras, 2006) (Cont'd)

	Premenopausal						Postmenopausal					
	Jalisco			Veracruz			Jalisco			Veracruz		
	No metabolic syndrome (n = 300)	Metabolic syndrome (n = 196)	No metabolic syndrome (n = 232)	Metabolic syndrome (n = 61)	No metabolic syndrome (n = 69)	Metabolic syndrome (n = 73)	No metabolic syndrome (n = 110)	Metabolic syndrome (n = 70)				
Alcohol, drinks/d												
None	83 (30.1)	46 (25.7)	59 (28.1)	13 (23.2)	21 (32.3)	17 (25.0)	24 (24.2)	16 (25.4)				
<0.1	137 (49.6)	94 (52.5)	107 (51.0)	30 (53.6)	29 (44.6)	36 (52.9)	45 (45.5)	35 (55.6)				
0.1-0.2	40 (14.5)	29 (16.2)	24 (11.4)	12 (21.4)	9 (13.9)	11 (16.2)	19 (19.2)	8 (12.7)				
>0.2	16 (5.8)	10 (5.6)	20 (9.5)	1 (1.8)	6 (9.2)	4 (5.9)	11 (11.1)	4 (6.3)				
SES												
Low	34 (12.4)	27 (15.6)	30 (14.9)	12 (23.5)	13 (20.0)	12 (19.7)	19 (19.6)	12 (19.0)				
Medium	123 (44.7)	76 (43.9)	90 (44.5)	25 (49.0)	23 (35.4)	22 (36.1)	45 (46.4)	31 (49.2)				
High	118 (42.9)	70 (40.5)	82 (40.6)	14 (27.5)	29 (44.6)	27 (44.2)	33 (34.0)	20 (31.8)				
Age at menopause, y												
<40					5 (8.0)	0 (0.0)	6 (5.7)	4 (5.8)				
40-44					12 (19.4)	15 (23.4)	22 (20.7)	14 (20.6)				
45-49					28 (45.2)	27 (42.2)	49 (46.2)	25 (36.8)				
50+					17 (27.4)	22 (34.4)	29 (27.4)	25 (26.8)				

Abbreviation: IQR, interquartile range.

Table 2. Difference in percent mammographic density (95% CI) by metabolic syndrome status and components of metabolic syndrome among premenopausal women stratified by state (ESMaestras, 2006)

	Jalisco (N = 496)				Veracruz (N = 293)			
	n (%) exposed	Age-adjusted ^a	MV-adjusted ^b	MV-adjusted with BMI ^c	n (%) exposed	Age-adjusted ^a	MV-adjusted ^b	MV-adjusted with BMI ^c
Metabolic syndrome								
Harmonized definition (waist ≥ 88 cm)	196 (39.5)	2.06 (-0.64 to 4.76)	2.63 (-0.18 to 5.44)	4.76* (1.72-7.81)	61 (20.8)	-5.28* (-9.1 to -1.45)	-5.84* (-9.86 to -1.82)	-2.91 (-7.19 to 1.38)
Harmonized definition (waist ≥ 80 cm)	235 (47.4)	2.71* (0.07-5.35)	3.20* (0.44-5.96)	4.79* (1.89-7.68)	79 (27.0)	-2.84 (-6.36 to 0.69)	-2.72 (-6.40 to 0.95)	-0.69 (-4.50 to 3.13)
Individual metabolic syndrome components								
Abdominal obesity (waist ≥ 88 cm)	284 (57.3)	-3.94* (-6.54 to -1.34)	-3.77* (-6.46 to -1.08)	-2.89 (-6.36 to 0.57)	146 (49.8)	-4.74* (-7.83 to -1.64)	-5.05* (-8.25 to -1.86)	-1.13 (-5.24 to 2.98)
Abdominal obesity (waist ≥ 80 cm)	422 (85.1)	-4.00* (-7.63 to -0.38)	-3.59 (-7.45 to 0.26)	-2.04 (-6.35 to 2.27)	228 (77.8)	-4.01* (-7.76 to -0.25)	-3.72 (-7.61 to 0.17)	0.20 (-4.28 to 4.68)
High fasting triglycerides (≥ 150 mg/dL)	185 (37.3)	1.25 (-1.44 to 3.93)	1.41 (-1.37 to 4.2)	2.06 (-0.77 to 4.88)	81 (27.7)	-1.03 (-4.55 to 2.49)	-0.52 (-4.16 to 3.12)	1.09 (-2.55 to 4.74)
Low HDL (<50 mg/dL)	328 (66.1)	3.30* (0.57-6.02)	3.56* (0.73-6.39)	4.62* (1.73-7.52)	164 (56.0)	-0.18 (-3.35 to 2.99)	0.46 (-2.88 to 3.80)	1.33 (-1.94 to 4.59)
High blood pressure (SBP ≥ 130 mmHg or DBP ≥ 85 mmHg)	189 (38.1)	1.04 (-1.73 to 3.81)	1.24 (-1.63 to 4.11)	1.60 (-1.28 to 4.47)	60 (20.5)	-2.06 (-5.98 to 1.86)	-2.86 (-6.97 to 1.26)	-2.33 (-6.39 to 1.74)
High fasting glucose (≥ 100 mg/dL)	76 (15.3)	0.34 (-3.31 to 3.99)	0.55 (-3.22 to 4.31)	1.40 (-2.42 to 5.22)	42 (14.3)	-3.43 (-7.9 to 1.03)	-2.97 (-7.72 to 1.79)	-1.12 (-6.82 to 3.58)
High fasting glucose (≥ 110 mg/dL)	36 (7.3)	1.42 (-3.67, 6.5)	1.91 (-3.31 to 7.13)	2.75 (-2.50 to 8.00)	24 (8.2)	-4.00 (-9.71 to 1.71)	-2.49 (-8.44 to 3.45)	-0.02 (-5.90 to 5.86)

^aModel 1: adjusted for age at mammography (continuous).

^bModel 2: Model 1 and family history of breast cancer (yes, no), history of BBD (yes, no), age at menarche (<12, 12, 13, 14+, unknown), hormonal contraceptive use (never, ever < 5, ever 5+), number of full-term pregnancies (nulliparous, 1, 2, 3, 4+), age at first pregnancy (nulliparous, <20, 20-24, 25-29, 30+), alcohol intake (none, <0.1, 0.1-0.2, 0.2+ drinks/d), smoking status (never, ever), and SES (low, medium, high).

^cModel 3: Model 2 and BMI at mammogram (continuous).

*P < 0.05.

Tables S1 and S2). None of the individual components were significantly associated in the fully adjusted model with percent density among premenopausal women in Veracruz (Table 2). While the association between metabolic syndrome and percent density varied significantly by state ($P < 0.01$), there was no significant effect modification by age, BMI, or parity among premenopausal women ($P = 0.39, 0.36, \text{ and } 0.61$ respectively).

Among postmenopausal women, there was no significant association between metabolic syndrome and percent density in age- and multivariable-adjusted models either Jalisco or Veracruz (multivariable adjusted difference = -0.62 ; 95% CI, -6.76 to 5.53 and -1.63 ; 95% CI, -5.97 to 2.71 , respectively; Table 3). None of the individual components were significantly associated with percent density in multivariable-adjusted models including BMI (Table 3). In fully adjusted models, metabolic syndrome was not significantly associated with dense area or nondense area in either state (Supplementary Tables S3 and S4). The association between metabolic syndrome and percent density did not vary significantly by state, age, BMI, or parity ($P = 0.64, 0.97, 0.57$ and 0.98 respectively). In addition, excluding women with self-reported diabetes did not substantially change the results for pre- or postmenopausal women (data not shown).

Discussion

In this population of Mexican women, we observed that premenopausal women in Jalisco who met the criteria for metabolic syndrome had higher percent mammographic density than those without metabolic syndrome. In particular, low HDL cholesterol was associated with higher percent mammographic density and greater dense area among premenopausal women in Jalisco. There was no association between metabolic syndrome or its individual components and mammographic density among premenopausal women in Veracruz or among postmenopausal women in either state.

Our results are somewhat inconsistent with a previous study on metabolic syndrome and mammographic density in pre- and perimenopausal women. In an analysis in SWAN, a multi-ethnic U.S. cohort, there was no association between metabolic syndrome and percent density after adjustment for BMI (8). Also, in SWAN, there was an inverse association between abdominal adiposity and percent density even after adjustment for BMI. While we did observe an inverse association between abdominal adiposity and percent mammographic density among premenopausal women, the association was attenuated after adjustment for BMI.

In general, previous studies have not observed an association between HDL cholesterol levels and percent mammographic density (8, 18–20) or have observed a positive association (21, 22). However, we observed that premenopausal women in Jalisco with low HDL levels had higher percent density than women with moderate or high HDL levels. Similar to our findings, low HDL levels

were associated with 60% higher risk of breast cancer in a nested case-control study in the ORDET cohort (5). In addition, high HDL levels were associated with a decreased risk of breast cancer in a small Danish cohort as well as among postmenopausal women in a Norwegian prospective study (23). However, other studies have not observed statistically significant associations between HDL levels and breast cancer risk (7, 24). Cholesterol has been hypothesized to increase breast cancer risk and therefore may influence mammographic density through its relationship with steroid hormones (2). In a cross-sectional study of 206 premenopausal women in the Norwegian EBBA study, increasing serum HDL levels were associated with lower salivary estradiol levels (22). However, in a different study population, postmenopausal use of oral estrogens increased HDL levels in a double-blind crossover study (25). Interestingly, while HDL levels were inversely associated with estradiol levels in the EBBA study, HDL levels were positively associated with breast density (22). Additional research is necessary to elucidate the relationship between HDL cholesterol, mammographic density, and breast cancer risk.

We observed significant effect modification by state among premenopausal women in our sample, which may be due to differences in the characteristics of women in the 2 states. Compared to premenopausal women in Veracruz, premenopausal women in Jalisco were almost twice as likely to have metabolic syndrome and have an approximately 5-percentage point higher average percent density, after adjusting for predictors of mammographic density. In addition, premenopausal women in Jalisco were slightly older and more likely to be nulliparous. However, we did not observe significant effect modification of the association between metabolic syndrome and percent density by these factors (or by BMI) among premenopausal women. The mammograms were conducted on different machines in the 2 states (Hologic Lorad M-III and Giotto Image M). Therefore, the absolute differences in the distribution of percent density by state may be due to differences in the sample populations or may be a result of varying degrees of measurement error by state. However, the mammography reader was blinded to both geographic state and metabolic syndrome status and any misclassification of density should be nondifferential with respect to metabolic syndrome status within each state. In general, differences in mammogram acquisition techniques have not been shown to confound the association between mammographic density and breast cancer risk (17). Further investigation is necessary to understand why risk factors, such as metabolic syndrome, may have different associations with percent density among premenopausal women in Jalisco compared with premenopausal women in Veracruz.

Our study has several limitations. Although the CVs for triglycerides, HDL, and glucose are low, there is likely some measurement error. This measurement error should be nondifferential as the laboratory was blinded to mammography measurements. Mammographic density

Table 3. Difference in percent mammographic density (95% CI) by metabolic syndrome status and components of metabolic syndrome among postmenopausal women stratified by state (ESMaestras, 2006)

	Jalisco (N = 142)				Veracruz (N = 180)			
	n (%) exposed	Age-adjusted ^a	MV-adjusted ^b	MV-adjusted with BMI ^c	n (%) exposed	Age-adjusted ^a	MV-adjusted ^b	MV-adjusted with BMI ^c
<i>Metabolic syndrome</i>								
Harmonized definition (waist ≥ 88 cm)	73 (51.4)	-2.60 (-7.32 to 2.12)	-2.87 (-8.31 to 2.58)	-0.62 (-6.76 to 5.53)	70 (88.9)	-3.68 (-7.56 to 0.20)	-2.70 (-6.89 to 1.48)	-1.63 (-5.97 to 2.71)
Harmonized definition (waist ≥ 80 cm)	85 (59.9)	1.64 (-3.18 to 6.46)	1.79 (-3.62 to 7.2)	3.98 (-1.71 to 9.68)	80 (44.4)	-4.69* (-8.51 to -0.86)	-3.45 (-7.61 to 0.71)	-2.71 (-6.93 to 1.51)
<i>Individual metabolic syndrome components</i>								
Abdominal obesity (waist ≥ 88 cm)	98 (69.0)	-7.50* (-12.45 to -2.54)	-6.61* (-12.47 to -0.74)	-5.03 (-11.92 to 1.86)	110 (61.1)	-6.33* (-10.09 to -2.58)	-5.55* (-9.67 to -1.44)	-4.69 (-9.70 to 0.33)
Abdominal obesity (waist ≥ 80 cm)	129 (90.9)	-3.14 (-11.29 to 5.01)	-0.76 (-9.91 to 8.39)	2.11 (-7.50 to 11.71)	160 (88.9)	-6.13* (-12.06 to -0.2)	-3.28 (-9.69 to 3.12)	-0.83 (-7.79 to 6.13)
High fasting triglycerides (≥ 150 mg/dL)	77 (54.2)	0.67 (-4.06 to 5.39)	-1.14 (-6.69 to 4.41)	0.64 (-5.10 to 6.38)	61 (63.9)	0.38 (-3.62 to 4.38)	0.63 (-3.73 to 4.99)	0.92 (-3.41 to 5.25)
Low HDL (<50 mg/dL)	93 (65.5)	0.66 (-4.29 to 5.61)	0.87 (-5.01 to 6.75)	2.57 (-3.55 to 8.70)	77 (42.8)	1.57 (-2.23 to 5.38)	3.42 (-0.72 to 7.56)	3.49 (-0.61 to 7.58)
High blood pressure (SBP ≥ 130 mmHg or DBP ≥ 85 mmHg)	73 (51.4)	-0.89 (-5.63 to 3.85)	-0.06 (-5.81 to 5.69)	2.01 (-4.06 to 8.07)	81 (45.0)	-1.02 (-4.96 to 2.92)	-0.03 (-4.34 to 4.28)	0.81 (-3.54 to 5.15)
High fasting glucose (≥ 100 mg/dL)	40 (28.2)	-3.87 (-9.14 to 1.40)	-3.55 (-10.04 to 2.93)	-2.66 (-9.37 to 4.05)	50 (27.8)	-3.72 (-7.92 to 0.47)	-2.11 (-6.69 to 2.47)	-1.53 (-6.11 to 3.05)
High fasting glucose (≥ 110 mg/dL)	24 (16.9)	-3.56 (-9.85 to 2.73)	-3.93 (-11.53 to 3.67)	-2.23 (-10.13 to 5.67)	28 (15.6)	-4.60 (-9.76 to 0.55)	-3.99 (-9.54 to 1.56)	-3.89 (-9.38 to 1.61)

^aModel 1: adjusted for age at mammogram (continuous).^bModel 2: Model 1 and family history of breast cancer (yes, no), history of BBD (yes, no), age at menarche (<12, 12, 13, 14+, unknown), oral contraceptive use (never, ever <5, ever 5+), number of full-term pregnancies (nulliparous, 1, 2, 3, 4+), age at first pregnancy (nulliparous, <20, 20-24, 25-29, 30+), alcohol intake (none, <0.1, 0.1-0.2, 0.2+ drinks/d), smoking status (never, ever), age at menopause (<40, 40-44, 45-49, 50+, unknown), and SES (low, medium, high).^cModel 3: Model 2 and BMI at mammogram (continuous).

*P < 0.05.

measurements are highly reproducible though there may be some random error. Any error should be nondifferential as the mammogram reader was blinded to metabolic syndrome status. The strengths of our study include the centralized measurement of mammograms, phlebotomy, and anthropometric measurements and detailed adjustment for potential confounders.

Conclusion

Metabolic syndrome was associated with 5-percentage point higher percent mammographic density among a sample of premenopausal women in Jalisco, Mexico, but was not associated with percent density among premenopausal women in Veracruz, Mexico, or among postmenopausal women in either state. These findings provide some support for a possible role of metabolic syndrome in mammographic density among premenopausal women; however, results were inconsistent across states and require further confirmation in larger studies.

Disclosure of Potential Conflict of Interest

R.M. Tamimi is a consultant/advisory board member of Pfizer. No potential conflicts of interest were disclosed by the other authors.

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