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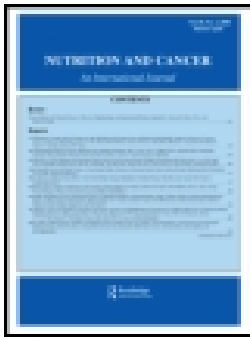
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Metabolic Syndrome and Mammographic Density in Premenopausal Chilean Women

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ABSTRACT

Background: Metabolic syndrome (MetS) has been previously associated with an increased risk of breast cancer in postmenopausal women. Mammographic density (MD) is a marker of breast cancer risk. There is little evidence of an association between MetS and MD in premenopausal women. **Methods:** Through a cross-sectional study, we evaluated 364 premenopausal Chilean women in which we measured anthropometric, blood pressure, and metabolic markers. MetS and its components were defined according to the National Cholesterol Education Program Adult Treatment Plan III criteria. We estimated MD by absolute dense volume (ADV, cm³), nondense volume (NDV, cm³), and percentage of dense volume (PDV, %). The relationship between MetS and MD was assessed by linear regression models. **Results:** After adjusting for sociodemographic and gynecologic-obstetric variables, nonsignificant association was found between MetS and ADV (log $\beta = 0.10$; 95%CI: $-0.01, 0.21$). However, abdominal obesity, high triglycerides, and number of components of MetS were directly related to higher ADV ($P < 0.05$). **Conclusion:** Our results showed no association between MetS and ADV; nevertheless, abdominal obesity and triglycerides were related to higher ADV. If MD could be modifiable through nutritional factors, it would open new perspectives for the prevention of breast cancer through obesity prevention strategies at population level.

ARTICLE HISTORY

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Introduction

Breast density, a measure of the extent of radiodense fibroglandular tissue in the breast, is a marker of breast cancer risk. Several studies have shown that women with higher absolute dense area (ADA) or higher percentage of dense tissue to total breast area (PDA) at the mammography are at a higher risk for developing breast cancer (1). More recently, measures of absolute dense volume (ADV) or relative dense fibroglandular volume (PDV) have been also associated with breast cancer risk (1,2).

The relationship between adiposity and breast density is complex. Body mass index (BMI = weight (Kg)/height (m)²) as a marker of general obesity and waist circumference (WC) as a marker of abdominal fat accumulation were strongly and inversely associated with PDA (3–5) or PDV (6). These relationships likely reflect correlations between body fat and fatty tissue in the breast (nondense tissue) (3,5,7). Studies that have evaluated the relationship between adiposity and absolute dense measures

(area or volume) are controversial with inverse (7–9), null (3), and direct associations reported (10–12).

Few studies have evaluated the relationship between metabolic syndrome (MetS), a cluster of interrelated metabolic risk factors (abdominal obesity, high blood pressure, hyperglycemia, and dyslipidemia), and breast density. In the Study of Women's Health Across the Nation, no association was found between MetS and PDA (13). The study ESMAestras in premenopausal Mexican women showed a positive relationship between ADA and PDA measures with MetS in the state of Jalisco and a negative relationship in the state of Veracruz (12). However, area-based methods for measuring breast density are not sensitive to breast thickness and may underestimate the true amount of dense tissue. Our aim is to assess the relationship between MetS and volumetric measures of breast density (ADV, NDV, and PDV) in premenopausal Chilean women of low and medium socioeconomic level.

Materials and methods

Study population

This is a cross-sectional study of the mothers of the girls participating in the Growth and Obesity Chilean Cohort Study (GOCS); objectives and methods of GOCS have been described elsewhere (14). Briefly, GOCS is a population-based ambispective cohort of 1195 children born in 2002 in six low- and medium-income towns from the South East area of Santiago, Chile (15,16). The study sample is representative of the population that receives health care at the National Health Services System (70% of the entire population) (17,18). In 2011–2012, 409 premenopausal mothers of the GOCS girls (mean age = 37 years, SD = 6 years) were included in a longitudinal study of breast cancer risk factors (determinants of breast cancer risk [DERCAM] cohort). Exclusion criteria were: postmenopausal status (no menstruation in the past year); history of cancer (except nonmelanoma skin cancer); current pregnancy; and current breastfeeding or breastfeeding in the past 9 months.

Data collection

Questionnaire

Women underwent a face-to-face structured questionnaire including sociodemographic (age, years of schooling) and gynecologic-obstetric variables (age of menarche, parity, age at first child, length of breastfeeding, and oral contraceptive ever).

Anthropometric measures

Weight, height, and WC were measured by a trained nutritionist. Weight was measured using a TANITA BC-418, in increments of 0.1 kg. Height was measured in increments of 0.5 cm using the height rod mounted to the scale, with the subject standing and dressed in light clothing without shoes. WC (i.e., minimum circumference between the iliac crest and the rib cage) was measured with a metal inextensible tape to the closest 0.1 cm. BMI was used to classify women in categories according to the World Health Organization (WHO) classification: underweight (BMI < 18.5 kg/m²), normal weight (BMI = 18.5–24.9 kg/m²), overweight (BMI = 25.0–29.9 kg/m²), and obese (BMI ≥ 30.0 kg/m²) (19).

Blood pressure

Blood pressure was measured using a digital monitor (OMRON) by a nutritionist who received special training for standardizing blood pressure measurements. The measurement was carried out after 10 min of chair rest during which women were sitting with their arm lying on a table. The measurement was recorded twice at an

interval of 5 min in order to diminish error. We used the average of the first and the second measurements to determine systolic and diastolic pressure.

Blood sample

A 10-ml fasting venous sample was collected in the first week of the follicular phase of the menstrual cycle. Insulin, glycemia, and lipids were measured. Analyses were conducted at the Institute of Maternal and Child Health Research of the University of Chile. Serum insulin concentrations were measured using a radioimmunoassay kit (Diagnostic Systems Laboratories, Inc., Webster Texas; intra- and interassay coefficients of variation (CV) 5% and 8%, respectively). Serum glucose concentrations were measured using enzymatic colorimetric techniques (HUMAN; Gesellschaft für Biochemica und Diagnostica, Wiesbaden, Germany). Triglycerides were measured using enzymatic colorimetric techniques (HUMAN). High-density lipoproteins (HDL) cholesterol was isolated by precipitation with a sodium phosphotungstate and magnesium chloride solution.

Mammograms

Digital mammograms were obtained using a Hologic Selenia Full-Field Digital Mammography System and conducted at the Clinica Las Condes of Santiago. Because breast density varies during the menstrual cycle, all women underwent the mammography in the follicular phase of the menstrual cycle. Raw images were obtained from the Digital Imaging and Communication in Medicine (DICOM) headers. Volumetric breast density was estimated using a fully automated, reproducible, and objective method (Volpara, Matakina Technology, Wellington, New Zealand, version 1.4.0) (20). ADV (cm³), NDV (cm³), and PDV (%) were estimated using the average of all views (mediolateral oblique, craniocaudal, left and right breast) available for each woman.

From the 409 DERCAM subjects, complete data were obtained for 364 women (total excluded = 45, 1 without complete questionnaire, 10 without blood pressure measurement and blood collection, and 34 without raw mammogram images).

MetS definition

The diagnosis of MetS was based on the criteria of National Cholesterol Education Program Adult Treatment Plan III (NCEP ATP III) (21). The criteria were to have the presence of any three or more of these five risk factors: WC: ≥88 cm (obesity abdominal); high triglycerides: ≥150 mg/dL (or on treatment for raised triglycerides); low HDL: <50 mg/dL (or on treatment for reduced HDL-c); high blood pressure systolic: ≥130

and/or diastolic: ≥ 85 mm Hg (or on treatment for hypertension); and increased fasting glucose ≥ 100 mg/dL (or on treatment for increased blood glucose).

Statistical analyses

Crude and adjusted linear regression models were used to estimate the relationship between the presence of MetS, as well as the individual components of MetS, and ADV, NDV, and PDV (all log transformed). Multivariable models were adjusted for age (years), schooling (≤ 8 years or > 8 years), age at menarche (years), parity (number of children), age at first birth (years), family history of breast cancer (yes/no), personal history of hormonal contraceptive use (yes/no), smoking status (yes/no), and alcohol consumption (yes/no).

Normality assumption was assessed using the residuals. A P -value < 0.05 was considered significant, and all statistical analyses were conducted using the STATA statistical software package version 11.2.

Ethical aspects

This study was approved by the Institutional Review Board at Institute of Nutrition and Food Technology (INTA), University of Chile. Written informed consent was obtained from all subjects.

Results

General characteristics of the study population are shown in Table 1. At the time of the visit, women had a median age of 36 years (IQR 32–42) and 2 children (IQR 2–3), and 88% had more than 8 years of schooling. Two of three women were overweight or obese, and one of four had MetS. Abdominal obesity (62%) and low HDL cholesterol (79%) were the components of MetS with the highest prevalence.

Women with MetS had higher ADV than women without MetS, but this difference did not reach statistical significance ($P > 0.05$). Women with abdominal obesity had higher ADV ($P = 0.001$), higher NDV ($P < 0.001$) and lower PDV ($P < 0.001$) than women without abdominal obesity (Table 2). Regarding NDV and PDV, women with MetS or low HDL cholesterol, abdominal obesity, high triglycerides, high glucose, or high blood pressure had higher NDV and lower PDV than their counterparts ($P < 0.05$).

In the adjusted linear regression models, we found no association between MetS and ADV ($\log\beta = 0.10$; 95% CI: $-0.02, 0.21$), but it was significantly associated with a 29% decrease in PDV ($\log\beta = -0.29$; 95% CI: $-0.40, -0.19$) and 43% increase in higher NDV ($\log\beta = 0.43$;

Table 1. Sample characteristics (n = 364).

	Median (interquartile range) or %
Sociodemographic	
Age (years)	36.0 (32.0–42.0)
≤ 8 years of schooling (%)	12.4
Gyneco-obstetric	
Age at menarche (years)	13.0 (12.0–14.0)
Total breastfeeding (months)	24.0 (12.0–42.0)
Age at first child (years)	20.8 (18.3–23.6)
Parity (number of children)	2.0 (2.0–3.0)
Oral contraceptives ever (%)	78
Morbid and lifestyle history	
Family history of breast cancer (%)	13.2
Diagnosis of type 2 diabetes mellitus (%)	3.3
Diagnosis of hypertension (%)	7.4
Diagnosis of dyslipidemia (%)	4.9
Current smoking (%)	51.4
Current alcohol (%)	37.1
Anthropometric	
Weight (kg)	66.7 (59.9, 76.8)
Height (cm)	156.9 (154, 160.6)
Waist circumference (cm)	92.5 (85.1, 100.7)
BMI (Kg/m ²)	27.2 (24.3, 31.1)
Nutritional status	
Underweight (%)	0.3
Normal (%)	31.3
Overweight (%)	38.2
Obese (%)	33.2
Diagnosis of metabolic syndrome (%)	
Abdominal obesity (waist circumference ≥ 88 cm)	62.0
High blood pressure (SBP ≥ 130 mmHg or DBP ≥ 85 mmHg)	9.9
High fasting glucose (≥ 100 mg/dL)	12.6
High fasting triglycerides (≥ 150 mg/dL)	23.3
Low HDL cholesterol (< 50 mg/dL)	79.9
Metabolic syndrome (number of components)	
0	10.4
1	22.8
2	41.8
3	17.6
4	6.0
5	1.4

95% CI: 0.30, 0.56) (Table 3). The components of MetS, the abdominal obesity ($\log\beta = 0.01$; 95% CI: 0.01; 0.01) and high triglycerides ($\log\beta = 0.0006$; 95% CI: 0.00004; 0.001), were directly associated with greater ADV. All components of MetS were positively associated with a higher NDV and lower PVD ($P < 0.05$) except for high blood pressure. The low HDL cholesterol was associated with a decrease in NDV ($\log\beta = -0.01$; 95% CI: $-0.02, -0.01$) and an increase in PDV ($\log\beta = 0.01$; 95% CI: 0.004, 0.01).

We also found a linear relationship between the number of MetS components present and higher ADV ($\log\beta = 0.06$; 95% CI: 0.01, 0.11) and NDV ($\log\beta = 0.27$, 95% CI: 0.22, 0.32) and lower PDV ($\log\beta = -0.19$; CI: $-0.23, -0.14$) (Table 3).

Discussion

In this population of premenopausal Chilean women, we found that the MetS was positively associated with NDV

Table 2. Difference in mammographic density (95% CI) by metabolic syndrome status and components of metabolic syndrome among premenopausal women (n = 364).

	ADV (cm ³) Median (IQR) ^a	P-value ^b	NDV (cm ³) Median (IQR) ^a	P-value ^b	PDV (%) Median (IQR) ^a	P-value ^b
Total sample: 364	59.7 (46.1–84.0)		629.4 (429.7–876.9)		8.8 (6.3–12.7)	
<i>Metabolic syndrome</i>						
No	58.4 (44.1–82.7)	0.079	562.7 (371.1–778.1)	<0.001	9.8 (7.0–13.8)	<0.001
Yes	67.7 (50.0–88.2)		870.9 (638.9–1170.5)		7.0 (5.3–8.6)	
<i>Metabolic syndrome components</i>						
<i>Abdominal obesity (waist circumference ≥88 cm)</i>						
No	54.6 (41.3–76.8)	0.001	383.5 (279.2–521.2)	<0.001	12.7 (8.9–17.8)	<0.001
Yes	63.6 (48.9–88.4)		775.3 (604.5–1052.4)		7.3 (5.5–10.1)	
<i>High blood pressure (SBP ≥130 mmHg or DBP ≥85 mmHg)</i>						
No	59.1 (45.1–84.5)	0.402	606.2 (404.3–866.7)	0.009	9.2 (6.3–12.8)	0.028
Yes	67.3 (49.6–80.0)		747.5 (604.7–1014.9)		7.2 (6.2–8.7)	
<i>High fasting glucose (≥100 mg/dL)</i>						
No	59.8 (45.0–84.6)	0.919	596.5 (395.9–845.2)	<0.001	9.4 (6.6–12.9)	<0.001
Yes	57.8 (49.5–75.6)		781.0 (638.7–1097.6)		6.7 (5.6–8.2)	
<i>High fasting triglycerides (≥150 mg/dL)</i>						
No	59.1 (44.6–82.1)	0.118	592.1 (383.5–830.9)	<0.001	9.4 (6.4–13.2)	0.006
Yes	63.8 (50.0–86.2)		730.3 (531.4–1077.3)		7.6 (5.6–10.9)	
<i>Low HDL cholesterol (<50 mg/dL)</i>						
No	56.0 (43.8–79.4)	0.251	461.9 (314.1–626.9)	<0.001	11.7 (8.3–16.4)	<0.001
Yes	60.3 (46.6–84.6)		660.8 (470.0–920.2)		8.1 (5.9–11.5)	
<i>Metabolic syndrome (number of components)</i>		0.148		<0.001		<0.001
0	51.7 (41.2–73.5)		327.7 (254.2–419.9)		13.6 (11.2–18.2)	
1	56.1 (41.8–76.8)		465.5 (311.0–626.9)		11.2 (8.5–16.4)	
2	60.5 (46.4–87.9)		689.3 (528.5–936.8)		8.0 (5.8–10.9)	
3	70.0 (49.4–90.3)		865.2 (622.5–1208.5)		6.9 (5.3–9.2)	
4	63.2 (53.1–72.6)		882.2 (689.4–1097.5)		7.1 (5.6–8.0)	
5	53.6 (51.8–77.9)		795.0 (661.8–1030.5)		7.0 (6.3–7.1)	

^aMedian and interquartile range.^bKruskal–Wallis test, $P < 0.05$.

and inversely related to PDV. MetS was not related to ADV, but abdominal obesity and high triglycerides had a positive relationship, yet of low magnitude.

We observe a positive directionality but of low magnitude and nonsignificance between MetS and the ADV. To our knowledge, only the published study ESMaestras of Mexico has evaluated the relationship between MetS and absolute breast density measurements in premenopausal women. They found inconsistent associations by geographic area, with a direct association in one state (Jalisco) and negative in the state of Veracruz. The authors of this study argue that women who lived in Jalisco were slightly older and had a higher percentage of MetS and a greater frequency of nulliparity (12). Sample size used in ESMaestras was higher, what could explain the statistical significance that they observed. The plausible mechanisms of this possible association are that MetS is characterized by a state of insulin resistance/hyperinsulinemia and subacute chronic inflammation; both conditions are risk factors for breast cancer (22). Insulin resistance is frequently observed in obese women or those with MetS. Insulin is known to have mitogenic, antiapoptotic, and angiogenic properties.

Furthermore, it has been observed that insulin stimulates the synthesis of insulin-like growth factor 1 (IGF-1), which has mitogenic properties on human breast stromal cell growth in primary culture (23). A study in premenopausal women showed a positive association between estrogen levels and IGF-I with density absolute, and this is consistent with the hypothesis that these hormones/growth factors may somehow promote growth of the fibroepithelial tissue in the breast (23,24). More studies are needed to clarify this relationship between absolute breast density and MetS.

Of the individual components, women with abdominal obesity had 1% more ADV than women without abdominal obesity ($P < 0.05$). Evidence between abdominal obesity and absolute breast measures in premenopausal women is scarce and inconsistent. The ESMaestras study found direct associations in the state of Jalisco, but without statistical significance after adjusting for BMI (12). Another study on Korean women found an inverse correlation with dense area (25), and a study on Chinese women living in the United States did not find associations (11). The main difference between the other studies is

Table 3. Regression models between breast density measurements and metabolic syndrome (n = 364).

	Log ADV ^a			Log NDV ^b			Log PDV ^c		
	Coef ^d	(95% IC)	P-value	Coef ^d	(95% IC)	P-value	Coef ^d	(95% IC)	P-value
Diagnosis metabolic syndrome	0.10	(−0.02, 0.21)	0.094	0.43	(0.30, 0.56)	<0.001	−0.29	(−0.40, −0.19)	<0.001
<i>Components of metabolic syndrome</i>									
Abdominal obesity (waist circumference ≥88 cm)	0.01	(0.01, 0.01)	<0.001	0.03	(0.03, 0.04)	<0.001	−0.02	(−0.02, −0.02)	<0.001
High fasting glucose (≥100 mg/dL)	0.002	(−0.0002, 0.01)	0.081	0.01	(0.003, 0.01)	<0.001	−0.003	(−0.01, −0.0004)	0.024
High fasting triglycerides (≥150 mg/dL)	0.0006	(0.00004, 0.001)	0.036	0.002	(0.001, 0.002)	<0.001	−0.001	(−0.001, −0.0001)	0.012
Low HDL cholesterol (<50 mg/dL)	0.003	(−0.01, 0.001)	0.227	−0.01	(−0.02, −0.01)	<0.001	0.01	(0.004, 0.01)	<0.001
High blood pressure (SBP ≥130 mmHg or DBP ≥85 mmHg)	0.03	(−0.13, 0.20)	0.678	0.16	(−0.04, 0.35)	0.111	−0.11	(−0.27, 0.05)	0.174
Number of components of metabolic syndrome	0.06	(0.01, 0.11)	0.011	0.27	(0.22, 0.32)	<0.001	−0.19	(−0.23, −0.14)	<0.001

^aLog absolute dense volume; ^blog nondense volume; ^clog percentage dense volume; ^dcoefficient β , Model: Adjusted by age, schooling, family history of breast cancer, menarche, hormonal contraceptive use, number of live-born children, age at first children, alcohol, smoking, breastfeeding.

that they used the area as a measure of absolute breast density. The dimensional methods are not sensitive to breast thickness and may underestimate the true amount of fibroglandular tissue for large-breast women (2).

On the other hand, we found a negative association between MetS and the PDV, which is consistent with other studies (12,13). These findings can be explained by the fact that women with MetS have a higher general and abdominal adiposity, which relate to a larger amount of nondense tissue in the breast, so the breast density ratio (in relative terms) is smaller.

The nondense tissue is not an indicator of density, but rather a measure of adiposity; thus, we find a strong association between MetS and its components and NDV. Breast adipose tissue is not only a fat storage tissue but also an endocrine organ that can secrete estrogens and cytokines and that could promote and enable a carcinogenic environment (26); however, the evidence of this relationship is not conclusive (1,27).

This study found a significant association, though weak, between the increasing numbers of MetS components and ADV, and of greater strength with lower PDV and higher NDV. The ORDET cohort in postmenopausal women found an increased risk of breast cancer for increasing number of components (*P* for trend 0.004) (28). The multiethnic study in premenopausal women found that for increasing number of components, the PD and density area decrease (29).

This study has several strengths. Subjects are representative of women of medium-low socioeconomic status of Chile. A trained and standardized nutritionist performed anthropometric measurements. Metabolic parameters and mammography were measured during the follicular phase of the menstrual cycle, and the samples were processed and analyzed in the same laboratory.

The software used to estimate density, “Volpara,” is a quantitative method and not a dependent operator, which reduces the measurement error.

As weaknesses of this study, we can mention the cross-sectional design; thus we cannot confirm causality. Furthermore, the possibility that the sample size was insufficient to prove the hypothesis is not excluded. If hyperinsulinemia or hyperglycemia is one of the mechanisms postulated in the relationship between MetS and MD, it is possible that this low frequency of hyperglycemia may have affected the power of the sample needed to find significant associations.

Conclusion

There are a few studies that have evaluated the relationship between MetS and its components with breast density measures in premenopausal women. The results of this study do not support the association between MetS and ADV, although it is possible that a larger sample size could prove this relationship. However, abdominal obesity and high triglycerides were very frequent in our sample and were associated with an increase in ADV. If MD could be modifiable through nutritional factors, it could open new perspectives for the prevention of breast cancer through obesity prevention strategies at population level.

Abbreviations

MetS	Metabolic syndrome
ADV	Absolute dense volume
NDV	Nondense volume
PDV	Percentage of dense volume
ADA	Absolute dense area
PDA	Percentage of dense area

Acknowledgments

The authors' responsibilities were as follows: MLG and AM: designed the study; MLG and HM: planned analyses; HM and AM: conducted the analyses; AM and MLG wrote the original draft of the article; and AP, HM, and MLG: helped in editing the drafts.

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