Published in final edited form as:
Cancer Prev Res (Phila). 2013 July ; 6(7): 701–710. doi:10.1158/1940-6207.CAPR-12-0475.

Metabolic syndrome and mammographic density in Mexican women

Megan Rice[1,2], **Carine Biessy**[3], **Martin Lajous**[1,4,5], **Kimberly A. Bertrand**[1,2], **Rulla M. Tamimi**[1,2], **Gabriela Torres-Mejía**[4], **Ruy López-Ridaura**[4], and **Isabelle Romieu**[3,4]

[1]Department of Epidemiology, Harvard School of Public Health, Boston, MA

[2]Channing Division of Network Medicine, Brigham & Women's Hospital, Boston, MA

[3]International Agency for Research on Cancer, Lyon, France

[4]Center for Research on Population Health, National Institute of Public Health, Mexico

[5]Center for Research in Epidemiology and Population Health (CESP), U1018, Villejuif, France

Abstract

Background—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.

Methods—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).

Results—Among premenopausal women in Jalisco, women with metabolic syndrome had higher percent density compared to those without after adjusting for potential confounders including BMI (difference = 4.76, 95%CI: 1.72, 7.81). Among the metabolic syndrome components, only low high-density lipoprotein levels (<50mg/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, 1.38), nor among postmenopausal women in either state.

Conclusion—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.

Corresponding author: Isabelle Romieu, MD, MPH, ScD, Instituto Nacional de Salud Pública, Av. Universidad 655, Col. Santa María Ahuacatitlán, C. P. 62100, Cuernavaca, Morelos, Mexico.

Conflict of Interest: The authors have no competing interests to declare.

Keywords

Metabolic syndrome; mammographic density; epidemiology

Introduction

Percent mammographic density, the percent 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 over 75 percent dense tissue on a mammogram have 4-6 times the risk of developing breast cancer compared to 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 two case-control studies, postmenopausal women with metabolic syndrome had a 75 percent higher risk of breast cancer compared to 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 two studies have not observed an association between metabolic syndrome and breast cancer risk (6, 7) and one study on metabolic syndrome and percent 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 over 40 percent 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).

Methods

Study population

The ESMaestras cohort has been described in detail previously (11). Briefly, ESMaestras was formed when 28,345 female teachers aged 35 years and over 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 at the time of their mammogram due to the known impact of hormone use on mammographic density (12). Our final analytic sample was comprised 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 three or more of the following components: waist circumference ≥88 cm, triglyceride levels ≥150 mg/dL, HDL cholesterol levels <50 mg/dL, systolic blood pressure (SBP) >130mmHg or diastolic blood pressure (DBP) >85 mmHg, and glucose levels ≥100 mg/dL. While the harmonized definition recommends a cutoff value of 80cm 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 ≥88cm in our primary analysis and was defined as ≥80cm 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 9am on the morning of the evaluation. Study personnel performed weight and height measurements using an electronic digital scale (Tanita Corp, Japan) to the nearest 0.1 kg and a wall stadiometer (Seca Corp., Hanover, MD) to the nearest millimeter. Waist circumference was measured in supine position at the umbilicus level using a fiberglass measuring tape (Seca Corp., Hanover, MD) registered to the nearest millimeter. Sitting blood pressure measurements were taken twice, five minutes apart, using a digital blood pressure monitor (Omron Corp., Japan). We used the average of the two measurements when available.

Trained nurses performed phlebotomy. Samples were centrifuged and aliquoted into cryotubes and kept in liquid nitrogen at -70 °C until stored at -70 °C in ultra-freezers. Triglyceride, high-density lipoprotein (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 HDL were measured using enzymatic hydrolysis in an automatic analyzer with a tungsten lamp (Prestige 24i, Tokyo Boeki Medical System LTD, Tokio, Japan). The interassay coefficients of variation (CVs) were 2.3% for glucose, 5.7% for triglycerides, and 5.3% for HDL cholesterol.

Mammographic density

A radiology technician performed mammography using the Giotto Image M (Internazionale Medico Scientifica, Bologna, Italy) in Jalisco and the Hologic Lorad M-III (Hologic, Bedford, MA) in Veracruz. Mammograms were developed using the Agfa CP1000 (Agfa-Gevaert Group, Belgium) developer. Craniocaudal and mediolateral oblique views were taken on each breast. Mammograms from the two states were combined and an Astra 2400S scanner (Umax, Fremont, CA) 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 non-dense 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 intraobserver 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 based on the date of the clinical visit and body mass index (BMI) was calculated based on measured height and weight during the clinical visit or the 2006 questionnaire if clinical data was unavailable. Socio-economic 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).(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, since 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 non-dense 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. Lastly, we performed a sensitivity analysis excluding women with self-reported diabetes. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Forty percent of premenopausal and 51 percent of postmenopausal women not on PMH in Jalisco were classified as having metabolic syndrome. In contrast, 21 percent of premenopausal women and 39 percent of postmenopausal women not on PMH were classified as having metabolic syndrome among women in Veracruz. On average, women in Jalisco had five percentage point higher percent mammographic density compared to 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 compared to 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 to those who did not in the age-adjusted model (difference = 2.06, 95% CI: -0.64, 4.76), however there was an inverse association among premenopausal women in Veracruz (difference=-5.28, 95% CI:-9.10, -1.45) (Table 2). These estimates did not substantially change in multivariate models excluding BMI (difference in Jalisco = 2.63; 95%CI: -0.18, 5.44; difference in Veracruz=-5.84, 95%CI: -9.86, -1.82). When we further adjusted for BMI, metabolic syndrome was significantly associated with an approximate five 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, 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, 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 (Supplemental Table 1). There was no significant association between metabolic syndrome and dense area among premenopausal women in Veracruz or non-dense area among premenopausal women in either state after adjustment for BMI and other covariates (Supplemental Tables 1 and 2). 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 non-dense area (difference in cm^2 = -6.58; 95%CI: -12.03, -1.12) in fully-adjusted models (Supplemental Tables 1 and 2). 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 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, 5.53 and -1.63, 95%CI: -5.97, 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 non-dense area in either state (Supplementary Tables 3 and 4). 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 compared to 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 US 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 compared to women with moderate or high HDL levels. Similar to our findings, low HDL levels were associated with 60 percent 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 two states. Compared to premenopausal women in Veracruz, premenopausal women in Jalisco were almost twice as likely to have metabolic syndrome and have an approximately five 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 performed on different machines in the two 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 non-differential 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 to premenopausal women in Veracruz.

Our study has several limitations. Though the CVs for trigylcerides, HDL, and glucose are low, there is likely some measurement error. This measurement error should be non-differential as the laboratory was blinded to mammography measurements. Mammographic density measurements are highly reproducible though there may be some random error. Any error should be non-differential 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 five 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work is supported by American Institute for Cancer Research Grant 05B047, CONACYT grant S0008-2009-1: 000000000115312, Ministry of Health Mexico, Avon cosmetics, Fundación Banorte, Fundación Gruma, Bicentennial Fund Travel Fellowship, the Harvard School of Public Health Department of Epidemiology, NIH T32 CA09001, NIH R25 CA098566.

References

1. Byrne C, Schairer C, Wolfe J, Parekh N, Salane M, Brinton LA, et al. Mammographic features and breast cancer risk: effects with time, age, and menopause status. J Natl Cancer Inst. 1995; 87:1622–9. [PubMed: 7563205]
2. Xue F, Michels KB. Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence. Am J Clin Nutr. 2007; 86:s823–35. [PubMed: 18265476]
3. Vona-Davis L, Howard-McNatt M, Rose DP. Adiposity, type 2 diabetes and the metabolic syndrome in breast cancer. Obes Rev. 2007; 8:395–408. [PubMed: 17716297]
4. Rosato V, Bosetti C, Talamini R, Levi F, Montella M, Giacosa A, et al. Metabolic syndrome and the risk of breast cancer in postmenopausal women. Ann Oncol. 2011; 22:2687–92. [PubMed: 21415236]
5. Agnoli C, Berrino F, Abagnato CA, Muti P, Panico S, Crosignani P, et al. Metabolic syndrome and postmenopausal breast cancer in the ORDET cohort: a nested case-control study. Nutr Metab Cardiovasc Dis. 2010; 20:41–8. [PubMed: 19361966]
6. Bjorge T, Lukanova A, Jonsson H, Tretli S, Ulmer H, Manjer J, et al. Metabolic syndrome and breast cancer in the me-can (metabolic syndrome and cancer) project. Cancer Epidemiol Biomarkers Prev. 2010; 19:1737–45. [PubMed: 20615887]
7. Kabat GC, Kim M, Chlebowski RT, Khandekar J, Ko MG, McTiernan A, et al. A longitudinal study of the metabolic syndrome and risk of postmenopausal breast cancer. Cancer Epidemiol Biomarkers Prev. 2009; 18:2046–53. [PubMed: 19567502]
8. Conroy SM, Butler LM, Harvey D, Gold EB, Sternfeld B, Greendale GA, et al. Metabolic syndrome and mammographic density: the Study of Women's Health Across the Nation. Int J Cancer. 2011; 129:1699–707. [PubMed: 21105041]
9. Rojas R, Aguilar-Salinas CA, Jimenez-Corona A, Shamah-Levy T, Rauda J, Avila-Burgos L, et al. Metabolic syndrome in Mexican adults: results from the National Health and Nutrition Survey 2006. Salud Publica Mex. 2010; 52 Suppl 1:S11–8. [PubMed: 20585723]
10. Romieu I, Lajous M. The role of obesity, physical activity and dietary factors on the risk for breast cancer: Mexican experience. Salud Publica Mex. 2009; 51 Suppl 2:s172–80. [PubMed: 19967272]
11. Lajous MLRR, Santoyo-Vistrain R, Garcia-Anaya A, Ortiz-Panozo E, Yunes-Diaz E, Sanchez-Zamorano LM, Torres-Mejia G, Lazcano-Ponce E, Hernandez-Avila M, Willet WC, Romeieu I. Cohort Profile: The Mexican Teachers' Health Study (ESMaestras). Int J Epidemiol. Accepted.

12. Martin LJ, Minkin S, Boyd NF. Hormone therapy, mammographic density, and breast cancer risk. Maturitas. 2009; 64:20–6. [PubMed: 19709825]
13. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009; 120:1640–5. [PubMed: 19805654]
14. Aschner P, Buendia R, Brajkovich I, Gonzalez A, Figueredo R, Juarez XE, et al. Determination of the cutoff point for waist circumference that establishes the presence of abdominal obesity in Latin American men and women. Diabetes Res Clin Pract. 2011; 93:243–7. [PubMed: 21632141]
15. Rojas-Martinez R, Aguilar-Salinas CA, Jimenez-Corona A. Optimal cutoff points for the detection of undiagnosed type 2 diabetes, hypertension and metabolic syndrome in Mexican adults. Salud Publica Mex. 2012; 54:13–9. [PubMed: 22286824]
16. Torres-Mejia G, De Stavola B, Allen DS, Perez-Gavilan JJ, Ferreira JM, Fentiman IS, et al. Mammographic features and subsequent risk of breast cancer: a comparison of qualitative and quantitative evaluations in the Guernsey prospective studies. Cancer Epidemiol Biomarkers Prev. 2005; 14:1052–9. [PubMed: 15894652]
17. Bollen KA, Glanville JL, Stecklov G. Socioeconomic status and class in studies of fertility and health in developing countries. Annual Review of Sociology. 2001; 27:153–85.
18. Aiello EJ, Tworoger SS, Yasui Y, Stanczyk FZ, Potter J, Ulrich CM, et al. Associations among circulating sex hormones, insulin-like growth factor, lipids, and mammographic density in postmenopausal women. Cancer Epidemiol Biomarkers Prev. 2005; 14:1411–7. [PubMed: 15941949]
19. Sung J, Song YM, Stone J, Lee K, Kim SY. High-density lipoprotein cholesterol, obesity, and mammographic density in Korean women: the Healthy Twin study. J Epidemiol. 2011; 21:52–60. [PubMed: 21071885]
20. Tamburrini AL, Woolcott CG, Boyd NF, Yaffe MJ, Terry T, Yasui Y, et al. Associations between mammographic density and serum and dietary cholesterol. Breast Cancer Res Treat. 2011; 125:181–9. [PubMed: 20464480]
21. Boyd NF, Byng JW, Jong RA, Fishell EK, Little LE, Miller AB, et al. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. J Natl Cancer Inst. 1995; 87:670–5. [PubMed: 7752271]
22. Furberg AS, Jasienska G, Bjurstam N, Torjesen PA, Emaus A, Lipson SF, et al. Metabolic and hormonal profiles: HDL cholesterol as a plausible biomarker of breast cancer risk. The Norwegian EBBA Study. Cancer Epidemiol Biomarkers Prev. 2005; 14:33–40. [PubMed: 15668473]
23. Furberg AS, Veierod MB, Wilsgaard T, Bernstein L, Thune I. Serum high-density lipoprotein cholesterol, metabolic profile, and breast cancer risk. J Natl Cancer Inst. 2004; 96:1152–60. [PubMed: 15292387]
24. Porto LA, Lora KJ, Soares JC, Costa LO. Metabolic syndrome is an independent risk factor for breast cancer. Arch Gynecol Obstet. 2011; 284:1271–6. [PubMed: 21249376]
25. Walsh BW, Schiff I, Rosner B, Greenberg L, Ravnikar V, Sacks FM. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. N Engl J Med. 1991; 325:1196–204. [PubMed: 1922206]

Abbreviations

MetS	metabolic syndrome
BMI	body mass index
HDL	high density lipoprotein
BBD	benign breast disease

CV coefficient of variation

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 (Percent)								
Age at menarche								
<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								

	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)
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 years	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+ years	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)
Alcohol (drinks/day)								
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)
Socio-economic status								
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								
<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)

Table 2

Difference in percent mammographic density (95% confidence interval) 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≥88cm)	196 (39.5)	2.06 (-0.64, 4.76)	2.63 (-0.18, 5.44)	4.76* (1.72, 7.81)	61 (20.8)	-5.28* (-9.1, -1.45)	-5.84* (-9.86, -1.82)	-2.91 (-7.19, 1.38)
Harmonized definition (waist≥80cm)	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, 0.69)	-2.72 (-6.40, 0.95)	-0.69 (-4.50, 3.13)
Individual metabolic syndrome components								
Abdominal obesity (waist≥88cm)	284 (57.3)	-3.94* (-6.54, -1.34)	-3.77* (-6.46, -1.08)	-2.89 (-6.36, 0.57)	146 (49.8)	-4.74* (-7.83, -1.64)	-5.05* (-8.25, -1.86)	-1.13 (-5.24, 2.98)
Abdominal obesity (waist≥80cm)	422 (85.1)	-4.00* (-7.63, -0.38)	-3.59 (-7.45, 0.26)	-2.04 (-6.35, 2.27)	228 (77.8)	-4.01* (-7.76, -0.25)	-3.72 (-7.61, 0.17)	0.20 (-4.28, 4.68)
High fasting triglycerides (≥150mg/dl)	185 (37.3)	1.25 (-1.44, 3.93)	1.41 (-1.37, 4.2)	2.06 (-0.77, 4.88)	81 (27.7)	-1.03 (-4.55, 2.49)	-0.52 (-4.16, 3.12)	1.09 (-2.55, 4.74)
Low HDL (<50mg/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, 2.98)	0.46 (-2.88, 3.80)	1.33 (-1.94, 4.59)
High blood pressure (SBP≥130mmgHg or DBP≥85mmgHg)	189 (38.1)	1.04 (-1.73, 3.81)	1.24 (-1.63, 4.11)	1.60 (-1.28, 4.47)	60 (20.5)	-2.06 (-5.98, 1.86)	-2.86 (-6.97, 1.26)	-2.33 (-6.39, 1.74)
High fasting glucose (≥100mg/dl)	76 (15.3)	0.34 (-3.31, 3.99)	0.55 (-3.22, 4.31)	1.40 (-2.42, 5.22)	42 (14.3)	-3.43 (-7.9, 1.03)	-2.97 (-7.72, 1.79)	-1.12 (-5.82, 3.58)
High fasting glucose (≥110mg/dl)	36 (7.3)	1.42 (-3.67, 6.5)	1.91 (-3.31, 7.13)	2.75 (-2.50, 8.00)	24 (8.2)	-4.00 (-9.71, 1.71)	-2.49 (-8.44, 3.45)	-0.02 (-5.90, 5.86)

[a] Model 1: adjusted for age at mammography (continuous)

[b] Model 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 per day), smoking status (never, ever), and SES (low, medium, high)

[c] Model 3: Model 2 and BMI at mammogram (continuous)

* p<0.05

Table 3

Difference in percent mammographic density (95% confidence interval) 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]
Metabolic Syndrome								
Harmonized definition (waist≥88cm)	73 (51.4)	-2.60 (-7.32, 2.12)	-2.87 (-8.31, 2.58)	-0.62 (-6.76, 5.53)	70 (38.9)	-3.68 (-7.56, 0.20)	-2.70 (-6.89, 1.48)	-1.63 (-5.97, 2.71)
Harmonized definition (waist≥80cm)	85 (59.9)	1.64 (-3.18, 6.46)	1.79 (-3.62, 7.2)	3.98 (-1.71, 9.68)	80 (44.4)	-4.69* (-8.51, -0.86)	-3.45 (-7.61, 0.71)	-2.71 (-6.93, 1.51)
Individual metabolic syndrome components								
Abdominal obesity (waist≥88cm)	98 (69.0)	-7.50* (-12.45, -2.54)	-6.61* (-12.47, -0.74)	-5.03 (-11.92, 1.86)	110 (61.1)	-6.33* (-10.09, -2.58)	-5.55* (-9.67, -1.44)	-4.69 (-9.70, 0.33)
Abdominal obesity (waist≥80cm)	129 (90.9)	-3.14 (-11.29, 5.01)	-0.76 (-9.91, 8.39)	2.11 (-7.50, 11.71)	160 (88.9)	-6.13* (-12.06, -0.2)	-3.28 (-9.69, 3.12)	-0.83 (-7.79, 6.13)
High fasting triglycerides (≥150mg/dl)	77 (54.2)	0.67 (-4.06, 5.39)	-1.14 (-6.69, 4.41)	0.64 (-5.10, 6.38)	61 (33.9)	0.38 (-3.62, 4.38)	0.63 (-3.73, 4.99)	0.92 (-3.41, 5.25)
Low HDL (<50mg/dl)	93 (65.5)	0.66 (-4.29, 5.61)	0.87 (-5.01, 6.75)	2.57 (-3.55, 8.70)	77 (42.8)	1.57 (-2.23, 5.38)	3.42 (-0.72, 7.56)	3.49 (-0.61, 7.58)
High blood pressure (SBP≥130mmgHg or DBP≥85mmgHg)	73 (51.4)	-0.89 (-5.63, 3.85)	-0.06 (-5.81, 5.69)	2.01 (-4.06, 8.07)	81 (45.0)	-1.02 (-4.96, 2.92)	-0.03 (-4.34, 4.28)	0.81 (-3.54, 5.15)
High fasting glucose (≥100mg/dl)	40 (28.2)	-3.87 (-9.14, 1.40)	-3.55 (-10.04, 2.93)	-2.66 (-9.37, 4.05)	50 (27.8)	-3.72 (-7.92, 0.47)	-2.11 (-6.69, 2.47)	-1.53 (-6.11, 3.05)
High fasting glucose (≥110mg/dl)	24 (16.9)	-3.56 (-9.85, 2.73)	-3.93 (-11.53, 3.67)	-2.23 (-10.13, 5.67)	28 (15.6)	-4.60 (-9.76, 0.55)	-3.99 (-9.54, 1.56)	-3.89 (-9.38, 1.61)

[a] Model 1: adjusted for age at mammogram (continuous)

[b] Model 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 per day), smoking status (never, ever), age at menopause (<40, 40-44, 45-49, 50+, unknown), and SES (low, medium, high)

[c] Model 3: Model 2 and BMI at mammogram (continuous)

* p<0.05