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Bone mineral density and mammographic density in Mexican women

Heidi Moseson^{1,*}, Megan S. Rice^{3,*}, Ruy López-Ridaura⁴, Kimberly A. Bertrand^{2,3}, Gabriela Torres⁴, Margarita Blanco⁵, Juan Alfredo Tamayo-Orozco⁶, Martin Lajous^{2,4,7}, and Isabelle Romieu⁸

¹Department of Epidemiology & Biostatistics, University of California San Francisco, San Francisco, CA, USA

²Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA

³Channing Division of Network Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, MA, USA

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

⁵Medical Direction, Social Security and Services Institute for the Employees of the State, Mexico City, Mexico

⁶Mexican Committee for the Prevention of Osteoporosis, Mexico City, Mexico

⁷Inserm (Institut National de la Santé et de la Recherche Médicale), Center for Research in Epidemiology and Population Health (CESP), U1018, Villejuif, France

⁸International Agency for Research on Cancer, Lyon, France

Abstract

Background—Bone mineral density (BMD) is a putative marker for lifetime exposure to estrogen. Studies that have explored whether BMD is a determinant of mammographic density (MD) have observed inconsistent results. Therefore, we examined this potential association in a sample of women (N=1,516) from the clinical sub-cohort in the Mexican Teachers' Cohort (N=115,315).

Methods—We used multivariable linear regression to assess the association between quartiles of BMD and percent MD, as well as total dense and non-dense area of the breast, stratified by menopausal status. We also examined the associations by body mass index (BMI) (<30 kg/m², 30 kg/m²).

Results—Overall, there was no association between BMD and MD among premenopausal women. However, when we stratified by BMI, there was a modest inverse association between BMD and percent MD (difference between extreme quartiles= -2.8, 95%CI: -5.9, 0.27, p-trend=0.04) among women with BMI <30 kg/m², but a positive association among obese women

Corresponding author: Martin Lajous, MD, ScD, 7^a Cerrada Fray Pedro de Gante #50, Mexico City 14000, Mexico, Telephone: +52 55 5487-1000 ext. 4622, mlajous@insp.mx.

*co-first authors

(comparable difference=5.1, 95%CI: 0.02, 10.1, p-trend=0.03; p-interaction<0.01). Among postmenopausal women, BMD and percent MD were positively associated after adjustment for BMI (p-trend<0.01). Postmenopausal women in the highest two quartiles of BMD had 4–5 percentage point higher percent MD compared to women in the lowest quartile. The association did not differ by BMI in postmenopausal women (p-interaction=0.76).

Conclusion—Among obese premenopausal women as well as postmenopausal women, BMD was positively associated with percent MD. Among leaner premenopausal women, BMD and percent MD were modestly inversely associated. These findings support the hypothesis that cumulative exposure to estrogen (as measured by BMD) may influence MD.

Introduction

Mammographic density (MD) is one of the strongest predictors of breast cancer risk.¹ Women with high breast density (>75%) have four to six times the risk of breast cancer compared to those with very low breast density^{2–5}. Hormone levels, including estrogen, are suspected to be a determinant of MD^{6–8}. Bone mineral density (BMD) is regarded as a marker for lifetime exposure to estrogen^{7–10} and higher BMD has been linked with increased risk of breast cancer in some^{11–17}, but not all studies^{9, 18}. While MD is responsive to hormonal interventions, including hormone therapy (HT) and tamoxifen,¹⁹ evidence for an association between cumulative lifetime exposure to estrogen, as measured by BMD, and MD is mixed^{9, 14, 20–25}. Further, no prior study has examined this association in Mexican women, a population that has increasing breast cancer incidence and mortality rates and may have unique risk factors.²⁶ Therefore, we examined the cross-sectional association between BMD and MD in a large sample of pre- and postmenopausal Mexican women.

Methods

Study population

The Mexican Teachers' Cohort (MTC or ESMaestras) is a prospective cohort study that was established in 2006–2008 and includes 115,315 female public school teachers in Mexico. Details on the cohort have been described elsewhere^{27–29}. The present analysis was based on a clinical sub-cohort of 2,084 MTC participants from the states of Jalisco and Veracruz who underwent mammography, anthropometry measurements, and an interview in 2007. Within this clinical sub-cohort, 1,707 women underwent a mammogram, of whom 1,679 also had their BMD measured. We excluded women with missing data on menopausal status (n=81), participants with a prior breast cancer diagnosis (n=11), missing data on body mass index (BMI) (n=6), and users of HT who reported they were currently using HT on the 2006 baseline questionnaire (n=65). Thus, the final analytic sample comprised 1,516 women (964 premenopausal and 552 postmenopausal).

Bone Mineral Density

Bone mineral density (BMD) was determined in the non-dominant forearm with a PIXI dual-energy x-ray absorptiometry densitometer (Lunar Corp., Madison, WI) following the recommendations of the International Society for Clinical Densitometry, and is measured as

grams per centimeter squared (g/cm^2).³⁰ All measurements took place within a mobile medical unit by trained personnel, and a bone specialist (A. Tamayo-Orozco) reviewed results. A prior study in younger Mexican women observed a correlation between BMD in the distal forearm with BMD as measured in the lumbar spine of 0.78 (95%CI: 0.73, 0.83).³¹

Mammographic Density

Using the Hologic Lorad M-III (Hologic, Bedford, MA, USA) in Veracruz and the Giotto Image M (Internazionale Medico Scientifica, Bologna, Italy) in Jalisco, a radiology technician carried out mammography on study subjects. The Agfa CP1000 developer (Agfa-Gevaert Group, Belgium) was used to develop mammograms and an Astra 2400S scanner (Umax, Fremont, CA) was used to digitize the mammograms. A single observer measured total area and total dense area of the craniocaudal view of the left breast using Mamgr, a computer assisted program developed at the Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine.^{32–34} Density was assessed only for the left breast as prior studies have demonstrated that breast density of the left and right breast are highly correlated.³⁵ We calculated percent density by dividing total dense area by the total area of the breast; non-dense area was calculated by subtracting total dense area from the total area. The Mamgr observer was blinded to participant characteristics including BMD.

Covariate Data

We obtained information on covariates [age at mammogram, family history of breast cancer, history of benign breast disease (BBD), metabolic equivalent of task (METs) per week, age at menarche, smoking, alcohol, parity, age at first birth, daily calcium intake and past HT use] from the 2006 self-reported questionnaire. Weight and standing height measurements were taken 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. These measurements were used to calculate BMI (kg/m^2) for each individual. For 91 women with missing measured height or weight, BMI was calculated based on self-reported height and weight.

Statistical Analyses

We categorized participants according to menopausal status specific BMD quartiles. Multivariable linear regression was used to estimate the association between quartiles of BMD and percent MD, as well as with natural log-transformed dense area, and natural log-transformed non-dense area. We adjusted for age, state of residence, family history of breast cancer, history of BBD, current BMI, METs per week, age at menarche, smoking, alcohol use, parity, age at first birth, calcium intake and past HT use (among postmenopausal women). To test for linear trend, we continuously modeled the median of the quartiles of BMD. To test for statistical interaction by BMI (<30 , ≥ 30 kg/m^2), we assessed the results of the Wald test in a model with an interaction term between ordinal BMD and binary BMI (<30 , ≥ 30). In sensitivity analyses, we restricted to never users of HT among postmenopausal women and stratified by state of residence (Jalisco, Veracruz). Analyses were completed using SAS (SAS version 9.3; SAS Institute; Cary, NC) and p-values <0.05 were considered statistically significant.

Results

Mean age was 43 years ($SD \pm 4.1$) among premenopausal women and 54 years ($SD \pm 5.3$) among postmenopausal women. Mean BMD was 0.45 g/cm^2 ($SD \pm 0.06$) and 0.40 g/cm^2 ($SD \pm 0.06$) among pre- and postmenopausal women, respectively. Mean percent MD was 37% ($SD \pm 14.6$) among premenopausal women and 28% ($SD \pm 13.4$) in postmenopausal women. As previously reported, percent mammographic density was higher among women in Jalisco compared to women in Veracruz.³⁶ Table 1 presents the distribution of characteristics by quartiles of BMD in pre- and postmenopausal women. Overall, women with higher BMD had greater BMI and higher levels of physical activity, while among postmenopausal women those with high BMD were also younger.

Overall, there was no association between BMD and percent MD in premenopausal women (difference between extreme quartiles = -0.21 percentage points; 95% CI: $-2.8, 2.4$; p-trend = 0.73) (Table 2), nor was there an association between BMD and dense area (p-trend = 0.68) or non-dense area (p-trend = 0.40), after adjusting for BMI and other predictors of MD. However, the association between BMD and measures of MD did vary by BMI in premenopausal women. Among women whose BMI was $<30 \text{ kg/m}^2$, there was a modest inverse association between BMD and percent MD. Those in the highest quartile of BMD had 2.8 percentage point lower percent MD than those in the lowest BMD quartile (95% CI: $-5.9, 0.27$; p-trend = 0.04) (Table 3). In contrast, BMD was positively associated with percent MD among obese premenopausal women (BMI $\geq 30 \text{ kg/m}^2$). Obese premenopausal women in the highest quartile of BMD had 5.1 percentage points greater percent MD than those in the lowest quartile (95% CI: $0.02, 10.1$; p-trend = 0.03 ; p-interaction < 0.01). Further, BMD was inversely associated with dense area among women whose BMI was $<30 \text{ kg/m}^2$ (p-trend < 0.01), but suggestively positively associated in obese women (p-trend = 0.09).

Among postmenopausal women, BMD was positively associated with percent MD (Table 2). Women in the highest two quartiles of BMD had 4 – 5 percentage point greater percent MD than those in the lowest quartile (p-trend < 0.01). BMD was suggestively positively associated with dense area (p-trend = 0.05) and inversely associated with non-dense area (p-trend < 0.01). There was no evidence for effect measure modification for the association between BMD and measures of MD by BMI among postmenopausal women (p-interaction = 0.16) (Table 3).

Results were similar, though slightly attenuated, for percent MD among postmenopausal women when we restricted to never users of HT (difference between extreme quartiles = 3.3 ; 95% CI: $-0.72, 7.3$; p-trend = 0.03) and did not differ by state of residence for either premenopausal (p-interaction = 0.24) or postmenopausal women (p-interaction = 0.52).

Discussion

In this population of Mexican women, there was no overall association between BMD and percent MD in premenopausal women. After stratification by BMI, we observed a significant positive association between BMD and percent MD among obese (BMI ≥ 30) premenopausal women. Among postmenopausal women, BMD was positively associated

with percent MD and dense breast area and inversely associated with non-dense area of the breast.

Given that BMD is considered a marker of cumulative estrogen exposure^{6–8} and some studies suggested positive associations between BMD and breast cancer risk^{10, 11, 13, 37}, researchers initially hypothesized that BMD may also be positively correlated with mammographic density^{9, 20}. However, no associations were found in these or the majority of subsequent studies^{9, 20, 22–25}, though some reported inverse associations^{14, 20}. Thus our results contradict the majority of published literature to date. Our findings of positive associations between BMD and MD in postmenopausal women do agree with one published cross-sectional study, however, which reported a 4–5 percentage point difference in MD among women in the top quartile of BMD compared to those in the bottom quartile²¹, effect sizes remarkably consistent with our findings. In addition, Sung et al. reported a positive association among premenopausal, but not postmenopausal women²⁴.

Few prior studies considered possible differences in associations of BMD with MD by BMI. One study reported no difference by BMI, while in another study of postmenopausal women, a modest inverse association was observed among lean women ($BMI < 25 \text{ kg/m}^2$), but not among women with $BMI \geq 25 \text{ kg/m}^2$.²⁰ Our findings of significant effect modification by BMI among premenopausal women should be interpreted with caution given the small sample sizes in stratified analyses.

One potential reason for the inconsistency in results in the published literature to date may be HT use in study populations. Several prior studies considered current versus past or ever use of HT⁹ while others were able to stratify more finely (e.g., recent past use vs. never use)^{14, 20–22, 24}. Some authors did not mention adjustment for HT use^{23, 25}. Given residual effects of HT use on breast density, the various considerations of HT use across previous analyses may contribute to divergent results. While it has been argued that recent exogenous hormone use may obscure an association between BMD and MD²¹, in the current analysis, we observed that significant positive associations in postmenopausal women persisted after adjustment for HT use and also after excluding ever users of HT.

Our analysis has some limitations. The use of BMD measured at the forearm in this study as opposed to the lumbar spine may have resulted in non-differential measurement error of BMD, potentially biasing our results towards the null. As this study is cross-sectional, we were unable to assess changes in bone and breast density over time. Strengths of this study include the standardized measurement of BMD and MD as well as the standardized collection of predictors of both breast and bone density and ability to adjust for potential confounding by these factors.

In conclusion, we observed that BMD and percent MD were positively associated in postmenopausal women as well as in obese premenopausal women in our sample of Mexican women and modestly inversely associated in leaner premenopausal women. These findings should reopen discussion of the possibility of a common cumulative estrogen-related pathway linking bone mineral density and breast density that may contribute to

breast cancer risk. Further research in this area should include particular emphasis on understanding how and why the association may differ by BMI.

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References

1. Brower V. Breast density gains acceptance as breast cancer risk factor. *J Natl Cancer Inst.* 2010; 102(6):374–5. Epub 2010 Mar 9. 10.1093/jnci/djq080 [PubMed: 20215595]
2. Boyd NF, Byng JW, Jong RA, Fishell EK, Little LE, Miller AB, Lockwood GA, Tritchler DL, Yaffe MJ. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. *J Natl Cancer Inst.* 1995; 87(9):670–5. [PubMed: 7752271]
3. Boyd NF, Rommens JM, Vogt K, Lee V, Hopper JL, Yaffe MJ, Paterson AD. Mammographic breast density as an intermediate phenotype for breast cancer. *Lancet Oncol.* 2005; 6(10):798–808. [PubMed: 16198986]
4. Vachon CM, Brandt KR, Ghosh K, Scott CG, Maloney SD, Carston MJ, Pankratz VS, Sellers TA. Mammographic breast density as a general marker of breast cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2007; 16(1):43–9. [PubMed: 17220330]
5. Boyd NF, Guo H, Martin LJ, Sun L, Stone J, Fishell E, Jong RA, Hislop G, Chiarelli A, Minkin S, Yaffe MJ. Mammographic density and the risk and detection of breast cancer. *N Engl J Med.* 2007; 356(3):227–36. [PubMed: 17229950]
6. Kawaguchi, H.; Pilbeam, CC.; Harrison, JR.; Raisz, LG. The role of prostaglandins in the regulation of bone metabolism; *Clin Orthop Relat Res.* 1995. p. 36-46.<http://www.ncbi.nlm.nih.gov/pubmed/7641496>
7. Cauley JA, Gutai JP, Kuller LH, LeDonne D, Sandler RB, Sashin D, Powell JG. Endogenous estrogen levels and calcium intakes in postmenopausal women. Relationships with cortical bone measures. *Jama.* 1988; 260(21):3150–5. [PubMed: 3240335]
8. Murphy S, Khaw KT, Sneyd MJ, Compston JE. Endogenous sex hormones and bone mineral density among community-based postmenopausal women. *Postgrad Med J.* 1992; 68(805):908–13. [PubMed: 1494513]
9. Kerlikowske K, Shepherd J, Creasman J, Tice JA, Ziv E, Cummings SR. Are breast density and bone mineral density independent risk factors for breast cancer? *J Natl Cancer Inst.* 2005; 97(5): 368–74. [PubMed: 15741573]
10. Nguyen TV, Center JR, Eisman JA. Association between breast cancer and bone mineral density: the Dubbo Osteoporosis Epidemiology Study. *Maturitas.* 2000; 36(1):27–34. [PubMed: 10989239]
11. Cauley JA, Lucas FL, Kuller LH, Vogt MT, Browner WS, Cummings SR. Bone mineral density and risk of breast cancer in older women: the study of osteoporotic fractures. Study of Osteoporotic Fractures Research Group. *JAMA.* 1996; 276(17):1404–8. [PubMed: 8892715]
12. Zhang Y, Kiel DP, Kreger BE, Cupples LA, Ellison RC, Dorgan JF, Schatzkin A, Levy D, Felson DT. Bone mass and the risk of breast cancer among postmenopausal women. *N Engl J Med.* 1997; 336(9):611–7. [PubMed: 9032046]
13. Buist DS, LaCroix AZ, Barlow WE, White E, Weiss NS. Bone mineral density and breast cancer risk in postmenopausal women. *J Clin Epidemiol.* 2001; 54(4):417–22. [PubMed: 11297892]

14. Crandall CJ, Zheng Y, Karlamangla A, Sternfeld B, Habel LA, Oestreicher N, Johnston J, Cauley JA, Greendale GA. The association between mammographic breast density and bone mineral density in the study of women's health across the nation. *Ann Epidemiol.* 2007; 17(8):575–83. [PubMed: 17532645]
15. Chen Z, Arendell L, Aickin M, Cauley J, Lewis CE, Chlebowski R. Hip bone density predicts breast cancer risk independently of Gail score: results from the Women's Health Initiative. *Cancer.* 2008; 113(5):907–15. [PubMed: 18666209]
16. Grenier D, Cooke AL, Lix L, Metge C, Lu H, Leslie WD. Bone mineral density and risk of postmenopausal breast cancer. *Breast Cancer Res Treat.* 2011; 126(3):679–86. [PubMed: 20838879]
17. Kim BK, Choi YH, Song YM, Park JH, Noh HM, Nguyen TL, Hopper JL. Bone mineral density and the risk of breast cancer: a case-control study of Korean women. *Ann Epidemiol.* 2014; 24(3):222–7. [PubMed: 24360852]
18. Fraenkel M, Novack V, Liel Y, Koretz M, Siris E, Norton L, Shafat T, Shany S, Geffen DB. Association between bone mineral density and incidence of breast cancer. *PLoS One.* 2013; 8(8):e70980. [PubMed: 23940680]
19. Boyd NF, Martin LJ, Bronskill M, Yaffe MJ, Duric N, Minkin S. Breast tissue composition and susceptibility to breast cancer. *J Natl Cancer Inst.* 2010; 102(16):1224–37. Epub 2010 Jul 8. 10.1093/jnci/djq239 [PubMed: 20616353]
20. Buist DS, Anderson ML, Taplin SH, LaCroix AZ. The relationship between breast density and bone mineral density in postmenopausal women. *Cancer.* 2004; 101(9):1968–76. [PubMed: 15386302]
21. Crandall C, Palla S, Reboussin BA, Ursin G, Greendale GA. Positive association between mammographic breast density and bone mineral density in the Postmenopausal Estrogen/Progestin Interventions Study. *Breast Cancer Res.* 2005; 7(6):R922–8. [PubMed: 16280044]
22. Dite GS, Wark JD, Giles GG, English DR, McCredie MR, Hopper JL. Is there a positive association between mammographic density and bone mineral density? *Breast Cancer Res.* 2006; 8(1):401. [PubMed: 16524454]
23. Gupta R, Alhajri FA, Mohammed AM, Chavan VN, Gupta P. Relationship between mammography breast density and bone mineral density. *J Clin Densitom.* 2008; 11(3):431–6. [PubMed: 18164638]
24. Sung J, Song YM, Stone J, Lee K. The relationship between bone mineral density and mammographic density in Korean women: the Healthy Twin study. *Breast Cancer Res Treat.* 2011; 129(2):583–91. [PubMed: 21512766]
25. Yong M, Atkinson C, Newton KM, Aiello Bowles EJ, Stanczyk FZ, Westerlind KC, Holt VL, Schwartz SM, Leisenring WM, Lampe JW. Associations between endogenous sex hormone levels and mammographic and bone densities in premenopausal women. *Cancer Causes Control.* 2009; 20(7):1039–53. [PubMed: 19280356]
26. Chavarri-Guerra Y, Villarreal-Garza C, Liedke PE, Knäul F, Mohar A, Finkelstein DM, Goss PE. Breast cancer in Mexico: a growing challenge to health and the health system. *Lancet Oncol.* 2012; 13(8):e335–43. [PubMed: 22846838]
27. Romieu I, Escamilla-Nunez MC, Sanchez-Zamorano LM, Lopez-Ridaura R, Torres-Mejia G, Yunes EM, Lajous M, Rivera-Dommarco JA, Lazcano-Ponce E. The association between body shape silhouette and dietary pattern among Mexican women. *Public Health Nutr.* 2011; 10.1017/s1368980011001182:1-10
28. Rice MS, Bertrand KA, Lajous M, Tamimi RM, Torres-Mejia G, Biessy C, Lopez-Ridaura R, Romieu I. Body size throughout the life course and mammographic density in Mexican women. *Breast Cancer Res Treat.* 2013; 138(2):601–10. Epub 2013 Mar 5. 10.1007/s10549-013-2463-8 [PubMed: 23460247]
29. Lajous ML-RR, 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.
30. Baim S, Binkley N, Bilezikian JP, Kendler DL, Hans DB, Lewiecki EM, Silverman S. Official Positions of the International Society for Clinical Densitometry and executive summary of the

- 2007 ISCD Position Development Conference. *J Clin Densitom.* 2008; 11(1):75–91.10.1016/j.jocd.2007.12.007 [PubMed: 18442754]
31. Hernandez-Prado B, Lazcano-Ponce E, Cruz-Valdez A, Diaz R, Tamayo J, Hernandez-Avila M. Validity of bone mineral density measurements in distal sites as an indicator of total bone mineral density in a group of pre-adolescent and adolescent women. *Arch Med Res.* 2002; 33(1):33–9. [PubMed: 11825629]
32. Byng JW, Boyd NF, Fishell E, Jong RA, Yaffe MJ. The quantitative analysis of mammographic densities. *Phys Med Biol.* 1994; 39(10):1629–38. [PubMed: 15551535]
33. Ursin G, Astrahan MA, Salane M, Parisky YR, Pearce JG, Daniels JR, Pike MC, Spicer DV. The detection of changes in mammographic densities. *Cancer Epidemiol Biomarkers Prev.* 1998; 7(1): 43–7. [PubMed: 9456242]
34. Torres-Mejia G, De Stavola B, Allen DS, Perez-Gavilan JJ, Ferreira JM, Fentiman IS, Dos Santos Silva I. 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(5):1052–9. [PubMed: 15894652]
35. Byng JW, Boyd NF, Little L, Lockwood G, Fishell E, Jong RA, Yaffe MJ. Symmetry of projection in the quantitative analysis of mammographic images. *Eur J Cancer Prev.* 1996; 5(5):319–27. [PubMed: 8972250]
36. Rice MS, Bertrand KA, Lajous M, Tamimi RM, Torres-Mejia G, Biessy C, Lopez-Ridaura R, Romieu I. Body size throughout the life course and mammographic density in Mexican women. *Breast Cancer Res Treat.* 2013; 138(2):601–10. [PubMed: 23460247]
37. van der Klift M, de Laet CE, Coebergh JW, Hofman A, Pols HA. Bone mineral density and the risk of breast cancer: the Rotterdam Study. *Bone.* 2003; 32(3):211–6. [PubMed: 12667548]

Table 1

Selected characteristics by quartiles of bone mineral density (g/cm²) and menopausal status (MTC, 2006).

	Premenopausal				Postmenopausal			
	Quartile 1 (<0.41) N=243	Quartile 2 (0.41–0.45) N=234	Quartile 3 (0.45–0.48) N=253	Quartile 4 (0.48+) N=234	Quartile 1 (<0.35) N=136	Quartile 2 (0.35–0.40) N=141	Quartile 3 (0.40–0.44) N=135	Quartile 4 (0.44+) N=140
Mean (SD)								
Age	43.6 (5.0)	43.5 (3.9)	42.8 (3.5)	43.1 (3.8)	56.0 (5.4)	53.1 (5.6)	53.3 (4.6)	52.0 (4.6)
BMI (kg/m ²)	26.6 (4.6)	27.9 (5.0)	29.2 (5.4)	29.8 (5.2)	27.0 (4.3)	28.9 (5.0)	29.4 (4.4)	31.4 (5.7)
Percent density	37.4 (15.2)	37.6 (15.0)	36.3 (13.6)	37.5 (14.8)	26.0 (13.3)	26.9 (13.1)	29.8 (13.5)	29.1 (13.7)
Percent (%)								
Family history of breast cancer	4.9	5.1	5.1	5.6	7.4	6.4	5.9	7.1
History of BBD	13.6	14.5	15.4	12.0	10.3	12.8	8.2	12.9
Physical activity (METs/week)								
Tertile 1	27.6	28.2	24.6	23.8	32.6	39.6	41.0	30.2
Tertile 2	39.1	37.6	37.3	39.8	40.0	33.1	33.6	34.5
Tertile 3	33.3	34.2	38.1	36.4	27.4	27.3	25.4	35.3
Age at menarche								
<12	22.4	19.0	24.1	27.0	24.2	22.6	21.6	31.1
12	27.4	29.7	29.3	29.1	22.7	25.6	34.3	25.9
13	21.6	27.1	23.3	22.6	24.2	13.1	16.4	17.8
14+	28.6	24.1	23.3	21.3	28.8	38.7	27.6	25.2
Smoking status								
Past	16.7	18.5	17.5	17.8	12.4	10.0	7.6	10.3
Current	9.1	13.6	16.7	10.6	15.9	20.8	9.3	20.5
Alcohol use								
Any	68.8	74.0	75.1	67.8	72.1	67.2	67.5	70.6
Speak or have parents who speak an indigenous language	6.3	2.6	3.2	5.2	6.1	5.0	2.3	3.6

	Premenopausal				Postmenopausal			
	Quartile 1 (<0.41) N=243	Quartile 2 (0.41–0.45) N=234	Quartile 3 (0.45–0.48) N=253	Quartile 4 (0.48+) N=234	Quartile 1 (<0.35) N=136	Quartile 2 (0.35–0.40) N=141	Quartile 3 (0.40–0.44) N=135	Quartile 4 (0.44+) N=140
Ever hormonal contraceptive use	52.4	59.6	46.7	52.4	55.6	48.1	45.7	52.2
Parity								
Nulliparous	14.1	9.3	12.9	12.6	12.4	15.9	12.0	15.4
1 child	15.8	15.0	15.4	10.8	14.0	13.6	19.2	12.5
2 children	36.3	35.4	34.2	36.0	32.6	26.5	32.8	22.8
3 children	23.5	31.4	27.1	27.9	30.2	27.3	20.0	37.5
4+ children	10.3	8.9	10.4	12.6	10.9	16.7	16.0	11.8
Age at first birth*								
<25	51.9	57.7	55.3	59.4	54.3	51.7	51.2	57.7
25+	48.2	42.3	44.7	40.6	45.7	48.4	48.8	42.3
Breastfeeding*								
Never	8.1	10.4	11.1	8.4	19.4	16.1	7.4	11.8
<12 months	36.7	42.1	42.7	37.1	38.7	38.7	39.5	40.9
12+ months	55.3	47.6	46.2	54.5	41.9	45.2	53.1	47.3
Calcium intake (mg/day)								
Quartile 1	23.2	22.7	25.7	24.6	29.4	32.1	21.6	25.0
Quartile 2	26.1	28.6	26.1	24.6	23.5	23.6	22.4	20.0
Quartile 3	26.1	24.4	27.3	23.7	19.9	15.7	30.6	28.6
Quartile 4	24.5	24.4	20.9	27.2	27.2	28.6	25.4	26.4
HT use								
Never					71.4	73.5	70.3	73.3
Past					20.3	19.9	17.2	18.5
Ever, current status unknown					8.3	6.6	12.5	8.2

Number of individuals with missing values: physical activity (n=9), age at menarche (n=26), smoking (n=185), alcohol (n=137), parity (n=72), age at first birth among parous (n=18), breastfeeding (n=26), calcium intake (n=10), indigenous language (n=20), hormonal contraceptive use (n=66), HT use (n=20)

Difference in mammographic density measures (95% CI) by quartile of bone mineral density (g/cm²) stratified by menopausal status

Table 2

	Premenopausal Women					Postmenopausal women				
	Quartile 1 (<0.41) N=243	Quartile 2 (0.41-0.45) N=234	Quartile 3 (0.45-0.48) N=253	Quartile 4 (0.48+) N=234	P- trend	Quartile 1 (<0.35) N=136	Quartile 2 (0.35-0.40) N=141	Quartile 3 (0.40-0.44) N=135	Quartile 4 (0.44+) N=140	P- trend
	Percent density					Percent density				
Model 1 ^a	Ref	-0.42 (-2.98,2.13)	-2.28 (-4.80,0.24)	-1.94 (-4.55,0.68)	0.08	Ref	0.21 (-2.95,3.36)	2.83 (-0.36,6.02)	1.79 (-1.45,5.03)	0.13
Model 2 ^b	Ref	-0.47 (-3.00,2.06)	-2.21 (-4.71,0.29)	-1.84 (-4.41,0.73)	0.09	Ref	-0.56 (-3.66,2.55)	3.38 (0.2,6.56)	1.63 (-1.56,4.82)	0.10
Model 3 ^c	Ref	0.2 (-2.30,2.71)	-0.91 (-3.42,1.61)	-0.21 (-2.82,2.40)	0.73	Ref	0.77 (-2.32,3.86)	5.06 (1.87,8.26)	4.44 (1.11,7.77)	<0.01
Ln dense area (cm ²)										
Model 1 ^a	Ref	0.09 (-0.02,0.20)	0.04 (-0.07,0.15)	0.08 (-0.03,0.19)	0.24	Ref	0.11 (-0.05,0.27)	0.25 (0.09,0.41)	0.19 (0.02,0.35)	0.01
Model 2 ^b	Ref	0.07 (-0.04,0.18)	0.02 (-0.09,0.13)	0.06 (-0.05,0.17)	0.41	Ref	0.06 (-0.10,0.21)	0.27 (0.11,0.43)	0.16 (0.00,0.32)	0.01
Model 3 ^c	Ref	0.04 (-0.06,0.15)	-0.03 (-0.14,0.07)	-0.01 (-0.12,0.10)	0.68	Ref	0.04 (-0.12,0.20)	0.25 (0.08,0.41)	0.11 (-0.06,0.28)	0.05
Ln non-dense area (cm ²)										
Model 1 ^a	Ref	0.10 (0.02,0.17)	0.14 (0.06,0.21)	0.16 (0.09,0.24)	<0.01	Ref	0.06 (-0.03,0.16)	0.06 (-0.03,0.16)	0.09 (-0.01,0.19)	0.09
Model 2 ^b	Ref	0.08 (0.01,0.16)	0.12 (0.05,0.2)	0.15 (0.07,0.23)	<0.01	Ref	0.06 (-0.03,0.16)	0.05 (-0.05,0.15)	0.07 (-0.02,0.17)	0.17
Model 3 ^c	Ref	0.01 (-0.05,0.08)	-0.02 (-0.08,0.05)	-0.02 (-0.09,0.04)	0.40	Ref	-0.05 (-0.13,0.04)	-0.08 (-0.16,0.01)	-0.15 (-0.24,-0.07)	<0.01

^aModel 1: Adjusted for age (continuous) and state of residence (Jalisco or Veracruz)

^bModel 2: Model 1 and family history of breast cancer (no, yes), history of BBD (no, yes), MET's per week (tertiles), age at menarche (<12, 12, 13, 14+, unknown), smoking (never, past, current, unknown), alcohol (none, any, unknown), number of full term pregnancies (nulliparous, 1, 2, 3, 4+, unknown), age at first pregnancy (<25, 25+, unknown), AmerIndian language (no, yes, unknown), oral contraceptive use (never, ever, unknown), breastfeeding (never, <12 months, 12+months, unknown), daily calcium intake (quartiles), postmenopausal hormone use (postmenopausal only: never, past, past or current, unknown), ln-dense area (in ln-non dense area models), and ln-non dense area (in ln-dense area models)

^cModel 3: Model 2 and BMI (continuous)

Table 3

Difference in percent mammographic density (95% CI) by quartile of bone mineral density (g/cm²) stratified by BMI (<30, 30 kg/m²) and menopausal status.

	Premenopausal Women						Postmenopausal women					
	Quartile 1 (<0.41)	Quartile 2 (0.41–0.45)	Quartile 3 (0.45–0.48)	Quartile 4 (0.48+)	P- trend	P-het	Quartile 1 (<0.35)	Quartile 2 (0.35–0.40)	Quartile 3 (0.40–0.44)	Quartile 4 (0.44+)	P- trend	P-het
	Percent density						Percent density					
Model 3 ^c	BMI<30						BMI<30					
	N=194	N=166	N=161	N=131			N=107	N=95	N=87	N=62		
	Ref	−0.13 (−2.91, 2.65)	−2.39 (−5.26, 0.47)	−2.82 (−5.90, 0.27)	0.04		Ref	0.03 (−3.59, 3.65)	3.12 (−0.73, 6.98)	3.32 (−0.96, 7.60)		0.06
	N=49	N=68	N=92	N=103		< 0.01	N=29	N=46	N=48	N=78		0.76
Model 3 ^c	BMI 30						BMI 30					
	Ref	1.24 (−4.12, 6.59)	3.44 (−1.66, 8.53)	5.05 (0.02, 10.07)	0.03		Ref	0.09 (−6.26, 6.44)	7.91 (1.49, 14.32)	4.48 (−1.57, 10.53)		0.05
	Ln dense area (cm ²)						Ln dense area (cm ²)					
	BMI<30						BMI<30					
Model 3 ^c	Ref	0.00 (−0.11, 0.12)	−0.11 (−0.23, 0.01)	−0.15 (−0.28, −0.02)	< 0.01		Ref	−0.03 (−0.21, 0.14)	0.12 (−0.07, 0.31)	0.04 (−0.17, 0.26)		0.40
Model 3 ^c	BMI 30						BMI 30					
	Ref	0.14 (−0.09, 0.38)	0.12 (−0.11, 0.34)	0.21 (−0.01, 0.43)	0.09	0.01	Ref	−0.01 (−0.35, 0.33)	0.34 (−0.01, 0.68)	0.06 (−0.26, 0.39)		0.58
	Ln non-dense area (cm ²)						Ln non-dense area (cm ²)					
	BMI<30						BMI<30					
Model 3 ^c	Ref	0.00 (−0.08, 0.07)	−0.02 (−0.09, 0.06)	−0.01 (−0.09, 0.07)	0.71		Ref	−0.07 (−0.17, 0.03)	−0.11 (−0.21, 0.00)	−0.18 (−0.29, −0.06)		< 0.01
Model 3 ^c	BMI 30						BMI 30					
	Ref	0.05 (−0.07, 0.17)	−0.05 (−0.16, 0.07)	−0.04 (−0.16, 0.07)	0.21	0.04	Ref	−0.03 (−0.19, 0.13)	−0.12 (−0.29, 0.04)	−0.18 (−0.33, −0.03)		0.16

^cModel 3: Adjusted for age (continuous), state of residence (Jalisco or Veracruz), family history of breast cancer (no, yes), history of BBD (no, yes), METs per week (tertiles), age at menarche (<12, 12, 13, 14+, unknown), smoking (never, past, current, unknown), alcohol (none, any, unknown), number of full term pregnancies (nulliparous, 1, 2, 3, 4+, unknown), age at first pregnancy (<25, 25+, unknown), AmerIndian language (no, yes, unknown), oral contraceptive use (never, ever, unknown), breastfeeding (never, <12 months, 12+months, unknown), daily calcium intake (quartiles), postmenopausal hormone use (postmenopausal only: never, past, past or current, unknown), BMI (continuous), In-dense area (in In-non dense area models), and In-non dense area (in In-dense area models).