# Does Breast Size Modify the Association between Mammographic Density and Breast Cancer Risk?

**Anne Stuedal,[1] Huiyan Ma,[2] Leslie Bernstein,[3] Malcolm C. Pike,[3] and Giske Ursin[1,3]**

[1]Department of Nutrition, University of Oslo, Oslo, Norway; [2]Institute for Health Promotion and Disease Prevention Research, University of Southern California, Alhambra, California; and [3]Department of Preventive Medicine, Keck School of Medicine, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, California

## Abstract

Background: **Both the absolute and the percent of mammographic density are strong and independent risk factors for breast cancer. Previously, we showed that the association between mammographic density and breast cancer risk tended to be weaker in African American than in White U.S. women. Because African American women have a larger breast size, we assessed whether the association between mammographic density and breast cancer was less apparent in large than in small breasts.**
Methods: **We assessed mammographic density on mammograms from 348 African American and 507 White women, 479 breast cancer patients and 376 control subjects, from a case-control study conducted in Los Angeles County. We estimated odds ratios (OR) for breast cancer with increasing mammographic density, and the analyses were stratified by mammographic breast area.**
Results: **Median breast size was 168.4 $cm^2$ in African American women and 121.7 $cm^2$ in White women ($P$ for difference <0.001). For absolute density, adjusted ORs (95% confidence intervals) per increase of 10 $cm^2$ were 1.32 (1.13-1.54), 1.14 (1.03-1.26), and 1.02 (0.98-1.07) in the first, second, and third tertiles of breast area, respectively ($P$ for effect modification by breast area = 0.005). The results for percent density were similar although weaker; adjusted ORs per 10% increase (absolute value) in percent density were 1.22 (1.05-1.40), 1.22 (1.06-1.41), and 1.03 (0.90-1.18 $P$ for effect modification by breast area = 0.34).**
Conclusion: **Our results indicate that the association between mammographic density and breast cancer may be weaker in women with larger breasts.** (Cancer Epidemiol Biomarkers Prev 2008;17(3):621–7)

## Introduction

Mammographic density is a strong, independent risk factor for breast cancer. Women with the highest mammographic density are at four to six times higher risk of breast cancer compared to those with no or very low densities (1-4). The biological basis for the increased risk associated with high mammographic density is not completely understood, however. The predominant histologic feature of breasts that are mammographically dense is a breast rich in stroma or collagen, although mammographic density is also correlated with the amount of epithelium (5, 6). The absolute amount of dense mammographic tissue, potentially reflecting the number of epithelial cells at risk, intuitively appears as a plausible explanation for the association between mammographic density and breast cancer risk. However, although absolute mammographic density has also been associated with breast cancer (2, 3, 7), percent mammographic density, that is, the ratio of the dense area to the total area of the breast as visualized by the mammogram, has been the most commonly used mammographic density measurement in relation to breast cancer risk (8). Contrary to absolute density, however, the measure of percent density does not specify the amount of dense tissue involved.

We have reported previously (3) that, although differences in mammographic density between ethnicities were small and not statistically different, the associations of both absolute and percent mammographic density with breast cancer were weaker for African American women than for White women. Per 10% increase in percent density odds ratio [OR 95% confidence interval (95% CI)] was 1.15 (1.04-1.27) for White women and 1.11 (0.98-1.26) for African Americans. For absolute density, ORs (95% CIs) per decile were 1.18 (1.02-1.36) and 1.09 (0.96-1.25) for White and African American women, respectively. Both breast area, as measured by the outline of the breast on the mammogram, and the amount of fibroglandular tissue, represented by the dense part of the breast on the mammogram, were higher in African American women than in White women (9). Here, we explore these relationships to determine whether breast size modifies the association between absolute and percent mammographic density and risk of breast cancer.

Received 9/7/07; revised 11/20/07; accepted 12/14/07.

**Grant support:** University of Oslo fellowship (A. Stuedal). Case identification was supported by USPHS grant N01-CN-67010 from the National Cancer Institute, NIH, Department of Health and Human Services and the California Department of Health Services as part of its statewide cancer reporting program mandated by Health and Safety Code Sections 103875 and 1033885. Data collection for the Women's Contraceptive and Reproductive Experiences Study was funded by the National Institute of Child Health and Human Development with additional support from the National Cancer Institute through a contract with the University of Southern California grant N01-HD-3-3175. The mammogram study was supported by California Breast Cancer Research Program grant 2RB-0058.

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**Requests for reprints:** Giske Ursin, Department of Preventive Medicine, Keck School of Medicine, University of Southern California/Norris Comprehensive Cancer Center, 1441 Eastlake Avenue 4407, Los Angeles, CA 90089. Phone: 323-865-0423; Fax: 323-865-0142. E-mail: gursin@usc.edu



doi:10.1158/1055-9965.EPI-07-2554

## Subjects and Methods

**Subject Identification.** Women included in this analysis were participants ages 35 to 64 years in a mammographic density study of Asian American, African American, and White women that we have described previously (3). For the present study, we restricted the analyses to White and African American women. This subgroup of women all came from the Los Angeles County component of the Women's Contraceptive and Reproductive Experiences (CARE) Study (10). The Women's Contraceptive and Reproductive Experiences Study was a multicenter, population-based case-control study of invasive breast cancer conducted among women ages 35 to 64 years in five areas of the United States, including Los Angeles County (10). Eligible case patients were U.S.-born White and African American women residing in Los Angeles County when diagnosed with a first primary invasive breast cancer between June 1994 and August 1998. Control subjects were selected by random-digit dialing among the residents of Los Angeles County and were frequency matched to case patients on age and ethnicity. All case patients were identified by the Los Angeles County Cancer Surveillance Program, an established population-based cancer registry that is part of the National Cancer Institute's Surveillance, Epidemiology and End Results registry program. Participation rates in Los Angeles were 71.9% for African American case patients, 70.6% for African American control subjects, 74.6% for White case patients, and 76.2% for White control subjects (10). Case and control recruitment was done concurrently; participants were interviewed at their homes or offices. Interviewers used structured questionnaires that contained a standard set of questions on established and suspected breast cancer risk factors, including information on previous mammograms. A reference date, created for each study subject, was the date of diagnosis for case patients, and the date on which the screening questionnaire was completed (at the first contact during random-digit dialing) for the control subjects.

For the mammographic density study, we identified breast cancer patients with unilateral cancer who reported having a diagnostic or prediagnostic mammogram of the contralateral breast within 5 years of their diagnosis date as well as control subjects who reported a mammogram within 5 years of their reference date or in the 1 year after their reference date (3).

From the 1,374 eligible women, we retrieved and scanned one or more mammograms for 949 women (531 case patients and 418 control subjects). The rate of mammograms that we obtained for the two ethnic groups was 72.7% (case patients, 71.1%; control subjects, 74.6%) for Whites and 64.7% (case patients, 69.3%; control subjects, 59.4%) for African Americans.

The scanned mammogram files of 20 women (16 case patients and 4 control subjects) could not be assessed for density as the digitized files were not usable, and we were unable to obtain the films a second time. We excluded mammograms of 4 case patients who had only one mammogram and were pregnant at the time of that mammogram. We therefore obtained mammographic density results for 925 women (511 case patients and 414 control subjects).

To use a consistent sample size for all analyses, we excluded 43 women (20 case patients and 23 control subjects) who had either undergone simple hysterectomy or had missing values for one or more variables included as covariates in our adjusted analyses. Our analyses of 855 women included 507 White women (280 case patients and 227 control subjects) and 348 African American women (199 case patients and 149 control subjects).

The study was approved by the Institutional Review Board at the University of Southern California. Each participant provided a signed informed consent and a release allowing us to request her mammograms.

**Processing of Mammograms.** We collected the most recent prediagnostic (25.7%) or diagnostic (74.3%) mammograms for the eligible case patients and the most recent mammogram within the defined period for the eligible control subjects. In case patients with prediagnostic mammograms, 61% had their mammogram within 1 year of diagnosis. In controls, 29.3% had their mammogram in the year of their reference date, and of the remaining controls, 51.1% had the mammogram within 1 year of the reference date.

All mammograms were digitized at a resolution of 150 pixels/in. (59 dots/cm). The mammograms were read in batches containing equal proportions of case patients and control subjects from each 5-year age group represented. For case patients, we read the mammogram from the contralateral (nondiseased) breast. For control subjects, we randomly selected the right or left breast while assuring that, within each batch, the control laterality distribution represented that of the unaffected (contralateral) breast of the case patients. The density assessments were done by G.U., whereas the breast area measurements were conducted by a research assistant trained by G.U. Assessment methods have been described and validated previously (11).

Briefly, these assessments use the digitized craniocaudal mammographic image. The computer software program assigns a pixel value of 0 to the darkest (black) shade in the image and a value of 255 to the lightest (white) shade with shades of gray assigned intermediate values. A reader first defines the total breast area using a special outlining tool. Next, the region of interest, excluding the pectoralis muscle, prominent veins, and fibrous strands, is defined. The reader then uses a tinting tool to apply a yellow tint to dense pixels with gray levels at or above some threshold $X$ and a pixel value of $\leq 255$. The reader searches for the best threshold where all pixels $X$ within the region of interest are considered to represent mammographic densities. The software estimates the total number of pixels and the number of tinted pixels within the region of interest. Absolute density represents the count of the tinted pixels within the region of interest. Percent density, or the fraction (%) of the breast with densities, is the ratio of absolute density to the total breast area.

**Statistical Methods.** Mammographic measures in our analyses include breast size, absolute density, and percent density. We used the total mammographic area as a proxy for breast size.

We present medians of age, body mass index (BMI), and mammographic density measures by breast area tertiles and ethnic group. $P$ values for case control differences are obtained from Mann-Whitney $U$ test.

We analyzed absolute and percent mammographic density as continuous and categorical variables (tertiles). When considering mammographic density as a continuous variable, the results are described in terms of intervals of 10 $cm^2$ for absolute density and intervals of 10% (absolute value) for percent density. We defined three strata of breast area (small, medium, and large) using tertiles (cut points: 109.8 and 174.9 $cm^2$). We estimated OR (95% CI) of breast cancer associated with increasing levels of mammographic density using standard multivariate unconditional logistic regression methods within strata (small, medium, and large) of breast area. In each stratum of breast area, we estimated the OR (95% CI) of breast cancer for women whose mammographic density were categorized in the second and third tertiles compared with those whose mammographic density was categorized in the first tertile (the category of lowest density). We also estimated the OR (95% CI) of breast cancer for mammographic density modelled as continuous variables.

We adjusted for the following variables: ethnicity (White, African American), age at mammogram in 5-year age groups (categorical), prediagnostic BMI (reported for the date 5 years before reference date, in $kg/m^2$, continuous), age at menarche (≤13, >13 years), breast cancer family history [none, breast cancer in a mother or a sister (first degree), breast cancer in an aunt or grandmother (second degree)], number of full-term pregnancies (0, 1-2, ≥3), a variable combining menopausal status and hormone therapy use at the time of the mammogram [premenopausal, postmenopausal and never hormone therapy use, postmenopausal and current estrogen therapy, postmenopausal and current estrogen + progestin therapy use, postmenopausal and ex-estrogen therapy, and postmenopausal and ex-estrogen + progestin therapy (including those who had used both estrogen therapy and estrogen + progestin therapy in the past)], and age at first full-term pregnancy (<30, ≥30 years).

To evaluate effect modification by breast area, we tested for homogeneity of trends using a likelihood ratio test. We compared the fit of the fully adjusted model with one trend variable for mammographic density with the fit of a fully adjusted model with a mammographic density trend variable for each breast size tertile. Test for homogeneity of trends were performed for both the continuous and tertile measure of density. In each case, the density variable was entered as a variable with 1 *df*.

To understand the magnitude of the joint effects of breast density and breast size, we constructed a nine-category variable by cross tabulating tertiles of breast area with tertiles of absolute mammographic density. We provide adjusted ORs for the joint effects using small breast/low absolute density as the reference category.

The statistical analyses were performed using SPSS for Windows version 14.0 (SPSS). All *P* values are two sided. We considered two-sided *P* values <0.05 statistically significant.

## Results

Median age of all women was 49 years (range, 32-64). Median BMI was 24.7 $kg/m^2$ (range, 16.7-53.1). A total of 44.7% of the women were postmenopausal; 29% of the women were current hormone therapy (estrogen therapy + estrogen plus progestin therapy) users. Current hormone therapy use was less common in African American (21.8%) than in White women (33.9%). The correlation coefficient (Spearman's rank) between BMI and breast size was 0.62 ($P < 0.001$). We have reported previously that case patients were more likely to have a later age at first birth and were more likely to have a first-degree family history of breast cancer than control subjects. Case patients were more likely to be premenopausal and less likely to currently use hormone therapy than control subjects. Case patients had statistically significant higher absolute and percent density than control subjects (3).

Table 1 shows age, BMI, and density measures by breast size tertiles and ethnic group. Case control differences in absolute and percent density were statistically significant, or near significant, for African American and White women in the lowest breast area tertile and for Whites in the middle tertile. However, there were no significant differences between cases and controls on mammographic density in the upper tertile of breast area.

Table 2 shows the associations between absolute and percent mammographic density and breast cancer risk stratified by tertiles of breast area. The association between absolute mammographic density and breast cancer was statistically significant for small- and medium-sized breasts only; no significant association was observed for large breasts. There was a statistical significant effect modification by breast area when we considered absolute mammographic density as a continuous variable ($P = 0.005$). The actual distribution of absolute density within small and large breasts (within the tertiles of absolute density provided) makes this finding even more noteworthy. In the medium-sized breast, the median of the highest tertile of absolute density was 72.1 $cm^2$ (respective median percent density was 52.8), whereas in the largest breast size the median of the highest tertile of absolute density was 90.4 $cm^2$ (respective percent density was 39.7%).

For percent mammographic density, the association between mammographic density and breast cancer risk in tertiles of mammographic area resembled that of absolute density, that is, there was a marked increase in risk with increasing percent density for women with small- and medium-sized breasts but no association observed among women with large breasts. However, for percent mammographic density, effect modification was not statistically significant ($P = 0.34$ for percent mammographic density considered as a continuous variable). In analyses stratified by age (<50 versus ≥50 years), we observed a similar pattern with the highest risk per increase in density in women with the smallest breast sizes and the smallest increase in the women with the largest breasts (results not shown).

When we stratified by race, the results were similar but not as striking among African American women. For absolute density, the adjusted ORs per 10 $cm^2$ increase, for small, medium, and large breasts, respectively, were 1.38 (1.14-1.67), 1.15 (1.01-1.31), and 1.06 (0.97-1.15) for White women and 1.18 (0.78-1.81), 1.13 (0.95- 1.35), and 1.02 (0.96-1.09) for African American women. The corresponding results for percent density were 1.25 (1.05-1.49), 1.22 (1.0-1.47), and 1.13 (0.90-1.41) for White women and 1.00 (0.65-1.55), 1.25 (0.97-1.62), and 1.01 (0.84-1.22) for African American women.

**Table 1. Median (range) of age, BMI, and mammographic density measures by breast area (tertiles) and ethnicity**

| | African American | | | White | | |
|---|---|---|---|---|---|---|
| | Cases | Control | P* | Cases | Control | P* |
| First tertile of breast area | | | | | | |
| No. subjects | 38 | 34 | | 121 | 92 | |
| Age | 44.5 (36-63) | 46.5 (35-59) | 0.79 | 45.0 (32-64) | 47.5 (34-63) | 0.66 |
| BMI | 23.6 (17.2-27.5) | 23.6 (18.9-31.6) | 0.50 | 21.1 (16.7-31.3) | 22.3 (17.1-32.3) | 0.01 |
| Absolute density | 37.1 (2.8-74.1) | 28.3 (1.3-67.5) | 0.06 | 37.0 (0.3-86.9) | 26.9 (0.8-78.3) | <0.001 |
| Breast size | 93.4 (24.5-109.6) | 89.2 (28.2-109.5) | 0.50 | 81.0 (29.9-109.4) | 79.4 (33.5-109.8) | 0.75 |
| % Density | 45.5 (2.8-79.4) | 34.0 (1.2-74.7) | 0.03 | 48.3 (0.4-85.7) | 42.7 (0.8-78.3) | 0.003 |
| Second tertile of breast area | | | | | | |
| No. subjects | 75 | 39 | | 96 | 75 | |
| Age | 50.0 (36-64) | 48.0 (35-63) | 0.52 | 48.0 (33-64) | 51.0 (34-64) | 0.22 |
| BMI | 26.3 (18.0-41.0) | 25.5 (20.6-38.4) | 0.62 | 24.2 (19.1-41.0) | 23.6 (18.2-41.8) | 0.71 |
| Absolute density | 47.0 (0.0-100.7) | 42.1 (0.0-99.8) | 0.23 | 46.5 (0.0-114.9) | 40.6 (0.2-118.7) | 0.02 |
| Breast size | 134.3 (111.7-174.3) | 141.9 (116.5-174.3) | 0.32 | 138.3 (109.8-174.8) | 132.8 (109.9-173.0) | 0.44 |
| % Density | 36.2 (0.0-84.8) | 27.3 (0.0-73.5) | 0.13 | 35.3 (0.0-82.4) | 28.1 (0.2-78.6) | 0.02 |
| Third tertile of breast area | | | | | | |
| No. subjects | 86 | 76 | | 63 | 60 | |
| Age | 50.5 (36-64) | 51.5 (35-64) | 0.16 | 49.0 (35-64) | 52.0 (34-64) | 0.23 |
| BMI | 28.8 (19.7-53.1) | 28.4 (21.6-51.6) | 0.66 | 27.2 (17.8-48.4) | 29.1 (20.8-48.7) | 0.01 |
| Absolute density | 53.9 (0.0-242.9) | 37.9 (0.0-187.6) | 0.35 | 57.6 (0.0-229.9) | 43.4 (0.0-214.6) | 0.19 |
| Breast size | 250.5 (175.0-620.6) | 236.2 (175.1-640.6) | 0.32 | 225.8 (175.7-747.4) | 220.6 (177.6-470.4) | 0.86 |
| % Density | 20.9 (0.0-82.2) | 15.6 (0.0-75.8) | 0.50 | 24.5 (0.0-76.5) | 19.3 (0.0-70.4) | 0.20 |

NOTE: Breast area cut points are 109.8 and 174.9 $cm^2$.
*$P$ values obtained from Mann-Whitney $U$ test.

When we did the statistical analyses stratified by breast area tertiles eliminating BMI from the model, or by restricting the analyses to women with BMI <30 $kg/m^2$ ($n$ = 693), or restricting the analyses to noncurrent hormone therapy users ($n$ = 607), results were similar (results not shown).

To understand further the joint effects of mammographic density and breast size, we created a composite variable of absolute mammographic density and breast size, with the reference group being the category of small breast/low absolute density. As reported above, the test for homogeneity of absolute density across tertiles of breast size was statistically significant only when the continuous measure of absolute density was used. The highest OR (95% CI) for the association with breast cancer was found for the combination of high absolute density and a small breast size [3.17 (1.35-7.46)]. Furthermore, the OR (95% CI) for the combination of medium absolute density in a medium-sized breast [3.01 (1.60-5.64)] was higher than the combination of high absolute density in a large-sized breast [2.19 (1.24-3.89)] despite the latter category having both higher absolute and percent density (Table 3).

When we did the cross-tabulation with breast size tertiles and percent mammographic density instead of absolute density, with small breast/low percent density as the reference category, the highest ORs (95% CIs) were found for the combinations of medium breast/medium percent density [3.36 (1.60-7.05)] and the medium breast/high percent density combination [3.18 (1.50-6.76)] rather than the large breast/high percent density category [2.19 (1.24-3.89)].

## Discussion

In the present study, we asked whether the relative risk of breast cancer associated with an increase in mammographic density, measured as either absolute or percent density, differs depending on a woman's breast size. Our results suggest that, when absolute mammographic density increases, the associated relative risks are lower if the increase in density takes place in a large rather than a small breast. Although the results were not statistically significant, breast size also appeared to modify the effect of percent density on breast cancer risk.

Although the biological mechanisms that underlie the association between mammographic density and breast cancer risk are not well understood, what is known can provide some clues to understanding our findings. Mammographic density is strongly associated with the amount of collagen or breast stroma (12). It may also be a measure of the number of epithelial cells at risk (1, 6) or fibroglandular growth factors (13).

One explanation for our findings could be that what we measure as dense tissue in women with large breasts is biologically different from what we measure as dense tissue in smaller breasts. Mammographic density reflects the stroma (collagen and fibrous supportive tissue) of the breast (6, 12). It could be hypothesized that a higher proportion of the dense tissue in the largest breasts may have a more ''supportive'' role than it does in the smaller breasts, that is, it may be less correlated with the number of epithelial cells at risk and be more weakly associated with breast cancer risk.

Another hypothesis that could explain our findings is that breast fat has a potential protective effect on the association between mammographic density and breast cancer risk. There is some, although limited, evidence for this from the experimental literature. The fat tissue secretes and/or produces a number of biologically active substances (14), commonly named adipo(cyto)kines (15). Several studies have suggested that adipocyte secreted proteins could stimulate proliferation in malignant cells (16-18). Further, estrogens synthesized from androgens by the aromatase enzyme in peripheral adipose tissues

**Table 2. OR (95% CI) for breast cancer per tertile of mammographic density, stratified by breast area (tertiles), *n* = 855**

Absolute mammographic density

| Tertiles of breast area ($cm^2$) | Density ($cm^2$) | No. cases/ controls | Crude OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|---|
| | Tertiles* (actual distribution) | | | |
| Small (24.5-109.7) | Low (0.3-26.9) | 42/60 | 1.00 | 1.00 |
| | Median: 15.7 | | | |
| | Medium (26.9-52.8) | 90/56 | 2.30 (1.37-3.85) | 2.17 (1.25-3.74) |
| | Median: 38.9 | | | |
| | High (53.1-86.9) | 27/10 | 3.86 (1.69-8.81) | 3.11 (1.27-7.62) |
| | Median: 61.3 | | | |
| | $P_{trend}$ | | <0.001 | 0.002 |
| | OR (95% CI) per 10 $cm^2$ increase | | 1.36 (1.18-1.58) | 1.32 (1.13-1.54) |
| Medium (109.8-174.9) | Low (0.0-26.7) | 39/43 | 1.00 | 1.00 |
| | Median: 8.6 | | | |
| | Medium (27.1-52.0) | 57/28 | 2.24 (1.20-4.20) | 2.16 (1.11-4.21) |
| | Median: 39.3 | | | |
| | High (53.7-118.7) | 75/43 | 1.92 (1.08-3.41) | 1.93 (0.98-3.82) |
| | Median: 72.1 | | | |
| | $P_{trend}$ | | 0.04 | 0.06 |
| | OR (95% CI) per 10 $cm^2$ increase | | 1.11 (1.03-1.21) | 1.14 (1.03-1.26) |
| Large (175.0-747.4) | Low (0.0-26.6) | 49/52 | 1.00 | 1.00 |
| | Median: 4.5 | | | |
| | Medium (27.1-53.0) | 23/31 | 0.79 (0.41-1.53) | 0.57 (0.27-1.20) |
| | Median: 39.9 | | | |
| | High (53.2-242.9) | 77/53 | 1.54 (0.91-2.60) | 1.14 (0.63-2.07) |
| | Median: 90.4 | | | |
| | $P_{trend}$ | | 0.09 | 0.57 |
| | OR (95% CI) per 10 $cm^2$ increase | | 1.04 (0.99-1.08) | 1.02 (0.98-1.07) |
| *P* for effect modification by breast size† | | | | |
| | Tertiles | | | 0.12 |
| | Continuous (per 10 $cm^2$ increase) | | | 0.005 |

Percent mammographic density

| Tertiles of breast area ($cm^2$) | Density (%) | No. cases/ controls | Crude OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|---|
| | Tertiles‡ (actual distribution) | | | |
| Small (24.5-109.7) | Low (0.4-21.0) | 17/32 | 1.00 | 1.00 |
| | Median: 10.7 | | | |
| | Medium (22.3-45.2) | 52/41 | 2.39 (1.17-4.89) | 2.35 (1.08-5.10) |
| | Median: 35.4 | | | |
| | High (45.4-85.7) | 90/53 | 3.20 (1.62-6.3) | 2.53 (1.17-5.50) |
| | Median: 57.3 | | | |
| | $P_{trend}$ | | 0.001 | 0.04 |
| | OR (95% CI) per 10% (absolute value) increase | | 1.27 (1.12-1.43) | 1.22 (1.05-1.40) |
| Medium (109.8-174.9) | Low (0.0-21.3) | 41/48 | 1.00 | 1.00 |
| | Median: 7.7 | | | |
| | Medium (21.3-45.3) | 68/34 | 2.34 (1.30-4.21) | 2.36 (1.25-4.48) |
| | Median: 32.4 | | | |
| | High (45.31-84.8) | 62/32 | 2.27 (1.25-4.12) | 2.58 (1.25-5.33) |
| | Median: 56.1 | | | |
| | $P_{trend}$ | | 0.007 | 0.01 |
| | OR (95% CI) per 10% (absolute value) increase | | 1.17 (1.04-1.31) | 1.22 (1.06-1.41) |
| Large (175.0-747.4) | Low (0.0-21.2) | 72/75 | 1.00 | 1.00 |
| | Median: 3.1 | | | |
| | Medium (21.3-45.2) | 48/42 | 1.19 (0.70-2.01) | 0.98 (0.55-1.76) |
| | Median: 33.4 | | | |
| | High (45.6-82.2) | 29/19 | 1.59 (0.82 3.09) | 1.23 (0.59-2.56) |
| | Median: 57.3 | | | |
| | $P_{trend}$ | | 0.17 | 0.65 |
| | OR (95% CI) per 10% (absolute value) increase | | 1.10 (0.98-1.24) | 1.03 (0.90-1.18) |
| *P* for effect modification by breast size‡ | | | | |
| | Tertiles | | | 0.52 |
| | Continuous (per 10% increase) | | | 0.34 |

NOTE: Adjusted for BMI ($kg/m^2$; continuous), age at mammography (5-y interval), breast cancer family history (none, first degree, second degree), age at menarche (≤13 y, >13 y), number of full-term pregnancies (0, 1-2, ≥3), age at first full-term pregnancy (<30 y, ≥30 y), menopausal status and use of hormone replacement therapy (premenopausal, postmenopausal and: current estrogen therapy, current estrogen plus progestin therapy, ex-estrogen therapy, ex-estrogen plus progestin therapy, never hormone therapy), and race.

*Absolute density tertile cut points are 26.9 and 53.1 $cm^2$.

†Test for homogeneity of trends using likelihood ratio test (see text).

‡Percent density cut points are 21.2% and 45.3%.

**Table 3. Adjusted OR (95% CI) for breast cancer associated with the joint effect of absolute mammographic density and breast size, with the corresponding crude values of absolute and percent mammographic densities**

| Absolute density, tertiles | Breast area, tertiles | | |
|---|---|---|---|
| | Small | Medium | High |
| Low | 1.0 (reference) | 1.46 (0.79-2.72) | 1.68 (0.88-3.20) |
| Cases/controls | 42/60 | 39/43 | 49/52 |
| Median absolute density ($cm^2$) | 15.7 | 8.6 | 4.5 |
| Median % density | 23.2 | 5.8 | 1.61 |
| Medium | 2.1 (1.24-3.57) | 3.01 (1.60-5.64) | 1.12 (0.55-2.29) |
| Cases/controls | 90/56 | 57/28 | 23/31 |
| Median absolute density ($cm^2$) | 38.9 | 39.3 | 39.9 |
| Median % density | 48.4 | 28.8 | 16.6 |
| High | 3.17 (1.35-7.46) | 2.38 (1.35-4.18) | 2.19 (1.24-3.89) |
| Cases/controls | 27/10 | 75/43 | 77/53 |
| Median absolute density ($cm^2$) | 61.3 | 72.1 | 90.4 |
| Median % density | 67.6 | 52.8 | 39.7 |

NOTE: Adjusted for BMI ($kg/m^2$; continuous), age at mammography (5-y interval), breast cancer family history (none, first degree, second degree), age at menarche (≤13 y, >13 y), number of full-term pregnancies (0, 1-2, ≥3), age at first full-term pregnancy (<30 y, ≥30 y), menopausal status and use of hormone replacement therapy (premenopausal, postmenopausal and: current estrogen therapy, current estrogen plus progestin therapy, ex-estrogen therapy, ex-estrogen plus progestin therapy, never hormone therapy), and race.

(19) could stimulate growth of breast carcinoma cells (20). However, a few studies have suggested that adipocytes could support normal breast epithelial proliferation, but inhibit growth of breast carcinoma cells (21). Although this evidence is not completely consistent (22, 23), it offers some basis for a hypothesis that breast fat may have a direct beneficial effect.

Another possible explanation is that our finding is due to measurement error. In our study, we used measures from standard two-dimensional mammographic images to represent volumes of fibroglandular mass and the breast size. Although this will probably inaccurately reflect the true volumes of these components, a recent study showed a high correlation between percent volumetric fibroglandular tissue from magnetic resonance images and mammographic percent dense area (24). Differences in compression during mammography may cause the amount of dense tissue evaluated from the mammograms to reflect the actual amount of fibroglandular mass differently for small and large breasts. The misclassification of fibroglandular tissue would most likely be nondifferential with respect to case-control status, and if misclassification is higher among those with the largest breasts, a bias towards the null would probably be more pronounced among the women with the largest breasts.

If our findings of a beneficial modifying effect of a large breast are true, so that mammographic density truly is less associated with breast cancer risk in large breasts than in small breasts, then one would expect a stronger association between mammographic density and breast cancer risk in women with smaller breasts. Our current analysis was limited to African American and White women. However, our findings may also be generalized to other ethnic groups. Asian women tend to have smaller breast sizes compared with Caucasian women. In a previous analysis of the case-control differences in this study and in a group of Asian American cases and controls, we reported no statistically significant ethnic differences in the risk of breast cancer associated with mammographic density (3). However, both absolute density and percent density were stronger risk factors for Asian American women than for White or African American women. On the other hand, Maskarinec et al. did not find higher risk among Asians than in Caucasians in a study from Hawaii (7). Whether the discrepancy between the two studies is due to unmeasured differences between the Asian populations in Los Angeles and Hawaii, or to other reasons is unknown. In a study of Japanese women (25), where mean breast size was considerably smaller than in the present study, the adjusted increases in risk per 1% mammographic density was 0.7% ($P_{trend}$ = 0.22) and 2.3% ($P_{trend}$ = 0.005) in premenopausal and postmenopausal, respectively. The corresponding value in our study as reported previously was 1.1% for African American, 1.5% for White, and 3.0% for Asian American women (3). Thus, although the Nagata et al. study did not find much stronger effects of density despite the smaller breast volumes, it is difficult to directly compare the numbers from the Nagata et al. study with ours because we used different methods of assessing mammographic density.

A weakness of our study is the relative small number of African American women. Furthermore, because BMI was reported retrospectively for the date 5 years before the reference date, these values could be inaccurate, and residual confounding by BMI is possible. Controls in general had the shortest time span between reported BMI and the mammogram. For any such confounding to have explained our results, the residual confounding by BMI would have had to be larger in women with a large breast size. Although we think this is unlikely, we cannot exclude the possibility.

When we restricted the analyses to women with <4 years span between the time of reported BMI and time of the mammogram, leaving 123 cases and 266 controls in the analyses, a pattern of a weaker association between density and breast cancer risk for a large breast size remained.

In conclusion, our results suggest that the association between both absolute (and, possibly, percent) mammographic density and breast cancer risk could be weaker in a large compared with a small breast. It would be important to confirm whether our results are true using methods that more accurately assess the exact volume of the breast and its fibroglandular and fat components. If

mammographic density truly is a weaker risk factor in large breasts, then it should be determined whether the composition of the fibroglandular tissue differs in small and large breast sizes. Furthermore, it will be important to clarify the role of the fatty tissue in the breast and in particular whether or how fat could modify epithelial cell proliferation and breast tumorigenesis.

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Anne Stuedal, Huiyan Ma, Leslie Bernstein, et al.

*Cancer Epidemiol Biomarkers Prev* 2008;17:621-627.