Risk Factors for Breast Cancer Associated with Mammographic Features in Singaporean Chinese Women

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Abstract

Background: **Mammographic density has been found to be a strong risk factor for breast cancer and to be associated with age, body weight, parity, and menopausal status. Most studies to date have been carried out in Western populations. The purpose of the study described here was to determine in a cross-sectional study in a Singaporean Chinese population the demographic, menstrual, reproductive, and anthropometric factors that are associated with quantitative variations in age-adjusted percentage mammographic densities and to examine the association of these factors with the dense and nondense areas of the mammogram.**

Method: **We used mammograms and questionnaire data collected from subjects in the Singapore Breast Screening Project. Women ages 45 to 69 years participated and 84% of those screened were Chinese. Mammograms were digitized and percentage density was measured and analyzed in relation to the questionnaire data.**

Results: **Percentage mammographic density was associated with several risk factors for breast cancer, most of them also associated, in opposite directions, with the dense and nondense components of the image. Percentage density was associated with age and weight (both negatively), height and age at first birth (both positively), and number of births and postmenopausal status (both negatively). Percentage density was weakly associated with a previous breast biopsy but was not associated with age at menarche or menopause, with use of hormones, or with a family history of breast cancer.**

Conclusion: **Percentage mammographic density in Singaporean Chinese women has similar associations with risk factors for breast cancer to those seen in Caucasians.** (Cancer Epidemiol Biomarkers Prev 2004; 13(11):1751–8)

Introduction

Mammographic density, which reflects the amounts of stroma and epithelium in the breast, has consistently been found to be a strong risk factor for breast cancer (1). Women with densities in ≥75% of the breast have a risk of breast cancer four to six times that of women of the same age with no densities, a difference in risk that persists for at least a decade from the time of the mammogram used in classification (2, 3). Most studies of this risk factor to date have been carried out in Western populations and have shown that older age and, after adjustment for age, greater body weight and greater parity are all associated with a smaller percentage of the breast occupied by radiologically dense breast tissue (1, 4, 5). However, less attention has been paid to the relationship of mammographic densities to risk of breast cancer (6, 7), or to the factors that influence them, in populations at lower risk of the disease. Further, variations in percentage density must be due to variations in one or both of the dense or nondense components of the mammogram. Although it has been shown the differences in the dense area account for much of the effect of percentage density on risk of breast cancer (3), little is known about the factors that are associated with variation in this measure.

The age-adjusted incidence of breast cancer is known to vary widely around the world. Age-standardized (to the world population) rates for Canada and Singaporean Chinese for 1988 to 1992 were 76.8 and 39.5 per 100,000, respectively (8). The purpose of the study described here was to determine in a cross-sectional study in a Singaporean Chinese population the demographic, menstrual, reproductive, and anthropometric factors that are associated with quantitative variations in age-adjusted percentage mammographic densities and to examine the association of these factors with the dense and nondense areas of the mammogram.

Methods

General Method. The general method was to use mammograms and questionnaire data already collected

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from subjects in the Singapore Breast Screening Project (SBSP). The SBSP is a population-based study designed to compare the prevalence of breast cancer in women ages 45 to 69 years randomized either to two-view mammography without physical examination or to observation. Women ages 45 to 69 years were randomly selected from the population registry of Singapore to participate in the SBSP and were issued written invitations for free screening. Forty-two percent of women who received invitations responded and a total of 29,193 women were screened by mammography in the SBSP between 1994 and 1997, when enrollment ended. Eighty-four percent (n = 24,609) of those screened were Chinese.

The data collected by questionnaire at the time of the baseline mammogram, administered by an interviewer, from all subjects in the SBSP included age, ethnic origin, education, occupation, prior breast screening history, age at menarche, menopausal status, number of pregnancies and deliveries, dates of the first and last delivery, history of breast feeding, use of oral contraceptives (OC) and hormone replacement therapy (HRT), family history of breast cancer (defined as having any relative with breast cancer), breast symptoms (of pain, tenderness, and swelling), and biopsies. Anthropometric measures of height, weight, and waist and hip circumferences were also taken.

Compared with the general population of Singapore, participants in the SBSP were more likely to be married, to have a formal education, and to be employed outside the home (9).

Selection of Subjects. Subjects for the present cross-sectional study to examine the association of mammographic features with demographic, menstrual, reproductive, and anthropometric factors were selected by a stratified random sample from all Chinese subjects who are members of the mammography arm of the SBSP. Subjects with invasive breast cancer were excluded. Subjects with breast implants or with augmentation or reduction mammoplasty were also excluded.

To ensure a wide range of risk factors, we selected subjects from a stratification of the SBSP by age, age at menarche, number of live births, weight, and menopausal status, all factors known to be associated with mammographic features in Western populations. Age, age at menarche, and weight were divided into quartiles. Number of children was divided into a group with none, and number of children for parous women was divided into three groups of approximately equal size. Menopausal status was divided into the two groups of premenopausal and perimenopausal or postmenopausal. The full SBSP population was divided into $4 \times 4 \times 4 \times 4 \times 2 = 512$ cells, and although we expected an average of 40 subjects per cell and planned to sample randomly two women from each cell, not all mammograms could be found and some cells were empty or contained only one subject. The final sample available for analysis was 803.

Measurement of Mammograms. The images assessed were the baseline mammogram taken at entry to the screening program. All SBSP mammograms were stored in one location under the jurisdiction of the Clinical Trials and Epidemiology Research Unit (D.H.). As in our previous work, one craniocaudal view was measured. For each subject, we randomly selected the side of the craniocaudal view that was used. The methods of digitization and measurement have been described previously (10). Films were read by one reader (N.F.B.) in sets of ~120 images composed of randomly ordered films. The interactive computer-assisted method was used to generate measurements of the areas of dense tissue and total area, and percentage density and nondense area were derived from these measurements. The reliability of the computer-assisted method of measurement was assessed by re-reading within each reading session a randomly selected 10% sample of images, randomly distributed among the images being read, and a further 10% of images were re-read between sessions.

Statistical Methods. The relationship of risk factors and anthropometric variables to the mammographic measures of percentage density, dense and nondense areas, was examined using linear regression. All models were inspected for normality and were satisfactory, with the exception of nondense area, which was log transformed. The linear assumption of all continuous explanatory variables was tested, particularly the relationship between mammographic density and age. Both univariate, adjusted for age, and multivariate models are given. Multivariate analysis involved fitting the most parsimonious model where only variables significantly associated with the mammographic measure ($P < 0.1$) were kept in the model. For illustrative purposes, explanatory variables that were excluded from the parsimonious model were added one at a time, and the regression coefficients were recorded and are shown in the tables in italics.

For the multivariate analysis, several changes in the coding of explanatory variables should be noted. For age at first birth, which is applicable to parous subjects only, nulliparous subjects were coded as zero and the mean age at first birth (among parous subjects) was subtracted from the age at first birth of each parous subject. In addition, for parous subjects, 1 was subtracted from the number of live births. Thus, the regression coefficient for the parity variable contrasts subjects with the mean age at first birth and only one child to nulliparous subjects. The regression coefficient for the age at first birth variable gives the effect of a 1-year difference in age at first birth (among parous subjects), and the effects of *additional* children (>1) can then be estimated through the regression coefficient of the number of live births variable.

Results

Characteristics of Subjects. Selected characteristics of the subjects studied are shown in Table 1. Their mean age was 57 years. Mean age at menarche was 14.5 years and mean age at first birth was 24.7 years. Seventy-eight percent of subjects were parous and the average number of deliveries was 2.9. Mean age at menopause was 49.2 years. Twenty-one percent of subjects had used HRT for an average of 40 months among users. Three percent had at least one first-degree relative with breast cancer and 5.7% reported a breast biopsy. Two percent had completed a degree or professional qualification and 5.7% had completed education to diploma or ''A'' level (usually taken at ages 17-18 years) and 18.7% to ''O'' level

Table 1. Characteristics of subjects

	Mean (SD) or %
Age (y)	56.68 (4.18)
Anthropometric	
Weight (kg)	57.09 (9.48)
Height (cm)	153.78 (5.50)
BMI (kg/m^2)	24.13 (3.80)
Waist (cm)	79.30 (9.32)
Hip (cm)	97.98 (7.97)
Waist/hip ratio	0.81 (0.07)
Menstrual and reproductive	
Age at menarche (y)	14.53 (1.75)
Parity (% parous)	77.83
Age at first delivery (y), n = 625	24.73 (5.09)
No. deliveries	2.91 (2.33)
Age at menopause (y), n = 494	49.16 (4.69)
Menopausal status (% post)	61.52
Exogenous hormones	
OC use (% ever)	34.62
HRT use (% ever)	20.92
Duration of HRT use (mo)	8.39 (25.55)
Duration of HRT use (mo), n = 168	40.10 (43.09)
Other	
Smoking status (% ever)	4.11
First-degree relative (% yes)	2.99
Education	
No formal education	54.30
PSLE	19.05
GCE ''O''/''N'' level	18.68
GCE ''A'' level/diploma	5.73
Degree/professional qualification	2.24
Breast symptoms (% yes)	3.74
Breast biopsy (% yes)	5.73
Mammographic density	
Percentage density (%)	27.80 (16.24)
Dense area (cm^2)	26.28 (16.02)
Nondense area (cm^2)	76.34 (37.66)

(usually taken at ages 15-16 years). There were no women with *in situ* cancer in the sample.

Compared with the entire population in the SBSP, subjects in our study were slightly less likely to be married (76% versus 80%), more likely to have a formal education (46% versus 39%), and more likely to work outside the home (41% versus 32%). The distribution of ages was similar in the SBSP and the present study (data not shown).

Distribution of Mammographic Measures According to Age. Box plots showing the distributions of percentage density, dense and nondense areas, according to age are shown in Fig. 1A-C and the association of age and mammographic measures is further examined in Tables 2, 3, and 4. Age was negatively associated with percentage density, and each additional year of age was associated in multivariate analysis with an average of 0.64 percentage points less density. Age was negatively associated with dense area, and each additional year of age was associated in multivariate analysis with an average of 0.52 cm^2 less dense tissue. Age was positively associated with nondense area, and each additional year of age was associated in multivariate analysis with an average of 0.1 cm^2 more nondense tissue. At all ages, there was wide variation in all of these measures. Because of the strong effect of age on these measures, all of the age-adjusted and multivariate analyses that are shown below were adjusted for age.

Factors Associated with Mammographic Features

Percentage Density. Table 2 shows the associations found between percentage mammographic density and other variables. Weight (negatively), height (positively), and body mass index (BMI; negatively) were all significantly associated with percentage density after adjustment for age and other variables. Each additional centimeter in height was associated with an average of 0.36 percentage points more percentage density.

Age at menarche was not associated with percentage density, but age at first delivery (positively), parity, and number of deliveries (both negatively) were all significantly associated with percentage density in multivariate analysis. Age at menopause was not significantly associated with percentage density, but postmenopausal women had an average of 5.4 percentage points less density than premenopausal women after adjustment for age and other variables.

Use of OC or HRT and duration of use of HRT were all associated with percentage density in age-adjusted analysis but not in multivariate analysis. Smoking and having first-degree relatives with breast cancer were not associated with percentage density in either age adjusted or multivariate analysis, although as shown in Table 1, only 4% and 3% of subjects fell into these categories, respectively.

Subjects with breast symptoms such as pain and tenderness had on average higher percentage density than those without symptoms, but this effect was statistically significant only in age-adjusted analysis. Women with a previous breast biopsy had an average of 6.5% more density than those who had not had a biopsy after adjustment for age and other variables.

A multivariate model containing age, height, weight, parity, age at first delivery, number of deliveries, menopausal status, and history of a breast biopsy explained 25% of the variance in percentage density.

Dense Area. Table 3 shows the associations found between the area of radiologically dense breast tissue and other variables. Weight and BMI (both positively) were significantly associated with dense area after adjustment for other variables. Height was significantly (positively) associated with dense area in age-adjusted analysis but not in multivariate analysis.

Dense area was not significantly associated with age at menarche or parity (except in age-adjusted analysis) but was associated with age at first delivery (positively) and number of deliveries (negatively) in multivariate analysis. Postmenopausal status, but not age at menopause, was significantly associated with a smaller area of dense tissue.

Use of exogenous hormones was not associated with the area of dense tissue in multivariate analysis, although HRT use was positively associated with dense area in age-adjusted analysis adjusted for age. Smoking and having first-degree relatives with breast cancer were not significantly associated with dense area. Formal education was positively associated with dense area in age-adjusted analysis but not in multivariate analysis.

Breast symptoms were associated with a greater area of dense tissue in both age-adjusted and multivariate analysis, and women with a previous breast biopsy had a significantly greater area of dense tissue in age-adjusted analysis but not in multivariate analysis.

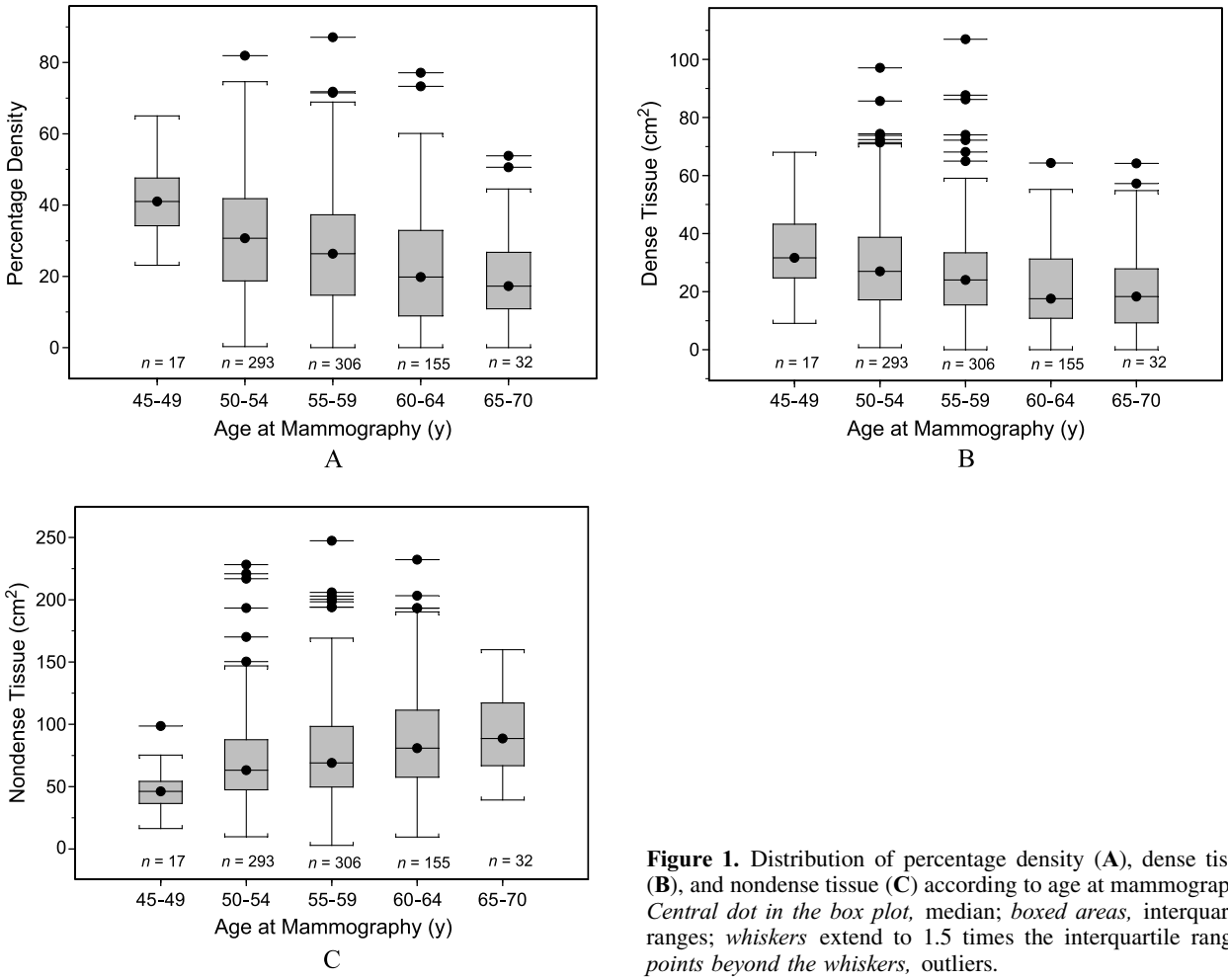

Figure 1. Distribution of percentage density (**A**), dense tissue (**B**), and nondense tissue (**C**) according to age at mammography. *Central dot in the box plot,* median; *boxed areas,* interquartile ranges; *whiskers* extend to 1.5 times the interquartile ranges; *points beyond the whiskers,* outliers.

A multivariate model containing age, weight, parity, age at first delivery, number of deliveries, menopausal status, and breast symptoms explained 13% of the variance in dense area.

Nondense Area. Table 4 shows the associations found between area of radiologically nondense breast tissue and other variables. As noted above, nondense area was not normally distributed and was log transformed in the analyses shown. Weight and BMI (both positively) and height (negatively) were significantly associated with nondense area after adjustment for age and other variables.

Nondense area was not significantly associated with age at menarche but was associated with parity (positively) and age at first delivery (negatively) in multivariate analysis. Menopausal status, but not age at menopause, was significantly associated with a larger area of nondense tissue.

Use of exogenous hormones, smoking, and having first-degree relatives with breast cancer were not associated with the area of nondense tissue in age-adjusted or multivariate analysis. Breast symptoms were not associated with the area of nondense tissue, but women with a previous breast biopsy had a smaller area of nondense tissue that was statistically significant in age-adjusted analysis and after adjustment for other variables.

A multivariate model containing age, height, weight, parity, age at first delivery, menopausal status, and history of a breast biopsy explained 44% variance in nondense area.

Discussion

The results of this cross-sectional study in Singaporean Chinese women show that measured mammographic density in the breast, treated as continuous variable, is associated with several factors that are known to influence risk of breast cancer. These factors are associated with variations in the percentage of the projected image of the breast that is occupied by radiologically dense breast tissue, and most factors were associated, in opposite directions, with both dense and nondense components of the image.

Percentage density was associated negatively with age, weight, parity, number of births, and postmenopausal

Table 2. Linear regression analysis of percentage density with risk factors for breast cancer (n = 803)

Variable	Age adjusted			Multivariate* R^2 = 0.25		
	Estimate	SE	P	Estimate	SE	P
Age (y)	−0.94	0.13	<0.0001	−0.64	0.13	<0.0001
Anthropometric						
Weight (kg)	−0.46	0.06	<0.0001	−0.50	0.06	<0.0001
Height (cm)	0.18	0.10	0.07	0.36	0.10	0.0003
BMI† (kg/m^2)	−1.32	0.14	<0.0001	*−1.17*	*0.13*	*<0.0001*
Menstrual and reproductive						
Age at menarche (y)	−0.002	0.32	0.99	*0.22*	*0.29*	*0.44*
Parity (parous)	−6.34	1.32	<0.0001	−3.15	1.54	0.04
Age at first delivery‡ (y), n = 625	0.74	0.12	<0.0001	0.35	0.14	0.01
No. deliveries§	−1.88	0.23	<0.0001	−1.20	0.36	0.001
Breast fed (yes), n = 625	−2.77	1.28	0.03	—	—	—
Age at menopause‖ (y), n = 494	−0.03	0.15	0.83	*0.10*	*0.14*	*0.47*
Menopausal status (post)	−5.51	1.19	<0.0001	−5.37	1.10	<0.0001
Exogenous hormones						
OC use ever (yes)	−3.16	1.18	0.01	*−1.32*	*1.15*	*0.25*
HRT use ever (yes)	4.49	1.36	0.001	*1.90*	*1.27*	*0.14*
Duration of HRT use (mo)	0.07	0.02	0.001	*0.03*	*0.02*	*0.15*
Other						
Smoking ever (yes)	−0.55	2.81	0.84	*2.35*	*2.54*	*0.35*
First-degree relative (yes)	4.25	3.27	0.19	*2.31*	*2.93*	*0.43*
Education (any formal vs. none)	4.98	1.12	<0.0001	*0.43*	*1.11*	*0.70*
Breast symptoms¶ (yes)	7.07	2.93	0.02	*4.25*	*2.71*	*0.12*
Breast biopsy (yes)	8.22	2.38	0.001	6.46	2.15	0.06

*Only variables significantly associated with percentage density (P < 0.10) are kept in the multivariate model. All estimates in italics are those calculated by adding that variable to the parsimonious multivariate model one at a time.

†BMI coefficient is estimated from the parsimonious multivariate model replacing weight and height.

‡The age-adjusted analysis is restricted on parous women. For the multivariate analysis, age at first delivery is centered on the mean: nonparous women are coded as 0, whereas the mean is subtracted from the age at first delivery of the parous women.

§The age-adjusted model is using the actual number of deliveries. For the multivariate analysis, no. deliveries = no. deliveries − 1 for parous women and 0 for nonparous women. See Statistical Methods for detail.

‖The age-adjusted analysis is restricted on postmenopausal women. For the multivariate analysis, age at menopause is centered on the mean.

¶Breast symptoms include pain/tenderness, lump, thickening, nipple eczema, nipple discharge, nipple inversion, or skin change.

status and positively with height and age at first birth. There was a positive association of borderline significance between percentage density and a previous biopsy but no association (after adjustment) with age at menarche, menopause, ever use of OCs or HRT, smoking, or family history of breast cancer. However, the characteristics of this population, in which there were few smokers and few with a family history of breast cancer, may have given rise to falsely null findings.

Both dense area, which reflects epithelium and stroma, and nondense area, which reflects fat, showed associations that were opposite in direction with age, age at first delivery, and menopausal status. Body weight was positively associated with both dense and nondense areas and negatively with percentage density. The dense area alone was associated positively with breast symptoms and the nondense area alone was associated positively with height and previous breast biopsy (both negatively; i.e., both greater height and a history of a breast biopsy were associated with a smaller nondense area).

The associations seen between risk factors for breast cancer and percentage mammographic density can thus be explained by associations of these factors with the dense and/or nondense areas of the mammogram. Similar associations of age, height, weight, parity, number of births, menopausal status, previous biopsy, and breast symptoms with mammographic density have been seen in studies conducted in Caucasians (4, 11, 12) and Hispanic and Alaskan Native women (13, 14). The multivariate model shown in Table 2 accounted for 27% of the variance in percentage density. The variables that were significant in this model explained a similar proportion (27%) of the variance in control subjects in our other studies[6] composed predominately of Caucasian subjects. Both results are similar to those published by Vachon et al. (15) in a population in Minnesota.

An association between mammographic pattern of the breast and risk of breast cancer was first described by Wolfe (16, 17) using four categories to classify the appearance of the mammogram designated N1, P1, P2, and DY. N1 indicates a breast in which the parenchyma is radiologically lucent and risk of breast cancer is lowest. DY indicates a breast in which the parenchyma is radiologically dense and risk of cancer is highest. P1 and P2 patterns are characterized by linear radiologic densities associated with intermediate increases in risk. Since Wolfe's first description, several cohort studies or case-control studies nested in cohorts have confirmed that this qualitative classification of mammographic patterns is associated with variations in risk of breast cancer (see ref. 18 for a review). Quantitative approaches that measure mammographic density have also been used and in general have given substantially larger gradients in risk than Wolfe's classification, and most studies have also found evidence of a dose-response

[6] Boyd NF, Jong R, Fishell E, Yaffe M, Martin L.

relationship, risk increasing with increasing density (2, 3, 11, 19-25).

To date, only four studies, all case-control in design, have examined the relationship of mammographic patterns to risk factor for breast cancer in Asian subjects, two in Japan, one in Singapore, and one in the United States. The Japanese studies both used Wolfe's classification and both found the higher risk patterns to be associated with an increased risk of breast cancer. The study of Nishiki et al. (26), with 59 cases and 204 controls, found an odds ratio (95% confidence interval) of 2.1 (1.1-3.9) in the combined P2/DY category compared with the N1/P2. The study of Kojima et al. (27), with 91 cases and 746 controls, found an odds ratio (95% confidence interval) of 12.2 (5.6-26.4) in the DY category relative to the N1 pattern.

Jakes et al. (28) examined the effect of mammographic parenchymal patterns on risk of breast cancer in Chinese women in Singapore in the same screened population as the present study. They used a case-control design with 174 breast cancer patients (of which 132 were prevalent cancers) who were age matched to 348 screened negative controls. The mammograms were classified according to Tabar's classification for parenchymal pattern (29). The risk of breast cancer for women with the high-risk Tabar pattern IV (defined as extensive nodular and linear densities, with nodular size larger than normal lobules) was significantly elevated when compared with the remaining patterns (odds ratio, 2.30; 95% confidence interval, 1.14-4.63) after adjustment for other risk factors.

Ursin, in a case-control study in the United States that included Asian American as well as African American and Caucasian women, assessed mammographic density using a computer-assisted method similar to the one used here and found that, in each ethnic group, women with the highest percentage density had 5-fold greater breast cancer risk than women with no density. These findings suggest that mammographic density is as strong a predictor of risk in Asian American women as in White women (7).

Mammographic density is associated with biological factors that make its association with risk of breast cancer, and with risk factors for the disease, biologically plausible. Mammographic density reflects breast epithelium and stroma, which attenuate X-rays more than does fat (30). Previous work by ourselves and others has shown that mammographic density is associated with higher blood levels of insulin-like growth factor-I and prolactin in premenopausal and postmenopausal women, respectively (31, 32). These breast mitogens have also been found to be associated with an increased risk of breast cancer and show the same associations with menopausal status as have been found with mammographic density (33, 34). Using immunohistochemistry and quantitative microscopy, we have also found that tissue from radiologically dense breasts had a greater area of stained insulin-like growth factor-I (35). The

Table 3. Linear regression analysis of dense area with risk factors for breast cancer (*n* = 803)

Variable	Age adjusted			Multivariate* $R^2 = 0.13$		
	Estimate	SE	*P*	Estimate	SE	*P*
Age (y)	−0.74	0.13	<0.0001	−0.52	0.13	0.0001
Anthropometric						
Weight (kg)	0.16	0.06	0.01	0.18	0.06	0.002
Height (cm)	0.22	0.10	0.03	*0.03*	*0.10*	*0.80*
BMI† (kg/m^2)	0.28	0.15	0.05	*0.39*	*0.14*	*0.01*
Menstrual and reproductive						
Age at menarche (y)	0.28	0.32	0.37	*0.44*	*0.30*	*0.15*
Parity (parous)	−4.42	1.33	0.001	−1.37	1.64	0.40
Age at first delivery‡ (y)	0.60	0.12	<0.0001	0.34	0.15	0.02
No. deliveries§	−1.50	0.23	<0.0001	−1.19	0.38	0.002
Breast fed (% yes) *n* = 625	−2.32	1.29	0.07	—	—	—
Age at menopause‖ (y)	0.13	0.15	0.38	*0.20*	*0.15*	*0.17*
Menopausal status (post)	−4.19	1.20	0.001	−4.09	1.16	0.001
Exogenous hormones						
OC use ever (yes)	−2.05	1.18	0.08	*−0.37*	*1.23*	*0.76*
HRT use ever (yes)	3.61	1.36	0.01	*1.66*	*1.35*	*0.22*
Duration of HRT (mo)	0.06	0.02	0.01	*0.02*	*0.02*	*0.29*
Other						
Smoking ever (yes)	−1.80	2.80	0.52	*1.02*	*2.71*	*0.71*
First-degree relative (yes)	0.41	3.26	0.90	*−0.92*	*3.12*	*0.77*
Education (any formal vs. none)	3.18	1.12	0.005	*−0.02*	*1.17*	*0.99*
Breast symptoms¶ (yes)	11.34	2.90	0.0001	9.78	2.81	0.001
Breast biopsy (yes)	5.83	2.38	0.01	*3.71*	*2.34*	*0.11*

*Only variables significantly associated with dense area ($P < 0.10$) are kept in the multivariate model. All estimates in italics are those calculated by adding that variable to the parsimonious multivariate model one at a time.

†BMI coefficient is estimated from the parsimonious multivariate model replacing weight and height.

‡The age-adjusted analysis is restricted on parous women. For the multivariate analysis, age at first delivery is centered on the mean: nonparous women are coded as 0, whereas the mean is subtracted from the age at first delivery of the parous women.

§The age-adjusted model is using the actual number of deliveries. For the multivariate analysis, no. deliveries = no. deliveries − 1 for parous women and 0 for nonparous women. See Statistical Methods for detail.

‖The age-adjusted analysis is restricted on postmenopausal women. For the multivariate analysis, age at menopause is centered on the mean.

¶Breast symptoms include pain/tenderness, lump, thickening, nipple eczema, nipple discharge, nipple inversion, or skin change.

Table 4. Linear regression analysis of nondense area (square root transformed) with risk factors for breast cancer (*n* = 803)

Variable	Age adjusted			Multivariate* R^2 = 0.45		
	Estimate	SE	*P*	Estimate	SE	*P*
Age (y)	0.11	0.02	<0.0001	0.08	0.01	<0.0001
Anthropometric						
Weight (kg)	0.13	0.01	<0.0001	0.14	0.01	<0.0001
Height (cm)	−0.0002	0.01	0.99	−0.07	0.01	<0.0001
BMI† (kg/m^2)	0.33	0.02	<0.0001	*0.32*	*0.01*	*<0.0001*
Menstrual and reproductive						
Age at menarche (y)	0.04	0.04	0.30	*0.02*	*0.03*	*0.50*
Parity (parous)	0.63	0.17	0.0003	0.40	0.17	0.02
Age at first delivery‡ (y)	−0.07	0.02	<0.0001	−0.03	0.02	0.05
No. deliveries§	0.17	0.03	<0.0001	0.07	0.04	0.09
Breast fed (% yes) *n* = 625	0.34	0.17	0.04	—	—	—
Age at menopause‖ (y)	0.003	0.02	0.87	*−0.004*	*0.02*	*0.82*
Menopausal status (post)	0.53	0.16	0.001	0.49	0.12	<0.0001
Exogenous hormones						
OC use ever (yes)	0.23	0.15	0.13	*0.12*	*0.13*	*0.36*
HRT use ever (yes)	−0.35	0.18	0.05	*−0.07*	*0.14*	*0.62*
Duration of HRT (mo)	−0.006	0.003	0.05	*−0.0007*	*0.002*	*0.76*
Other						
Smoking ever (yes)	0.07	0.36	0.85	*−0.20*	*0.28*	*0.48*
First-degree relative (yes)	−0.44	0.42	0.30	*−0.33*	*0.32*	*0.31*
Education (any formal vs. none)	−0.50	0.15	0.001	*−0.15*	*0.13*	*0.24*
Breast symptoms¶ (yes)	−0.16	0.38	0.67	*−0.03*	*0.30*	*0.91*
Breast biopsy (yes)	−0.75	0.31	0.02	−0.44	0.24	0.06

*Only variables significantly associated with nondense area ($P < 0.10$) are kept in the multivariate model. All estimates in italics are those calculated by adding that variable to the parsimonious multivariate model one at a time.

†BMI coefficient is estimated from the parsimonious multivariate model replacing weight and height.

‡The age-adjusted analysis is restricted on parous women. For the multivariate analysis, age at first delivery is centered on the mean: nonparous women are coded as 0, whereas the mean is subtracted from the age at first delivery of the parous women.

§The age-adjusted model is using the actual number of deliveries. For the multivariate analysis, no. deliveries = no. deliveries − 1 for parous women and 0 for nonparous women. See Statistical Methods for detail.

‖The age-adjusted analysis is restricted on postmenopausal women. For the multivariate analysis, age at menopause is centered on the mean.

¶Breast symptoms include pain/tenderness, lump, thickening, nipple eczema, nipple discharge, nipple inversion, or skin change.

factors shown in the present article to be associated with variations in mammographic density may act by modulating exposure of the breast to mitogens and other regulatory proteins to cause variations in breast tissue composition.

Although mammographic density is influenced by several risk factors for breast cancer, it is not clear whether populations at different risks for the disease have different average levels of breast density. Four of the six studies published to date show that the population group at lower risk of breast cancer had less dense mammographic patterns. In the United States, compared with Hispanic and non-Hispanic White women, American Indians, at lower risk of breast cancer, had a higher prevalence of the less dense, low-risk patterns (36), as did premenopausal Japanese women in Japan compared with British women (37) and Southeast Asian women attending a mammographic screening program in the United Kingdom compared with Caucasians (38). Further, Maskarinec et al. (6) found that the area of dense tissue in the mammogram was smaller in Asian women in Hawaii than in Caucasian or Native Hawaiian women. However, in another study from Hawaii, ethnic group (Chinese, Japanese, or Caucasian) was unrelated to mammographic pattern (4) and White et al. (39) found a higher prevalence of dense breasts in Asian women ages 40 to 49 years than in other ethnic groups.

Few of these studies have taken into account the substantial differences in body size that exist between different ethnic groups, and none has yet assessed the volume of the breast or of the dense tissue that it contains. The development of methods that allow measurement of the quantities of the different tissues in the breast, rather than their projected areas as is done now, may resolve some of these discrepancies and improve risk discrimination. However, the present study shows that the percentage mammographic density in Chinese women has similar associations with risk factors for breast cancer to those seen in Caucasians.

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