Correlates of Mammogram Density in Southwestern Native-American Women[1]

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Abstract

Little is known about the breast cancer risk factors or mammogram characteristics among Native-American women. Southwestern Native-American women have a low risk of breast cancer and a high risk of diabetes. Our purpose was to determine the prevalence of known clinical risk factors for breast cancer and their association with mammogram density in a sample of Southwestern Native-American women undergoing breast cancer screening. A retrospective review was performed of screening mammogram examinations in 455 women. Density was classified by American College of Radiology Breast Imaging Reporting and Data System (BIRADS) density patterns 1 to 4 (fat to dense). Clinical data including patient age, weight, body mass index, parity, lactation, age at first birth, menopause status, hormone replacement therapy, diabetes status, and family history of breast cancer were obtained. Multivariate analyses were performed. Among the entire group, 152 women (33.4%) had diabetes. Patient age ($P = 0.0012$), weight ($P < 0.0001$), menopause status ($P = 0.0134$), estrogen use ($P = 0.0311$), age at first birth ($P = 0.0035$), and diabetes ($P = 0.0015$) were associated with mammogram density. Diabetes was associated with mammogram density in premenopausal women ($P = 0.0032$) but not in postmenopausal women ($P = 0.3178$) in stratified analyses. Diabetes, hormone replacement therapy, age, weight, menopause status, parity, and age at first birth were significantly associated with mammogram density. The association of mammogram density with diabetes varied by menopause status and was significant only for premenopausal women.

Introduction

Mammogram density has significant implications related to breast cancer. Density affects the accuracy of mammography in the detection of breast cancer, and density appears to be an intermediate biomarker of breast cancer risk (1, 2). Although controversy remains, there is substantial evidence indicating that dense mammographic tissue is a breast cancer risk factor and may be a partial biomarker for some of the other risk factors (2). The breast is a heterogeneous composition of adipose tissue, epithelial cells, and fibrous tissue. Because fat is translucent, density results from fibrous and epithelial cells (3). There is some corresponding correlation of breast composition with histological features of risk, with reports that women with extreme proportions of density are at an elevated risk for cancer *in situ*, atypical hyperplasia, and hyperplasia, which indicates a connection between density and high risk histological changes in breast epithelium (4). Multiple studies indicate that breast cancer risk increases steadily with increasing density and that the risk persists when considering age (2–8). The magnitude of the risk associated with increased density is between 4-fold and 6-fold, exceeding that of most other predictors of breast cancer (2–4, 9). In addition, a considerable amount of research has been done to investigate the relationship between density and the other known breast cancer risk factors. Associations of density have been found chiefly with parity, childbirth, menopausal status, and HRT[3] (2, 6, 10–12). An additional implication of mammogram density is decreased sensitivity in mammography screening, which is associated with dense patterns (12).

Although there are many studies of mammogram density, there are few studies among populations having different breast cancer risks. Breast cancer incidence rates from Surveillance, Epidemiology, and End Results (SEER) data in 1992 showed a lower incidence in Native-American women of New Mexico (31.6/100,000, age adjusted), as compared with white women (115.7/100,000).[4] Southwestern Native-American women have had a much lower risk of a death from breast cancer (9.8/100,000, 1989–1993), compared with the mortality rates for all United States races (27.1/1000,000, 1988–1992) and compared with overall Native-American breast cancer mortality rates (15.2/100,000, 1989–1993; Ref. 13).[5]

Two small autopsy studies in New Mexico reported previously that the mean mammogram density is lower in Native-American women as compared with white or Hispanic women (14, 15). In these studies, the low density was considered to be independent of clinical factors that alter density, such as BMI

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[3] The abbreviations used are: BMI, body mass index; PIMC, Phoenix Indian Medical Center; BIRADS, Breast Imaging Reporting and Data System; OR, odds ratio; CI, confidence interval; HRT, hormone replacement therapy.

[4] Internet address: http://seer.cancer.gov/publications/ethnicity/breast.pdf.

[5] Indian Health Service: Regional Differences in Indian Health, 1998–99. Internet address: http://www.ihs.gov/publicinfo/publications/trends98/region98.asp.

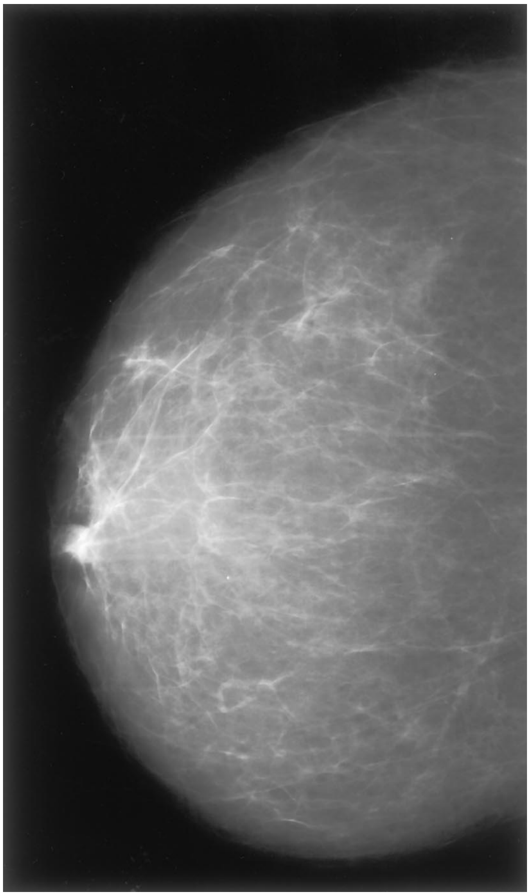

Fig. 1. BIRADS category 1 mammogram. The breast is almost entirely fat.

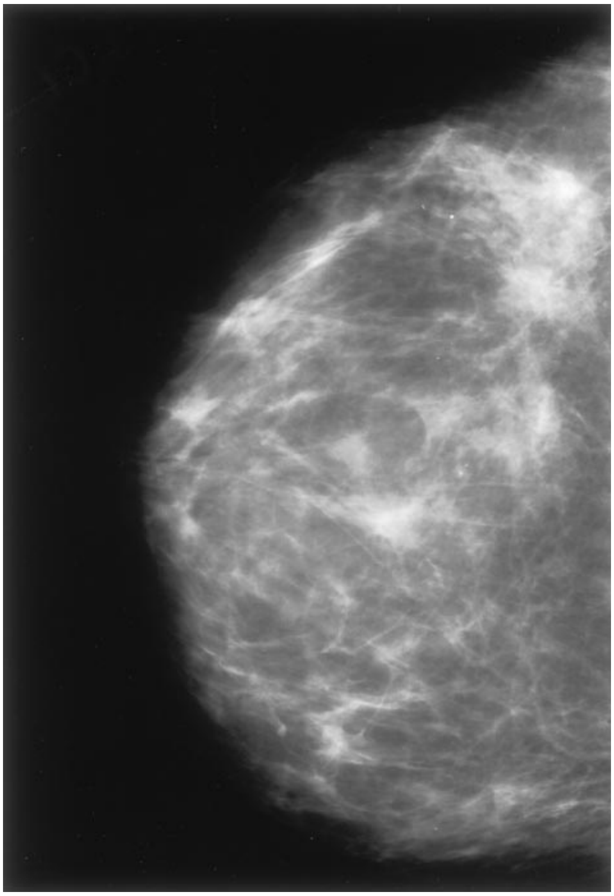

Fig. 2. BIRADS category 2 mammogram. There are scattered fibroglandular densities.

and age at first birth. The low-density mammograms were presumed to be a manifestation of the lower risk of breast cancer in this population, but the exact etiology was not determined. There have been studies in Caucasians and other ethnic groups that analyze factors that relate to mammogram density, (2, 12, 16–20) but no studies in living Native-American women in the Southwest, a group that has had a low risk of breast cancer. Type 2 diabetes has a very high prevalence among Southwestern Native-Americans, found in up to one-half of adults, and this factor has not been studied as to whether it could relate to mammogram density (21, 22).

Patients and Methods

Subjects. A retrospective review was performed of a sample of all sequential screening mammography examinations that were performed at the PIMC Department of Radiology between September 1, 1997, and February 28, 1998. Screening mammograms are mammograms performed in patients who are without breast physical examination abnormalities, such as nipple discharge, lumps, or thickening. The mammography log book contained a notation for whether each patient mammogram examination was a screening mammogram or a diagnostic mammogram, and diagnostic mammograms were not included in the study. Patients were not in an organized screening study but had been referred from a variety of clinics in this region of the Indian Health Service for mammogram screening. Consent from the Institutional Review Board of the Indian Health Service, the PIMC Institutional Review Board, grants CA86098 and U10CA25224 was obtained. A report was made available to the PIMC and to the area Tribal Health Boards before the preparation of this report.

Mammograms consisted of original standard mediolateral oblique and craniocaudal views obtained on dedicated mammographic equipment at the PIMC. The mammograms were reviewed by a Food and Drug Administration-certified radiologist (M. A. R.) with 10 years of mammography experience in an ethnically diverse but non-Native-American population at an academic medical center. Mammogram density was assessed using the American College of Radiology (BIRADS) density patterns (23), a four-category ordinal scale from 1 to 4 (fatty tissue to dense). During assessment of the mammograms, the mammographer was unaware of the age of the patient and blinded to all clinical data. The standard American College of Radiology (ACR) BIRADS overall breast composition patterns are (*a*) almost entirely fat; (*b*) predominantly fat with scattered fibroglandular densities; (*c*) heterogeneously dense; and (*d*) extremely dense (23). These are illustrated by examples in Figs. 1–4. The clinical information was recorded from the history forms completed by each patient and by the mammography technologist, which were contained in the mammogram jacket. These were the sources of information regarding breast cancer risk factors, (patient age, age at first birth, family history of breast cancer, HRT, lactation, age at menarche, hysterectomy, parity) and the presence or absence of diabetes. These

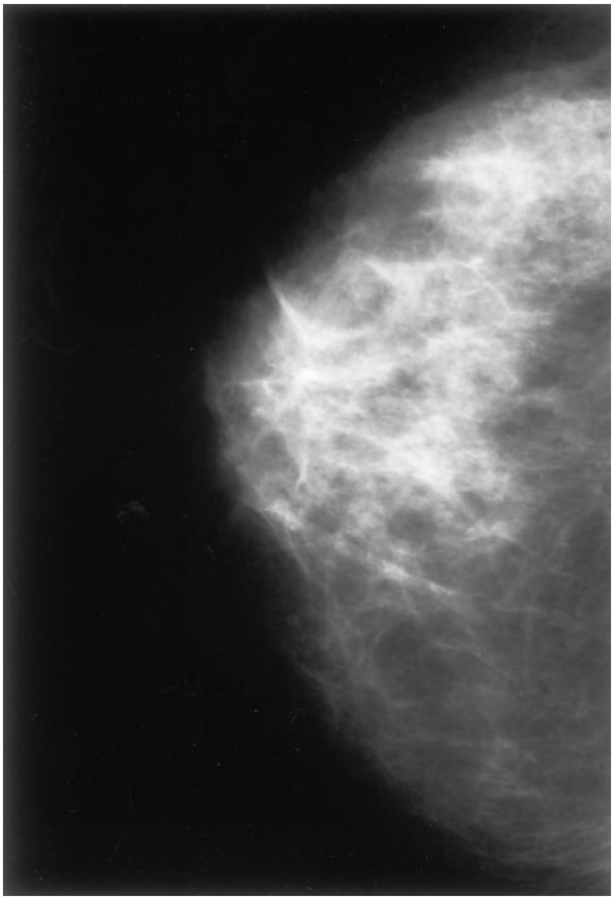

Fig. 3. BIRADS category 3 mammogram. The breast tissue is heterogeneously dense.

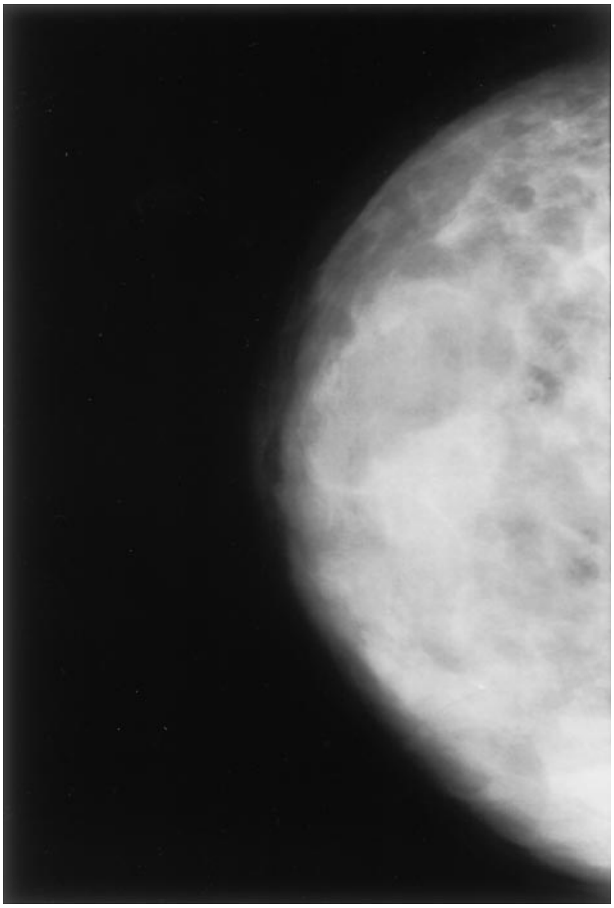

Fig. 4. BIRADS category 4 mammogram. The breast tissue is extremely dense.

data were recorded by a separate observer (J. S. K.). Weight, height, and BMIs were obtained from the Registration and Patient Management System database of the PIMC by another observer (C. W.), who was blinded to the other data.

Statistical Methods. Mammographic breast density was analyzed for significant associations with the following covariates; age, weight, nulliparous *versus* parous status, number of childbirths, age at first childbirth, estrogen use, positive lactation history, menopause status, indicator for hysterectomy, and diabetes status. Associations with density score were modeled as ORs, using a cumulative logit, multinomial model, also called the proportional-odds model (SAS, version 8.2; Ref. 24). The proportional odds model was chosen because of the ordinal nature of the breast density outcome, with breast density strictly following the series of inequalities across BIRADS categories; I < II < III < IV. The log odds (logits) for each level of breast density were cumulated over lower levels; therefore, the estimated odd ratios measure the odds of a higher breast density score compared with the odds of a lower score. The assumption of proportionality was tested using the score test statistic, with a P of <5% suggesting that the assumption was violated. All of the above covariates were offered to the model in a forward stepwise fashion, with a Wald-type P of ≤10% necessary for the covariate to be retained in the model. For covariates retained in the final, parsimonious model, the ORs and 95% CIs were estimated. In all of the modeling steps, a complete-case method was used, with unknown (missing) data assumed to be missing completely at random. Because height and BMI were missing for nearly 24% of the subjects, the covariate weight, which was available for 95% of subjects, was used in multivariate models to adjust for body composition. Because weight is known *a priori* to be strongly associated with breast density, these covariates were modeled as mean-centered linear covariates and using indicators for the quartiles of their distributions, in separate models, for comparison of the association. Additionally, menopausal status is known *a priori* to be significantly associated with breast density, and, hence, multivariate proportional-odds models were computed stratified by menopause status.

Data were collected and stored electronically using Microsoft Excel and were analyzed statistically using SAS, version 8.2.

Results

Demographic characteristics for the sample of 455 Native-American women are presented in Table 1. Women were 19 to 85 years of age at mammography screening with a mean ± SD of 52.9 ± 10.7 years. Height and weight were recorded from patient chart information and were obtained from 78 and 95% of the sample, respectively. NIH BMI categories are: <20, lean; 20–24.9, normal; 25–29.9, overweight; >30, obese. BMI was high in this population, with a mean ± SD of 32.4 ± 7.1, but was calculated for only 76% of the sample because of missing information for height. Because BMI was missing for

Table 1 Sample characteristics (n = 455)

Characteristics	n (%)	Mean	SD	Range
Age, yrs	455 (100)	52.9	10.7	19–85
Height, cm	355 (78.0)	159.3	6.2	132.1–179.1
Weight, kg	433 (95.2)	81.3	17.8	40.3–150.4
BMI	347 (76.3)	32.4	7.1	18.0–60.5
Diabetes				
Yes	152 (33.4)			
No	303 (66.6)			
BIRADS breast density				
1	140 (30.8)			
2	145 (31.8)			
3	161 (35.4)			
4	9 (2.0)			
Breast cancer history				
No family history	375 (82.4)			
First- or second-degree relative	65 (14.3)			
Unknown	15 (3.3)			
Parity				
Nulliparous	39 (8.6)			
Unknown	3 (0.6)			
Parous	413 (90.8)			
Age at first birth	401 (97.1)	20.3	4.1	13–35
Number of childbirths	413 (100)	4.2	2.4	1–15
Breastfeeding history				
Yes	252 (61.0)			
No	160 (38.7)			
Unknown	1 (0.2)			
Menopausal status				
Pre	144 (31.7)			
Post	311 (68.3)			
Age at menopause	230 (74.0)	44.6	6.5	22–63
Estrogen use				
Yes	146 (47.0)			
No	165 (53.0)			
Hysterectomy				
Yes	62 (19.9)			
No	242 (77.8)			
Unknown	7 (2.3)			

nearly 25% of the sample, the covariate weight rather than the BMI was used in multivariate analyses. Diabetes was reported for 152 (33.4%) of women and was significantly related to higher BMI and heavier weight than nondiabetics (data not shown). Sixty-five women, or 14% of the sample, reported a positive family history of breast cancer, defined as either a first- or second-degree relative with a diagnosis of disease. Most women (90.8%) were parous with a mean age (±SD) at first birth of 20.3 ± 4.1 years and a mean number of childbirths of 4.2 ± 2.4); 61% of parous women reported breastfeeding at some time. A total of 311 women were postmenopausal at mammography screening, with the mean age at menopause of 44.6 years ± 6.5, calculated using information from 230 (74%) of the 311 women. Estrogen use as hormone replacement was reported in 146 women or 47% of postmenopausal women, with hysterectomy reported for 62 (19.9%) women. Forty-three (69%) of 62 women who report hysterectomy also reported estrogen use.

The distribution of BIRADS breast density scores favored less dense breast, scores of 1 or 2, in 62.6% of women. An additional 35.4% of women were scored as 3, with only 2% or 9 women receiving the highest BIRADS score. Interestingly, women reporting diabetes were more likely to have lower BIRADS scores than nondiabetics in univariate analyses. Seventy-five % of diabetic women received BIRADS scores of 1 and 2 compared with 56% for nondiabetic women ($\chi_{df\ =\ 32}$ = 27.82; $P < 0.0001$).

Table 2 Proportional odds model for BIRADS breast density (n = 418)

Covariate	OR	95% CI	P
Age[a]	0.817	0.723–0.923	0.0012
Weight[b]	0.824	0.778–0.873	<0.0001
Menopausal status (post *vs.* pre)	0.466	0.254–0.853	0.0134
Estrogen use (yes *vs.* no)	1.657	1.047–2.622	0.0311
No. of births	0.894	0.827–0.967	0.0051
Age at first birth[c]	1.234	1.072–1.420	0.0035
Diabetes (yes *vs.* no)	0.519	0.346–0.778	0.0015

[a] OR is calculated for a difference of 5 years (*e.g.,* a 50-year-old woman compared with a 45-year-old woman).
[b] OR is calculated for a difference of 5 kg (*e.g.,* an 85-kg woman compared with an 80-kg woman).
[c] OR is calculated for a difference of 5 years (*e.g.,* a woman who was 30 at first birth compared with a woman who was 25 at first birth).

Multivariate analysis, using the cumulative logit, multinomial model with BIRADS scores as the outcome, indicates that age at screening, weight, menopausal status, estrogen use, number of childbirths, age at first birth, and diabetes status were all significantly associated with breast density (Table 2). Older women on average had a lower odds of a high breast density score than younger women. For a 5-year age difference at mammography screening, the odds of a high breast density score decreased by 9.3%. Increasing weight of the woman also lowered the odds of a high breast density score. For example, a 5-kg increase in weight decreased the odds by 7.6%. Postmenopausal women had dramatically lower odds of high breast density when compared with premenopausal women. Estrogen use in postmenopausal women, however, increased the odds of high breast density by 65.7%. Childbearing decreased the odds of high breast density with increasing childbirths (*e.g.,* for women with two childbirths compared with women with a single childbirth the odds were reduced by 10.6%). The age at childbirth was significantly associated with breast density, with women having their first child at older ages having higher odds of high breast density scores. For example, a woman having her first child at 35 years of age had 23% higher odds of a high breast density score than a woman having her first child at 30 years of age.

Diabetes in women in this sample was associated with decreased odds of high breast density scores, similar in magnitude to menopausal status. Women with diabetes had 48.1% lower odds of a high breast density score when compared with nondiabetic women, even after adjusting for the other significant covariates in the multivariate model.

To explore the extent of the diabetes association across age, menopausal status, and weight, the proportional-odds model was stratified by menopause status with the diabetes effect modeled within each quartile of the weight distribution in the sample. The distribution of weight, in kilograms, was similar between pre- and postmenopausal women in this sample, with the 25th, 50th, and 75th percentiles calculated as 68.7, 78.4, and 91.7 and as 68.9, 78.3, and 92.2 for pre- and postmenopausal women, respectively. Age was modeled as a linear covariate, centered to the mean of pre- and postmenopausal women respectively. Like the overall model, covariates were offered to the stratified models (pre- and postmenopausal) with a P of ≤0.1 necessary for the covariate to be retained. Only those covariates retained in the overall model were offered; age, weight, estrogen use, number of births, age at first birth, and diabetes. Because only postmenopausal women reported estro-

Table 3 Proportional-odds model for premenopausal women (n = 140)

Covariate	OR	95% CI	P
Age at first birth[a]	1.453	1.159–1.822	0.0012
No. of births	0.835	0.709–0.984	0.0310
Weight			<0.0001
1st quartile	Referent		
2nd quartile	0.341	0.116–1.002	0.0504
3rd quartile	0.359	0.102–1.268	0.1116
4th quartile	0.081	0.027–0.248	<0.0001
Diabetes			
1st weight quartile	0.113	0.017–0.747	0.0236
2nd weight quartile	0.324	0.110–0.960	0.1978
3rd weight quartile	0.220	0.058–0.839	0.0267
4th weight quartile	0.165	0.025–1.097	0.0623

[a] OR is calculated for a difference of 5 years (*e.g.,* a woman who was 30 at first birth compared with a woman who was 25 at first birth.

Table 4 Proportional-odds model for postmenopausal women (n = 308)

Covariate	OR	95% CI	P
Age[a]	0.825	0.728–0.936	0.0027
Estrogen use	1.630	1.038–2.560	0.0339
No. of births	0.918	0.845–0.997	0.0420
Weight			0.0029
1st quartile	Referent		
2nd quartile	0.620	0.304–1.265	0.1890
3rd quartile	0.668	0.327–1.363	0.2675
4th quartile	0.221	0.101–0.488	0.0002
Diabetes			0.3178
1st weight quartile	0.798	0.329–1.934	0.6172
2nd weight quartile	1.077	0.431–2.691	0.8732
3rd weight quartile	0.742	0.307–1.791	0.5065
4th weight quartile	0.358	0.132–0.971	0.0436

[a] OR is calculated for a difference of 5 years (*e.g.,* a 60-year-old woman compared with a 55-year-old woman).

gen use, this variable was excluded from the premenopausal model.

Tables 3 and 4 report the proportional-odds model for pre- and postmenopausal women, respectively. For both models, the proportional odds assumption was found to be valid (score test, $\chi_{df\ =\ 18 \cdot 2} = 17.34$, $P = 0.50$, and score test, $\chi_{df\ =\ 20 \cdot 2} = 16.84$, $P = 0.66$, for pre- and postmenopausal models, respectively). For premenopausal women, the age at first birth, the number of births, weight, and diabetes were significantly associated with breast density, whereas the age at screening was not. The magnitude of the diabetes association across quartiles of weight was similar (OR, 0.113, 0.324, and so forth), and all indicated a decreased odds of high-breast-density score compared with the odds of a lower-density score. The association was statistically significant ($P < 0.05$) for the first and third quartiles of weight and marginally significant ($0.05 < P < 0.1$) for the heaviest women in the fourth quartile. Overall, diabetes was significantly related to breast density in premenopausal women ($P = 0.0032$). For postmenopausal women, breast density was significantly associated with age at screening, estrogen use, the number of childbirths, and weight as stratified by quartiles (Table 4). Breast density was not significantly associated with age at first birth. Diabetes, if modeled as a single covariate (not stratified by weight), is not significantly associated with breast density ($P = 0.1468$; not shown in table). If modeled as interaction terms with each quartile of weight (stratifying the effect of diabetes by weight quartiles), the women in the heaviest weight quartile with diabetes have a significantly lower odds of high-breast-density scores than women without diabetes (OR, 0.358). This association is apparent only for the heaviest women; the estimated ORs (and associated *P*s) for the women in the other weight quartiles do not suggest a significant association. In fact, diabetes when considered across all weight quartiles is not significantly associated ($P = 0.3178$).

To compare the magnitude of the independent effect of diabetes for premenopausal women in this population, BIRADS scores were predicted for premenopausal women by using their typical characteristics for the significant covariates in the model: age at first birth, number of births, and weight, with and without diabetes (Table 5). A typical premenopausal woman was 82 kg in weight (third weight quartile), who had had three children, and with a mean age at first birth of 18 years. The model estimates that women with diabetes more typically have a BIRADS score of 1 or 2, and are less likely to have a score of 3, when compared with nondiabetics in this premenopausal sample population.

Because the correlation of density with diabetes was an unexpected finding, we compared diabetes to the strongest risk factor for breast cancer, family history. Positive family history of breast cancer occurred in 8 (5.2%) of 152 women with, and in 57 (18.8%) of 303 women without, diabetes ($P = 0.002$). A history of a first-degree relative with breast cancer occurred in 5 (3.3%) of 152 of women with, and 35 (11.6%) of 303 women without, diabetes ($P = 0.001$).

Discussion

Mammogram density is an estimate of the proportion of fibroglandular tissue to fat in the breast. With increasing age and menopause, the proportion of breast fat increases and the epithelium involutes, causing mammograms to become less radiodense with age (1, 2, 12, 25). In addition to age and menopause, density is known to vary with anthropomorphic factors (weight, BMI) and reproductive factors related to breast cancer risk, such as age at first birth, parity, and HRT (3,10–12, 26). Unknown genetic factors have also been proposed (27, 28). Several studies have quantitated mammogram density and have confirmed the association with risk as well as with risk factors (2, 3, 7, 8, 28–30). Women with extensive dense breast tissue visible on a mammogram have a risk of breast cancer that is up to 6.0 times greater than those who have low density or no density (28–30). About one-third of breast cancer cases can be attributed to the presence of dense tissue in more than 50% of the breast (3, 31). The risk associated with mammographic density is greater than that associated with almost all other risk factors for breast cancer, and the increase in risk has been shown to persist for at least a decade after the date of the mammogram used to classify density (3).

There is a 6-fold variation in breast cancer incidence and mortality rates among Native-American women, with Southwestern Native-Americans having the lowest rates, and the Alaskan and the Northern Plains regions having the highest rates (13).[4,5] Previous studies of mammogram density among groups having disparate breast cancer risk have been performed among Asian and Caucasian women in England; Japanese women, black, white, and Native-American Women in Seattle; and Caucasian, Hispanic, and Native-American women in New Mexico (14–20). Southwestern Native-American women in New Mexico were reported to have lower density mammograms than did Caucasians or Hispanics (14, 15). Because obesity has become very common among Native-Americans, low density mammograms would not be surprising, but the

Table 5 Model estimated percentages of BIRADS scores by diabetes status for premenopausal women in this study's population

Diabetes status[a]	BIRAD scores			
	1	2	3	4
Yes	28.8	41.8	28.4	1.0
No	8.2	26.5	61.0	4.3

[a] Percentages for BIRADS scores were estimated from the cumulative logit, multinomial model of Table 3. Estimates are based on typical premenopausal women in sample population defined in "Patients and Methods."

finding was independent of BMI as well as of clinical risk factors for breast cancer (14, 15). The hypothetical cause for this finding was early breast epithelial involution of unknown etiology, and the low density was considered to reflect the lower risk of breast cancer in Native-American women (14, 15, 25).

Our findings are that mammogram density correlates with previously observed factors (menopause, weight, age, parity, HRT), but also correlates with diabetes status in premenopausal women independent of obesity. It is uncertain why the relationship of density to diabetes varies by menopause status. It is possible that the BIRADS measures are too insensitive to detect smaller differences in density in postmenopausal women. The low density in Southwestern Native-American women appears to be multifactorial and related to overweight, high parity, and to diabetes in this population.

Mammogram density patterns have not been systematically studied in a group of patients with either type I or type 2 diabetes (MEDSEARCH 1965–2002). There are a few case reports of type 1 diabetes mellitus of many years duration being associated with fibrous, lymphocytic mastopathy, resulting in higher mammogram density (32). Our opposite findings of fat density patterns in association with type 2 diabetes might be explained by the increased upper body fat distribution associated with type 2 diabetes. Nearly all diabetes in the Southwestern Native-American population is type 2, which correlates with the high BMI in the study group (21, 33, 34).

Those with diabetes had a lower rate of first-degree positive family history (3%) compared with those without diabetes (12%), with those of other screening mammography groups (11%), and with those reported among Sioux Indians (10%; Ref. 17, 35, 36). Similarly, Hispanic Americans, who also have a high prevalence of type 2 diabetes mellitus, are reported to have a low incidence of positive family history of breast cancer (37, 38). A correlative study has reported that women with a negative family history of breast cancer have higher insulin levels than women with a family history of breast cancer (39). To our knowledge, there are no other studies comparing rates of family history of breast cancer with the presence of type 2 diabetes (MEDSEARCH 1965–2002), although there is one study that has compared rates of family history of breast cancer in women with a family history of diabetes, and found no correlation (40). It is not known, therefore, whether these findings are unique to Native-American women.

The prevalence of obesity and diabetes in Native-Americans is high, particularly in the Southwestern United States where it occurs in about one-third to one-half of adults (21, 41). Women with a BMI of 32, are three times more likely to have higher-stage breast cancers (42). Poor survival rates in Native-Americans are considered attributable to delayed diagnosis and higher stage at detection (43). It is not known whether obesity is a contributing factor. Obese women have larger breast cancers, higher stage at diagnosis, higher recurrence rates, and poorer survival, independent of socioeconomic factors (44–45). This may be attributable to increased metastatic potential from local and circulatory estrogens, or to delayed detection because of difficulty in palpation (44–48). The potential adverse effect of obesity on breast cancer stage at detection in Native-American women might be ameliorated by screening mammography (45). However, screening rates in these women have been below national averages with 23% of Southwestern Native-American women >50 years of age reporting having a mammogram and clinical breast exam in the previous 2 years as compared with 66% of women nationally (49, 50).

Mammogram density affects accuracy. Most studies report that sensitivity and specificity are higher in low-density mammograms and in postmenopausal women (2, 51–54). Given the prevalence of low-density mammograms, screening mammography should be particularly effective in Native-American women. This is indicated by a report of unusually high mammographic sensitivity in Native-American women, 95% compared with 77% in Hispanic women, 80% in white women in New Mexico, and 70% in white women in New Hampshire (51, 54).

A limitation of our study was the subjective and semiquantitative nature of the BIRADS classification scheme for mammogram density. There were no computerized methods to measure density at the institution of study. Because of Institutional Review Board requirements, mammograms could be neither copied nor transferred for computerized analysis, or for comparison with another population. Therefore, this study cannot determine whether density is lower in this group than in other groups. The BIRADS system is used in mammography research and clinical practice, (2, 5, 6, 16, 21, 51–56), and although interobserver variability exists in density assessments, interobserver agreement is excellent in the fat density (BIRADS-1) category and good in other categories (56, 57). Another limitation is that the precise formulation of HRT was also not known. Although the finding that density varies with diabetes is new, the other findings that density varies with weight, parity, age, age at first birth, and HRT have been verified in many other studies (12).

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