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ORIGINAL ARTICLE – BREAST ONCOLOGY

Breast Density in a Contemporary Cohort of Women With Ductal Carcinoma In Situ (DCIS)

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ABSTRACT

Background. Mammographic breast density (MBD) is an independent risk factor for breast cancer. Information regarding the relationship of MBD and breast cancer biology in women with ductal carcinoma in situ (DCIS) is currently lacking. This study aimed to examine the clinicopathologic characteristics of DCIS in women stratified by MBD.

Methods. A retrospective review was performed to identify women with pure DCIS who underwent preoperative mammography between 2010 and 2018. Clinicopathologic and demographic data were collected. For the purpose of analysis, MBD was categorized as "non-dense" (Breast Imaging-Reporting and Data System [BI-RADS] density categories A and B) or "dense" (BI-RADS C and D) according to its identification in radiology reports.

Results. Of 3227 patients with a breast cancer diagnosis enrolled in the institutional Breast Cancer Database during the study period, 658 (20%) had pure DCIS. Of these 658 patients, 42% had non-dense breasts, and 58% had dense breasts. Most lesions were non-palpable (92%) and detected by mammography (84%). Patients with dense breasts were more likely to be younger at the time of diagnosis ($p < 0.001$), premenopausal ($p < 0.001$), and Asian ($p = 0.018$), and to have higher-grade disease ($p = 0.006$; Table 2). Family history, BRCA status, parity, mammogram frequency, palpability, method of presentation, lesion size, hormone receptor status, comedo histology, and recurrence did not differ significantly between the two groups (Table 1). The median follow-up period was 7.1 years.

Conclusion. Women with pure DCIS and higher MBD are more likely to be younger at the time of diagnosis, premenopausal, and Asian, and to present with higher-grade disease. Further research on the relationship of age, MBD, and tumor biology in DCIS is warranted.

In 2017, ductal carcinoma in situ (DCIS) was diagnosed for an estimated 63,410 women, and invasive breast cancer was diagnosed for an additional 252,710 women in the United States.[1] Recognized as a "stage 0" cancer, DCIS already possesses many of the molecular abnormalities that allow progression to invasive disease. Therefore, DCIS often is managed with the intention of preventing progression or recurrence as an invasive cancer.[2,3]

In most cases, DCIS is asymptomatic and diagnosed during routine screening mammography. As widespread mammography screening programs have become available worldwide, rates for the detection of DCIS have increased significantly.[4,5]

The composition of each breast is unique, with parenchyma, fat, and connective tissue existing in varying quantities in each patient.[6–8] The volume of parenchyma and the density of this tissue are an important variable in the performance of breast imaging because they affect the ability to assess abnormalities accurately. The presence of dense breast tissue is known to diminish the sensitivity of

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screening mammography.[6] In addition, mammographic breast density (MBD) is known to be an independent risk factor, with an approximately fivefold increase in risk in the general population for the development of DCIS in those with dense breasts.[4,6,9,10]

Breast density is such an important risk factor for breast cancer that many states have adopted laws requiring disclosure of breast density on mammogram reports.[9]

Although much has been written about the significance of breast density and invasive disease, our understanding of the relationship between MBD and patient and tumor characteristics of patients with DCIS still is lacking. This study aimed to examine the clinicopathologic characteristics of women with DCIS stratified by their MBD.

METHODS

The institutional Breast Cancer Database was queried to identify women with a diagnosis of pure DCIS who underwent preoperative mammography between 2010 and 2018. The NYU Breast Cancer Database, established in January 2010, prospectively follows all patients with newly diagnosed breast cancer who had their definitive surgery at our institution. All patients 18 years of age or older undergoing breast cancer surgery at NYU are eligible to enroll in the institutional review board (IRB)-approved database.

All data were obtained from detailed questionnaires completed by the patients and from electronic medical record (EMR) review. Mammograms were performed either at our institution or at outside facilities with reports available for review in the EMR.

The inclusion criteria specified women older than 18 years with a diagnosis of pure DCIS and records available for review. Any patient without a BI-RADS density classification available on mammography or a diagnosis of invasive disease was excluded from the study. Clinicopathologic and demographic data including age, menopausal status, race, strong family history (having a first-degree relative with breast cancer), BRCA status, body mass index (BMI), parity, mammogram frequency, tumor palpability, method of presentation, tumor size, hormone receptor status, histologic grade, comedo histology, and recurrence status were recorded. Mammographic breast density was classified according to the four-point scale of the American College of Radiology (ACR) Breast Imaging-Reporting and Data System (BI-RADS) categories as follows: A (the breasts are almost entirely fatty), B (there are scattered areas of fibroglandular density), C (the breasts are heterogeneously dense, which may obscure small masses), or D (the breasts are extremely dense, which lowers the sensitivity of mammography).[11] The patients then were grouped into "non-dense" (BI-RADS A and B) and "dense" (BI-RADS C and D) groups for analysis purposes. Statistical analysis was performed with Pearson's Chi square, Wilcoxon rank-sum tests, multivariate logistic regression, and Cox proportional hazards regression.

RESULTS

During our study period, 3227 patients with a cancer diagnosis were enrolled in the database. Of these patients, 658 (20%) had pure DCIS and known mammographic breast density, including 276 patients with non-dense breasts (42%) and 382 patients with dense breasts (58%). The median follow-up period for this cohort was 7.1 years (range, 0.4–7.8 years). The majority of the patients presented with non-palpable disease (92%) detected by mammography (84%). The median age of the patients with dense breasts was 55 years, whereas those with non-dense breasts had a median age of 64 years ($p < 0.001$).

We performed logistic regression analysis, adjusting for age at diagnosis and race, and found that patients with dense breasts were more likely to be younger ($p < 0.001$), premenopausal ($p < 0.001$), and Asian ($p = 0.044$) and to have a lower BMI ($p < 0.001$) and a higher tumor histologic grade ($p = 0.019$) than those with non-dense breasts (Table 1). Strong family history, BRCA status, parity, mammogram frequency, palpability, method of presentation, tumor size, hormone receptor status, comedo histology, and recurrence did not differ significantly between the two groups (Table 1). Recurrence still did not differ significantly between the two groups after adjustment for surgery type, systemic therapy, and radiation therapy ($p = 0.501$), nor after time to recurrence was taken into account ($p = 0.353$).

In the multivariable analysis, age, menopausal status, race, and histologic grade remained significantly different between the two groups. The women with dense breasts had slightly higher odds of being younger (odds ratio [OR] 0.96; 95% confidence interval [CI] 0.94–0.98), premenopausal (OR 2.62; 95% CI 1.50–4.57), and Asian (OR 2.00; 95% CI 1.13–3.56) and of having high-grade histology (OR 1.61; 95% CI 1.13–2.29) than the women with non-dense breasts (Table 2).

DISCUSSION

In our study of patients with pure DCIS, high mammographic breast density was associated with younger age, premenopausal status, Asian race, and high-grade histology. In general, breast density decreases with increasing age.[12] Younger age and lower BMI are correlated with increased breast density.[10,12,13] However, the existing

TABLE 1 Clinical and pathologic characteristics by mammographic breast density (n = 658)

Variable	Total (n = 658)	BI-RADS A & B (n = 276) n (%)	BI-RADS C & D (n = 382) n (%)	p Value[a]	Adjusted p value[b]
Median age at diagnosis: years (range)[c]	59 (29–89)	64 (35–89)	55 (29–89)	< 0.001	< 0.001
Menopausal status				< 0.001	< 0.001
Premenopausal	206 (31.4)	34 (12.4)	172 (45.0)		
Postmenopausal	451 (68.6)	241 (87.6)	210 (55.0)		
Race				0.004	0.044
White	463 (70.6)	213 (77.2)	250 (65.8)		
Black	56 (8.5)	26 (9.4)	30 (7.9)		
Hispanic	49 (8.5)	17 (6.2)	32 (8.4)		
Asian	88 (13.4)	20 (7.2)	68 (17.9)		
Strong family history (1st-degree relative)				0.523	0.958
Yes	220 (33.9)	96 (35.3)	124 (32.9)		
No	429 (66.1)	176 (64.7)	253 (67.1)		
BRCA1/2 status				0.634	0.990
Positive	23 (10.1)	9 (11.4)	14 (9.4)		
Negative	205 (89.9)	70 (88.6)	135 (90.6)		
BMI: median (range)[c]	26 (16–46)	27 (17–46)	24 (16–42)	< 0.001	< 0.001
Parity				0.042	0.185
Nulliparous	212 (32.4)	77 (28.0)	135 (35.5)		
≥1 live births	443 (67.6)	198 (72.0)	245 (64.5)		
Mammogram frequency in last 6 years				0.008	0.510
0–2	79 (13.3)	21 (8.5)	58 (16.8)		
3	48 (8.1)	15 (6.0)	33 (9.6)		
4–6	390 (65.8)	175 (70.6)	215 (62.3)		
7–11	66 (11.1)	31 (12.5)	35 (10.1)		
≥12	10 (1.7)	6 (2.4)	4 (1.2)		
Palpability				0.010	0.124
Yes	52 (7.9)	13 (4.7)	39 (10.2)		
No	606 (92.1)	263 (95.3)	343 (89.8)		
Method of presentation				0.020	0.106
Breast exam	55 (8.4)	15 (5.4)	40 (10.6)		
Mammogram	547 (83.9)	243 (88.4)	304 (80.6)		
Ultrasound	19 (2.9)	4 (1.5)	15 (4.0)		
MRI	31 (4.8)	13 (4.7)	18 (4.8)		
Median size: cm (range)[c]	1.2 (0.1–10.0)	1.1 (0.1–10.0)	1.4 (0.1–8.6)	0.064	0.505
ER status				0.699	0.130
Positive	537 (83.4)	225 (82.7)	312 (83.9)		
Negative	107 (16.6)	47 (17.3)	60 (16.1)		
PR status				0.545	0.351
Positive	465 (72.2)	193 (71.0)	272 (73.1)		
Negative	179 (27.8)	79 (29.0)	100 (26.9)		

TABLE 1 continued

Variable	Total (n = 658)	BI-RADS A & B (n = 276) n (%)	BI-RADS C & D (n = 382) n (%)	p Value[a]	Adjusted p value[b]
Histologic grade				0.020	0.019
Low	38 (5.8)	21 (7.6)	17 (4.5)		
Intermediate	292 (44.8)	135 (48.9)	157 (41.8)		
High	322 (49.4)	120 (43.5)	202 (53.7)		
Histology				0.756	0.471
Comedo	183 (27.8)	75 (27.2)	108 (28.3)		
Non-comedo	475 (72.2)	201 (72.8)	274 (71.7)		
Recurrence				0.832	0.501[d]
Yes	32 (4.9)	14 (5.1)	18 (4.7)		0.354[e]
No	626 (95.1)	262 (94.9)	364 (95.3)		

BI-RADS breast imaging-reporting and data system, *BMI* body mass index, *MRI* magnetic resonance imaging, *ER* estrogen receptor; *PR* progesterone receptor

[a]Chi square or Fishers exact test p values

[b]Logistic regression model adjusted for age at diagnosis and race

[c]Wilcoxon rank-sum test p values

[d]Logistic regression

[e]Cox proportional hazard model adjusted for age at diagnosis, race, surgery type, systemic therapy, and radiation therapy

literature on breast density and tumor characteristics is mixed, and the reason for the apparent relationship between high-density breast tissue and high-grade histology in breast disease, both in situ and invasive, is not clear.

We found an association between Asian race and higher breast density. This association has been examined in previous studies, including the study by del Carmen et al.[14] Their study also showed a relationship between Asian race and higher breast density. However, when adjustment was made for age, BMI, and bra cup size, this relationship was less significant, a factor that the authors attributed to the sample size of their study.

In our study, after adjustment for age at diagnosis, menopausal status, race, and histologic grade, a significant association remained between density and Asian race in our results. Despite a significantly smaller overall study population, we had a much greater enrichment for Asian patients in our cohort. Interestingly, despite their higher breast density, Asian patients are known generally to have a lower age-adjusted breast cancer incidence rate than African American or Caucasian patients.[14] This underscores the complexity of the relationship between breast density and cancer development and provides an area for future study.

Multiple studies have demonstrated that tumors developing in areas of high-density tissue are more likely to have adverse features, such as high histologic grade, as seen in our study cohort of DCIS patients.[4,13,15] In a study of breast density and tumor histology, Sala et al.[16] also found that increased density is correlated with higher-grade tumor histology in invasive carcinoma. Yaghjyan et al.[6] reported similar findings.

Conversely, Masarwah et al.,[17] in their study of outcomes for women with invasive cancer, found that very low mammographic breast density, classified as density lower than 10%, was an independent poor prognostic feature after controlling for all other variables. Ding et al.[18] also found a relationship between low tumor grade and high breast density. Porter et al.[19] found that women with increased mammographic density have slightly larger tumors, but observed no difference in lymph node stage, lymphovascular invasion, tumor type, or histologic grade.

Pathology studies have correlated increasing mammographic breast density and the proportion of fibrous stroma in the breast, with concomitant decreasing proportion of fatty tissue.[9,20] As the volume of fibroglandular tissue in the breast increases, the volume of epithelial cells at risk of carcinogenesis also may increase, which could explain some of the relationship between density and breast cancer risk.[21]

Mammography has lower sensitivity in the diagnosis of breast disease for women with dense breasts.[19,22]. Fasching et al.[23] demonstrated that the difference between pathologic tumor size and size shown on mammography increased for patients with increasing breast density. Similarly, Boyd et al.[13] found an elevated risk for a breast cancer diagnosis with a greater percentage of mammographic breast density in the 12 months after a negative

TABLE 2 Multivariable logistic regression analysis

Variable	BI-RADS A & B (n = 276) n (%)	BI-RADS C & D (n = 382) n (%)	OR (95% CI)[a]	p value[a]
Median age at diagnosis: years (range)	64 (35–89)	55 (29–89)	0.96 (0.94–0.98)	< 0.001
Menopausal status				
Premenopausal	34 (12.4)	172 (45.0)	2.62 (1.50–4.57)	< 0.001
Postmenopausal	241 (87.6)	210 (55.0)	Ref	
Race				0.049
White	213 (77.2)	250 (65.8)	Ref	
Black	26 (9.4)	30 (7.9)	0.78 (0.42–1.45)	0.432
Hispanic	17 (6.2)	32 (8.4)	1.47 (0.75–2.86)	0.259
Asian	20 (7.2)	68 (17.9)	2.00 (1.13–3.56)	0.018
Histologic grade				0.011
Low	21 (7.6)	17 (4.5)	0.73 (0.35–1.55)	0.139
Intermediate	135 (48.9)	157 (41.8)	Ref	
High	120 (43.5)	202 (53.7)	1.61 (1.13–2.29)	0.006

BI-RADS breast imaging-reporting and data system; *OR* odds ratio, *CI* confidence interval

[a]Adjusted for age at diagnosis, menopausal status, race, and histologic grade

screening mammogram, suggesting that some tumors may be masked on imaging by the density of the breast tissue. This suggests the utility of adjunctive imaging methods such as ultrasound and magnetic resonance imaging (MRI) for patients with dense breasts.

Findings have shown that compared with mammography alone, MRI is more sensitive for diagnosing pure DCIS, and previous studies have demonstrated the utility of MRI for detecting cancers missed on mammography.[24] In the American College of Radiology Imaging Network (ACRIN) 6666 trial, an additional 4.3 per 1000 cancers were detected by addition of ultrasound, and an additional 14.7 per 1000 cancers were detected with addition of screening MRI.[25] This study specifically analyzed women with heterogeneously or extremely dense breast tissue.

In our study, ultrasound identified 4 additional cancers in the non-dense breasts and 12 in the dense breasts, whereas MRI identified an additional 5% of lesions in each group. Although it has become increasingly popular to order adjunctive imaging methods for screening of women with dense breast tissue, our results demonstrated that the vast majority of DCIS lesions in both more dense and less dense breasts were identified using mammography. Routine physical exam and screening mammography accounted for 91.4% of diagnoses in the dense breast group and 93.4% in the less dense group. This suggests that even in the presence of dense breast tissue, adjunctive imaging should be performed on a case-by-case basis at the discretion of the ordering physician.

Weigel et al.[26,27] examined the role of screening mammography in DCIS and found that when a screening program was implemented, the DCIS detection rates increased significantly for the whole population and that this was driven by detection of intermediate- and high-grade DCIS subtypes. These higher-grade subtypes also tended to increase with advancing age.

In contrast, we found that our patients with increased breast density who were enriched for the higher-grade histology proved to be substantially younger than their counterparts with lower density. We also found that women with greater breast density were less likely to have had regular mammography. Due to less frequent screening of the dense group, some of these lesions may qualify as interval cancers, which have been shown in previous studies to present with a worse phenotype and to occur with greater likelihood in women with increased breast density.[23,28,29] In one study of interval cancers, Mandelson et al.[29] found that patients with interval cancers were more likely to have lower body weight and increased breast density, similar to our findings for patients with DCIS. However, their study also noted that cancers developing in lower-density areas tended to have higher-grade histology, which contradicts our findings.

Finally, we noted no differences in recurrence rates between the two groups after controlling for treatment-related variables. This may have been influenced by the small number of recurrences overall as well as by the relatively short follow-up time.

CONCLUSION

In our study of MBD in patients with a diagnosis of DCIS, higher breast density was associated with higher-grade disease, lower BMI, Asian race, and younger age. Because routine imaging identified an overwhelming number of DCIS cases in our study, it does not appear that a delay in diagnosis should necessarily be implicated in those cases with a diagnosis of higher-grade disease. However, the trend showing that patients with higher breast density have fewer imaging tests suggests that perhaps not all patients were undergoing routine screening despite the finding that the median age of the dense-breast cohort was 52 years. Although young age and low BMI have a well-established correlation with higher breast density, the relationship of higher-grade histology with increased MBD is interesting. The existing literature on this topic is heterogeneous, and the mechanism for this relationship merits further study.

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