Association of Mammographic Density and Molecular Breast Cancer Subtype

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San Antonio Breast Cancer Symposium
December 9-13, 2014

Background

Mammographic density impacts both an individual's risk of developing breast cancer and the sensitivity of imaging modalities to detect it. Limited yet conflicting data exists on an association between density and developing specific molecular subtypes of breast cancer.

Methods

- Eligible patients included women with invasive breast cancer diagnosed between 2003-2012 and enrolled in a larger study on breast density.
- Exclusion criteria from the larger study included inadequate follow-up or pathologic information, lack of digital mammography preceding systemic therapy, history of breast implants or reduction surgery, and development of bilateral breast cancer within one year of diagnosis.
- Demographics were collected through chart review and patient survey.
- Mammographic Density was classified qualitatively from existing radiology reports according to Breast Imaging Reporting and Data System (BIRADS) classification and quantitatively by volumetric density measurements using Volpara Solutions™ software.
- Relevant pre-cancer factors including age, race, BMI, family history of breast cancer, and biopsy showing LCIS were included in analysis.
- Molecular Subtype was assigned by hormone receptor status, tumor grade and mitotic score (MS) (**Table 1**).

Table 1. Molecular subtype classification by hormone receptor status, tumor grade and mitotic score (MS)

Luminal A	Luminal B	Her-2-Neu	Triple Negative
ER+/PR+ & grade 1	ER+ & grade 3 or MS=3	Her-2-neu +	ER-/PR- & Her-2-neu -
ER+/PR+ & grade 2 & MS=1	ER+/PR- & grade 2		
ER+/PR- & grade 1	ER+/PR+ & grade 2 & MS=2		

Results

- Of 604 eligible patients, 457 had sufficient imaging and pathology information for analysis.
- 233 (51%) had Luminal A, 79 (17%) Luminal B, 59 (13%) Her-2 +, and 86 (19%) Triple Negative tumors.
- Younger women and those with denser breasts based on quantitative measurements were more likely to have Her-2+ tumors (**Table 2**); this association was not seen using the standard BIRADS classification.
- Triple Negative tumors were less common in patients with LCIS and more common in African Americans.

Results cont.

Table 2. Association between patient factors and molecular breast cancer subtype

Variable n = 457	Luminal A n = 233 (51%)	Luminal B n = 79 (17%)	Her-2-Neu n = 59 (13%)	Triple Negative n = 86 (19%)	P value
Age (median, IQR)	61 (54, 70)	58 (50,67)	54 (46, 70)	59 (48, 67)	0.006
BMI (median, IQR)	27.1 (22.9, 30.5)	25.7 (23.0, 30.0)	26.0 (22.7, 32.6)	28.1 (24.3, 32.6)	0.173
Volpara™ breast density (median,IQR)	7.18 (4.74, 11.25)	8.68 (5.68, 14.34)	10.25 (5.96, 16.51)	7.00 (4.97, 11.89)	0.002
BIRADS density (n,%)					
Fatty	42 (18.0%)	15 (19.0%)	5 (8.5%)	16 (18.6%)	0.183
Scattered	103 (44.2%)	27 (34.2%)	20 (33.9%)	36 (41.9%)	
Heterogeneous	74 (31.8%)	30 (38.0%)	25 (42.4%)	26 (30.2%)	
Extreme	14 (6.0%)	6 (7.6%)	9 (15.2%)	7 (8.1%)	
Unspecified	0	1 (1.2%)	0	1 (1.2%)	
Race (n,%)					
Caucasian	202 (86.7%)	65 (82.3%)	51 (86.4%)	61 (70.9%)	0.002
African American	23 (9.9%)	13 (16.5%)	6 (10.2%)	23 (26.7%)	
Other	2 (0.9%)	0	2 (3.4%)	0	
Unspecified	6 (2.6%)	1 (1.2%)	0	2 (2.3%)	
Presence of LCIS (n,%)	48 (20.6%)	8 (10.1%)	8 (13.6%)	5 (5.8%)	0.004
1st or 2nd degree Family History of breast cancer (n,%)	107 (45.9%)	34 (43.0%)	21 (35.6%)	39 (45.35)	0.625

- Multinomial logistic regression controlling for pre-cancer patient factors demonstrated that **while quantitative breast density does not significantly differentiate between all molecular subtypes (p=0.140), the association between Her-2-neu positive tumors and denser breasts using continuous quantitative measurements is significant (p=0.035).**
- In a second multinomial logistic regression utilizing categorical BIRADS breast density, **this association is not clearly seen among women classified as having heterogeneously dense (p=0.671) or extremely dense breast (p=0.099).**

Conclusion

Women with denser breasts by continuous-scaled quantitative measurements are at higher risk for Her-2+ tumors, an association not delineated using standard BIRADS density classification. Delineating risk factors specific to molecular breast cancer subtype may promote individualized risk prediction models and prevention strategies.