Original Article Open Access

Archives Of Breast Cancer

DOI: 10.32768/abc.2024113xxx-xxx

Association Between Radio-pathological Breast Tumor Characteristics and Mammographic Breast Density

Mahnaz Roayaei[a], Fatemeh Bahrami[b], Fatemeh Karami[c], Hoda Mahdavi*[d]

[a]*Radiation Oncology Department, School of medicine, Isfahan University of Medical Sciences, Isfahan, Iran*

[b]*School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran*

[c]*Shafa Radiology Center, Isfahan, Iran*

[d]*School of Medicine, Iran University of Medical Sciences, Tehran, Iran*

ARTICLE INFO

Received:
17 May 2024
Revised:
21 July 2024
Accepted:
22 July 2024

Keywords:
Breast cancer, breast density, mammography, tumor characteristics, HER2

ABSTRACT

Background: Although mammographic density is a strong indicator of breast cancer risk, it is unclear whether there is any association between breast density and certain breast cancer subtypes. This study aimed to investigate the relation between radiologic breast density category and tumor characteristics.

Methods: Patients with histologically proven breast cancer who had undergone diagnostic mammography were reviewed retrospectively from 2016 to 2019. The American College of Radiology BI-RADS mammographic density categories were recorded and grouped into low (a and b), and high (c and d). Patient characteristics as well as tumor size, border, pathology, ER, PR, and Her2 immunohistochemistry were extracted from the mammography, ultrasonography, and core needle pathology reports. Binary logistic regression model was used to analyze the association between breast density and receptors, molecular subtypes, or tumor features.

Results: The present study was comprised of 129 patients, with 7, 47, 41, and 34 patients in the density categories a, b, c, and d, respectively. Patients who had a higher breast density were significantly younger (P=0.001). Those with a lower density were more likely to have HER2, IHC 0 tumors (Odds ratio adjusted for age = 4.9, 95% CI 1.25-18.27, P=0.022). Mammographic density was not related to molecular subtypes and other tumor features.

Conclusion: Mammographic dense breast may be associated with Her2 positive breast cancer.

INTRODUCTION

Breast cancer is one of the most frequently diagnosed malignancies among women [1] in which death rates have largely decreased by utilizing screening programs. Mammography is a widely accepted screening modality even though it is limited by low detection rates.[2,3] Mammographic density, referred as the percentage of dense tissue associated with stromal and epithelial proliferation of the entire breast tissue, is considered a known risk factor for the development of breast cancer. Accordingly, women who possess mammographically dense breasts are at a three-to-five-fold heightened risk of developing breast cancer than that of women with mammographically fatty breasts.[4-6] This phenomenon may be related to microenvironmental factors of the tumor and stroma. [7] In addition, sensitivity in detecting malignant lesions and microcalcifications is reduced in mammograms of dense breasts [2, 8], causing delayed diagnoses, and as described in a number of studies, revealing cancer at more advanced stages, e.i., larger tumors and nodal involvement.[7,9–11]

***Address for correspondence:**
Hoda Mahdavi, MD,
School of Medicine, Iran University of Medical Sciences, Tehran, Iran
Firoozgar hospital, Beh-Afarin St., Karimkhane-Zand Blvd., Tehran, Iran, PO Box: 1593747811,
Tel: +98912498677
Email: Mahdavi.h@iums.ac.ir

Her2 amplification which is present in about 15% of breast cancer patients, is a negative prognostic factor for breast cancer. Lack of Her2 overexpression is detected by immunohistochemistry score of either 0 or 1+, considered as negative. However, Her2 0 tumors may be biologically distinct from 1+ tumors since new Her2 targets have shown efficacy in low positivity of 1+ or 2+ unamplified Her2. [12] Ongoing studies are exploring the biology of Her2 expressing tumors.

It is suspected that there may be differences in clinicopathological reports of categories of breast density according to hormone receptor status and Her2 IHC score. This study aims to investigate potential associations between breast density and clinicopathological features of breast cancer.

METHODS

Study design and participants

This cross-sectional study was conducted on all women who underwent diagnostic mammography at the Shafa Imaging Center, Isfahan, Iran between 2016 to 2019. We identified and reviewed medical records of all patients who had undergone diagnostic mammography with a documented diagnosis of a malignant breast mass based on their pathological reports. Women with a second breast cancer, or those with previous breast surgery or radiotherapy were excluded.

Mammographic and Ultrasonographic data

Mammography was performed using a digital system in the craniocaudal (CC) and mediolateral oblique (MLO) positions using Hologic, Selenia mammography system with similar settings. We evaluated breast density using the American College of Radiology (ACR) breast composition classification, with breast density categorized as follows: a) almost entirely fatty; b) scattered areas of fibro-glandular density; c) heterogeneously dense; and d) extremely dense. Breast malignancies are typically irregular hypoechoic nodular lesions with ill-defined or spiculated borders and microcalcifications; however, the radiologist will not be able to distinguish all malignant from benign lesions exclusively by the mammogram or ultrasonogram.[2,13] Margins of the tumor were documented in mammograms to be ill-defined, spiculated, or otherwise (partially obscured, micro lobulated, lobulated, or normal), and mass density was documented as iso dense or highly dense. Based on the ultrasound reports performed at the time of diagnosis, the reported information regarding mass dimension in millimeters, vascularity (positive or negative), and morphology (irregular or oval) was extracted.

Pathological characteristics

Medical records and pathology reports were studied to obtain information regarding histological tumor type, histological grade, and ER, PR, and HER2 status. Positive results for ER and PR were defined as the presence of stained nuclei in 1% or more of the tumor cells. Regarding Her2 status, tumors were scored as 0, 1+, 2+, and 3+ using the immunohistochemical stain. The ER, PR, Her2, Ki67 kits used included rabbit anti-human monoclonal antibody (Master diagnostica, Granada, Spain). Due to biological differences in the amount of Her2 expression [12], negative tumors were grouped as negative: IHC 0 and compared to otherwise (IHC 1+, 2+, 3+), and again grouped as not overexpressed: IHC 0 or 1+ and compared to the rest. The results of in situ hybridization of equivocal cases (2+) were not adopted. The tumor subtypes were classified into four distinct categories: luminal A, luminal B, HER2 enriched, and basal. Luminal A and luminal B breast cancers were explained as follows: Luminal A: ER and/or PR positive, ki67 low (< 14%). Luminal B: ER and/or PR positive with ki67 high (>14%). HER2-enriched tumors demonstrated overexpression of HER2 which did not express estrogen and progesterone receptors. Basal tumors were identified by the absence of estrogen, progesterone and HER2 receptors.

Statistical analysis

The data in the study were presented in terms of frequencies and percentages for categorical variables and mean and standard deviation (SD) for continuous variables. The Kolmogorov-Smirnov test was employed to assess the normality of all continuous variables. Clinicopathologic variables were analyzed for differences among the four density groups using the chi-square test for categorical variables and the one-way ANOVA or Kruskal-Wallis test for continuous variables. The four density groups were aggregated into two groups as follows: high density group, composed of heterogeneously dense and extremely dense (ACR density c and d), and low-density group, as totally fatty and scattered densities (ACR density a and b). The relationship between breast density and ER, PR, and HER-2 status was investigated using binary logistic regression. Similarly, binary logistic regression was used to examine the associations between high or low breast density and each radiological and pathological variable. Next, a multivariable logistic regression was run for predictors of mammographic high-density categories that were related to breast density with a predetermined P-value of 0.2 or less. Statistical significance was defined as P-value $\leq$ 0.05. IBM SPSS Statistics, version (ver. 26.0 IBM Corp.,

Armonk, NY, USA) was used for all statistical analyses.

RESULTS

Overview of Study Participants.

Among 187 patients with a newly diagnosed breast cancer in diagnostic mammography, 58 patients were excluded due to lack of adequate radiological or pathological information, and finally a total of 129 cases fulfilled the eligibility criteria and were included in the study. The mean age of the participants was 52.86 (10.7), and 12.4% reported a family history of breast cancer. The most frequent histological type of breast cancer was Invasive Ductal Carcinoma (IDC) (91.4%), and the majority of patients, 48.3%, had a grade II tumor.

Table 1. Baseline characteristics of patients diagnosed with breast cancer compared across mammographic breast density groups.

Variables		Total n=129	breast density				P-Value
			A (n=7)	B (n=47)	C (n=41)	D (n=34)	
Age, mean in years (SD)		52.86 (10.7)	61.6 (9.6)	57.2 (8.8)	52.2 (12.1)	46.0 (6.8)	0.00*
Tumor size, mean in millimeters (SD)		20.9 (16.4)	2.0 (0.8)	2.2 (1.95)	1.8 (1.47)	2.3 (1.49)	0.19
Family history of breast cancer, n (%)	negative	113 (87.6%)	7 (100%)	43 (91.4%)	32 (78%)	31 (91%)	0.139
	positive	16 (12.4%)	0 (0%)	4 (8.6%)	9 (22%)	3 (9%)	
mass border, n (%)	ill-defined	32 (26.6%)	1 (14.2%)	11 (23.4%)	8 (19.5%)	12 (35.2%)	0.4
	spiculated	75 (58.1%)	6 (85.8%)	27 (57.4%)	27 (65.8%)	15 (64.8%)	
	other	13 (10.8%)	0 (0%)	6 (12.7%)	3 (7.3%)	4 (11.7%)	
calcification in mass	negative	70 (57.9%)	4 (57.2%)	25 (53.2%)	25 (61%)	16 (47%)	0.63
	positive	51 (42.1%)	3 (42.8%)	16 (34%)	15 (36.5%)	17 (50%)	
mass density (%)	iso-dense	38 (34.5%)	1 (14.3%)	12 (25.5%)	9 (22%)	16 (47%)	0.009*
	high- density	72 (65.4%)	6 (85.7)	29 (61.7%)	27 (65.8%)	10 (29.4%)	
mass morphology, n (%)	irregular	121 (93.7%)	7 (100%)	45 (95.7%)	41(100%)	28 (82.3%)	0.026*
	oval	3 (2.4%)	0 (0%)	0 (0.00%)	0 (0.00%)	3 (8.8%)	
tumor grade, n (%)	I	18 (14.7%)	1 (14.2%)	8 (17%)	4 (9.7%)	5 (14.7%)	0.794
	II	59 (48.3%)	4 (57.1%)	23 (48.9%)	18 (43.9%)	14 (41.1%)	
	III	45 (36.9%)	1 (14.2%)	14 (29.7%)	16 (39%)	14 (41.1%)	
histological type, n (%)	IDC	118 (91.4%)	6 (85.7%)	41 (87.2%)	38 (92.6%)	33 (97%)	0.748
	ILC	3 (2.3%)	0 (0%)	2 (4.2%)	1 (2.4%)	0 (0%)	
	MC	7 (5.4%)	0 (0%)	4 (8.5%)	2 (4.8%)	1 (2.9%)	
ER, n (%)	negative	22 (18.0%)	0 (0%)	10 (21.2%)	6 (14.6%)	6 (17.6%)	0.562
	positive	100 (82.0%)	6 (85.7%)	35 (74.4%)	33 (80.4%)	26 (76.4%)	
PR, n (%)	negative	32 (27.1%)	0 (0%)	14 (29.7%)	8 (19.5%)	10 (29.4%)	0.262
	positive	86 (72.9%)	6(85.7%)	29 (61.7%)	30 (73.1%)	21 (61.7%)	
HER2, n (%)	IHC 0	104 (82.5%)	6(85.7%)	43 (91.4%)	27 (65.8%)	28 (82.3%)	0.004*
	IHC 1+, 2+, 3+	22 (17.5%)	0(0%)	3 (6.3%)	14 (34.1%)	5 (14.7%)	
	IHC 0 or 1+	165 (88%)	6 (100)	43 (93.5)	30 (73.2)	28 (84.8)	0.044*
	IHC 2+, 3+	19 (10.3%)	0 (0)	3 (6.5)	11 (26.8)	5 (15.2)	
Ki67, n(%)	14≥	45 (31.7%)	3(42.8%)	18(38.2%)	15(36.5%)	9 (26.4%)	0.79
	14<	41 (47.7%)	2 (28.5%)	13 (27.6%)	15 (36.5%)	11 (32.3%)	
Breast cancer subtype, n (%)	Luminal A	66 (51.1%)	4 (57.1%)	27 (57.4%)	18 (43.9%)	17 (50%)	0.63
	Luminal B	33 (25.5%)	2 (28.5%)	8 (17%)	15 (36.5%)	8 (23.5%)	
	HER2 enriched	6 (4.6%)	0 (0%)	2 (4.2%)	2 (4.8%)	2 (5.8%)	
	Triple-negative	18 (13.9%)	0 (0%)	9 (19.1%)	4 (9.7%)	5 (14.7%)	

IDC: Invasive Ductal Carcinoma; ILC: Invasive Lobular Carcinoma; MC: Mucinous Carcinoma; ER: Estrogen Receptor; PR: Progesterone Receptor; HER2: Human Epidermal growth factor Receptor 2. Sums of percentages are less than 100% when missing data exists.
*Significant difference at the 0.05 level

Tumor size ranged from 3 to 120 millimeters. The majority of the patients (93.7%) had an irregular mass morphology and most (58.1%) had a spiculated type of margin. Data from the ultrasonography showed

that 23.4% of the masses had positive vascularity. Positive ER and/or PR status was present in 81.4% of the patients. The mean (SD) of Ki67 was 22.2 (16.8). Other descriptive characteristics are presented in Table 1 which shows that age (r = -.47) was significantly different across breast density categories.

A binary logistic regression was performed to evaluate the effect of age on the likelihood of breast density when categorized as high versus low that was statistically significant (β = -0.085, OR= 0.92. P<0.0001).

Relationships between breast density categories and radio-pathological characteristics of tumor.

In the BI-RADS mammographic density categories a, b, c, and d, there were 7 (5.4%), 47 (36.4%), 41 (31.8%) and 34 (26.4%) patients, respectively. Significant differences in mass density, mass morphology and HER2 status were observed in the four groups (Table 1) which shows that categories of mass density (χ^2,=11.6), mass morphology (χ^2,=8.5), and Her2 stain (χ^2,= 13.1) were significantly different across breast density categories.

Table 2. Association between mammographic breast density and features of tumors in patients diagnosed with breast cancer using binary logistic regression

independent variable	Univariate model			Multivariable model		
	OR	CI 95%	P-value	OR	CI 95%	P-value
general						
age	0.92	0.88-0.96	<0.001*	0.89	0.82-0.96	0.002*
radiological						
Tumor size	0.99	0.99-1.05	0.58	-	-	-
mass border						
ill-defined	1	-	0.29	1	-	0.95
spiculated	0.49	0.49-1.19	0.11	1.23	0.29-5.18	0.78
other	0.65	0.20-2.0	0.47	0.97	0.14-6.63	0.97
calcification in mass						
negative vs positive	0.8	0.35-1.83	0.6	-	-	-
mass density						
iso- vs high-density	0.55	0.24-1.24	0.15	0.41	0.11-1.53	0.19
mass vascularity						
negative vs positive	0.26	0.10-0.7	0.008*	0.34	0.09-1.33	0.12
pathological						
tumor grade						
I	1	-	0.33	-	-	-
II	1.18	0.41-3.40	0.75	-	-	-
III	2.0	0.65-6.08	0.22	-	-	-
histological type						
IDC	1	-	0.46	-	-	-
ILC	0.33	0.02-3.75	0.37	-	-	-
MC	0.49	0.10-2.32	0.37	-	-	-
Breast cancer subtype				-	-	-
Luminal A	1	-	0.659	-	-	-
Luminal B	1.05	0.34-3.30	0.92	-	-	-
HER2 enriched	1.8	0.54-6.00	0.33	-	-	-
Triple-negative	2	0.29-13.81	0.48	-	-	-
Immunohistochemistry						
ER*	0.83	0.32-2.11	0.70	-	-	-
PR*	0.88	0.38-2.00	0.76	-	-	-
HER2						
IHC 0*	0.18	0.04-0.064	0.008*	0.07	0.01-0.68	0.022*
IHC 0-1+**	0.22	0.6-0.81	0.022*	0.09	0.01-0.90	0.04*
Ki67***	1.51	0.63-3.5	0.34	-	-	-

Breast density as the dependent variable is defined by American College of Radiologists' as a or b versus c or d, ER: Estrogen Receptor; PR: Progesterone Receptor; HER2: Human Epidermal growth factor Receptor 2; OR: Odd Ratio; CI: Confidence Interval, * positive IHC versus negative, ** negative or one plus stain versus 2 or 3 plus. *** Ki67 14≥ versus 14<significance level 0.05. IDC: Invasive Ductal Carcinoma; ILC: Invasive Lobular Carcinoma; MC: Mucinous Carcinoma

Relationships between breast density and hormone receptor and other features of tumor.

Binary logistic regression showed that dense breast versus fatty breast was associated with HER-2 expression in breast cancer (OR 5.56, 95% CI 1.57-

20.23, P<0.008). The association remained for Her2 score 0 versus otherwise expression when entered in the multivariate model. Age was associated with breast density; however, there was no significant relationship between breast density and other features of tumor such as grade, size, molecular subtypes, and mass margin (Table 2).

Finally, predictors which were related to breast density with a predetermined p value of 0.2 or less were used in a multivariable regression. These variables were age, Her2 status, mass border, mass vascularity, and mass density. The results are demonstrated in table 2.

DISCUSSION

In this retrospective study, our results suggest that there might be a positive association between breast density and HER2 expressing breast tumors. Patients who had higher breast density categories demonstrated greater likelihood of manifesting tumors with positive scores of Her2 IHC as opposed to those demonstrating lower breast density. In particular, this significance remained when the data was controlled in the multivariate model.

Apart from age, which is a known negative confounding factor affecting breast density[7], results of this study showed that regarding the ER and PR status, no difference was observed between the groups categorized as low-density and high-density in contrast to studies showing a positive relation.[14-17] These results are on the basis of evidence which suggests that the precursors of the dense composition of the breast may be driven by environmental factors and epi-genetics similar to risk factors for ER-positive breast cancers. These include low parity, use of exogenous estrogen in combination with progestin, and postponed menopause. Genetics may also have a large impact on many unidentified inherited factors. [15] However, the results of the relatedness of receptor markers and dense breasts are contradictory.[11] Consistent with some studies, this study found no obvious relation between density and the development of a particular intrinsic molecular subtype of breast cancer, or ER, PR, and Ki67 [18-20], while there are other studies which show different results.[21-23] Inconsistency in findings may reflect differences in research populations, assessment methods, screening patterns, different adjustments for covariates, or the presence of possible biases. [24] Above all, breast density is a risk factor of all breast cancer subtypes and should be considered for screening and monitoring subjects at risk. [24, 15] Regarding our findings of the Her2 receptor positivity and higher breast density, there is evidence in the literature associating the risk of HER2-Breast Cancer and higher mammographic breast density in a study on a Canadian screening population. [25] Breast density and distribution of receptor status are known to vary by race. In particular, a study conducted on the Asian population showed that women with BI-RADS D were more likely to be diagnosed with HER2-enriched tumors. The Asian decent is known for lower breast cancer incidence but a higher proportion of dense breasts poses more frequent Her2 enriched tumors. [26] A recent systematic review and meta-analysis have showed that higher breast density might contribute to the heightened incidence of HER2-positive subtypes among Asian women. [27] Another study has reported that individuals with high breast density and HER2-positive breast cancers show an increase in STAT3 signaling pathway which promotes tumorigenesis of breast cancer [28], suggesting a connection between HER2 and the molecular pathways of breast density.[29] Notably, the earliest trials on the Her2 receptor investigated the population who benefited most from the first Her2 targeted therapy. Those with 3+ (complete, intense circumferential membranous staining in > 10% of tumor cells) or 2+ (weak to moderate complete membrane staining in >10% of tumor cells) with a positive FISH test, have long been considered the only Her2 positive subgroup and eligible to receive trastuzumab. Now, weak expressions of Her2 are also of interest because newer targets of this receptor have shown efficacy in this population. The results of the later studies reflect biological and clinical differences between Her2 non-expressing tumors and those with Her2 expression.[12,30]

Our investigation did not discover any association between breast density and typical tumor prognostic features, such as size and grade. The relation is inconsistent among different studies but some [31, 32] have suggested a link between high breast density and adverse breast tumor clinical characteristics, such as larger tumor size, nodal involvement, and advanced stage at diagnosis, possibly due to screening and early detection limitations in dense breasts.

This study was strengthened by use of a multivariable model method which allows for controlling the effect of a number of potential process factors simultaneously, but was methodologically restricted as causality and risk cannot be recognized. The number of the cases included was not large enough to make the study sufficiently rigorous for detecting a difference in breast density across tumor hormone receptors. Furthermore, no documented data related to BMI or menopausal state of patients at diagnosis was available. Also, the analysis may have been best interpreted if the results of in situ hybridization of Her2 2+ cases were incorporated. However, as discussed about population-based

studies, the results of this single-center cross-sectional study may inspire the evaluation of histopathological characteristics of an Iranian cohort. We suggest future research on the possible shared underlying mechanisms of breast density and incidence of Her2 positive breast cancers.

CONCLUSION

In conclusion, this study suggests considering breast density as a plausible risk factor for HER2-positive breast cancer but this possibility needs to be proven in population-based studies. While treatment decisions are currently based on pathology, mammographic features of different cancer subtypes could provide additional information to refine a patient's risk profile. The knowledge of dominant subtypes of cancers across breast compositions may have distinct implications. Firstly, in terms of the biological aspects, shared underlying etiologies and molecular pathways which contribute to the linkage of stromal-epithelial proliferation and receptor expression can be explored. Secondly, from a clinical point of view this can result in setting different thresholds of tumor detection for mammogram density categories in women susceptible to certain subtypes of breast cancer. Therefore, further investigation is required to validate the results and to discover the underlying mechanisms.

ETHICAL CONSIDERATIONS

Research approval was obtained from Isfahan University of Medical Sciences Ethics Committee (IR.MUI.MED.REC.1399.1090).

ACKNOWLEDGEMENTS

None.

CONFLICTS OF INTEREST

None.

FUNDING

None.

DATA AVAILABILITY

Data was presented in the article.

REFERENCES

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*. 2024;74(3):229-63. doi: 10.3322/caac.21834.
2. Ramadan SZ. Methods Used in Computer-Aided Diagnosis for Breast Cancer Detection Using Mammograms: A Review. *Journal of healthcare engineering*. 20;2020(1):9162464. doi: 10.1155/2020/9162464.
3. Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. *N Engl J Med*. 2012;367(21):1998–2005. doi: 10.1056/NEJMoa1206809.
4. Wang AT, Vachon CM, Brandt KR, Ghosh K. Breast density and breast cancer risk: a practical review. In: Mayo Clinic Proceedings. *Elsevier*; 2014. p. 548–57. doi: 10.1016/j.mayocp.2013.12.014.
5. Ali EA, Raafat M. Relationship of mammographic densities to breast cancer risk. *Egypt J Radiol Nucl Med*. 2021;52:1–5. doi: 10.21608/ejrnm.2021.13788.
6. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2006;15(6):1159–69. doi: 10.1158/1055-9965.epi-06-0034.
7. Huo CW, Chew GL, Britt KL, Ingman W V, Henderson MA, Hopper JL, et al. Mammographic density—a review on the current understanding of its association with breast cancer. Breast Cancer Res Treat. 2014;144:479–502. doi: 10.1007/s10549-014-2901-2.
8. von Euler-Chelpin M, Lillholm M, Vejborg I, Nielsen M, Lynge E. Sensitivity of screening mammography by density and texture: a cohort study from a population-based screening program in Denmark. *Breast Cancer Res*. 2019;21:1–7. doi: 10.1186/s13058-019-1203-3.
9. Yaghjyan L, Esnakula AK, Scott CG, Wijayabahu AT, Jensen MR, Vachon CM. Associations of mammographic breast density with breast stem cell marker-defined breast cancer subtypes. *Cancer Causes Control*. 2019;30:1103–11. doi: 10.1007/s10552-019-01207-w.
10. Pizzato M, Carioli G, Rosso S, Zanetti R, La Vecchia C. Mammographic breast density and characteristics of invasive breast cancer. *Cancer Epidemiol*. 2021;70:101879. doi: 10.1016/j.canep.2020.101879.
11 Yaghjyan L, Colditz GA, Collins LC, Schnitt SJ, Rosner B, Vachon C, et al. Mammographic breast density and subsequent risk of breast cancer in postmenopausal women according to tumor characteristics. *J Natl Cancer Inst*. 2011;103(15):1179–89. doi: 10.1093/jnci/djr225.
12. Won HS, Ahn J, Kim Y, Kim JS, Song JY, Kim HK, Lee J, Park HK, Kim YS. Clinical significance of HER2-low expression in early breast cancer: a nationwide study from the Korean Breast Cancer Society. *Breast Cancer Research*. 2022 Mar 21;24(1):22. doi: 10.1186/s13058-022-01519-x.
13. Gokhale S. Ultrasound characterization of breast masses. *Indian J Radiol Imaging.* 2009 Jul;19(03):242-7. doi: 10.4103/0971-3026.54878.
14. Cullinane C, Brien AO, Shrestha A, Hanlon EO, Walshe J, Geraghty J, et al. The association between breast density and breast cancer pathological response to neoadjuvant chemotherapy. *Breast Cancer Res*

Treat. 2022;194(2):385–92. doi: 10.1007/s10549-022-06616-1.
15. Conroy SM, Pagano I, Kolonel LN, Maskarinec G. Mammographic density and hormone receptor expression in breast cancer: the Multiethnic Cohort Study. *Cancer Epidemiol*. 2011;35(5):448–52. doi: 10.1016/j.canep.2010.11.011.
16. Shaikh AJ, Mullooly M, Sayed S, Ndumia R, Abayo I, Orwa J, et al. Mammographic breast density and breast cancer molecular subtypes: the Kenyan-African aspect. *Biomed Res Int*. 2018;2018. doi: 10.1155/2018/6026315.
17. Sajjad B, Farooqi N, Rehman B, Khalid IB, Urooj N, Sajjad S, et al. Correlation of Breast Density Grade on Mammogram With Diagnosed Breast Cancer: A Retrospective Cross-Sectional Study. *Cureus*. 2022;14(7). doi: 10.7759/cureus.27028.
18. Arora N, King TA, Jacks LM, Stempel MM, Patil S, Morris E, et al. Impact of breast density on the presenting features of malignancy. *Ann Surg Oncol*. 2010;17:211–8. doi: 10.1245/s10434-010-1237-3.
19. Phipps AI, Buist DSM, Malone KE, Barlow WE, Porter PL, Kerlikowske K, et al. Breast density, body mass index, and risk of tumor marker-defined subtypes of breast cancer. *Ann Epidemiol*. 2012;22(5):340–8. doi: 10.1016/j.annepidem.2012.02.002.
20. Fasching PA, Heusinger K, Loehberg CR, Wenkel E, Lux MP, Schrauder M, et al. Influence of mammographic density on the diagnostic accuracy of tumor size assessment and association with breast cancer tumor characteristics. *European journal of radiology*. 2006 Dec 1;60(3):398-404. doi: 10.1016/j.ejrad.2006.08.002.
21. Ma H, Luo J, Press MF, Wang Y, Bernstein L, Ursin G. Is there a difference in the association between percent mammographic density and subtypes of breast cancer? Luminal A and triple-negative breast cancer. *Cancer Epidemiol biomarkers Prev*. 2009;18(2):479–85. doi: 10.1158/1055-9965.epi-08-0805.
22. McCarthy AM, Friebel-Klingner T, Ehsan S, He W, Welch M, Chen J, et al. Relationship of established risk factors with breast cancer subtypes. *Cancer Med*. 2021;10(18):6456–67. doi: 10.1002/cam4.4158.
23. Balema WA, Moseley TW, Weaver O, Hess KR, Brewster AM. The association between volumetric breast density and breast cancer subtypes among women newly diagnosed with breast cancer. *American Society of Clinical Oncology*; 2019: e13115-e13115. doi: 10.1200/jco.2019.37.15_suppl.e13115.
24. Antoni S, Sasco AJ, dos Santos Silva I, McCormack V. Is mammographic density differentially associated with breast cancer according to receptor status? A meta-analysis. *Breast Cancer Res Treat*. 2013;137:337–47.
25. Tan V, Payne J, Paquet N, Iles S, Rayson D, Barnes P, et al. The association between breast density and HER2-positive breast cancer: A population-based case-control study. *American Society of Clinical Oncology*; 2020: e12556-e12556. doi: 10.1200/jco.2020.38.15_suppl.e12556.
26. Li E, Guida JL, Tian Y, Sung H, Koka H, Li M, et al. Associations between mammographic density and tumor characteristics in Chinese women with breast cancer. *Breast Cancer Res Treat*. 2019;177:527–36. doi: 10.1007/s10549-019-05325-6.
27. Bai S, Song D, Chen M, Lai X, Xu J, Dong F. The association between mammographic density and breast cancer molecular subtypes: A systematic review and meta-analysis. *Clin Radiol*. 2023;78(8):622-32. doi: doi.org/10.1016/j.crad.2023.04.008.
28. Ma JH, Qin L, Li X. Role of STAT3 signaling pathway in breast cancer. Cell *Communication and Signaling*. 2020 Dec;18:1-3. doi: 10.1186/s12964-020-0527-z.
29. Radenkovic S, Konjevic G, Gavrilovic D, Stojanovic-Rundic S, Plesinac-Karapandzic V, Stevanovic P, et al. pSTAT3 expression associated with survival and mammographic density of breast cancer patients. *Pathol Pract*. 2019;215(2):366–72. doi: 10.1016/j.prp.2018.12.023.
30. Marchiò C, Annaratone L, Marques A, Casorzo L, Berrino E, Sapino A. Evolving concepts in HER2 evaluation in breast cancer: Heterogeneity, HER2-low carcinomas and beyond. InSeminars in cancer biology 2021 Jul 1 (Vol. 72, pp. 123-135). *Academic Press*. doi: 10.1016/j.semcancer.2020.02.016.
31. Sartor H, Borgquist S, Hartman L, Zackrisson S. Do pathological parameters differ with regard to breast density and mode of detection in breast cancer? *The Malmö Diet and Cancer Study. The Breast.* 2015;24(1):12–7. doi: 10.1016/j.breast.2014.10.006.
32. Pollán M, Ascunce N, Ederra M, Murillo A, Erdozáin N, Alés-Martínez JE, et al. Mammographic density and risk of breast cancer according to tumor characteristics and mode of detection: a Spanish population-based case-control study. *Breast Cancer Res*. 2013;15(1):1–11. doi: 10.1186/bcr3380.

How to Cite This Article

Roayaei M, Bahrami F, Karami F, Mahdavi H. Association Between Radio-pathological Breast Tumor Characteristics and Mammographic Breast Density. Arch Breast Cancer. 2024; 11(3):269-75.
Available from: https://www.archbreastcancer.com/index.php/abc/article/view/947