

# **RESEARCH ARTICLE**

### CORRELATION OF MAMMOGRAPHIC AND HISTOPATHOLOGICAL CHARACTERISTICS OF BREAST LESIONS

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Abstract

..... **Introduction:** Breast Imaging Reporting and Data System (BI-RADS) is the universal standard developed bythe American College of Radiology characterize breast lesions on to mammography.Histopathological assessment is usually doneaftersurgery, helpstocorrelate the BI-

RADSscoringsystem.).Molecular markers including estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2(Her2) have prognostic and predictive values and hence can be used to recommend treatmentguidelines.

Methodology: A 2-year prospective cross-sectional observational study was conductedin the Departments of Pathology and Radiodiagnosis, Christian Medical College, Ludhiana. Atotalof62caseswhichhadundergonemammographyfollowedbyabreastb iopsywereincludedinthe study. Mammograms and Histopathology slides of all cases were reviewed independently by tworadiologists and pathologists respectively.

**Results:** Lesions with smaller diameters on mammography and biopsy showed a stroke positive correlation (r =0.5461,p=0.0007). Significant associations of biomarkers with mammography characteristics were observed(ER with architectural distortion, p=0.005; ER with margins, p=0.005; PR with architecturaldistortion,p=0.009;PRwithmargins,p=0.005;Her2witharchi tectural distortion, p=0.007; Her2with margins, p=0.006).

Conclusion: Significant associations between histopathological biomarkers and mammography characteristics could provide additional information at the first contact of a patient with a breast lesion.

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### Introduction:-

One in eight cancers diagnosed in the world today are breast cancers, having a high globaldisease burden. Breast cancers had for 2.3 million newly diagnosed cases in 2020, with 6,85,000 deaths from this disease(Arnold et al., 2022). It is the most common cancer in the Indian female population,

Havingsurpassedcervicalcancersincetheyear2003(Malvia et al., 2017), (Gupta et al., 2016).In addition to the lack of anationwide screening program, the increasing incidence in our country can attributed to the conservative Indian society, reluctance among women to seek medical help, age oldcustoms, illiteracy, and unawareness (Satishkumar et al., 2021).

It is imperative to diagnose breast cancer in its preliminary stages in view of its high mortality. Variousscreeningtoolsincludeself-

breastexamination, clinical examination, mammography, ultrasonography, and fine needle aspiration biopsies of suspiciousl esions. Out of these, mammography is a highly sensitive and effective tool for early detection of non-palpable breast cancer in asymptomatic women (Kumar et al., 2017). Even though the cost benefit ratio for the wide application of mammography as ascreening tool in the Indian population does not seem financially feasible, studies still show that mammography in conjunction with breast examination has a role in reducing mortality, instead of breast examination as an independent modality (Ngan et al., 2020).

Breast Imaging Reporting and Data System (BI-RADS) is the universal standard developed bythe American College of Radiology to characterize breast lesions on mammography. BI-RADSclassification includes seven categories, from 0 to 6, reflecting the radiologist's level of suspicionof malignancy (Breast imaging reporting & data system, n.d.). Although studies have shown that this system proves good correlationwith likelihood of malignancy, there can be significant interobserver variation in interpretation ofmammograms, thus mandating a tissue biopsy. Histopathological assessment is usually doneaftersurgery,helpstocorrelatetheBI-RADSscoringsystembesidesprovidinga confirmatorydiagnosis,guidingtreatmentandassessingprognosis (Hu et al., 2018).Molecular markers includingestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2(Her2) have prognostic and predictive values and hence can be used to recommend treatmentguidelines(Tamaki et al., 2011).

Interdisciplinary studies comparing mammographic findings with histopathology are few in theIndian population, especially concerning biomarkers. Hence, it was considered pertinent toconduct this study to enhance our understanding of mammography and bring forth its diagnosticaccuracyandlimitationsinoursetupwhilstalsoplanningfuturestrategiesandrecommendationspostmammographicevaluationofapatient.

### Materialsandmethods:-

### Patient Population:

A 2-year prospective cross-sectional observational study was conducted in the Departments of Pathology and Radiodiagnosis, Christian Medical College, Ludhiana, Punjab from October 2017 till April 2020. Atotalo f62 cases which had undergone mammography followed by a breas stbiopsy were included in the study while cases with unsatisfactory mammogram or inadequate biopsy material were excluded. Clinical data of all enrolled cases were obtained from the medical records and archived biopsy requisition forms.

### Mammographic Evaluation:

Mammograms of all cases were reviewed independently by tworadiologists who were blinded to the final histopathological diagnosis and clinical outcome of thepatients. Characteristic features like lesion location, margin, breast composition, architecturaldistortion, dilated ducts, skin thickening, and nipple retraction were recorded for each patient. Marginswere classified intotwobroadcategories of ill-defined and well-defined but alsoincludedothergroupslikelobulated, indistinct, spiculatedetc. Calcificationshapewastentatively classified into punctate, amorphous, pleomorphic, and linear. Final BIRAD score wasnoted in accordance with the grading system by American College of Radiology. Figure 1A and 1B show representative mammographic findings.



Figure 1 A and 1B: - Mammographic images of Left breast (1A) and Right breast (1B) showing lesion with ill-defined margins.

### Histopathological Evaluation:

Histopathology slides of all the cases were reviewed independently by two pathologists based on the World Health Organization (WHO) histological classification of tumors of breast and Rosen's Breast Pathology. Characteristics of the lesionrecordedincludedmassmargins, largest diameter of lesion, presence of necrosisal on gwith its grade, nodal presence involvement, and final diagnosis. The of ER was determined by  $nuclear staining and was graded from 0 to 8 using the All redscore, with positivity defined as a score of \geq 3.$ For the HER2 evaluation, membranous staining was graded as 0-1+, 2+, and 3+. The Ki-67 immunoreactivity was evaluated by examining high-power fields and counting 1000tumor cells in the hot spots. The pathologists were blinded to the mammographic BIRAD score.

In those cases where discrepancies arose between the two observers, consensus was reached by mutual discussion.

### Statistical analysis:

To compare mammographic findings with histopathological findings, multivariate analysis was used. All analyses we reperformed using SPSS version 21.0 (SPSSInc., Chicago, IL, USA), with P<0.05 taken to indicate significant differences.

## **Results:-**

The mean age of the populationwas  $54.9 \pm 12.9$  years, with an almost equal distribution into three age groups. (See Table 1) Core biopsy wasthemostcommontypeofbiopsyperformed on histopathological specimens, with more than 70% of lesions being malignant (41.4% being grade 3). The majority (40.3%) of lesions were categorized as BIRADs 4 on mammography with 56.5% of the lesions being the most commonly detected at the upper-outer quadrant of breast.

DESCRIPTIVE CHARACTERISTICS	FREQUENCY	PERCENTAGE		
Age(54±12.97years)				
<45	20	32.3%		
45-60	22	35.5%		

	10	20 (0)						
>60	19	30.6%						
Typeofbiopsy								
Core	23	37.1%						
Excision	18	29.0%						
Incision	4	6.5%						
Mastectomy	12	19.4%						
Lumpectomy	5	8.1%						
BIRADs								
1.0	1	1.6%						
2.0	7	11.3%						
3.0	17	27.4%						
4.0	25	40.3%						
5.0	12	19.4%						
LocationonMammogram								
RA	5	8.1%						
UO	35	56.5%						
UI	7	11.3%						
LO	3	4.8%						
LI	11	17.7%						
TypeofLesiononPathology								
Non-neoplastic	4	6.5%						
Inflammatory	3	4.8%						
Benign	11	17.7%						
Malignant	44	71.0%						
Gradeofmalignancy								
1	8	19.5%						
2	16	39%						
3	17	41.4%						

**Table 1:-** Descriptive Characteristics of Lesions on Mammogram and Histopathology.

On identifying the lesion based on the diameter by mammography and histopathology, lesions with smaller diameters showed a stroke positive correlation (r = 0.5461, p=0.0007) on mammography and histopathology (See Figure 2)

## Largest Diameter of Lesion



Figure 2:- Correlationbetweenlargestdiameteroflesion(inmm)onMammographyandHistopathology.

The presence of biomarkerslikeER,PR,Her2andKi67andtheirpositivityratesamongdifferentbreastcarcinomas were identified (See Table 2).InvasiveductalcarcinomahadthehighestpositivityforER(n=28,80%),PR (n=28, 80%), Her2 (n=26, 78.8%), Ki67 (n=27, 79.4%). Invasive lobular carcinoma and Ductalcarcinoma in situ have the second highest ER and PR positivity (n=2, 5.7%) for both. InvasivelobularcarcinomahasthehighestpositivityrateforHer2receptor(n=2,6.1%)outofallbreastcarcinomasincludedino urstudy.

Biomark	ers	DuctalC arcinom ainSitu	Invasive DuctalC arcinom a	Invasive Lobular Carcino ma	MixedIn vasiveDu ctalandL obularC arcinom a	Invasive Cribrifo mCarcin oma	EccrineAd enocarcino ma	Total
	Present	2(7.4%)	21 (77.7%)	2(7.4%)	1(3.7%)	1(3.7%)	0(0.0%)	27
ER	Absent	0(0.0%)	7(87.5%)	0(0.0%)	0(0.0%)	0(0.0%)	1(12.5%)	8
	Total	2(5.7%)	28(80%)	2(5.7%)	1(2.8%)	1(2.8%)	1(2.8%)	35
	Present	2(7.7%)	21 (80.8%)	1(3.8%)	1(3.8%)	1(3.8%)	0(0.0%)	26
PR	Absent	0(0.0%)	7(77.8%)	1(11.1%)	0(0.0%)	0(0.0%)	1(11.1%)	9
	Total	2(5.7%)	28(80%)	2(5.7%)	1(2.8%)	1(2.8%)	1(2.8%)	35
	Absent	0(0.0%)	15 (78.9%)	1(5.3%)	1(5.3%)	1(5.3%)	1(5.3%)	19
	1+	0(0.0%)	7(87.5%)	1(12.5%)	0(0.0%)	0(0.0%)	0(0.0%)	8
	2+	0(0.0%)	4(100%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	4
Her2	3+	0(0.0%)	2(100%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	2
	Total	0(0.0%)	26 (78.8%)	2(6.1%)	1(3%)	1(3%)	1(3%)	33
	<2%	0(0.0%)	2(100%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	2
	2-20%	2(15.4%)	7(53.8%)	2(15.4%)	1(7.7%)	1(7.7%)	0(0.0%)	13
Ki67	>20%	0(0.0%)	18 (94.7%)	0(0.0%)	0(0.0%)	0(0.0%)	1(5.3%)	19
	Total	2(5.9%)	27 (79.4%)	2(5.9%)	1(2.9%)	1(2.9%)	1(2.9%)	34

 Table2: Frequencyofpositivebiomarkersindifferenttypesofbreastcarcinoma.

The characteristics of breast lesions observed on mammography and their association with biomarkers. (See Table 3) Out of multiple mammography characteristics observed, we found significant associations of biomarkers with architectural distortion and margin of breast lesions(ER with architectural distortion, p=0.005; ER with margins, p=0.005; PR with architecturaldistortion,p=0.009;PRwithmargins,p=0.005;Her2witharchitecturaldistortion,p=0.007;Her2with margins, Non-significant with p=0.006). association was seen for Ki67 breast

composition(p=0.051)andwithbreastlesionmargins(p=0.058)

MammographicCharacteristic	ER	PR	Her2			Ki67		
s			1+	2+	3+	<2%	2-	>20%
							20%	
BreastComposition								
Fibro-fatty	17	17	3	3	1	2	12	7
Fibro-glandular	6	5	1	1	0	0	1	6
Mixed	5	5	4	0	1	0	1	6
ArchitecturalDistortion	20	19	7	3	0	1	7	14
DilatedDucts	1	1	0	1	0	0	0	1

Table3:- AssociationofBiomarkerswithMammographyCharacteristics.

Calcification	5	4	2	1	0	0	2	4
NodalInvolvement	2	2	0	1	0	0	1	1
SkinThickening	6	5	3	1	1	0	2	7
NippleRetraction	7	6	2	1	1	0	2	5
Margins								
Ill-Defined	4	4	7	3	2	2	9	18
Well-Defined	2	2	1	1	1	0	5	1

TherelationshipbetweenmarginsofbreastlesionsasseenonmammographyandhistopathologywiththefinalBIRADsscorea ndhistopathologicaldiagnosticcategory were compared. (See Table 4) A majority (87%)ofbreastlesionshavingill-defined marginsonmammographyandhistopathology had BIRADs score of  $\geq$ 4. All breast lesions with well-defined margins onmammography and histopathology had BIRADs score of  $\leq$ 3 but 16.7% of them were diagnosed to be malignant on biopsy.

Margins	<b>BIRADs</b>	Score	HistopathologicalDiagnosticCategories				
	≤3	≥4	Non- neoplastic	Inflammatory	Benign	Malignant	
Ill-defined onBiopsy&							
Ill-defined	2(13%)	13	1(6.7%)	0(0.0%)	3(20%)	11	
onMammography		(87%)				(73.3%)	
Well-definedon							
Biopsy&	2(29%)	5(71%)	0(0.0%)	0(0.0%)	0	7(100%)	
Ill-defined					(0.0%)		
onMammography							
Well-definedon							
Biopsy&	6	0(0.0%)	1(16.7%)	0(0.0%)	4	1(16.7%)	
Well-	(100%)				(66.7%)		
definedonMammography							
Ill-definedon							
Biopsy&	7	0(0.0%)	1(14.3%)	0(0.0%)	2	4(57.1%)	
Well-	(100%)				(28.6%)		
definedonMammography							

 Table4: Ill- and Well-defined

margins of breastlesions seen on Biopsy and Mammography correlation with benign and malign ant categories of BIRAD sscore and Histopathology.

## **Discussion:-**

Increasing amounts of clinical data imply that prognostic variables affecting breast cancer gobeyond the conventional tumor histological grade. This requires clinicians to expand prognosticefforts beyond consideration of histological grade, which is well known to have a strongcorrelation with clinical outcome in patients with breast cancer. The same has been linked to a number of variables, including ER positivity, HER2 status, and lymph node invasion. However, these are accounted for viain vasive methods. Therefore, an accurate correlation between non-invasive findings and their corresponding histopathological features may be considered of great value incancer evaluation.

Shape and biomarkers play an essential role in the management of patients with invasive breastcancer. Estrogen receptors (ERs) and progesterone receptors (PRs) should both be assessed all newly diagnosed invasive breast cancers in order to select individuals likelv respond toendocrinetreatment.Specifically,spiculatedmasseswerestronglyassociated(p=0.005)withPRexpression and spiculated tumors were more likely to be PR+ than PR- compared toa distinct mass. This is in congruence with other studies that have looked at mammographic features inrelation to the traditional factors used to subgroup breast cancer and found evidence to relatespiculated masses with good outcome; and excellent prognosis if the masses are smaller than15mm.PRpositivityisalsosignificantlycorrelatedtoarchitecturaldistortion(p=0.009).

It is important to note that this study shows a greater correlation between mammographic andhistopathological lesion sizes at smaller diameters. Prior research has shown that tumors that appear on mammography as poorly defined masses and asymmetric densities had biggerdimensions than those that appear as architectural distortions and

#### spiculated

masses.

We

findsignificantassociations of ER positivity with architectural distortion (p=0.005) and mammography margins (p=0.005). Over the years, multiple studies have successfully correlated HER2 expression particularly with specifications like oval shape. This not only a distinct curate prognostication of the transmission of tr

The immunohistochemical identification of the surrogate genotype has been reported to require the use of Ki-67 antisera to establish the proliferation rate in the largest immunophenotype, those carcinomas which are estrogen receptor positive, HER-2/neu negative. Recognition of the utility of Ki-67 in characterizing molecular phenotypes of breast carcinoma is recent and hence worth studying. This study finds significant associations between Ki67 and breast composition (p=0.051) and Ki67 with mammographic margins (p=0.058).

To our knowledge, this is the first study that attempts to correlate these biomarkers with mammography features from the Indian subcontinent. While considerable research has been performed to assess the accuracy of detection of breast cancers by mammography, usage of biomarkers in the same is understudied. The results found in this study may provide huge potential for further studies researching breast cancer subtypes in specific demographics or ethnicities which can be further translated into effective screening guidelines.

The study has some limitations. Our study included a small sample size. Breast density is also known to affect mammographic appearance, this has not been adjusted for. Further studies are recommended on the topic with bigger sample sizes and focus on demographic information to uncover any occult diversity in biomarker subtypes.

### Conclusion:-

Histopathological biomarkers can provide imperative information regarding patient prognosis and clinical outcome. Despite it being an invasive procedure, it continues to be the gold standard investigation for breast carcinoma patients. Mammography is universally used primary investigation done in patients with breast lesions before biopsy. Significant associations between histopathological biomarkers and mammography characteristics could provide additional information at the first contact of a patient with a breast lesion.

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