

RESEARCH ARTICLE

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Mammographic Microcalcifications and Breast Cancer: A Case - Control Study

Muhammad Usman Sami^{1*}, Maira Saeed², Sadia Nazeem³, Mehreen Afridi⁴

Abstract

Background: Microcalcifications are among the earliest radiographic findings suggestive of breast malignancy and are often detected in women undergoing diagnostic mammography. Their association with breast cancer, independent of other risk factors, is clinically important but not fully understood. **Objective:** To investigate the associations between mammographic microcalcifications and breast cancer risk in women undergoing diagnostic mammography. **Design:** Case–control study. **Setting:** Breast Care Unit (BCU), Rehman Medical Institute (RMI), Peshawar, Pakistan. **Participants:** Three hundred women aged 30 years and above who underwent diagnostic mammography; 150 patients with histologically confirmed breast cancer and 150 (age, menopausal status and ACR density) matched controls with normal breasts. **Main outcome measures:** The presence of microcalcifications on mammography. **Covariates:** ACR breast density, menopausal status, and age group. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated via multivariable logistic regression. **Results:** Microcalcifications were significantly more common in patients (50.7%) than in controls (20.7%) and were independently associated with breast cancer (adjusted OR 5.51, 95% CI: 3.02–10.05; $p < 0.001$). Compared with premenopausal women, perimenopausal women had the highest odds of having breast cancer (adjusted OR 14.30, 95% CI: 3.80–53.78, $p < 0.001$), followed by postmenopausal women (adjusted OR 4.50, 95% CI: 1.74–11.63, $p = 0.002$). The ACR breast density categories B and C were significantly associated with microcalcifications but not independently with breast cancer. **Conclusion:** Mammographic microcalcifications are strong independent predictors of breast cancer, particularly among peri- and postmenopausal women, highlighting their clinical value in risk stratification and diagnostic evaluation.

Keywords: Mammography- microcalcifications- breast cancer- ACR density- menopausal status

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Introduction

Breast cancer remains a leading cause of morbidity and mortality worldwide, and early detection is pivotal to improving patient outcomes and survival [1]. According to the national cancer registry of Pakistan, the incidence of breast cancer is 21.4% (most common) in both sexes, 38.8% in women, and the incidence of the top 5 cancers is the highest [2]. The key screening tool in the detection of breast cancer is mammography, which is a low-energy X-ray used for the detection of abnormalities in the breast. Two types of views are taken: cranio-caudal (CC) and mediolateral oblique (MLO). In CC view, the image is taken from above, whereas in MLO, it is taken from the sides so that the pectoralis muscle is visible [3]. The mammograms are reviewed by radiologists for any signs of malignancy, including microcalcifications. Microcalcifications appear as bright white spots on the X-ray film. Benign lesions are larger in size and fewer in number and have the same size and shape,

whereas malignant lesions are clustered and small and irregular in size, shape and branching orientation [4]. Microcalcifications are small bright dots < 1 mm in size on mammography [5]. A study performed in Sweden revealed that microcalcification clusters were significantly related to in situ breast cancers and that microcalcification clusters increased with age, although the increase was slow in premenopausal patients but sharper after menopause [6]. Breast microcalcifications by themselves are not only breast cancer but also prominent risk factors for breast cancer [6, 7]. Additionally, sometimes a tumor is concealed (i.e., dense tissue) and not detected via mammography, as shown by a study performed in Japan; three patients who had breast cancer with microcalcifications and no tumor detected via mammography and microcalcifications were the only findings detected via mammography [8]. Microcalcifications associated with mass lesions warrant careful assessment, as malignant processes such as ductal carcinoma in situ colonizing benign tumors, including fibroadenomas, may occur [9]. Although the presence of

¹Department of Ophthalmology, Rehman Medical Institute, Peshawar, Pakistan. ²Department of Breast and General Surgery, Rehman Medical Institute, Peshawar, Pakistan. ³Bachelor of Medicine and Bachelor of Surgery, Rehman Medical College, Peshawar, Pakistan. *For Correspondence: muhammad.usman-19@rmi.edu.pk

mammographic microcalcifications is associated with an increased risk of breast cancer, existing evidence remains inconsistent regarding their independent predictive value, particularly in relation to breast density and menopausal status [10]. Furthermore, data from low- and middle-income settings are limited, where patterns of presentation and screening practices may differ. Given that mammographic calcifications often represent the earliest radiographic manifestation of malignancy, a clearer understanding of their clinical significance is essential to optimize risk stratification and diagnostic decision-making. This highlights the need for studies evaluating the association between mammographic microcalcifications and breast cancer while accounting for key demographic and imaging-related factors. The objectives of this study were (1) to compare the prevalence and characteristics of mammographic microcalcifications in cases and controls to assess their diagnostic significance and (2) to determine the association of mammographic microcalcifications with an increased risk of breast cancer.

Materials and Methods

Study population

Ethical approval for this case-control study was obtained from the Department of Medical Research, Rehman Medical Institute. Informed consent was obtained from all participants prior to data collection. The confidentiality of participant information was strictly maintained. The study was conducted at the Breast Care Unit (BCU) of the Rehman Medical Institute (RMI), Peshawar, from April 1 to May 31, 2025. On the basis of the OpenEpi sample size calculation, with a 95% confidence interval, 5% margin of error, a prevalence of 20.7% (controls), and an odds ratio of 3.07, a total sample size of 136 participants was calculated, with a 1:1 case-to-control ratio. A convenience sampling technique was employed to recruit biopsy-proven breast cancer patients (cases) and women without breast cancer (controls) from the same tertiary care center, reflecting the retrospective nature of the study and the availability of complete mammographic and clinical data. Controls were selected to be comparable to cases with respect to age, menopausal status, and American College of Radiology (ACR) breast density. The inclusion criteria included all women with confirmed breast cancer diagnoses and those without breast cancer whose digital mammograms were available. Patients with incomplete records, missing mammograms, or inadequate histopathology reports were excluded. Data were collected retrospectively from the BCU database at RMI via histopathology and mammography reports. Cases were identified on the basis of biopsy-confirmed malignancy, whereas controls included women with normal mammograms. Mammograms were retrospectively reviewed on the Synapse PACS (Fujifilm Medical Systems) by radiologists blinded to case or control status and subsequently correlated with archived radiology reports available in the institutional health cloud. Mammographic microcalcifications were classified according to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) lexicon

based on their morphology (e.g., amorphous, coarse heterogeneous, fine pleomorphic, or fine linear/branching) and distribution (diffuse, regional, grouped, linear, or segmental). For analysis, microcalcifications were dichotomized as present or absent. Controls were selected using frequency matching to achieve comparability with cases across age groups, menopausal status, and ACR breast density; however, exact individual matching was not performed, and these variables were further adjusted for in multivariable analysis. Patient record number (PR number), age, menopausal status, microcalcification presence, and ACR breast density were recorded in a Microsoft Excel spreadsheet. Data analysis was performed via SPSS version 27. Descriptive statistics were computed for categorical variables, including the presence of mammographic microcalcifications, menopausal status, ACR breast density categories, and age groups, as well as for the continuous variable age. Inferential analyses were performed using chi-square tests for categorical variables and independent-sample t tests for continuous variables. Binary logistic regression analysis was conducted to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer in relation to microcalcifications, ACR breast density, and menopausal status, with adjustment for potential confounders.

Covariates

In this study, several covariates were considered to assess their potential influence on the association between microcalcifications and breast cancer. Age was categorized into decade-based groups (30–39, 40–49, 50–59, 60–69, 70–79, and 80+ years). Menopausal status was defined as premenopausal (<45 years), perimenopausal (45–55 years), or postmenopausal (>55 years) on the basis of age [11]. Breast density was recorded using ACR categories: A (almost entirely fatty), B (scattered fibroglandular densities), C (heterogeneously dense), and D (extremely dense) [12]. These covariates were included in the analysis to adjust for their potential confounding effects on the relationship between microcalcifications and breast cancer.

Results

Baseline characteristics

Our case-control study of 300 participants revealed significant differences in baseline characteristics between groups (Table 1). The cases were markedly older than the controls were (mean age 54.99 vs. 46.97 years, $p < 0.001$), with more than twice as many cases (40.0% vs. 14.0%) aged ≥ 60 years. Microcalcifications were 2.5 times more prevalent in patients (50.7% vs. 20.7%, $p < 0.001$). Striking menopausal status disparities were observed, with half of the cases being postmenopausal, whereas only 16.7% of the controls were postmenopausal ($p < 0.001$). While the ACR density distributions were clinically similar ($p = 0.15$), the cases presented a nonsignificant trend toward a lower prevalence of extremely dense breasts (ACR-D: 6.0% vs. 8.7%) Table 1.

The association between microcalcifications and ACR density was significant ($p = 0.028$), with the highest prevalence in the ACR-B subgroup (38.3%) and the

Table 1. Demographic and Clinical Characteristics by Patient Status

Characteristic	Cases (n=150)	Controls (n=150)	p value
Age (years), mean \pm SD	54.99 \pm 12.36	46.97 \pm 8.93	<0.001
Age Group, n (%)			<0.001
30-39	19 (12.7%)	26 (17.3%)	
40-49	37 (24.7%)	72 (48.0%)	
50-59	34 (22.7%)	34 (22.7%)	
60-69	41 (27.3%)	15 (10.0%)	
70+	19 (12.7%)	6 (4.0%)	
Microcalcifications, n (%)	76 (50.7%)	31 (20.7%)	<0.001
ACR, n (%)			<0.491
A	45 (30.0%)	36 (24.0%)	
B	62 (41.3%)	60 (40.0%)	
C	34 (22.7%)	41 (27.3%)	
D	9 (6.0%)	13 (8.7%)	
Menopausal Status, n (%)			<0.001
Premenopausal	33 (22.0%)	75 (50.0%)	
Perimenopausal	42 (28.0%)	50 (33.3%)	
Postmenopausal	75 (50.0%)	25 (16.7%)	

SD, standard deviation; ACR, Breast Imaging Reporting and Data System density categories. P values were obtained from independent t tests (age) and chi-square tests (microcalcification, ACR, menopausal status). Post hoc test for microcalcification, menopausal status, age group and ACR ($p = 0.05$).

ACR-C subgroup (29%). While menopausal status showed a nonsignificant trend ($p = .070$), premenopausal women had the highest microcalcification incidence (39.8%). Age group differences were nonsignificant ($p = 0.115$), peaking in the 40 s (37.4%) and 60 s (18.7%) participants Table 2.

Regression Analysis

Logistic regression analysis indicated that microcalcifications significantly increased the risk of breast cancer. Women with microcalcifications were nearly 4 times more likely to have breast cancer than those without (OR = 3.84, 95% CI: 2.31 - 6.39, $p < 0.001$), and this association remained strong after adjusting for age, breast density, and menopausal status (adjusted OR [aOR] = 5.51, 95% CI: 3.02 - 10.05, $p < 0.001$). Multicollinearity

was not observed (variance inflation factors < 2), and the Hosmer - Lemeshow test indicated good model fit ($p = 0.72$). Table 3. Menopausal status was a strong independent predictor. Compared with premenopausal women, perimenopausal women had the highest risk about 14 times greater (aOR = 14.30, 95% CI: 3.80 - 53.78, $p < 0.001$), while postmenopausal women had a 4.5 - fold higher risk (aOR = 4.50, 95% CI: 1.74 - 11.63, $p = 0.002$). Age and breast density alone were not significant predictors (age per decade: aOR = 1.25, $p = 0.349$; ACR density: aOR = 1.14, $p = 0.408$), highlighting that menopausal transition is a key risk factor requiring closer surveillance. Table 4. Breast density was strongly associated with the presence of microcalcifications. Compared with women with ACR A density, those with

Table 2. Distribution of Microcalcifications by ACR, Menopause, and Age Group

Microcalcifications	ACR	Menopausal Status	Age Group
Yes (n=107)	A: 22 (20.6%)	Pre: 43 (40.2%)	30-39: 17 (15.9%)
	B: 41 (38.3%)	Peri: 24 (22.4%)	40-49: 40 (37.4%)
	C: 31 (29.0%)	Post: 40 (37.4%)	50-59: 17 (15.9%)
	D: 13 (12.1%)		60-69: 20 (18.7%)
			70-79: 11 (10.3%)
No (n=193)	A: 59 (30.6%)	Pre: 65 (33.7%)	80+: 2 (1.9%)
	B: 81 (42.0%)	Peri: 68 (35.2%)	30-39: 28 (14.5%)
	C: 44 (22.8%)	Post: 60 (31.1%)	40-49: 69 (35.8%)
	D: 9 (4.7%)		50-59: 51 (26.4%)
			60-69: 36 (18.7%)
		70-79: 8 (4.1%)	
		80+: 1 (0.5%)	
Chi-Square (p value)	$p = 0.028$	$p = 0.070$	$p = 0.115$

ACR (Breast Imaging Reporting and Data System), menopausal status; pre = < 45 years, peri 45-55 years, post > 55 years

Table 3. Microcalcifications and Breast Cancer Risk.

Predictor	Unadjusted OR (95% CI)	P - value	Adjusted OR (95% CI)	P - value
Microcalcifications (Present)	3.84 (2.31–6.39)	<0.001	5.51 (3.02–10.05)	<0.001
Menopausal Status (Ref: Pre)	—	—	—	—
Perimenopausal	—	—	14.30 (3.80–53.78)	<0.001
Postmenopausal	—	—	4.50 (1.74–11.63)	0.002
ACR Density (A→D)	—	—	1.14 (0.84–1.55)	0.408
Age Group (per decade)	—	—	1.25 (0.79–1.97)	0.349

OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; Ref, reference group. Note: Unadjusted ORs taken from the model without confounders; adjusted ORs from the model including menopausal status, ACR and age group.

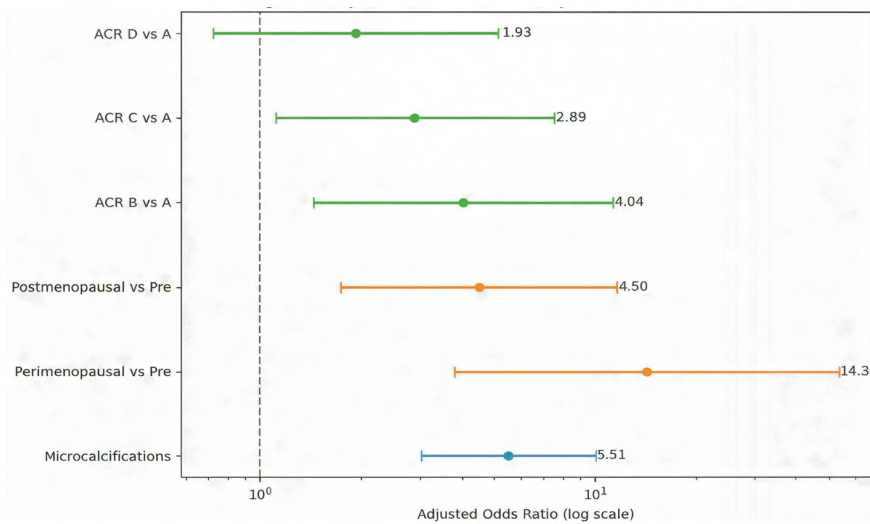


Figure 1. Adjusted Odds Ratios for Key Predictors of Breast Cancer among Women Undergoing Diagnostic Mammography. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) are shown on a logarithmic scale. The vertical dashed line at OR = 1 represents no effect. Color coding: Blue = microcalcifications; Orange = menopausal status; Green = ACR density. Values at the end of the error bars indicate exact aORs. Microcalcifications and menopausal status are independent predictors of breast cancer, while higher ACR density is associated with microcalcifications but not independently with breast cancer in this cohort.

ACR B and C density had a 3 - 4 times higher likelihood of having microcalcifications (aOR = 4.04 and 2.89, respectively), independent of age and menopausal status. Multiple comparisons were considered, and adjustment (e.g., Bonferroni) did not materially affect significance. Age and menopausal status did not independently predict microcalcifications. Clinically, this suggests that women with higher breast density may benefit from more careful mammographic evaluation for microcalcifications, which are important markers of breast cancer risk Table 5. The adjusted odds ratios for key predictors of breast cancer are summarized in Figure 1, highlighting the strong association of microcalcifications and menopausal status with disease risk.

Discussion

This case-control study involving 300 participants revealed a significant association between microcalcifications, menopausal status, and breast cancer risk [6, 13-15]. Notably, microcalcifications were present in 50.7% of the cases compared with 20.7% of the controls, indicating a strong association with breast cancer after adjusting for breast density, menopausal status and age. The odds were high, showing an independent association not confounded by other variables (aOR = 5.51), which is greater than that reported in a study conducted in Seoul (aOR = 3.07) [16]. A key novel finding of our study is that perimenopausal women exhibited the highest

Table 4. Menopausal Status and Breast Cancer Risk

Predictor	Unadjusted OR (95% CI)	P - value	Adjusted OR (95% CI)	P - value
Premenopausal (Ref)	1.00 (Reference)	—	1.00 (Reference)	—
Perimenopausal	6.82 (3.70–12.57)	<0.001	14.30 (3.80–53.78)	<0.001
Postmenopausal	3.57 (1.94–6.58)	<0.001	4.50 (1.74–11.63)	0.002
Adjustment Variables	None		Microcalcifications, ACR density, age	

OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; Ref, reference group. Note: Unadjusted ORs taken from the model without confounders; adjusted ORs from the model including microcalcifications, ACR breast density, and age group.

Table 5. Microcalcifications and ACR (Breast Density)

ACR Category	Unadjusted OR (95% CI)	P - value	Adjusted OR (95% CI)	P - value
ACR A (Ref)	1	–	1	–
ACR B	3.874 (1.45–10.37)	0.007	4.044 (1.44–11.32)	0.008
ACR C	2.854 (1.12–7.24)	0.027	2.893 (1.11–7.56)	0.029
ACR D	2.050 (0.78–5.39)	0.145	1.931 (0.72–5.15)	0.189

OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; Ref, reference group. Note: Unadjusted ORs taken from the model without confounders; adjusted ORs from the model including age group and menopausal status.

odds of breast cancer (aOR = 14.30), exceeding the risk in postmenopausal women (aOR = 4.50) relative to premenopausal women [6, 17]. Age and menopausal status were significantly different between the cases and controls in our study. A greater proportion of breast cancer patients are postmenopausal and aged >60 years, echoing the global trend where advanced age and hormonal transitions significantly influence breast cancer risk [16, 18]. However, in our adjusted model, age was not an independent predictor, suggesting that microcalcifications and menopausal status may serve as more robust risk indicators in this population. However, most studies have associated postmenopausal status with elevated breast cancer risk [19]. While most prior studies have primarily linked postmenopausal status with elevated breast cancer risk, our results suggest that the hormonal transition during the perimenopausal period may play a particularly critical role in tumorigenesis. This finding provides new insight into timing-specific risk stratification, which could inform targeted screening and closer surveillance in perimenopausal women [20–22]. Our analysis also demonstrates that although ACR breast density is associated with the presence of microcalcifications (aORs = 4.04 for ACR B and 2.89 for ACR C), it is not independently predictive of breast cancer after adjustment. This contrasts with studies that have suggested dense breast tissue alone is a risk factor and emphasizes that microcalcifications themselves, rather than density alone, are strong independent indicators of malignancy [23, 24]. This could be due to our sample size or confounding from microcalcifications. However, density was significantly associated with microcalcifications in our study [16, 25]. In our study, women with ACR B and C densities had significantly greater odds of having microcalcifications (aORs = 4.04 and 2.89, respectively). Age, in our multivariable model, was similarly not an independent predictor, suggesting that imaging features and menopausal status provide more discriminative information in this population. In sum, this study reinforces the diagnostic significance of microcalcifications and highlights perimenopausal status as a critical risk modifier, findings that warrant integration into clinical decision – making and guideline development.

Limitations

This study has several limitations, which were addressed where possible. First, although the single-center design may limit generalizability and introduce selection bias, it allows for standardized imaging protocols,

consistent diagnostic criteria, and uniform data collection methods, thereby enhancing internal validity. Second, while some clinical variables such as genetic predisposition and detailed hormonal history were not included because of the study's emphasis on imaging and demographic predictors, the study focused on well-established radiologic and demographic predictors of breast cancer, which are routinely documented and clinically relevant for risk stratification. Finally, menopausal status was determined on the basis of available medical records, which may pose a risk of misclassification; however, such documentation is routinely updated in institutional records and provides a practical, noninvasive means of categorization in retrospective studies.

In conclusion, our study highlights a positive association between mammographic microcalcifications and breast cancer, supporting their utility as important radiological markers for early detection. In particular, perimenopausal women were more likely to have breast cancer, and an increasing trend toward microcalcifications was observed with increasing breast density. These results emphasize the importance of integrating both radiologic findings and demographic variables into screening strategies. Future large-scale, prospective research is warranted to validate these associations and contribute to the development of evidence-based clinical guidelines.

Author Contribution Statement

Muhammad Usman Sami conceived the study design and methodology, contributed to data collection and entry, performed the statistical analysis, and wrote the results and discussion sections. Maira Saeed contributed to data collection and writing of the discussion. Mehreen Afridi contributed to the development of methodology and conducted the literature search. Dr Sadia Nazeem supervised the entire project. All authors critically reviewed and approved the final version of the manuscript.

Acknowledgements

Scientific Approval / Thesis Status

This study was not part of any approved student thesis or dissertation and did not receive formal approval from any scientific or regulatory body, as it was conducted as a retrospective observational analysis of anonymized institutional data.

Ethics Approval and consent to participate

Ethical approval was obtained from the Rehman

Medical Institute Research Ethics Committee (Reference: RMI/RMI-REC/Approval/253). Written informed consent was obtained from all participants. All the data was deidentified before analysis to ensure that no individual can be identified from the study data.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Study Registration

This study was not registered in any public clinical trial or research registry, as registration is not mandatory for retrospective observational studies with no prospective intervention or patient recruitment.

Conflict of Interests

The authors declare that they have no competing interests.

Abbreviations

ACR: American College of Radiology
OR: Odds ratio
CI: Confidence interval
RMI: Rehman Medical Institute
PACS: Picture Archiving and Communication System
REC: Research Ethics Committee.

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