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Predictors of Malignancy in Isolated Mammographic Microcalcifications: A Retrospective Cohort Study of Patients Undergoing Stereotactic Biopsy

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Abstract

Introduction: In breast cancer screenings, while mammography effectively detects microcalcifications for breast cancer, their association with benign and premalignant lesions is unclear. We evaluated pathology results and malignancy-related factors in patients who underwent stereotactic biopsy for mammographic microcalcifications.

Materials and Methods:

This retrospective study included 173 patients who underwent stereotactic biopsy for suspicious mammographic microcalcifications between May 2019 and July 2024. Clinical, radiological, and pathological data were reviewed. Patients were classified according to histopathological findings, and factors associated with malignancy were analyzed using multivariate logistic regression.

Results:

Malignant pathology was identified in 37 patients (21.4%), whereas 136 patients (78.6%) had benign lesions. Among malignant cases, 32 (86.5%) were diagnosed with DCIS and 5 (13.5%) with invasive carcinoma. Microcalcification distribution and morphology differed significantly between benign and malignant groups. Multivariate logistic regression analysis demonstrated that regional distribution (OR: 7.27, 95% CI: 1.12–47.15, p = 0.037), linear distribution (OR: 10.91, 95% CI: 1.81–65.78, p = 0.009), and pleomorphic morphology (OR: 4.93, 95% CI: 1.20–20.25, p = 0.027) were independently associated with malignancy.

Conclusion:

Malignancy was detected in approximately one-fifth of patients undergoing stereotactic biopsy for suspicious mammographic microcalcifications. Regional and linear distribution patterns, as well as pleomorphic morphology, were independent predictors of malignancy and may assist in risk stratification and clinical decision-making.

1. Introduction

Breast cancer is the most commonly diagnosed malignancy among women worldwide and remains a leading cause of cancer-related mortality despite advances in diagnosis and treatment [1]. Mammographic screening has been shown to reduce breast cancer mortality through earlier detection and treatment of disease [2]. Among mammographic findings, microcalcifications are of particular importance because they may represent the earliest radiological manifestation of breast cancer, especially ductal carcinoma in situ (DCIS) [3].

Microcalcifications are frequently detected in asymptomatic women and demonstrate a broad spectrum of morphologic and distribution patterns. While most are benign, certain imaging characteristics are associated with an increased likelihood of malignancy [4, 5]. However, imaging findings alone are often

insufficient to reliably distinguish benign from malignant lesions, and histopathological evaluation remains the diagnostic gold standard.

Stereotactic biopsy is the preferred minimally invasive technique for sampling suspicious mammographic microcalcifications and provides accurate pathological diagnosis with low morbidity [6]. Although several imaging characteristics have been associated with malignancy, accurately predicting pathological outcomes remains challenging in clinical practice. Identification of radiological features associated with malignancy may improve patient selection for biopsy and facilitate risk stratification.

The aim of this study was to evaluate the pathological outcomes of patients undergoing stereotactic biopsy for isolated mammographic microcalcifications and to identify clinical and radiological factors associated with malignancy.

2. Methods

This retrospective study was conducted at the General Surgery Breast and Endocrine Surgery Clinic of Ankara Bilkent City Hospital. Hospital records of 1105 patients who underwent stereotactic biopsy for suspicious microcalcifications detected during breast cancer screening between May 2019 and July 2024 were reviewed. Ethical approval was obtained from the Ankara Bilkent City Hospital Scientific and Ethical Review Board for Medical Research (Approval Date: 08/05/2024; Study No: 179), and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients at the time of registration.

Patients with palpable breast masses, lesions primarily evaluated by ultrasound-guided core needle biopsy, previous breast cancer, previous breast surgery, male sex, and age younger than 40 years were excluded. The study population consisted of 173 patients referred for stereotactic biopsy because of suspicious mammographic microcalcifications. Additional ultrasonographic findings identified during pre-procedural evaluation were recorded and analyzed; however, these findings were not considered exclusion criteria because the indication for biopsy was based on mammographic microcalcifications. Patients were classified as benign or malignant according to histopathological results and evaluated in terms of demographic, clinical, and radiological characteristics.

Preoperative data were obtained from archived medical records and included age, body mass index, smoking and alcohol use, reproductive history, hormone replacement therapy and oral contraceptive use, and family history of breast cancer. Radiological features such as breast density, localization, type and distribution of microcalcifications, associated mammographic findings, and the presence of a corresponding mass on ultrasonography were also assessed.

2.1.Statistical Analysis:

Descriptive statistics were presented as numbers (n) and percentages (%) for categorical variables. The normality of distribution for continuous variables was assessed using the Shapiro-Wilk test and

graphical methods. Continuous variables were summarized as mean ± standard deviation (SD) or median (minimum–maximum), depending on data distribution. For comparisons between benign and malignant groups, categorical variables were analyzed using cross-tabulations and the chi-square test, with results expressed as frequencies (n) and percentages (%). Continuous variables such as age, body mass index (BMI), age at menarche, parity, age at first birth, and breastfeeding duration were compared using the Mann-Whitney U test. To identify independent risk factors associated with malignancy, multivariate logistic regression analysis was performed. Results were presented as odds ratios (OR) with 95% confidence intervals (CI). All statistical analyses were conducted using IBM SPSS Statistics version 21.0 (IBM Corp., 2012) and Microsoft Excel 2007. A p-value of < 0.05 was considered statistically significant.

3. Results

The mean age of the 173 patients was 50.10 ± 7.48 years, and the mean age at menarche was 13.10 ± 1.63 years. Oral contraceptive use was reported by 31.8% (n = 55) of patients, hormone replacement therapy by 13.9% (n = 24), and a family history of breast cancer by 24.9% (n = 43). (Table 1)

Table 1
Demographic and Clinical Characteristics of the Patients (n = 173)

Variable	Category	Mean ± SD / n (%)	Median (Min–Max)
Age (years)		50.10 ± 7.48	49.0 (36–74)
BMI (kg/m²)		26.76 ± 5.22	26.0 (15–46)
Smoking Status	No	115 (66.5)	
	Yes	58 (33.5)	
Alcohol Status	No	164 (94.8)	
	Yes	9 (5.2)	
Age at Menarche		13.10 ± 1.63	13.0 (9–18)
Menopausal Status	No	91 (52.6)	
	Yes	82 (47.4)	
Parity		2.74 ± 1.63	3.0 (0–9)
Age at First Birth (years)*		23.15 ± 4.75	22.0 (13–38)
Breastfeeding Duration (years)*		2.83 ± 2.22	2.5 (0.16–12.5)
Oral Contraceptive Use	No	118 (68.2)	
	Yes	55 (31.8)	
Hormone Replacement Therapy (HRT)	No	149 (86.1)	
	Yes	24 (13.9)	
Family History	No	130 (75.1)	
	Yes	43 (24.9)	
*Individuals with a parity of at least 1			

Microcalcifications were located in the right breast in 43.9% (n = 76), the left breast in 53.2% (n = 92), and bilaterally in 2.9% (n = 5) of patients, most commonly in the upper outer quadrant (44.5%, n = 77). Grouped distribution was the predominant pattern (84.4%, n = 146). Morphologically, microcalcifications were most frequently punctate (32.9%, n = 57) or mixed amorphous–punctate (32.4%, n = 56). (Table 2)

Table 2
Breast Density and Distribution of Imaging Characteristics

Variable	Category	n (%)
Breast Density	A	3 (1.7)
	B	23 (13.3)
	C	96 (55.5)
	D	51 (29.5)
Which Breast	Right	76 (43.9)
	Left	92 (53.2)
	Both	5 (2.9)
Quadrant	Upper outer	77 (44.5)
	Upper inner	7 (4.0)
	Upper middle	15 (8.7)
	Lower outer	9 (5.2)
	Lower inner	17 (9.8)
	Lower middle	10 (5.8)
	Outer middle	20 (11.6)
	Inner middle	9 (5.2)
	Retroareolar	8 (4.6)
	Subareolar	1 (0.6)
Associated Finding	None	125 (72.3)
	Structural distortion	4 (2.3)
	Asymmetric density	29 (16.7)
	Nodular density	15 (8.7)
Microcalcification Distribution	Clustered	146 (84.4)
	Regional	7 (4.0)
	Segmental	11 (6.4)
	Linear	8 (4.6)
	Diffuse	1 (0.6)
Microcalcification Morphology	Punctate	57 (32.9)

Variable	Category	n (%)
	Amorphous	30 (17.3)
	Amorphous-Punctate	56 (32.4)
	Pleomorphic	15 (8.7)
	Coarse heterogeneous	14 (8.1)
	Linear	1 (0.6)
Breast USG Lesion	Absent	153 (88.4)
	Present	20 (11.6)

Histopathological evaluation revealed benign lesions in 136 patients (78.6%) and malignant lesions in 37 patients (21.4%). Malignant pathology consisted of 32 cases of ductal carcinoma in situ (DCIS) and 5 cases of invasive carcinoma. Lobular carcinoma in situ (LCIS) was detected in 5 patients and was included in the benign category because it is currently regarded as a non-obligate precursor lesion rather than an invasive malignancy. (Table 3)

Table 3
Distribution of Pathology Results

Pathology Result	n (%)
Benign (Benign, LCIS)	136 (78.6)
Malignant (Malignant, DCIS)	37 (21.4)

The mean age at menarche was significantly higher in the malignant group compared with the benign group (13.49 ± 1.56 vs. 13.00 ± 1.64; p = 0.049). No significant differences were observed between groups regarding age, BMI, smoking or alcohol use, menopausal status, reproductive factors, use of oral contraceptives or hormone replacement therapy, or family history of breast cancer (p > 0.05). (Table 4)

Table 4
Comparison of Clinical and Demographic Characteristics Between Benign and Malignant Groups

Variable	Benign (n = 136)	Malignant (n = 37)	Test statistic	p value
Age (years)	49.60 ± 7.27 / 51.0 (36–74)	49.0 ± 8.05 / 51.0 (41–69)	z = 1.492	0.136
BMI	26.54 ± 5.12 / 26.0 (16–45)	27.57 ± 5.58 / 27.0 (15–46)	z = 1.173	0.241
Smoking, n (%)	46 (33.8) / 90 (66.2)	12 (32.4) / 25 (67.6)	χ^2 = 0.025	0.874
Alcohol use, n (%)	7 (5.1) / 129 (94.9)	2 (5.4) / 35 (94.6)	–	0.611*
Menarche age	13.00 ± 1.64 / 13.0 (10–18)	13.49 ± 1.56 / 14.0 (9–18)	z = 1.968	**0.049**
Menopause, n (%)	64 (47.1) / 72 (52.9)	18 (48.6) / 19 (51.4)	χ^2 = 0.029	0.864
Parity	2.83 ± 1.63 / 3.0 (0–9)	2.41 ± 1.61 / 2.0 (0–8)	z = 1.693	0.090
First birth age (years)	23.26 ± 4.77 / 23.0 (13–38)	22.70 ± 4.71 / 21.0 (16–34)	z = 0.749	0.454
Breastfeeding duration (years)	2.73 ± 2.15 / 2.5 (0.16–12.5)	3.17 ± 2.50 / 2.5 (0.16–12.0)	z = 0.824	0.410
Oral contraceptive use, n (%)	43 (31.6) / 93 (68.4)	12 (32.4) / 25 (67.6)	χ^2 = 0.009	0.925
Hormone Replacement Therapy use, n (%)	20 (14.7) / 116 (85.3)	4 (10.8) / 33 (89.2)	χ^2 = 0.369	0.543
Family history, n (%)	33 (24.3) / 103 (75.7)	10 (27.0) / 27 (73.0)	χ^2 = 0.119	0.730

*z: Mann-Whitney U Test,x^2 : Chi-square Test, * Fisher's Exact test results are presented*

Microcalcification distribution differed significantly between benign and malignant groups ($p < 0.001$). Grouped distribution was more common in benign cases (90.4%), whereas regional and linear distributions were more frequent in malignant cases. Pleomorphic morphology was significantly associated with malignancy (24.3% vs. 4.4%, $p = 0.003$). Breast density, lesion side or quadrant, additional mammographic findings, and ultrasonographic correlates were not significantly associated with malignancy. (Table 5)

Table 5
Comparison of Imaging Features Between Benign and Malignant Groups

Variable	Benign (n = 136)	Malignant (n = 37)	χ^2	p value
Microcalcification distribution			X^2=22.142	**< 0.001**
Grouped	123 (90.4)	23 (62.2)		
Regional	2 (1.5)	5 (13.5)		
Segmental	8 (5.9)	3 (8.1)		
Linear	2 (1.5)	6 (16.2)		
Diffuse	1 (0.7)	0 (0.0)		
Microcalcification morphology			X^2=18.000	**0.003**
Punctate	48 (35.3)	9 (24.3)		
Amorphous	27 (19.9)	3 (8.1)		
Amorphous–punctate	43 (31.6)	13 (35.2)		
Pleomorphic	6 (4.4)	9 (24.3)		
Coarse heterogeneous	12 (8.8)	2 (5.4)		
Linear	0 (0.0)	1 (2.7)		
x^2 : *Chi-square Test*				

On multivariate logistic regression analysis, regional distribution (OR: 7.274, p = 0.037) and linear distribution (OR: 10.914, p = 0.009) were independently associated with an increased risk of malignancy compared with grouped distribution. (Table 6)

Table 6
Valuation of Potential Risk Factors Associated with Malignancy Using Multivariate Logistic Regression Analysis

Variable	β	SE	Wald	p value	OR (Exp(B))	95% CI (Lower–Upper)
Constant	-3.496	1.715	4.152	0.042	0.030	—
Microcalcification distribution			10.716	0.030		
Regional	1.984	0.954	4.329	**0.037**	7.274	1.122–47.155
Segmental	0.642	0.750	0.733	0.392	1.901	0.437–8.266
Linear	2.390	0.916	6.801	**0.009**	10.914	1.811–65.784
Diffuse*		—	—	—	—	—
Microcalcification morphology			6.466	0.263		
Amorphous	-0.165	0.733	0.050	0.822	0.848	0.202–3.570
Amorphous–punctate	0.577	0.511	1.278	0.258	1.781	0.655–4.845
Pleomorphic	1.596	0.721	4.904	0.027	4.932	1.201–20.248
Coarse heterogeneous	-0.075	0.893	0.007	0.933	0.928	0.161–5.343
Linear*	—	—	—	—	—	—

*: Diffuse distribution and linear morphology categories were represented by very small sample sizes, precluding reliable estimation of regression coefficients and odds ratios.

4. Discussion

Breast cancer is the most commonly diagnosed malignancy among women worldwide, and mammography remains the standard screening modality for its early detection [1, 2]. Reported sensitivity rates for mammography vary across studies. Pisano et al. reported an overall sensitivity of 70.3%, whereas Kerlikowske et al. reported a sensitivity of 77% in a meta-analysis [3, 4].

Although numerous studies have investigated the relationship between mammographic microcalcifications and breast cancer, many have included heterogeneous patient populations with palpable masses, associated imaging abnormalities, or a prior history of breast malignancy [5, 6]. In contrast, the present study focused exclusively on patients with isolated mammographic microcalcifications who underwent stereotactic biopsy. This relatively homogeneous cohort allowed a more focused evaluation of imaging characteristics associated with malignancy and may provide a clearer understanding of risk stratification in screening-detected lesions.

Microcalcifications are among the most important mammographic findings for the early detection of breast cancer [7]. Their detection rate during screening ranges from 12.7% to 41.2% in the general population, and approximately 15–25% of patients with detected microcalcifications are diagnosed with breast cancer [5, 8]. In our study, malignancy was identified in 21.4% of patients, consistent with previous reports. In 30–50% of non-palpable breast cancers, diagnosis relies solely on mammographically detected microcalcifications. Furthermore, 72–90% of screening-detected ductal carcinoma in situ (DCIS) cases are associated with microcalcifications [5, 8]. In our cohort, DCIS accounted for 18.4% of all cases and represented the majority of malignant lesions (86.5%), whereas invasive carcinoma was identified in only a small proportion of patients. These findings emphasize the pivotal role of mammographically detected microcalcifications in the diagnosis of preinvasive breast cancer. The predominance of DCIS among malignant lesions suggests that suspicious microcalcifications are frequently associated with disease at an early stage, highlighting the value of screening mammography in facilitating timely diagnosis and intervention before progression to invasive cancer.

Evaluation of breast density, lesion localization, morphology, and distribution patterns is essential in the assessment of mammographic microcalcifications. Boyd et al. reported that 40–50% of women have dense breasts, a factor associated with an increased risk of breast cancer [8]. Although breast density was not significantly associated with malignancy in our study, dense breast tissue (BI-RADS categories C and D) was present in 86.4% of malignant cases, supporting previous observations. Similarly, while microcalcifications were most commonly located in the upper outer quadrant of the left breast, lesion localization was not associated with malignancy risk.

The morphology and distribution patterns of microcalcifications are among the most important imaging predictors of malignancy. Previous studies have demonstrated an increased risk of malignancy in association with pleomorphic morphology and suspicious distribution patterns, particularly linear and segmental distributions [7, 9]. Consistent with these observations, we found significant differences in both morphology and distribution between benign and malignant lesions. Linear and regional distribution patterns were independently associated with a 10.9-fold and 7.2-fold increased risk of malignancy, respectively. In addition, pleomorphic microcalcifications were significantly associated with malignancy and were observed considerably more frequently in the malignant group than in the benign group ($p = 0.003$).

The observed association between linear and regional distribution patterns and malignancy may be explained by the growth characteristics of ductal carcinoma in situ. According to the BI-RADS lexicon, linear calcifications are suggestive of deposits within a single ductal system, whereas regional distributions may reflect involvement of a larger volume of breast tissue that does not conform to a single ductal segment [9]. These imaging patterns may therefore correspond to the anatomical spread of neoplastic cells within the breast ductal system, supporting their value as predictors of malignancy.

From a clinical perspective, the identification of linear or regional distribution patterns together with pleomorphic morphology may facilitate risk stratification in patients with isolated mammographic

microcalcifications. Recognition of these high-risk imaging characteristics may support patient counseling, multidisciplinary evaluation, and timely histopathological assessment. Given the predominance of DCIS among malignant lesions in our cohort, early identification of such findings may contribute to diagnosis at a potentially curable stage of disease [5, 6, 9].

In addition to imaging characteristics, we evaluated demographic and clinical variables potentially associated with malignancy. No significant associations were observed between malignancy and several established breast cancer risk factors, including BMI, smoking and alcohol use, parity, age at first birth, breastfeeding duration, menopausal status, hormone exposure, and family history of breast cancer [10–15]. Although age at menarche was slightly higher in the malignant group, the clinical relevance of this finding remains uncertain. The absence of significant associations may be related to the relatively small number of malignant cases and the lack of detailed exposure data for certain variables.

This study was conducted at one of the largest breast surgery centers in the country, providing access to a high-volume patient population and a comprehensive institutional database. A major strength of the study is the inclusion of a relatively homogeneous cohort consisting exclusively of patients who underwent stereotactic biopsy for isolated mammographic microcalcifications. Patients with a previous history of breast cancer, prior breast surgery, palpable breast masses, or lesions primarily evaluated by ultrasound-guided biopsy were excluded, thereby reducing potential confounding factors. Furthermore, detailed radiological, surgical, and pathological data were available for all patients, and mammographic findings were reviewed in collaboration with experienced radiologists, ensuring accurate characterization of microcalcification morphology and distribution patterns. The use of histopathological diagnosis as the reference standard further strengthens the reliability of the findings.

Despite these strengths, several limitations should be acknowledged. First, the retrospective and single-center design may limit the generalizability of the results to other populations and clinical settings. Second, the relatively small number of malignant cases may have affected the precision of the multivariate analyses, as reflected by the wide confidence intervals observed for some estimates. Third, detailed information regarding certain established breast cancer risk factors, such as the duration of hormone replacement therapy, oral contraceptive use, alcohol consumption, and smoking exposure, was not consistently available, precluding more comprehensive risk assessment. Finally, interobserver variability in the interpretation of mammographic microcalcification patterns could not be evaluated. Prospective multicenter studies with larger patient populations are needed to validate these findings and further refine risk stratification models for patients presenting with isolated mammographic microcalcifications.

Declarations

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