









# Imaging Findings and Clinicopathological Correlation of Breast Cancer in Women under 40 Years Old

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## ABSTRACT

**Objective:** The aim of this study was to evaluate the clinical, imaging and histopathological features of breast cancer in patients aged under 40 years of age. The relationship between radiological characteristics and histopathological features was also investigated.

**Materials and Methods:** The study included 131 patients aged under 40 years, diagnosed pathologically with breast cancer. A retrospective evaluation was made of the imaging and clinicopathological findings and the relationship between pathological and imaging findings was investigated.

**Results:** Most of the cancers were detected from clinical symptoms, especially a palpable mass (76.3%). The most common histological type of tumor was invasive ductal carcinoma and 64.8% of the tumors were high grade tumors. The predominant features were irregular borders (92.4%), microlobulated-angulated contours (43.5%), hypo-homogeneous internal echogenicity (80.9%) on ultrasonography, and the presence of a mass (41.2%) and suspicious microcalcifications (40.2%) on mammography. Magnetic resonance imaging commonly showed mass enhancement (66.7%) with type 2 or 3 dynamic curve (92.6%). High-grade tumors were associated with posterior acoustic enhancement ( $p: 0.03$ ) while low-grade tumors presented with spiculated margins more than high grade tumors ( $p: 0.04$ ).

**Conclusion:** Breast cancer in women aged under 40 years usually presents with a self-detected palpable mass and can show different imaging findings according to the histological grade. Ultrasonography is the main modality for the diagnosis of breast cancer in young women, but mammography and magnetic resonance imaging can help in both diagnosis and evaluation of the extent of disease.

**Keywords:** Young women, breast cancer, radiological findings, pathology features

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## Introduction

Breast cancer is less common in women under 40 years old and this age group constitutes approximately 7% of all women diagnosed with breast cancer (1, 2). However, it can have a worse prognosis and more aggressive biological behavior than breast cancer in older patients. Previous studies have shown that young women are diagnosed at a later stage with highly proliferative, poorly differentiated, estrogen receptor negative tumors with the presence of lymphovascular invasion (3-5).

The radiological findings of breast cancer in young women can vary and the diagnosis of cancer can be more challenging than in an older population as there are also different histopathological features (6, 7). Most medical associations, including the American College of Radiology and Society of Breast Imaging, recommend annual breast cancer screening starting at the age of 40 and the sensitivity of mammography is lower in young women due to denser breast tissue (8, 9). The use of breast ultrasonography (US) is preferred for women under 40 years old in the diagnosis of breast disease, but mammography or Magnetic Resonance Imaging (MRI) should be performed if there is a suspicious finding for malignancy (10).

Therefore, the aim of this study was to evaluate the clinical, imaging and histopathological features of breast cancer in patients aged <40 years. The secondary objective was to investigate the relationship between radiological characteristics and histopathological features.

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## Materials and Methods

### Patients

Approval for the study was granted by the Hacettepe University Ethics Commission. Informed consent was not required because of the retrospective nature of the study.

A retrospective review was made of 2619 women applied with breast core needle biopsy between June 2011 and December 2017. A total of 443 patients were under 40 years old. Those with benign pathology results were excluded from the study and thus 131 patients diagnosed with breast cancer were included for evaluation in the study.

### Imaging

All patients underwent ultrasonography, 107 patients had mammography and only 27 patients had MRI. Patients aged >35 years with a family history and those with a personal history of breast cancer underwent mammography as the initial modality. For other patients, US was applied first and then mammography was performed because of suspicious findings. MRI was applied to 27 patients to evaluate the extent of breast cancer before breast-conserving surgery.

The US images were obtained using a 12 MHz linear probe on a Toshiba Aplio 400 device (Toshiba Medical Systems Corporation, Otawara, Japan). For the mammograms, standard mediolateral oblique and craniocaudal images were obtained using Seno essential mammography systems (General Electric, USA). The MRI scans were acquired with the patient in the prone position in a 1.5-Tesla MRI scanner (Signa HD, GE Medical Systems, USA) using a four-channel phased array breast coil. The imaging protocol included the following sequences: axial T2-weighted fat saturated (TR/TE 5100/90 ms, slice thickness=2 mm, flip angle 90°, matrix 256x256), axial echo-planar DWI (TR/TE 2500/72, slice thickness =3 mm, matrix 256x256, diffusion gradient with b values of 0 and 500 s/mm<sup>2</sup>), and axial T1-weighted fast spin echo pre-contrast MR images (TR/TE 4.3/2.1 ms, slice thickness=2 mm, flip angle 90°, matrix 512x512). Dynamic breast examination was performed after the injection of intravenous contrast material (Dotarem, Guerbet, Roissy, France) through the antecubital vein at a dose of 0.1 mmol/kg using a power injector (Medrad, Bayer HealthCare, Netherlands). After pre-contrast T1-weighted images, the following 5 axial T1-weighted post-contrast dynamic sequences (TR/TE 4.5/2.1 ms, slice thickness=2 mm, flip angle 10°, matrix 512x512) were obtained at intervals of 90 seconds.

### Pathological examination

The pathological reports were reviewed to determine histopathological type, tumor grade and immunohistochemical findings including Estrogen Receptor (ER), Progesterone Receptor (PR) and Human Epidermal Growth Receptor 2 (HER 2) status. HER 2 status was defined as positive for tumors with a score of 3+ and negative for tumors with scores of 0 and 1+. In tumors with a 2+ score, gene amplification using Fluorescence in situ Hybridization (FISH) analysis was used to confirm the HER 2 status. Testing negative for all three hormone receptors was defined as triple negative breast cancer.

### Statistical Analysis

Descriptive statistics including patient age, tumor size, clinical presentation, histopathological type, grade, immunohistochemical and radiological findings were presented as frequencies and percentages of categorical variables and means and standard deviations of quan-

titative variables. The Independent Samples t-test was performed to compare the means of two groups (grade1-2 and grade 3) and Pearson chi-square test, Yates' chi-square test or Fisher Exact tests were used to compare differences between groups for categorical variables including radiological findings and histopathological findings. Spearman's rho correlation was used to examine the relationship between two quantitative variables. A value of p<0.05 was accepted as statistically significant. All statistical analyses were performed using The Statistical Package for Social Sciences version 23.0 software (IBM Corp.; Armonk, NY, USA).

## Results

### Clinical and histopathological data

The clinical and histopathological features are presented in Table 1. Most cancers were detected from clinical symptoms, especially a palpable mass (101/131, 77% symptomatic, 100/131 patients with a palpable mass). 22.9% of patients were asymptomatic and were diagnosed with breast cancer when they underwent breast US due to personal or family breast cancer history. The most common histological type of tumor was invasive ductal carcinoma, 64.8% of tumors were high-grade, and 17.6% of tumors were triple negative.

**Table 1. Clinical and pathological characteristics of 131 patients**

Characteristics	Number (%)
Mean age (year±SD)	34.2±3.6
Clinical presentation	
-Palpable mass	100 (76.3)
-Personal breast cancer history	10 (7.6)
-Family breast cancer history	20 (15.3)
-Bone metastasis	1 (0.8)
Histopathological type	
-Invasive ductal carcinoma	96 (73.3)
-Invasive lobular carcinoma	5 (3.8)
-Mixed carcinoma	20 (15.3)
-Mucinous type	3 (2.3)
-DCIS	7 (5.3)
Tumor Grade	
-Grade 1	4 (3.1)
-Grade 2	42 (32.1)
-Grade 3	85 (64.8)
Immunohistochemical findings	
ER positivity	87 (66.4)
PR positivity	71 (54.2)
HER 2/Cerb positivity	34 (26.0)
Triple negative	23 (17.6)

SD: Standard deviation; DCIS: Ductal carcinoma in situ; ER: Estrogen receptor; PR: Progesterone receptor; HER 2: Human epidermal growth factor receptor-2

Table 2. Radiological findings of lesions

Findings	Number (%)
Size ( $\pm$ SD) mm	36.3 ( $\pm$ 28.3)
Axillary lymphadenopathy in US	79 (60.3)
Skin thickening	24 (18.3)
Multifocality	49 (37.4)
BI-RADS category according to US-MMG	
-BI-RADS 4A	8 (6.1)
-BI-RADS 4B	16 (12.2)
-BI-RADS 4C	16(12.2)
-BI-RADS 5	91 (69.5)
US Findings (131 patients)	
-No abnormality	5 (3.8)
-Shape	
-Irregular	121 (92.4)
-Oval-round	5 (3.8)
-Margin	
-Circumscribed	2 (1.5)
-Microlobulated and angulated	57 (43.5)
-Indistinct	45 (34.4)
-Spiculated	22 (16.8)
-Posterior acoustic feature	
-No feature	76 (58.0)
-Acoustic enhancement	29 (22.1)
-Acoustic shadowing	26 (19.8)
-Echogenicity	
-Iso-homogeneous	2 (1.5)
-Hypo-homogeneous	106 (80.9)
-Heterogeneous	18 (13.8)
Mammography findings (107 patients)	
-No abnormality	17 (15.9)
-Abnormality	90 (84.1)
-Microcalcifications	43 (40.2)
-Asymmetrical density	29 (27.1)

-Distortion	7 (6.5)
-Mass	44 (41.2)
-Mass shape	
-Oval-round	9 (8.3)
-Irregular	35 (32.7)
-Mass margins	
-Circumscribed	1 (0.9)
-Microlobulated	5 (4.6)
-Indistinct	13 (12.1)
-Obscured	17 (15.8)
-Spiculated	8 (7.4)
MRI findings (27 patients)	
-Mass	18 (66.7)
-Non-mass enhancement	9 (33.3)
- Kinetic curve	
-Type 1	2 (7.4)
-Type 2 and 3	25 (92.6)
-T2W signal intensity	
-Isointense	18 (66.7)
-Hyperintense	9 (33.3)
Grade 1-2 (46)	
-Spiculated margins	12 (26.1)
-Posterior acoustic enhancement	5 (10.9)
-Heterogeneous internal echogenicity	4 (8.7)
-Microcalcifications	19 (50)
-Mass enhancement in MRI	4 (57.1)
-T2W signal intensity	1 (14.3)
Grade 3 (85)	
-Spiculated margins	10 (11.8)
-Posterior acoustic enhancement	24 (28.2)
-Heterogeneous internal echogenicity	14 (16.5)
-Microcalcifications	24 (34.8)
-Mass enhancement in MRI	14 (70)
-T2W signal intensity	8 (40)

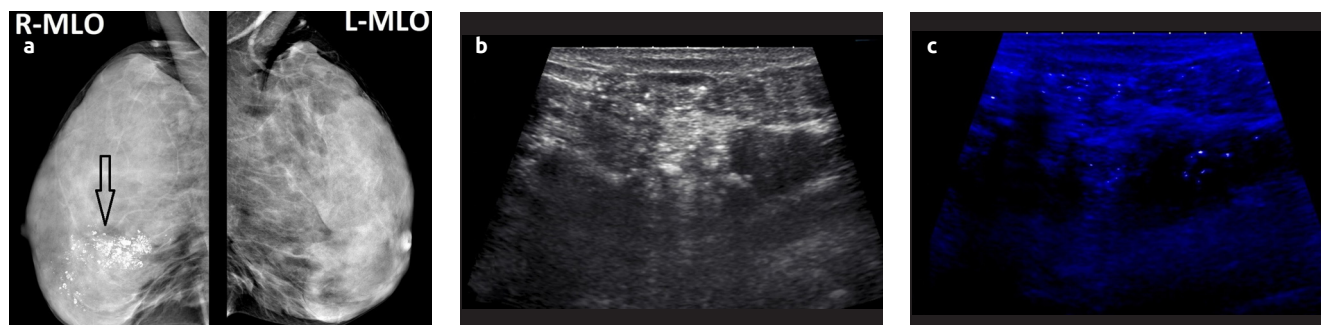
SD: Standard deviation; US: Ultrasonography; MMG: Mammography; MRI: Magnetic resonance imaging; BI-RADS: Breast imaging reporting and data system

### Imaging findings

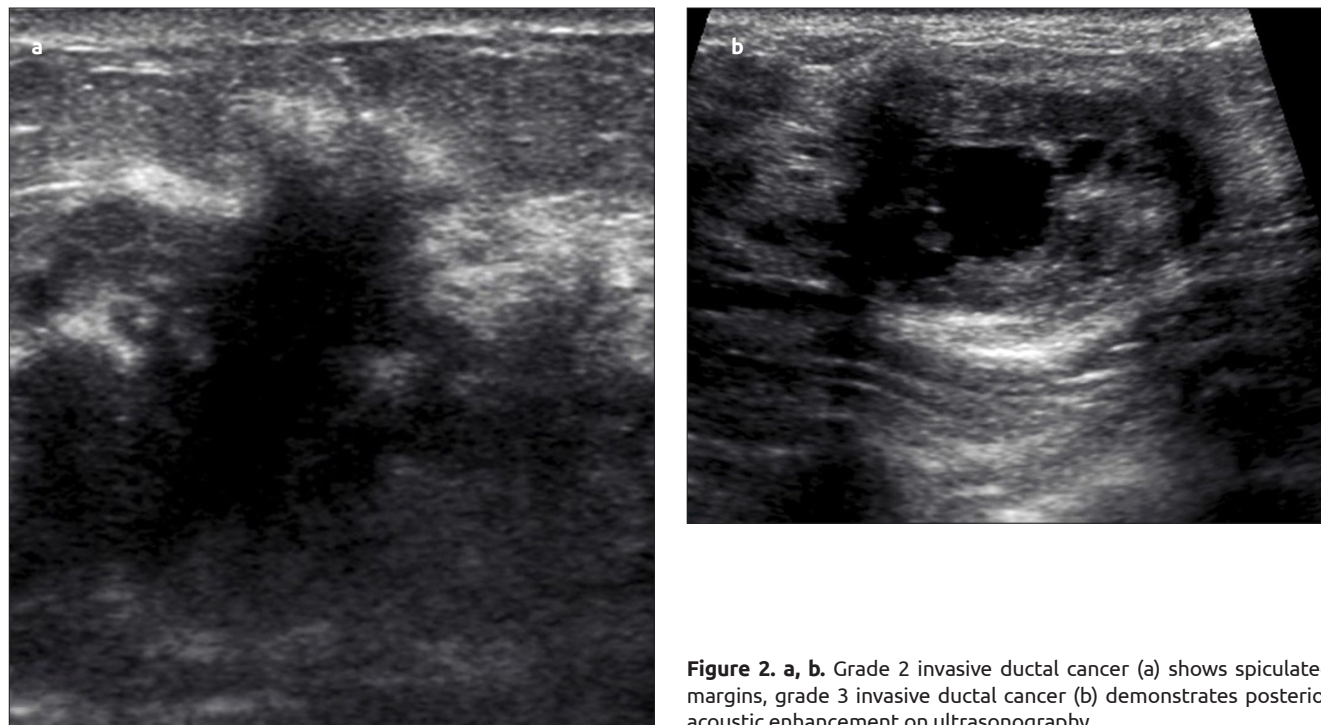
The radiological findings of tumors are summarized in Table 2. Breast Imaging Reporting and Data System (BI-RADS) categorisation was applied according to the US and mammography findings. Most patients were categorized as BI-RADS 5, and only 8 patients as BI-RADS 4A. The mean size of tumors was 36.3 mm. 60.3% of patients had axillary lymphadenopathy, which was also proven to be malignant pathologically. Skin thickening was present in 24 (18.3%) patients, and multifocal/multicentric tumors were seen in 49(37.4%).

### US

Ultrasonography was performed on all the patients. In 5 (3.8%) patients, no abnormality was determined on US and these cases were diagnosed with microcalcifications seen on mammography. The predominant features on US were irregular shape (121, 92.4%), microlobulated-angulated margins (57, 43.5%) and hypo-homogeneous internal echogenicity (106, 80.9%). Most patients (76, 58%) did not have a posterior acoustic feature, and 22.1% of patients demonstrated posterior acoustic enhancement.



**Figure 1. a-c.** Malignant pleomorphic microcalcifications are seen on mammography (a), ultrasonography (b) and micropure imaging (c) in a 27-year old patient with grade 3 breast cancer



**Figure 2. a, b.** Grade 2 invasive ductal cancer (a) shows spiculated margins, grade 3 invasive ductal cancer (b) demonstrates posterior acoustic enhancement on ultrasonography

### Mammography

Mammography was applied to 107 patients (81.6%) and on 84.1 % of these images an abnormality was determined. The most common abnormality on mammography was the presence of a mass (44/107, 41.2%), followed by suspicious microcalcifications (43/107, 40.2%) (Figure 1). In 5 patients, the diagnosis was made based on the presence of microcalcifications on mammography only. The most frequently seen shape on mammography was irregular, and the most common margin feature was obscured.

### MRI

All of the patients were diagnosed with US and mammography findings. MRI was applied to 27 (20.6%) patients to evaluate the extent of the disease before surgery. Of these 27 cases, 18 (66.7%) presented with mass enhancement, and 9 (33.3%) presented with non-mass enhancement. Most patients demonstrated type 2 or 3 dynamic curve (25/27, 92.6%). In 9 of 27 (33.3%) patients the cancer was hyperintense, and the T2W signal intensity was predominantly isointense in 18 (66.7%).

### Relationship between histopathological features and imaging findings

High-grade tumors were associated with posterior acoustic enhancement (grade1, 2: 10.9%, grade 3: 28.2% p: 0.03), and low-grade tu-

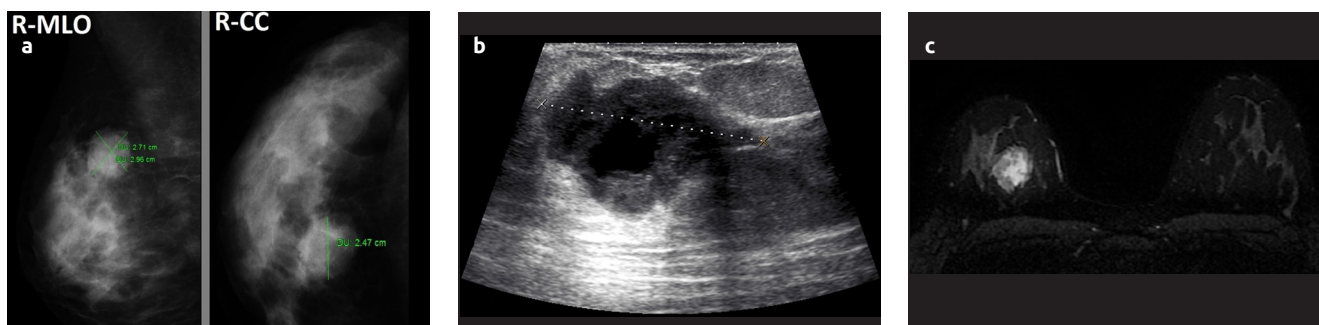
mors presented with spiculated margins more than high-grade tumors (grade 1-2: 26.1%, grade 3: 11.8% p: 0.04) (Figure 2).

High pathological grade tumors showed more internal heterogeneity than grade 1 and 2 tumors (grade1-2: 8.7%, grade 3:16.5% p: 0.09) (Figure 2). On MRI, T2W hyperintensity was more commonly seen in high-grade tumors than low-grade tumors (grade1, 2: 14.3%, grade 3: 40% p: 0.3). (Figure 3). Skin thickening (grade 1, 2: 13%, grade 3: 21.2% p: 0.3) and the presence of axillary lymphadenopathy (grade 1, 2: 50%, grade 3: 65.9% p: 0.1) were more frequently seen in high-grade tumors than low-grade tumors, but these findings did not reach statistical significance.

The histopathological grade did not show any association with the other radiological findings including shape, margins, and microcalcifications. No statistically significant relationship was determined between immunohistochemical findings and imaging findings.

### Discussion and Conclusion

Breast cancer in young women is uncommon but shows more aggressive histopathological features and has a poorer prognosis (5, 11, 12). In the current study, the majority of breast cancers in women under



**Figure 3. a-c.** Imaging findings are shown of a 26-year old patient with grade 3 invasive ductal carcinoma. Mediolateral and craniocaudal mammography images (a) demonstrate round shape, ultrasonography image (b) shows internal heterogeneity and posterior acoustic enhancement and magnetic resonance image (c) indicates T2W hyperintensity

40 years old presented symptomatically especially with a palpable mass and more than half of the patients had axillary lymphadenopathy on US at the time of diagnosis. With the exception of the high-risk group, young women are not included in breast screening programs. The reason for a poorer prognosis may be a late diagnosis and axillary or distant metastasis at diagnosis. However, several studies have shown that breast cancer in young women has a higher percentage of negative ER and PR receptors, higher lymphovascular invasion, grade and expression of proliferation markers including KI-67 and cyclins (12-14). Similar to a previous study, the findings of the current study showed that breast cancer in women under 40 years old was associated with a higher histological grade (6).

Radiological diagnosis of breast cancer in young women is more challenging compared to older counterparts. Most medical associations recommend annual breast cancer screening starting at the age of 40 years old for women at average risk. Mammography is the main modality for breast cancer screening (9, 15). Breast density can hide breast cancer and therefore mammography sensitivity is decreased in young women because of the higher breast tissue density (16). Due to the higher density, overdiagnosis and accumulation of radiation in young women, ultrasonography is the primary modality for the diagnosis of breast cancer. In the current study, ultrasonography was performed on all patients and with the exception of 5 patients, there was an abnormality in all patients. Of the patients who underwent mammography, an abnormality was detected in 84.1%. Moreover, 5 patients who could not be diagnosed by US were diagnosed by mammography. On mammography the most common findings of tumors were microcalcifications and mass. The shape of the masses was usually irregular, which was consistent with the findings of previous studies (6, 17). The predominant margin features were microlobulated-angulated on US and obscured in mammography. In contrast to the current study, Bullier et al. (17) found a predominance of spiculated margins in women with breast cancer aged <40 years. The lower rate of spiculated margins in the current study could be attributed to the higher percentage of high-grade tumors.

Magnetic Resonance Imaging was performed on patients for evaluation of the extent of cancer before breast cancer conserving surgery. Most patients showed mass enhancement, T2 isointensity and type 2 or 3 dynamic curves similar to the results of previous studies (6, 17, 18). Dynamic curves (92.6 % of patients have type 2/3 curves) in particular could help the radiologist in the diagnosis of breast cancer in young women whose diagnosis can be more challenging than in an older population.

The association between radiological findings and histological grade was also investigated. High-grade tumors were related to posterior acoustic enhancement, while low-grade tumors were related to spiculated margins. Moreover, on MRI T2W, hyperintensity was more commonly seen in high-grade tumors than in low-grade tumors, but this finding could not reach statistical significance probably due to the low number of patients with MRI findings. The results of previous studies supported the current study findings and it has been reported that high-grade and triple negative tumors can mimic benign lesions with circumscribed margins and posterior enhancement (17, 19). High-grade tumors are known to demonstrate higher cellularity and necrosis, which could be the reason for the internal heterogeneity, posterior acoustic enhancement and T2W hyperintensity. However, low-grade tumors usually show higher stromal reaction and desmoplasia which may cause spiculated margins (17, 20, 21). Women under 40 years old show a diverse distribution of histological grades, as 64.8% of our patients had higher grade tumor. Therefore, due to the different imaging findings of high-grade tumors, breast cancer under 40 years old can show distinct radiological findings from their older counterparts.

There were some limitations of the current study. The major limitation was the retrospective design. Second, the number of patients evaluated with MRI was low and this may have caused the lack of statistical significance. Finally, although the immunohistochemical findings were investigated, molecular subtypes could not be evaluated due to the lack of Ki 67 data in some patients.

In conclusion, breast cancer in women under 40 years old usually presents with a self-detected palpable mass and can show different imaging findings including posterior enhancement, T2W hyperintensity and less spiculated margins due to a higher histological grade. US is the main modality for diagnosis of breast cancer in young women, but mammography and MRI can help both diagnosis and evaluation of the extent of the disease. Awareness of imaging and clinicopathological findings of breast cancer in young women helps the radiologist to make an early and accurate diagnosis, and the clinician to provide the correct treatment.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Ethics Committee of Hacettepe University School of Medicine.

**Informed Consent:** Informed consent was not received due to the retrospective nature of the study.

**Peer-review:** Externally peer-reviewed.

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