
ORIGINAL ARTICLE

Characteristic Features of Breast Cancer in Women Aged ≤ 30 Years

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ABSTRACT

Objective: To identify and describe the imaging, clinicopathological and biological characteristics of breast cancer for women aged ≤ 30 years and to correlate the imaging features with clinical and molecular prognostic factors of breast cancer.

Methods: A total of 47 women aged ≤ 30 years with diagnosed breast cancer were included in this study. The patients' clinic visit, radiology, and pathology reports were retrospectively reviewed. We analysed the associations between features and outcomes using Fisher's exact test.

Results: The most common ultrasonographic feature was a mass with suspicious features for malignancy, which was assessed as Breast Imaging-Reporting and Data System (BI-RADS) category 4 (82.2%, 37 / 45) or 5 (17.8%, 8 / 45) in all cases. Of the invasive tumours, 69.0% (29 / 42) had a high histological grade, 61.4% (27 / 44) were oestrogen receptor-positive, 56.8% (25 / 44) were progesterone receptor-positive, and 25.6% (11 / 43) were human epidermal growth factor receptor type 2-positive. There was a significant correlation between mammographic mass margin and BRCA mutation ($p = 0.0217$); ultrasonographic mass features including margin, echo pattern, posterior feature and hormone receptor status ($p = 0.0117$ - 0.0467); and BI-RADS assessment and lymph node metastasis ($p = 0.0076$). BRCA mutation positive correlated significantly with a high histological grade ($p = 0.0243$) of tumour.

Conclusion: Breast cancer in women aged ≤ 30 years more frequently presents as a palpable mass with malignant imaging features and a high histological grade. The imaging and clinical features are significantly associated with prognostic factors of breast cancer in this patient population.

Key Words: Biopsy; Breast; Mammography; Neoplasms; Pathology

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Ethics Approval: This study (#13-799) was approved by our institutional review board and is compliant with federal Health Insurance Portability and Accountability Act regulations. The requirement for signed informed consent was waived.

中文摘要

30歲及以下女性乳癌的典型特徵

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目的：確定和描述30歲或以下女性乳癌患者的影像學、臨床病理學和生物學特徵，並將影像學特徵與乳癌的臨床和分子預後因素聯繫起來。

方法：納入47名確診乳癌的30歲或以下女性患者，回顧分析檢視患者的門診就診、放射學和病理報告。我們使用Fisher精確檢驗分析特徵和結果之間的關聯。

結果：最常見的超聲波特徵是具有可疑惡性腫瘤特徵的腫塊。當中屬乳腺影像學報告及數據系統（BI-RADS）第4類佔82.2%（37/45），第5類佔17.8%（8/45）。在浸潤性腫瘤中，69.0%（29/42）屬高組織學級別，61.4%（27/44）的雌激素受體呈陽性，56.8%（25/44）的黃體素受體呈陽性，25.6%（11 / 43）的人類表皮生長因子受體二型呈陽性。乳房X光造影檢查的腫瘤邊緣與*BRCA*突變（ $p = 0.0217$ ）、超聲波掃描的腫瘤特徵包括其邊緣、回音模式和腫瘤後部特徵與激素受體狀態（ $p = 0.0117-0.0467$ ），以及BI-RADS評估與淋巴結轉移（ $p = 0.0076$ ）均顯著相關。*BRCA*突變呈陽性與腫瘤的高組織學級別顯著相關（ $p = 0.0243$ ）。

結論：30歲或以下的女性乳癌患者，呈現可觸及的腫塊，具有惡性影像學特徵和較高的組織學分級。成像和臨床特徵與患者人群的乳癌預後因素顯著相關。

INTRODUCTION

Approximately 6.6% of all breast cancers are diagnosed before age 40 years, 2.4% are diagnosed before age 35 years, and 1% are diagnosed before age 30 years.¹ Although breast cancer in young women is an uncommon condition, these cancers are considered particularly aggressive and are associated with poor prognosis.²⁻⁴ However, because benign breast lesions are much more common than malignant tumours in young women, especially for those in their twenties, doctors may not take young women seriously when they express concerns about breast cancer.⁵ Doctors usually recommend follow-up for these patients; this may lead to delay in the diagnosis of breast cancer. In addition, because screening mammography is not recommended for young women, most breast cancers are diagnosed by detection of a palpable mass. These and other factors contribute to younger women having larger and more advanced tumours at the time of diagnosis, compared with older women.^{6,7}

Several studies have reported the imaging features of breast cancer in young women with different age cut-offs of 35 or 40 years⁸⁻¹⁸; however, the imaging features of breast cancer in women aged of ≤ 30 years have not been fully characterised. Therefore, the purpose of the

present study was to identify and describe the imaging, clinicopathological, and biological characteristics of breast cancer in women aged ≤ 30 years, and to correlate imaging features with clinical and molecular prognostic factors of invasive breast cancer in this age-group.

METHODS

Patient Selection

This retrospective study was approved by the institutional review board of UNC-CH (University of North Carolina–Chapel Hill) with a waiver of informed consent. Data of female patients aged ≤ 30 years who presented to the UNC-CH Breast Clinic from 2 January 2004 until 31 December 2012 and who also underwent breast imaging, a core needle biopsy, or surgical excision of a breast lesion that resulted in the diagnosis of breast cancer were extracted from hospital records. We reviewed the clinical data including age at time of diagnosis, symptoms, breast cancer gene mutations (*BRCA 1/2*), and family history of breast cancer in any first- or second-degree relatives.

Image Analysis

For women aged ≤ 30 years, ultrasonography was the initial imaging modality for evaluation of a breast lesion at our institution. If the ultrasonography examination demonstrated a suspicious mass, a bilateral mammogram

was then performed. All images that were obtained at our institution or at outside hospitals were used for the analysis. Mammograms were available for 42 patients, ultrasonograms for 45, and magnetic resonance imaging (MRI) scans for 17. Mammography consisted of baseline mediolateral oblique and craniocaudal projections and, if necessary, additional images such as spot compression view with or without magnifying obtained at the time of evaluation. Dedicated machines of both digital (Senographe 2000D; General Electric, US) and analogue (film-screen) [Siemens Nova 3000 with Fuji UM-MA HC film, US] techniques were initially used in our institution. Analogue imaging was no longer performed after 2005. Ultrasonography examinations (Logiq 7; General Electric, US) were performed by breast imaging radiologists with the knowledge of the clinical findings. MRI was performed using a 1.5-T system (Magnetom Avanto; Siemens, US) with a Sentinelle 7-channel breast coil (Invivo, US).

Mammograms, ultrasonograms, and MRI scans were reviewed by a breast imaging radiologist (JHL) with 10 years of experience. The radiologist was unblinded to other information. All images were analysed according to the 5th edition of the American College of Radiology Breast Imaging Reporting and Data System (ACR BI-RADS) lexicon with final assessment¹⁹ and all analyses were presented per lesion. In case of multifocal or multicentric disease, only the main tumour, not each single lesion, was analysed to avoid data clustering.

Histopathological Analysis

Histologically reviewed data included tumour size, histological type, grade, lymph node (LN) metastasis, existence or absence of multiple or bilateral tumours, and immunohistochemical analysis to evaluate the expression of oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor type 2 (HER2). The histological type of all tumour specimens was defined according to the World Health Organization's classification system²⁰ and the histological grade was defined according to the Elston-Ellis method.²¹ In immunohistochemical analysis, ER and PR positivity was defined as nuclear staining in more than 1% of invasive tumour cells and the intensity of HER2 staining was scored as 0, 1+, 2+ or 3+. Tumours with a score of 3+ were classified as HER2 positive; tumours with a score of 0 or 1+ were classified as negative. Tumours with a HER2 staining intensity score of 2+ underwent further fluorescence in situ hybridization analysis to confirm the HER2 status.

Statistical Analyses

Statistical analyses were performed using SPSS (Windows version 20.0; IBM Corp, Armonk [NY], US). We used Fisher's exact test for correlations between imaging features and clinical and molecular prognostic factors; $p < 0.05$ was considered statistically significant.

RESULTS

Clinical Data

Of 48 consecutive patients, we excluded one patient who had metastatic rhabdomyosarcoma to the breast; 47 patients were finally included in this study. The patients were aged 17 to 30 years (mean age 26.8 years). Two patients (4.3%) were aged \leq 20 years, five (10.6%) were aged 21 to 25 years, and 40 (85.1%) were aged 26 to 30 years. Forty-six (97.9%) of the 47 patients were symptomatic with a palpable mass at the time of diagnosis. One patient (2.1%) had no breast symptoms and was referred to the breast clinic in the process to evaluate the cause of thrombocytopenia. Seven patients (14.9%) had a family history of breast cancer. Of 43 cases in this study where *BRCA* mutations were known, 10 (23.3%) were positive.

Imaging Features

Table 1 presents the imaging features. Tumour sizes ranged from 7 to 120 mm (mean, 31 mm). Mammograms were available for 42 patients; of them, 34 (81.0%) had heterogeneously or extremely dense breast composition. The overall sensitivity of mammography was 95.2% (40 / 42). The most common lesion type was a mass with or without calcifications. Other findings included asymmetries in three patients (7.1%), focal asymmetries in two (4.8%), architectural distortion in one (2.4%), and skin and trabecular thickening in one (2.4%). The predominant mammographic features of the mass-type lesions were an irregular shape (77.8%) and indistinct margins (33.3%).

Ultrasonography was performed in 45 patients. Mass was the most frequent (97.8%) lesion type seen. In addition, these masses had suspicious features for malignancy, which were assessed as category 4 (82.2%) or 5 (17.8%) in all cases. Only one lesion (2.2%) was a non-mass lesion with the appearance of a hypoechoic region with internal echogenic foci, and it was assessed as a category 4 lesion. After final assessment based on both mammography and ultrasonography, 29.7% of lesions originally assessed as category 4 based on ultrasonography only were reassessed as category 5

Table 1. Imaging features.*

	Value
Mammography features	
Breast composition (n = 42)	
Fatty [†]	8 (19.0%)
Dense [‡]	34 (81.0%)
Mammography abnormality (n = 42)	
Negative	2 (4.8%)
Calcification	6 (14.3%)
Mass ± calcifications	27 (64.3%)
Others	7 (16.7%)
Shape (n = 27)	
Oval, round	6 (22.2%)
Irregular	21 (77.8%)
Margin (n = 27)	
Circumscribed	3 (11.1%)
Obscured	6 (22.2%)
Microlobulated	1 (3.7%)
Indistinct	9 (33.3%)
Spiculated	8 (29.6%)
Ultrasonography features	
Ultrasonography abnormality (n = 45)	
Mass	44 (97.8%)
Non-mass	1 (2.2%)
Shape (n = 44)	
Oval	4 (9.1%)
Irregular	40 (90.9%)
Margin (n = 44)	
Circumscribed	2 (4.5%)
Indistinct	15 (34.1%)
Angular	9 (20.5%)
Microlobulated	11 (25.0%)
Spiculated	7 (15.9%)
Echo patterns (n = 44)	
Complex cystic and solid	4 (9.1%)
Hypoechoic, heterogeneous	39 (88.6%)
Isoechoic	1 (2.3%)
Posterior features (n = 44)	
No	13 (29.5%)
Enhancement	20 (45.5%)
Shadowing	11 (25.0%)
Ultrasonography BI-RADS assessment (n = 45)	
Category 4	37 (82.2%)
Category 5	8 (17.8%)
Mammography / ultrasonography BI-RADS assessment (n = 47)	
Category 4	28 (59.6%)
Category 5	19 (40.4%)
Magnetic resonance imaging features	
Magnetic resonance imaging abnormality (n = 17)	
Mass	16 (94.1%)
Non-mass enhancement	1 (5.9%)
Shape (n = 16)	
Oval	2 (12.5%)
Irregular	14 (87.5%)
Margin (n = 16)	
Circumscribed	2 (12.5%)
Irregular	7 (43.8%)
Spiculated	7 (43.8%)
Enhancement (n = 16)	
Homogeneous	1 (6.3%)
Heterogeneous	10 (62.5%)
Rim	5 (31.3%)

Abbreviation: BI-RADS = Breast Imaging Reporting and Data System.

* Data are shown as No. (%).

[†] The breasts are almost entirely fatty. There are scattered areas of fibroglandular density.

[‡] The breasts are heterogeneously dense, which may obscure small masses. The breasts are extremely dense, which lowers the sensitivity of mammography.

(Figure 1). Of the 17 patients who underwent MRI, 16 (94.1%) of the lesions presented as a mass on MRI. Only one (5.9%) lesion presented as non-mass enhancement. Of the MRI masses, 87.5% had an irregular shape. The most common mass margin features were irregular or spiculated (87.5%) and the most common enhancement pattern was heterogeneous (62.5%).

Histopathological Data

Table 2 summarises the histopathological and molecular characteristics of the patients included in the present study. Of the 47 patients, 40 underwent surgery and 25 of these patients had neoadjuvant chemotherapy before surgery. Of the 47 patients, 41 (87.2%) had invasive ductal carcinoma, three (6.4%) of whom had ductal carcinoma in situ. Tumour sizes ranged from 0.1 to 56 mm (mean 19 mm), and tumours <20 mm accounted for 25 (62.5%) of the 40 patients who underwent surgery. Invasive tumours were predominately high nuclear grade (grade 3; 69.0%), and 25.6% of the tumours were triple-negative (TN) breast cancer.

Statistical Analysis

There was a significant positive correlation between the mammographic mass margin features and expression of *BRCA* mutation ($p = 0.0217$). In patients with a *BRCA* mutation, 83.3% (5 / 6) of the tumours had indistinct margin on mammogram. The ultrasonogram mass margin features, echogenicity, and associated posterior features were significantly correlated with the expression of ER ($p = 0.0176, 0.0135, 0.0467$, respectively) and PR ($p = 0.0117, 0.0235, 0.0305$, respectively). Eighty-six percent (6 / 7) of the masses with a spiculated margin on ultrasonography were both ER- and PR-positive and 75% (3 / 4) of the complex cystic and solid masses were TN subtypes. A BI-RADS assessment based on both mammography and ultrasonography was significantly correlated with the presence of LN metastasis ($p = 0.0076$). Of the cases without axillary LN metastasis, 80% (16 / 20) were assessed as category 4; of the cases with axillary LN metastasis, 66.7% (12 / 18) were assessed as category 5 (Figure 2).

In the correlation of clinical characteristics with histopathological and prognostic factors, the expression of *BRCA* mutation correlated significantly with the histological grade ($p = 0.0243$). All 10 tumours in patients with *BRCA* mutation were high grade 3, and 84.6% (11 / 13) of low-grade (grade 1 and 2) tumours were in patients with no *BRCA* mutation.

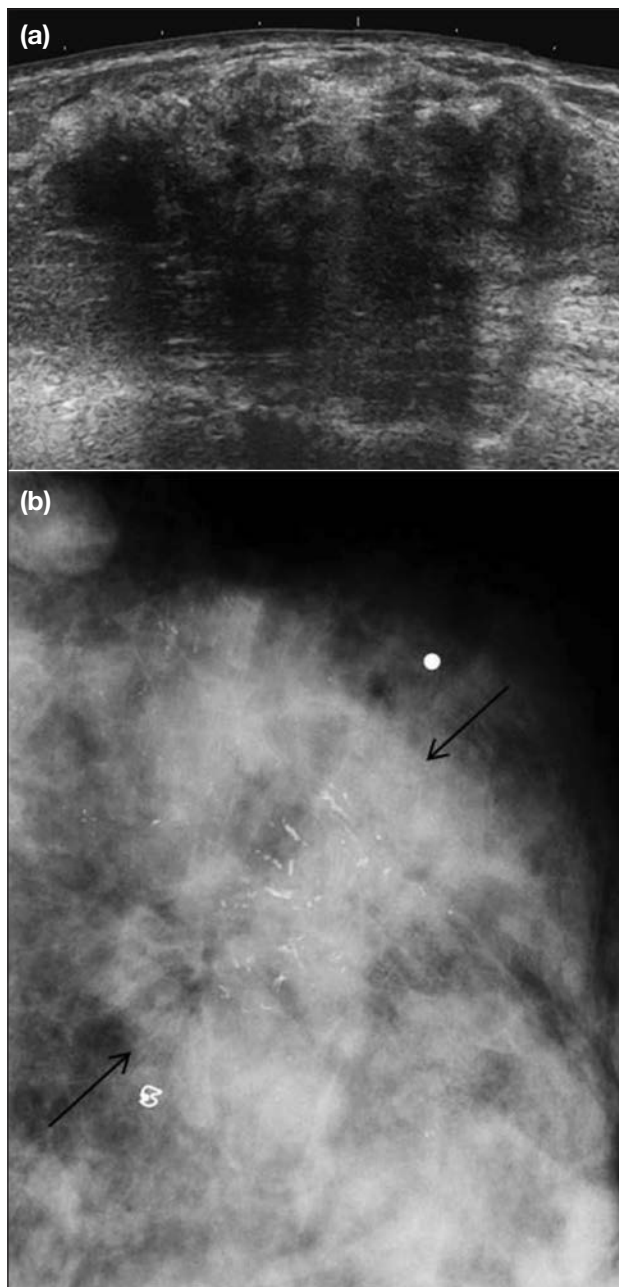


Figure 1. A 24-year-old woman presenting with a palpable mass in the upper outer quadrant of the left breast. (a) Ultrasonogram showing a large hypoechoic mass with an irregular shape and indistinct margins is visible in the palpable area of the left breast. Ultrasound Breast Imaging Reporting and Data System assessment was category 4. (b) Left mediolateral oblique spot compression magnification mammographic view showing an irregular hyperdense mass with fine-linear branching calcifications at the palpable skin marker area (arrows) in a dense breast. Final assessment based on both mammogram and ultrasonogram was reassessed as category 5. Histopathological results confirmed invasive ductal carcinoma with histological grade 2, negative oestrogen receptor and progesterone receptor, and positive human epidermal growth factor receptor type 2.

Table 2. Histopathological and molecular characteristics.*

Characteristics	Value
Histopathological type (n = 47)	
Invasive ductal carcinoma, not otherwise specified	41 (87.2%)
Ductal carcinoma in situ	3 (6.4%)
Invasive lobular carcinoma	1 (2.1%)
Malignant phyllodes tumour	1 (2.1%)
B cell post-transplant lymphoproliferative disorder	1 (2.1%)
Tumour size (n = 40)	
<20 mm	25 (62.5%)
20-50 mm	13 (32.5%)
>50 mm	2 (5.0%)
Axillary lymph node metastasis (n = 38)	
No	20 (52.6%)
Yes	18 (47.4%)
Histological grading (n = 42)	
Grade 1	3 (7.1%)
Grade 2	10 (23.8%)
Grade 3	29 (69.0%)
Oestrogen receptor status (n = 44)	
Negative	17 (38.6%)
Positive	27 (61.4%)
Progesterone receptor status (n = 44)	
Negative	19 (43.2%)
Positive	25 (56.8%)
Human epidermal growth factor receptor type 2 status (n = 43)	
Negative	32 (74.4%)
Positive	11 (25.6%)
Multiple cancer (n = 47)	
No	33 (70.2%)
Yes	14 (29.8%)
Bilateral cancer (n = 47)	
No	44 (93.6%)
Yes	3 (6.4%)

* Data are shown as No (%). Of these 47 patients, 40 underwent surgery and 25 had neoadjuvant chemotherapy before surgery.

DISCUSSION

Current literature reports that breast cancers occurring in young patients may be different from those arising in older women.²² However, there is a wide range in the definition of “young” (aged ≤ 25 ,⁴ ≤ 30 ,¹⁸ ≤ 35 ,^{7,10-12,14} ≤ 40 ,^{2,5,8,9} ≤ 45 ,^{13,15} or even ≤ 50 ²³ years). The selected age range of subjects was decided with consideration of the age commonly applied in clinical practice in deciding first-line imaging.¹⁵ To the best of our knowledge, there has been only one study on characteristic imaging features and the correlation with imaging features and clinical and molecular prognostic factors of breast cancer in women aged ≤ 30 years, and this was conducted in only Asian women.²⁴

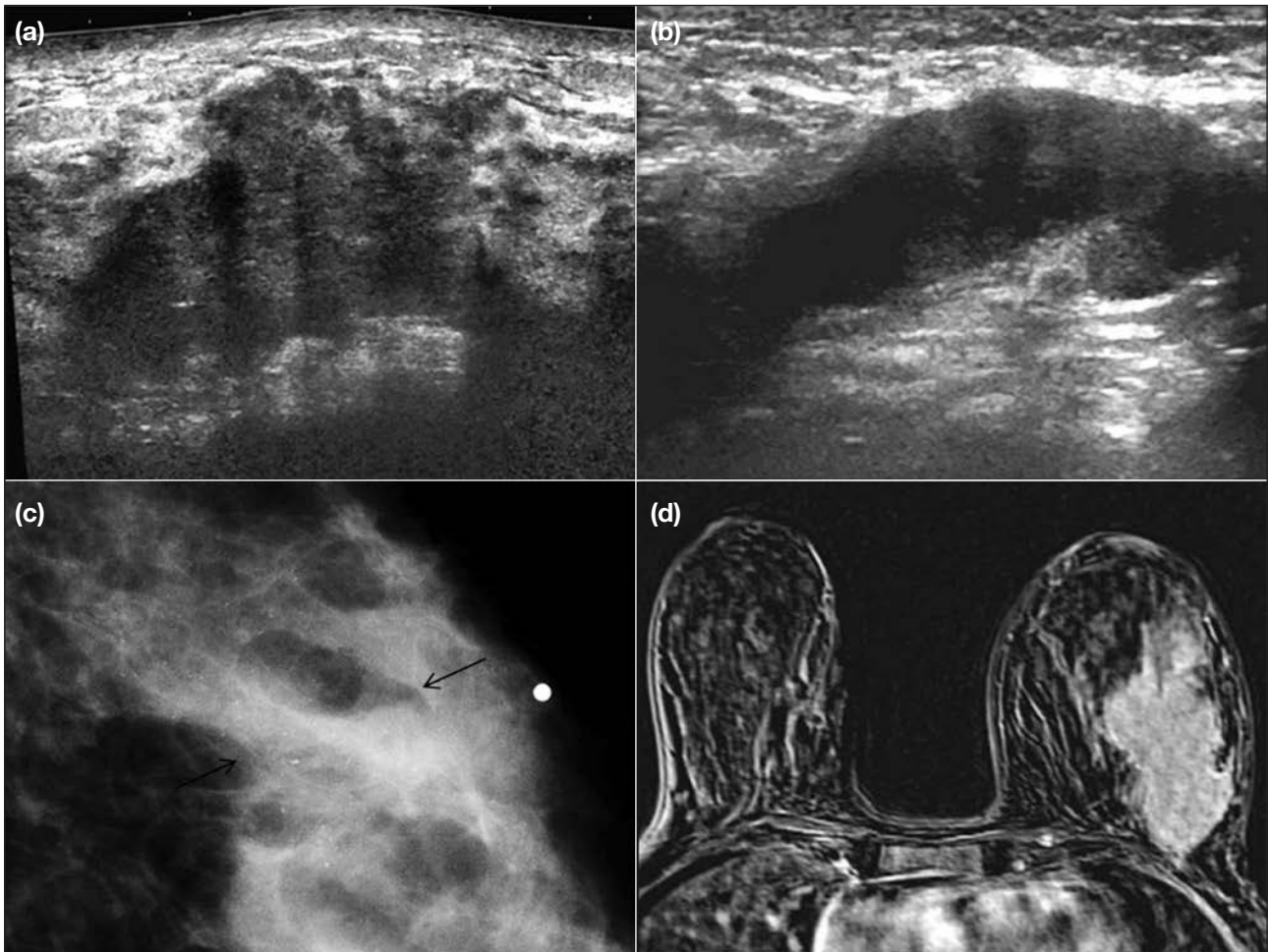


Figure 2. A 27-year-old woman presenting with a palpable mass in the lower outer quadrant of the left breast. (a) Ultrasonogram showing a 5-cm hypoechoic mass with an irregular shape and angular margin in the palpable area of the left breast. (b) Left axillary ultrasonogram showing an enlarged hypoechoic lymph node suggesting metastatic lymphadenopathy. (c) Left craniocaudal spot compression magnification mammogram showing fine pleomorphic calcifications (arrows) in a dense breast. Final assessment based on both mammogram and ultrasonogram was category 5. (d) Subtraction image of breast magnetic resonance imaging scans showing a large mass with heterogeneous enhancement and irregular margins in the left breast. Histopathological results confirmed invasive ductal carcinoma with histological grade 3, positive oestrogen receptor and progesterone receptor, and negative human epidermal growth factor receptor type 2. Left axillary lymph node metastasis was also confirmed.

Patients enrolled in breast cancer screening programmes were excluded from analysis; these patients are likely to have dense breast tissue on mammography, making it more difficult to differentiate between tumours and normal breast tissue.^{8,9} Our results showed that most patients had palpable symptoms (97.9%) and invasive carcinoma (89.4%), likely owing to the non-screened population and the poorer prognosis of breast cancers in young women.⁹

Family history of breast cancer is more common in women aged ≤ 40 years than in postmenopausal women.^{8,22,25} Although family history of breast cancer

in young breast cancer patients is common, Loman et al²⁵ reported that only 9% of patients had *BRCA 1/2* mutations. In the present study of women aged ≤ 30 years, only 14.9% of patients had a family history of breast cancer, but 23.3% had *BRCA 1/2* mutations. This may be attributed to the differences in the ethnicity and the age cut-off of enrolled patients compared with the study by Loman et al.²⁵

Older studies on imaging features of breast cancer in young women have used analogue techniques or had incomplete radiological data without following the guidelines of ACR BI-RADS. These older studies

reached conclusions on the frequent pseudo-benign presentation of cancers in young women, and found that detection rates for breast cancer by mammography were low.¹¹⁻¹³ More recent studies have reported sensitivities of mammography, ranging from 76% to 89% in the diagnosis of breast cancer in young women.^{9,14,15,24} The higher sensitivity in recent studies may be due to advances in breast imaging technologies, including digital mammography and computer-aided diagnosis, and the introduction of ACR BI-RADS guidelines for image analysis. In the present study, sensitivity of mammography was 95.2%, despite the high percentage of dense breast composition (81.0%). In addition to technological improvements, these favourable results may be because most cases (78.6%) in this study had suspicious calcifications that were easily detected by mammography and because the tumours tended to be large (mean size, 31 mm).

Although mammography is the gold standard for the diagnosis of breast cancer, many studies have reported that ultrasonography is an appropriate initial imaging test for symptomatic young women.¹⁴⁻¹⁸ In our study, the sensitivity of ultrasonography was 100%. There are several reasons for this result. First, there have been significant technical improvements in ultrasonography equipment, including high-frequency linear probes with high spatial resolution. Also, software advancements such as compound image, harmonic image, elastography and colour Doppler image are helpful for characterising breast lesions. Second, radiologists trained in breast imaging perform real-time ultrasonography. This may lead to more accurate and valid diagnoses than using static ultrasonogram images collected by a technologist. Third, the use of the precise descriptive lexicon and assessment categories in accordance with ACR BI-RADS may improve the characterisation of a mass. Finally, the radiologist reported the final assessment of the ultrasonogram with knowledge of the clinical information and the mammogram result; this was considered a positive factor influencing to the diagnosis.

The most common ultrasonography features of the masses—irregular shape, indistinct margins, and hypoechoicity or heterogeneity echotexture—recorded in the present study (90.9%, 34.1%, and 88.6%, respectively) are consistent with those reported in a study by An et al (75.6%, 57.8% and 77.8%, respectively).²⁴ The histopathological and biological results of the present study—including the incidence of high grade 3 (69.0%), ER-negative lesions (38.6%), PR-negative

lesions (43.2%), HER2 overexpression (25.6%), and LN metastasis (47.4%)—are similar to those of previous studies of young women aged ≤ 40 years,^{8,14,22,26} but higher than those of postmenopausal women.^{22,23,27-29} These results demonstrate that breast cancers in women aged ≤ 40 years have a more aggressive profile and a poorer prognosis than those in postmenopausal women.

The correlation of imaging features with molecular prognostic factors of invasive breast tumours has recently been described in all age-groups and in younger age-groups: significantly more spiculated lesions are found in ER/PR-positive groups^{8,30,31}; and tumours with *HER2* overexpression are significantly correlated with the presence of calcifications on mammograms.^{14,24,31} Our study also demonstrated a significant correlation between the ultrasonography mass features and expression of ER and PR. Most spiculated masses on ultrasonography were both ER- and PR-positive (85.7%). There were no ER- and PR-negative lesions with spiculated margins. Most complex cystic and solid masses (75%, 3 / 4) were TN breast cancer, reflecting tumoural necrosis in these high-grade tumours.³¹ The higher assessment category (category 5) was significantly correlated with LN metastasis ($p = 0.008$), likely because the radiologists reported the comprehensive imaging results and could upgrade the categories of the lesions from 4 to 5 when the patients had LN enlargement with suspicious features in their axilla in addition to the suspicious masses in their breasts (Figure 2).

Previous studies have reported that the TN subtype is often associated with *BRCA* mutations and that 10.6% to 14% of TN breast cancers are *BRCA 1/2* mutations.³²⁻³⁴ Our study showed that 27.3% (3 / 11) of the TN breast cancer was in patients with a *BRCA* mutation. The expression of *BRCA* mutation was significantly correlated with the histological grade ($p = 0.0243$). In addition, in all patients with *BRCA* mutation, the tumours were grade 3. In contrast, in patients with no *BRCA* mutation, the majority (11 / 13) of the tumours were of low histological grade 1 and 2. This is consistent with the results of the study by Schrading and Kuhl,³⁵ who found that 70% of tumours in women of all ages with *BRCA* mutations were high grade.

There are several limitations of this study. First, this was a retrospective study at a single institution with a small sample size. The number of cases could limit statistical outcomes. Second, the reviewing radiologist was unblinded to the clinical and histological information

and this might be influencing the image analysis. The results may have differed if the radiologist was blinded to the results and if there was more than one reviewing radiologist. Third, a number of clinicopathological data were missing or unavailable for review and this could have also affected the results. A large prospective multicentre study is recommended to decrease these limitations and to further evaluate breast cancer in these patients.

CONCLUSIONS

Breast cancer in young women aged ≤ 30 years frequently presents as a palpable mass with suspicious imaging features that are assigned BI-RADS category 4 or 5. Some imaging and clinical features are significantly associated with prognostic factors of breast cancer. Radiologists should be aware of the characteristic features in women aged ≤ 30 years to avoid delaying the diagnosis of breast cancer in this patient population.

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