Association between mammographic features and clinicopathological characteristics in invasive ductal carcinoma of breast cancer

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Received January 10, 2014; Accepted May 5, 2014

DOI: 10.3892/mco.2014.297

Abstract. The aim of the present study was to evaluate the association between mammographic features and clinicopathological characteristics in invasive ductal carcinoma. A total of 231 patients were retrospectively reviewed from January, 2011 to December, 2012. Statistical analysis was performed using Fisher's exact test, χ^2 test, Spearman's correlation and logistic regression, as appropriate. Of the 231 patients who underwent mammography, malignant calcifications were significantly more frequent in carcinomas that were human epidermal growth factor receptor 2 (HER2)-positive (P=0.001) or had a >2 cm size tumor (P=0.006). The pleomorphic-type was correlated with a p53-positive status (P=0.039) or lymph node metastasis (P=0.048), whereas the indistinct amorphous-type was associated with a HER2-positive status (P=0.026). An evident mass was frequently observed in higher Ki-67 expression-level tumors (P=0.002). In conclusion, the aforementioned correlations are noteworthy as they potentially reflect tumor attributes and may serve as a guide for treatment.

Introduction

Mammography detection is a widely-used screening technique for breast cancer (1). Typical features characteristic of invasive malignant carcinoma include evident mass, micro-calcification, architectural distortion or asymmetric density. Tumors with various clinical and pathological characteristics have different appearances on mammography, leading to variable prognoses (2). It has been reported that HER2/neu is a factor that influences specific mammographic appearances (3). Regarding the image features of certain special histology types, Yang *et al* (4) compared metaplastic breast cancer and invasive ductal carcinomas (IDCs). Increasing attention has focused on the clinical and pathological characteristics of breast carcinomas, which may exhibit various types of biological behaviors over the years of treatment and prognosis (5). However, few studies have been conducted with regard to this aspect.

The aim of the present study was to investigate the association between mammographic image features and clinicopathological characteristics in IDC.

Materials and methods

Patient data and mammography studies. The clinical and pathological results and mammography reports of 231 patients were retrospectively analyzed. The mammographic appearances were assessed according to the analytical criteria of the Breast Imaging Reporting and Data System from the database of Tianjin Oncology Hospital Breast Cancer Center (6). All the patients were female, and underwent breast radical mastectomy between 2011 to 2013. Mammography screening detection was obtained prior to surgery.

Study design and conduction. Pathological information was prospectively collected according to patient age, estrogen2 level in circulation, tumor size, the grade of IDC, the molecular type of carcinoma, estrogen receptor (ER) and progesterone receptor (PR) status, HER2/neu status, Ki-67 expression level, p53 status and lymph node metastasis status. Mammograms were assessed by five radiologists who specialize in breast radiology at the Department of Oncology Center (Tianjin Medical University Cancer Institute and Hospital, Tianjin, China), without any information of the pathological results. The mammography studies were collected and divided into five groups according to the traditional identification of malignant breast cancer in general. The five groups were i) evident mass without calcifications (Fig. 1A), ii) malignant calcifications without mass (Fig. 1B), iii) evident mass with calcifications (Fig. 1C), iv) architectural distortion or asymmetric density

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Key words: mammography, breast neoplasm, clinic, invasive ductal carcinoma, pathology

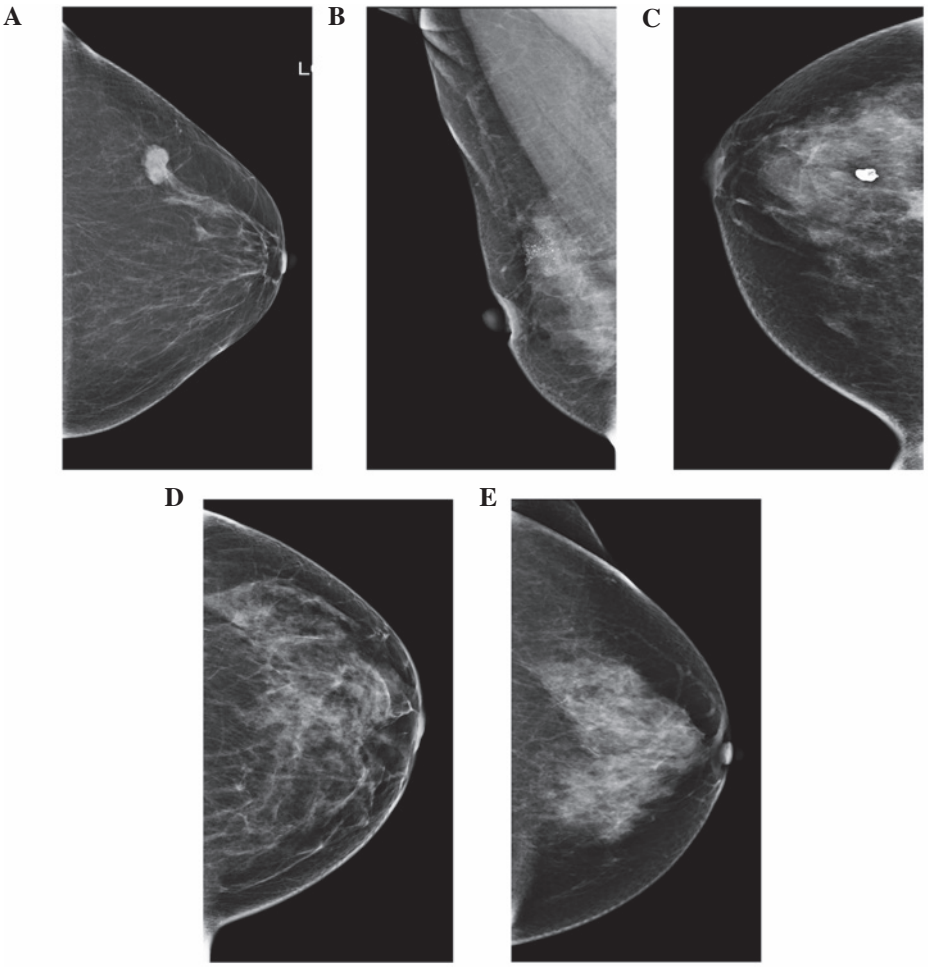

Figure 1. (A) Evident mass without calcifications; (B) malignant calcifications without mass; (C) evident mass with calcifications; (D) architectural distortion or asymmetric density without mass or calcifications and (E) no visible changes.

without mass or calcifications (Fig. 1D) and v) no visible changes (Fig. 1E), respectively.

Statistical analysis. Pathological information was correlated with mammographic appearances. The data were analyzed by the SPSS 17.0 statistical program (SPSS, Inc., Chicago, IL, USA). Statistical analysis was performed to assess the association using Fisher's exact test, the χ^2 test, Spearman's correlation and logistic regression, as appropriate.

Results

Several factors generally associated with mammographic appearances. Table I demonstrates that there were significant differences between mammographic appearances in general and age, estrogen2 level in circulation, tumor size, grade of IDC, HER2 expression status, Ki-67 expression index and the molecular type of the tumor (P=0.005, 0.044, 0.020, 0.037, 0.001, 0.001 and 0.013, respectively).

Comparison of mammographic features with the immunohistochemistry labeling index of the tumor. In the HER2 group, significant differences were identified between the presence and absence of malignant calcifications and indistinct or amorphous calcifications on mammography (P=0.001 and P=0.026). In the Ki-67 index group, significant differences were identified between the presence and absence of an evident mass (P=0.002). In the expression of the p53 group, significant differences were identified between the presence and absence of pleomorphic calcifications on mammography (P=0.039). These results are shown in Tables II-V, respectively.

Comparison of mammographic features with the pathological index of the tumor. There were significant differences between the presence and absence of malignant calcifications in the size of the tumor group (P=0.006) (Table II). Furthermore, in the group of an evident mass on mammogram, there were significant differences between irregular and lobular or oval mass shape in various grades of IDC (P=0.001) (Table VI).

Comparison of mammographic features with the nodal involvement status of the tumor. In terms of the nodal involvement of the tumor, the data in Table IV demonstrated that there were significant differences between the presence and absence of pleomorphic calcifications (P=0.048).

Discussion

In previous years, the mammogram has become one of the most significant diagnostic approaches of breast tumor.

Table I. Association between mammographic appearance and clinical characteristics.

Characteristics	Mammographic appearance, %					P-value	χ^2
	1	2	3	4	5		
Age, years						0.005	14.91
>50	26.1	16.8	51.3	5.0	0.8		
≤50	26.1	31.5	30.6	7.2	4.5		
Estrogen2 level in circulation						0.044	9.794
>40	26.2	31.0	32.1	6.0	4.8		
≤40	25.9	19.6	47.6	6.3	0.7		
Tumor size, cm						0.020	11.668
≤2	29.9	23.9	32.5	9.4	4.3		
>2	21.9	23.7	50.0	2.6	1.8		
Lymph node status						0.365	4.319
Negative	27.7	23.1	37.7	8.5	3.1		
Positive	23.8	24.8	45.5	3.0	3.0		
Grade of IDC						0.037	16.393
I	37.5	16.7	29.2	16.7	0.0		
II	24.8	28.0	37.9	5.6	3.7		
III	23.9	13.0	58.7	2.2	2.2		
Estrogen receptor						0.561	2.984
Negative	21.7	20.0	45.0	8.3	5.0		
Positive	27.5	25.1	39.8	5.3	2.3		
Progesterone receptor						0.726	2.054
Negative	23.7	19.7	46.1	6.6	3.9		
Positive	27.1	25.8	38.7	5.8	2.6		
HER2 expression status						0.001	19.993
Negative	36.3	27.5	22.5	10.0	3.8		
Positive	20.5	21.9	51.0	4.0	2.6		
Ki-67 expression index						0.001	17.650
≥45%	22.4	13.4	59.7	1.5	3.0		
<45%	27.8	28.4	32.7	8.0	3.1		
p53 status						0.066	8.794
Negative	29.3	25.6	35.4	7.3	2.4		
Positive	18.5	20.0	53.8	3.1	4.6		
Molecular type						0.013	25.423
Luminal A	34.8	29.0	24.6	8.7	2.9		
Luminal B	22.5	23.5	50.0	2.9	1.0		
HER2 overexpression	18.4	18.4	53.1	6.1	4.1		
Triple negative	40.0	20.0	10.0	20.0	10.0		

Mammogram appearance: 1, mass without malignant calcification; 2, malignant calcification without mass; 3, mass with malignant calcification; 4, architectural distortion or asymmetric density without mass or calcification; 5, none; IDC, invasive ductal carcinoma.

Findings of previous studies (7-10) have indicated that various types of breast tumor present different appearances on mammogram. Several typical mammographic appearances can reflect the tumor attributes and its biological behaviors, which may provide valuable information to the clinicians. Mammographic features can be used as predictors of prognosis and pathological characteristics, which influence the subsequent treatment. Therefore, the mammographic pattern is considered a risk factor for subsequent development of breast cancer (11).

Table II. Association between malignant calcification and clinical characteristics.

	Malignant calcification, %							
Characteristics	Positive	Negative	χ^2	P-value	r	Sig	HR (adjusted)	95% CI
HER2 (n=231)			11.989	0.001	0.228	0.000	3.205	1.617-6.354
Negative	50.0	50.0						
Positive	72.8	27.2						
Molecular type (n=230)			13.496	0.004	0.080	0.227		
Luminal A	53.6	46.4						
Luminal B	73.5	26.5						
HER2 overexpression	71.4	28.6						
Triple negative	30.0	70.0						
p53 (n=229)			3.373	0.066	0.121	0.067		
Negative	61.0	39.0						
Positive	73.8	26.2						
Ki-67 (n=229)			2.997	0.083	0.114	0.084		
≥45%	73.1	26.9						
<45%	61.1	38.9						
Tumor size, cm (n=231)			7.567	0.006	0.181	0.006	1.913	1.075-3.405
≤2	56.4	43.6						
>2	73.7	26.3						

CI, confidence interval; HR, hazard ratio.

Table III. Association between breast mass and clinical characteristics.

	Mass, %							
Characteristics	Positive	Negative	χ^2	P-value	r	Sig	HR (adjusted)	95% CI
Age, years (n=230)			11.041	0.001	0.219	0.001		
>50	77.3	22.7						
≤50	56.8	43.2						
Estrogen2 level l in circulation (n=227)			5.501	0.027	-0.156	0.019		
>40	26.6	73.4						
≤40	58.3	41.7						
HER2 (n=231)			3.865	0.049	0.129	0.050		
Negative	58.8	41.3						
Positive	71.5	28.5						
Ki-67 (n=229)			9.969	0.002	0.209	0.001	2.741	1.265-5.940
≥45%	82.1	17.9						
<45%	60.5	39.5						
Grade of invasive ductal carcinoma (n=231)			6.405	0.041	0.128	0.052		
I	66.7	33.3						
II	62.7	37.3						
III	82.6	17.4						

CI, confidence interval; HR, hazard ratio.

Table IV. Association between pleomorphic calcifications and clinical characteristics.

	Pleomorphic calcifications, %							
Characteristics	Positive	Negative	χ^2	P-value	r	Sig	HR (adjusted)	95% CI
HER2 (n=231)			3.186	0.074	0.117	0.075		
Negative	15.0	85.0						
Positive	25.2	74.8						
p53 (n=229)			4.246	0.039	0.136	0.040	2.049	1.051-3.997
Negative	18.3	81.7						
Positive	30.8	69.2						
Ki-67 (n=229)			3.556	0.059	0.125	0.059		
≥45%	29.9	70.1						
<45%	18.5	81.5						
Tumor size, cm (n=231)			2.895	0.089	0.112	0.090		
≤2	17.1	82.9						
>2	26.3	73.7						
Lymph node status (n=231)			3.909	0.048	0.130	0.048	1.993	1.049-3.785
Negative	16.9	83.1						
Positive	27.7	72.3						

CI, confidence interval; HR, hazard ratio.

Table V. Association between indistinct and amorphous calcifications and clinical characteristics.

	Indistinct and amorphous calcifications, %							
Characteristics	Positive	Negative	χ^2	P-value	r	Sig	HR (adjusted)	95% CI
Age, years (n=230)			3.319	0.071	-0.120	0.068		
>50	20.2	79.8						
≤50	30.6	69.4						
HER2 (n=231)			5.085	0.026	0.149	0.024	2.155	1.077-4.315
Negative	16.2	83.8						
Positive	29.8	70.2						
Tumor size, cm (n=231)			3.729	0.068	0.127	0.053		
≤2	19.7	80.3						
>2	33.7	66.3						
p53 (n=229)			3.657	0.066	0.127	0.056		
Negative	6.1	93.9						
Positive	13.8	86.2						
Ki-67 (n=229)			3.497	0.061	-0.124	0.061		
≥45%	3.0	97.0						
<45%	10.5	89.5						

CI, confidence interval; HR, hazard ratio.

It is known that specific types of breast tumor, including colloid or tubular, manifest particular appearances on mammogram (12,13). However, the IDC is the most frequent histological type among breast tumors. In general, breast tumors exhibit up to five different radiological patterns corresponding to the biological heterogeneity of these tumors.

Table VI. Association between the shape of mass and clinical characteristics.

Characteristics	Shape of mass (%)		χ^2	P-value	r	Sig	HR (adjusted)	95% CI
	Regular	Irregular						
Tumor size, cm (n=155)			4.841	0.036	0.177	0.027		
≤2	61.6	38.4						
>2	43.9	56.1						
Grade of invasive ductal carcinoma (n=155)			10.604	0.001	0.268	0.001	2.365	1.263-4.430
I	62.5	37.5						
II	60.4	39.6						
III	26.3	73.7						

CI, confidence interval; HR, hazard ratio.

The data of the present study have demonstrated that several typical mammographic features are correlated with certain indices of immunohistochemistry and pathology, and lymph node metastasis status. The aforementioned evidence may reflect tumor attributes to a certain extent.

In terms of the HER2 expression level, the data indicated that the ratio of malignant calcifications on mammogram was significantly high in HER2-positive cases. In particular, differences existed between the HER2-positive or -negative group on mammogram. A study by Gajdos *et al* (14) suggested that calcifications were associated with HER2 overexpression. The presence of calcifications in a mass or segmental calcifications on mammography were significantly associated with a positive HER2 status. Studies have been conducted on ER-negative breast cancer patients, which demonstrated that in the ER-negative group, HER2-positive breast cancers are more likely to be irregular masses, with spiculated margins associated with pleomorphic calcifications, whereas the HER2-negative breast cancers have been more frequently identified as round/variform-shaped masses with indistinct margins and have shown a great diversity of morphological types of calcifications comparatively (15). Thus far, a few studies have reported the association between HER2 overexpression of various types of tumor and malignant-appearing calcifications with regard to ductal carcinoma *in situ* (DCIS), non-palpable breast carcinomas and invasive breast carcinomas (3,13,16). These studies demonstrated that, regardless of the type, the malignant calcifications on mammography were correlated with HER2 status, tending to exist in the HER2 overexpression cases. As for the IDCs, the results were concordant with previous studies conducted concerning this aspect (3). Based on the aforementioned evidence, it may be inferred that patients who exhibit the malignant calcifications on mammography tend to be HER2 overexpressed when they are newly diagnosed. As is widely known, the HER2 status is an important prognostic factor for overall survival and disease-free survival of patients with breast cancer (17), which is closely associated with the HER2 receptor-targeted trastuzumab therapy.

Previous studies have demonstrated the association between p53 and Ki-67 expression with mammography. Gilliland *et al* (18) concluded that rapidly growing and aggressive tumors are responsible for a considerable amount of breast cancer detection failure by mammography. The identification of cancer within 12 months following a negative mammogram is defined as 'interval breast cancer.' The dysregulation of the cell cycle and potential genetic instability were measured by p53 expression, whereas the proliferation rate of the tumor was measured by the Ki-67 index. The results of the study indicated that the proportion of pleomorphic calcifications on mammography in p53-positive expression cases was significantly higher compared with the negative cases. The rates of evident breast mass on mammography in the high Ki-67-expression level group were significantly higher than those with low expression levels. The study by Porter *et al* (19) also indicated that screening mammography may miss certain rapidly proliferating, high-grade tumors. Thus, the studies highlight that more concerns should be taken for patients with pleomorphic calcifications or evident breast mass on mammogram. It is likely that these mammographic appearances are correlated with p53 or Ki-67 expression status, which are prognostic factors of great importance (20,21).

In addition, the present study examined the correlation between the mammographic feature of nipple retraction and PR expression status. No specific mammographic findings were significantly associated with ER or PR status in the study by Gajdos *et al* (14). Another study found that non-spiculated margins or hyperdense masses were associated with a negative ER status (22). The results of the data in the present study showed that the presentation ratio of the nipple retraction symptom was significantly higher in PR-positive expression patients compared with negative expression of PR. Therefore, this finding may indicate that patients who showed symptoms of nipple retraction on mammogram prior to surgery were likely to exhibit PR-positive expression, which may provide particular guidance for further endocrine treatment (23).

As for the pathological characteristics of tumors, the results of the present study demonstrated significant differences between the tumor size, various histological types and grades of IDC with mammographic features, malignant or pleomorphic calcifications, and the shape of the breast mass on the mammogram. Among the type of evident mass on mammogram, irregular shapes of mass were more frequently

present in tumors with grade 3 IDC. By contrast, the studies by Rotstein and Neerhut (24) and Lamb *et al* (25) indicated that high-grade IDCs may paradoxically exhibit features similar to those of benign breast masses, including a well-defined margin. Masses with non-spiculated margins on mammography were associated with a higher histological grade (22).

To a certain extent, it can account for the phenomenon that tumor attributes contribute to the variety of mammographic appearance types. However, due to the fact that the majority of patients in the present study were IDC type, the number of IDC accompanied by DCIS or other histological types was relatively small. Therefore, further studies are required to clarify this aspect. The aforementioned information on mammography can offer accurate pre-operative evaluation for breast-conserving surgery.

Regarding the nodal involvement, the data have demonstrated that pleomorphic calcifications, overlying skin thickening or dimpling on mammogram were more frequently present in the positive lymph node status group. Awareness of this information prior to surgery would aid clinicians in formulating the most suitable choices of surgical treatment modality for patients, including mastectomy or breast-conserving surgery (26). Another study revealed that the presence of calcifications alone or masses associated with calcifications on mammography was significantly associated with positive extensive intraductal component, and this contraindicates breast-conserving surgery and other mammographic features, including irregular shape, indistinct margin, calcifications within a mass and segmental calcifications (23).

In conclusion, it is of note that there are significant differences between the mammographic appearances with breast carcinoma attributes. The correlation of mammography image features and clinical and pathological characteristics exist in IDCs. Based on these findings, we believe that the mammography image appearances may reflect certain biological behaviors of tumors prior to surgery, which are useful for future evaluation and treatment of patients.

Acknowledgements

The present study was supported by the Program for the Applied Basic Research and Cutting-edge Technology Project of Tianjin Science and Technology Commission to Professor Cao (grant no. 11JCZDJC28000).

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