MR Imaging Phenotypes and Features Associated with Pathogenic Mutation to Predict Recurrence or Metastasis in Breast Cancer

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Abstract

Objectives: To develop a multiple-feature model using clinico-pathological and radiologic characteristics adding pathogenic mutations associated signs for predicting recurrence or metastasis in breast cancers at high familial risk women.

Methods: Genetic testing for breast-related gene mutations was performed in 54 patients with breast cancers. Breast MRI findings were retrospectively evaluated in 64 tumors of 54 patients. The relationship between pathogenic mutation and clinico-pathological and radiologic features was examined, and disease recurrence or metastasis was estimated. Multiple logistic regression analyses were performed to identify independent factors of pathogenic mutation and disease recurrence or metastasis. Based on the above significant factors, a multivariate logistic regression was adopted to establish two models for predicting disease recurrence or metastasis in breast cancer by using R software.

Results: On the 64 breast cancers, the patients on 17 cancers have pathogenic mutation and no pathogenic mutation on 47 cancers. The clinico-pathogenic and radiologic features associated with pathogenic mutation included six signs: biologic features ($p=0.000$), nuclear grade ($p=0.045$), breast density ($p=0.005$), MRI lesion type ($p=0.000$), internal enhancement pattern ($p=0.004$), and spiculated margin ($p=0.049$). Necrosis within the tumors was only feature associated with increased disease recurrence or metastasis ($p=0.006$). The model including clinico-pathologic and radiologic factors showed good discrimination in predicting disease recurrence or metastasis. The comprehensive model including model combined pathogenic mutations significantly associated signs is more effective.

Conclusions: The multiple-feature model in addition to pathogenic mutations associated parameters can more effective in predicting disease recurrence or metastasis.

Key Points

- 1) Only two MRI phenotypes – “internal enhancement patterns” and “central necrosis” were associated with disease recurrence or metastasis.
- 2) The MRI phenotypes associated with pathogenic mutation adding to the model for predicting disease recurrence or metastasis, the comprehensive model is an improvement based on multivariate analyses in breast cancer.

Introduction

Breast cancer is the most commonly diagnosed cancer, ranking fifth in the mortality of cancers in women in China ^[1]. Breast cancer risk is strongly influenced by genetic factors. The *BRCA1* and *BRCA2* are key genes associating with the development of breast cancer ^[2, 3]. *BRCA1* mutation carriers are more likely to have triple-negative and higher nuclear grade, which tend to have bad prognoses ^[4]. In addition, patients with metastasis or recurrence have also worse prognoses. Thus, many efforts to predict metastasis or recurrence in breast cancer patients, especially adding factors associated with pathogenic gene mutations have been made.

Magnetic resonance imaging (MRI) has been widely used for screening women at increased risk for breast cancer^[5]. The sensitivity of MRI for detecting breast tumors ranges from 77–91%, which is higher than mammography (33%-40%), in women at high familial risk for breast cancer^[6, 7]. Breast MRI can both diagnose breast cancer accurately and predict prognosis using variable imaging features. Previous studies identified that peritumoral edema on T2-weighted images and higher degree of background parenchymal enhancement (BPE), and increased vascularity around the tumor, indicate poor prognosis in breast cancer^[8–10]. Some studies have also demonstrated breast cancers with gene mutations had characteristic performances. The tumors with *BRCA* mutation carriers are associated with round shape, sharp margins, and rim enhancement^[11–13]. However, the current reported studies were little the relationship between pathogenic mutations and MRI features. In addition, multigene panel testing using NGS (next generation sequencing) technology could identify up to 50% more individuals with cancer susceptibility gene mutations in comparison with testing only for *BRCA1* and *BRCA2*^[14]. Moreover, NGS technology has become possible to study a wider range of hereditary cancer related genes. The sequential analysis of genes has the disadvantage of been expensive, laborious and time consuming.

Therefore, the aim of the study was to retrospectively identify signs associated with pathogenic mutations in 16 genes, and furthermore to develop a multiple-feature model using clinico-pathological features and radiologic characteristics in addition to pathogenic mutations associated signs for predicting metastatic or recurrence in breast cancers at high familial risk women.

Materials And Methods

Patients

This retrospective study included patients with histologically confirmed invasive ductal carcinomas and ductal carcinomas in situ from July 2014 to January 2016. All patients had obtained informed consent. A total of 100 patients initially were included in study according to the following inclusion criteria: (a) preoperative MR images were acquired, (b) available pathological and immune-histochemical reports, (c) available test results for gene mutation status, (d) available clinical data, including age, familiar history of breast cancer, and TNM stage. Among them, 44 patients were excluded due to the following exclusion criteria: (a) patients confirmed benign lesions (n=23), (b) patients received preoperative neoadjuvant chemotherapy treatment (n=11), (c) patients received local resection of lesion before MRI examination (n=10). Finally, 64 tumors of 56 patients were included, unilateral breast cancers on 48 patients, bilateral breast cancers on 6 patients, and two tumors of unilateral breast on 2 patients.

Imaging Technique

Dynamic breast MR imaging was performed using a 3.0 T magnet (GE Discovery 750) with patients in the prone position using a dedicated double-breast coil. Both breasts were imaged with axial T1-weighted sequence (TR=622ms, TE=10ms), fat-suppressed axial T2-weighted sequence (TR=6330ms, TE=68ms), and axial DWI sequence (TR=3235ms, TE=64ms) with *b* values of 0 and 1000s/mm². The contrast enhancement scan was used sagittal T1-weighted fat-suppressed volume imaging for breast assessment

(VIBRANT) sequence (TR=6.1ms, TE=2.9ms, flip angle=15°, matrix=256×128, slice thickness=1.8mm, phase acquisition time=90~100s), obtained before and continuous five times after intravenous injection of 0.1 mmol/L gadolinium chelate per kilogram body weight (Gadovist, Bayer Schering Pharma, Berlin, Germany).

Imaging Interpretation

The MR imaging characteristics of tumors were described by using terminology according to BI-RADS ^[15]. Breast density included dense (heterogeneously dense and extremely dense) and non-dense (entirely fatty and scattered fibroglandular density). The lesion type was classified as mass, asymmetry/distortion, and calcification on mammogram and as mass and nonmass enhancement on MRI. The shape (regular or irregular), internal enhancement pattern (heterogeneous mass-enhancement, rim mass-enhancement, or line/segmental nonmass-enhancement), spiculated margin (yes or no), central necrosis within tumor (yes or no), peritumoral edema (yes or no) and tumor localization (edge or central) were then evaluated on MRI.

Histologic Evaluation and Pathogenic Mutation Analysis

Histopathology, nuclear grade, tumor stage (T\N\M), and the status of immunohistochemical (IHC) staining for ER, PR, p53, Ki67, and HER2 were recorded, and positive for ER and PR was defined by the ASCO-CAP guideline ^[16]. Positive HER2 status was determined using IHC 3+ staining, or amplification using fluorescence in situ hybridization. Molecular subtypes were classified into Luminal A, Luminal B, HER2 over-expression, and Triple negative, and further classified into two groups including triple-negative (ER, PR, and HER negative) and non triple-negative. Biologic features were classified into three groups—unfavorable group (intermediate nuclear grade and ER negative/ PR negative, high nuclear grade and ER negative/ PR negative, high nuclear grade and ER negative/PR positive, high nuclear grade and ER positive/PR negative), favorable group (low nuclear grade and ER positive/ PR positive, low nuclear grade and ER negative/PR positive, low nuclear grade and ER positive/PR negative), and intermediate group (other nuclear grade and ER/PR). Disease recurrence or metastasis was defined as recurrence of breast cancer at any site (including local, regional, or distant).

Ion Ampliseq Designer (<https://ampliseq.com/> Browse. action) was used to design the multiplex PCR amplification primers of the exon regions of 16 inherited breast cancer related genes (*BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *BRIP1*, *TP53*, *PTEN*, *STK11*, *CDH1*, *ATM*, *BARD1*, *MLH1*, *MRE11A*, *MSH2*, *MSH6*, and *BAP1*) with a coverage rate of 99.8%, and Sanger sequencing was used to detect areas that could not be covered. According to the kit instructions, genomic DNA was extracted from the peripheral blood of breast cancer patients, and the DNA was amplified by multiplex PCR. The amplified products were connected, purified, oil-in-water reaction and enrichment of positive templates. Samples were sequenced in Ion Proton using GPM 314 chip. After sequencing, Coverage Analysis and Variant Caller were downloaded, and IGV software was used to analyze the results and determine whether there were pathogenic mutation genes in the 16 genes.

Statistical Analysis

The chi-square or Fisher exact tests were used to compare proportions between two groups (pathogenic mutation vs. no pathogenic mutation and disease recurrence or metastasis vs. no disease recurrence or metastasis) by using SPSS software (version 20.0). Multiple logistic regression analyses were performed to identify independent factors that can be used to predict pathogenic mutation and disease recurrence or metastasis. Based on the above significant factors, a multivariate logistic regression was adopted to establish two models for predicting disease recurrence or metastasis in breast cancer by using R software (version 6.1, R Foundation for Statistical Computing, Vienna, Austria). Two-sided $P < 0.05$ indicated a significant difference. Model 1 include clinico-pathologic features and radiologic variables, and Model 2 include clinico-pathologic features and radiologic variables in addition to pathogenic mutations associated parameters. The performance was evaluated by area under the receiver operating characteristic (ROC) curve, accuracy, sensitivity, and specificity. The difference in the area under the curve (AUC) between Model 1 and Model 2 was analyzed by Delong's test.

Results

Gene Mutations Status

All 64 tumors of 56 patients (mean age, 43.5 years; age range, 26-72 years) were included. All patients have a family history of breast cancer. Of 64 tumors, gene mutations were detected in 28 tumors (43.8%) (Fig. 1), pathogenic mutations were identified in 17 (26.6%) of 64 tumors, with 11 (17.2%) carrying *BRCA1* mutation, 2 (3.1%) carrying *BRCA2* mutation, and 4 (6.3%) had been found pathogenic mutation in other genes including *ATM* (n=1), *BAP1* (n=1), *BRIP1* (n=1), and *MSH6* (n=1), respectively. Table 1 summarizes the 17 identified pathogenic mutations, which contain 10 (58.8%) frameshift, 4 (23.5%) nonsense, and 3 (17.6%) splice-site variants in 17 breast cancers. No pathogenic mutations were identified in 11 of 64 tumors (17.2%), with 4 carrying *ATM* mutation, 2 carrying *MSH2* mutation, and *BRIP1/BRCA1/PALB2/CDH1/TP53* had been found no pathogenic mutation on only one tumor, respectively. Table 2 summarizes the 11 identified no pathogenic mutations, which all were missense in 11 breast cancers. The other 36 tumors had no gene mutations in the 16 genes.

Clinico-pathological and Radiologic Features associated with Pathogenic Mutations

Associations between clinico-pathological factors and pathogenic mutation status are presented (Table 3). The women younger than 40-year-old with breast cancer have been more detected pathogenic gene mutation ($p=0.039$). Pathogenic gene mutations subgroup had a significantly higher number of cancers with high nuclear grade (6 of 17 [35.3%], $p=0.017$), ER negative (7 of 17 [41.2%], $p=0.004$), PR negative (7 of 17 [41.2%], $p=0.007$). No significant association was observed between histopathology, T stage, N stage, HER2 overexpression, p53 status and the pathogenic gene mutation. And there were almost significant difference in Ki67 status ($p=0.057$) between pathogenic mutation and no pathogenic mutation. Pathogenic mutations were more likely to be the triple-negative phenotype (9 of 17 [52.9%]) than other subtype (3 of 17 [17.6%]) ($p=0.000$). Significantly pathogenic mutation rates were observed in unfavorable biological behavior cancers (10 of 17

[58.8%], $p=0.000$). Breast cancers carrying pathogenic mutations were more likely to being recurrence or metastasis (5 of 17 [29.4%] and 3 of 47 [6.4%]) ($p=0.014$).

The mammographic and contrast-enhanced MR characteristics of the tumors in each genetic subgroup are presented in Table 4. On mammogram, dense breast in patients with pathogenic mutation (16 of 17 [94.1%]) were significantly shower than those in patients with no pathogenic mutation (30 of 47 [63.8%]) ($p=0.025$). No mammographic lesion features were significantly associated with the pathogenic mutation status ($p=0.722$). On MRI scan, cancers were identified as mass type in all 17 lesions (100%) with pathogenic mutation, and as mass type in 37 lesions (78.7%) and nonmass type in 10 lesions (21.3%) with no pathogenic mutation ($p=0.038$). We found difference in internal enhancement pattern ($p=0.000$), spiculated margin ($p=0.005$), or necrosis within tumor ($p=0.009$) when comparing the pathogenic and non-pathogenic mutation subtypes. Breast cancers carrying pathogenic mutations showed more frequently ring mass enhancement with non-spiculated margin and necrosis within tumor. No significant associations were found between pathogenic mutation status with the shape ($p=0.253$), edema around tumor ($p=0.847$), or the location of the cancer ($p=0.623$).

Clinico-pathological and Radiologic Features associated with Disease Recurrence or Metastasis

The 5-year rate of disease recurrence or metastasis was 12.5% (8/64) for all patients, 29.4% (5/17) for pathogenic mutation subgroup and 6.4% (3/47) for no pathogenic mutation subgroup, which was significant difference ($p=0.014$). Tumors with five features including high nuclear grade (4 of 8 [50.0%], $p=0.004$) ER negative (5 of 8 [62.5%], $p=0.030$), PR negative (5 of 8 [62.5%], $p=0.041$), p53 positive (7 of 8 [87.5%], $p=0.046$) and triple negative subtype (4 of 8 [50.0%], $p=0.015$) had more disease recurrence or metastasis during 5 years after surgery (Table 5). Only two radiologic features – “internal enhancement patterns” ($p=0.045$) and “central necrosis” ($p=0.000$) were associated with disease recurrence or metastasis (Table 6). Breast cancers performing ring mass enhancement and central necrosis were more likely to being recurrence or metastasis.

Multivariable Analyses of predicting Pathogenic Mutations and Disease Recurrence or metastasis and ROC Analyses

These six features including biologic feature, nuclear grade, breast density, MRI lesion type, internal enhancement pattern and non-spiculated margin were proved to be independent prognostic factors predicting pathogenic mutations using multivariable logistic regression combined clinic-pathologic with radiologic features (Table 7). The AUC was 0.890 (95%CI: 0.793-0.988) (Fig.2), the sensitivity and specificity was 0.937 and 0.875, respectively.

For predicting disease recurrence or metastasis, evaluating these seven clinico-pathologic and radiologic features including nuclear grade, ER, PR, p53, molecular subtype, internal enhancement pattern, and central necrosis, but the only one important and significantly independent prognostic factor was central necrosis within tumor as the Model Ⅱto predict disease recurrence or metastasis using multivariable logistic regression.

The AUC was 0.839 (95%CI: 0.675-1.000) (Fig.3), the sensitivity and specificity was 0.963 and 0.600, respectively. When pathogenic mutation status were added to the model χ^2 , there were consistent results on the AUC, the sensitivity, and the specificity as the model χ^2 .

For the Model χ^2 predicting disease recurrence or metastasis with the only one radiologic feature—"central necrosis within tumor" (Model χ^2) combined these six prognostic signs significantly associated with pathogenic mutations, the AUC was 0.857 (95%CI: 0.695-1.000) (Fig.3), the sensitivity and specificity was 0.964 and 0.750, respectively. When clinico-pathologic and imaging features significantly associated with pathogenic mutations were added, the AUC increased from 0.839 to 0.857, but had not significantly difference ($P=0.153$), and the specificity increased from 0.600 to 0.750 (Fig.3).

Discussion

In our study, there were a 26.6% carrier rate of pathogenic mutation in the 64 breast cancers, consisting of 20.3% (13/64) in high-penetrance and 6.3% (4/64) moderate/low- penetrance of the pathogenic mutation genes, and the prevalence of *BRCA* mutation was 20.3% (13/64). Tsaousis et al. ^[17] showed that the pathogenic mutation frequencies of high-risk and moderate-risk genes was 16.5% and 6.2% respectively. Wang et al. ^[18] detected a 13.5% carrier rate of pathogenic germline mutation in the 20 genes, but a 26.6% higher carrier rate of pathogenic mutation in this study. The underlying reasons may be that our enrolled women had high risk with family history of breast cancer.

Our results indicated that pathogenic mutation associated with younger than 40 years old, higher nuclear grade, triple-negative subtype, and unfavorable biological behavior, as well as dense breast on mammography. We also found that breast cancers with pathogenic mutations exhibited ring mass enhancement with non-spiculated margin on MRI. Although it was different from other studies focusing on the *BRCA* mutations that comparing the pathogenic mutation subgroup and the non-pathogenic mutation subgroup, 76.5% (13/17) were *BRCA* mutations in pathogenic mutations in this study. In agreement our observations, a significantly number of lesions described as rounded, with sharp margins, and with ring-enhancement was found to be higher in the *BRCA* mutation ^[13, 19]. Yip et al. ^[20] found that in the Asian population there is a significant association between triple negative and *BRCA1* but not *BRCA2* status and a trend toward a higher percentage of grade 3 cancers in the *BRCA1* carriers but not in the *BRCA2* carriers. These above results were consistent to these characteristics observed in the current studies. In this study, we also found breast cancers with central necrosis were more frequently identified pathogenic mutation and disease recurrence or metastatic. The association of rim-enhancement with central necrosis or insufficient microvessel growth can be an indicator for the growth rate of tumors. Jimenez and coworkers have described centrally necrotizing carcinomas to have an accelerated clinical course and early systemic metastasis ^[21]. An accelerated growth rate can be associated with a high mitotic activity index (MAI) ^[19, 22]. Several authors have implied that, due to the rapid growth rate of tumors in gene mutation carriers, the risk of recurrence or metastasis could high, so the screening frequency should be increased and ^[23, 24].

In this study, the 5-year rate of disease recurrence or metastasis was 12.5% (8/64) for all patients, 29.4% (5/17) for pathogenic mutation subgroup, and 6.4% (3/47) for no pathogenic mutation subgroup. Wang et al. ^[18] found that the rate of disease-free survival at 5 years was 73.3% among *BRCA* mutation carriers, as compared

with 91.1% among non-carriers. Previous studies demonstrated that some factors including tumour size, multiple masses, fat-saturated T₂WI signal, were confirmed to be associated with distant metastasis^[25–26]. Some independent clinicopathologic factors were previously confirmed to be associated with distant metastasis. Age, T stage, N stage, lymphovascular invasion, and hormone receptor status were associated with bone metastasis in breast cancer^[27]. The study found that sex, histological type, N stage, grade, age, ER status, PR status can predict liver metastasis^[28]. Lee et al.^[29] showed that increased ipsilateral vascularity and higher positive skewness of texture analysis were independently associated with disease recurrence, whereas rim enhancement showed no association with disease recurrence. In our study, central necrosis on MRI was the only factor associated with disease recurrence or metastasis, and the 5-year rate of disease-free survival was 50% (5/10) in the breast cancer with central necrosis, and 96.3% (52/54) in the breast cancer without central necrosis. Although disease recurrence or metastasis differed among patients with nuclear grade, ER or PR status, p53 status, molecular subtype, and internal enhancement pattern were not confirmed to be a significant factors. The underlying reasons will be clarified with a larger sample size. Although adding the pathogenic mutation status could not improve the predicting efficiency, the six signs adding to the model for predicting disease recurrence or metastasis, the comprehensive model is an improvement of predictive models based on multivariate analyses. Spanberger et al.^[30] found that the extent of peritumoral edema on the preoperative T2-weighted conventional MR scan showed to be related to the degree of angiogenesis, brain invasiveness, and overall survival. However, peritumoral edema is not a significant factor for predicting metastasis in this study, the possible reason maybe that there were brain metastases in only two patients (Fig. 4), and need to be further analyze with a larger sample size. Hence, using MRI as a screening tool enables the detection of breast cancer with pathogenic mutations in women with familial risk of breast cancer.

Our study had limitations. The sample size is very small which means that the differences or similarities regarding the clinical and pathological characteristics. Hence, these findings should to be confirmed by larger trials. Also, in this study all enrolled women had family history of breast cancer and were analyzed not only *BRCA* mutation but also sixteen genes related breast cancer so it may be not reasonable to generalize these results to the entire population. Therefore, future studies may need broader inclusion criteria and enroll sporadic breast cancer cases from the general population. In addition, as the multigene panel testing is becoming widely adopted, studies should develop evidence-based practice guidelines.

In summary, clinico-pathologic and radiologic features of breast cancers can be effective in predicting pathogenic mutations and disease recurrence or metastasis, combined pathogenic mutations associated parameters enable more effective discrimination of disease recurrence or metastasis than use of clinico-pathologic and radiologic variables alone.

Abbreviations

MRI: Magnetic resonance imaging; BPE: Background parenchymal enhancement; NGS: Next generation sequencing; TR: Time of repetition; TE: Time of echo; DWI: Diffusion weighted imaging; VIBRANT: Volume imaging for breast assessment; BI-RADS: Breast imaging reporting and data system; IHC: Immunohistochemical; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor-2; ASCO-CAP: American Society of Clinical Oncology-College of American

Pathologists;PCR:Polymerase chain reaction;GPM:Global proteome machine;IGV:Integrative genomics viewer;ROC:Receiver operating characteristic;AUC:Area under the curve;MAI:Mitotic activity index.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

ZZS, JPY, and HL designed the study. ZZS wrote the research. JPY analysed the expression of pathogenic gene mutations. YNC wrote the section of Pathogenic Mutation Analysis. WJM provided statistical advice for this manuscript. PFL reviewed the paper. All authors have read and approved the manuscript writing.

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Availability of data and materials

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

Ethics approval and consent to participate

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Tianjin medical university cancer institute and hospital (NO.: Ek2018125). Written informed consent was obtained from all subjects (patients) in this study.

Consent for publication

Not applicable.

Competing interests

All authors states that there are no potential competing interests.

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Tables

Table 1

Pathogenic genes mutations in 15 patients with 17 cancers

Gene	Mutation	Age at diagnosis	Family history	Mutation type
<i>BRCA1</i>	c.3359_3363delTTAAT	48	Sister	frameshift
	c.5470_5477delATTGGGCA	30	Aunt	frameshift
	c.5136G>A*	29	Mother	nonsense
	c.5153-1G>A*	47	Sister	splice-site variants
	chr17:41246509delG	41	Mother	frameshift
	chr17:41226484insC	44	Sister	frameshift
	c.5470_5477delATTGGGCA	53	Aunt	frameshift
	chr17:41226455delG	49	Mother	frameshift
	c.2138C>G	34	Mother, Aunt	nonsense
<i>BRCA2</i>	chr13:32913702DelTACT	51	Mother	frameshift
	chr13:32914936InsTA	41	Sister	frameshift
<i>BAP1</i>	chr3:52440911InsC	26	Mother	frameshift
<i>BRIP1</i>	chr17:59793425C>A	41	Sister	splice-site variants
<i>MSH6</i>	chr2:48010546delC	49	Mother	frameshift
<i>ATM</i>	c.2414C>T	32	Aunt	nonsense

* indicate that the patients included two tumors.

Table 2

No pathogenic genes mutations in 11 patients with 11 cancers

Gene	Mutation	Age at diagnosis	Family history	Mutation type
<i>BRIP1</i>	chr17:59938867C>A	75	Sister	missense
<i>BRCA1</i>	c.154C>T	46	Sister	missense
<i>PALB2</i>	c.3296C>T	43	Sister	missense
<i>ATM</i>	c.8716G>C	47	Sister	missense
	c.275A>C	49	Mother	missense
	c.125A>G	43	Aunt	missense
	c.8495G>A	38	Mother	missense
<i>CDH1</i>	c.1888C>G	45	Sister	missense
<i>MSH2</i>	c.970C>T	42	Mother	missense
	c.14C>A	63	Mother	missense
<i>TP53</i>	c.733G>A	32	Mother	missense

Table 3				
Clinico-pathological characteristics of breast cancers carrying or not pathogenic mutations				
Variable	Pathogenic N=17	No Pathogenic N=47	No. of all	P value
Age				
≤40 years	7 (41.2%)	7 (14.9%)	14 (21.9%)	0.039
≥40 years	10 (58.8%)	40 (85.1%)	50 (78.1%)	
Histopathological type				
Ductal carcinoma in situ	1 (5.9%)	7 (14.9%)	8(12.5%)	0.434
Invasive ductal carcinoma	16 (94.1%)	40 (85.1%)	56 (87.5%)	
Tumor size				
T1	8 (47.1)	15 (31.9)	23 (35.9)	0.534
T2	7(41.2)	26 (55.3)	33 (51.6)	
T3	2 (11.8)	6 (12.8)	8 (12.5)	
Node metastasis				
N-	10 (58.8)	34 (72.3)	44 (68.8)	0.365
N+	7 (41.2)	13 (27.7)	20 (31.2)	
Recurrence or Metastasis				
Yes	5 (29.4)	3 (6.4)	8 (12.5)	0.014
No	12 (70.6)	44 (93.6)	56 (87.5)	
Biologic feature				
unfavorable	10(58.8)	6(12.8)	16(25.0)	0.000
Intermediate/ favorable	7(41.2)	41(87.2)	48(75.0)	
Nuclear grade				
Low/Intermediate	11 (64.7)	43(91.5)	54 (84.4)	0.017
high	6 (35.3)	4 (8.5)	10(15.6)	
ER				
ER-	10 (58.8)	9(19.1)	19 (29.7)	0.004
ER+	7 (41.2)	38 (80.9)	45 (70.3)	
PR				

PR-	10(58.8)	10(21.3)	20(31.2)	0.007
PR+	7(41.2)	37 (78.7)	44 (68.8)	
HER2				
HER2-	13 (76.5)	29 (61.7)	42 (65.6)	0.375
HER2+	4 (23.5)	18 (38.3)	22 (34.4)	
p53				
p53-	5 (29.4)	24 (51.1)	29 (45.3)	0.160
p53+	12 (70.6)	23 (48.9)	35 (54.7)	
Ki67				
Ki67-	1 (5.9)	13 (27.7)	14 (21.9)	0.057
Ki67+	16 (94.1)	34 (72.3)	50 (78.1)	
Molecular subtype				
Luminal A	3 (17.6)	15 (31.9)	18 (28.1)	0.000
Luminal B	5 (29.5)	24 (51.1)	29 (45.3)	
HER2 over-expression	0 (0.0)	5 (10.6)	5 (7.8)	
Triple negative	9 (52.9)	3 (6.4)	12 (18.8)	
Triple negative				
No	8 (47.1)	44 (93.6)	52 (81.2)	0.000
Yes	9 (52.9)	3 (6.4)	12 (18.8)	

Table 4

Radiologic Features of breast cancers carrying or not pathogenic mutations

Variable	Pathogenic N=17	No Pathogenic N=47	No. of all	Pvalue
MG				
Breast density				
Dense	1(5.9)	17(36.2)	18(28.1)	0.025
Non-dense	16(94.1)	30(63.8)	46(71.9)	
Lesion type				
Calcification	3 (17.6)	5 (10.6)	8 (12.5)	0.722
Mass	7 (41.2)	19 (40.4)	26 (40.6)	
Asymmetry/ Distortion	7(41.2)	23 (48.9)	30 (46.9)	
MRI				
Lesion type				
Mass	17(100.0)	37 (78.7)	54 (84.4)	0.038
Nonmass	0(0.0)	10 (21.3)	10 (15.6)	
Internal enhancement pattern				
Heterogeneous mass-enhancement	4 (23.5)	30 (63.8)	34 (53.2)	0.000
Rim mass-enhancement	13 (76.5)	7 (14.9)	20 (31.2)	
Line/segmental nonmass-enhancement	0 (0.0%)	10 (21.3)	10 (15.6)	
Shape				
Regular	6 (35.3)	10 (21.3)	16 (25.0)	0.253
Irregular	11 (64.7)	37 (78.7)	48 (75.0)	
Spiculated margin				
Yes	0 (0.0)	16 (34.0)	16 (25.0)	0.005
No	17 (100.0)	31 (66.0)	48 (75.0)	
Central necrosis				
Yes	6 (35.3)	4 (8.5)	10 (15.6)	0.009
No	11 (64.7)	43 (91.5)	54 (84.4)	
Peritumoral edema				

Yes	4 (23.5)	10 (21.3)	14 (21.9)	0.847
No	13 (76.5)	37 (78.7)	50 (78.1)	
Tumor localization				
Edge	14 (82.4)	36 (76.6)	50 (78.1)	0.623
Central	3 (17.6)	11 (23.4)	11 (21.9)	

Table 5

Clinico-pathological characteristics of breast cancers with or not recurrence or metastasis

Variable	Recurrence or Metastasis N=8	No Recurrence or Metastasis N=56	No. of all	Pvalue
Age				
≤40 years	3 (37.5)	11 (19.6)	14 (21.9)	0.253
≥40 years	5 (62.5)	45 (80.4)	50 (78.1)	
Histopathological type				
Ductal carcinoma in situ	1 (12.5)	7 (87.5)	8(12.5)	1.000
Invasive ductal carcinoma	7 (12.5)	49 (87.5)	56 (87.5)	
Tumor size				
T1	2 (25.0)	21 (37.5)	23 (35.9)	0.073
T2	3 (37.5)	30 (53.6)	33 (51.6)	
T3	3 (37.5)	5 (8.9)	8 (12.5)	
Node metastatic				
N-	5 (62.5)	39 (69.6)	44 (68.8)	0.683
N+	3 (37.5)	17 (30.4)	20 (31.2)	
Biologic feature				
unfavorable	4(50.0)	12(21.4)	16(25.0)	0.081
Intermediate/ favorable	4(50.0)	44(78.6)	48(75.0)	
Nuclear grade				
Low/Intermediate	4 (50.0)	50(89.3)	54 (84.4)	0.004
high	4 (50.0)	6 (10.7)	10(15.6)	
ER				

ER-	5 (62.5)	14 (25.0)	19 (29.7)	0.030
ER+	3 (37.5)	42 (75.0)	45 (70.3)	
PR				
PR-	5 (62.5)	15 (26.8)	20 (31.2)	0.041
PR+	3 (37.5)	41 (73.2)	44 (68.8)	
HER2				
HER2-	7 (87.5)	35 (62.5)	42 (65.6)	0.164
HER2+	1 (12.5)	21 (37.5)	22 (34.4)	
p53				
p53-	1 (12.5)	28 (50.0)	29 (45.3)	0.046
p53+	7 (87.5)	28 (50.0)	35 (54.7)	
Ki67				
Ki67-	0 (0.0)	14 (25.0)	14 (21.9)	0.110
Ki67+	8(100.0)	42 (75.0)	50 (78.1)	
Molecular subtype				
Luminal A	0 (0.0)	18 (32.1)	18 (28.1)	0.052
Luminal B	3 (37.5)	26 (46.4)	29 (45.3)	
HER2 over-expression	1 (12.5)	4 (7.2)	5 (7.8)	
Triple negative	4 (50.0)	8 (14.3)	12 (18.8)	
Triple negative				
No	4 (50.0)	48 (85.7)	52 (81.2)	0.015
Yes	4 (50.0)	8 (14.3)	12 (18.8)	

Table 6

Radiologic Features of breast cancers with or not recurrence or metastasis

Variable	Recurrence or Metastasis N=8	No Recurrence or Metastasis N=56	No. of all	Pvalue
MG				
Breast density				
Dense	1 (12.5)	17 (30.4)	18(28.1)	0.293
Non-dense	7 (87.5)	39 (69.6)	46(71.9)	
Lesion type				
Calcification	1 (12.5)	7 (12.5)	8 (12.5)	0.831
Mass	3 (37.5)	22 (39.3)	26 (40.6)	
Asymmetry/ Distortion	4 (50.0)	27 (48.2)	30 (46.9)	
MRI				
Lesion type				
Mass	6(75.0)	48 (85.7)	54 (84.4)	0.435
Nonmass	2(25.0)	8 (14.3)	10 (15.6)	
Internal enhancement pattern				
Heterogeneous mass-enhancement	1 (12.5)	33 (58.9)	34 (53.1)	0.045
Rim mass-enhancement	5 (62.5)	15 (26.8)	20 (31.2)	
Line/segmental nonmass-enhancement	2 (25.0)	8 (14.3)	10 (15.6)	
Shape				
Regular	4 (50.0)	12 (21.4)	16 (25.0)	0.081
Irregular	4 (50.0)	44 (78.6)	48 (75.0)	
Spiculated margin				
Yes	0 (0.0)	16 (28.6)	16	0.081

			(25.0)	
No	8 (100.0)	40 (71.4)	48 (75.0)	
Central necrosis				
Yes	6(75.0)	4 (7.1)	10 (15.6)	0.000
No	2(25.0)	52 (92.9)	54 (84.4)	
Peritumoral edema				
Yes	3 (37.5)	11 (19.6)	14 (21.9)	0.253
No	5 (62.5)	45 (80.4)	50 (78.1)	
Tumor localization				
Edge	6 (75.0)	44 (78.6)	50 (78.1)	0.819
Central	2 (25.0)	12 (21.4)	14 (21.9)	

Table 7

Multiple logistic regression analysis predicting pathogenic mutation and recurrence or metastasis on breast cancers

Variable	Odds ratio	95%CI	Pvalue
<i>Pathogenic mutations</i>			
Age			
<40 years	Reference	NA	0.418
≥40 years	0.914	0.736-1.134	
Recurrence or Metastasis			
No	Reference	NA	0.039
Yes	1.402	1.024-1.916	
Biologic feature			
unfavorable	Reference	NA	0.000
Intermediate/ favorable	0.409	0.259-0.647	
Nuclear grade			
Low/Intermediate	Reference	NA	0.045
high	0.736	0.551-0.986	
ER			
ER+	Reference	NA	0.416
ER-	1.368	0.646-2.896	
PR			
PR+	Reference	NA	0.304
PR-	1.399	0.742-2.642	
Molecular subtype			
Non-Triple negative	Reference	NA	0.634
Triple negative	1.099	0.721-1.676	
Breast density			
Non-dense	Reference	NA	0.005
Dense	1.315	1.093-1.582	
MRI Lesion type			
Nonmass	Reference	NA	0.000
Mass	1.315	1.093-1.582	

Mass	2.705	1.739-4.207	
Internal enhancement pattern			
Other enhancement types	Reference	NA	0.004
Rim mass-enhancement	1.404	1.121-1.758	
Spiculated margin			
Yes	Reference	NA	0.049
No	0.803	0.649-0.994	
Central necrosis			
No	Reference	NA	0.388
Yes	0.875	0.649-1.181	
Recurrence or metastasis			
Nuclear grade			
Low/Intermediate	Reference	NA	0.056
high	1.242	0.998-1.544	
ER			
ER+	Reference	NA	0.888
ER-	1.042	0.590-1.839	
PR			
PR+	Reference	NA	0.920
PR-	0.973	0.573-1.653	
p53			
p53-	Reference	NA	0.348
p53+	1.069	0.930-1.230	
Molecular subtype			
Non-Triple negative	Reference	NA	0.498
Triple negative	0.909	0.691-1.196	
Internal enhancement pattern			
Other enhancement types	Reference	NA	0.439
Rim mass-enhancement	1.037	0.946-1.138	
Central necrosis			
No	Reference	NA	0.000

Figures

Figure 1

Distribution of the 16 susceptibility mutations in 64 breast carcinomas. Genes not shown (*PTEN*, *STK11*, *CHEK2*, *BARD1*, *MLH1*, *MRE11A*) are those without identified mutations in the study cohort.

Figure 2

Receiver operating characteristic curves used to predict pathogenic mutation with clinico-pathologic and radiologic features

Figure 3

Receiver operating characteristic curves used to predict recurrence or metastasis with clinico-pathologic and radiologic features alone (Model I) and combined with signs significantly associated with pathogenic mutation (Model II)

Figure 4

A 29-year-old woman with *BRCA1* mutation. (A) An axial fat-suppressed T2-weighted magnetic resonance image demonstrated central necrosis. (B) An axial contrast-enhanced T1-weighted magnetic resonance image demonstrated rim enhancement. (C and D) This patient experienced brain metastasis after 5 years from the date of surgery. Axial contrast-enhanced T1-weighted images demonstrated multiple lesions showing rim enhancement.