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A Cross-Sectional Observational Study to Compare the Role of Ultrasound with Mammography in Women Identified at High Risk for Breast Cancer in a Population in China

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCF **Peili An**
BCF **Shujuan Zhong**
ACF **Rong Zhang**
ABC **Xiaoxia Hou**
ADF **Ruru Xi**
CEF **Yingjin Wang**

Medical Ultrasound Center, Northwest Women's and Children's Hospital, Xi'an, Shaanxi, P.R. China

Corresponding Author: Yingjin Wang, e-mail: 736509037@qq.com
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Background: Currently, there is no national breast cancer screening program in China. In countries that have screening programs, screening mammography is used. This study aimed to compare the imaging parameters and diagnostic findings between ultrasound and mammography in women at high risk who had a histologically confirmed diagnosis of breast cancer in a population in China.


Material/Methods: A cross-sectional observational study included 1,687 women with a risk score of ≥ 30 , according to the cancer risk assessment model, who underwent breast ultrasound and mammography. Women who had a Breast Imaging-Reporting and Data System (BI-RADS) score of 4 or 5 were identified, and 155 women had breast cancer confirmed by breast biopsy and histology. The ultrasound and mammography findings were evaluated and compared.

Results: Breast ultrasound resulted in significantly fewer inconclusive results (BI-RADS score, 0), when compared with mammography ($p=0.046$). In cases with a histologically confirmed diagnosis of breast cancer (BI-RADS score, 4), the diagnostic sensitivity of breast ultrasound and mammography were 0.989 and 0.859, respectively. In cases with a histologically confirmed diagnosis of breast cancer (BI-RADS score, 5), the diagnostic sensitivity of breast ultrasound and mammography were 1.000 and 0.984, respectively. In cases with a histologically confirmed diagnosis of benign breast lesions (BI-RADS score, 2), there was no significant difference between breast ultrasound and mammography.

Conclusions: In a population of women in China, breast ultrasound was a more sensitive diagnostic imaging method for women with high risk BI-RADS 4 and 5 breast lesions.

MeSH Keywords: **Biopsy • Early Detection of Cancer • Histology • Inflammatory Breast Neoplasms • Mammography • Ultrasonography, Doppler**

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Background

Currently, there is no national breast cancer screening program in China. In countries that have screening programs, screening mammography is used. Ultrasound uses high-frequency sound waves to detect abnormalities in the breast, and mammography uses X-rays. During the last two decades, the incidence of breast cancer has increased worldwide [1]. Breast cancer is now the most common cancer in women [2,3], and is the leading cause of cancer-related death in Chinese women [1]. Breast cancer screening of women at 40 years and above reduces mortality from breast cancer by 30–50% [4]. The United States Preventive Services Task Force (USPSTF) recommends screening mammography every two years for women aged between 50–74 years [5].

Mammography is widely used for breast cancer screening [6,7]. However, Chinese women have been reported to have increased breast density with age [3]. Mammography has higher sensitivity for fatty breast tissue and lower sensitivity for dense breast tissue [6]. Also, the peak age for the diagnosis of breast cancer in Chinese women is 45–49 years, which is 10–20 years less than in Caucasian women [1,2]. However, mammography is less effective in younger women compared to older women, due to increased breast density with age [7,8].

The Breast Imaging-Reporting and Data System (BI-RADS) has been developed as a quality assurance and risk assessment method by the American College of Radiologists (ACR). BI-RADS is used in the reporting of breast ultrasound, mammography, and magnetic resonance imaging (MRI). In China, most women are diagnosed with breast cancer from fine-needle aspiration cytology (FNAC) or histology of core needle biopsy of the breast [9]. However, women who present with a palpable breast mass and are diagnosed with breast cancer by cytology or histology are more likely to have distant metastases at diagnosis [10], and to have local recurrence after diagnosis and treatment [11]. Therefore, there is a need for an accurate non-invasive method for the screening of breast cancer in Chinese women. Ultrasound is found to be sensitive for screening of breast cancer in Chinese women who are at high risk of breast cancer on imaging [6]. However, currently, there are no national guidelines for screening breast cancer in China [1,6].

This cross-sectional observational study aimed to compare the imaging parameters and diagnostic findings between ultrasound and mammography in women at high risk of breast cancer in a population in China, in women who had a diagnosis confirmed by breast histopathology.

Material and Methods

Ethical approval and patient consent

The study design and protocol were approved by the Human Ethics Committee of the Northwest Women's and Children's Hospital (Approval number: NWCH/CL/14/19, dated 24th July 2019). The study was conducted according to the legal requirements for human studies in China. The cross-sectional study was designed and conducted according to the strengthening of the reporting of observational studies in epidemiology (STROBE) statement [12], and the 2008 Helsinki Declaration. Informed consent was signed by all participating women or their relatives or their legally authorized person for diagnosis, anesthesia (if required), biopsies, histopathology, radiology, or performing additional diagnostic procedures as part of the study. Personal data and images in all formats were anonymized to ensure patient confidentiality.

Study participants

Between 1st June 2016 to 30th June 2019, a breast cancer screening program was conducted at the Northwest Women's and Children's Hospital, China, and the referring hospitals. A total of 3,579 women completed questionnaires regarding their breast health, their lifestyle, demographical characteristics, clinical conditions, and reproductive history. The risk of breast cancer was assessed using a model that was recommended by the Institutional Review Board, with a risk score that ranged from 0–100 [13]. There were 1,892 women who had a risk score of <30 who were considered to be at low risk for breast cancer. Therefore, these women were excluded from further investigations. There were 1,687 women who were screened with a risk score of 30 or more, and these women were advised to undergo either mammography or breast ultrasound.

Data collection

Data from the clinical questionnaires, mammography, breast ultrasound, and breast biopsy and histopathology were collected from the institutional medical records. The flowchart of the study design is shown in Figure 1. The mean age of women at the time of enrollment into the study was 45.45 years, 55% of women were <50 years, and 20% of women were postmenopausal. The demographic and clinical characteristics and the reproductive history of the women are presented in Table 1.

Mammography

A standard two-view (cranial-caudal and medial-lateral oblique) mammography was performed using Senographe™ Crystal full-field digital mammography (GE Healthcare, Chicago, IL, USA) [3]. The mammographs were reported by radiologists

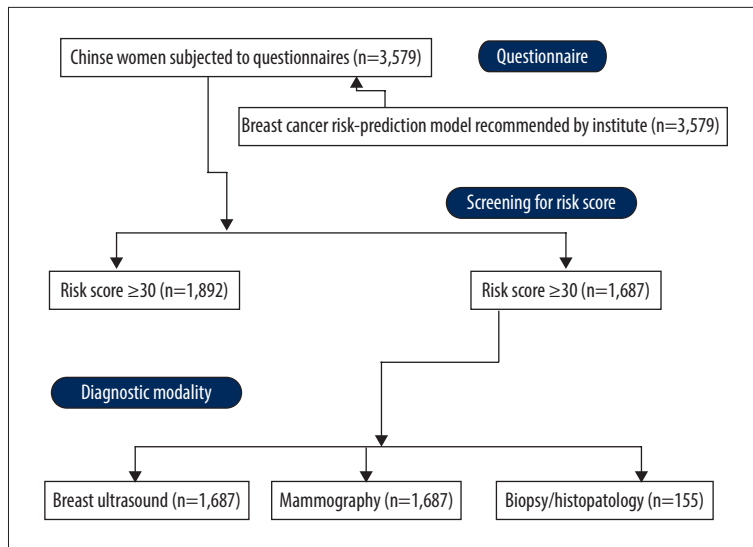


Figure 1. The flowchart of the study design.

Table 1. Questionnaires results of the enrolled women.

Characteristics		Results
Numbers of women enrolled		1,687
Age (years)	Minimum	35
	Maximum	65
	Mean±SD	45.45±7.39
	Body mass index (kg/m ²)	24.89±1.88
Ethnicity	Han Chinese	1,535 (91)
	Mongolian	117 (7)
	Tibetan	19 (1)
	North Korean refuge	16 (1)
Education	Primitive	945 (56)
	Below graduation	456 (27)
	Graduate or more	286 (17)
Marital status	Married	1,152 (68)
	Divorced/widowed	290 (17)
	Unmarried/single	245 (15)
Mental stress*	≤1	201 (12)
	2–5	884 (52)
	6–9	602 (36)

Characteristics		Results
Alcohol habit	Never	1,563 (93)
	Past	82 (5)
	Current	42 (2)
Smoking	Never	1,453 (86)
	Past	135 (8)
	Current	99 (6)
Oral contraceptive used any time in life	Yes	312 (18)
	No	1,375 (82)
Menopausal status	Premenopausal	1,347 (80)
	Postmenopausal	340 (20)
Family history of breast cancer	Yes	162 (10)
	No	1,525 (90)
Risk score**		38.85±3.62

Categorical variables are shown as frequency (percentage) and continuous variables are shown as mean±SD. * 0: minimum and 9: maximum; ** accessed by the breast risk assessment model recommended by the institutional review board.

with a minimum of three years of experience who was unaware of the data in the clinical questionnaires.

Breast ultrasound

Breast ultrasound was performed by color Doppler using a LOGIQ E9 XDclear 2.0 radiology ultrasound system (GE

Healthcare, Chicago, IL, USA) using a 12 MHz XDclear 2.0 transducer (GE Healthcare, Chicago, IL, USA). Transverse and sagittal planes were scanned by ultrasound technologists with a minimum of three years of experience who were unaware of the data in the clinical questionnaires and the mammographic findings [6].

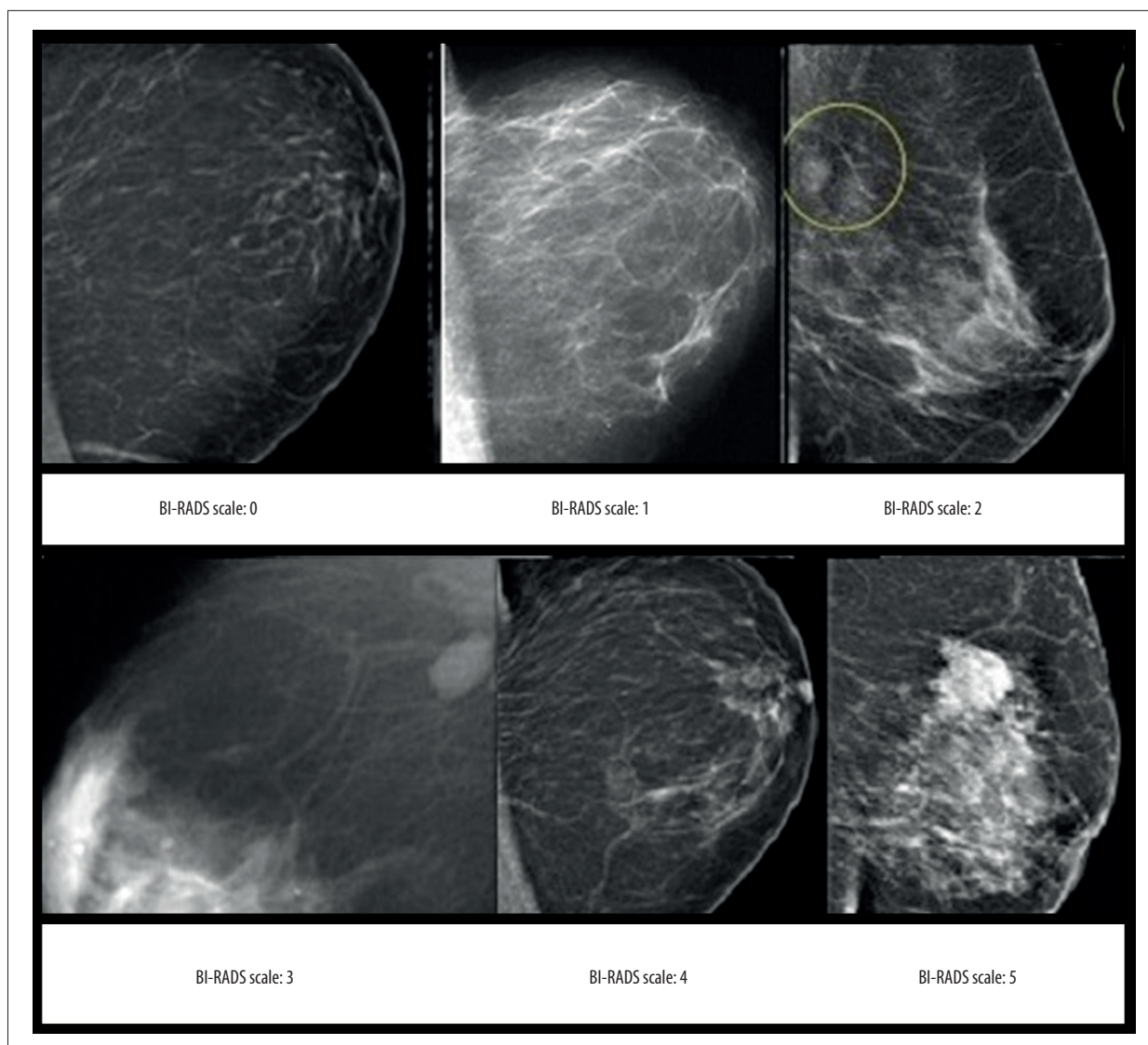


Figure 2. The Breast Imaging-Reporting and Data System (BI-RADS) scores according to the mammography.

Imaging analysis using the Breast Imaging-Reporting and Data System (BI-RADS)

Breast ultrasound and mammographic examinations were interpreted using the Breast Imaging-Reporting and Data System (BI-RADS) using scores between 0–5. BI-RADS 0, inconclusive results requiring further mammography; BI-RADS 1, no areas of architectural distortion, suspicious calcifications, or masses (tumor was absent); BI-RADS 2, simple cysts, secretory calcifications, calcified fibroadenomas, implants, fat-containing lesions, and intramammary lymph nodes (benign tumor); BI-RADS 3, a solitary mass of punctate calcifications, or a circumscribed and non-palpable mass, or focal asymmetry (probably benign); BI-RADS 4, suspicious for malignancy; and BI-RADS 5, highly suggestive of malignancy (Figures 2, 3) [6]. Radiologists and ultrasound technologists had a minimum of

three years of experience and were unaware of the data in the clinical questionnaires.

Breast biopsies

Women with BI-RADS scores of 4 or 5 (Figure 4) underwent breast biopsies and histopathology [8]. Breast sampling was ultrasound-guided using a LOGIQ™ E9 ultrasound system (GE Healthcare, Chicago, IL, USA) for fine-needle aspiration cytology (FNAC), core needle biopsy, using an 18 G biopsy needle (BD Biosciences, Chicago, IL, USA), and excision biopsy. Breast biopsies were performed by physicians with a minimum of three years of experience who were unaware of the data in the clinical questionnaires and the mammographic and ultrasound data [14].

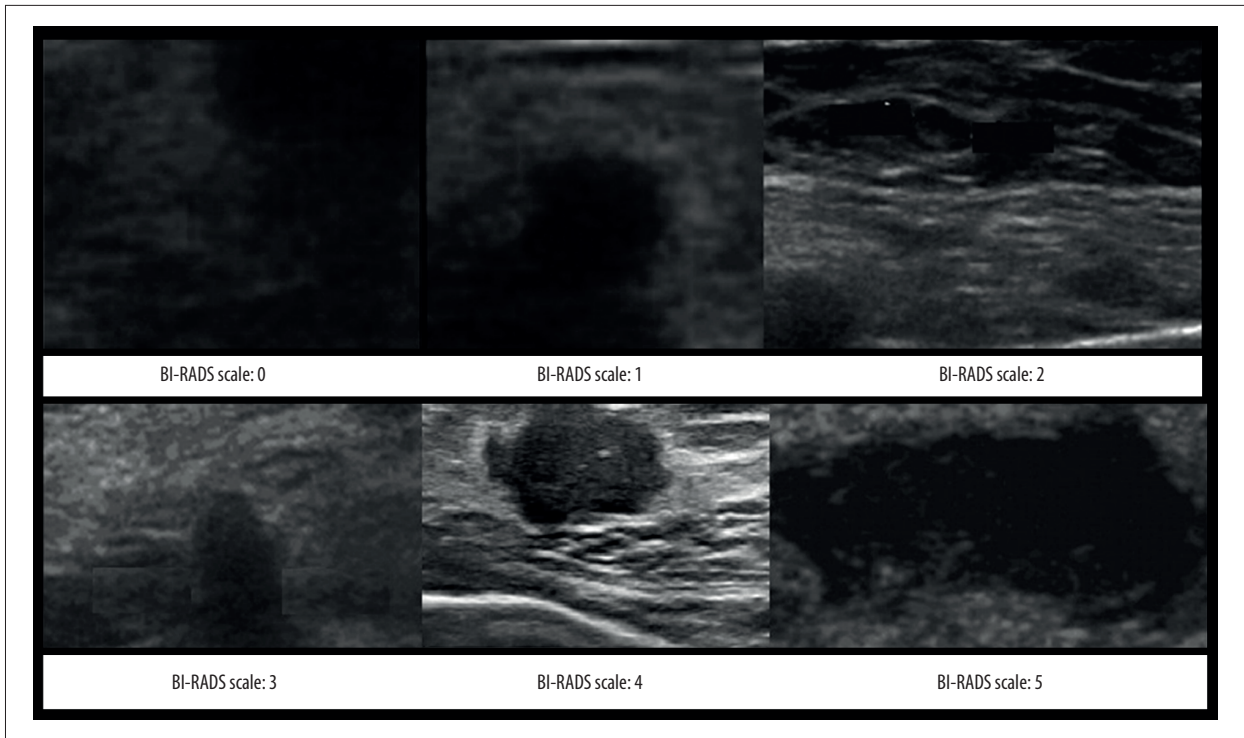


Figure 3. The Breast Imaging-Reporting and Data System (BI-RADS) scores according to the breast ultrasound.

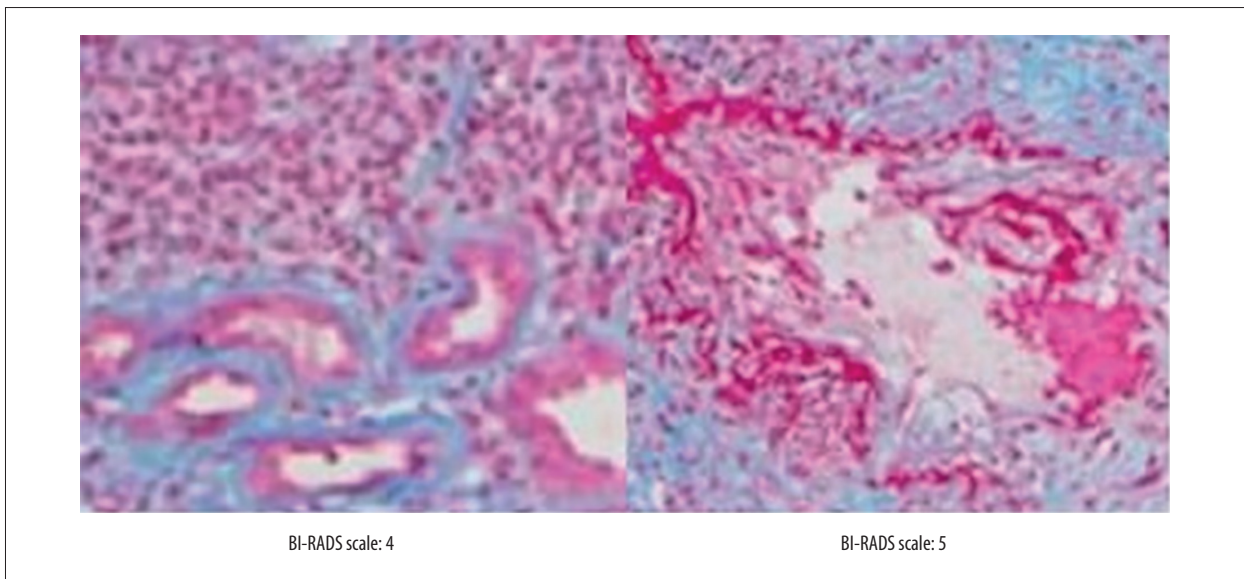


Figure 4. The Breast Imaging-Reporting and Data System (BI-RADS) scores according to the histopathology of the breast biopsies.

Breast histopathology

The histological analysis was performed by histopathologists with a minimum of three years of experience who were unaware of the data in the clinical questionnaires and the mammographic and ultrasound data.

Beneficial score analysis

The beneficial score for each diagnostic modality was evaluated according to Equation 1 of the BI-RADS level of evidence [15]:

$$\text{Beneficial score} = \frac{\text{PCD}}{N} - \left(\frac{\text{NCD}}{N} \times \text{Risk of underdiagnosis} \right) \quad (1)$$

Where,

Table 2. Specification for diagnostic parameters of adopted modalities.

BI-RADS scale	Diagnostic method							Comparisons between mammography and ultrasound	Comparisons between mammography and ultrasound + mammography
	Biopsies/histopathology	Ultrasound		Mammography		Ultrasound + mammography			
Numbers of women enrolled	155	1,687	*p-value	1,687	*p-value	1,687	*p-value	p-value	p-value
0	0 (0)	1,037 (61)	N/A	1,094 (65)**	N/A	945 (56)**	N/A	0.046	<0.0001
1	N/A	201 (12)	N/A	189 (11)	N/A	220 (13)	N/A	0.554	0.114
2	N/A	142 (8)	N/A	115 (7)	N/A	202 (12)**	N/A	0.092	<0.0001
3	N/A	153 (9)	N/A	148 (9)	N/A	165 (10)	N/A	0.809	0.342
4	92 (59)	91 (6)	0.962	79 (5)	0.645	92 (5)	N/A	0.3866	0.346
5	63 (41)	63 (4)		62 (3)		63 (4)	N/A	0.927	0.927

N/A – not applicable. Variables are shown as frequency (percentage). * Comparison with respect to biopsies/histopathology. BI-RADS – The Breast Imaging-Reporting and Data System. 0 – Inconclusive results; 1 – tumor was absent; 2 – benign tumor; 3 – probably benign; 4 – suspicious abnormality; 5 – highly suggestive of malignant. Fischer’s exact test or Chi-square independence test was used for statistical analysis. ** Significant difference with respect to mammography.

$$\text{Risk of underdiagnosis} = \frac{5 - \text{BI-RADS score}}{\text{BI-RADS score}}$$

Where, PCD is the true positive tumor detected; NCD, is the true negative tumor detected; N, is the total number of women included in the analysis.

Cost analysis

Cost data regarding imaging modalities and the biopsies and histopathology were obtained from the medical and institutional records.

Statistical analysis

Data were analyzed using InStat version 3.0 (GraphPad, San Diego, CA, USA). The study sample size was calculated on the basis that the sensitivity of each diagnostic method varied from 50–90% and the maximum missing data was estimated to be 30%. Categorical data were presented as the frequency (number), and continuous data were presented as the mean ± standard deviation (SD). Categorical data were analyzed by Fisher’s exact test or the chi-squared (χ^2) test. Continuous data were analyzed by one-way analysis of variance (ANOVA) following Tukey’s post hoc test, with a critical value (q) >3.25 considered to be significant. Data were considered significant, with a 95% confidence level [6].

Results

Diagnostic parameters

There were 141 women who were reported to have a Breast Imaging-Reporting and Data System (BI-RADS) score of 4 or 5 by mammography, and 155 women were reported to have a BI-RADS score of 4 or 5 by ultrasound. Breast biopsy and histopathology were performed in 155 women and included 98 fine-needle aspiration cytology (FNAC) samples, 32 core needle biopsies, and 25 excision biopsies. Breast ultrasound combined with mammography resulted in fewer inconclusive results (BI-RADS score, 0) than breast ultrasound (p=0.002) and mammography (p<0.0001). Breast ultrasonography resulted in fewer numbers of inconclusive results (BI-RADS score: 0) than mammography (p=0.046). The sensitivity of breast biopsy and histopathology for the detection of BI-RADS score 4 on breast ultrasound, mammography, and breast ultrasound plus mammography were 0.989, 0.859, and 1.000, respectively. The sensitivity of breast biopsy and histopathology for the detection of BI-RADS score 5 on breast ultrasound, mammography, and breast ultrasound plus mammography were 1.000, 0.984, and 1.000, respectively. Breast ultrasound and mammography both had the same specificity (p=0.34). The analysis of imaging and biopsy results are presented in Table 2. The histological diagnosis of breast cancers are presented in Table 3.

Table 3. The histological diagnosis of the breast cancers diagnosed.

Category	Population
Numbers of women	155
Invasive ductal carcinoma	27 (17)
Invasive lobular carcinoma	31 (20)
Ductal carcinoma <i>in-situ</i>	97 (63)

Variables are shown as frequency (percentage).

Beneficial score analysis

For inconclusive results (BI-RADS score, 0), benign lesion or no tumor (BI-RADS score, 1), and highly suggestive of malignancy (BI-RADS score, 5), breast ultrasound and mammography had the same sensitivity. For the detection of benign lesions (BI-RADS score, 2), probably benign tumor (BI-RADS score, 3), and suspicious for malignancy (BI-RADS score, 4), the sensitivity for the detection of breast cancer was significantly greater for breast ultrasound than mammography. For the detection of benign breast lesions (BI-RADS score, 2), there was a

significant difference between breast ultrasound and mammography (Figure 5). When breast ultrasound combined with mammography was considered as a reference standard, there was a significant difference between the results predicted by breast ultrasound and mammography ($p < 0.0001$) (Table 4).

Cost analysis

Breast ultrasound (75 ± 7 ¥ per patient) had a significantly lower cost than mammography (210 ± 15 ¥/patient; $p < 0.0001$; $q = 86.255$) and biopsy and histopathology (315 ± 35 ¥/patient, $p < 0.0001$, $q = 153.34$) (Figure 6).

Discussion

This study reported fewer numbers of inconclusive results for breast ultrasonography than mammography. Breast biopsy and histopathology had a sensitivity for the detection of Breast Imaging-Reporting and Data System (BI-RADS) scores of 4 and 5 tumors, which was significantly higher for breast ultrasound than mammography. The study results were consistent with a previously reported multicenter randomized trial

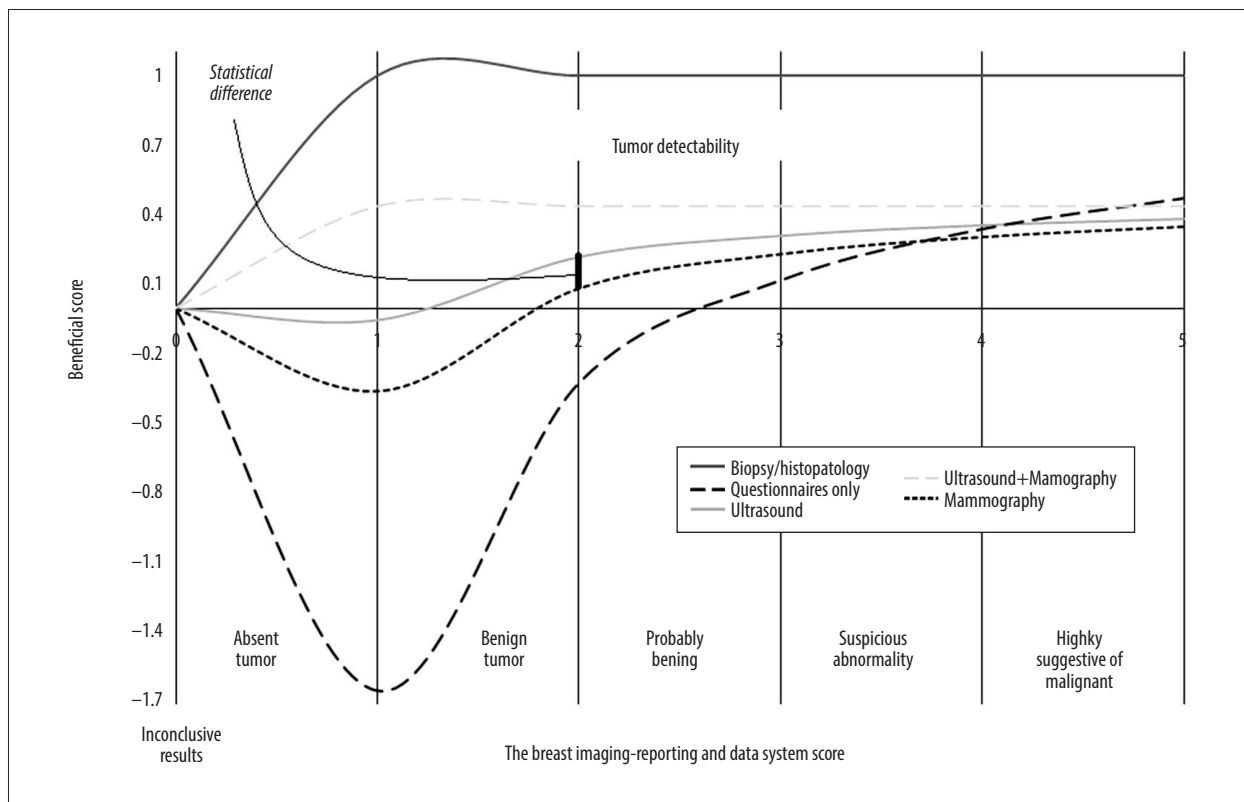


Figure 5. The beneficial score analysis. Physicians performed the biopsies. Pathologists performed the histological analysis. Radiologists performed the mammography. Ultrasound technologists performed breast ultrasound. All had a minimum of three years of experience. 0, inconclusive results; 1, tumor was absent; 2, benign tumor; 3, probably benign; 4, suspicious abnormality; 5, highly suggestive of malignancy.

Table 4. Data of diagnostic parameters used in the analysis.

Diagnostic modality		Numbers of women used for analysis	True positive detected*	True negative detected**
Biopsy/histopathology		155	155***	0
Breast ultrasound	Value	1687	650	184
	#p-value	N/A	0.002	<0.0001
Mammography	Value	1687	593	298
	#p-value	N/A	<0.0001	<0.0001
Questionnaires only	Value	3579	1687	1893
	#p-value	N/A	0.035	<0.0001
Breast ultrasound+mammography	Value	1687	742	0

Data are presented as frequency. * BI-RADS score: 2 to 5; ** BI-RADS score: 1; *** BI-RADS score: 4 or 5. # With reference to breast ultrasound+mammography results. N/A – not applicable. The Chi-square independence or Fischer exact test was performed for the statistical analysis. A $p < 0.05$ was considered as significant.

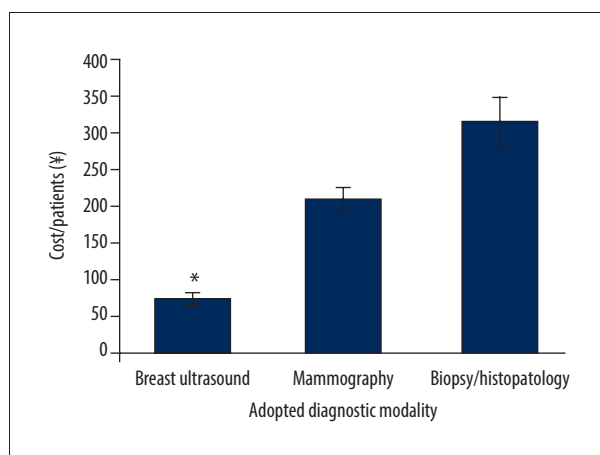


Figure 6. Cost analysis of the diagnosis. Data are presented as the mean±standard deviation (SD). Data were analyzed by one-way analysis of variance (ANOVA) following Tukey's post hoc test. A $p < 0.05$ and $q > 3.25$ were considered significant. * Significantly lower than mammography and biopsy/histopathology.

of Chinese women [6] and a previously published retrospective cross-sectional study [16]. The low sensitivity of mammography may be due to the increased breast density of Chinese women [3], the younger age of the women enrolled in this study, and fewer postmenopausal women who had breast glandular tissue replaced by fat [6]. There has been previously reported to be an inverse relationship between age and breast density [8]. However, ultrasound scans of the breast are less affected by age [6]. The findings from the present study support that breast ultrasonography has a higher sensitivity than mammography in Chinese women.

Comparatively high numbers of inconclusive results, with a BI-RADS score of 0, were reported by both imaging modalities, and the results of the present study were consistent with these findings from breast cancer screening programs of Chinese women [6,16]. This study program for early detection of breast cancer included women who volunteered for the study who may or may not have required further imaging methods. There are several models available for breast cancer risk assessment. For example, the Claus model and extended formula and tables, the Gail model, the Gail-2 model, the BOADICEA model of the genetic susceptibility to breast cancer, the Jonker model, and the Tyrer-Cuzick model [13]. Therefore, there is a need to establish a suitable national breast cancer risk-prediction model in China to reduce inconclusive results.

In this study, for the detection of benign breast tumors (BI-RADS score, 2), breast ultrasound had a significantly higher detection rate than mammography. Ultrasound has previously been shown to have high specificity for the detection of malignant and benign lesions of the breast [15]. In premenopausal Chinese women, increased glandular breast tissue affects the mammographic findings [8], and mammography has a higher risk of overdiagnosis [17]. Breast cancer screening has a recognized limitation of underdiagnosis because life-threatening breast cancers may not be diagnosed easily with a single imaging modality [18]. Breast ultrasound may be the best diagnostic modality for the detection of slow-growing tumors in Chinese women, which have a better prognosis than the faster-growing tumors that women may identify by self-examination of the breasts.

The findings from the present study showed that breast ultrasound had the least cost for breast cancer screening, which

was consistent with previous studies on breast cancer screening programs in China [6,16]. The cost factor is an important part of the screening of cancer in developing countries [6]. Digital mammography is more expensive than conventional mammography and breast ultrasound [4]. In China, a higher percentage of women do not participate in breast cancer screening programs because of family needs, financial issues, and social inconvenience [6]. Ultrasonography is more convenient for the screening of breast cancer in Chinese women compared with mammography.

The study has several limitations. This study was of short duration, and there was a lack of patient follow-up to determine survival data. Women with a low risk of breast cancer were excluded from the program, which may have affected the performance of the diagnostic imaging modalities. The women's demographic and clinical conditions also are recognized to have effects on the results of imaging modalities [3]. The study did not evaluate the effects of demographic and clinical parameters on the results of the imaging modalities. Breast biopsy and histopathology were performed in only 155 women, and the observational period of the study was short.

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Conclusions

This study aimed to compare the imaging parameters and diagnostic findings between ultrasound and mammography in women at high risk who had a histologically confirmed diagnosis of breast cancer in a population in China. Women who had a Breast Imaging-Reporting and Data System (BI-RADS) score of 4 or 5 were identified and 155 women had breast cancer confirmed by breast biopsy and histology. Breast ultrasound was a more sensitive diagnostic imaging method for women with high risk BI-RADS 4 and 5 breast lesions.

Acknowledgments

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Conflict of interest

None.