

# A multicenter hospital-based diagnosis study of automated breast ultrasound system in detecting breast cancer among Chinese women

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## Abstract

**Objective:** The automated breast ultrasound system (ABUS) is a potential method for breast cancer detection; however, its diagnostic performance remains unclear. We conducted a hospital-based multicenter diagnostic study to evaluate the clinical performance of the ABUS for breast cancer detection by comparing it to handheld ultrasound (HHUS) and mammography (MG).

**Methods:** Eligible participants underwent HHUS and ABUS testing; women aged 40–69 years additionally underwent MG. Images were interpreted using the Breast Imaging Reporting and Data System (BI-RADS). Women in the BI-RADS categories 1–2 were considered negative. Women classified as BI-RADS 3 underwent magnetic resonance imaging to distinguish true- and false-negative results. Core aspiration or surgical biopsy was performed in women classified as BI-RADS 4–5, followed by a pathological diagnosis. Kappa values and agreement rates were calculated between ABUS, HHUS and MG.

**Results:** A total of 1,973 women were included in the final analysis. Of these, 1,353 (68.6%) and 620 (31.4%) were classified as BI-RADS categories 1–3 and 4–5, respectively. In the older age group, the agreement rate and Kappa value between the ABUS and HHUS were 94.0% and 0.860 ( $P < 0.001$ ), respectively; they were 89.2% and 0.735 ( $P < 0.001$ ) between the ABUS and MG, respectively. Regarding consistency between imaging and pathology results, 78.6% of women classified as BI-RADS 4–5 based on the ABUS were diagnosed with precancerous lesions or cancer; which was 7.2% higher than that of women based on HHUS. For BI-RADS 1–2, the false-negative rates of the ABUS and HHUS were almost identical and were much lower than those of MG.

**Conclusions:** We observed a good diagnostic reliability for the ABUS. Considering its performance for breast cancer detection in women with high-density breasts and its lower operator dependence, the ABUS is a promising option for breast cancer detection in China.

**Keywords:** Automated breast ultrasound system; breast neoplasms; China

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## Introduction

The global burden of breast cancer is high and continues to increase, with an estimated 1.67 million new diagnoses and 0.52 million deaths in 2017 (1). Although North America and Europe remain the regions with the highest incidence of breast cancer worldwide, the largest contributors to the global burden are East and South Asia, including countries such as China and India (2,3). In these regions, a high proportion of women present with an advanced stage of the disease, leading to a poor prognosis (3-5).

Early detection and treatment of breast cancer, which can be achieved by the clinical diagnosis of symptomatic breast cancer and by screening asymptomatic women, can reduce mortality and other severe consequences of advanced-stage disease. Substantial evidence from extensive high-quality observational studies and randomized controlled trials (RCTs) has shown that mammography (MG)-based screening can decrease mortality by detecting breast cancer during the early stage (6,7). Although MG is widely used in Western countries for breast cancer screening, its performance declines among young women because of its low sensitivity and the exposure to radiation. More importantly, its performance is lower among women with heterogeneously dense (50%–74% dense tissue) or extremely dense ( $\geq 75\%$  dense tissue) breasts. Previous studies reported that having dense breasts is a risk factor for breast cancer (8-10). Chinese women, like other Asian women, typically have smaller and denser breasts than Caucasian women (4). Meanwhile, their average age at the diagnosis of breast cancer is approximately ten years younger than that of Western women (4). Thus, MG may not be the optimal breast cancer screening test for Chinese women.

Recent studies found that handheld ultrasound (HHUS) can detect small and node-negative breast cancer in young women and in those with dense breasts (11). Compared to MG, HHUS is non-invasive, non-radioactive, and inexpensive, making it an attractive method for breast cancer detection. At present, HHUS is regarded as a supplemental tool to MG in the United States and other Western countries. In some Asian countries, such as China and Japan, ultrasound is the primary tool for breast cancer screening in women with denser breasts due to its lower cost, even though evidence showing its effectiveness is inadequate (12,13). The diagnostic accuracy of HHUS heavily depends on the operators' ability of image acquiring and interpretation, which constrains its broad applications in developing countries.

In recent years, the automated breast ultrasound system (ABUS), an emerging and promising technology for the clinical diagnosis of breast cancer in women, has received increasing attention (14,15). Compared to HHUS, the ABUS depends less on the operator for image selection and his/her ability of image interpretation as it allows radiologists to review the entire dataset and to interpret the images remotely. A study conducted in the United States showed that adding the ABUS to MG screening in women with heterogeneously and extremely dense breasts contributed to better breast cancer detection (16). However, the diagnostic value of the ABUS alone has not been rigorously evaluated so far. Therefore, we designed a multicenter hospital-based study to evaluate the clinical performance of the ABUS for breast cancer detection in Chinese women.

## Materials and methods

### *Study design and sample size calculations*

This study was a hospital-based multicenter diagnostic research that evaluated the diagnostic performance of the ABUS for breast cancer detection by comparing it to HHUS and MG in Chinese women.

We estimated the sample sizes to ensure that a sufficient number of women with breast cancer were included to evaluate the performance of the ABUS, HHUS and MG. According to estimated sensitivities from previous studies (17,18), a power of 0.8 and non-inferiority value of 0.06, approximately 60 and 188 breast cancer cases were required for the younger (30–39 years) and older (40–69 years) age groups, respectively. Considering the prevalence of breast cancer in China, this study planned to include 450 women aged 30–39 years and 1,050 women aged 40–69 years.

Given a possibly high variability of breast cancer prevalence across hospitals, we defined specific sample sizes for each Breast Imaging Reporting and Data System (BI-RADS) category (19). According to the American College of Radiology (ACR) BI-RADS distribution, the following specific sample size proportions were allocated to the BI-RADS categories: 40%, 35%, 12.5% and 12.5% for BI-RADS categories 1–2, 3, 4 and 5, respectively. Accordingly, the estimated required sample sizes for BI-RADS 1–2, 3, 4 and 5 were 180, 158, 56 and 56 women, respectively, in the younger age group; in the older age group, they were 420, 368, 131 and 131 women, respectively.

**Participants**

This study was conducted at five high-level tertiary hospitals in China between February 2016 and March 2017. The hospitals included the Cancer Hospital, Chinese Academy of Medical Sciences in Beijing (BJ), Sun Yat-sen University Cancer Center in Guangzhou (GZ), Tianjin Medical University Cancer Institute and Hospital (TJ), Xin Hua Hospital in Shanghai (SH), and First People’s Hospital of Hangzhou (HZ).

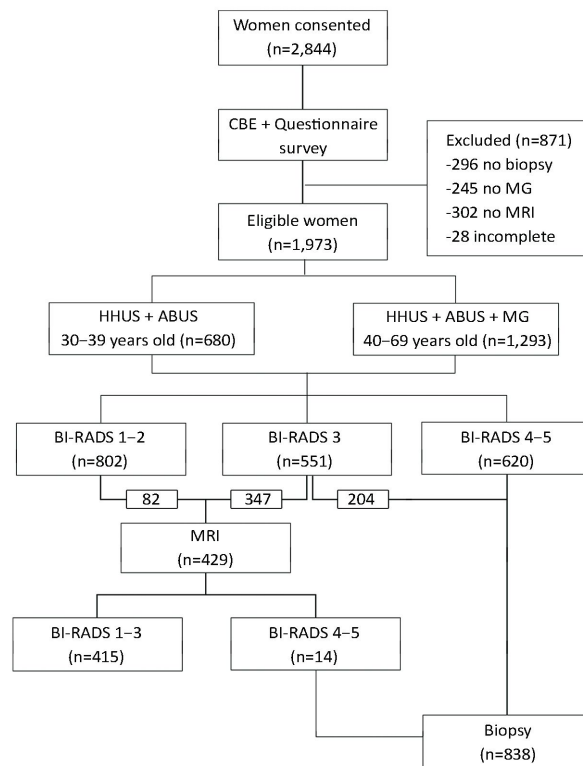
Female outpatients who visited these hospitals with breast-related complaints were proportionally selected and included in this study. We excluded women aged <30 and ≥ 70 years. We also excluded those who had previously received a diagnosis of or treatment for breast cancer; had undergone surgical or percutaneous breast procedures in the past 12 months; had a history of lumpectomy, contra-lateral mastectomy, or breast augmentation; and those who were currently pregnant, breastfeeding, or planning to become pregnant.

The study was approved by the institutional review board of the Cancer Institute, Chinese Academy of Medical Sciences (IRB approval number 15-061/988) and the institutional review boards of all participating hospitals. Informed consent was obtained from all study participants.

**Flow of the study**

One-on-one questionnaire interviews including items on the participants’ sociodemographic characteristics and potential breast cancer risk factors were conducted by trained healthcare staff. Then, all enrolled participants underwent successive HHUS and ABUS examinations. The women in the older age group also underwent MG; those in the younger age group did not undergo MG due to concerns of radiation (20,21) (Figure 1).

According to the ACR BI-RADS classification system, the BI-RADS assessment results for HHUS, ABUS and MG were classified into 6 categories: 0 = incomplete, 1 = normal, 2 = benign, 3 = probably benign, 4 = suspicious, and 5 = highly suggestive of malignancy. In this study, the highest BI-RADS result among HHUS, ABUS and MG was selected as the referral reference for further magnetic resonance imaging (MRI) and/or biopsy testing (e.g., if a woman was classified as BI-RADS categories 1, 2, and 4 by HHUS, ABUS and MG, respectively, she was classified as BI-RADS category 4). Women categorized as BI-RADS 3 underwent MRI or biopsy to distinguish true-negative and false-negative results. For BI-RADS categories 1 and 2, no



**Figure 1** Study flowchart.

referral was provided, based on the expectation that 10% of these women were randomly selected for an MRI examination. For women with BI-RADS categories 4 or 5, core aspiration or surgical biopsy was performed, and a pathological diagnosis was made.

We also assessed the MRI-based BI-RADS categories. Women with BI-RADS categories 1–3 in the MRI were considered negative. Those with MRI-based BI-RADS categories 4–5 underwent a biopsy and pathological diagnosis.

**ABUS, HHUS and MG**

The ABUS (Invenia ABUS, GE Healthcare, Sunnyvale, CA, USA) is a computer-based system for evaluating the complete breast. Each breast was imaged in three views: lateral (LAT), anteroposterior (AP), and medial (MED), with an automated 6–14 MHz linear array transducer attached to a rigid compression plate (covering areas of 15.4 cm × 17.0 cm × 5.0 cm). Each view acquired up to about 300 2D images and reconstructed the breast in the coronal plane, from the skin to the chest wall. The standardized review process involves using a patented thick-slice coronal plane for quick navigation through the

breast and the use of the “survey mode”, which is similar to cine and allows the radiologist to rapidly interpret many images. The acquisition time for each view was approximately 60 seconds, with about 3 to 4 min per breast.

According to the clinical routine, HHUS was performed in the supine position by board-certified radiologists who were experienced in breast imaging. The devices used for the examinations included the GE LOGIQ9 (GE Medical Systems, Milwaukee, WI, USA), Aixplorer system (Supersonic Imagine, Aix en Provence, France), iU22 Ultrasound System (Philips Medical Systems, Bothell, WA, USA), and s2000 (Siemens Medical Solutions, Mountain View, CA, USA).

The devices used for obtaining MG images included the GE Sengraphe DS (GE Medical Systems, Milwaukee, WI, USA), Hologic Selenia (Hologic, Bedford, MA, USA), and Fujifilm FDR MS-2500 (Fujifilm Corp, Tokyo, Japan). All procedures strictly followed the clinical routine.

### Statistical analysis

Double entry checks using EpiData version 3.1 (EpiData Association, Odense, Denmark) were independently conducted by each of the five hospitals. The Cancer Hospital, Chinese Academy of Medical Sciences was responsible for qualifying and pooling the collected data from the five hospitals into the final dataset. To exclude verification bias, the biopsy results were considered as the gold standard for the diagnostic outcome. Women with no biopsy results who tested negative in all available tests were deemed to be true negatives in this study.

The distributions of the BI-RADS categories and pathology result are shown as specific numbers and proportions. The participants' sociodemographic characteristics are described using means and standard deviations for continuous variables and percentages for categorical variables. Differences in sociodemographic characteristics by BI-RADS categories (1–3 vs. 4–5) and between malignant and benign findings were compared using the chi-square test for categorical variables and the Student's *t*-test for continuous variables. Kappa coefficients test was calculated to compare the diagnostic results among the ABUS, HHUS and MG.

SPSS software (Version 17.0; SPSS Inc., Chicago, IL, USA) was used to perform all statistical analyses. Statistical significance was assessed by two-tailed tests with an  $\alpha$  level of 0.05.

## Results

A total of 2,844 women were recruited, all of whom signed a written informed consent form at 1 of the 5 hospitals. Of these, 296 were excluded because they declined a biopsy. In the older age group, 245 women were excluded because they declined to undergo MG. We also excluded 302 women with BI-RADS category 3 because they refused to undergo MRI or biopsy and 28 women with incomplete information. Therefore, the sample size for the final analysis included 1,973 women (375, 542, 315, 325 and 416 from the BJ, GZ, TJ, SH and HZ, respectively).

Of the 1,973 women that were included in the final analysis, 680 were in the younger age group (30–39 years) and therefore underwent both HHUS and ABUS testing. The remaining 1,293 women were in the older age group (40–69 years); thus, they underwent HHUS, ABUS and MG testing. Based on the BI-RADS results, 429 women underwent further MRI examinations, and 838 women had a biopsy. The distribution of the BI-RADS results confirmed that the sample size of this study had enough power to compare the performances of HHUS, ABUS and MG.

### Participant characteristics

The mean age of the 1,973 participants was  $45.4 \pm 9.7$  years. The majority (1,432/1,973; 72.6%) of the women had a normal body mass index (BMI). Of all women, 75.7% (959/1,267) had heterogeneously dense or extremely dense breasts, 71.8% (1,416/1,973) were pre-menopausal, and 81.1% (1,600/1,973) had breastfed. Furthermore, 92.8% (1,831/1,973), 90.5% (1,786/1,973), 97.1% (1,916/1,973), and 90.7% (1,789/1,973) of the women never used oral contraceptives, had no family history of breast cancer, and had no smoking history, and had no history of alcohol consumption, respectively (*Table 1*).

A total of 1,353 women (68.6%) were classified as BI-RADS categories 1, 2, or 3; they had a mean age of  $44.3 \pm 9.5$  years. In contrast, 620 participants (31.4%) were defined as BI-RADS categories 4 or 5; they had a mean age of  $48.0 \pm 9.8$  years. A total of 417 women (21.1%) women were diagnosed with a malignancy, whereas the remaining 1,556 women (78.9%) women had benign test results (*Table 1*).

We then analyzed the sociodemographic and clinical characteristics of the participants by BI-RADS group (BI-RADS 1–3 vs. BI-RADS 4–5). The proportions of women with overweight and obesity were significantly higher in the BI-RADS 4–5 group than in the BI-RADS 1–3 group ( $P=0.029$ ). We also detected differences for breast density

Table 1 Demographic, clinical and pathological characteristics at enrollment

Characteristics	Total (N=1,973)	BI-RADS category		P	Pathology result		P
		Type 1–3 (n=1,353)	Type 4–5 (n=620)		Malignant (n=417)	Benign (n=1,556)	
Age (year)							
$\bar{x}\pm s$	45.4±9.7	44.3±9.5	48.0±9.8	<0.001	49.4±9.7	44.4±9.5	<0.001
30–39	680 (34.5)	528 (39.0)	152 (24.5)	<0.001	86 (20.6)	594 (38.2)	<0.001
40–69	1,293 (65.5)	825 (61.0)	468 (75.5)		331 (79.4)	962 (61.8)	
BMI (kg/m <sup>2</sup> )							
$\bar{x}\pm s$	23.0±3.1	22.8±3.0	23.4±3.3	<0.001	23.6±3.3	22.9±3.0	<0.001
Under weight (≤18.49)	97 (4.9)	69 (5.1)	28 (4.5)	0.029	16 (3.8)	81 (5.2)	0.023
Normal weight (18.50–24.99)	1,432 (72.6)	1,003 (74.1)	429 (69.2)		287 (68.8)	1,145 (73.6)	
Overweight (25.00–29.99)	392 (19.9)	251 (18.6)	140 (22.6)		97 (23.3)	295 (19.0)	
Obesity (≥30.00)	52 (2.6)	30 (2.2)	23 (3.7)		17 (4.1)	35 (2.2)	
Breast density							
<25%	26/1,267 (2.1)	20/801 (2.5)	6/466 (1.3)	0.022	5/329 (1.5)	21/938 (2.2)	<0.001
25%–50%	282/1,267 (22.3)	168/801 (21.0)	114/466 (24.5)		96/329 (29.2)	186/938 (19.8)	
51%–75%	731/1,267 (57.7)	452/801 (56.4)	278/466 (59.7)		189/329 (57.4)	542/938 (57.8)	
>75%	228/1,267 (18.0)	161/801 (20.1)	68/466 (14.6)		39/329 (11.9)	189/938 (20.1)	
Menopausal status							
Pre-menopausal	1,416 (71.8)	1,026 (75.8)	390 (62.9)	<0.001	238 (57.1)	1,178 (75.7)	<0.001
Menopausal	557 (28.2)	327 (24.2)	230 (37.1)		179 (42.9)	378 (24.3)	
Breastfeeding							
Yes	1,600 (81.1)	1,091 (80.6)	509 (82.1)	0.489	351 (84.2)	1,249 (80.3)	0.109
No	364 (18.4)	255 (18.8)	109 (17.6)		66 (15.8)	298 (19.2)	
Unknown	9 (0.5)	7 (0.5)	2 (0.3)		0 (0)	9 (0.6)	
Use of oral contraceptives							
Yes	137 (6.9)	93 (6.9)	44 (7.1)	0.379	29 (7.0)	108 (6.9)	0.103
No	1,831 (92.8)	1,258 (93.0)	573 (92.4)		385 (92.3)	1,446 (92.9)	
Unknown	5 (0.3)	2 (0.1)	3 (0.5)		3 (0.7)	2 (0.1)	
Family history of breast cancer							
Yes	182 (9.2)	125 (9.2)	57 (9.2)	0.387	41 (9.8)	141 (9.1)	0.517
No	1,786 (90.5)	1,226 (90.6)	560 (90.3)		374 (89.7)	1,412 (90.7)	
Unknown	5 (0.3)	2 (0.1)	3 (0.5)		2 (0.5)	3 (0.2)	
Smoking history							
Never	1,916 (97.1)	1,321 (97.6)	595 (96.0)	0.080	399 (95.7)	1,517 (97.5)	0.128
Used	31 (1.6)	19 (1.4)	12 (1.9)		9 (2.2)	22 (1.4)	
Current	26 (1.3)	13 (1.0)	13 (2.1)		9 (2.2)	17 (1.1)	
Alcohol drinking history							
Never	1,789 (90.7)	1,230 (90.9)	559 (90.2)	0.212	371 (89.0)	1,418 (91.1)	0.195
Used	132 (6.7)	93 (6.9)	39 (6.3)		30 (7.2)	102 (6.6)	
Current	52 (2.6)	30 (2.2)	22 (3.5)		16 (3.8)	36 (2.3)	

BMI, body mass index; BI-RADS, Breast Imaging Reporting and Data System.

( $P=0.022$ ) and menopausal status ( $P<0.001$ ) between the two groups. However, we found no differences for breastfeeding, the use of oral contraceptives, a family history of breast cancer, smoking history, and a history of alcohol consumption (Table 1).

Then, the participants' characteristics were compared by malignant and benign findings. The proportions of women with overweight and obesity ( $P=0.023$ ), dense breasts ( $P<0.001$ ), and those who were menopausal ( $P<0.001$ ) were different among women with malignant findings and in those with benign findings. Again, we found no differences for breastfeeding, the use of oral contraceptives, a family history of breast cancer, smoking history, and a history of alcohol consumption between the two groups (Table 1).

### Agreement rates

Table 2, 3, 4 depict the agreement rates between HHUS, ABUS and MG for the older age group. The agreement rate and Kappa value between the ABUS and HHUS were 94.0% and 0.860 ( $P<0.001$ ), respectively (Table 2). Between the ABUS and MG, they were 89.2% and 0.735 ( $P<0.001$ ), respectively (Table 3). Last, the agreement rate and Kappa value between HHUS and MG were 89.6% and 0.752 ( $P<0.001$ ), respectively (Table 4).

### Pathology results

Almost half of the pathology results were precancerous lesions or cancer in this study. Among them, non-special type invasive carcinoma (NTIC) was the dominant pathologic subtype (316/417; 75.8%), followed by special-type invasive carcinoma (STIC; 40/417; 9.6%), ductal carcinoma *in situ* (DCIS; 38/417; 9.1%), and atypical ductal hyperplasia (ADH; 9/417; 2.2%). Among the subtypes of benign lesions, fibroadenoma (FA) accounted for the highest proportion of diagnoses (218/421; 51.8%) (Table 5).

Table 5 shows the joint distribution of pathology and

**Table 2** Agreement rate between HHUS and ABUS in women aged 40–69 years

ABUS	HHUS		Total	Agreement rate (%)	$\kappa$	P
	Positive	Negative				
Positive	356	19	375			
Negative	58	860	918	94.0	0.860	<0.001
Total	414	879	1,293			

HHUS, handheld ultrasound; ABUS, automated breast ultrasound system; Positive, BI-RADS 4 or BI-RADS 5; Negative, BI-RADS 1, BI-RADS 2 or BI-RADS 3.

**Table 3** Agreement rate between ABUS and MG in women aged 40–69 years

ABUS	MG		Total	Agreement rate (%)	$\kappa$	P
	Positive	Negative				
Positive	299	76	375			
Negative	64	854	918	89.2	0.735	<0.001
Total	363	930	1,293			

ABUS, automated breast ultrasound system; MG, mammography; Positive, BI-RADS 4 or BI-RADS 5; Negative, BI-RADS 1, BI-RADS 2 or BI-RADS 3.

**Table 4** Agreement rate between HHUS and MG in women aged 40–69 years

HHUS	MG		Total	Agreement rate (%)	$\kappa$	P
	Positive	Negative				
Positive	321	93	414			
Negative	42	837	879	89.6	0.752	<0.001
Total	363	930	1,293			

HHUS, handheld ultrasound; MG, mammography; Positive, BI-RADS 4 or BI-RADS 5; Negative, BI-RADS 1, BI-RADS 2 or BI-RADS 3.

diagnostic imaging results, providing essential information on the consistency between testing and pathology results (the gold standard of the diagnostic outcome). For HHUS, 84.0% (21/25) and 93.1% (242/260) of cases classified as BI-RADS 1–2 and BI-RADS-3, respectively, were benign lesions based on pathology. For BI-RADS 4–5, 71.4% (395/553) of the cases had precancerous lesions or cancer. For ABUS, 83.0% (39/47) and 91.4% (278/304) of cases identified as BI-RADS 1–2 and BI-RADS-3, respectively, were benign lesions. For BI-RADS 4–5, 78.6% (383/487) of the cases had precancerous lesions or cancer. For MG, 72.5% (79/109) and 85.7% (96/112) of cases categorized as BI-RADS 1–2 and BI-RADS 3, respectively, were benign lesions. For BI-RADS 4–5, 78.9% (285/361) of the women had precancerous lesions or cancer (Table 5).

### Discussion

This study, to the best of our knowledge, is the first multicenter hospital-based study to evaluate the clinical performance of the ABUS for breast cancer detection by comparing it to HHUS and MG among Chinese women.

MG has been widely used for the early detection of breast cancer worldwide. However, MG has some limitations, including exposure to radiation and a relatively high rate of false-positive results (22–24). More importantly,

Table 5 Joint distribution of pathology results and imaging diagnostic results

Method	Benign lesions [n (%)]					Precancerous lesions or cancer [n (%)]					
	DH	AD	FA	Others	Total	DCIS	ADH	NTIC	STIC	Others	Total
<b>HHUS</b>											
No. 1,2	1 (4.0)	9 (36.0)	6 (24.0)	5 (20.0)	21 (84.0)	1 (4.0)	1 (4.0)	1 (4.0)	0 (0)	1 (4.0)	4 (16.0)
No. 3	11 (4.2)	48 (18.5)	160 (61.5)	23 (8.8)	242 (93.1)	7 (2.7)	5 (1.9)	5 (1.9)	0 (0)	1 (0.4)	18 (6.9)
No. 4,5	7 (1.3)	50 (9.0)	52 (9.4)	49 (8.9)	158 (28.6)	30 (5.4)	3 (0.5)	310 (56.1)	40 (7.2)	12 (2.2)	395 (71.4)
Total	19	107	218	77	421	38	9	316	40	14	417
<b>ABUS</b>											
No. 1,2	2 (4.3)	19 (40.4)	11 (23.4)	7 (14.9)	39 (83.0)	2 (4.3)	1 (2.1)	5 (10.6)	0 (0)	0 (0)	8 (17.0)
No. 3	14 (4.6)	59 (19.4)	170 (55.9)	35 (11.5)	278 (91.4)	4 (1.3)	4 (1.3)	12 (3.9)	3 (1.0)	3 (1.0)	26 (8.6)
No. 4,5	3 (0.6)	29 (6.0)	37 (7.6)	35 (7.2)	104 (21.4)	32 (6.6)	4 (0.8)	299 (61.4)	37 (7.6)	11 (2.3)	383 (78.6)
Total	19	107	218	77	421	38	9	316	40	14	417
<b>MG</b>											
No. 1,2	6 (5.5)	28 (25.7)	34 (31.2)	11 (10.1)	79 (72.5)	3 (2.8)	2 (1.8)	17 (15.6)	4 (3.7)	4 (3.7)	30 (27.5)
No. 3	6 (5.4)	21 (18.8)	58 (51.8)	11 (9.8)	96 (85.7)	2 (1.8)	2 (1.8)	9 (8.0)	0 (0)	3 (2.7)	16 (14.3)
No. 4,5	3 (0.8)	21 (5.8)	26 (7.2)	26 (7.2)	76 (21.1)	21 (5.8)	1 (0.3)	229 (63.4)	28 (7.8)	6 (1.7)	285 (78.9)
Total	15	70	118	48	251	26	5	255	32	13	331

HHUS, handheld ultrasound; ABUS, automated breast ultrasound system; MG, mammography; DH, ductal hyperplasia; AD, adenosis; FA, fibroadenoma; DCIS, ductal carcinoma *in situ*; ADH, atypical ductal hyperplasia; NTIC, non-special type invasive carcinoma; STIC, special-type invasive carcinoma.

its performance is worse in young women and in women with heterogeneously dense or extremely dense breasts, which are highly prevalent among women from Asian countries such as Malaysia, Korea, and China (25-27). Therefore, researchers in these countries have been searching for new methods to substitute MG.

HHUS is the primary tool for breast cancer screening in some Asian countries; however, little evidence has shown its effectiveness and accuracy (13). Moreover, HHUS is operator-dependent and has poor repeatability, constraining its use in developing countries. Recently, researchers have been paying considerable attention to the ABUS because of its good performance in detecting breast cancer in women with high-density breasts and because it is less dependent on the operator than HHUS. These features make the ABUS a promising breast cancer screening tool for women in Asian countries.

The results of this study show that the ABUS had a good diagnostic performance. In the comparisons between the ABUS and HHUS, we found that the results of the ABUS were more in line with the pathology results in the BI-RADS 4-5 groups. Specifically, 78.6% of women who were classified as BI-RADS 4 or 5 based on the ABUS were diagnosed with precancerous lesions or cancer; this was 7.2% higher than the proportion of women who were classified in the same BI-RADS categories based on

HHUS. For the BI-RADS 1-2 group, the false-negative rate of the ABUS was almost identical to that of HHUS. The heterogeneity in the operator skills across the different hospitals of this study might have been the main reason for the inferior performance of HHUS.

The false-negative rate of the ABUS was much lower than that of MG (17.0% vs. 27.5%, respectively), while the detection rates of the ABUS and MG were similar (78.6% vs. 78.9%, respectively). Moreover, the sensitivity and specificity of ABUS were higher than that of MG; ABUS had less false positive findings (high specificity) with a slightly decrease in sensitivity. These findings imply that the ABUS is a promising method for breast cancer detection among women with breast-related complaints. Further studies should determine whether the ABUS can be used in large-scale population-based screening programs in China and other Asian countries.

In this study, we were also able to identify the risk factors for breast cancer in Chinese women. A higher BMI and post-menopausal status were associated with higher BI-RADS scores and malignant findings, while a smoking history and a history of alcohol consumption were not correlated to higher BI-RADS scores or malignant findings. These results are consistent with previous studies on the risk factors of breast cancer among Chinese women (4,28,29) and in agreement with relevant studies from other

Asian countries (30,31). Interestingly, breastfeeding, a family history of breast cancer, and the use of oral contraceptives were not associated with the BI-RADS category in this study; this is inconsistent with previous findings (29-31). The reasons for these differences remain obscure. They might be attributed to the limited sample size of this study or selection bias.

The findings of this study need to be considered in light of its limitations. First, selection bias is possible because the participants were all recruited at high-level hospitals located in well-developed regions in China, which might not be representative of all hospitals across China. Second, 871 women were excluded from this study for different reasons. We cannot do a test to determine whether or not these excluded women have significant difference with women recruited in this study. However, we predefined the proportions of sample sizes according to BI-RADS categories to avoid disproportionate enrollment. We recruited another woman who has the same BI-RADS classification given that one woman did not comply with the study procedure. Hence, we believe that non-compliance is likely to have limited effects on the results of this study. Last, data quality depends on the experience of the radiologists, pathologists, and healthcare staff who interviewed the participants.

## Conclusions

We observed a good reliability for the ABUS when compared to HHUS and MG in our analysis. Considering its reliable performance for detecting breast cancer among women with high-density breasts, its lower operator dependence, and its feasibility (radiologists only require training for a short period to become proficient in lesion interpretation), the ABUS is a promising diagnostic method for detecting breast cancer among large populations in Asian and developing countries such as China.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interests to declare.

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