RESEARCH ARTICLE

Effects of Age, Breast Density and Volume on Breast Cancer Diagnosis: A Retrospective Comparison of Sensitivity of Mammography and Ultrasonography in China's Rural Areas

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Abstract

Purpose: Mammography has been confirmed as the only effective mode to improve the prognosis of patients with breast cancer in Western developed countries, but might not be a good choice in other areas of the world. One of the major challenges in China is to determine an optimal imaging modality for breast cancer screening. This study was designed to clarify the sensitivity of ultrasonography compared with that of mammography in rural China. Methods: We retrospectively studied the sensitivity of mammography and ultrasonography based on 306 breast cancer patients detected by the program of "screening for cervical cancer and breast cancer" performed in Chinese rural areas between January 2009 and December 2011, and analyzed the effects of age, breast density and volume on the sensitivity. Results: Stratified analysis showed that the sensitivity of breast ultrasonography was significantly higher than that of mammography in premenopausal patients (81.4% vs. 61.1%, *p*=0.02), in women ≤ 55 years of age (82.2% vs. 63.4%, *p*<0.01), in the high breast density group (American College of Radiology [ACR] levels 3-4) (85.9% vs. 60.6%, *p*<0.01) and in the small breast volume group (≤400 ml) (87.1% vs. 66.7%, *p*<0.01). Age had a significant effect on sensitivity of mammography (breast density and volume-adjusted odds ratio, 6.39; 95% confidence interval, 2.8-14.4 in age group > 55 compared to age group ≤ 45), but not that of ultrasonography. Neither breast density nor volume had significant effect on sensitivity of mammography or ultrasonography. Conclusions: Ultrasonography is more sensitive than mammography in detecting breast cancer in women under 55 year-old Chinese, especially in those with high-density and relatively small breasts.

Keywords: Breast cancer screening - mammography - ultrasonography - sensitivity - rural China

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Introduction

Breast cancer is one of the most common malignancies in women, and is second only to lung cancer as a cause of cancer death in the United States (Jemal et al., 2010). The survival rate of patients with breast cancer keeps improving with the development of early detection and comprehensive treatment in recent years. The 5-year survival rate of early breast cancer has ascended to nearly 95%, while the prognosis of advanced patients is poor with the survival rate less than 30% (Etzioni et al., 2003). In the absence of effective primary prevention measures, screening and early detection of breast cancer has been an important way to reduce the mortality rate and prolong patients' life. In China, the widely adopted measures for breast cancer screening are mammography (MG) and breast ultrasonography (BUS).

Breast screening based on mammography in the developed countries has been confirmed as a cost-effective way to reduce the death rate of breast cancer (Humphrey et al., 2002; Nemec et al., 2007). Although mammography is the most commonly used imaging modality for breast screening, its effectiveness may be reduced in women with dense breasts and its sensitivity is poor for young women (Moss, 1999; Sardanelli et al., 2004; Berg et al., 2008).

Breast cancer has been one of the most common cancers and the fourth-leading cause of cancer death among women in China (Yang et al., 2005; Yang et al., 2006). As compared with cases in some western countries, patients with breast cancer in Asia including China have their unique epidemiological characteristics and physiological features. For example, there are more patients diagnosed at the younger age, and the density of mammary tissue is higher (Fan et al., 2009; Lee et al., 2009; Han et al., 2011; Li et al., 2011). This leads to the controversy on the application of mammography.

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Moreover, patients always concern about the radiation exposure and its high cost. Therefore, ultrasonography, an alternative imaging modality is also widely used in China, especially in rural areas.

It has been widely reported that ultrasonography is more sensitive than mammography in breast cancer diagnosis (Kang et al., 2007; Huang et al., 2012; Lehman et al., 2012; Ya-Jie et al., 2012). Although the specificity of mammography is higher than that of ultrasonography (Birdwell, 2009), in the view of breast cancer screening, the higher sensitivity is more beneficial for early diagnosis of breast cancer. Mammography or ultrasonography, which one is the best choice for breast cancer screening in China has gained much more concerns. Since 2009, the Ministry of Health of China initiated a program of "screening for cervical cancer and breast cancer" in rural areas. In Nanjing city of Jiangsu province, some rural areas have thus been involved. We provide mammogram and ultrasonography service for women in this program. Patients with suspected cancers are ultimately diagnosed at Nanjing Maternity and Child Health Care Hospital.

Based on the data from this program, we performed a retrospective study: to compare the sensitivity of mammography and ultrasonography; to analyze the effects of menstrual status, age, breast density and volume on the sensitivity; and to establish an optimal strategy of breast cancer screening under relatively poor economic conditions, and thus to provide evidence for screening of breast cancer in China's rural areas.

Materials and Methods

Between January 2009 and December 2011, 306 breast cancer patients were detected by the program of "screening for cervical cancer and breast cancer". All patients have accepted mammography and ultrasonography before treatment and been confirmed with pathological evidence.

The mammography device was manufactured by Siemens Co. Ltd. All mammographic examinations were read by two imaging experts using blind method, respectively. The imaging interpretation was based on the American College of Radiology (ACR) BI-RADS (Breast Imaging Reporting and Data System) lexicon (D'Orsi et al., 2003). The total breast density was classified into ACR level 1 to 4 referring to the following criteria (D'Orsi et al., 2003): level 1, almost entirely fatty; level 2, scattered fibroglandular densities; level 3, heterogeneously dense; and level 4, extremely dense. Mammographic density of ACR levels 1–2 were defined as low density, and levels 3–4 were defined as high density. We measured the volume of the breast using the following formula proposed by Kalbhen et al (1999), which had been demonstrated in previous studies (Kayar et al., 2011): breast volume $=\pi/4 \times(W\times H\times C)$, where W=breast width, H=breast height, and C=compression thickness in craniocaudal mammography. Breast width, height and compression thickness were all measured on the craniocaudal mammogram by the computer.

We used color Doppler ultrasonography device (made by ESAOTE, Italy) in ultrasonographic examinations. The probe frequency was 10-18 Hz. The ultrasonographic examinations were performed by board-certified radiographers and classified by the latest ACR BI-RADS US standard.

According to ACR BI-RADS Category for grading probability of malignancy in mammographic and ultrasonographic findings, BI-RADS Categories 1-3 indicate negative with benign or probably benign findings, and BI-RADS Categories 4-5 indicate positive which requires a tissue diagnosis (D'Orsi et al., 2003).

After informed consent, a brief interview was performed and patient's clinical and histopathological data were collected. SPSS software (version 18.0, Chicago, IL) was used for the statistical analysis. Chi-squared test was used for stratified comparison of the sensitivity between MG and BUS. Logistic regression was used to analyze the effect of age, breast density and volume on the sensitivity of MG and BUS, respectively. All reported p values were two-sided. P value less than 0.05 was set as the threshold for significance. All confidence intervals (CIs) are reported at the 95% level.

Results

Characteristics of the patients

Of the 306 cases, 169(55.2%) cases were premenopausal and 137(44.8%) were postmenopausal at the time of cancer diagnosis. The age of the patients ranged from 22 to 78, with the mean age of 51 years. Among them, 246(80.4%) cases were invasive ductal carcinoma (IDC),

Table 1. Participants' Characteristics

Characteristics	N(%)
Age	
≤45	101(33.0%)
45-55	103(33.7%)
>55	102(33.3%)
Menstrual status	
Premenopausal	169(55.2%)
Postmenopausal	137(44.8%)
Pathology	
IDC	246(80.4%)
ILC	14(4.6%)
DCIS	26(8.5%)
Others	20(6.5%)
Tumor size(cm)	
≤2	160(52.3%)
2-5	140(45.8%)
>5	6(2.0%)
Breast Density[a]	
ACR1	14(4.6%)
ACR2	41(13.4%)
ACR3	190(62.1%)
ACR4	61(19.9%)
Breast Volume(ml)	
≤400	94(30.7%)
400-800	174(56.9%)
>800	38(12.4%)

IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ; ILC, invasive lobular carcinomas; ACR, American College of Radiology; [a]Breast density is classified into 4 levels: ACR 1, almost entirely fatty; ACR 2, scattered fibroglandular densities; ACR 3, heterogeneously dense; ACR 4, extremely dense

Table 2. The Stratified Analysis of Sensitivity of MG and BUS According to Menstrual Status, Age, Density and Volume of Breast

Method		BUS	MG		Total	P Value
			- [a]	+ [b]		
Menstrual Status	Premenopausal	-	18	13	31(18.6%)	0.02
		+	47	89	136(81.4%)	
		Total	65(38.9%)	102(61.1%)	167(100%)	
	Postmenopausal	-	2	15	17(12.4%)	0.79
		+	17	103	120(85.6%)	
		Total	19(13.9%)	118(86.1%)	137(100%)	
Age(year)	≤45	-	10	4	14(14.1%)	<0.01
		+	29	56	85(85.9%)	
		Total	39(39.4%)	60(60.6%)	99(100%)	
	45-55	-	9	13	22(21.4%)	0.05
		+	26	55	81(78.6%)	
		Total	35(34.0%)	68(66.0%)	103(100%)	
	>55	-	1	11	12(11.8%)	0.82
		+	9	81	90(88.2%)	
		Total	10(9.8%)	92(90.2%)	102(100%)	
Breast Density	Low[c]	-	3	7	10(18.2%)	1.00
		+	8	37	45(81.8%)	
		Total	11(20.0%)	44(80.0%)	55(100%)	
	High[d]	-	17	21	38(15.3%)	<0.01
		+	56	155	211(84.7%)	
		Total	73(29.3%)	176(70.7%)	249(100%)	
Breast Volume(ml)	≤400	-	8	4	12(12.9%)	<0.01
		+	23	58	81(87.1%)	
		Total	31(33.3%)	62(66.6%)	93(100%)	
	400-800	-	11	19	30(17.3%)	0.05
		+	34	109	143(82.7%)	
		Total	45(26.0%)	128(74.0%)	173(100%)	
	>800	-	1	5	6(15.8%)	0.77
		+	7	25	32(84.2%)	
		Total	8(21.1%)	30(78.9%)	38(100%)	

BUS, breast ultrasonography; MG, mammography; ACR, American College of Radiology; BI-RADS, Breast Imaging-Reporting and Data System; [a]Negative, BI-RADS 1-3; [b]Positive, BI-RADS 4-5; [c]Low density group, ACR1-2; [d]High density group, ACR3-4

26(8.5%) were ductal carcinoma in situ (DCIS), 14(4.6%) were invasive lobular carcinoma (ILC), and 20(6.5%) cases had other pathological features including medullary carcinoma, mucinous carcinoma, basal-like breast cancer, Paget's disease, metaplastic carcinoma, invasive micropapillary carcinoma, solid papillary carcinoma, intracystic papillary carcinoma and lobular carcinoma in situ. The average tumor size was 23mm (range 5–100 mm). As showed in Table 1, 14(4.6%) cases were classified as ACR level 1; 41(13.4%) were level 2; 190(62.1%) were level 3; and 61(19.9%) were level 4. The average breast volume of the 306 cases was 528.9 ml (range134.4-1342.8 ml), in which 94(30.7%) were ≤ 400 ml, 174(56.9%) were 400-800 ml, and 38(12.4%) were > 800 ml. The clinical data of all the patients are shown in Table 1.

The comparison of sensitivity between BUS and MG

We excluded two patients who did not take MG preoperatively. The overall sensitivities of BUS and MG were 84.2% and 72.4%, respectively. The sensitivity of BUS was significantly higher than that of MG in premenopausal patients (81.4% vs. 61.1%, p=0.02), while no difference was observed in postmenopausal cases (85.6% vs. 86.1%, p=0.79). In women ≤ 45 years of age, BUS was remarkably more sensitive compared to MG (85.9% vs. 60.6%, p<0.01); in women aged 45-55 years, BUS was slightly more sensitive than MG (78.6% vs. 66.0%, p=0. 05). After combining the two subgroups, we found that BUS still remained more sensitive than MG (82.2% vs. 63.4%, p<0.01). However, in women >55 years, the sensitivity of BUS was slightly lower than MG (88.2% vs. 90.2%, p=0.82). In patients with high breast parenchymal density (ACR levels 3-4), BUS was markedly more sensitive than MG (84.7% vs. 70.7%, p<0.01), while in low density group, no difference was observed (81.8% vs. 80.0%, p=1.00). Take breast volume into consideration, the sensitivity of BUS was remarkably higher than that of MG in large breast group (>800 ml) (87.1% vs. 66.7%, p<0.01), while no difference was observed in small breast group (≤400 ml) and medium volume group (400-800 ml) (Table 2).

Factors associated with the sensitivity of BUS and MG

We analyzed the effects of age, density as well as breast volume on the sensitivity of BUS and MG by multivariate analysis with odds ratios (ORs) as indicators of effect. The crude ORs of age, density and volume have been adjusted for both of the other two variables.

Sensitivity of BUS increased as the growth of age. The adjusted OR of sensitivity of BUS was 1.57(95%, CI 0.67-3.71) in women aged > 55 years compared to that in women aged ≤ 45 years, but without statistical

Table 3. Crude and Adjusted ORs with 95% CI of Positive Findings by BUS and MG According to Age, Density and Volume of Breast

Method		BUS		MG	
		Crude OR (95 % CI)	Adjusted OR (95 % CI)	Crude OR (95 % CI)	Adjusted OR (95 % CI)
Age	≤45	1	1	1	1
	45-55	0.69 (0.34-1.41)	0.71 (0.35-1.45)	1.26 (0.71-2.24)	1.25 (0.71-2.23)
	>55	1.41 (0.63-3.16)	1.57 (0.67-3.71)	5.98 (2.78-12.88)	6.39 (2.83-14.43)
Breast Density[a]	ACR1	1	1	1	1
	ACR2	0.27 (0.03-2.38)	0.4 (0.05-3.67)	0.24 (0.03-2.06)	0.45 (0.05-4.05)
	ACR3	0.4 (0.05-3.13)	0.83 (0.09-7.42)	0.18 (0.02-1.43)	0.61 (0.07-5.30)
	ACR4	0.44 (0.05-3.83)	0.97 (0.10-9.63)	0.2 (0.02-1.61)	0.71 (0.08-6.60)
Breast Volume(ml)	≤400	1	1	1	1
	400-800	0.74 (0.37-1.50)	0.74 (0.36-1.50)	1.42 (0.82-2.46)	1.43 (0.81-2.53)
	>800	0.86 (0.30-2.45)	0.86 (0.30-2.46)	1.88 (0.77-4.57)	1.98 (0.80-4.94)

BUS, breast ultrasonography; MG, mammography; OR, odds ratio; 95% CI, 95% confidence interval; ACR, American College of Radiology; [a]Breast density is classified into 4 levels: ACR 1, almost entirely fatty; ACR 2, scattered fibroglandular densities; ACR 3, heterogeneously dense; ACR 4, extremely dense

significance. BUS was less sensitive as breast density increased. The adjusted OR of sensitivity of BUS was 0.97 (95%, CI 0.10-9.63) in patients with high-density breast compared with that in those with low-density breast. In addition, sensitivity of BUS declined as breast volume increased. The adjusted OR for sensitivity of BUS was 0.86 (95%, CI 0.30-2.46) in large breast group (>800 ml) and 0.74 (95%, CI 0.36-1.50) in medium volume group (400-800 ml), as compared with that in small breast group (≤400 ml). None of the three variables had a statistically significant effect on the sensitivity of BUS.

The effects of age and density on sensitivity of MG were parallel to that on sensitivity of BUS, respectively. Sensitivity of MG also increased as the growth of age. The adjusted OR of sensitivity of MG was 6.39 (95%, CI 2.83-14.43) in the oldest age group (>55) and 1.25 (95%, CI 0.71-2.23) in the middle age group (45-55) compared to that in the youngest age group (≤45). Similar to BUS, sensitivity of MG also decreased as the density of breast parenchyma increased. The adjusted OR for sensitivity of MG was 0.71 (95%, CI 0.08-6.60) in patients with high-density breasts compared with that in those with low-density breasts. The breast volume had a reverse effect on sensitivity of MG compared to that on sensitivity of BUS. Sensitivity of MG slightly improved with the increase of breast volume. The adjusted OR of sensitivity of MG was 1.98 (95%, CI 0.80-4.94) in large breast group (>800 ml) and 1.43 (95%, CI 0.81-2.53) in medium volume breast group (400-800 ml) compared to that in small breast group (≤400 ml).

The effect of age on the sensitivity of MG remained statistically significant when we adjusted for both the density and volume of the breast. Other two variables, breast density or volume, had no significant effect on sensitivity of MG (Table 3).

Discussion

The incidence of breast cancer in women has been rapidly increasing in Asia (Matsuno et al., 2007; Lin et al., 2009). Mammographic screening has a significant effect to decrease breast cancer mortality. However, recommendations for breast cancer screening with mammography have become increasingly controversial (Nelson et al., 2009; US Preventive Services Task Force, 2009; Lee et al., 2010). Our study demonstrated that mammography was less sensitive than ultrasonography in detecting breast cancer, especially in women under 55 year-old, and those with high-density and relatively small breasts. We are considering ultrasonography could also be an important option for breast cancer screening in China.

The financial appropriation for health care in China was deficient in the past ten years. According to the international convention, expenditure on health care shall account for at least 15% of the aggregate expenditure of the government. The proportion of China was only 10.3% in 2009 and the average expenditure for one person is less than $100 each year which is greatly lower than that in other countries (Lu et al., 2005; Lu et al., 2010). Rural areas cover the majority areas in China, which have even much less resources. For physicians in rural areas of China, we face challenges to deal with breast cancer screening with so limited resources. To find out a practical method for breast cancer screening in China is becoming critical.

Mammography has been widely accepted as a primary examination for breast cancer screening in western developed countries. Randomized clinical trials have demonstrated that screening mammography lowers the death rate of breast cancer (Humphrey et al., 2002; Nemec et al., 2007), with a reported overall sensitivity of about 75% (Carney et al., 2003). In our study, the overall sensitivity of mammography was 72.4%. Stratified analysis showed that it ascended to 80.0% in low-density breasts, 86.1% in postmenopausal women and 90.2% in women older than 55 years of age, showing its superiority in old women with fatty breasts. Furthermore, mammography provides an overall view of the breast and facilitates for contrast of the bilateral breasts especially in women with relatively large breasts. However, Chinese patients have their unique physiological features: relatively smaller breasts with denser breast tissue, and an earlier age (before menopause) to contract breast cancer (Fan et al., 2009; Han et al., 2011), as compared to women with breast cancer in western countries. Our data revealed that the mean age of the 306 cases was 51 years, the average breast volume was 528.9 ml, and patients with high-density breast tissue accounted for 82%, which further confirmed Chinese patients' different physiological and epidemiological characteristics from women in western countries. Stratified analysis indicated that the sensitivity of mammography declined to 70.7% in high-density breasts, 61.1% in premenopausal women and 60.6% in women younger than 45 years, suggesting that mammography might not be an optimal choice for screening in Chinese women.

Additionally, the observation from our clinical practice was also consistent with our data in research: breast masses and calcifications could be easily identified on mammography in breasts with low density, while most signs such as focal asymmetry or even masses were hardly observed in high-density breasts or young women except calcification. Low sensitivity of mammography was also partially due to low incidence of intraductal carcinoma (8.49%) in China, which presented with microcalcifications and could only be detected by mammography (Cheng et al., 2000).

Ultrasonography is also one of the most commonly used methods to detect breast cancer. Three biggest advantages for the method are: firstly, the cost is only half of that of mammography; secondly, it has the ability to monitor the shape, size, border and blood flow situation of the tumors dynamically that are occult on mammography; finally, high accuracy, especially with the development of instruments and more widespread use by experienced physicians. Ultrasonography has become a routine diagnostic tool for breast cancer in China.

Several factors have been identified that profoundly affect the sensitivity of ultrasonography and mammography including: age, breast density and volume. Age is an independent factor to influence the sensitivity of imaging examinations. Ultrasonography has been previously found to be more sensitive than mammography in detecting breast cancer in patients under 40 in a U.S. population (Lehman et al., 2012). Our data showed that ultrasonography was markedly more effective than mammography in diagnosis for most Chinese patients who are under 55 years of age. The difference in sensitivity between the two imaging modalities in the population under 55 year-old may be related to the basic features such as small and dense breasts of Chinese women. In women with dense breasts, ultrasonography was significantly superior to mammography in terms of diagnostic accuracy, which was also confirmed by other investigators (Pediconi et al., 2009). Dense breast tissue may be difficult for X-ray to penetrate during mammographic examination and thus limit the sensitivity of mammography. For patients with small breasts (<400 ml), we found that ultrasonography was remarkably more sensitive than mammography. It may have the advantage of avoiding missing the lesions located on the edge or in the deep of the breast which may hardly be included in mammogram. In all, our data demonstrated that ultrasonography was more sensitive than mammography in women less than 55 year-old, especially in those with high-density and small breasts.

Non-mammographic screening methods, particularly ultrasonography, have supplemented mammography to compensate for the limitations of mammographic screening (Kuhl et al., 2005). There is a trend in China that ultrasonography is becoming widely used for breast cancer screening because it is a relatively simple, convenient and cost-effective imaging method. Therefore, it is specifically suitable for breast cancer screening in rural areas in China.

The joint detection of mammography and ultrasonography can further improve the diagnostic sensitivity. Our results indicated that the combination of mammography and ultrasonography had substantially higher sensitivity than mammography or ultrasonography alone. It is suggested that we should take "ultrasonography + selective mammography" for premenopausal women and "mammography + selective ultrasonography" for postmenopausal women as a screening mode for breast cancer in China's rural areas. For joint detection, cost is the major concern. Whether ultrasonography will replace mammography as the first-line screening tool needs further study.

One limitation for this study is that our samples are all from breast cancer patients only. The specificity of the study would be discussed in the following study, for the false positive cases were diagnosed at the out-patient department.

In addition, we should take a second-look of ultrasonography if mammography shows positive findings while the lesion is not detected on the initial ultrasonography. When mammography shows negative while the lesion is observed by ultrasonography, we need to read the mammogram once again. Clinical physicians should re-evaluate the mammography and ultrasonography outcomes combined with physical examination before surgical biopsy.

To sum up, ultrasonography is more sensitive than mammography in detecting breast cancer in Chinese women under 55 year-old, especially in those with high-density and relatively small breasts. Considering its low cost and convenience, ultrasonography is feasible for breast cancer screening in China's rural areas.

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