

Application of Breast Ultrasound in a Mammography-Based Chinese Breast Screening Study

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Abstract We evaluated the clinical significance of the combined use of mammography + ultrasound as a new breast screening strategy. The inclusion criteria were: (1) females aged >40yrs; (2) breast cancer diagnosis by the breast image screening personnel at FUSCC; (3) screening by both ultrasound and mammography; (4) mammographic/sonographic images analyzed independently by different radiologists; and (5) follow-up for at least 1 year. Fifty-four women were enrolled. The analysis included diagnostic sensitivity of mammography, ultrasound, and mammography + ultrasound. The sensitivities of mammography and mammography + ultrasound were compared overall as well as among different age groups/breast densities. The screening sensitivity of mammography, ultrasound, and mammography + ultrasound was 79.6, 57.4, and 92.6 %, respectively. The difference between mammography and mammography + ultrasound was significant ($P < 0.05$). The benefit of including ultrasound with mammography as a new breast image screening strategy was found statistically significant in patients with dense breast on mammogram while it was non-significant in younger (<50 years) women. We, therefore, concluded that mammography + ultrasound increased the diagnostic sensitivity of breast screening; hence it was more desirable for women with dense breast on mammography.

Keywords Mammography · Ultrasound · Breast cancer · Screening

Introduction

Breast cancer is one of the most common malignant tumors among women worldwide, especially in the western countries [1, 2]. However, the incidence of breast cancer has increased dramatically in the urban areas of developing countries over the past decade [3]. This is especially noticeable in Shanghai where the incidence of breast cancer has surpassed that of all other cancers in China [4].

Mammography screening has been under scrutiny in the developed countries. With the fast-pace development in sonographic technology over the past few years, its use as a supplementary imaging procedure to mammography has been documented in several studies [5–7]. Chinese women generally have small dense breasts. Most breast cancer patients are premenopausal females. The cases without calcification lesions and classic morphology are prone to be overlooked in mammography. If included as a supplementary screening strategy, the ultrasound can make up for such outcomes of mammography [8]. Furthermore, ultrasound is an economic, simple, safe, non-invasive, and painless imaging screening method. Kolb et al. [9] reported that only 48 % of breast cancer cases could be diagnosed by mammography alone, and that the diagnostic sensitivity could be raised to 97 % if mammography and ultrasound were used together for screening.

In the present study, we analyzed the data regarding breast screening performed at the Fudan University Shanghai Cancer Center (FUSCC) and evaluated the diagnostic sensitivity of the combined use of mammography and ultrasound for breast imaging screening.

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Patients and Methods

Screening Projects and Study Population

An Employee Breast Screening Project (EBSP) was launched in August 2005 which organized the employees of several enterprises to undergo breast screening at FUSCC. The ages of the population were requested to be over 35 years. These individuals were subjected to mammography screening during the period from 1 to 1.5 years. The population could choose from the options of clinical breast examination (CBE) and ultrasound. There were three imaging screening strategies adopted as follows: mammography + ultrasound + CBE, mammography + CBE, or mammography alone. The Shanghai Society-based Breast Screening Project (SBSP) was launched in May 2008 which organized residents in a community to participate in breast screening program at the FUSCC. The population with ages from 35 to 74 years was subjected to CBE. The imaging population of age groups 35–44, 45–69, and 70–74 years, having high risk factors or CBE with suspiciously palpable mass in breast underwent three cycles of free combo-examination by mammography + ultrasound. The three cycles of this imaging strategy were scheduled to be repeated in the following 6 years.

Inclusion Criteria

The women who wished to be enrolled in the screening project were explained the study and asked to sign the informed consent forms. The study was approved by the institutional ethics committee (Approval #: 20080460-5). Inclusion criteria were as follows: (1) the EBSP-selected breast cancer cases were diagnosed during the time period from August 2005 to August 2008 while the SBSP-selected cases were diagnosed in the time period from May 2008 to February 2011; (2) the females were aged over 40 years; (3) the blinding method was applied at baseline evaluation and both mammography and ultrasound were performed at the same time. In the blinding method used, the mammo-radiologist and the ultrasound (US) operator completed their imaging reports separately and were unaware of each other's report; and (4) follow-up for at least 1 year.

Overall, 18 breast cancer cases were found in enterprise screening and 16 of the 18 cases met with the inclusion criteria of the study; 40 breast cancer cases were found in community screening and 38 of the 40 cases met with the inclusion criteria of the study. Thus, a total of 54 breast cancer cases were enrolled in this study.

Imaging Examination and Evaluation

All imaging screening was performed at the Breast Diagnostic Center in FUSCC. This center has staff facilities

comprising of surgeons, physicians, radiologists, and pathologists.

In digital mammography (GE, 2000DTM (SD) or LORAD), exposure controls of mammography units were set at 25 kV with film density between 1.6 and 1.8D and daily calibration. Lateral image of each breast was obtained on two films (CC and MLO). The data were digitally stored and backed-up once a year. A multidisciplinary team was involved to enhance the quality assurance standards. The mammogram films of each patient were read independently by two radiologists whereby each radiologist interpreted the films on high-resolution screen (BARCO) and were unaware of the interpretation made by other radiologist. The interpretation was based on three categories including breast density (low, average, high, very high) and description of the lesion (mass, calcification, dense shadow, structure distortion), following the Breast Imaging Reporting and Data System (BI-RADS) guidelines of the American College of Radiology (ACR) [10]. The diagnosis was based on the recommendations by ACR BI-RADS [10]. ACR BI-RADS breast densities were defined as follows: (1) low-ACR I: almost entirely fat (low density, up to 25 % mammary gland parenchyma); (2) average-ACR II: scattered fibroglandular densities (average density, 26–50 % gland parenchyma); (3) high-ACR III: heterogeneously dense (high density, 51–75 % gland parenchyma); and (4) very high-ACR IV: extremely dense (very high density, more than 75 % gland parenchyma).

In Doppler sonography, images with high-frequency transducers at 7.5–10 MHz were obtained by two ultrasound operators who did both the scanning and interpreting. The scanning region and body position were according to the guidelines of FUSCC. Specifically, the guidelines required ultrasound operators to scan in vertical and horizontal parallel stripes covering the breast, axillary tail, and areola region so that each side of the entire breast volume was scanned twice. Axillary region was routinely scanned regardless of whether there was a significant abnormality in the ipsilateral breast. The daily workload of each ultrasound operator was restricted to fewer than forty cases and average time per case was at least 5 min to guarantee the screening quality. There were images taken of concerning lesions. The diagnosis was based on ACR BI-RADS [10]. The mammo-radiologist and the ultrasound operator completed respective imaging reports independently of each other and were blinded to each other's report.

Statistical Analysis

Statistical analyses were performed using SPSS software (version 15.0, SPSS Inc, Chicago, IL, USA). The diagnostic sensitivities of three imaging screening methods (mammography alone, ultrasound alone, and mammography

combined with ultrasound) were calculated. The diagnostic sensitivity of a method was defined as the percentage of malignant cases determined by the screening method among the total malignant cases diagnosed. The difference of diagnostic sensitivity between breast mammography alone and mammography combined with ultrasound was analyzed by χ^2 test, and Fisher's exact test was performed when the χ^2 test was unavailable. Furthermore, the differences of two screening methods were analyzed among the various age groups (less than 50 years and 50 years or over) and breast density groups (low, average, high and very high; according to BI-RADS ACR categories and/or criteria). For comparisons, differences at P values < 0.05 were considered statistically significant.

Results

Basic Screening Characteristics

From August 2005 to August 2008, a total of 7,417 women participated in EBSP project and 18 were diagnosed with breast cancer. The 1,414 women whose ages were over 40 years underwent the blinded combo screening using mammography and ultrasound during the baseline evaluation; 16 cases met with the inclusion criteria. The ages of these 16 cases were from 41 to 66 (median age 51) years. From May 2008 to February 2011, 13,873 women participated in SBSP project, 3,715 women entered the second round, and 42 were diagnosed to have breast cancer. The 9,822 women whose ages were over 40 years underwent the blinded combo screening using mammography and ultrasound during the baseline evaluation; 38 cases met

with the inclusion criteria. The ages of these 38 cases were from 42 to 77 (median age 58.5) years. Thus, a total of 54 breast cancer cases were included in this study and their ages ranged from 41 to 77 (median age 56) years.

Overall Sensitivity

A true positive was defined as the breast cancer case determined correctly by the examination method used. A false negative was defined as the breast cancer case determined incorrectly as benign by the examination method used. The diagnostic sensitivity was defined as the percentage of malignant cases determined by the examination method used out of the total malignant cases. The diagnostic sensitivities of mammography alone, ultrasound alone, and mammography combined with ultrasound were 79.6, 57.4, and 92.6 %, respectively (Table 1). The difference of overall sensitivity between mammography alone and mammography combined with ultrasound was statistically significant ($P < 0.05$) (Table 2).

Correlation Between Sensitivity of Mammography Alone or Mammography Combined With Ultrasound and Age

The 9 of 54 breast cancer cases were 40–49 years old and 45 of 54 cases were aged over 50 years. Comparing the diagnostic sensitivity with age (≤ 50 or > 50 years), there was no significant correlation found ($P > 0.05$), (Table 2).

Correlation Between Sensitivity of Mammography Alone or Mammography Combined With Ultrasound and Breast Density

Based on BI-RADS system, 14 cases were classified as ACRI/ACRII and 40 cases were classified as ACRIII/ACRIV. The diagnostic sensitivity of mammography alone or mammography combined with ultrasound in ACRI and ACRII groups was 92.9 %. In ACRIII and ACRIV groups, there were 10 false-negative cases by mammography alone. In this regard, 7 cases were detected by ultrasound while 3 cases were followed up to be interval cancers. As shown in table 2, the correlation between sensitivities of two

Table 1 Overall sensitivities of different image screening methods

Screening methods	True positive	False negative	Diagnosis sensitivity
Ultrasound	31	23	57.4 %
Mammography	43	11	79.6 %
Mammography + ultrasound	50	4	92.6 %

Table 2 Diagnostic sensitivity comparison between mammography and mammography + ultrasound in different age/breast density groups

Screening methods	Overall sensitivity	Age		Breast density	
		<50 years	≥ 50 years	Low and average	High and very high
Mammography	79.6 % (43/54)	77.8 % (7/9)	77.8 % (36/45)	92.9 % (13/14)	75.0 % (30/40)
Mammography + ultrasound	92.6 % (50/54)	88.9 % (8/9)	93.3 % (42/45)	92.9 % (13/14)	92.5 % (37/40)
χ^2 value	3.794	0.4	3.462	–	4.501
P value	0.046	>0.05	0.059	>0.05	0.033

Table 3 Features of 11 false-negative cases using mammography alone

	1	2	3	4	5	6	7	8	9	10	11
Age	<i>41</i>	51	49	54	55	<i>56</i>	59	63	42	<i>61</i>	<i>60</i>
Mammography	X	X	X	X	X	X	X	X	X	X	X
Ultrasound	X	O	O	O	O	X	O	O	O	X	X
CBE	X	O	O	O	X	X	X	O	X	X	X
Density	<i>ACR IV</i>	ACR III	ACR IV	ACR III	ACR IV	<i>ACR III</i>	ACR III	ACR III	ACR IV	<i>ACR III</i>	<i>ACR II</i>
Lesion size	?	30	15	15	18	<i>20</i>	28	15	20	<i>10</i>	<i>20</i>
Stage	?	IIa	I	I	I	<i>I</i>	IIa	I	IIa	<i>I</i>	<i>IIa</i>

Note Data in italics indicates four cases of interval cancer

imaging screening methods and high densities was found to be significant ($P < 0.05$). Table 3 shows features of these 10 false-negative cases by mammography alone.

Discussion

Shanghai is one of the biggest cities in China. With rapid socioeconomic growth, breast cancer has become the leading public health concern over the past 30 years. Overall, the age-adjusted incidence increased by 134.0 % between 1975 and 2004 [11] and, to date, a population-based mammographic screening program has not been carried out in Shanghai. In this concern, to explore the suitable approach for an organized breast screening, FUSCC launched the project studies aimed at an early detection of breast cancer in women of different ages.

Besides recommending case by case screening, efforts were also made to perform mass screening at FUSCC. An EBSP project was launched in August 2005 in which the women who worked in several enterprises were enrolled in breast screening and subjected to three types of screening imaging methods i.e., mammography + ultrasound + CBE, mammography + CBE, or mammography alone. The SBSP project was launched in Qi-bao Community in May 2008. It was a community-based mass breast screening project that was supported by different social organizations. At baseline, all participants were required to undergo a clinical breast examination (CBE) and imaging population was subjected to both mammography and ultrasound. This study found that the combined use of mammography and ultrasound as a screening technique increased the detection rate of early breast cancers in this Shanghai community population. Thus, the prognosis and treatment of breast cancer could be improved.

The results of this study indicated that the sensitivity of mammography alone was higher than that of ultrasound alone. This supported the finding that mammography was a highly competitive technique for the diagnosis of ductal

carcinoma in situ (DCIS) which presented as micro-calcification and the early breast cancer [12, 13]. Whereas, ultrasound as a screening method is time-consuming (median time: 19 min), expensive, and also requires a great deal of operator expertise and automatic entire breast detection [13]. Due largely to these reasons, the use of ultrasound as a breast cancer screening method is restricted in the Western countries [13].

Of note, the sensitivity of mammography combined with ultrasound was significantly higher than that of mammography alone ($P < 0.05$). In our study, 50 of 54 cases were identified by this imaging screening strategy and, thus, the diagnostic sensitivity was 92.6 %. Among this population, 45 of 54 (83.3 %) were females aged over 50 years. Among these patients, the sensitivity of mammography combined with ultrasound was higher than that of mammography alone; however, the difference was non significant ($P = 0.059$). Regarding other 9 females aged below 50 years, the sensitivities of mammography with and without ultrasound were 88.9 and 77.8 %, respectively. Obviously, the diagnostic sensitivity was improved as ultrasound was included in screening; however, the difference was non significant ($P > 0.05$).

In this study, 80 % (40/50) of breast cancer cases were ACR III and ACR IV type breast density; 14 cases were types ACR I and ACR II. The diagnostic sensitivity of ACR I/ACR II type cases was 92.6 %. In case of ACR I and ACR II, one case of interval cancer was not detected by both mammography and ultrasound. After reviewing mammography films, the dense breast was classified as ACR II and the lesion presented as unsymmetrical dense shadow. During follow-up after 1 year, mammography was still negative but ultrasound detected the mass. Among the 40 cases of ACR III and ACR IV types, 10 cases were not detected by mammography alone and the number of false-negative cases was reduced to 3 cases after the addition of ultrasound. It incarnates the advantage of using ultrasound as it makes up the lack in diagnostic sensitivity of mammography in certain cases [14].

Arguably, parallel inclusion of more imaging screening methods will even more improve the diagnostic sensitivity. On the other hand, it will also increase the screening cost. Thus, the question whether it is necessary to use both mammography and ultrasound methods for breast cancer screening in Chinese population deserves attention? To this end, as our data show, the combined use of mammography and ultrasound is a more useful screening approach, especially for high density breast. This study also provides an imaging screening strategy for the future national breast screening projects. In this regard, the baseline mammography evaluation is instrumental in the first round of screening to classify the breast density. The patients of ACR I and ACR II only undergo mammography in the following screening rounds. On the other hand, the patients of ACR III and ACR IV will undergo the combined examination by mammography and ultrasound. By doing so, the diagnostic sensitivity will be enhanced at no considerable rise in cost of screening.

In summary, this study aimed at the efficient and cost-effective detection of early-stage breast cancers. The major results are summarized as follows: (1) the sensitivity of mammography is higher than that of ultrasound and the former remains the preferred imaging method for breast screening; (2) the addition of ultrasound to initial mammographic evaluation improves the diagnostic sensitivity of breast screening; (3) the combined use of mammography and ultrasound is specifically useful for women with dense breast on mammogram.

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