Original Article

Supplementary Breast Ultrasound Screening in Asian Women with Negative But Dense Mammograms—A Pilot Study

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Abstract

Introduction: Dense breasts are common in Asian women and they limit the sensitivity of mammography. This study evaluates the performance of supplementary breast ultrasound screening in Asian women with dense mammograms. Materials and Methods: The study was approved by the hospital's Institutional Review Board. A prospective clinical trial was performed between September 2002 and November 2004. Asymptomatic Asian women with negative and dense mammograms were offered supplementary ultrasound screening for breast cancer. Ultrasound assessment was categorised as U1 to U4. U1 and U2 cases were recommended routine interval screening mammography. U3 cases were recommended follow-up ultrasound in 6 months and routine interval screening mammography and U4 cases were recommended biopsy. Results: One hundred and forty-one women with mean age of 45.1 years were enrolled into the study. Mean scan time was 13.0 minutes (± 5.6 minutes) for bilateral vs 11.0 minutes (± 1.4 minutes) for unilateral scans. There were 10 patients and 14 patients in the in the U3 and U4 categories, respectively. Two U4 category patients were diagnosed with malignancy—a-6 mm ductal carcinoma-in-situ and a 13-mm invasive ductal carcinoma. The breast cancer detection rate was 1.4%. Sensitivity and specificity were 100% (2/2) and 88.5% (92/104) respectively. The positive predictive value was 14.3% (2/14) and the negative predictive value was 100% (92/92). Conclusion: This pilot study reveals the usefulness of supplementary ultrasound screening in detecting early stage mammographically and clinically occult breast cancers in Asian women with dense breasts. A larger long-term study is, however, needed to assess its feasibility and impact on breast cancer prognosis.

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Introduction

Mammogram has been the gold standard for breast cancer screening and Magnetic Resonance Imaging (MRI) has been advocated for screening of high-risk individuals. However, there is currently no recommendation for supplementary ultrasound scan in breast cancer screening.[1-4] Moreover, it is known that dense breasts, which are common in Asian women, reduce the sensitivity of detecting breast cancers on mammogram by as much as 50%[5-8] compared to fatty breasts. Furthermore, increased breast density is associated with a higher risk for breast cancer and development of interval cancers between screening mammograms.[7,9,10]

This study highlights the potential of complementing screening mammograms with ultrasound to detect mammographically occult breast cancers. Ultrasound is easily available and is largely inexpensive. Ultrasound had been shown in the Western population to detect mammographically occult cancers in mammographically dense breasts.[8,11-17] The aim of this research was to perform a study to prospectively evaluate the performance of breast ultrasound screening in Asian women with dense breasts and negative screening mammograms.

Materials and Methods

This single centre study was approved by the Institutional Review Board.

Study Population

Consecutive, asymptomatic women of Asian racial ethnicity who came to our hospital for routine mammographic

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screening were invited to participate in the study between September 2002 and November 2004 if they were assessed to have mammographically dense breasts and negative mammograms. The women were recruited from the general population but women with known high-risk factors were not excluded from the study.

Mammographic final assessment and breast density were categorised according to the Breast Imaging Reporting and Data System (BI-RADS).[18] The BI-RADS is a quality assurance tool, published by the American College of Radiologists, designed to standardise reporting for breast imaging. Only BI-RADS mammogram assessment categories of 1 and 2 were assigned as negative mammograms for the purpose of this study. A BI-RADS 1 assessment category refers to a negative mammogram with nothing to comment on. BI-RADS 2 refers to the presence of findings that are benign on mammogram. For breast density, heterogeneously dense and extremely dense breast compositions were designated as mammographically dense breasts. Verbal informed consent was obtained from the patients for this study.

Ultrasound Assessment

Mammograms were carried out on a General Electric Senographe DMR unit and breast ultrasound examinations were performed on a Toshiba PowerVision scanner with a 7 to 10 MHz probe. The breasts were scanned in radial and anti-radial planes.

Each breast ultrasound examination was performed by a sonographer and verified by a radiologist. Three experienced breast sonographers were involved in obtaining the ultrasound images. Each of them had 4 to 12 years of breast ultrasound imaging experience. There were 4 breast radiologists who provided conventional sonographic assessment. Each of them had 3 to 15 years of breast ultrasound imaging experience.

Ultrasound Assessment Categories and Follow-up

Ultrasound assessment was classified into categories U1 to U4, as shown in Table 1. U1 and U2 cases were asked to return for routine mammographic screening after 1 or 2 years, depending on the age. Those below 50 years were advised to undergo mammographic screening annually while those 50 years and above were asked to screen every 2 years. U3 category of lesions were asked to return for sonographic follow-up after 6 months. Histopathological correlation would be recommended for U4 lesions.

The follow-up protocol for ultrasound detected lesions was largely based on the prevalent practice at our hospital during that time. We did not follow the ultrasound management

Table 1. Summary of the Ultrasound Assessment Categories and Their Management

Category	Definition	Follow-up Recommendation
U1	Negative finding	Return to regular interval mammographic screening
U2	Benign findings	Return to regular interval mammographic screening
U3	Probably benign findings	Follow-up ultrasound in 6 months' time and return to regular interval mammographic screening
U4	Suspicious finding	Biopsy recommended

guidelines recommended by the American College of Radiology[19] as they were only developed in 2003 which was after the conception of our study. In view of this belated development, the patients' records were also retrospectively reviewed for the outcome of any breast imaging at 2 years after the initial breast screen.

Data Analysis

U1 and U2 cases were considered true negatives if there was no development of breast cancer by the next mammographic screening at 1 or 2 years, depending on the age as detailed above. U3 cases were considered true negatives if their follow-up ultrasound scans at 6 months and the next mammographic screening showed no suspicious interval change. U4 patients would be given advice for biopsy for histopathological confirmation. Biopsy methods included core needle biopsy, vacuum-assisted biopsy and surgical excision biopsy following hookwire localisation.

Data were collected prospectively and included patient demographics, personal history of previous breast cancer, risk factors for breast cancer, mammogram and ultrasound results, radiologists' assessment of lesions, the time taken to complete each breast ultrasound study, biopsy results and outcome of subsequent follow-up. For the purpose of this study, women with a personal history of prior breast cancer, family history of breast cancer in the first and second degree relatives, prior chest wall irradiation for Hodgkin's disease, breast cancer (BRCA) mutations or other genetic conditions, and prior history of atypical ductal hyperplasia and lobular neoplasia were considered to be at elevated risk for breast cancer.

The breast cancer detected rate, sensitivity, specificity, positive predictive value, negative predictive value and biopsy or recall rate were calculated. Breast cancer detection rate was based on the number of breast cancer cases that were detected amongst all the women who were enrolled. Sensitivity was the true positive cases divided by the true positive cases and false negative cases. A true positive

was defined as a U4 classified lesion with evidence of malignancy on histology while a false positive referred to a U4 lesion with benign histopathology on biopsy. Specificity was calculated by taking all true negative cases in the U1 to U3 categories and dividing them by the true negative cases and false positive cases. Cases lost to follow-up were not included in the assessment of specificity. The positive predictive value was the number of breast cancers that were detected out of the number of lesions that required further biopsy evaluation (U4 cases). Negative predictive value was the proportion of true negatives among all negative cases (U1 to U3) assigned on ultrasound screening and it would exclude cases that were lost to follow-up. The biopsy rate or recall rate, was the number of cases that required biopsy (U4 cases) out of all the women who enrolled. Statistical tests were performed with SPSS version 17 and Graphpad Quickcals.

Results

One hundred and forty-one asymptomatic women with mean age of 45.1 years (range, 30 to 64 years) who satisfied the criteria of negative but dense mammograms were enrolled in the study. The racial distribution was predominantly Chinese which made up 94% of the study group. Four percent were Indian, 1% Malay and 1% Eurasian. They were all asymptomatic with no known clinical findings. Thirty-six women (25.5%) had elevated risk for breast cancer. Twenty-four (17.0%) of these women had family history of first degree relatives with breast cancer while 5 (3.5%) had family history of second degree relatives with breast cancer. None of the patients had known BRCA gene mutations, prior chest irradiation or previously detected high-risk lesions like atypical ductal hyperplasia and lobular neoplasia. Seven (5%) women had previously been treated for breast cancer and were known to be in remission and asymptomatic at the point of recruitment.

One hundred and thirty nine women underwent ultrasound screening of both breasts and 2 women who had unilateral mastectomy for previous breast cancer had unilateral screening of the contralateral breast. The mean time taken to complete a bilateral breast ultrasound was 13.0 minutes (± 5.6 minutes) and a unilateral breast examination was 11.0 minutes (± 1.4 minutes, $P = 0.61$).

One hundred and six women or 75.2% of the enrolled women returned for follow-up. There were no confirmed cancers detected in U1 to U3 lesions at the end of the follow-up period (Table 2). A patient in the U2 category had requested for a biopsy of her breast lesion and an ultrasound guided vacuum-assisted large core needle biopsy was performed. The lesion proved to be a fibroadenoma. Another patient who had a U3 category lesion also underwent

Table 2. Breakdown of the Number of Patients for Each Ultrasound Assessment Category

Ultrasound Assessment Categories	Number of Patients (%)	Number (%) of Patients Who Completed Follow-up	Number of Cancers Detected
U1	42 (29.8%)	30 (71.4%)	0
U2	75 (53.2%)	54 (72.0%)	0
U3	10 (7.1%)	8 (80%)	0
U4	14 (9.9%)	14 (100%)	2

a vacuum-assisted large core needle biopsy at the physician's request and the histopathology was fibrocystic change. All other U3 lesions remained stable on follow-up ultrasound and had negative screening mammography after 1 year. All U4 lesions underwent ultrasound-guided core needle biopsy. Their final histopathology revealed 2 malignant tumours: a 6-mm ductal carcinoma-in-situ (DCIS) (Fig. 1) and a 13-mm invasive ductal carcinoma (Fig. 2). There was no nodal disease or evidence of metastasis in these 2 cases. The mammograms of the 2 positive cases were also retrospectively reviewed. Both lesions were again not mammographically identifiable by 2 experienced breast radiologists as the lesions were well hidden by the dense breast tissue and there were no abnormal microcalcifications or architectural distortion. Both were also not clinically palpable. The other biopsied lesions were benign (Table 3).

1a

1b
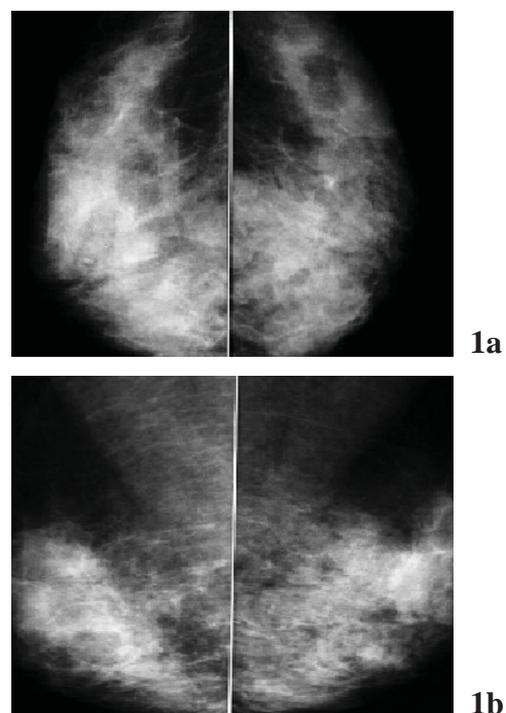
Figs. 1a and 1b. Heterogeneously dense breasts on cranio-caudal and mediolateral oblique mammographic views. No obvious mammographic abnormality was detected.
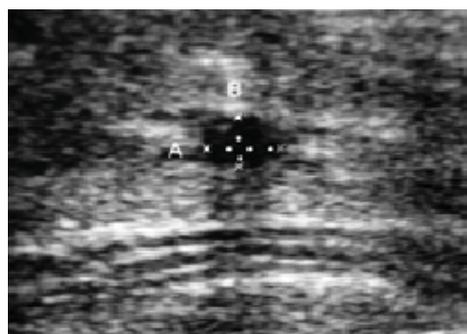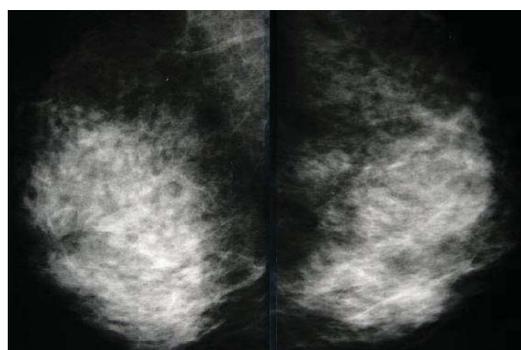
1c

1d

Figs. 1c and 1d. Supplementary ultrasound screening revealed a left 3 o'clock nodule with slightly irregular margins, increased vascularity and posterior acoustic shadowing. Ultrasound-guided needle core biopsy and eventual surgical specimen confirmed ductal carcinoma-in-situ.

2a

Fig. 2a. Mediolateral oblique and cranio-caudal mammograms of the right breast show extremely dense breast tissues. No obvious mammographic abnormality was detected.
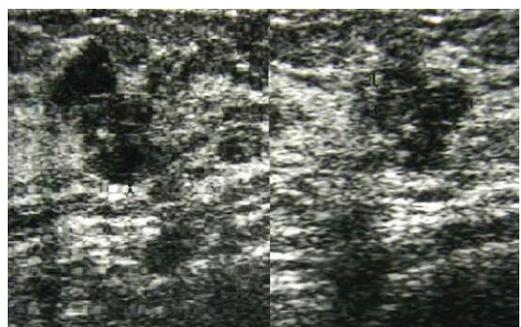
2b

Fig. 2b. Supplementary ultrasound screening revealed a right 8 o'clock 13 mm heterogeneously hypoechoic lesion that is slightly tall in orientation and has angular and ill-defined margins. Ultrasound-guided core needle biopsy revealed invasive ductal carcinoma.

Table 3. Final Histopathology of the U4 Lesions

Histopathology	Number of Cases
Ductal Carcinoma-in-situ	1
Invasive Ductal Carcinoma	1
Fibroadenoma	1
Blood Clot	1
Papilloma	2
Fibrocystic Change	8

The breast cancer detection rate for supplementary breast ultrasound screening was 1.4% (2/141). The sensitivity and specificity were 100% (2/2) and 88.5% (92/104) respectively. The positive predictive value was 14.3% (2/14) and the negative predictive value was 100% (92/92). The biopsy rate was 9.9% (14/141).

A retrospective review of patients' records revealed that 22 out of 42 U1 (52.4%), 41 out of 75 U2 (54.7%), 6 out of 10 U3 (60.0%) and 6 out of 14 U4 (42.9%) women had mammograms or mammograms and ultrasound imaging at 2 years. There were no cancers detected for the U1 and U2 cases and no further suspicious lesions detected for the U4 patients. One U3 case was diagnosed with invasive ductal carcinoma at 2 years.

Discussion

For a screening test to be effective in reducing breast cancer mortality, the test has to be sensitive, be able to detect the cancers at an earlier stage compared to those detected in unscreened patients and the screening intervals should preferably be half of the lead time gained. This was outlined by Pelikan in 1993[20] and Moskowitz in 1996.[21] Currently, mammography is the only breast cancer screening tool that has demonstrated evidence of reduction of breast cancer mortality.[22-27] With the use of screening mammography, it had been shown that breast tumours could be identified when they were small and non-palpable with the absence of nodal disease. Duffy et al[28] observed in the Swedish Two-County Trial that the reduction in the 20-year breast cancer mortality rate in the population that received mammographic screening could be attributed to increased discovery of cancers at stage I of the disease rather than at stage II or later.

While screening mammography is effective as a screening modality for breast cancer, it also has a false negative rate of approximately 10% to 15%. One of the main reasons for this is due to the presence of dense breast tissue which can obscure cancers on mammography. Mammographic sensitivity in dense breasts may be as low as 48%.[5-8] This problem presents as a frequent diagnostic challenge in Asian

women where smaller breast volumes and less body fat result in relatively dense breasts.[29-33] Marcela G del Carmen et al[34] reported that 83.2% of Asians who presented for mammography at the Massachusetts General Hospital from 2003 to 2004 had breast density categories of BI-RADS 3 and 4. After adjustment for age and body mass index (BMI), Asian women had higher breast density than the other racial groups. Furthermore, dense breast tissue is also associated with elevated breast cancer risk.[35] These reasons encourage the background for evaluation of other radiologic modalities that can supplement screening mammography to detect early breast cancers in Asian women.

Currently, the use of MRI screening in addition to mammographic screening is advocated in high-risk patients.[36] MRI screening had demonstrated high sensitivity and high negative predictive value which are better than those of combined mammography and sonography.[37-40] However, MRI is costly and has been plagued by a high false positive rate with meta-analysis suggesting specificity of approximately 67%.[41] This has also resulted in a recall rate that is 3 to 5 times higher than that of screening mammography.[42] Hence, MRI screening is not currently recommended for the average risk woman except perhaps in cases with breast augmentation that may obscure breast malignancy on mammography and ultrasound. In light of this, there may be a role for ultrasound breast screening in the average or intermediate risk patients.

Benefits of Ultrasound Screening

Ultrasound is easily accessible and relatively inexpensive. It is better able to detect cancers that are obscured by dense breast tissue on mammography and has been shown in previous studies[8,11,14] to detect breast cancers at an early and preclinical stage. Ultrasound and mammography are also complementary with ultrasound being more sensitive for invasive cancer than DCIS and vice versa.[6] For these reasons, ultrasound appears to be a cost-effective screening test to supplement screening mammography and to the best of our knowledge, there has been no study that has evaluated ultrasound breast screening in Asian women.

The cancer detection rate in this study was 1.4% or 14 per 1000 women. It is very much higher than the 4.6 cancers detected per 1000 women in Singapore's national breast screening programme from 2002 to 2007[43] which has not been adjusted for breast density, and more than the calculated expected rate of 6.9 per 1000 women screened for the United Kingdom Breast Screening Programme[44] of which Singapore's screening programme is partially modelled after.[45] The cancer detection rate was also higher than that of the other similar ultrasound screening studies on Caucasian women[8,12-14,17] (Table 4) although there were no statistically significant difference. The relatively high cancer detection rate might be spurious and related to pure chance in this small sample size study. However, other factors should also be considered. Firstly, the disease might be more prevalent than previously thought. More recent epidemiological data had indicated a rising incidence of breast cancer in Singapore and Asian women.[46,47] The crude incidence rate of breast cancer in Singapore, had risen from 67.3 per 100,000 from 1998 to 2002[48] to 77.8 per 100,000 from 2003 to 2007.[49] Another possible reason was that there might be a higher proportion of cancers presenting as mammographically occult but sonographically detectable lesions in dense breasts, especially in Asian women. Indeed, some studies have indicated that ultrasound screening identified equal or more number of cancers than mammography, sensitivity ranging from 50% to 88% for ultrasound compared to 50% to 57% for mammography.[8,15,50] These reports highlight that ultrasound can detect more invasive cancers than mammography in women with dense breasts although it is not as good as mammography in the detection of DCIS. The biopsy rate in our study was also higher compared to the other studies and a higher recall or biopsy rate might be another contributing factor to the high cancer detection rate as explained by Moskowitz.[21] Regardless of the reasons,

Table 4. Comparison of the Sample Size, Cancer Detection Rate, Biopsy Rate and Positive Predictive Value Among Ultrasound Screening Studies of Dense Breasts

	Number of Supplementary Screening Ultrasound Examinations	Cancer Detection Rate	Biopsy Rate	Positive Predictive Value
Our study	141	1.4% (2/141)	9.9% (14/141)	14.3% (2/14)
Kolb et al[8]	12,193	0.3% (33/12193), *P* = 0.08	2.6% (320/12193)	10.3% (33/320)
Buchberger et al[12]	8103	0.4% (32/8103), *P* = 0.11	4.5% (362 / 8103)	8.8% (32/362)
Kaplan et al[13]	1862	0.3% (6/1882), *P* = 0.10	3.1% (57/1862)	10.5% (6/57)
Crystal et al[14]	1517	0.5% (7/1517), *P* = 0.17	2.5% (38/1517)	18.4% (7/38)
Corsetti et al[17]	6449	0.5% (29/6449), *P* = 0.14	7.5% (486/6449)	6.0% (29/486)

Note: Using the Fisher's Exact Test, our Study's breast cancer detection rate shows no significant difference from those obtained from the other studies.

the fact remained that despite the small sample size and the supposedly lower prevalence of breast cancer in Asian women, there were mammographically occult breast cancers detected by ultrasound and the merits of supplementary sonographic screening should be further evaluated and not simply dismissed.

As mentioned earlier, one of the important tenets of breast cancer screening is identifying malignant disease at an early stage. The 2 cancers that were detected in the study were small and of early stage. The invasive ductal carcinoma detected in the study measured 13 mm and there was no nodal disease. Further work-up also did not reveal any evidence of metastatic disease. The second case was a 6-mm intermediate grade DCIS. Interestingly, although ultrasound examination is known to be relatively poor in the detection of DCIS,[12,13] this small lesion was not demonstrated on mammogram because it did not present with any microcalcifications.

Limitations of Ultrasound Screening

The value of identifying additional cancers on ultrasound screening must be weighed against the increased biopsy risk and increased workload. Our study revealed a specificity of 87.8% for ultrasound and this is better than that of MRI. The 9.9% biopsy rate and the positive predictive value of 14.3% achieved in this study are probably acceptable if screening mammographic standards were applied.[21,51-54] However, it would potentially mean that approximately 7% to 8% more women who enter a combined mammographic and sonographic screening programme would be recalled for sonographic findings assuming 80% of them have dense breasts. Added cost and effort of the ultrasound screening would also include the additional 30.6 hours of scan time for these 141 women in order to detect 2 additional cancers, as well as the 10 follow-up ultrasound studies for the U3 cases and the 13 biopsies performed for the 13 U4 cases. The advent of automated breast ultrasound (ABUS) may be able to significantly reduce the time and workload for ultrasound breast scans. Kelly et al[55] also reported that an increase in cancer detection rate of 0.36% when adding ABUS to mammographic screening in women with dense breasts and/or at elevated breast cancer risk. ABUS may prove to be a more practical way to perform ultrasound screening.

There are also other issues that need to be addressed if an ultrasound breast screening programme is to be implemented. While much has been said about identifying early stage cancers with supplementary breast ultrasound screening, it is, however, still unclear as to whether this will lead to better prognosis or reduction in mortality. The effect of lead-time bias has yet to be assessed. In lead-time

bias, early detection of cancer from a screening programme only results in the disease being observed and treated for a longer period of time but not necessarily prolonging life or affecting mortality outcome. While mammographic screening has been shown to reduce mortality from breast cancer, it remains to be seen if early cancer detection from breast ultrasound screening will eventually contribute to additional decrease in the mortality rate. Logically, ultrasound screening should lead to the identification of more small breast cancers and hence, improvement of prognosis and possibly reduction of mortality. However, one may argue that these mammographically occult cancers, if missed in the initial mammographic screen, may ultimately manifest on subsequent mammographic screens and may not have significant impairment to the patient's prognosis even if diagnosed later. Hence, long-term data are clearly needed to clarify ultrasound's impact on prognosis and mortality. There are also questions about the need for interval screenings and about the duration between interval screens. The prevalent cancer detection rate which is the cancer detection rate at the first screen may be followed by a lower incidence rate at subsequent screenings as seen in mammographic screening programmes[56-58] and the effectiveness of subsequent ultrasound screenings may be limited, especially if they are scheduled too closely to each other. The ongoing ACRIN 6666 trial in the United States (Berg et al[59]) is looking into the effectiveness of subsequent ultrasound screens in women with elevated risk and will hopefully shed some light on this matter.[50,59]

Study Limitations

The main limitation in this pilot study was the small sample size that meant that even a difference of 1 positive case might cause spurious results, especially in the context of screening for a relatively low-prevalence disease. The sample population was also fairly heterogeneous with a mixture of women with average and elevated risk. We did not separately analyse the statistics between the women of these 2 groups primarily because the number of women with elevated risk was small. In addition, none of the 36 patients with elevated risk were found to have breast cancer and they could not have contributed any bias towards the breast cancer detection rate in this study. There was also only a single radiologist involved in the assessment of each ultrasound case and this precluded evaluation of inter-observer variability.

The other limitation was the high drop-out rate of 35 women from the follow-up during this study. This would make it difficult to accurately assess sensitivity, specificity and negative predictive value of the study. It was observed that most of the women who were lost to follow-up were from the U1 and U2 categories. They were probably clinically

well and might not have felt the need for another screening study. This is a common problem encountered in most screening programmes. Some might have also chosen to have their next screening mammogram performed outside of our institution and hence we would be unable to trace their breast imaging results. We did, however, find that 24 out of the 35 women who defaulted radiological follow-up (68.6%, 9 U1 and 15 U2 patients) were seen in the clinic by their primary breast care physicians for routine check-ups within 3 years of the initial mammographic and sonographic screening. There were no significant physical breast findings detected in these women and were likely to have no significant breast disease.

There was also the issue of the follow-up duration of 1 year being too short for the U3 lesions. At the time of conceptualisation of the study, there was no general consensus for the ultrasound follow-up duration. However in 2003, the ACR BI-RADS classification was introduced for breast ultrasound assessment which recommended that probably benign lesions be followed-up for 2 years to ensure benignity. In view of this, we decided to retrospectively review the records of all patients to determine if any interval cancers were detected in women who had some form breast imaging at 2 years. Interestingly, 1 of the U3 cases was discovered to have a mammographically occult stage I breast cancer 2 years after her initial breast ultrasound screen. The patient complained of focal left breast hardening which turned out to be an 8-mm cancer visualised only on ultrasound examination. It did not correspond in location or appearance with the original U3 lesions detected in the initial screening ultrasound examination and was in all likelihood of a newly developed cancer. The original U3 lesions had remained stable on sonographic follow-up at 6 months as well as at 2 years.

Conclusion

This pilot study on breast ultrasound screening in Asian women with mammographically dense breasts reveals the usefulness of ultrasound in detecting early stage mammographically and clinically occult breast cancers. A larger long-term study is however, needed to assess its feasibility and impact on breast cancer prognosis.

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