RESEARCH COMMUNICATION

Breast Elastography: A Hospital-Based Preliminary Study in China

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Abstract

The performance of ultrasound elastography in the characterization of 170 breast lesions with histologic correlation was evaluated in 150 consecutive patients who were diagnosed as having benign or malignant masses on B mode sonography. Each lesion was classified with ACR's BI-RADS lexicon (benign=2 and 3, malignant 4 and 5) using Ueno elastography classification scores (benign=1-3, malignant=4-5). Of the 170 lesions, 70 were histologically malignant, and 100 were benign. Ultrasound elastography was superior in detecting breast cancer, since the accuracy (95.8%), sensitivity (98.6%), specificity (96.0%), and positive predictive values (94.5%) were higher than those of B mode sonography (90.6%, 91.4%, 90.0% and 86.5% respectively). The sensitivity (98.57%) and false discovery rate (1.1%), when both modalities were jointly used (sonography and /UE) was better then those of sonography and UE singly. However, the specificity (90%) was found similar to sonography. In conclusion, ultrasound elastography is superior to B mode sonography in assessing the nature of breast lesions.

Keywords: Ultrasound elastography - sonography - breast lesions - histopathology

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Introduction

Breast is a highly modified sudoriferous gland. It is an organ of female beauty and pride. From puberty to death; the breast is subjected to constant physical and physiological alterations that are related to menses, pregnancy and menopause. Cancer of breast is the most common cancer in women and the second most common cause of cancer-related mortality (Jemal et al., 2005). According to the WHO 2007, globally 1 in 10 women is affected by breast cancer during their life time. Over 0.7 million of new cases of carcinoma of breast cancer are detected every year globally, with nearly 0.3 million death, affecting 28 per 100,000 females in the age group of 35-60 years. Despite being the most common cancer, 5-year relative survival rate of breast carcinoma is still over 90 % when they are detected in early phase (Brenner et al., 2007).

The incidence of breast cancer varies greatly around the world, being comparatively lower in less-developed countries then in the more-developed countries. Though the incidence of breast cancer in China is comparatively lower than the Western countries, research has revealed that it has been increasing annually (Tian et al., 2005). Larger cities like Shanghai, Beijing, Tianjing, Wuhan, Guangzhou etc, have higher mortality and morbidity rates than small cities and even higher than in rural areas (四川省乳腺治疗网 , 2008). The rate of incidence from 1978 (17/100,000 to 52/100,000) to 2009 has tripled. In China, breast cancer is the second most common cancer overall but the first most common cancer in the female populations living in the city areas. According to the Ministry of Health, PRC, Shanghai and Beijing are the two larger cities having incidence of 52/100,000 and 45/100,000 respectively. The increasing incidence rate was due to the change of risk, change of life style and change of society rather than the change of population structure and size (Yang et al., 2005). The estimated breast cancer mortality rate has been increased between 1991 and 2005. The increase was sharper in the younger age group than in the older age group (Yang et al., 2004). Similarly, in another study, the analysis of Center for Health Information and Statistics (CHIS) dataset showed that the increasing mortality rate of breast cancer was confined to the younger age group (Yang et al., 2003). Both increased risk and change of population structure/size contributed to the increase of mortality rates (Yang et al., 2004).

As we know that early detection of abnormalities is associated with the better prognosis of breast cancer. Mammography and sonography are the most sensitive modalities for detecting breast cancer. Most Chinese women have relatively small dense breasts, which is one of the factors leading to false negative findings in mammography (Saarenmaa et al., 2001). The feasibility of US machine, no radiation effect, cheap and quick has made it as the first modality in screening for breast cancer in China.

Ultrasonographic elastography(UE) is a novel

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modality; currently it is the subject of hot research for clinical applications, primarily the breast lesion imaging. Breast elastography is a technique that maps relative tissue stiffness, and has been concluded that this new technique may be useful for differentiating malignant from benign lesions (Robert, 2007). Generally, breast cancer tissue is harder than the adjacent normal breast tissue. This property serves as the basis for some examinations, such as palpation, which is being currently used in the clinical assessment of breast abnormalities, as well as for elastography. The elastography based on the principle, that tissue compression produces strain (displacement) with in the tissue and that the strain produced is smaller in harder tissue than in softer tissue. Therefore by measuring the tissue strain induced by compression, we can estimate tissue hardness, which may be useful in diagnosing breast cancer. Research has shown that normal tissue and fat have lower elasticity profiles, while hard areas, such as cancers, have higher (Garra et al., 1997).

Materials and Methods

Patients

From December 2009 to April 2010, 150 patients with 170 lesions in the breast were included in the study. Examination was carried out in the tertiary centre of West China i.e. (Huaxi Hospital of West China Medical School), which is also a largest hospital in China. Patients mean age was 44.65years, with a range of 15 to 79 years. All patients were first examined with sonography and those patients with mass were further analyzed with UE. Informed consent for diagnostic procedures was obtained from each patient. All the examinations were performed before any biopsy, fine needle aspirations or surgeries were performed.

Study Design

In each patient, bilateral whole breast sonography was performed in the transverse and longitudinal planes using a Siemens Acuson Antares 5.0 US scanner equipped with 7.5-13.0MHz liner-array transducer. Sonographic features of lesions (size, shape, margin, internal echogenicity, presence/absence of calcification, posterior acoustic phenomena, anterior posterior-width ratio, and presence/absence of lymph node enlargement, presence/absence of intra-tumoral blood flow) were prospectively recorded in a computer database system. With these features they were classified to BIRADS lexicon by single observer (XZ), who had 15 years of experience on breast sonography.

Ultrasound elastography was performed simultaneously as the scanner was equipped with sonoelastography unit; hence the stiffness of lesion could be measured using different colors. On B-mode, we displayed the target lesion and moved the ROI(region of interest) around the lesion, making sure that the target tissue occupied no more than one third of the total area of the ROI. Hence besides the lesion area, surrounding tissue, including subcutaneous fat was also the region of interest. The probe was moved superior and inferior to obtain the elasticity images. Importantly to obtain images that were appropriate for analysis, we applied more coupling gel on the skin surface, above the target lesions, so that no any manual pressure interfere with the vibrations(pressure) induced by the sonoelastographic unit. The probe was held lightly and perpendicular to the ROI during the elastography.

Image Analysis

The final assessment of the lesions as seen on conventional US were classified according to the American College of Radiology Breast Imaging Reporting and Data System(BIRADS). Findings were classified as following category 1: normal appearance; category 2: benign finding; category 3: probably benign finding; category 4: suspicious abnormality; category 5: highly suggestive of malignancy.

The elasticity images were evaluated by using the score system described by Itoh et al; 2006, which includes a five point scale:

Score 1: even strain over the whole hypoechoic area .The entire lesion is evenly shaded in green, as in the breast tissue.

Score 2: strain over most of the hypoechoic area with some areas spared. The hypoechoic area is a mosaic pattern of green and red.

Score 3: strain at the periphery with sparing of the centre lesion. The central part of the lesion is red, the peripheral part is green.

Score 4: no strain over the entire hypoechoic lesion .The entire area is red.

Score 5: no strain over the entire hypoechoic lesion or in the surrounding area .Both the lesion and its surrounding area are red.

Green indicates medium tissue stiffness, blue indicating soft tissue and red indicating hard tissue as classified on Siemens sonoelastography Unit. Elasticity images were evaluated according to the score pattern above. Elasticity Score of 1, 2 and 3 was considered as Benign and the Score 4, 5 was considered as malignant.

Statistical Analysis

The software package SPSS 12 for Windows was used for statistical data analysis. Cross Table Tests Fischer`s test was carried out to assess the diagnostic value of conventional US and UE compared with the histopathology results. Two-sided $p<0.05$ was considered statistically significant. The diagnostic sensitivity, specificity, accuracy, positive and negative predictive value and false discovery rate were calculated.

Results

All 170 lesions of 150 patients underwent breast biopsy. The patient mean age was 44.6 years range (15-79). Histological analysis revealed that out of 170, 70 (41.2%) were malignant and 100 (58.2%) were benign. The histological diagnoses are summarized in Table 1. The result showed that fibroadenoma (68%) and invasive ductal carcinoma (54%) were the commonest benign and malignant lesions respectively.

With regard to sensitivity, specificity and accuracy value, UE was superior to sonography ($P<0.005$; Table 2). Combining UE and sonographic diagnostic

Table 1. Histopathological Diagnosis of the 170 Breast Lesions

Pathologic diagnosis	Number
Benign	
Fibroadenoma	68
Fibrocystic Mastopathy	8
Hyperplasia	6
Chronic Inflammation	5
Phyllodes Tumor	3
Plasma cell granuloma	3
Intraductal Pappiloma	2
Fat necrosis	1
Galactocele	2
Hamartoma	2
Lymphangioma	1
Sub-total	100
Malignant	
Invasive Ductal Carcinoma	54
Ductal Carcinoma in situ	10
Papillary carcinoma	2
Paget's disease	1
Others	3
Sub-total	70

methods yielded the better results in detecting the breast cancer (Table 2). Though the accuracy in detecting the characteristics of lesions by UE was better compared to sonography and when combinedly examed, but the false discovery rate was lower in UE, than when they were combinedly examed (Table 2). Sonographic findings were false negative in 6 of 70 cancers; and 3 of 67 cancers were

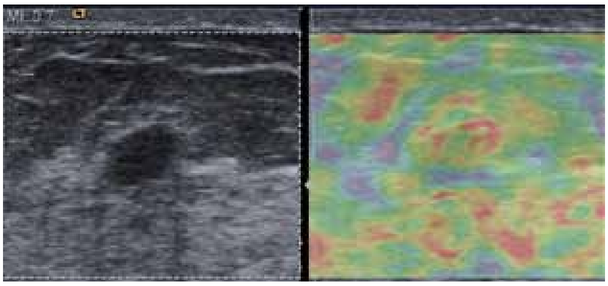

Figure 1. A 41 Year-old Woman with Medullary Carcinoma. Left: On US, the lesion with sonographic features of benign entity in shape, margin, echotexture was classified as BI-RADS category 3. Right: UE revealed the hypoechoic area as a mosaic pattern of green and red (UE 2 Score)

Table 2. Comparative Study of Conventional Sonography, UE and Combined Modalities of Sonography and UE in the Differentiation of Malignant from Benign Lesions

Modality	Conventional USG	UE	Combined
Sensitivity	91.4 (64/70)	95.7 (65/70)	98.5 (69/70)
Specificity	90 (90/100)	96 (96/100)	90 (90/100)
PPV	86.4 (64/74)	94.3 (67/71)	87.3 (69/79)
NPV	93.7 (90/96)	96.9 (96/99)	98.9 (90/91)
Accuracy	90.5(154/170)	95.8 (163/170)	93.5 (159/170)

missed by UE. Cancers that were missed on UE were found to be in early stages of invasive ductal carcinoma. Of the 6 cancers missed by sonography, 4 were detected by UE. When the diagnoses from the sonography and UE were combined, the false negative rate decreased to 1.4% (1 of 70 cancers), which was significantly lower than that of other two diagnostic methods.

The pathologic finding of the missed cancer when both modalities were combined was medullary carcinoma (Figure 1). The false positive rate of UE 4 %(4/100) was lower than the sonography 10 %(10/100) (Figure 2) as well as for them when they were combinedly used 10 %(10/100). Among the false positive findings most of them were giant lobulated fibroadenoma (Figure 3) with heterogeneous internal echotexture, chronic inflammation (Figure 4) and galactocele (Figure 5) which was missed by UE had the EI scores of 5. Although we combined the two different methods, the false positive was 10 of 100 lesions, which was the same as for sonography alone. Any modalities that suspects the lesion to be malignant is considered to be malignant but for benign both the modalities should suspect benign lesions. Hence, when combined, we improve the sensitivity but the specificity remained similar to that of sonography. But when individually used, UE has better results in sensitivity and specificity.

The distributions of BI-RADS score for benign and malignant lesions are shown in Table 3. 90 %(90/100) of benign lesions were scored (1-3). Benign lesions that were suspected malignant as per BIRADS classification by sonography were 10. Among 10, 7 were scored 4 and the remaining 3 were scored 5. Similarly, of the total 70 cancers, except 6, rests of the 64 lesions were scored 4 and 5. Hence, when we make the cut-off point of 4 as a malignant, the sensitivity of sonography to rule out the benign and malignant lesions according to BIRADS

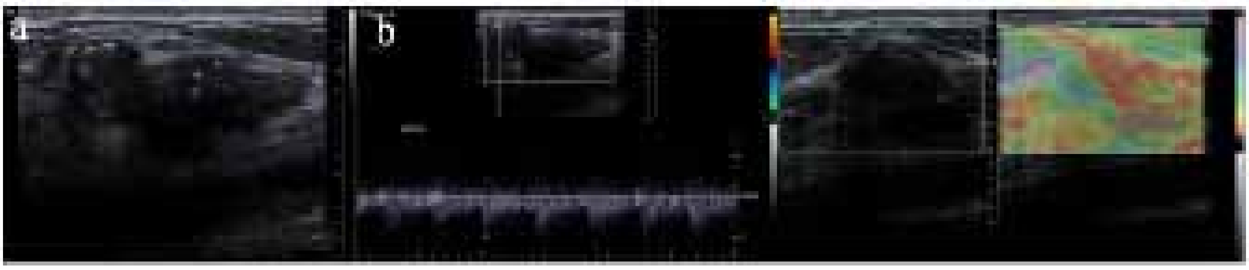

Figure 2. A 29 year-old-woman with Fibroadenoma. Left: On US image, the mass showed has malignant feature. Presence of calcification (a), presence of intra-tumoral blood flow (b), lobulated shape and ill-defined margin mass was classified as BI-RADS category 4. Right: UE score was 3

Table 3. BI-RADS Categories Based on Conventional US of Breast Lesions (n=170)

BI-RADS Score	Benign	Malignant
2	26	0
3	64	6
4	7	17
5	3	47
Total	100	70

Table 4. Elasticity Scores in Breast Lesions (n=170)

Elasticity Score	Benign	Malignant
1	23	0
2	43	1
3	30	2
4	2	27
5	2	40
Sub-total	100	70

lexicons turned to be, 90.0% (90/100) benign, and 91.4% (64/70) malignant. Similarly, when we considered the EI score of 1, 2 and 3 as a benign, and 4, 5 as a malignant. The sensitivity to rule out benign and malignant for UE were 96% (96/100) and 95.7% (67/70) respectively (Table 4). Hence, when cutoff point of 4 was used to describe malignancy of lesions, UE imaging modality has better sensitivity than sonography.

Discussion

Breast is the most common malignancy among the female population worldwide. Screening and awareness among the female population can reduce the mortality rate. Early detection of cancer through screening has better prognosis (Tabar et al., 2003). Annually, the screening patient for breast cancer has been increasing. According to the data collected from our department, in 2002 there were 6,346 patients, but, in 2009 there were 48,314 patients who underwent for breast sonography. The scenario clearly explains that the rising in patients for screening, follow up or rising in incidence for breast lesion has certainly given a burden to patients,family,society,hospital and ultimately to the country. With the emerging of new technology worldwide, ultrasound elastography(UE) is the new approach in detecting and identifying lesions in the breast. Though the first clinical results of UE were published in 1997-2001 (Garra et al., 1997; Hiltawsky et al., 2001), but only in 2003-2004 the development of Sonography equipment with dedicated software for real time processing enabled UE utilization simultaneously with routine sonography examinations (Konofagou 2004; Ueno and Iboraki, 2004). The scoring system proposed by Itoh and his co-workers (Itoh et al., 2006) was useful for preliminary studies. The ability of UE to evaluate the mechanical properties of different tissue is a very useful diagnostic tool that provides further information about the breast lesions in addition to the shape, orientation, margin and internal structure and presence of calcifications. These additional findings may be very useful in differentiating malignant lesions with benign lesions. The strain and stiffness can noninvasively be determined by UE and can be color mapped. Red indicating the regions with low elasticity (harder tissue areas) and blue indicating the regions with high elasticity (soft tissue).

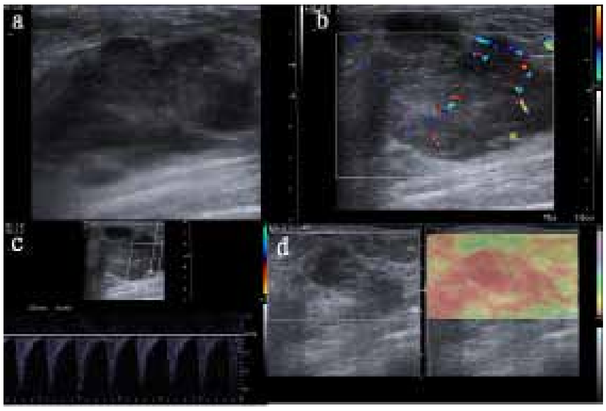

Figure 3. A 40 Year-old-woman with Lobulated Fibroadenoma. 2D ultrasound image showed a large lobulated hypoechoic mass (a), with heterogeneous internal echotexture. Intra-tumoral blood flow was profuse (b), RI=0.92(c). The UE score was 4 (d)

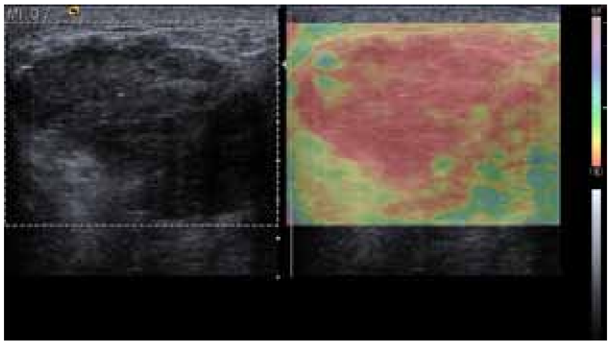

Figure 4. A 38 Year-old-woman with Chronic Inflammation. Sonographically, and UE (score 4) imaging misdiagnosed as a breast cancer

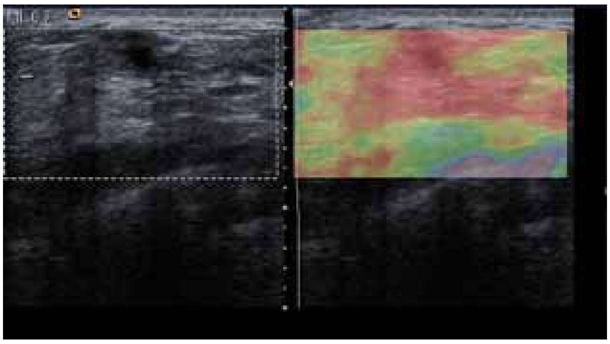

Figure 5. Galactocele in a 29 Year-old-woman with Heterogenous Internal Echotexture with Posterior Acoustic Enhancement. Though the margin of the lesion is not clearly visible, correlating clinically it was defined as benign from 2D sonography. On UE there was no strain over the entire hypoechoic lesion or in the surrounding area. Both the lesion and its surrounding area are red (Score 5)

The elastic properties with in the normal tissue, fibroadenoma and cancer are different (Walz et al., 1993; Sarvazyan et al., 1995) assessing that the neo-plastic tumors are significantly harder than the fibroadenomas. However, we should recognize some development features of fibroadenoma and cancer, when they are in various stages of growth. If we consider the FN(false negative) result, when both UE and sonography were used, should be aware that the sonographic and elastographic features of medullary carcinoma which resembled like benign, with round shape and circumscribed margin. (Figure 1). Most of them also lack desmoplastic reaction (Sewell, 1995). Similarly, poor stroma and lack of sonographic conspicuousness features may misguide the results. Hence, two invasive ductal carcinomas that were in very early stages were missed by UE. Even by using both methods of UE and sonography, interpretative difficulties occurred in 10 instances, False positive (FP), especially in the chronic inflammation, hyperplasia and giant lobulated fibroadenoma, leading to upgrading and worsening in classification both at sonography and UE.

UE was superior to sonography both in sensitivity (95.7% vs. 91.4%) and specificity (96% vs. 90%). Our results were similar to those reported by (Garra et al., 1997; Itoh et al., 2003; Luo et al., 2005; Wang et al., 2005; Yu et al., 2005; Thomas et al., 2006). Similarly in a study performed at Singapore General Hospital the sensitivity of UE was 100% vs.88.5% (sonography) (The Medical News, 2009).

In a study conducted by Q. Zhu et al., 2008, 10 cancers were below score 3, of them 3 were scored 3 and 7 were scored 2 according to EI score classification. Cancers that scored 3 were, low grade DCIS, poorly differentiated IDC and mucinous carcinoma. Similarly in our study, out of 70 malignant lesions, 2 were scored 3 and 1 was scored 2 on UE. The missed cancers were pathologically on early stage of invasive ductal carcinoma and medullary carcinoma. These cancers had sonographically benign features; round, circumscribed, with no desmoplastic reaction (medullary carcinoma). Similarly, giant lobulated fibroadenoma, chronic mastitis, hyperplasia with presence of calcifications were missed on sonography and UE and leading to False Positive.

As we know that, conventional US are operator-dependant, and there may be an inter-observer variability. Similarly UE also requires training and practice to learn the appropriate technique. In our experience, most of the images which were excluded from the study belonged to the initial period of the learning curve. Perpendicularly firmly held US probe on the breast surface overlying the lesion is mandatory to obtain correct elasticity images. When the operator is well trained, the UE can be performed straightforwardly after the US conventional study, and it needs only a short extra time of 5min on average.

Among sonography BI-RADS scores, when cutoff point of 4 was used to describe the malignancy of lesions, 91.42%(64/70) of the total cancers were detected alone by sonography. Also, when we used EI score of 4 as the cutoff point, UE detected 95.7%(67/70) of the cancers. In our study the joint use of sonography and UE statistically showed an improvement in detecting the cancer(sensitivity 98.5%; 69/70) but there was no statistically improvement in the specificity. It may be due to that most of the malignant cases that were studied had suspicious sonographic features of malignancy. And those benign cases which were not recognized on a joint study have conspicuous features of malignancy. As the study is solely performed by single observer, some biasness in image interpretation may have occurred.

There are several limitations in our study. First, the area of the target lesion occupied in the ROI should be less than one third .The ROI in a large lesion only included the lesion itself and left out the surrounding breast tissue that affected the strain and presentation of both normal and abnormal structures. Second, to compare the target lesion elasticity with that of normal breast tissue, both types of tissue should be present in the ROI. Thirdly, the probe should be handled firmly and perpendicularly so that no any manual pressure should be applied during the acquisition of images.

In conclusion, ultrasound elastography(UE) is a simple, non-invasive diagnostic examination that provides information about the stiffness of a mass. Thus,utilizing the newly emerged technology along with conventional sonography will be of great clinical value in detecting the malignant lesions. Combined use of UE and sonography in routine examination may help the investigator to rule out the different characteristics of the lesions and will help to increase the sensitivity for detecting the malignant lesions.

References

Brenner H, Gundos A, Arndt V (2007). Recent major progress in long term cancer patient survival disclosed by modeled period analysis. *J Clin Oncol*, **25**, 3274-80.

Garra BS, Cespedes EI, Ophir J, et al (1997). Elastography Of breast lesions: initial clinical results. *Radiology*, **202**, 79-86.

Hiltawsky KK, Kruger M, Starke C, et al (2001). Freehand ultrasound elastography of breast lesions: clinical results. *Ultrasound Med Biol*, **27**, 1461-69.

Itoh A, Ueno E, Tohno E, et al (2006). Breast disease: clinical application of US elastography for diagnosis. *Radiology*, **239**, 341-50.

Jemal A, Murray T, Ward E, et al (2005). Cancer statistics. *CA Cancer J Clin*, **55**, 10-30.

Konofagou EE (2004). Quo vadis elasticity imaging. *Ultrasonics*, **42**, 331-336.

Luo Bm, Ou B, Feng X, et al (2005). Breast diseases: Comparative study of real-time tissue elastography with pathology. *Chin J Ultrasound Med*, **21**, 662-4.

Robert A. Smith (2007). Effect of mammographic services screening on stage at presentation of breast cancers in Sweden. *Cancer*, **109**, 2205-12.

Saarenmaa I, Salminen T, Geiger U, et al (2001). The effect of age and density of the breast on the sensitivity of breast cancer diagnostic by mammography and ultrasonography. *Breast Cancer Res Treat*, **67**, 117-23.

Sarvazyan AP, Skovoroda AR, Emelianov SY, et al (1995). Biophysical bases of elasticity imaging. *Acoustical Imaging*, **21**, 223-40.

Sewell CW (1995). Pathology of benign and malignant breast disorders. *Radiol Clin North Am*, **33**, 1067-80.

Tabar L, Yen MF, Vitak B, et al (2003). Mammography service screening and mortality in breast cancer patients: 20-year follow up before and after introduction of screening. *Lancet*, **361**, 1405-10.

The Medical News (2009). Breast elastography allows for a more accurate diagnosis of breast cancer; Available from http://www.news-medical.net/news/2009/04/23/48795.

Thomas A, Kummel S, Fritzsche F, et al (2006). Real-time sonoelastography performed in addition to B-mode

ultrasound and mammography : Improved differntiation of breast lesions. *Acad Radiol*, **13**, 1496-504.
Tian Fg, Guo XY, Zhong HY (2005). Advanced in diagnosis and treatment of breast cancer. *Cancer Res Clinic*, **17**, 58-60.
Ueno E, Iboraki P (2004). Clinical application of US elastography in the diagnosis of breast disease. European Congress of Radiology, Vienna.
Walz M, Teubner J, Georgi M, et al (1993). Elasticity of benign and malignant breast lesion: imaging, application and results in clinical and general practice. 8th International Congress on the Ultrasonic Examination of the breast.
Wang Y, Wang Y, Zhang XM, et al (2005). Evaluation of elastography application in differentiating benign and malaignanat breast tumors. *Chin J Med Imaging Technol*, **21**, 1704-6.
Yang L, Parkin DM, Li L, et al (2003). Time trends in cancer mortality in China: 1987-1999. *Int J Cancer*, **106**, 771-83
Yang L, Parkin DM, Li LD, et al (2004). Estimation and projection of the national profile of cancer mortality in China 1991-2005. *Br J Cancer*, **90**, 2157-66.
Yang L, Parkin DM, Ferlay J, et al (2005). Estimates of cancer incidence in China for 2000 and projections for 2005. *Cancer Epidemiol Biomarkers Prev*, **14**, 243-50.
Yu Q, Xu ZZ, Mao F, et al(2005). Preliminary application of elastography in diagnosis of breast diseases. *Shanghai Med Imaging*, **14**, 102-3.
Zhu Q, Jiang Y, Liu J, et al (2008). Real-time ultrasound elastography: its potential role in assessment of breast lesions. *Ultrasound Med Biol*, **34**, 1232-8.
四川省乳腺治疗网，2008.乳腺癌警示月：我国乳腺癌发病率30年增长3倍多. Available from http://www.120rx.com/jiaoan/html/?220.html (Chinese article).