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Methods of early detection: would clinical breast examination and breast ultrasonography be a good alternative to mammography?

Adrian YS Yip, WP Chu, Louis WC Chow, Wings TY Loo, Eleanor YY Ong, Wincy Chan

Breast cancer is one of the leading causes of cancer deaths among women[1]. In the past 40 years, breast cancer incidence has doubled or even tripled in developed countries such as South Korea and Japan; whereas it is about 20% to 30% in China and India in the past decade[2-4]. An increasing incidence rate of 3% each year was observed in mainland China[5]. It is getting more common that especially in low- and middle-income countries (LMCs), where about 45% of new cases and over 55% of deaths in Asian countries were reported[6], with an annual increase rate of 5%[7]. However in Africa, it is difficult to evaluate the trend, due to the inaccurate population data. It has been estimated that up to 70% of breast cancer new cases will occur in developing countries by 2020[8] and that 84 million people will die from it in the next 10 years if no actions will be taken according to World Health Organization (WHO)[9].

In the last decades, infection was still the leading public health problem in the LMCs. However, non-communicable disease such as cancer is increasingly burdening the health community and it has become the focus of attention of health authorities which are reallocating resources to cope with the health issue now. Breast cancer is used to be more common in western countries than in eastern countries. But now, "westernisation" might explain the increased incidence in developing countries. Westernised lifestyle, industrialisation, delayed fertility, longer life expectancy, poor dietary habits, and low exercise rates are recognised as risk factors of breast cancer[10-11]. In any case, breast cancer has already become a global health burden.

Early detection of breast cancer is deemed as the major preventive strategy and many studies have been carried out. Breast cancer mortality rate has been reduced in developed countries due to the application of early detection and effective treatment. Known as "secondary prevention", with the use of mass mammography (MMG) screening and clinical breast examination (CBE), breast cancer screening could detect cancer in earlier stage such that about 70% of the newly diagnosed cases in developed countries are in stages 0 and 1[12]. However, in

Authors' address: Organisation for Oncology and Translational Research, Hong Kong (Adrian YS Yip, WP Chu, Louis WC Chow, Wings TY Loo, Eleanor YY Ong); Clinical Trials Centre, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong (Louis WC Chow); Comprehensive Centre for Breast Diseases, UNIMED Medical Institute, Hong Kong (Louis WC Chow, Wings TY Loo, Wincy Chan)

Corresponding author: Louis WC Chow, E-mail: lwcchow@ootr.org

LMCs, due to the lack of awareness, limited healthcare infrastructure, inadequate manpower and uneven distribution of resources, about 75% of the cases are usually diagnosed at late and untreatable stages (clinical stages Ⅲ and Ⅳ)[13-15]; for example, in less developed regions in China, 12.7%, 48.3%, 18.2% and 3.7% of cases were diagnosed at stage Ⅰ, Ⅱ, Ⅲ, and Ⅳ respectively and 18% was unknown for clinical stage at diagnosis[16]; in India, 1%, 23%, 52%, and 24% of cases were diagnosed at stage Ⅰ, Ⅱ, Ⅲ, and Ⅳ respectively[17]. More patients were diagnosed at the advanced stage of the disease. Nevertheless, in more developed regions, for example, in China, more patients were diagnosed at an earlier stage. It is evident that mortality rates in LMCs are higher than those in developed countries[3]. As breast cancer care might heavily rely on cancer treatments that are already limited, it is essential to uphold the cancer prevention strategy to save more resources by increasing breast cancer awareness and organizing screening control programmes.

It is well recognised that the purpose of a screening programme is to reduce mortality, and the patient might receive a less aggressive treatment by early detection which allows detecting an early-stage tumour of less than 1 cm size, negative lymph node status and no distant spread[18]. In fact, the use of preventive service is closely linked to a healthy lifestyle of an individual[19]. An accurate screening and diagnostic tool could definitely give clinicians a better decision for selection of appropriate therapy to cure cancer. As more people utilize the preventive service, burden to the healthcare system could be mitigated in a long run given that the service has to be accurate and reliable enough to avoid unnecessary checkups.

However, many other factors could still hamper early detection in the first place despite the availability of advanced breast cancer therapies. Socioeconomic status (SES) is significantly associated with negative health outcomes in USA[20-21], and a high SES is considered as a risk factor of breast cancer[22]. Differences in culture and knowledge have been associated with health status and behaviours[23], in which education, knowledge, and income are major predictors for a woman to receive a MMG or not[24-25]. Several studies have also reported that there is an association between increased uptake of MMG and the place of residence with more physicians[26-27]. Compliance is another important determinant for the success of a screening program which requires continuous implementation to accumulate health capital of a society; however the compliance to different screening methods is affected by the availability of resources and the initiatives of women. The use of breast cancer screening varies among different ethnic groups[28-32] and it has been suggested that different communication strategies are needed for promotion of a screening programme among patients with different ethnic backgrounds[33].

To improve the health of a community, health education is an important initial step to change the healthy lifestyle such that, taking breast cancer as an example, the public will realise the importance of early detection for better therapeutic outcome. Education is part of the early detection programmes and it involves the

least resources. This is particularly important in the LMCs, because any misconceptions about breast cancer might hinder women from participating in any screening programming and consulting doctors for any change in health status. Stockton et al[34] found that the rate of advanced breast cancer dropped in the 1980s in the United Kingdom, even before the National Breast Screening Programme had begun. This dramatic fall was aided by public education and the increased awareness about early detection. Unfortunately, there are still many people not having much knowledge about breast cancer. According to a report about the introduction of screening programme in Ukraine, some women did not believe in the result obtained from CBE and refuse further clinical investigation which might contribute to the failure of a screening programme[35]. Different countries might require different screening modalities which are acceptable and accessible to the public.

1 Cost-effectiveness

The WHO suggests that the start of breast cancer screening should be based on the available resources and cancer incidence. She also suggested that 70% of the population at risk should be screened in order to effectively reduce mortality from breast cancer[36]. However, existing guidelines and studies are primarily from countries with high-level resources, but not LMCs. As a result, it is essential to produce a more suitable guideline for LMCs, and more studies are needed to evaluate the true cost-effectiveness in those countries.

The true benefit to the health of a community by a screening programme depends not only on the efficacy of a screening tool, but also on its cost-effectiveness such that a screening programme will not incur an imbalance of resource allocation in a society. The cost-effectiveness of the screening methods can be measured by the cost per year of life expectancy gained. It is calculated by dividing the total cost of the screening programme by the years of life expectancy gained (YLEG) by all women who benefit from screening. YLEG is the difference between the lifespan of women who have had and benefited from screening and those who have not.

The estimates of cost-effectiveness of screening vary in different studies due to the different methods of calculation, benefits and costs assumptions. As estimated by Rosenquist and Lindfors[37], it would cost US $18 000 per year of life expectancy saved with an annual MMG beginning from age 40 to age 79 years. With the assumption of this screening benefit, the annual MMG screening might reduce breast cancer mortality by 36% for women aged 40–49 years and 45% for women aged 50–79 years. In previous studies, both annual and biennial screenings are suggested to be cost-effective for all ages in the women[38-40], but it might only be feasible in well developed countries where resources are available. MMG might not be appropriate for LMCs due to its high cost of skilled manpower and stringent quality control[41].

Breast cancer screening strategy employed in a developed country might not be feasible in LMCs. In Australia, the Australian National Breast Cancer Centre

recommends the 'triple test', the combination of CBE, imaging and biopsy, which provides a more accurate diagnosis of breast cancer. In LMCs, due to inadequate funding and uneven distribution of resources, the quality of healthcare services varies from clinics with basic services to specialised hospitals with specialists and equipments for cancer prevention, detection and treatment. Furthermore, in most of the hospitals in LMCs, the cancer services are very limited and fundamental. Less than 5% of the resources are used for cancer control, and over 80% of cancer patients are unable to receive any treatments after diagnosis[42]. The lack of radiotherapy service is definitely an obvious example of poor cancer service in LMCs. In India, radiotherapy is usually available in private hospitals and the 21 regional cancer centres[43]. The International Atomic Energy Agency has reported that only about 30% of the world radiotherapy services are in the LMCs, where 85% of the world's population live there. At least 50% - 60% of breast cancer patients can suffer from less pain and prolong their lives with radiotherapy[44]. In the LMCs, the treatment plan which a breast cancer patient receives is totally dependent on where she lives.

A successful screening programme is attributed to not only an appropriate and accurate screening tool, but also a comprehensive planning before commencement of a programme. A population- or community-based screening programme might give a large demand to the hospitals and healthcare centres. Therefore, healthcare service such as breast cancer treatment has to be standardized and necessary supporting healthcare policy should be fully implemented before a screening programme can be established. In addition, insurance coverage is closely related to the access of preventive services[45]. To prepare a country with availability and accessibility to preventive service, a well-structured financial support is essential even though a very effective preventive method is available. In the LMCs, finance is a very important factor to secure the success of a screening program with no doubt.

All these indicate that there is an urgent need in the introduction of a cost-effective and accurate screening method for the LMCs. However, the efficacies of different screening methods vary by age, types of carcinomas, societies and cultures. Nowadays, CBE and MMG remain the standard practice in many countries while other imaging method such as ultrasonography (USG) has not yet been approved for general screening[46]. It is also crucial to take into consideration that screening might create unnecessary anxiety to women. A highly accurate screening tool therefore plays a particularly important role to avoid many unnecessary worries and cost.

2 Different Screening Tools

2.1 Clinical breast examination (CBE)

CBE is a common breast cancer screening especially in countries with limited resources. It is carried out by a trained clinician who follows the guidelines and recommendations to maximise the effectiveness[47-48]. Abnormalities and lymph node evaluation may be detected by visual inspection and palpation at an early

stage[49]. Some evidence has suggested that CBE is able to detect most of breast cancers found by MMG and some that missed by MMG and other methods among pre-menopausal women[50-51].

Although CBE is not standardised in terms of performance and documentation and it might be unable to detect very small tumours, it could improve the situations of the patients who are diagnosed at very late stage[52]. In addition, it is a useful screening method for women who are not recommended to undertake MMG because it is cheap and simple. In the LMCs, the easily accessible and relatively cheap screening tool might be a good choice for regular screening which might improve the cancer detection rate and subsequently the survival rate when screening mammography is not available or barely accessible. As part of routine health examination, CBE might increase the breast cancer awareness of the women and healthcare practitioners could encourage the women to come for a health check-up more often, and subsequently earlier detection of breast cancer at lower disease stage could be achieved. It might be useful for some countries which are planning to set up a breast cancer screening programme.

Breast self-examination (BSE) was considered as another tool for earlier breast cancer diagnosis at an earlier stage[53-56] long time ago, but BSE alone was unable to reduce mortality from breast cancer in the absence of other screening tools according to two randomised studies[57-58]. Therefore, BSE is not recommended for screening purpose at the moment[59]. Comparatively, CBE is better[60], but there is also lack of randomised studies evaluating the effectiveness of CBE independently contributing to the reduction in breast cancer mortality. Recently, an annual CBE has been recommended for the women aged 40 or above by the American Cancer Society[61] and the combined use of CBE and MMG has been suggested by many national organisations, such as the American Medical Association, American College of Obstetricians and Gynecologists, and American College of Radiology[62]. As a result, most of the trials have only investigated either the single use of MMG or a combination with CBE for early detection of breast cancer. The effectiveness of CBE is only derived based on its performance. In women who have had regular screening, the sensitivity of CBE is only 31%, when compared to 69% in those who have not had much screening; in addition, its sensitivity is higher in women under the age of 50 years[63,64]. Barton et al[65] examined six studies and concluded 54.1% for CBE sensitivity and 94.0% for its specificity. Sankaranarayanan et al[66] conducted a cluster randomised controlled trial in India to evaluate three rounds of triennial CBE for healthy women. The sensitivity of 51.7% and the specificity of 94.3% were observed. These values are similar to the published results from 752,081 CBE reports with 58.8% sensitivity and 93.4% specificity by the US national screening program[67].

The sensitivity of CBE is dependent on different factors, such as age, tumour size and characteristics, ethnicity, hormonal status, and breast tissue[51]. Furthermore, in Barton's silicone models, significant results were found in CBE that was taken longer

than 2 minutes with more accurate techniques, such as systematic search pattern, thoroughness, different palpation pressure, three fingers, finger pads, and circular motion[65]. More studies are definitely needed to evaluate the true CBE effectiveness. However, its accuracy may be increased with better techniques.

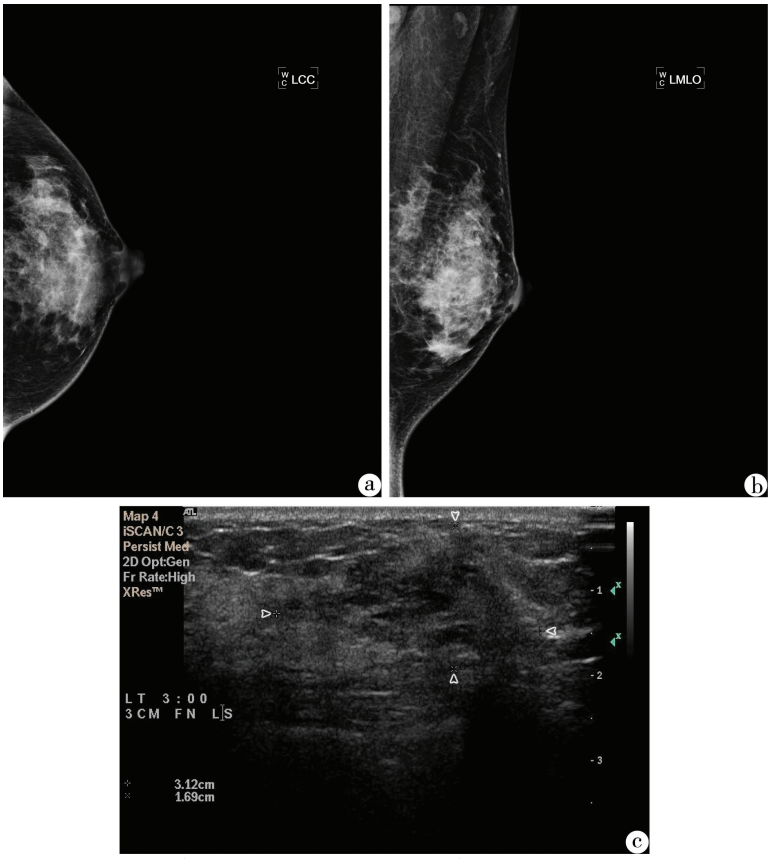
2.2 Ultrasonography (USG)

USG gives a real-time image of breast tissue structure by the reflected high-frequency sound waves which pass through the breast tissue. It is well tolerated and is widely available. A decade ago, USG was mainly performed by breast surgeons, but nowadays, it can be performed by primary practitioners who are less experienced, or even by the patients[68]. Notwithstanding the relatively worse resolution than MMG, the primary use of USG is to differentiate cystic masses from solid lesions, benign solid lesions or malignant solid lesions[69]. It is therefore not considered as a screening tool[70]. However, an experienced clinician is definitely able to obtain more accurate information from the images to give a correct diagnosis, and might be able to estimate the likelihood of malignancy in a solid mass by USG[69]. In addition, it can guide tissue sampling for pathology diagnosis as well[71-72]. Unfortunately, its limited field of view is another disadvantage which makes it unable to assess the whole breast.

USG has recently been used as a supplement imaging procedure to MMG[69,73], or a complementary assessment method for clinically detected breast masses[49] so as to avoid unnecessary aspiration and surgery. On the whole, USG is still regarded as a complementary diagnostic tool; however, with improving technology in differentiation and characterization of benign and malignant lesions by elastography, the advanced USG producing the mean sensitivity of 83.4% and specificity of 84.2% for the diagnosis of malignant breast lesions[74] might possess another role in the future . It is noteworthy that early age at breast cancer onset is observed in Asian women and the sensitivity of USG will be higher for women with higher breast densities among young women in Asia. USG is therefore more commonly used in Asian countries, for example, in mainland China, many physicians would prefer the use of USG to screen for breast cancer in young women because it is sensitive and able to detect smaller lesion in a dense breast.

A study of 796 breast cancer patients showed that USG is significantly better than MMG for detecting invasive breast cancer[75]. Promising results in detecting breast cancer by USG were also demonstrated in other studies[76-79]. A study of 165 breast cancer patients also showed that USG is more sensitive than MMG (99% vs. 85%) when detecting breast invasive carcinoma in women aged 30 to 39 years[80]. Another prospective study comparing the accuracy of CBE, MMG and USG in predicting the size of histological malignant breast cancers demonstrated that USG was the best predictor among the three[81]; a lower sensitivity than MMG was also observed in other studies as well[82-83]. A systematic review of breast cancer screening with high-frequency USG in Asian women has demonstrated that the combined sensitivity and specificity were 0.785 (95% CI: 0.726-0.837) and 0.975

(95% CI: 0.973-0.977) respectively[84]. The area under the Summary Receiver Operating Characteristic curve was 0.98 and, at follow up, 96.9% of patients diagnosed with breast cancer were at clinical stage Ⅱ or below, which highlighted a high accuracy of screening USG for breast cancer in Asian women characterised by younger age of onset and higher breast density than western counterparts. In addition to the accuracy of the detection method, compliance is another important element for a screening programme. In another study of 1 239 asymptomatic young Asian women screened for breast cancer, the compliance rate with USG is significantly higher than with MMG (80.1% vs. 73.5%, $P = 0.006$)[85]. Assessment-induced pain and unsatisfactory examination results (BI-RADS category 0) were major barriers for follow-up MMG while embarrassment and unsatisfactory examination results were major barriers for follow-up USG. With the high accuracy and better compliance among Asian, breast cancer screening using USG might be feasible in Asian countries. In our clinical experience, USG is a more useful diagnostic tool to provide clinicians with better breast radiological findings of younger patients than MMG (Fig 1).



(a) Left breast-CC view; (b) Left breast-MLO view; (c) Left breast lesion 3.12 cm×1.69 cm

Fig 1 First radiological assessment of a 31-year-old patient presented with breast pain. Her mammogram (a, b) was read as excessively dense breasts which decrease the sensitivity of mammogram and her ultrasound (c) was read as hypoechoic lesion highly suggestive of malignancy with infiltrative feature at left breast 3 : 00. Pathology of the left breast and axilla revealed invasive mucinous carcinoma with metastasis of sentinel and axillary lymph nodes, pT3, G1, N2, M0.

2.3 Mammography (MMG)

MMG gives X-ray images of the breast at mediolateral oblique and cranial-caudal views. It has been the "gold standard" of breast cancer detection for decades, and some data even showed that its sensitivity is up to 90%. Some randomised controlled trials showed that MMG may reduce breast cancer mortality by up to 21%[86]. According to a large-scale clinical study with 42 760 patients from USA and Canada, MMG demonstrated a sensitivity of 70.0%, specificity of 92.0%, and a diagnostic accuracy of 78.0%[87]. Similarly in Europe, the sensitivity and specificity of MMG from a randomised screening trial with 23 929 patients from Norway was 77.4% and 96.5%, respectively[88]. Therefore, MMG screening tests have become popular in Europe, North America, Australia, Japan, and some other developed countries[89].

Despite a good standard against other imaging techniques with higher sensitivity and specificity, MMG still has its limitation in different situations. MMG is unable to detect small and lobular breast cancers, and it has got a poor resolution in dense breasts. Younger women have a higher breast density, and therefore the sensitivity of MMG is reduced for premenopausals[90]; the sensitivity of MMG was increased by age and the fattiness of breast[91]. Kerlikowske et al[92] found that women aged 50 or over with a less dense breast had a higher MMG sensitivity (98.4%) than that with predominantly dense breasts (83.7%); whereas in women aged 50 or below, the sensitivity in fatty breasts was 81.8% compared to 85.4% in dense breasts. An even greater difference was found in Mandelson's study which showed that the MMG sensitivity in women with fatty breasts was 80%, but only 30% in those with extremely dense breasts[93]. Several studies have reported a relatively lower sensitivity of screening MMG in women with dense breasts than those with fatty breasts after adjustment for confounding factors including age and menopausal status[93-94]. Thus, the breast density is regarded as one of the major factors causing false-negative findings[95-96].

It is important to note that a dense breast does not only give a poor resolution to MMG, but is also highly associated with breast cancer risk, and that women with a dense breast have a four- to six-fold higher risk of developing breast cancer[97-98]. A careful selection of an appropriate screening modality for women with dense breast is therefore necessary. In some other MMG studies, results have shown that MMG might detect about 35%-45% of non-palpable cancers[99], although they may be visualised by modern USG already. In addition, as shown in some conceptual models, the use of MMG may be influenced by individual and environmental characteristics[26,100-102] and about 10%-12% of the breast cancer cases are missed[103]. Furthermore, women with germ-line mutations have got an increased breast cancer risk and more than 50% of them may get the cancer before 50 years old[104]. Therefore, they are recommended to start screening at an early age. However, MMG might not be sensitive enough to screen for breast cancer when they are still young, so MMG might not be an ideal option for them.

Except for genetic and environmental factors, the risk of breast cancer may be increased by radiation[105]. Mattsson et al[106] also showed that there was a statistically significant increase in breast cancer incidence after receiving radiation treatment of benign breast diseases. A strong association had also been found between radiation-induced breast cancer and radiation dose ($P<0.0001$)[107]. The mean glandular radiation dose of 2-view MMG is about 4 to 5 mGy, and the dosage is variable among different facilities. The dosage increases with breast density, and the cumulative exposure is about 60 mGy during a decade[108]. Nevertheless, a review of 117 studies about MMG concluded that the reduction in breast cancer mortality from early detection outweighed the breast cancer death risk due to MMG radiation[109].

3 Evaluation

The efficacies of USG and MMG greatly differ in different situations and that the clinical applications for cancer detection remain controversial. Both of them have been found to be more reliable in estimating the size of pre-operative breast cancer than palpation. A similar sensitivity and accuracy of their performances have been reported as well[110-111]. Potterton et al[112] suggested that USG was useful in assessing and localising small tumours detected by MMG and Pierie et al[113] demonstrated that USG was the most reliable method for pre-operative assessments. In recent years, the combination use of USG and MMG for treatment planning has also been suggested[114] and a randomised controlled study to recruit 100 000 subjects is being conducted in Japan[115], although a number of false positives might increase[116].

The question about which screening method should be used in the LMCs requires heedful consideration. The diagnostic efficacy is an important factor. However, the choice is dependent on how much the health authorities are able to pay. Majority of the population are unable to receive screening and treatment due to the rapid increase in healthcare cost. Although MMG is the only screening method which might reduce breast cancer mortality[117-123], and it is the fundamental screening resource in countries with high-level of resources, while USG is used as a supplement imaging procedure to MMG.

The use of MMG might be a barrier in the LMCs due to the use of expensive X-ray film. Likewise, although digital MMG does not use the X-ray film, the machine itself is expensive. Furthermore, the use of MMG is solely for breast imaging; whereas USG can be used in many other parts of the body for real-time imaging, and the film is not necessary. In addition, MMG requires manpower, and technical expertise. Only about less than 10% of MMG have been carried out in LMCs[124]. In some places where MMG is merely available, the service is usually reserved primarily for diagnosis rather than for screening. MMG might not be affordable in most of the LMCs. Instead, USG might be used in the LMCs before MMG screening will be carried out.

In countries with limited resources, almost half of the breast cancer cases are

diagnosed at an advanced stage and are therefore unable to undergo resource-intensive breast-conserving therapy[125] Also, it has suggested that MMG is necessary to determine the presence of cancer in the same quadrant or in different quadrants if breast conservation is available. In this case, when the use of screening MMG might not be accompanied by adequate surgical and drug treatment options in LMCs, it might not be cost-effective for implementation of screening MMG. After considering about the advantages and disadvantages of CBE, MMG and USG, the combined use of CBE and USG may be an option for early detection of breast cancer. CBE may give an idea of where the lesions are before the use of USG, which may increase the USG sensitivity. Benson et al[74] suggested that the USG could be used as an extension of "clinician's fingers", and that USG might be a useful tool for evaluation after a positive CBE. It is a useful method to diagnose symptomatic disease, confirm the presence of a breast mass and document the tumor size. It is particularly important in places where MMG is not available. The cost effectiveness of biennial CBE in India was found to be US $522 per life-year saved in a population of 1 million women[126]. In LMCs with limited resources, CBE might be an ideal option for breast cancer screening.

In addition, USG is accessible to all parts of the breasts, and it does not give out any ionising radiation. Patients in the LMCs usually suffer from locally advanced and palpable invasive cancers, and the average age at diagnosis tends to be young. A young diagnosed age means they usually have dense breasts, in which USG seems to be a better diagnostic tool. The efficacies of CBE and USG are highly dependent on the skills of the clinical staff performing them, but the skills improve after training and practice.

4 Conclusion

The best way to reduce breast cancer mortality rate is to combine early detection with appropriate treatment before we could get a definitive cure against it. If breast cancer patients are unable to receive systemic treatment, the screening programme might have a limited value. However, the use of CBE and USG which are effective and accessible but less expensive should be considered in LMCs, where resources are limited. According to the present economic situations in the LMCs, CBE should be given the priority, whereas screening MMG should be introduced when sufficient resources may be allocated in the future.

【Key words】 breast neoplasms; early detection; clinical breast examination; ultrasonography; mammography; low- and middle-income countries

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(Received September 30, 2011)
(Edited by ZHAO Bin)

Adrian YS Yip, WP Chu, Louis WC Chow, et al. Methods of early detection: would clinical breast examination and breast ultrasonography be a good alternative to mammography? [J/CD]. 中华乳腺病杂志:电子版,2011,5(6):646-659.