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乳房超音波在乳癌篩檢的效益評估

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計畫主持人：黃俊升

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Abstract

Keywords：breast ultrasound, breast cancer screening

As Taiwan is an area of low breast cancer incidence, the breast cancer prevention policy of the Department of Health for many years has been breast self-examination. However, a large randomized trial of breast self-examination in Shanghai, by Thomas et al, found that self-examination is not an effective method for early detection of breast cancer. Although it is well documented that mass screening using mammography lowers the mortality of breast cancer among women over the age of 50, women aged 40 to 49 do not appear to benefit to the same extent. In contrast to Western countries, breast cancer in Taiwan is characterized by an earlier onset, with peak incidence at age 40-49 and more than half of breast cancers arising in premenopausal women.

Since premenopausal women have denser breasts than postmenopausal women and Taiwanese women have smaller breasts and a higher percentage of dense breasts, increased mammography screening frequency may be not the sole solution to increase the detection rate in this age group. The addition of other screening modalities, such as breast ultrasound, may be helpful. We reviewed breast tumor cases with histopathological diagnosis and examinations of ultrasound and mammography at National Taiwan University Hospital. The false negative rate of breast ultrasound and mammography for diagnosis of palpable breast cancers were 7.1% and 18.6%, respectively. We furthered linked the ID numbers of women having undergone examinations of breast ultrasound and/or mammography at National Taiwan University Hospital to the data file of National Cancer Registry.

The results of ultrasound and mammography were reviewed for those cancers not operated at National Taiwan University Hospital but had examinations within 6 months before surgery. The re-calculated false-negative rate of breast ultrasound and mammography were 4.5% and 17.5%, respectively. Twenty five percent of palpable cancers were not visible in patients younger than 50 years of age, while only 5% in patients older than 50. About 90% of palpable cancers with false-negative mammography were diagnosed as cancer by ultrasound. These results support the idea that ultrasound should be helpful in detecting cancers missed by mammography in dense breasts, more frequently present in premenopausal women, which indicates the role of breast ultrasound in breast cancer screening and justifies a randomized mass screening using breast ultrasound and mammography in Taiwan.

摘要

關鍵詞：乳癌篩檢, 超音波

台灣仍屬乳癌低發生率的地區，因此衛生署乳癌防治的政策向來是乳房自我檢查。然而，在上海執行的大規模隨機分配試驗發現，乳房自我檢查並不能早期發現乳癌。至於使用乳房 X 光攝影進行大規模乳癌篩檢，雖然可以降低 50 歲以上婦女的乳癌死亡率，然而在 40 歲到 49 歲的婦女，並未能顯現效果。相較於歐美國家，台灣的乳癌發生的年齡層高峰為 40 歲到 49 歲，一半以上的乳癌發生於停經前的婦女。

由於停經前的婦女乳房較為緻密，而且 台灣婦女乳房緻密的比率較高，因此增加乳房 X 光的篩檢頻率，並不見得是提高乳癌偵測的適當方法。採用其他篩檢工具，例如乳房超音波，可能較有幫助。吾人分析在台大醫院檢查且有切片結果者發現，乳房超音波與

乳房 X 光攝影在乳房腫瘤診斷的偽陰性分別為 7.1%及 18.6%。吾人進一步將民國 84 到 86 年在台大醫院做乳房超音波及乳房 X 光攝影的名單與全國癌症登記相連，發現未在台大醫院手術的病例，經查其乳房超音波及乳房 X 光攝影檢查結果，重新計算偽陰性為 4.5%及 17.5%。結果亦顯示，在乳房較為緻密的年輕婦女，乳房 X 光攝影較易遺漏一些摸不到或甚至摸得到的乳癌，而乳房超音波可能早期偵測這些乳癌。本研究結果將有助於確定乳房超音波在乳癌篩檢的地位，並確定台灣需要進行大型隨機分配研究，以了解乳房超音波及乳房 X 光攝影在台灣乳癌篩檢的效益。

前言

Although breast cancer in Taiwan has a low incidence compared to that in high incidence areas of the world, it has been markedly increasing in recent years and now has the second highest incidence of all cancers in female Taiwanese (1). The mortality of breast cancer has also increased and it is even higher than that of cervical cancer, the highest incidence cancer. The reason for the lower mortality of cervical cancer may be the high prevalence of in situ cancer detected by pap smear. In 1995, 36% of cervical cancers in Taiwan were in situ cancers, while only 4.7% of breast cancers were non-invasive.

As Taiwan is an area of low breast cancer incidence, the breast cancer prevention policy of the Department of Health for many years has been breast self-examination, which does not involve a large financial outlay. In addition, theoretically, women may be able to detect subtle changes in their own breasts that might be missed on clinical breast examination by doctors. Since Taiwanese women have relatively small breasts, it was assumed that self-examination would be able to detect breast cancer earlier. However, many breast cancers were diagnosed in the late stage.

Although many factors contribute to the late discovery of cancer (2), many clinicians doubted that self-examination was an effective method for the early detection of breast cancer. Doubts about self-examination were supported by the results of a randomized trial of breast self-examination in Shanghai, published in 1997 by Thomas et al. (3), in which about a quarter of a million Chinese women were randomized to either a self-examination instruction group or a control group. After 5 years of follow-up, the number of breast cancers detected in the two groups was equal, and the breast cancers detected in the self-examination group were not diagnosed at an earlier stage or smaller size than those in the control group. Cumulative breast cancer mortality rates during the 5 years from entry into the trial were also almost identical in the two groups.

Although it is well documented that mass screening using mammography lowers the mortality of breast cancer among women over the age of 50, women aged 40 to 49 do not appear to benefit to the same extent. The reduction in breast cancer mortality for women who began screening between the ages of 35 and 49 years varies from 18% to 35% (4-7). The National Cancer Institute therefore recommends mammographic screening every 1-2 years for all women in their 40s (8), while the American College of Radiology, the American Cancer Society, and the American Medical Association advise annual screening for all women in this age group (9-11). Most people who are against annual screening for women in their 40s believe that both the incidence and detection rate of breast cancer in younger women is lower (12).

In contrast to Western countries, breast cancer in Taiwan is characterized by an earlier onset, with peak incidence at age 40-49 and more than half of breast cancers arising in premenopausal women (13,14). Data from one hospital for 811 Taiwanese breast cancers showed that 63% of their breast cancer patients were premenopausal and 29.3% of all patients were early onset (age

≦ 40) (13). The follow-up data showed that early onset breast cancer had a more aggressive behavior than that in the older age group. Screening women aged 40-49 may be more important than, or at least as important as, screening women older than 50. The dilemma of breast cancer screening in Taiwan can be summarized by Taiwan having a rapidly increasing incidence of breast cancer, especially in premenopausal women, while the incidence is still low compared to Western countries. Since premenopausal women have denser breasts than postmenopausal women and Taiwanese women have smaller breasts and a higher percentage of dense breasts, increased mammography screening frequency may be not the sole solution to increase the detection rate in this age group. The addition of other screening modalities, such as breast ultrasound, may be helpful, as breast ultrasound can detect some breast cancers in dense breasts that are missed by mammography (15,16).

研究目的

1. To determine the sensitivity and specificity of breast ultrasound and mammography in breast examination.
2. To determine tumor size, histological grading, axillary lymph node status of palpable and non-palpable cancers.
3. To determine the false negative rate of breast ultrasound and mammography in breast examination mimic breast cancer screening.
4. To determine the rate of interval cancers after last breast ultrasound or mammography examination.

文獻探討

Two population-based breast cancer screenings using mammography, with or without clinical examination, were conducted in Singapore and Hong Kong, most of the participants being Chinese women. As in Taiwan, Singapore is also experiencing an increasing incidence of breast cancer. A randomized trial of screening using mammography without clinical examination in women aged 50-64 years was started in 1994 (17). For every 1,000 women screened, 4.8 cancers were detected. The percentage of stage 0 and stage I cancers was 64% in the screening group compared to 26% in non-screened women. When only invasive cancers were considered, 65% of cancers detected in screened women were node-negative compared with 47% in non-screened women. As this trial only screened women aged 50-64 years, it cannot give any information on whether, or how, younger women should be screened.

Clinical breast examination and mammography were used in another mass screening program in Hong Kong between 1993 and 1995 (18). A total of 13,033 women aged 40-70 years were screened, and 8,504 women underwent mammography. In all, 42 cancers were detected, 16 of which were non-palpable. Four palpable cancers were not detected by mammography. The cancer detection rate was 4.61/1,000 in the 40-49 year age group and 6.46/1,000 in the over-50s age group. When these two trials were compared, mammography screening plus clinical examination achieved a better detection rate than mammography alone in women over the age of 50, which is consistent with literature reviews that a screening program using both mammography and clinical examination can achieve a higher sensitivity than either modality alone (review in ref 19). The lower detection rate in younger women raises the question whether the incidence in this age group is lower (which is not the case in Taiwan, and probably not in Hong Kong) or the sensitivity of mammography in younger women is lower. Mammography alone failed to detect 15% of breast cancers identified by clinical examination and the sensitivity was lower in younger women (review in ref 19). Thus, combined clinical examination and mammography is desirable.

Although the reasons for the discrepancy in screening efficacy between different age groups are not well understood, different tumor biology and mammographic test characteristics in younger women must be considered. The doubling time for breast cancer in women under the age of 50 is 80 days, while that in women aged 50 to 70 is 157 days (20). The Swedish Two-County trial found that, in younger women, the tumor types tended to be more aggressive (21), which screening results suggest these women are less likely to benefit. The lower benefit from screening women aged less than 50 compared with those over 50 is due to a shorter sojourn time in the younger age group (22). It has also been suggested that 2- or 3-yearly screening might be sufficient in women aged 50 years or older, while women aged 40 to 49 years might require annual screening (21). As a high incidence of interval cancers represents either rapid progression of breast tumors or poor sensitivity of the screening method, the shorter sojourn time indicates a rapid progression of breast tumors in younger patients, which necessitates a shorter screening interval or a more sensitive screening modality.

The ability of mammography to detect breast cancer is affected by breast density (15,23), its sensitivity being 80% in women with fatty breasts and only 30% in women with extremely dense breasts (23). After adjustment for age, menopausal status, use of hormone replacement therapy, and body mass index, the odds ratio for interval cancer in women with extremely dense breasts compared with those with fatty breasts is about 6. As regards age and breast density, more premenopausal women than postmenopausal women have dense breasts (23). The chance of having biopsy after mammography examination is also different between young (40-49) and old (≥50) age groups. One study noted that the probability of abnormal mammograms at first screening is the same in different age groups, but the positive predictive value of screening mammography declines from about 18% in women older than 60 to 4% in women aged 40 to 49 (24), which means that women younger than 50 will undergo more unnecessary intervention procedures.

A consensus statement by the European Group for Breast Cancer Screening (EGBCS) is against the use of ultrasound in population screening at any age due to the high rates of both false-positive and false-negative results associated with mass screening using breast ultrasound (25). Many of the false-negative results are due to difficulty in microcalcification detection using breast ultrasound, although we found that it is not impossible to detect microcalcifications, not necessarily associated with mass, in nonpalpable breast lesions using this method (26), and others have reported that they could use ultrasound to localize microcalcifications detected by mammography (27).

Moreover, ultrasound is the only tool that can demonstrate microcalcifications in women younger than 35 years of age, for whom mammography is not usually requested. One study demonstrated that 0.3% of 12,706 examinations performed, or 2.8% of 1,575 lesions detected, by ultrasound were cancers that were detected by ultrasound, but not by mammography or physical examination (16). The EGBCS concludes that the high rates of false-positive outcomes would lead to unnecessary further investigation. However, in this particular study, ultrasound was used to examine contralateral or ipsilateral breasts of cancer patients for multifoci lesions, in addition to primary cancer. The probability of finding another lesion is expected to be low and the intention of the examiner to biopsy the detected lesion in these high-risk patients will be high. Thus, the cancer detection rate was low and the false-negative rate high in this study. In another prospective study, when breast ultrasound was used to screen 3,626 women with dense breasts and normal mammographic and physical examination findings, 11 (0.3%) were found to have cancers (15). These cancers, identified by ultrasound alone, did not differ in terms of tumor size and stage from nonpalpable cancers detected by mammography and were smaller and at a lower stage than palpable breast cancers. In women with dense breasts, overall cancer detection

increased by 17%, and the number of tumors detected only by imaging increased by 37%. These results support the idea that ultrasound is very helpful in detecting nonpalpable cancers missed by mammography of dense breasts, more frequent in premenopausal women.

One retrospective study in Japan reported the use of breast ultrasound in a non-randomized mass screening (28). In one group of 15,935 women, only physical examination was performed and 5 breast cancers were detected, while, in another group of 18,539 women, ultrasound plus physical examination was performed and 22 cancers were detected. Sixteen of these 22 women had early breast cancer and 13 (59.1%) of the 22 cancers were not palpable. Half of the 22 women were younger than 50. Although the overall cancer detection rate was low, which might be due to the low incidence of breast cancer in Japan or the low sensitivity of the screening modalities, breast ultrasound is useful in mass screening for the detection of early breast cancers, many of which will be in women under the age of 50 and missed by physical examination.

研究方法

All the patients who underwent breast ultrasound or mammography examination from 1995 to 1997 at National Taiwan University Hospital (NTUH) were enrolled in the study. There were 11840 examinations of breast ultrasound and 7579 examinations of mammography. Surgical biopsies were performed for 1390 breast tumors after examinations of ultrasound and mammography in 1995 and 1996 and 393 primary breast cancers were diagnosed. The diagnoses of breast ultrasound and mammography were categorized into malignant, suspicious and benign. Histopathological diagnoses of all surgical biopsies were collected for further estimation of false negative results of image studies.

All incident cases of breast cancers in Taiwan since 1995 were collected from Cancer Registry of the Department of Health. The ID numbers of patients undergoing examinations of breast ultrasound and mammography from 1995 to 1997 at NTUH were matched with those of incident cases of breast cancers found at Cancer Registry since 1995. If the incident cases had had examinations of breast ultrasound and mammography at NTUH but had not been diagnosed as breast cancers at that time, these are considered as possible interval cancers. These patients will be interviewed by a research nurse via telephone. The frequency and results of breast ultrasound and mammography examinations, after examinations at NTUH from 1995 to 1997 but before diagnosis of cancer, will be recorded so that the interval between diagnosis of cancer and the last examination can be determined.

The pathological features, including tumor size, histological grade and lymph node status, will be recorded for all the breast cancers diagnosed by breast ultrasound or mammography at NTUH from 1995 to1997, and treated at NTUH or other hospitals. Whether these cancers were palpable or not will also be reviewed from charts.

Since this a retrospective study, the quality of chart records may affect the determination of parameters, especially whether the tumors were palpable or not. It may be not easy to contact those patients not treated at NTUH and to get detailed information of pathology.

結果與討論

In 1995 and 1996, 1,390 breast tumor cases, who underwent surgery with histopathological diagnosis in the National Taiwan University Hospital, were reviewed. Of these, 1131 had breast ultrasound examination and 332 had mammography, i.e. many had only ultrasound or mammography. There were 393 cancers and 997 benign lesions. Ninety-four of the 1,390 cases were nonpalpable lesions and 26 were nonpalpable cancers. Most of the patients underwent surgical biopsy if the findings of breast ultrasound and/or mammography were positive or suspicious, while some patients refused biopsy or visited other hospital for surgery, which may affect the prediction of false positive rate. Some patients with benign findings of image studies did not proceed to biopsy, which may cause underestimation of false negative rate.

If the above bias are neglected, the sensitivity of breast ultrasound in the diagnosis of palpable breast tumors was much higher than that of mammography (95% vs. 78%). The specificity of breast ultrasound was also higher (79% vs. 70%). While ultrasound and mammography had similar positive predictive values (67% and 70%, respectively), ultrasound had a significantly higher negative predictive value than mammography (97% vs. 78%). In the case of nonpalpable lesions, mammography had a higher sensitivity (83% vs. 54%), but a lower specificity (39% vs. 82%) than ultrasound (not every nonpalpable lesion underwent both examinations). Of the nonpalpable cancers detected by mammography or ultrasound, 47.6% (10/21) or 31% (5/16), respectively, were noninvasive; in contrast, 95% of palpable cancers detected by mammography or ultrasound were invasive.

Thirty one percent (5/16) of nonpalpable breast cancers detected by ultrasound were ductal carcinoma in situ (DCIS), 43.7% (7/16) were invasive cancers with tumor smaller than 1.5 cm, 18.8% (3/16) were invasive cancers between 1.5 cm to 2 cm, and 6.3% were invasive cancers larger than 5 cm (detected in one breast in one woman with bilateral indurated breasts due to direct silicon injection). Sixteen percent of palpable cancers were not visible by mammography. Age or breast density affected the detection of cancer by mammography; in patients younger than 50 years of age, 25% of palpable cancers were not visible, while the corresponding value for patients older than 50 was only 5%. About 90% of palpable cancers with false-negative mammography were diagnosed as cancer by ultrasound.

In mammography examinations of 22 non-palpable cancers, 7 (31.8%) revealed malignant mass and microcalifications, while 14 (63.6%) revealed malignant microcalcifications only; the other one (4.5%) were not visible by mammography, which was detected as cancer by ultrasound. Six non-palpable breast cancers missed by ultrasound were detected by mammography due to the presence of microcalifications which ultrasound failed to detect.

We furthered linked the ID numbers of women having undergone examinations of breast ultrasound and/or mammography at National Taiwan University Hospital to the data file of National Cancer Registry. There were 753 breast cancers identified in Cancer Registry, and 131 of those were operated outside NTUH. Among those patients operated outside NTUH, 87 of them were operated within 6 months of examinations at NTUH. For palpable cancers operated at NTUH, 504 had breast ultrasound examinations. The false-negative rate was 7.1%. All tumors were visible on ultrasound and the missed cases were recognized as benign tumors. Two hundred and twenty five palpable cancers had mammographic examinations. The false-negative rate was 18.6%. Thirty cancers(13.3%) were not visible on mammograms. For those cancers not operated at NTUH, the reports of breast ultrasound and mammography were reviewed. The re-calculated false-negative rate of breast ultrasound and mammography were 4.5% and 17.5%, respectively.

Since 4.5% of nonpalpable cancers and 13.3% of palpable cancers were not visible by mammography, ultrasound is helpful in detecting nonpalpable cancers, most of which will be DCIS or early invasive cancers, in women aged 40-49 with dense breasts. One criterion for evaluating screening efficacy is that more than 50% of screen-detected cancers should be smaller than 15 mm (29), and breast ultrasound seems to be able to do this.

If the main limitation of ultrasound in mass screening is the difficulty in detecting microcalcifications-associated DCIS, the significance of DCIS needs to be clearly understood. Although many pathological and molecular biological studies suggest that many cases of DCIS will progress to invasive carcinoma if undetected or untreated (review in ref 30, 31), it is estimated that only 30-50% of DCIS will progress to invasive cancer, with the remainder regressing or remaining indolent (32, 33). In addition, it is not documented whether all invasive carcinomas arise from *in situ* cancers. In the first mammography screening conducted on 1,000 women aged 40 to 49 and first screened by mammography, 1.5 cases were DCIS and 1.5 cases

invasive cancer, compared with 2 DCIS and 7 invasive cancer for every 1,000 women aged 50 to 69 (24).

In Sickle's series, in which most of the patients were Caucasians, microcalcifications suggesting malignancy constituted 42% of nonpalpable breast cancers(34), whereas, in our series, nearly all the nonpalpable cancers detected by mammography in Taiwanese women were because of the presence of microcalcifications. Ultrasound is probably more sensitive than mammography in detecting nonpalpable cancers; however, it fails to detect microcalcifications. Mammography is the best tool to detect microcalcification-associated DCIS, which probably will not progress rapidly to invasive cancer, and can therefore be performed over a longer interval, with ultrasound being added to detect nonpalpable cancers not associated with microcalcifications.

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