Clinical Study

Are Both Ultrasonography and Mammography Necessary for Cancer Investigation of Breast Lumps in Resource-Limited Countries?

Rungnapa Chairat,1,2 Adisorn Puttisri,3 Asani Pamarapa,4 Sahatham Samintharapanya,5 Chamaiporn Tawichasri,6 and Jayanton Patumanond7

1 Program in Clinical Epidemiology, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand
2 Department of Nursing, Uttaradit Hospital, Uttaradit 53000, Thailand
3 Department of General Surgery, Nakon Swan General Hospital, Nakon Swan 60000, Thailand
4 Department of General Surgery, Uttaradit General Hospital, Uttaradit 53000, Thailand
5 Department of General Surgery, Lampang General Hospital, Lampang 52000, Thailand
6 Clinical Epidemiology Society, Chaing Mai 50200, Thailand
7 Clinical Epidemiology Unit, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand

Correspondence should be addressed to Jayanton Patumanond; j.patumanond@yahoo.com

Received 27 April 2013; Accepted 28 July 2013

Academic Editors: G. Gatti and A. Goussia

Copyright © 2013 Rungnapa Chairat et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Objective. To reevaluate the diagnostic value of breast imaging in the diagnosis of breast cancer in areas where health resources are limited. Methods. Patients were women presenting with breast lumps in two university-affiliated tertiary hospitals, Thailand, during 2006 and 2010. Clinical data were abstracted from the breast cancer registration database and patient records. The diagnostic predictive ability of ultrasonography and mammography was obtained from logistic regression analysis and presented with areas under the receiver operating characteristics (AuROCs) curves. Results. Among 3129 breast lumps (3069 women), 854 were diagnosed with breast cancer by certified pathologists. Age and size of lumps alone already predicted cancer correctly in 77.45% (AuROC = 77.45). Additional ultrasonography increased the prediction to 96.22% (P < 0.001). Additional mammography also increased the prediction to 95.99% (P < 0.001). Performing both imaging modalities did not increase the prediction clinically (0.01%–0.24%). More accurate prediction (2.07%–2.21%) may be added by fine needle aspiration cytology (FNAC). Conclusions. Breast imaging is still valuable in settings where health resources are limited. Single breast imaging (only either ultrasonography or mammography) is adequate for cancer diagnosis. It is therefore unnecessary to perform both imaging modalities. Accuracy of the diagnosis may be improved by FNAC, if available.

1. Introduction

Breast cancer is increasingly common in women worldwide. It is one of the leading causes of death among female malignancies [1]. The incidence varies from region to region, more in developed countries (>80 per 100,000 populations) than in developing countries (<40 per 100,000 populations). In southeast Asian women, it was 31.0 per 100,000 populations [2]. Cancer of the breast in Thailand is the highest among all female cancers and is continuously rising. The incidence increased from 34.4 to 40.6 per 100,000 populations during 2006 to 2009. The mortality also increased from 6.3 to 7.3 per 100,000 populations in the corresponding years [3].

The standard diagnosis of breast cancer recommended triple diagnostic investigations [4], comprising (1) clinical breast examination; (2) breast imaging, ultrasonography, or mammography, (3) cytopathologic with fine needle aspiration cytology (FNAC) or histopathologic findings with a core needle biopsy with cutting needle biopsy. The same recommendation was also used by The National Institute of Cancer of Thailand, for women presenting with breast lumps [5]. Ultrasonography is recommended in women under 35
years old, and both ultrasonography and mammography are recommended in those 35 years old or above. Although breast images have been proved effective in diagnosing cancer in women presenting with breast lumps [6], their uses are, however, limited, either by lack of trained medical personnel or their unavailability. Referral of patients to better equipped hospitals only for imaging investigations may somehow cause the delay in diagnosis and treatments [7].

In routine practice, physicians in countries with limited resources approach women with breast lumps with history taking clinical breast examination and breast pathology by FNAC or biopsy and skipped breast imaging (mammography or ultrasonography) to shorten the time of diagnosis and treatment. However, clinical breast examination alone lacks reliability for cancer diagnosis [8]. Although researches indicated that diagnosis of cancer may be adequately made by FNAC [7], the results may still contain false-negatives and false-positives [9]. The procedure (FNAC) also cannot differentiate in situ from invasive breast cancer. There are still not enough evidences to conclude which investigations should be used when considering effectiveness together with availability, leading to varying recommendations and guidelines [10].

The present study evaluated the ability of breast imaging (mammography and ultrasonography) in diagnosing cancer in women presenting with breast lumps, in the presence of patient profiles, with or without FNAC. The study also considered their combinations, sequences, and availability of each investigative modality, in order to reflect situations where health resources are limited.

2. Subjects and Methods

2.1. Subjects and Settings. Patients were women who presented with breast lumps in two university-affiliated tertiary care hospitals, Lampang Hospital and Uttaradit Hospital, located in the northern part of Thailand. Patient medical records between 2006 and 2010 were retrieved under the ICD-10 specification. Case tracing was made for at least 12 months after the first presentation to the hospitals to verify any changes in final diagnosis. Women with a history of breast biopsy, or breast silicone implantation were not included. In this nested case-control analogue design, cases were women verified as cancer by breast pathology (biopsy or operative specimen). Controls were those with noncancerous lumps proved by the same criteria or clinical breast examination and/or breast imaging and/or FNAC.

2.2. Data and Source. The keyed information, age (years), body mass index (BMI, kg/m$^2$), duration of lumps (month), size of lumps (cm), side of lumps, quadrant, clinical characteristics, and final histopathology, was retrieved from the medical registration and patient records.

2.3. Diagnostic Investigations. For breast imaging results, mammography and ultrasonography were interpreted by the hospital radiologists under routine practices. The classification of breast imaging followed the BI-RADS (Breast Imaging Reporting and Data System) [11] (Table 1).
Table 2: General characteristics of patients (3069 subjects, 3129 lumps).

| Characteristics | Malignant mean (SD) | Benign mean (SD) | P value |
|-----------------|---------------------|------------------|---------|
| Age (years)     | 53.2 (11.6)         | 43.1 (12.0)      | <0.001  |
| BMI (kg/m²)     | 23.7 (6.2)          | 22.7 (2.2)       | 0.003   |
| Duration (month)| 4.0 (9.9)           | 4.4 (14.0)       | <0.001  |
| Size (cm)       | 3.1 (1.9)           | 1.6 (1.1)        | <0.001  |
| Side (n, %)     |                    |                  |         |
| Right           | 419/49.1            | 1,102/48.4       | 0.779   |
| Left            | 435/50.9            | 1,173/51.6       |         |
| Quadrant (n, %) |                    |                  |         |
| Upper outer     | 467/54.7            | 1,157/50.9       | 0.121   |
| Upper inner     | 188/22.0            | 556/24.4         |         |
| Subareolar      | 55/6.5              | 145/6.4          |         |
| Lower outer     | 95/11.1             | 239/10.5         |         |
| Lower inner     | 49/5.7              | 178/7.8          |         |
| Clinical          |                      |                  |         |
| manifestations   | (n, %)              |                  |         |
| Fixed lump      | 346/47.1            | 40/2.5           | <0.001  |
| Retracted skin  | 30/4.5              | 9/0.7            | <0.001  |
| Nipple discharge | 19/2.8              | 41/2.7           | 1.000   |
| Rugged edge     | 74/10.9             | 141/10.3         | 0.702   |
| Wound/ulcer     | 13/2.0              | 26/2.1           | 1.000   |

Cytopathologic diagnosis was verified by certified university hospital pathologists. FNAC classification followed the Cytologic Category Code System [12, 13] (Table 1).

2.4. Data Analysis. General characteristics and clinical characteristics were presented with descriptive statistics and compared between patients with and without cancer by exact probability tests, t-tests, or Wilcoxon’s rank sum tests, as appropriate.

Logistic regression techniques were used to obtain diagnostic values of age, size, imaging techniques, and FNAC and presented with diagnostic odds ratios (dORs), 95% confidence interval (CI), and P value.

The diagnostic abilities of the 3 main diagnostic investigations (ultrasonography, mammography, and FNAC) in combination with clinical baseline (age and size of lumps) were compared with the clinical baseline alone, by area under the receiver operating characteristics (AUROC’s) curves.

The differences in predictive abilities of diagnostic modality were compared by the likelihood ratio tests (LR tests) under the logistic models. Application utilities of the investigation sequences were calculated by predictive ability (%) times availability (%) to guide clinical approaches in real situations.

3. Results

From 3129 breast lumps (3069 patients), there were 854 lumps with definite (postoperative histopathology) diagnosis of breast cancer and 2275 lumps without. Review of the index investigation, ultrasonography, mammography, and FNAC showed significant different results between those with and without cancer (P < 0.001) (Table 1).

Patients were between 15 and 93 years old (mean = 45.8 ± 12.8). Those with cancer were older (53.2 ± 11.6 versus 43.1 ± 12.0 years, P < 0.001) and had higher body mass index (23.7 ± 6.2 versus 22.7 ± 2.2 kg/m², P = 0.003). The duration of noticing breast lumps was shorter (4.0 ± 9.9 versus 4.4 ± 14.0 months, P < 0.001). Lump sizes ranged from 0.5 to 15 cm, larger in those with cancer (3.1 ± 1.9 versus 1.6 ± 1.1 cm, P < 0.001). More than half of the lumps were palpable in the upper outer quadrants. Right and left sided lumps were similar in both groups. Fixed lumps, retracted skin, and retracted nipple were more frequent in those with cancer (P < 0.001) (Table 2).

The independent predictive ability of the three investigative modalities in the presence of baseline information (age and size) under the multivariable logistic regression showed high diagnostic odds ratios of 3.85 for ultrasonography, 2.08 for mammography, and 3.52 for FNAC (Table 3).

Baseline information, age and lump sizes, alone predicted cancer correctly in 77.45% (AuROC = 77.45, 95% CI = 73.31–81.60). Single investigation on top of baseline showed the...
highest to the lowest prediction for ultrasonography (AuROC = 96.22%, 95% CI = 94.77–97.67), mammography (AuROC = 95.99%, 95% CI = 94.46–97.52), and FNAC (AuROC = 92.47%, 95% CI = 90.32–94.62) (Figure 1).

Modality combination with the highest prediction was breast imaging (either ultrasonography or mammography) with FNAC. FNAC after ultrasonography added 2.07% (P < 0.001). FNAC after mammography also increased the prediction by 2.21% (P < 0.001). Ultrasonography after mammography added very little prediction (0.24%, P = 0.015). Ultrasonography after mammography added very little prediction (0.01%, P = 0.609) (Figure 2).

The investigative modality sequence that yielded high additional prediction leading to high final prediction was breast imaging (either ultrasonography or mammography) followed by FNAC.

4. Discussion

Breast imaging (either ultrasonography or mammography) increased cancer prediction beyond baseline information with AuROCs of 96.22% and 95.99%. Their utilities were among the highest (38.45% and 30.71%). Previous studies also reported high reliability of the two modalities, but there were no reports on availability or utility in routine practice, nor reports on appropriate combination or sequences of investigations [6, 14–18]. It is therefore difficult to compare diagnostic accuracies of investigative modalities across studies [7].

In the area with restricted health resources, clinicians may diagnose breast cancer using clinical breast examination and FNAC, without any of breast imaging modalities. The present study agreed that clinical breast examination alone was not adequate for cancer diagnosis [8, 19]. Although FNAC on top of baseline information might be efficient (AuROC = 92.47%, OR = 3.52, P < 0.001) [7, 20–23], but false-negative results from FNAC may lead to delayed and/or under treatment, while false-positive results may lead to overtreatment [24]. Additional ultrasonography or mammography after FNAC increases cancer prediction by 5.82% and 5.73%, clinically and statistically significant, but its application utility decreased profoundly to 8.36% and 7.30%.

Comparing between the two imaging modalities, ultrasonography had higher cancer prediction and utility than mammography. Mammography may have some limitations in diagnosing dense breast [25, 26], while ultrasonography may have more advantages in diagnosing breast cyst. The accuracy of ultrasonography in diagnosing cyst was as high as 92%, but only 65% in diagnosing cancer [27]. Ultrasonography may also detect cancer from stage 1 to stage 4. Microcalcification was detected in 74% of patients with
ductal carcinoma in situ of the breast (54 in 73 patients) [28]. Ultrasonography also detected abnormality when mammography reported Bi-RADS = 0 [29]. Subgroup analysis also showed that patients with Bi-RADS below 4 might gain more benefit from additional ultrasound investigation, while for those with Bi-RADS 4 and above who already had high possibility for cancer, ultrasound might not gain any additional information.

The findings indicated that breast imaging was valuable in diagnosing cancer in patients presenting with breast lumps with high utility. In health restricted resource countries, performing both imaging modalities (ultrasonography and mammography) may be unnecessary [30]. However, a better prediction may be gained by a combination of different modalities ultrasonography followed by FNAC, or mammography followed by FNAC, depending on availability and/or preference.

Breast imaging investigation should therefore be encouraged and made available countrywide in order to reduce cancer mortality in women presenting with breast lumps suspicious of breast cancer [10].

5. Conclusions

Breast imaging, either ultrasonography or mammography, had high additional diagnostic value of cancer prediction over baseline in patients presenting with breast lumps. However, both mammography and ultrasonography may be unnecessary. Which modality should be performed first was due to its availability and/or center preferences. However, additional FNAC, if available, may increase cancer prediction, both clinically and statistically.

Ethical Approval

The study was approved by The Research Ethics Committee, Faculty of Medicine, Chiang Mai University and The Research Ethics Committee of Lampang and Uttaradit hospitals. Informed consents were not required in this retrospective data collection. Patient hospital numbers, other traceable information, and private information were kept confidential and omitted in all analytic processes.

Conflict of Interests

The authors declare that they have no conflict of interests.

Acknowledgments

The authors wish to thank the medical and nursing staff of the two hospitals for their support in database provision and missing data verification. The study was partially supported by The Basic and Applied Health Sciences Research Grant, Faculty of Medicine, Chiang Mai University.

References

[1] B. K. Edwards, M. L. Brown, P. A. Wingo et al., “Annual report to the nation on the status of cancer, 1975–2002, featuring population-based trends in cancer treatment,” Journal of the National Cancer Institute, vol. 97, no. 19, pp. 1407–1427, 2005.
[2] J. Ferlay, H.-R. Shin, F. Bray, D. Forman, C. Mathers, and D. M. Parkin, “Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008,” International Journal of Cancer, vol. 127, no. 12, pp. 2893–2917, 2010.
[3] 2010, http://bps.ops.moph.go.th/Healthinformation/index2.html.
[4] B. Ghimire, M. I. Khan, T. Bibhusal, Y. Singh, and P. Sayami, “Accuracy of triple test score in the diagnosis of palpable breast lump,” Journal of the Nepal Medical Association, vol. 47, no. 172, pp. 189–192, 2008.
[5] National Cancer Institute of Thailand, “Clinical practice guideline for diagnostic and treatment in breast cancer,” 2007.
[6] S. Teavirat, V. Hirunvivathanakul, and S. Jadsapadaparakthar, “Diagnosis performance of combined mammogram and ultrasound in diagnosis of breast cancer,” Vajira Medical Journal, vol. 46, no. 2, pp. 115–123, 2002.
[7] J. Patumanond, T. Kayee, and U. Sukkasem, “Empirical accuracy of fine needle aspiration cytology (FNAC) for preoperative diagnoses of malignant breast lumps in hospitals with restricted health resources,” European Journal of Gynaecological Oncology, vol. 30, no. 3, pp. 295–299, 2009.
[8] T. Ratanachaikanont, “Clinical breast examination and its relevance to diagnosis of palpable breast lesion,” Journal of the Medical Association of Thailand, vol. 88, no. 4, pp. 505–507, 2005.
[9] A. Nerurkar and P. Osin, “The diagnosis and management of pre-invasive breast disease: the role of new diagnostic techniques,” Breast Cancer Research, vol. 5, no. 6, pp. 305–308, 2003.
[10] C. Smigal, A. Jemal, E. Ward et al., “Trends in breast cancer by race and ethnicity: update 2006,” CA: A Cancer Journal for Clinicians, vol. 56, no. 3, pp. 168–183, 2006.
[11] The American College of Radiology, BI-RADS ATLAS and MQSA: Frequently Asked Questions, 2009.
[12] “The uniform approach to breast fine-needle aspiration biopsy. National Cancer Institute Fine-Needle Aspiration of Breast Workshop Subcommittees,” Diagnostic Cytopathology, vol. 16, no. 4, pp. 295–311, 1997.
[13] P. Sampatanaukul, D. Boonjuwewat, V. Thanakit, and P. Pak-Art, “Integrated criteria of fine-needle aspiration cytology and radiological imaging for verification of breast cancer in non-palpable lesions,” Journal of the Medical Association of Thailand, vol. 89, no. 2, pp. 236–241, 2006.
[14] S. N. Prasad and D. Housekrova, “A comparison of mammography and ultrasonography in the evaluation of breast masses,” Biomedical Papers Medical Faculty of the University Palacky Olomouc Czechoslovakia, vol. 151, no. 2, pp. 315–322, 2007.
[15] E. Devolli-Disha, S. Manxhuka-Kërliu, H. Ymeri, and A. Kut-llovi, “Comparative accuracy of mammography and ultrasound in women with breast symptoms according to age and breast density,” Bosnian Journal of Basic Medical Sciences, vol. 9, no. 2, pp. 131–136, 2009.
[16] S. J. Shen, Q. Sun, Y. L. Xu et al., “Comparative analysis of early diagnostic tools for breast cancer,” Zhonghua Zhong Liu Za Zhi, vol. 34, no. 11, pp. 877–880, 2012.
N. Zimmermann and R. Ohlinger, “Diagnostic value of palpation, mammography, and ultrasonography in the diagnosis of fibroadenoma: impact of breast density, patient age, ultrasonographic size, and palpability,” *Ultraschall in der Medizin*, vol. 33, no. 7, pp. E151–E157, 2012.

W. A. Berg, J. D. Blume, J. B. Cormack et al., “Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer,” *The Journal of the American Medical Association*, vol. 299, no. 18, pp. 2151–2163, 2008.

G. C. Wishart, J. Warwick, V. Pitsinis, S. Duffy, and P. D. Britton, “Measuring performance in clinical breast examination,” *British Journal of Surgery*, vol. 97, no. 8, pp. 1246–1252, 2010.

R. Ariga, K. Bloom, V. B. Reddy et al., “Fine-needle aspiration of clinically suspicious palpable breast masses with histopathologic correlation,” *American Journal of Surgery*, vol. 184, no. 5, pp. 410–413, 2002.

R. Arora, A. A. El Hameed, T. Al Ajrawi, O. Al Harbi, and A. A. Elbasmy, “The accuracy of abnormal cytology report in breast fine needle aspiration alone and in combination with clinical and imaging findings—a hospital based five year study in Kuwait,” *The Gulf Journal of Oncology*, no. 4, pp. 33–38, 2008.

S. Mizzuno, S. Isaji, T. Ogawa et al., “Approach to fine-needle aspiration cytology-negative cases of breast cancer,” *Asian Journal of Surgery*, vol. 28, no. 1, pp. 13–17, 2005.

K. T. Morris, J. T. Vetto, J. K. Petty et al., “A new score for the evaluation of palpable breast masses in women under age 40,” *The American Journal of Surgery*, vol. 184, no. 4, pp. 346–347, 2002.

P. J. Carder, “Fine needle aspiration cytology of the breast—time for a re-think?” *Cytopathology*, vol. 15, no. 6, pp. 336–337, 2004.

A. S. Majid, E. S. de Paredes, R. D. Doherty, N. R. Sharma, and X. Salvador, “Missed breast carcinoma: pitfalls and pearls,” *Radiographics*, vol. 23, no. 4, pp. 881–895, 2003.

U. Fischer, “X-ray mammography. Calcifications, masses and architectural distortions,” *Radiologe*, vol. 48, no. 8, pp. 785–798, 2008.

K. Singh, T. Azad, and G. D. Gupta, “The accuracy of ultrasound in diagnosis of palpable breast lumps,” *JK Science*, vol. 10, no. 4, pp. 186–188, 2008.

T. Nagashima, H. Hashimoto, K. Oshida et al., “Ultrasound demonstration of mammographically detected microcalcifications in patients with ductal carcinoma in situ of the breast,” *Breast Cancer*, vol. 12, no. 3, pp. 216–220, 2005.

P. A. Zanello, A. F. C. Robim, T. M. G. de Oliveira et al., “Breast ultrasound diagnostic performance and outcomes for mass lesions using breast imaging reporting and data system category 0 mammogram,” *Clinics*, vol. 66, no. 3, pp. 443–448, 2011.

P. Korpraphong, O. Tritanon, W. Tangcharoensathien, A. Tamnit, and C. Suebwong, “Ultrasonographic characteristics of mammographically occult small breast cancer,” *Journal of Breast Cancer*, vol. 15, no. 3, pp. 344–349, 2012.