

Original article

A comparison of mammography, ultrasonography, and far-infrared thermography with pathological results in screening and early diagnosis of breast cancer

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Background: Many breast-imaging techniques have been developed as primary clinical methods for identifying early-stage breast cancers and differentiating them from benign breast tumors. For the large population of China, any screening method that is rapid, economical, and accurate is worthy of evaluation.

Objective: To compare the effectiveness of mammography, color Doppler ultrasonography, and far-infrared thermography in the screening and early diagnosis of breast cancer.

Methods: Data from 2036 women with breast disease between January 2007 and May 2011 were included in this study. All patients underwent mammography, ultrasonography, and far-infrared thermography imaging. The diagnostic accuracy of the three methods was determined using postoperative pathological results as the diagnostic criterion standard.

Results: There were 480 patients found to have breast malignancies on pathological examination. The lesion diameter was <2 cm in 853 cases. Among them, breast cancer was found in 73 patients and carcinoma in situ in 22 patients. There was no difference in the accuracy of mammography and ultrasonography (96.1% versus 95.8%). However, there were significant differences between the accuracy of far-infrared thermography (97.1%) and ultrasonography and mammography. The sensitivity and specificity of far-infrared thermography was superior to that of mammography and ultrasonography in lesions <2 cm in diameter.

Conclusion: Far-infrared thermography is more accurate for breast cancer screening than ultrasonography and mammography for lesions <2 cm. It has comparable diagnostic accuracy to ultrasound and better diagnostic accuracy than mammography for lesions >2 cm in diameter.

Keywords: Breast cancer, color Doppler ultrasonography, far-infrared thermography, mammography

There are many different kinds of breast disorders (malignant and benign tumors) that display similar symptoms. Therefore, breast-imaging techniques have been developed as primary clinical methods for identifying early-stage breast cancers and differentiating them from benign breast tumors. At present, the main screening tests include mammography and ultrasonography. Mammography is the most commonly used imaging examination for the screening of breast cancer; however, the rate of false negative rates can reach up to 30% and expose patients to ionizing radiation [1]. In addition, mammography is less effective in younger

women and those with denser breast tissue [2]. Ultrasonography is primarily used for differentiating between cystic and solid properties of breast lesions identified by mammography; it can examine dense breast tissue, and guide aspiration biopsy and preoperative localization. Because of the time needed to perform an examination, the need for appropriate operator training, and other constraints, ultrasonography alone is not suitable as a screening method for breast cancer. Indeed, ultrasound and mammography may miss many cases where the tumor is <0.5 cm.

Infrared breast imaging for the detection of breast cancer was first tested in the 1970s, but did not achieve widespread clinical use, because the technology of the time was cumbersome and the false negative and false positive rates were relatively high [3-5]. The

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technical principle behind far-infrared thermography is relatively vigorous intracellular glucose metabolism in malignant lesions, which causes greater angiogenesis, producing more thermal energy than normal tissues [6]. Advances in technology and computer modeling have led to renewed interest in using thermography as a screening tool for breast cancer [1, 6-8]. Advantages of thermography include simple and fast test administration, and quantitative computer software result analysis; it requires less advanced technical operator training relative to other screening methods and testing is relatively inexpensive [1, 2]. Thus, far-infrared thermography is a workable imaging technique for breast cancer patients.

The incidence of breast cancer in Chinese women has been increasing, making screening an important healthcare objective in China [9]. The limitations of mammography are especially apparent in Chinese women with small breasts and dense glands; therefore, ultrasonography has become more important. However, ultrasonography examination is time consuming as whole breast images cannot be obtained and diagnostic accuracy is strongly related to operator experience. In addition, the large population of China mandates that any screening method be rapid, economical, and accurate.

This study compared the effectiveness of mammography, color Doppler ultrasonography, and far-infrared thermography in both screening and early diagnosis of breast cancer, using pathological results as the diagnostic criterion standard.

Materials and methods

Subjects

The current study included 2036 women with breast disease who were diagnosed by open surgery or needle biopsy between January 2007 and May 2011 at both Renmin Hospital of Wuhan University and Hubei Tumor Hospital. Inclusion criteria were an age >35 years, and abnormal mammography and/or ultrasound results that required a biopsy or surgical excision. All patients first underwent far-infrared thermography, which was followed up with ultrasound and mammography on the same day. Our institution routinely carries out far-infrared thermography one day before surgical excision or biopsy of the lesion in breast disease patients. Thus, all patients had mammography, ultrasonography, and far-infrared thermography imaging data. Exclusion criteria included a previous history of breast surgery or breast exposure

to radiation. Patients were instructed to not smoke, consume alcohol, perform strenuous exercise, or apply lotion to the breast within 4 hours before the examination. In addition, far-infrared thermography was not performed if the patient had a fine needle aspiration within 2 days or a thick needle aspiration or vacuum-assisted biopsy within 2 weeks before the examination, because these may affect the results of far-infrared thermography. This study was approved by the Institutional Review Board of our hospital, and all patients provided their written informed consent.

Far-infrared thermography

The breast far-infrared thermography system was produced by Wuhan University and Wuhan Hao Technology Co. (Wuhan, Hubei, People's Republic of China) and the examinations were performed by experienced surgeons. The room temperature was $25 \pm 3^\circ\text{C}$ and there were no sources of thermal energy in the room and no direct sunlight. The breasts were not touched before the examination. Patients were asked to take off their coats and rest for 15 minutes before examination, which achieved a balance between body and room temperatures. Subsequently, 2–3 images were taken within five minutes. The patients either had arms raised or placed on their hips 2 m from the thermography device lens. If necessary, another image was obtained as a marking image indicating the lesion. The images were analyzed automatically using software to obtain a layer-to-layer analytical curve. Benign and malignant disease states were determined by the curve characteristics and the curve angle. The image acquisition time was between 15–20 minutes per image. The analytical software was developed by the authors and based on results of previous work [7, 8]. A thermal curve of the area surrounding the lesion was developed and a malignancy diagnosis was based on the angle between the beginning of the curve and the horizontal line (**Figure 1**). Malignancy is defined as an angle of $30\text{--}45^\circ$, an angle $>45^\circ$ is defined as inflammation and a lesion with angle $<30^\circ$ is defined as a benign tumor.

Color Doppler ultrasonography and mammography

Doppler ultrasonography was performed by professional ultrasound technicians using a color Doppler ultrasound (ESAOTE Megas GPX FD570A, Milan, Italy) with a 25 MHz high-frequency probe. In most cases, the patient was supine on the examination

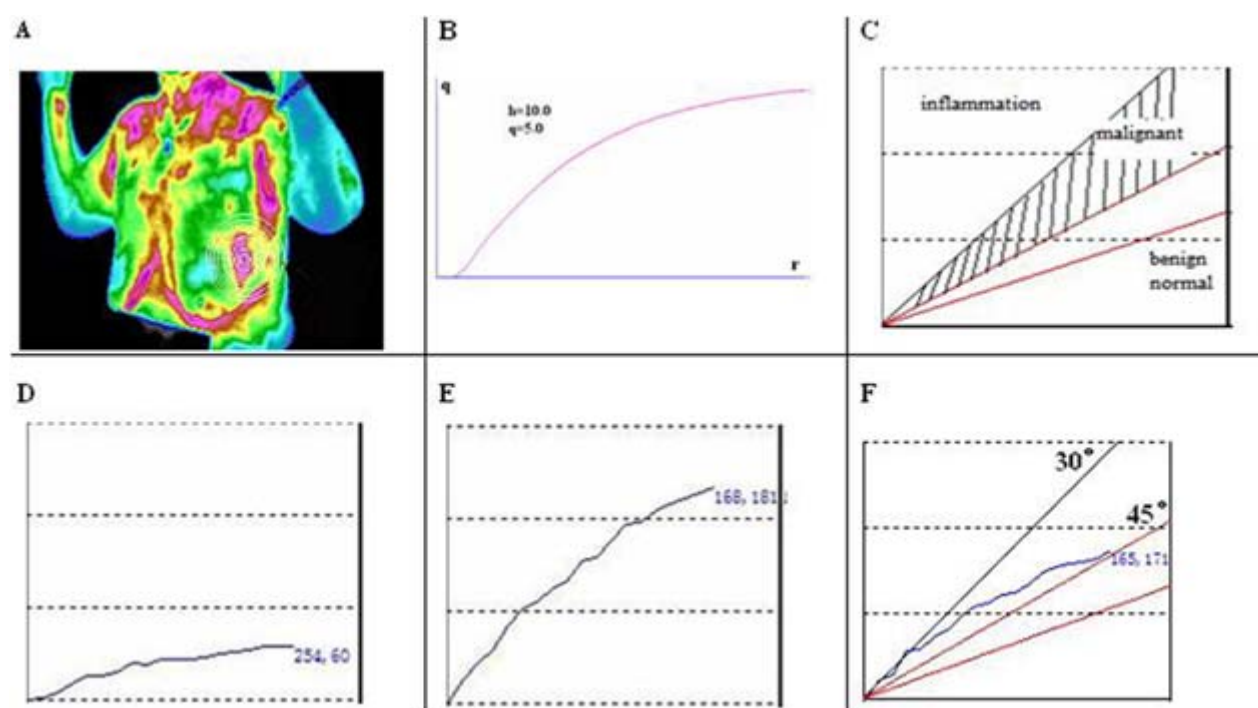


Figure 1. Thermal releasing curve used for the diagnosis of breast lesions. (A) Thermographic image. (B) A thermal map is created from concentric circles surrounding the lesion, which is then used to produce a thermal releasing curve (q - r curve). (C) The curve angle indicated the nature of the lesion. (D) Thermal curve of normal tissue. (E) Thermal curve of a malignant lesion. (F) Malignancy is defined as an angle of 30° – 45° , an angle $>45^{\circ}$ is defined as inflammation and a lesion with angle $<30^{\circ}$ is defined as a benign tumor.

table; however, if the disease was located laterally, the patient was placed in a lateral recumbent position. The breast was sufficiently exposed and the probe was placed directly on the breast. Scanning was performed in a standard manner. Digital mammography (GE Healthcare, Milwaukee, WI, USA) was performed and mediolateral oblique (MLO) views and craniocaudal (CC) views were obtained in accordance with the current technological requirements and standards of the American College of Radiology (ACR) for breast X-ray examination.

Diagnostic criteria of color Doppler ultrasonography and mammography were in accordance with the fourth edition of the Breast Imaging-Reporting and Data System (BI-RADS) [10]. There were 5 degrees (grades) in both examinations. Grade 5 was diagnosed as breast cancer and grades 2, 3, 4 were diagnosed as benign lesions.

Image interpretation

Two radiologists independently and separately interpreted each examination. The radiologists tried to achieve consensus on image interpretation and they were blinded to the results of examinations by the

other radiologist. If the results were not consistent, more experienced radiologists interpreted the images. All the radiologists had comparable training in breast imaging interpretation.

Pathological diagnosis

This study used the 2003 version of the World Health Organization (WHO) pathological classification and grading of breast tumors. Grading was conducted in accordance with three indices: gland formation, nuclear morphology, and mitotic figures [11]. The pathological diagnosis was performed by an experienced pathologist, who was at the level of an associate professor at our institution.

Statistical analysis

Sensitivity, specificity, and diagnostic accuracy calculations were performed for the three imaging examinations. Sensitivity is the true positive rate, defined as " $a/(a+c)$ " where " a " is the number of cases with correctly diagnosed real disease and " c " is the number of cases without real disease but diagnosed to have disease. Specificity is the true negative rate, defined as " $d/(b+d)$ " where " d " is the number of cases

without real disease and correctly diagnosed to have no disease and “b” represents the number of cases with real disease, but diagnosed to have no disease. Diagnostic accuracy is the proportion of total number of the true positive and true negative cases in all subjects who underwent examinations. The chi-square test (χ^2) or Fisher’s exact test were used for group comparisons. All analyses were performed with SPSS version 13.0 statistical software (SPSS, Chicago, IL, USA); a value of $p < 0.05$ was considered to indicate statistical significance.

Results

The mean age of the 2,036 patients included in the current study was 42.4 years (range: 16 to 78 years). Our criterion standard comparison was the pathological comparison of mammography, ultrasonography, and far-infrared thermography results in the 2036 patients. Among the 2036 patients, 480 patients had breast cancers, 73 had stage I disease, 241 had stage II disease, 111 had stage III disease, and 55 had stage IV disease. Among the 1,556 patients with benign lesions, 405 had adenosis, 317 had cystic diseases, 709 had fibroadenomas, 79 had granulomatous mastitis, and 46 had plasma cell mastitis. The results comparing the three methods are shown in **Table 1**. The accuracy of mammography was higher than ultrasonography ($\chi^2 = 11.41$, $p = 0.001$) and far-infrared thermography ($\chi^2 = 4.94$, $p = 0.026$), but there was no significant difference between the accuracy of ultrasonography and far-infrared thermography ($\chi^2 = 0.245$, $p = 0.245$). The sensitivity of far-infrared thermography was superior to that of mammography. Meanwhile, the diagnostic specificity of mammography was superior to that of

ultrasonography and far-infrared thermography.

The results of the three examination methods in the diagnosis of breast lesions <2 cm in diameter are shown in **Table 2**. The diameter of the lesion was <2 cm in 853 cases; among these patients, breast cancer was found in 73 patients and carcinoma in situ in 22. There were significant differences in the diagnostic accuracy between the three methods for lesions <2 cm in diameter ($\chi^2 = 7.664$, $p = 0.022$). There was no difference in the accuracy between mammography and ultrasonography ($\chi^2 = 0.864$, $p = 0.353$). However, there were significant differences between far-infrared thermography and ultrasonography and mammography ($p < 0.05$). The sensitivity and specificity of far-infrared thermography was superior to that of mammography and ultrasonography (**Table 2**).

The results of the three examination methods in diagnosing breast lesions >2 cm in diameter are shown in **Table 3**. The diameter of the lesion was >2 cm in diameter in 1193 cases; among them breast cancer was found in 407 patients, with no carcinoma in situ cases. There were significant differences in diagnostic accuracy for lesions >2 cm in diameter between mammography and ultrasound ($\chi^2 = 26.06$, $p < 0.01$) as well as mammography and far-infrared thermography ($\chi^2 = 41.46$, $p < 0.01$). However, there was no significant difference in diagnostic accuracy between far-infrared thermography and ultrasound ($\chi^2 = 1.95$, $p = 0.16$). Ultrasound had greater sensitivity than mammography and far-infrared thermography, while far-infrared thermography had greater specificity than ultrasound and mammography groups.

Table 1. Comparison of mammography, ultrasonography, and thermography in the diagnosis of breast cancer (n = 2036)

	Pathological examination		Accuracy*	Sensitivity	Specificity
	Malignant	Benign			
Mammography					
Malignant	376	27	93.56%	78.3%	98%
Benign	104	1529			
Color Doppler ultrasound					
Malignant	399	108	90.7%	83.1%	93.1%
Benign	81	1448			
Far-infrared thermography					
Malignant	405	93	91.7%	84.4%	94.0%
Benign	75	1463			

The diagnostic accuracy of mammography was higher than the ultrasonography ($\chi^2 = 11.41$, $p = 0.001$) and far-infrared thermography ($\chi^2 = 4.94$, $p = 0.026$), but there was no significant difference in diagnostic accuracy between ultrasonography and far-infrared thermography ($\chi^2 = 0.245$, $p = 0.245$).

Table 2. Comparison of mammography, ultrasonography, and thermography in the diagnosis of breast lesions <2 cm in diameter (n = 853)

	Pathological examination		Accuracy*	Sensitivity	Specificity
	Malignant	Benign			
Mammography					
Malignant	59	19	96.1%	80.8%	97.6%
Benign	14	761			
Color Doppler ultrasound					
Malignant	63	26	95.8%	86.3%	96.6%
Benign	10	754			
Far-infrared thermography					
Malignant	66	17	97.1%	90.4%	97.8%
Benign	7	763			

*There was no difference in the diagnostic accuracy between mammography and ultrasonography ($\chi^2 = 0.864$, $p = 0.353$). However, there were significant differences in diagnostic accuracy between far-infrared thermography and both ultrasonography and mammography ($p < 0.05$).

Table 3. Comparison of mammography, ultrasonography, and thermography in the diagnosis of breast lesions >2 cm in diameter (n = 1193)

	Pathological examination		Accuracy*	Sensitivity	Specificity
	Malignant	Benign			
Mammography					
Malignant	354	116	85.0%	84.9%	85.1%
Benign	63	660			
Color Doppler ultrasound					
Malignant	396	78	91.7%	95.0%	90.0%
Benign	21	698			
Far-infrared thermography					
Malignant	375	39	93.2%	90.0%	95.0%
Benign	42	737			

*There were significant differences in diagnostic accuracy between mammography and ultrasound ($\chi^2 = 26.06$, $p < 0.01$) as well as mammography and far-infrared thermography ($\chi^2 = 41.46$, $p < 0.01$). However, there was no significant difference in diagnostic accuracy between far-infrared thermography and ultrasound ($\chi^2 = 1.95$, $p = 0.16$).

Representative cases

Case 1. Invasive ductal carcinoma

A 43-year-old woman was seen with a complaint of a lump in her left breast. Physical examination revealed a mobile mass of approximately 1.5×2.0 cm at the 12 to 1 o'clock position in her left breast. The texture was hard and the boundaries unclear. Thermography revealed that the temperature of the left breast was higher than that of the right (Figure 2A) and the thermal releasing curve (q-r curve) was consistent with malignancy (Figure 2B). Mammography and ultrasonography (Figures 2C and D) were also consistent with a malignant lesion.

The pathological diagnosis was invasive ductal carcinoma.

Case 2. Low-grade ductal carcinoma in situ

A 45-year-old woman was seen for a complaint of bloody discharge from her left breast. Physical examination was only remarkable for bloody discharge from the nipple when pressing the upper outer quadrant of the left breast. Thermography showed the mean temperature of the left breast was similar to that of the right breast, but the temperature was slightly elevated in the lateral side of the left breast (Figure 3A). Analysis of the thermal curve

was consistent with malignancy (**Figure 3B**). Mammography with contrast injection revealed microcalcifications (**Figure 3C**), whereas ultrasonography revealed no suggestions of malignancy (**Figure 3D**). The final pathological diagnosis was early-stage ductal carcinoma in situ.

Case 3. Granulomatous mastitis

A 35-year-old woman was admitted to the hospital for evaluation of a mass at her right periareolar region. Physical examination showed the patient had symmetrical breasts; however, the right nipple was depressed and the left nipple was normal. There was

no orange peel syndrome or dimple syndrome present. A hard mass 2×3 cm in size was present located near the right areola and had an unclear border. There was skin redness, swelling, and tenderness present. The mass was considered breast cancer by both ultrasound (**Figure 4A**) and mammography (**Figure 4B**). Far-infrared thermography showed a significantly increased temperature in the right breast compared with that of the left breast, suggesting a lesion (**Figure 4C**). The thermal characteristic curve was consistent with inflammation (**Figure 4D**). The final pathological diagnosis was granulomatous mastitis.

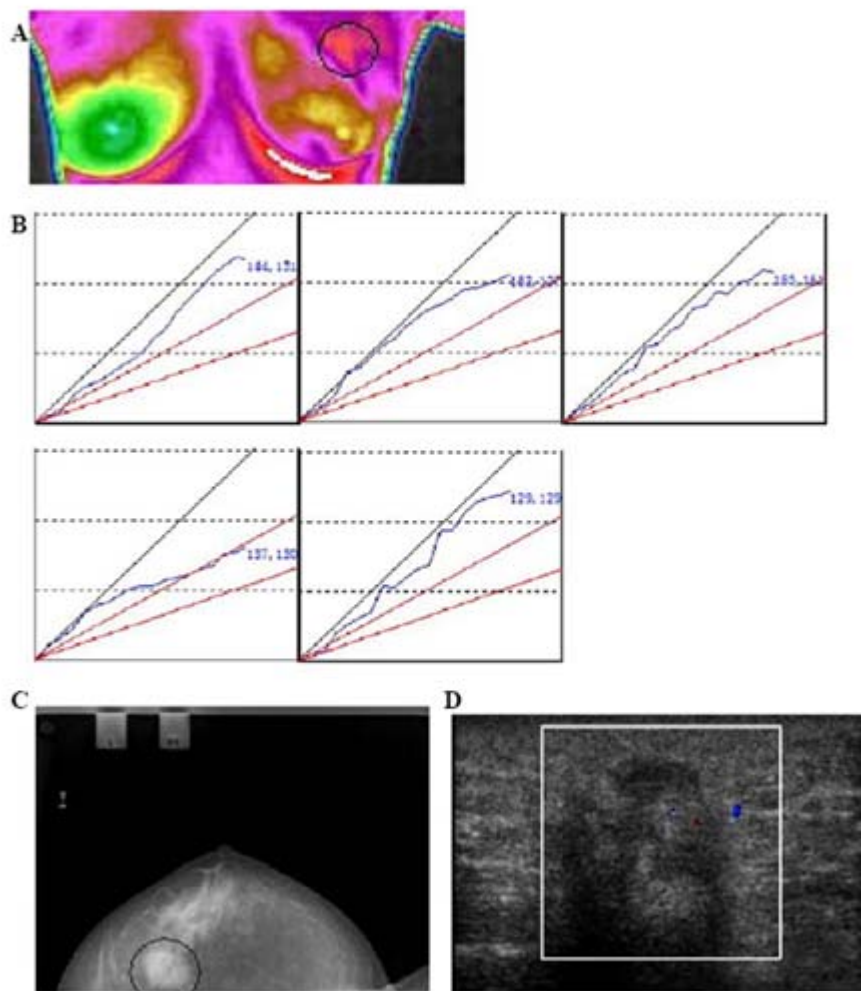


Figure 2. Case 1: invasive ductal carcinoma. (A) Thermograph obtained with far-infrared thermography. The temperature of the left breast was significantly higher than that of the right breast, suggesting a lesion. (B) Thermal releasing curve (q-r curve) consistent with malignancy. (C) Mammography (cranial-caudal view) showed a mass within the left breast. Structural disorder of the local gland posterior to the areola, increased density, and small calcifications near the skin margin were noted. (D) Ultrasound revealed a hypoechoic mass with blurred margins and a rich blood supply.

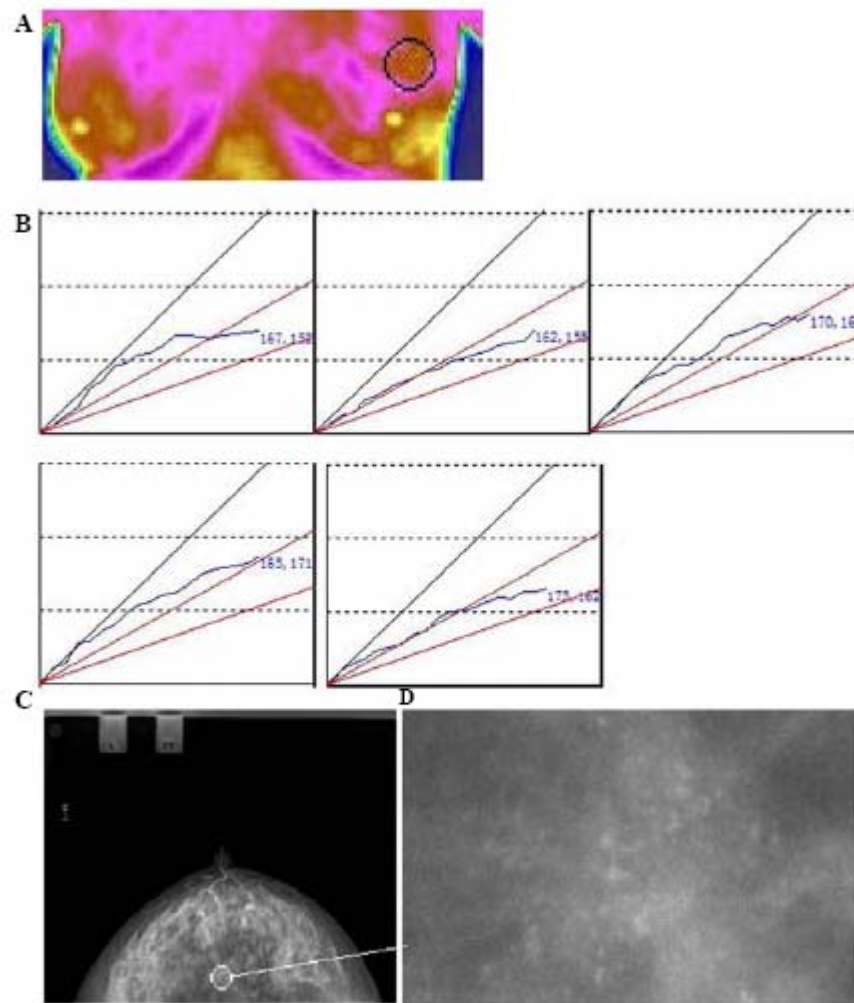


Figure 3. Case 2: low-grade ductal carcinoma in situ. (A) Far-infrared thermography revealed left and right breast temperatures were almost the same; however, the temperature was slightly elevated in the lateral side of the left breast. (B) Thermal characteristic curve was consistent with malignancy. (C) Mammography (cranial-caudal view) after contrast injection into the mammary duct revealed microcalcification clusters in the upper outer quadrant of the left breast. (D) Ultrasound revealed a hypoechoic mass that was relatively even with irregular margins. No blood flow was observed.

Discussion

This study showed that the sensitivity of far-infrared thermography was superior to that of mammography in diagnosing breast malignancy. The sensitivity and specificity of far-infrared thermography was superior to mammography and ultrasonography in the diagnosis of lesions <2 cm in diameter. Further work on differentiating the tumor pathology based on thermographic results is necessary for future clinical use.

As noted previously, mammography remains the most commonly used imaging examination for breast cancer screening, even with high false negative rates and increased exposure to radiation [1].

Ultrasonographic examinations are time consuming; whole breast images cannot be obtained, and accurate diagnosis is strongly related to the operator experience. Hence, both mammography and ultrasonography have significant shortcomings for diagnosing breast cancers and other related pathologies.

By comparison, technological advances and computer modeling analyses [1, 6-8] have renewed interest in thermographic imaging for the breast cancer screening and detection. This is because thermographic imaging is completely non-invasive, fast, and economical. These characteristics make thermographic imaging ideal for use in countries such as China that have a large population.

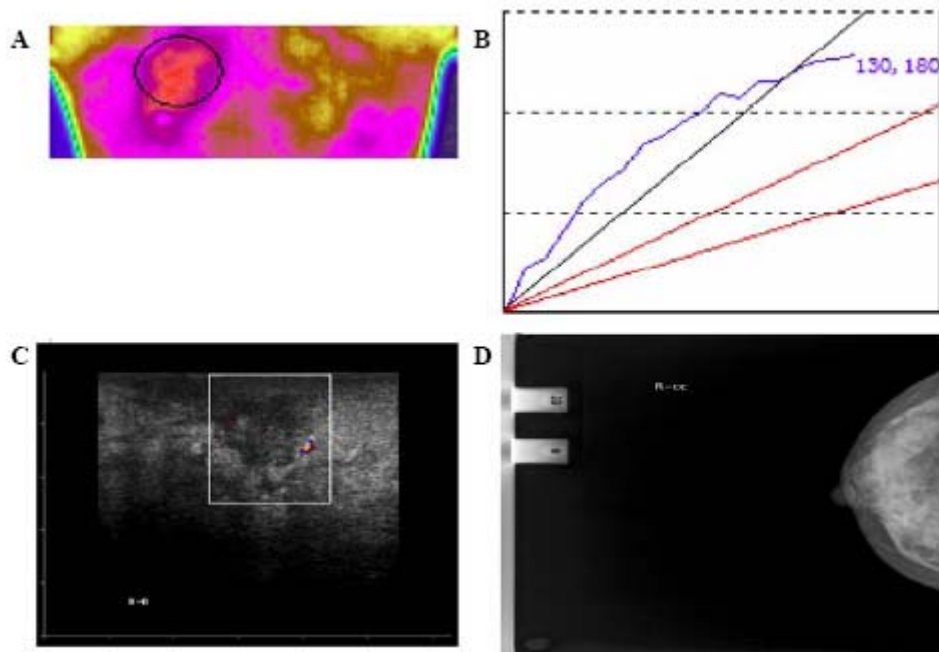


Figure 4. Case 3: granulomatous mastitis (A) Mammography showed depression of the right nipple and thickened skin. Enhanced gland density was observed at 10 o'clock. There was a mass-like image without a clear boundary, which suggested a malignant mass. (B) Color Doppler ultrasound showed a large uneven hypoechoic region in the right breast with obscure boundaries. Many blood flow signals were observed peripherally. (C) Far infrared thermography showed an increased temperature in the right breast that was significantly higher than that of the right breast, suggesting a lesion. (D) Thermal characteristic curve was consistent with inflammation; the final diagnosis proven by pathological examination was granulomatous mastitis.

Although few current studies have examined thermography as a screening tool for breast cancer, their results are encouraging. Arora et al. [12] used thermography to examine 92 patients with 94 breast lesions who received surgical excision. Sixty of the 94 biopsies were malignant and 34 were benign; thermography identified 58 of the 60 malignancies for a sensitivity, specificity, and NPV of 97%, 44%, and 82%, respectively. Whishart et al. [2] performed thermography on 100 women prior to needle core biopsy, analyzed the results by four different methods, and reported a maximal sensitivity and specificity of 78% and 75%, respectively. Wang et al. [13] studied five thermography signs by age-adjusted multivariate logistic regression models in 276 women who received thermography before excisional biopsy and at the most optimal cutoff; they reported a sensitivity, specificity, PPV, and NPV of 72.4%, 76.6%, 81.3%, and 66.4%, respectively. Interestingly, however, Kontos et al. [14] studied thermography in 63 patients and found a respective sensitivity, specificity, PPV, and NPV of 25%, 85%, 24%, and 86%. These conflicting results may be the consequence of the lack of a uniform

diagnostic standard for far-infrared thermography, and varying methods used to analyze the data.

The second presented case is notable. The patient presented with a primary symptom of bloody nipple discharge, requiring the injection of a contrast agent and repeat mammography. The shortcoming of this is that contrast injection is a relatively complex, invasive and painful procedure. Because the ultrasonographic images were unremarkable in this case, a missed diagnosis may easily have occurred. However, far-infrared thermography has none of the above-mentioned shortcomings and was accurate in the lesion diagnosis.

This study had several limitations. First, it only differentiated tumors based on size, using a cut-off point of 2 cm. It did not account for stratifications based on other categories, such as histology and types of breast masses. As the populations were evaluated at a single institution in one country, the outcomes reflect only one patient population segment. A multicenter study in which patients are classified into different groups according to age, disease, or other demographic factors is necessary to confirm

outcomes. Moreover, because not all imaging centers use far-infrared thermography for breast imaging, this study may have limited utility for certain groups of patients.

Conclusions

In conclusion, our study results indicate that far-infrared thermography is suitable as a screening tool for breast cancer, and its sensitivity and specificity are better than those of ultrasonography and mammography for lesions <2 cm in diameter. The procedure is completely non-invasive, fast, and economical, making it suitable for screening in large populations. Further study and standardization of this image analysis is warranted.

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