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Cancer risk assessment with a second generation infrared imaging system

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ABSTRACT

Infrared imaging of the breasts for breast cancer risk assessment with a second generation Amber indium antimonide focal plane staring array system was found to produce images superior to a first generation Inframetrics scanning mercury cadmium telluride system. The second generation system had greater thermal sensitivity, more elements in the image and greater dynamic range, which resulted in a greater ability to demonstrate asymmetric heat patterns in the breasts of women being screened for breast cancer. Chi-square analysis for independence of the results from 220 patients with both the scanning and focal plane infrared imaging systems demonstrated that the results from the two systems were strongly associated with each other (p=.0001). However, the improved image from the second generation focal plane infrared imaging system allowed more objective and quantitative visual analysis, compared to the very subjective qualitative results from the first generation infrared imaging system. The improved image also resulted in an increase in the sensitivity for asymmetric heat patterns with the second generation focal plane system and yielded an increase in the percentage of patients with an abnormal asymmetric infrared image of the breasts from 32.7% with the scanning system to 50.5% with the focal plane system. The greater sensitivity and resolution of the digitized images from the second generation infrared imaging system has also allowed computer assisted image analysis of both breasts, breast quadrants and hot spots to produce quantitative measurements (mean, standard deviation, median, minimum and maximum temperatures) of asymmetric infrared abnormalities.

Keywords: thermography, infrared imaging, breast cancer, focal plane array, risk assessment

1. INTRODUCTION

Early studies of infrared imaging of the breast concentrated on its ability to detect and diagnose breast cancer. Mammography and infrared imaging, commonly called thermography in medicine, were compared for detection and diagnostic ability in the United States during the Breast Cancer Detection and Demonstration Projects between 1973 and 1981, but infrared imaging was discontinued after only a few years. Collection of infrared images of the breast was discontinued because of the poor quality of the infrared images being collected. The poor quality of the images was a result of the lack of standardization of instrumentation, the lack of trained technical personnel to maintain high quality infrared imaging, and the lack of trained radiologists to interpret the infrared images. Unfortunately the collection of infrared image was abandoned before enough data could be collected to be analyzed for significance in terms of detection and diagnosis. Further no risk assessment or prognostic significance information for infrared imaging was generated from the Breast Cancer Detection and Demonstration Projects.

Beginning in the 1980s studies supporting the use of infrared imaging in breast cancer risk assessment[1,2,3] began to be published. Gautherie and Gros[1] in a study of 58,000 patients found 784 patients with normal physical, mammographic and ultrasound findings who had abnormal infrared images of the breasts. Of these 784 patients 298 (38%) were diagnosed with breast cancer within 4 years, and this was the first compelling evidence that asymmetric infrared abnormalities of the breasts is a high risk marker for breast cancer. Stark[2] followed with a second study in 1985 which demonstrated that 23% (346 of the 1499 women with abnormal infrared images of the breast, while screening a total of 11,249 women) of the women with abnormal infrared images of the breast were diagnosed with cancer within the next ten years. This study further showed that women with abnormal infrared images of their breasts had a higher incidence of breast cancer (23%) than nulliparitous women (8.1%) or women with a family history of breast cancer (8.6% with either one or two first degree relatives). Although women with breast biopsies containing extensive hyperplasia and atypia had a 30% to 50% incidence of breast cancer in this study[2] there were only 34 women who had previous breast biopsies, and this is too small a number of woman at risk to allow major changes in incidence through prevention or intervention.

Although several studies have been reported supporting the application of infrared imaging for risk assessment in breast cancer, there still remained an unacceptably high false positive rate (women with an asymmetric infrared abnormality and a normal mammogram) of about 25% for infrared imaging of the breasts. This high false positive rate was due to the low quality of the first generation infrared imaging technology and the very subjective qualitative visual analysis of the results. We believe that the application of second generation infrared imaging systems, with greater sensitivity, improved resolution and the ability to do sophisticated real time computer assisted image analysis of the digitized images of breast heat patterns, should yield standard, reproducible qualitative and quantitative results, that will be applicable to risk assessment, detection, diagnosis and prognosis of breast cancer. Thus, the present study was undertaken to determine if improvements in infrared technology that have been incorporated into the second generation focal plane staring array Amber infrared imaging system can improve the images used for risk assessment in breast cancer.

2. MATERIALS AND METHODS

We recorded 3 breast views (right lateral, left lateral and frontal views) of 220 patients with the Amber focal plane staring array infrared imaging system at the Elliott Mastology Center. The 3 images were digitized and stored on computer hard disk during the study period. We independently analyzed the same 220 patients with the Inframetrics scanning infrared imaging system (right lateral, left lateral and frontal views) using hard copy photographic images (color frontal view and the three black and white views comparable to the Amber digitized images) of the patients that were being screened with mammography and routinely undergoing infrared imaging of their breasts during the study.

The first methodological decision we made, concerning infrared data analysis, was to try to quantitate the asymmetric abnormalities that were present in the Amber images (Table 1). Previously, with the Inframetrics system, we called breast infrared images abnormal if any of the six asymmetric abnormalities were definitely present. Inframetrics images that only had a borderline infrared abnormality were called slightly abnormal (3 levels of results: normal, slightly abnormal, abnormal). For the Amber data we created a quantitative index by adding together the individual scores (Table 1) for the six possible asymmetric abnormalities (small hot spot, large hot spot, global heat, vascular heat, areolar heat and edge heat). The Amber Index could therefore range from 0 to 8 but the highest Amber Index that we computed was five.

TABLE 1
SCORING OF RESULTS FORM THE INFRAMETRICS AND AMBER SYSTEMS

ABNORMALITY	INFRAMETRICS SYSTEM SCORE	AMBER SYSTEM SCORE
ASYMMETRIC SMALL FOCAL HOT SPOT	YES OR NO	0, 1
ASYMMETRIC LARGE FOCAL HOT SPOT	YES OR NO	0, 2
ASYMMETRIC GLOBAL HEAT	YES OR NO	0, 3
ASYMMETRIC VASCULAR HEAT	YES OR NO	0, 1, 2, 3
ASYMMETRIC AREOLAR HEAT	YES OR NO	0, 1
ASYMMETRIC EDGE HEAT	YES OR NO	0, 1

3. RESULTS

Table 2 presents a comparison of the features of the Amber and Inframetrics imaging systems. The Amber system produced a much better image because of the focal plane staring array that contained far greater elements, and increase in dynamic range from 8 to 12 bits/element and an increase in thermal sensitivity from 100mK to 25mK. In addition the Amber image was outputed in a digital format that lends itself to image analysis.

TABLE 2
COMPARISON OF FEATURES BETWEEN THE INFRAMETRICS AND AMBER SYSTEMS

INFRAMETRICS SYSTEM	AMBER SYSTEM
First Generation	Second Generation
Scanning Mercury Cadmium Telluride Detector	Indium Antimonide Focal Plane Array
Liquid Nitrogen Cooler	Stirling Cycle Cooler
175 Elements/Line @Line Rate: 7866Hz RS-170/NTSC	256 x 256 Elements - Staring Array
Dynamic Ratings: 8 Bits/Element	Dynamic Range: 12 Bits/Element
Thermal Sensitivity: 100mK@30°C	Thermal Sensitivity: 25 mK@30°C
Spectral, Range: 8-12 Microns	Spectral Range: 3-5 Microns
External Calibration	Internal Calibration
Video Output: Analog	Video Output: Either Digital or Analog

The first comparison (Table 3) we made on the normal and high risk patients being screened for breast cancer was to

TABLE 3
COMPARISON OF INFRARED RESULTS WITH THE INFRAMETRICS AND AMBER SYSTEMS

AMBER SYSTEM	INFRAMETRICS SYSTEM		
AMBER INDEX	NORMAL	SLIGHTLY ABNORMAL	ABNORMAL
0	87/220 (39.5%)	12/220 (5.5%)	10/220 (4.5%)
1	23/220 (10.5%)	5/220 (2.3%)	4/220 (1.8%)
2	22/220 (10.0%)	16/220 (7.3%)	10/220 (4.5%)
3	10/220 (4.5%)	1/220 (0.5%)	4/220 (1.8%)
4	5/220 (2.3%)	0/220 (0.0%)	6/220 (2.7%)
5	1/220 (0.5%)	1/220 (0.5%)	3/220 (1.4%)

p=.0001, chi-square analysis for independence determine if the results from the second generation Amber infrared imaging system differed from the results from the Inframetrics system. Chi-square analysis for independence showed that the two methods produced results that were not independent and therefore were strongly associated (p=.0001). The most interesting result was that there appeared to be an increase in the sensitivity for picking up asymmetric heat patterns with the Amber system, as 50.5% (111 of 220 patients without breast cancer) had abnormal infrared imaging, whereas only 32.7% (72 of 220 patients) had asymmetric heat patterns with the Inframetrics system. Analysis of the six asymmetric abnormalities individually (Table 4) showed that most of the increase in sensitivity could not be attributed to the small and insignificant (p=.1434) increase in small hot spots, large hot spots and global heat from 22.9% (50 of 218 patients) with the Inframetrics system to 29.5% (65 of 220 patients) with the Amber system. However there was a significant increase (p=.0054) in vascular asymmetry from 19.7% (43 of 218 patients) with the Inframetrics scanning system to 31.8% (70 of 220 patients) with the Amber focal plane system.

TABLE 4

DISTRIBUTION OF ABNORMALITIES FOR INFRAMETRICS AND AMBER INFRARED IMAGING SYSTEMS

ABNORMALITY	INFRAMETRICS SYSTEM	AMBER SYSTEM
ASYMMETRIC SMALL FOCAL HOT SPOT	41/218 (18.8%)	28/220 (12.7%)
ASYMMETRIC LARGE FOCAL HOT SPOT	3/218 (1.4%)	35/220 (15.9%)
ASYMMETRIC GLOBAL HEAT	6/218 (2.8%)	2/220 (0.9%) p=.1434
ASYMMETRIC VASCULAR HEAT	43/218 (19.7%)	70/220 (31.8%) p=.0054
ASYMMETRIC AREOLAR HEAT	6/218 (2.8%)	14/220 (6.4%)
ASYMMETRIC EDGE HEAT	1/218 (0.5%)	0/220 (0.0%)

Two known risk factors (family history of breast cancer and previous breast biopsy) were compared to the infrared imaging results from the Inframetrics scanning and Amber focal plane systems. Neither of these risk factors were found to correlate with the infrared imaging results and therefore infrared imaging results were found to be an independent risk factor in breast cancer. Women being screened for breast cancer, who come from a family with a history of breast cancer, are at 2- to 5-fold increased risk of developing breast cancer, if one or more first degree female relatives (mother, sister or daughter) have had breast cancer. In this study women were divided into two risk categories by either the presence or absence of a family history of breast cancer and compared by group to the results of their breast infrared imaging. When patients' results from infrared imaging, either levels determined by analysis of Inframetrics infrared imaging (Table 5) or the Amber Index (Table 6), were compared to patients' family history of breast cancer, it was found that there was no relationship between having a family history of breast cancer and having an abnormal asymmetric infrared pattern of the breasts. So it seems that an abnormal infrared image is a high risk marker for breast cancer that is independent of family history of breast cancer.

TABLE 5
INFRAMETRICS SYSTEM RESULTS BY FAMILY HISTORY OF BREAST CANCER

INFRAMETRICS SYSTEM	RISK ASSESSMENT	
	NORMAL (NO FAMILY HISTORY)	HIGH (FAMILY HISTORY)
NORMAL	80/213 (37.6%)	64/213 (30.0%)
SLIGHTLY ABNORMAL	21/213 (9.9%)	12/213 (5.6%)
ABNORMAL	17/213 (8.0%)	19/213 (8.9%)

p=.3903, chi-square analysis for independence

TABLE 6
AMBER SYSTEM RESULTS BY FAMILY HISTORY OF BREAST CANCER

AMBER SYSTEM	RISK ASSESSMENT	
AMBER INDEX	NORMAL (NO FAMILY HISTORY)	HIGH (FAMILY HISTORY)
NORMAL (0)	57/213 (26.8%)	49/213 (23.0%)
SLIGHTLY ABNORMAL (1,2)	45/213 (21.1%)	32/213 (15.0%)
ABNORMAL (>2)	16/213 (7.5%)	14/213 (6.6%)

p=.7971, chi-square analysis for independence

The second risk factor that we looked at was previous breast biopsy. It has been clearly shown in studies done by other investigators that patients who have had one or more previous breast biopsies are at increased risk of being diagnosed with breast cancer. This increased risk of developing breast cancer, that has been associated with having had a previous breast biopsy, is probably due to the ability of mammography to detect not only invasive cancerous lesions but also noninvasive cancerous lesions and benign lesions (such as atypical hyperplasia and microcalcifications) that put woman at increased risk of developing breast cancer. In other words, mammographic abnormalities, that lead to open surgical biopsy, are highly associated with invasive carcinomas and further are often caused by precursors of invasive carcinoma that put woman at increased risk of developing breast cancer. These abnormalities that are present in mammograms are probably also the cause of abnormal infrared images in breast cancer screening and at diagnosis of breast cancer. The Inframetrics analysis (Table 7) showed that there was a trend (p=.0747, chi-square analysis for independence) towards patients with abnormal infrared images of the breast having breast biopsies. This trend was not confirmed (p=.3582, Table 8) when the infrared images were digitized and saved with the Amber infrared system and the Amber Index compared to the history of breast biopsy.

Digitization of the higher quality infrared Amber images allowed quantitation of infrared abnormalities by computer assisted image analysis. The location of cancer in the breast is not random and each quadrant of the breast has been shown to have its own rate of occurrence with the upper outer quadrant containing the greatest proportion of tumors. Therefore, we devised a computer analysis method that would quadrant the breast by a defined reproducible method. In all the digital images a line is drawn from the chin to the nipple, then a second line is drawn to the lowest contour of the breast, and finally a third and forth line are drawn horizontally to the left and right margins of the breast (Figure 1). The same is done for both the right and left breast and we determine the mean, standard deviation, median, minimum and maximum temperatures for each quadrant of the breast. Then these quantitative measurements were compared between the left and right breast to quantitate asymmetric infrared abnormalities.

TABLE 7
INFRAMETRICS SYSTEM RESULTS BY HISTORY OF PREVIOUS BREAST BIOPSY

INFRAMETRICS SYSTEM	RISK ASSESSMENT	
	NORMAL (NO PREVIOUS BIOPSY)	HIGH (PREVIOUS BIOPSY)
NORMAL	116/212 (54.7%)	28/212 (13.2%)
SLIGHTLY ABNORMAL	24/212 (11.3%)	9/212 (4.2%)
ABNORMAL	22/212 (10.4%)	13/212 (6.1%)

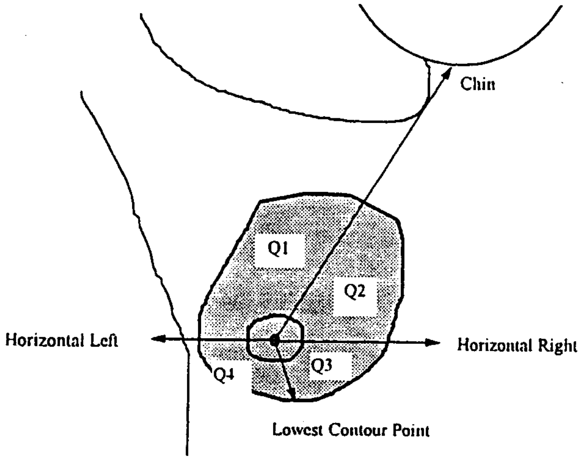
p=.0747, chi-square analysis for independence

TABLE 8
AMBER SYSTEM RESULTS BY HISTORY OF PREVIOUS BIOPSY

AMBER SYSTEM	RISK ASSESSMENT	
AMBER INDEX	NORMAL (NO PREVIOUS BIOPSY)	HIGH (PREVIOUS BIOPSY)
NORMAL (0)	84/212 (39.6%)	22/212 (10.4%)
SLIGHTLY ABNORMAL (1,2)	58/212 (27.4%)	18/212 (8.5%)
ABNORMAL (>2)	20/212 (9.4%)	10/212 (4.7%)

p=.3582 chi-square analysis for independence

FIGURE 1
GUIDELINES FOR BREAST QUADRANTS



4. DISCUSSION

Infrared imaging of the breast for breast cancer risk assessment with a second generation focal plane staring array system was found to produce images superior to a first generation scanning system. The second generation system had greater thermal sensitivity, more elements in the image and a greater dynamic range, which resulted in a greater ability to demonstrate asymmetric heat patterns in the breasts of women being screened for breast cancer. Comparison of the infrared images from the two systems showed that the 12 bit Amber image was better than the 8 bit Inframetrics image, but the digitized images that were stored on the hard drive were not as good in either case as the analog output from either system. The 16 bit capacity of the Amber system will probably be needed in order for the quality of the recalled digitized image to reach that of the analog output, and for image analysis to reach its full potential. However we did conclude that the second generation Amber infrared images both analog and digital are better for medical applications than the first generation Inframetrics Images.

The improved imaging of the second generation infrared system increased the proportion of women with abnormal breast infrared images in a group of women being screened for breast cancer, and also allowed more objective and quantitative visual analysis, compared to the very subjective qualitative results of the first generation infrared system. Eventually we hope to demonstrate that the application of a simple index (the summation of a semiquantitation of asymmetric hot spots, global heat, vascularity, areolar heat and edge heat) and an appropriate cut-off level can decrease the high false positive rate to an acceptable level. This will require us to determine what types, levels or combination of types and levels of asymmetric abnormalities are most predictive of risk of developing breast cancer. The Amber Index seems to be more suited to this purpose, than the 3 levels of results from the Inframetrics system, because there are many levels (0 to 8 levels) with the Amber Index and we actually had 6 levels of the Amber Index. In this study 50% (111 of 220) of the patients were found to have some infrared abnormality of the breasts, when an Amber Index of zero was considered normal, but if an index of one is considered to be such a small abnormality that a patient's risk of developing breast cancer is not significantly increased, then approximately 36% (79 of 220) of the patients being screened for breast cancer would be categorized as high risk individuals. If an amber index of two is considered insignificant then 14% (31 of 220) of the patients being screened for breast cancer would have sufficiently abnormal infrared images to be at increased risk of developing breast cancer. We feel that 14% would be approximately the proportion of patients in our study group that would be at increased risk of developing breast cancer and therefore an index greater than two would put a patient at increased risk of developing breast cancer. However, a clinical follow-up study will be needed to determine how well we have delineated the women at high risk of developing breast cancer. From Table 3 it can also be seen that the patients, who are determined to be at increased risk of developing breast cancer, are different with the two systems, as 16 patients who have completely normal breast infrared images with the Inframetrics system had abnormal images (Amber Index greater than 2) with the Amber system and 24 other patients with normal Amber images (Amber Index less than or equal to 2) were abnormal with the Inframetrics system. Thus 18% (40 of 220) of the patients had significantly different infrared imaging results with the two systems and we are presently doing clinical follow-up studies to determine if the Amber Index is a better predictor of risk of developing breast cancer than the previous results with the Inframetrics system.

In the past the major shortcoming of infrared imaging of the breast has been its high false positive rate which is typically between 1/4 and 1/3 of women being screened for breast cancer. This seemingly high false positive rate is partly due to mammographers calling all abnormal infrared images of the breast false positives in woman with normal mammograms, instead of being considered at high risk of developing breast cancer -- mammographers have not accepted that an abnormal infrared image is an early predictor of breast cancer. Even though women with an abnormal infrared image of their breasts is very prevalent in the screening population and this would therefore require many high risk women to be followed at shorter intervals with mammography and clinical breast exam, the fact that approximately 25% of the women with abnormal infrared images will develop breast cancer warrants its inclusion in all breast cancer screening programs. We also believe that further improvements in infrared imaging systems and analysis, such as the Amber Index, will eventually allow the clinician to better define infrared abnormalities of the breast that translate into increased risk of breast cancer and therefore decrease the high false positive rate of infrared imaging of the breast.

Patients found to have abnormal infrared images during screening for breast cancer have previously been shown to be at higher risk of developing breast cancer[1,2,3]. This study has clearly shown that the presence of an abnormal infrared image in patients being screened by mammography for breast cancer is a high risk marker independent of the commonly used high risk markers of family history and previous breast biopsy. The improvement in risk assessment that could be achieved by integrating infrared image analysis with family history and previous breast biopsy results could have significant impact on the selection of patients for breast cancer prevention studies. For example, in hormonal intervention studies with the antiestrogen tamoxifen the addition of infrared imaging results to the other parameters presently used to select patients for these hormonal therapy prevention study might define a group of women at high enough risk of developing breast cancer to warrant the extension of hormonal therapy intervention from only postmenopausal women to both premenopausal and postmenopausal women. This extension to premenopausal women would be possible because of an increase in the therapeutic index of the hormone prevention therapy, caused by decreasing the number of women treated (higher risk women being treated) and therefore increasing the proportion of women that benefit from the hormonal therapy, while the side effects and toxicities remain the same.

The greater sensitivity and resolution of the digitized images of the second generation infrared system has allowed image analysis of total breasts, breast quadrants and hot spots to produce mean, standard deviation, median, minimum and maximum temperatures. This will allow future analysis to be both quantitative and objective as opposed to the subjective qualitative analysis that has been the standard in the past for infrared imaging of the breasts.

In conclusion we believe that infrared imaging of the breast should be an integral part of any breast cancer screening program due to its value as an independent risk factor for breast cancer and its value as a prognostic indicator[4]. The use of improved second generation focal plane staring array infrared technology for breast cancer detection, diagnosis and as a high risk and prognostic indicator should lead to both earlier detection of breast cancer, thus increasing the overall survival of breast cancer patients, and aid in determining which node negative breast cancer patients should receive adjuvant chemotherapy. Continued development of objective computer assisted analysis methods of infrared images of the breast, that compare quantitative thermal parameters of the right and left breasts, will eventually eliminate the problems inherent in the presently used subjective qualitative analysis methods. Accomplishment of these goals should significant decrease the morbidity, mortality and overall cost of therapy for breast cancer patients.

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