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A Comparative Review of Thermography as a Breast Screening Technique

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Breast cancer is the most frequently diagnosed cancer of women in North America. The probability of developing breast cancer increases with age and the largest risk factors associated with its development, specifically age and gender, are not modifiable. Despite advances in treatment that have reduced breast cancer mortality over the past two decades, next to lung cancer, this disease still remains the second leading cause of cancer induced death in women. Several well established tools are currently used to screen for breast cancer including clinical breast exams, mammograms, and ultrasound. Mammography has been the gold standard for screening breast cancer, though as a screening tool its sensitivity and specificity are limited. Ultrasound and clinical breast exams are adjunctive tools used in the breast screening process, particularly for women with mammographically dense breasts. Thermography, first introduced as a breast-screening tool in 1956 has been approved for use by the FDA since 1982 and was initially well accepted. However, after a 1977 study found thermography to lag behind both mammography and ultrasound, the medical community quickly lost interest in this tool and its application has been greatly limited. In this review, each of the breast screening tools and their associated limitations are discussed, with a focus brought to thermography. No single screening tool provides excellent predictability but a combination of tools that also incorporates thermography has been shown to boost both sensitivity and specificity. In light of developments in computer technology, and the maturation of the thermographic industry, additional research is required to confirm and/or continue to develop the potential of this technology to provide a more effective noninvasive adjunctive tool to provide early detection of breast cancer.

Keywords: breast cancer screening; thermography; mammography; ultrasound; clinical breast exams

Breast cancer is the most frequently diagnosed cancer of women in North America. The National Cancer Institute of Canada estimates that 1 in 9 women will develop breast cancer in their lifetime and 1 in 27 will die from the disease.[1] The statistics on the United States are similar with incidence estimated to be 1 in 8 women developing breast cancer.[2] The probability of developing breast cancer increases with age (see Table 1) and the largest risk factors associated with the development of breast cancer, specifically age and gender, are not modifiable.[1]

Despite advances in treatment that have reduced breast cancer mortality over the past two decades, next to lung cancer, breast cancer still remains the second leading cause of cancer death in women.[3] Clinical breast exam (CBE) and mammography are the two most widely used breast screening tools. Breast cancer screening guidelines vary in North America. In the United States, the US Preventive Services Task force (USPSTF) "recommends screening mammography, with or without clinical breast exam, every 1 to 2 years for women aged 40 or older."[4] In addition, there are no recommendations for or against the use of CBE or breast self exam (BSE) in screening. In Canada, mammography and CBE are accepted procedures for breast cancer screening. There are, however, different recommendations based on age. For women aged 50 and older, mammography screening

Table 1. Percentage Probability of Developing Breast Cancer

Age	Canada[1]	United States[2]
<40	0.4	0.43
40 to 45	1.2	1.44
46 to 50	2.3	2.63
51 to 60	3.0	3.65
61 to 70	3.1	n/a
71 to 80	2.5	n/a

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is recommended every two years with consideration for annual mammography given in circumstances of increased risk. Routine mammographic screening for women under age 40 is not recommended, and for women ages 40 to 49 access to screening mammography is recommended at the discretion of the woman and her physician.[5]

Current Screening Techniques

Mammography

Since the early 1960s, the gold standard for early detection of breast cancer has been, and still is mammography.[6] The sensitivity of mammography in the general population is believed to reside between 75% to 90% with a positive predictive value of only 25%.[7-10] However, numerous studies indicate that there may be a wider variation in mammography's sensitivity and specificity.[11] Furthermore, mammography's sensitivity may be influenced by such factors as age, breast density, and family history.[12,13]

Mammography is used to assess the anatomical structures of the breast and identify any abnormalities.[14,15] Elmore et al[9] estimated that in the US, 1 in 2 women will have at least 1 false–positive mammogram result, and 1 in 5 women will have at least 1 false–positive clinical breast examination result. Brewer et al[16] conducted a systematic review of the long term effects of false–positive mammograms. Their findings indicate that women who received false–positive mammograms experienced an increase in thoughts regarding breast cancer, increased anxiety and worry, and increased anticipation regarding receiving positive results for breast cancer.[16] These issues and the associated increase in stress occur in addition to an increase in cost to the health care system resulting from the additional procedures.

Challenges and Risks of Mammography

Breast density. Mammography is not well suited for women with dense breasts, implants, fibrocystic breasts, or on hormone replacement therapy.[17,18] For example, on mammography, both dense breast tissue and cancer appear white, making it difficult to distinguish between the two tissue types.[19,20] In a study reported on by the American Cancer Society, the density of breast tissue was graded into 4 categories. Grade 1 represented the least dense breast tissue and grade 4 the densest. Mammogram detection rates were found to be 83% for grade 2, 68% for grade 3, and 55% for grade 4.[19] As the density of a woman's breast tissue increased the mammography's ability to detect abnormalities was reduced. The incidence of dense breasts and/or fibrocystic breast is higher in younger aged women though this can occur in women of any age.[19] It is worth noting that breast density is known to correlate with increased risk of breast cancer.[21,22] Thus a higher proportion of women with a higher potential of risk may be less likely to benefit from the proven sensitivity of mammography in women with low density breast tissue.

Rupture risk. With mammography there is a risk of rupture of the encapsulation of a cancerous tumor, as the process of taking a mammogram involves the compression of the breast tissue. Twenty-two pounds of pressure is sufficient to rupture the encapsulation around a cancerous tumor.[18] Today's mammogram equipment uses 42 pounds of pressure.[18] Depending on the location of the tumor, this would be sufficient force to rupture the encapsulation and potentially release malignant cells into the bloodstream.

Radiation exposure. Mammography also confers a slightly increased risk of causing radiation induced breast cancer. Younger women's breast tissue is more susceptible to the effects of radiation versus older women because undifferentiated cells are more vulnerable to the effects of ionizing radiation.[18] It has also be found that proliferation of these mutated cells under the influence of estrogen increases by 10%.[18] The latent period for the development of breast cancer after low dose radiation exposure is a minimum of 10 years. There is some evidence to even suggest that low dose radiation carries a higher risk versus higher dose radiation of the past.[23,24] Feig[25] estimates that while the risk is small for radiation induced breast cancer in women before the age of 50, the benefits of earlier detection still outweigh the costs. Berrington de Gonález and Reeves[26] developed several models to assess the risk of radiation exposure through screening of women beginning at age 20, 30, and 40. Their estimates suggest that if screening were begun at age 20 this would cause more radiation-induced breast cancer deaths that it would prevent. If screening were begun at age 30 it was unlikely to result in a reduction of breast cancer mortality and at age 40 the benefits from screening would only be evident if mortality was reduced by 20%.[26] An article by Law et al[27] further suggests that screening prior to age 35 presents a higher risk to benefit ratio versus screening after age 40.

Age. The younger the patient the less effective mammography is likely to be. Some of the challenges associated with mammography in younger women have been discussed above. Furthermore, Berrington de González and Reeves,[26] in their study of mammographic screening determined that "mammogram is less effective before the age 50." This may be related to a tendency for younger women to have relatively higher breast tissue density.

BRCA1/2 mutations. There is also some concern regarding the use of mammography in women with a family history of breast cancer and/or the BRCA1/2 gene mutations. Women with a BRCA1/2 gene mutation are at a

greater risk for the development of breast cancer. The BRCA1/2 genes are responsible for correcting DNA mutations; mutations that may well result from radiation damage. Friedenson[28] theorizes that exposure to ionizing radiation by screening mammograms might well be more dangerous for women with this mutation. While the Narod et al[29] case control study of 1600 women with either BRCA1 or 2 mutations concluded that screening mammography does not contribute "substantially to the burden of breast cancer." However, in a subgroup analysis, they did find an associated increased risk of breast cancer diagnosis prior to age 40 when screening mammographs were initiated when women were in their 30s.[29]

Ultrasound

Ultrasound is an adjunctive tool used in conjunction with mammography and clinical breast exam in screening for breast cancer. Breast ultrasound has been considered a useful tool in mammographically dense breasts and in characterizing an abnormality detected in mammograms.[12] Osako et al[20] conducted a study that graded the tumor size, by palpation, and breast density in 165 women, and then compared the effectiveness of mammography and ultrasound in detecting these tumors. It was found that sensitivity of mammography declines with decreasing tumor size and increasing breast density, while ultrasound remained effective regardless of tumor size. However, the sensitivity of ultrasound declines in detecting nonpalpable tumors such as microcalifications.[20] The overall accuracy of ultrasound has been found to depend on three factors: quality of the tools, expertise of the physician in conducting the procedure and in interpreting the image, and the use of a multidisciplinary approach for breast cancer detection.[30]

Clinical Breast Exam

CBE and SBE are manual exams that are performed by the clinician or the patients themselves. Well-performed SBE and CBE have been found to detect at least 50% of asymptomatic cancers.[31] Oestricher et al[32] found that although the sensitivity of CBE alone (21%) is not comparable to the sensitivity of mammography (78%), the two combined tend to improve the sensitivity of breast cancer detection (82%). Park et al[33] showed that the importance of CBE lies in its ability to detect cancers missed by mammography. In a study by Park et al,[33] 489 asymptomatic women were screened for breast cancer with 46 women diagnosed with breast cancer. Of these 46 women diagnosed, 54% were detected by mammography alone, 13% were detected by CBE alone, and the remaining 32% were detected by both screening methods. This study showed that mammography has a false–negative rate in detecting breast cancer of about 13%, which could delay diagnosis and treatment. By performing a thorough CBE one could detect breast cancer that mammography may not detect, thus avoiding a critical delay in diagnosis and treatment.[33]

As mentioned in previous sections, the sensitivity of mammography decreases with increased density of breast tissue. Density of breast tissue correlates with age, as younger women tend to have denser breasts, which also makes it more difficult to palpate lesions within the tissue. The pronounced limitations of mammography for women with dense mammary tissue is highlighted by a study of Oestricher et al[32] that found women with dense breasts were twice as likely to be diagnosed with breast cancer using CBE alone. While mammography is the currently accepted gold standard for breast cancer screening, there are clearly limitations to this tool.[11]

What is Thermography?

Infrared radiation is emitted from objects with a temperature above absolute zero.[34,35] The human body radiates heat energy from the surface of the skin and the emissivity of human skin is 0.98, which is close to that of a perfect black body.[34-36] Therefore, accurate temperature values can be created from measurements of the infrared radiation from the skin.[34] Infrared thermography is the recording of temperature distribution of a body using the infrared radiation emitted by the surface of that body at wavelengths between 0.8 μm and 1.0 μm.[37] An infrared camera is used to detect the infrared heat energy that is emitted from the skin. The amount of the energy that is recorded is converted into an energy signal that, along with other parameters, is used to calculate the actual temperature of the object. With this information it is possible to create a visual map or thermogram of the distribution of temperatures on the surface of the object imaged.[36] The sensitivity of modern infrared cameras is such that temperature differences to 0.025°C can be detected.[34]

Breast infrared thermography is a noninvasive procedure that does not involve compression of the breast tissue or exposure to radiation, and functions through an assessment of physiological function, through high resolution temperature measurements of breast tissue.

Thermography as a breast cancer risk assessment tool in the US has been approved by the FDA since 1982, and as a screening tool for breast cancer, thermography was first introduced in 1956 and was accepted widely by medical professionals at that time.[38] However, this acceptance rapidly ended in 1977 after a report written by Feig et al[39] tested the sensitivity of thermography compared to other methods of breast cancer detection. The results of this study, in the Breast Cancer Detection Demonstration Project (BCDDP), showed that thermography came out third, after ultrasound and mammography, with a sensitivity of only 39% and a specificity of 82%.[39] However,

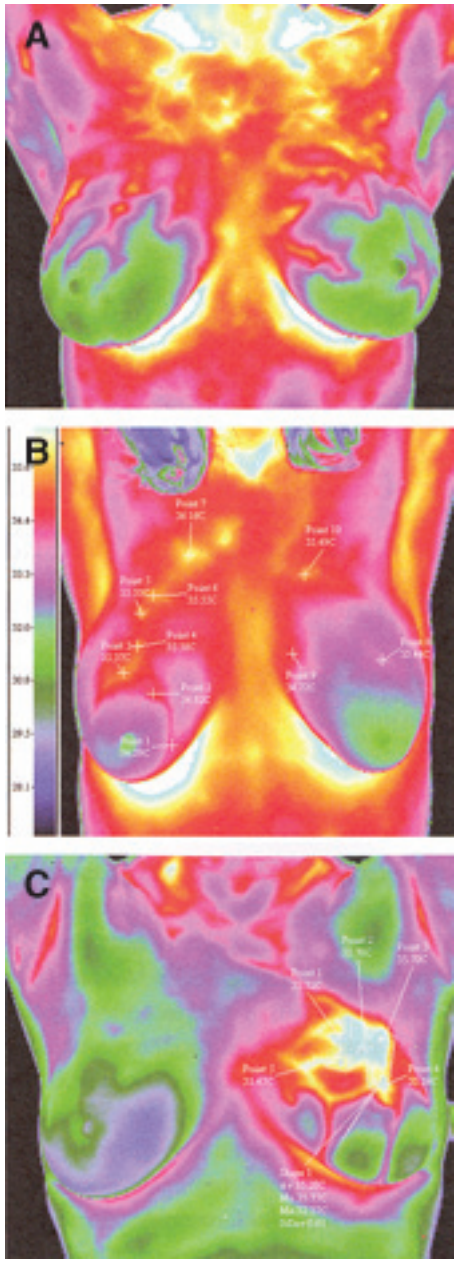

Figure 1. Thermographic breast images: (A) normal; (B) showing early stage of cancer in the right breast; (C) showing advanced cancer in the left breast

some thermography researchers have criticized the BCDDP study for its lack of quality control around the thermography procedures, images, and interpretation.[40] Since the release of the 1977 report the medical community has largely lost interest in thermography and focused its efforts on improving mammography.

In the past, thermography was restricted to such techniques as infrared thermograms, plate thermograms, and liquid crystal imaging. Although these produced a foundation of information for current researchers to build on, consistent results of high sensitivity were never achieved. Since these early beginning's, thermography's use of temperature measurements on the surface of the breast to detect abnormalities in breast tissue has improved dramatically. Technological improvements have led to increases in the sensitivity of thermography. In a collaborative effort, the top thermography researchers of the 1970s were able to come up with criteria for interpreting thermograms. These included recognition of diffuse heat patterns involving a quadrant, half, or the entire breast; asymmetric focal hotspots on the thermogram; or an increase in areolar heat.[41] An analysis by Head et al[42] also included increases in periareolar heat, blood vessel discrepancy, and a global diffused heat pattern. Standardized procedures were also introduced at this time.

How is Thermography Performed?

Laboratory Procedure

Temperature and humidity control in the imaging room must be maintained at a stable temperature within the range of 18°C to 25°C and maintained within 1°C during the examination.[34, 36] Potential sources of additional heat generated by windows permitting sun to shine through, additional heat generated by computer equipment, and other such devices must be eliminated from the imaging room in order to reduce thermal artifacts. Drafts and air flow from air conditioners must be directed away from the patient in order or reduce the opportunity for additional physiological stress that would negatively impact the procedure.[34]

Patient Procedure

After filling out a breast history form, patients are asked to undress to the waist in a private dressing room to allow the surface of the breasts to cool to room temperature (18°C to 22°C) taking about 15 minutes. For the scan, the patient is asked to stand about 10 feet in front of the camera with her arms raised over her head while three views of the breast (anterior and two lateral views) are taken. The next step in the process is a "cold challenge" where the patient is asked to place both hands in cold water at 10°C for one minute; then these same three images are retaken.[43,44] The breasts exhibit thermal patterns that are captured by the infrared camera. It is these thermal captured image patterns that are interpreted by a trained thermographer. The necessity of the inclusion of a cold challenge as part of the imaging procedure is currently being questioned. In 2004, Amalu[45] conducted a review of the literature and found that the results of the "cold challenge" did not contribute additional information that would change the clinical follow-up of a patient.

A trained thermographer will analyze the thermogram for specific thermal features. Thermal features are divided into signs and criteria based on their established characterization of breast disease. In all instances the contra lateral breast is used as reference for some degree of control. According to Hoekstra[46] thermology signs are:

- Asymmetric and hyperthermic vascular patterns
- Focal patterns with +2.5°C differential
- Asymmetric and atypical complexity of a vascular pattern
- Asymmetric and diffusely hyperthermia (+2°C differential) patterns involving the peri-areolar area or entire breast
- Localized heat along an abnormal physical contour (edge sign)
- Lack of an adaptive response to an autonomic challenge procedure

Thermology criteria are:

- Anarchic or complex vascular features
- Hyperthermic focal patterns greater than 3°C differential
- Asymmetric and abnormal complexity of a vascular pattern
- Asymmetric and abnormal physical contour of more than one quadrant of a breast
- Any combination of these thermology signs

Biological Rationale for Thermal Changes Indicating Underlying Pathology

Blood is the main heat exchanging fluid in the body; therefore pathologies identified by thermography are generally associated with changes in blood perfusion.[47] Gautherie et al[48] reported that in normal breast tissue there is a constant positive curve of thermal conductivity, where temperature gradually increases from skin to deep tissue, whereas in breasts with a cancerous lesion, the thermal conductivity resembled a bell-shaped curve. The evidence of a discrepant temperature profile implies that there is something in the middle of this breast type of tissue that releases large amounts of heat.[48] Anbar[47] identified that "abnormal behavior of skin temperature can be manifest in two principal modalities: (1) pathological changes in the spatial distribution of temperature over the skin surface, (2) pathological changes in the dynamic temperature behavior, ie, warming, cooling, or periodic cooling of a given sub area of skin." There are a number of possible explanations for these changes including angiogenesis, nitric oxide, inflammation, and estrogen.

Angiogenesis

Endocrine changes, inflammation, and the presence of tumors modify the temperature and vascularization of the breasts.[49] In order to grow, Cancer tumors must develop blood vessels to deliver the necessary nutrients and oxygen to support their growth. These blood vessels, developed in a process of pathologic angiogenesis, provide the cancer tumor with a dedicated blood supply. In this pathological and chaotic process of angiogenesis there is a lack of smooth muscle cells rending the blood vessels unable to vasoconstrict normally.[50] A 1996 study by Gamagami on angiogenesis by infrared imaging, reported that hypervascularity and hyperthermia could be shown in 86% of nonpalpable breast cancers.[7,51] Yahara et al,[52] using contact thermography, reported that an elevation in temperature in the tissue surrounding the tumor was correlated to women in a high-risk for cancer group.

Nitric Oxide

Nitric oxide is a vasodilatory substance in the body.[40,51] While cells of the immune system produce nitric oxide as a defense mechanism, it has also been demonstrated that other cancer cells, including breast cancer cells, produce nitric oxide as well.[53,54] Nitric oxide is used as a local vasodilator by these cells to enhance the nutrient and oxygen delivery to the cancerous cells, thereby increasing local temperature.[53]

Inflammation

The presence of inflammation is another mechanism by which local increases in heat may be generated. As in the case of infection or wound healing, cancer creates its own conditions leading to vasodilation and the rapid recruitment of the variety of cells and blood involved in the process of inflammation.[53]

Estrogen

Estrogen also mediates vasodilation by increasing the local production of nitric oxide, therefore estrogen imbalances could result in vasodilation of the estrogen sensitive tissues leading to localized temperature changes.[55]

Sensitivity of Thermography

Early clinical trials conducted in the 1960s and 1970s indicated that thermography's ability to detect breast cancer had a true positive rate of between 84% to 95% and a false positive rate of between 6% to 13%.[40] In a study by Head et al[56] three different groups of patients from the Elliott Mastology Center who had undergone breast infrared imaging as part of their breast exam beginning in 1973 were studied. The patients had all received infrared imaging of their breasts at least one year prior to their diagnosis of breast cancer. Group 1 was comprised of 126

patients who had died from breast cancer, group 2 was comprised of 100 patients who had been diagnosed with breast cancer, and group 3 was comprised of 100 patients who had a variety of mastopathies but did not have breast cancer during the screening. In a retrospective analysis of the infrared imaging versus the outcomes, it was found that 88% of the infrared images in group 1, 65% of the infrared images in group 2, and 28% of the infrared images in group 3 were abnormal.[56]

In a 2003 study conducted by Parisky et al[15] assessing the effectiveness of infrared imaging to evaluate mammographically suspicious lesions found thermography to have a 97% sensitivity and positive predictive value of 25%. The study was a 4-year clinical trial that evaluated 875 suspicious mammographic lesions for which breast biopsy had been recommended.

The Ville Marie study was conducted on 100 patients who were referred to by the Comprehensive Breast Center and met the following criteria: (1) minimal evaluation including clinical examination, mammography, and infrared imaging; (2) a definitive surgical management constituted the preliminary therapeutic modality; and (3) the final stage was either noninvasive carcinoma, stage 1 invasive breast cancer, or stage 2 invasive breast cancer.[40] Results of the study indicate that the sensitivity of infrared imaging was 83%, while that of mammography was 66%.

Predictive Ability of Thermography

A high rate of false positives for thermography has been identified as one of the drawbacks of the tool. However, it should be noted that investigators Ng et al[49] made the statement that, "It was reported that the results of thermography can be correct 8-10 years before mammography can detect a mass and that the error in thermography is that it is 'too right too early.'"

Indeed there is some support to this claim, as in the study by Head et al,[56] a small group of 20 patients had serial infrared imaging and at least one infrared image one year prior to their diagnosis of breast cancer. Fifty percent of those patients (10/20) had abnormal infrared images and 70% (7/10) of those patients had abnormal infrared images one year prior to the diagnosis of breast cancer. A 1980 study by Gautherie and Gros[57] showed that 38% of patients with abnormal infrared images were diagnosed with breast cancer in the 4-year period following the abnormal infrared images. In 1985, Stark[58] reported that 23% of the patients in his study with abnormal infrared images developed breast cancer within 10 years.

Based on the results of a study done by Gautherie and Gros, Head and Elliot[59] commented that the presence of an abnormal symmetric infrared heat pattern of the breasts increases a women's risk of getting breast cancer at least 10-fold. Head et al[56] compared the infrared imaging results of a group of 220 patients who were screened with both first and second generation infrared technology. Part of the analysis included assessing known risk factors, family history of breast cancer, previous estrogen replacement hormone therapy, and previous breast biopsy, with the infrared results. The analysis indicated that the infrared results could be an independent risk factor for cancer as there was no correlation to any of the above mentioned known risk factors.

From the Ville Marie study, the authors concluded that "infrared imaging's most tangible contribution was to signal an abnormality in a younger cohort of breast cancer patients who had noncontributory mammograms and also nonspecific clinical exams who conceivably would not have been passed on for second line evaluation."[40] Isard,[60] in his study of 10 000 patients with infrared imaging and mammography commented on the remarkable stability of infrared images from one year to the next in healthy individuals.

Limitations of Thermography

As with mammography, there are limitations regarding the technology's ability to detect abnormalities in breast tissue. Thermography, because it is a thermal picture of the skin, is unable to localize a lesion or tumor since abnormalities found by infrared imaging do not define an area that can be surgically biopsied.[56] The interpretation of the thermal images relies on identification of areas of increased temperature making areas of low metabolic activity or "cold"[56] tumors more difficult to identify.[61] In a 2003 study on the efficacy of thermography, all false negative infrared results were microcalcifications, suggesting that infrared imaging may not be able to detect these abnormalities as well as mammography does.[15]

Conclusion

Thermography does not provide information on the morphological characteristics of the breast, but it does provide functional information on thermal and vascular conditions of the tissue. These functional changes are hypothesized to change before the onset of structural changes that occur in a diseased or cancerous state. It is known that physiological changes in tissue precede pathological changes,[14] and studies support thermography's potential role in the early detection of breast abnormalities that may lead to cancer. Since the late 1970s there have been a number of studies that have tested the effectiveness of this modality.[42,57,62] If abnormal, thermograms are early indicators of functional abnormalities

Table 2. Classification System[43,44,46]

TH-1	No unusual features, normal breast tissue
TH-2	Area(s) of increases in heat that are responsive to the cold challenge
TH-3	Area(s) of atypical increases in heat that are not responsive to the cold challenge
TH-4	Area(s) of abnormal increases in heat that are not responsive to the cold challenge
TH-5	Area(s) of severely abnormal increases in heat that are not responsive to cold challenge

NOTE: Thermographic findings are categorized as a risk assessment into the following system termed the Marseille system. This analytic method provides for a TH1 to TH5 scale as a summary based on specific, objective and quantitative thermal features, and differential levels of infrared energy. "The recommendations are that further assessments and screening be performed when there is a classification of TH3 through TH5."[63]

that lead to breast cancer, then there may be opportunities for early intervention to reverse the abnormal function toward normal.

There is no one screening tool currently available that provides 100% predictability of the presence of a cancerous tumor. The only definitive diagnostic tool is a biopsy. In the past 30 years there have been numerous studies that have demonstrated thermography to have the ability to detect breast abnormalities that other screening methods may not have identified. The Ville Marie study demonstrated that thermography alone had a sensitivity of 83% in detecting breast cancer, while the combination of mammography and thermography had a 95% sensitivity.[40] In light of developments in computer technology, and the maturation of the thermographic industry, additional research is required to confirm and/or continue to develop the potential of this technology to provide effective noninvasive early detection of breast cancer.

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