Infrared Physics and Technology 97 (2019) 244–257

Contents lists available at ScienceDirect

Infrared Physics & Technology

journal homepage: www.elsevier.com/locate/infrared

Review

Infrared imaging for breast cancer detection: An objective review of foundational studies and its proper role in breast cancer screening

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ARTICLE INFO

Keywords:
Infrared imaging
Breast cancer
Thermography
Digital infrared thermal imaging
Cancer screening

ABSTRACT

Infrared imaging, or digital infrared thermal imaging (DITI), is an FDA-approved adjunct to mammography that can detect thermal abnormalities in the breast associated with breast cancer. Seminal studies in the United States and Europe demonstrated the ability of infrared thermography to detect breast cancer and assess a patient's associated risk and prognosis. This review introduces infrared thermography in the context of breast cancer screening to the scientist or engineer and objectively outlines the clinical evidence for and against the screening technique based on large-population and long-term studies. The progression of infrared technology is briefly summarized, a historical timeline of infrared thermography is outlined, its limitations are discussed, and finally the proper role of infrared thermography in breast cancer screening is presented.

1. Introduction

Infrared thermography is a method of measuring surface temperatures of an object by detecting the infrared radiation (i.e., thermal energy) emitted by the object. It is routinely used in many scientific and engineering industries to obtain the surface temperature distribution of an object or system for analysis and design. Various research studies have assessed the medical applications of infrared imaging, ranging from cancer detection to the diagnosis of abnormalities in several organs in the human body [1–3].

In the context of breast cancer screening, infrared thermography measures the skin temperatures of a patient's breasts for the purpose of detecting thermal abnormalities associated with cancer and assessing the patient's associated risk and prognosis. The thermography of the breast provides thermal information such as the temperature distribution, temperature gradients, and heat patterns, as well as localized or generalized thermal features, all of which can be useful inputs in a cancer screening environment.

The driving principle behind the thermographic detection of cancer is capturing the thermal effects on the skin resulting from pathophysiological changes in the breast caused by cancer. By its nature, infrared thermography is a surface measurement. Therefore, in order to thermally detect the metabolic and vascular changes that are characteristic of cancer, the screening technique is highly dependent on the thermal characteristics of the tumor and breast, discussed in proceeding sections.

The goal of this review is to objectively outline the clinical evidence for and against infrared thermography as a screening and diagnostic technique. Clinical studies that formed the foundation of thermography are reviewed in detail [4–14], including those with unfavorable findings [15–19]. Notable recent thermography studies (after the year 2000) are also surveyed [20–27]. Finally, based on the clinical studies surveyed, the proper role of infrared thermography in breast cancer screening is presented.

2. Background

2.1. Infrared thermography overview

Infrared (IR) thermography measures skin temperatures by the natural infrared radiation emitted by the human body. At normal 37°C core body temperature (approximately 310 K), the human body naturally emits heat—that is, electromagnetic radiation primarily in the infrared spectrum according to Planck's law. The IR spectrum ranges in wavelengths between approximately 0.7–100 μm [28] and can be categorized into at least four spectral bands (ranges approximated): short-wave (SWIR, 1–3 μm), mid-wave (MWIR, 3–5 μm), long-wave (LWIR, 8–12 μm), and very long-wave (VLWIR, 12–30 μm). See Fig. 1. The IR radiation emitted by the human body peaks at a wavelength between 9–10 μm per Wein's displacement law, which corresponds to the long-wave IR spectral band. The emissivity of human skin is very high (near

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https://doi.org/10.1016/j.infrared.2018.12.017
Received 11 October 2018; Received in revised form 12 December 2018; Accepted 15 December 2018
Available online 17 December 2018
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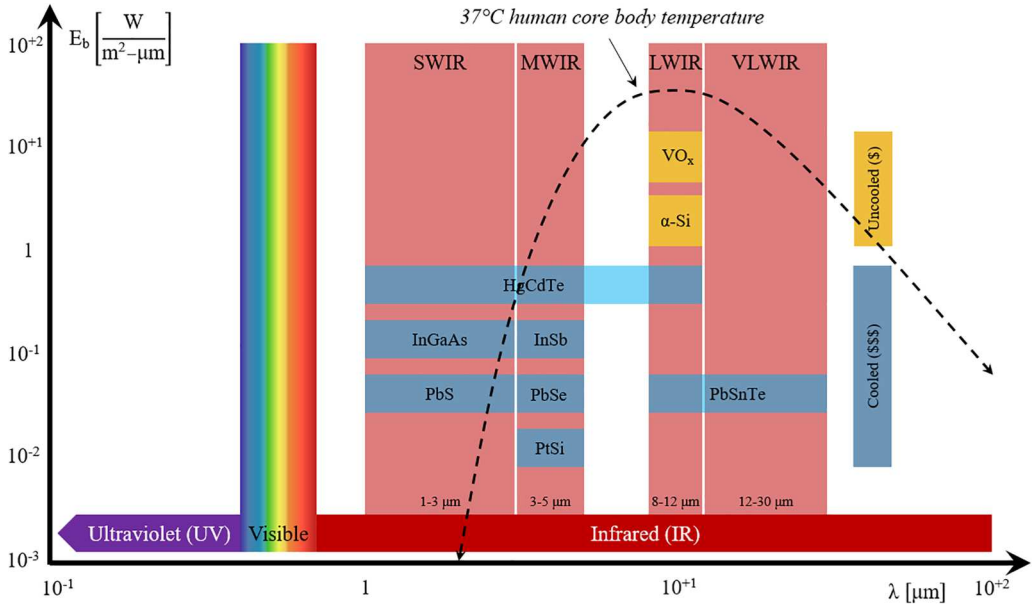

Fig. 1. Typical infrared (IR) detector materials used across IR spectral bands [37,38]. The monochromatic emissive power for a blackbody at 37°C over the infrared spectrum is shown for reference.

that of a blackbody), empirically measured to be between 0.98–1.0 in the 1–14 μm infrared spectral band [29,30].

An infrared image provides a temperature map of a patient's breasts and is referred to as a "breast thermogram," or simply a "thermogram," as seen in Fig. 2. Typically, a frontal view and external lateral views are taken. A thermogram is assessed by a thermographer to be normal (negative) or abnormal (positive). The general criteria for an abnormal thermogram have been previously established by thermography researchers [31,32], as have protocols for properly recording a thermogram [33].

The greatest attraction to medical infrared thermography has been the fact that it is, by its nature, entirely safe for the patient, as no exposure to radiation is required. The imaging procedure is a non-invasive, non-contact, and harmless screening technique. In contrast, mammography, the current standard breast cancer screening technique, exposes the patient to a low dose of ionizing radiation (X-rays), which inherently carries a risk to the patient that can outweigh the benefit based on the patient's age and frequency of screening [34,35].

2.2. Infrared equipment and technological progression

Infrared equipment is used to obtain IR images of a patient and generally consists of an IR camera (similar to a photo camera) and ancillary equipment, such as lenses for magnification, an accompanying computer (for IR cameras without a visual display), and vendor-provided software to post-process IR images or video. An IR camera consists of IR-transparent lenses (e.g., Ge), a scanning system, and an IR detector [36]. In order to record an IR image or video, an IR camera

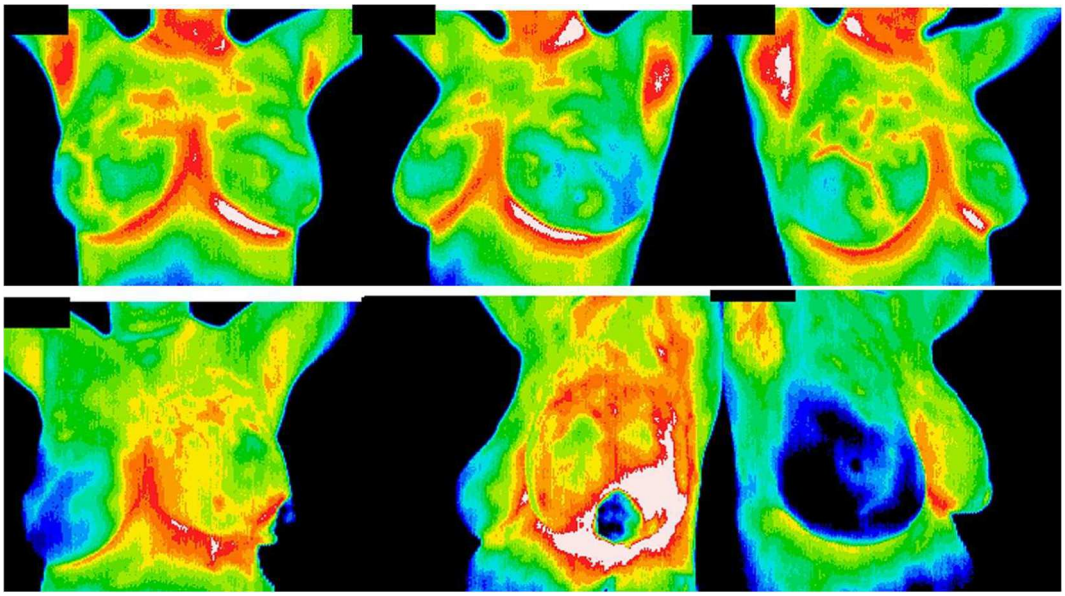

Fig. 2. Infrared images (thermograms) of 2 patients' breasts [25]. Thermal asymmetry, localized hyperthermia, and generalized hyperthermia are factors considered in assessing thermograms [31,32]. **Top:** Thermogram assessed as normal; patient confirmed without cancer. **Bottom:** Thermogram assessed as abnormal; cancer confirmed in the patient's left breast. The IR equipment used to record both IR images was a Meditherm med2000 (IR detector resolution not specified). Used with permission.

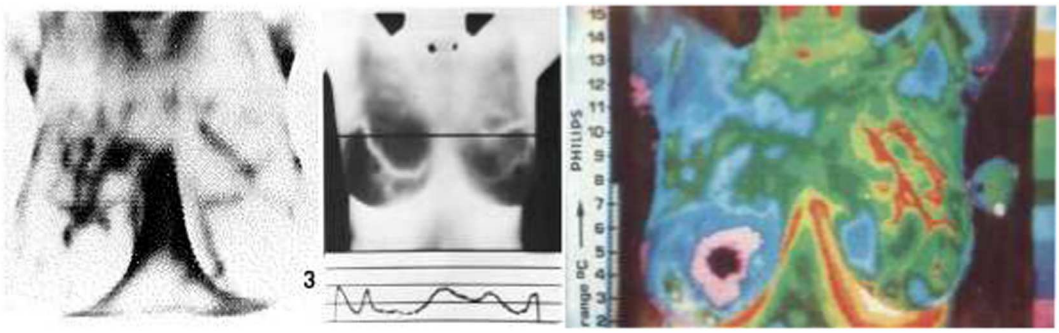

Fig. 3. Early IR thermograms from the 1960s–1970s. All three thermograms were assessed as abnormal. **Left:** IR image (equipment unspecified) of a patient diagnosed with cancer in the right breast [16]. **Center**: IR image recorded with a Spectrotherm of a patient with a blood vessel temperature rise in the right breast indicating an abnormality (final diagnosis unspecified) [32]. **Right**: IR image recorded with a Philips Thermograph of a patient with Stage 2 cancer in the left breast [5]. Used with permission.

does not require contact for measurement and is therefore non-invasive.

IR detectors are categorized as either thermal detectors or photon detectors [37,38]. Thermal detectors (e.g., a microbolometer) rely on changes in electrical resistivity upon incident radiation due to heating; they are uncooled and typically made of vanadium oxide or amorphous silicon. Photon detectors are photoconductive or photovoltaic in nature; they require cryogenic cooling and are made of a semiconductor compound (e.g., InGaAs, InSb, or HgCdTe, depending on IR spectral band). Thermal detectors are limited to LWIR, while photon detector materials can be selected and fine-tuned for SWIR, MWIR, or LWIR detection. See Fig. 1. For human core body temperature ranges (nominally 37°C), LWIR or MWIR detectors are appropriate.

Infrared technology has advanced significantly the past 5 decades from single-point scanners to focal plane arrays due to military research and development, as seen by comparing Fig. 3 with Fig. 2. For example, early IR cameras used by medical thermography researchers in the 1960s–1970s were AGA Thermovision models; these IR cameras had a cooled InSb detector resolution of approximately 100 × 100 and a sensitivity of 0.2°C (200 mK) [39]. Later, in the late 1990s, commercially-available industrial-grade uncooled IR cameras had a 320 × 240 detector resolution or similar, temperature range of 0–500°C, sensitivity of < 0.1°C (< 100 mK), and 2°C accuracy. Today, a commercially-available industrial-grade uncooled IR camera offers a resolution up to 1024 × 768 (10× improvement), temperature range of −40–2,000°C, sensitivity of < 0.02°C (< 20 mK), and 1°C accuracy.

However, the significant downside to IR equipment is, and has been, cost. Today, expenses range from approximately $10,000–$45,000 for an uncooled IR camera with detector resolutions between 320 × 240 to 1024 × 768, respectively, and approximately $60,000–$250,000 for a cooled IR camera with detector resolutions between 640 × 512 to 1024 × 1024, respectively. In contrast, a low-end IR camera offering a very low resolution (e.g., 80 × 60) will cost a few hundred US dollars.

3. A brief history of infrared thermography in breast cancer screening

Breast thermography as a medical field of study began in 1956 when Ray N. Lawson, MD, of Canada first observed that breast tumors were locally warmer than surrounding healthy breast tissue [40]. Then, in 1957, Lawson first proposed infrared thermography as a method of clinically measuring the local temperature rise of the breast tumor [41]. Lawson's 1956 publication is generally attributed to mark the beginning of breast thermography.

In subsequent decades, early thermography researchers like Harold J. Isard, MD [6,7], JoAnn D. Haberman, MD [12], Istvan Nyirjesy, MD [13], Agnes M. Stark, MD [8,42,43], and Michel Gautherie [4,5,44], conducted large-population studies evaluating thermography as a breast cancer screening technique. Their conclusions supported the use of thermography in breast cancer screening. However, other notable thermography researchers like Myron Moskowitz, MD [17,45,46], and B.E. Nathan [19], also conducted studies that strongly disfavored the role of thermography in breast cancer screening.

As a result, the topic of infrared thermography in breast cancer screening became a point of contention among researchers within the medical community; proponents and opponents debated and contested results and methodologies of each other's clinical studies. Specifically, opponents noted that the topic of thermography had become "somewhat emotive" and filled with "religious zeal"; some opponents even called for claims supporting thermography "be put to rest" and to "pull the plug" on thermography [19,46,47]. These exchanges in the literature collectively indicated how the subject evolved from a scientific research pursuit into a controversial topic.

In 1973, the United States American Cancer Society (ACS) and the National Cancer Institute (NCI) established the Breast Cancer Detection Demonstration Projects (BCDDP), a network of 29 breast cancer screening centers across 27 locations nationwide [48]. Motivated by favorable results from a 1960s NCI-sponsored study by the Health Insurance Plan (HIP) of Greater New York, the objective of the ACS/NCI BCDDP was to evaluate the benefits of 4 screening modalities for the early detection of breast cancer: medical history, physical examination (clinical breast exam), mammography (xeroradiography), and thermography [48,49]. Some of the physicians noted earlier led BCDDP centers, most notably Isard for the Philadelphia, PA, BCDDP and Moskowitz for the Cincinnati, OH, BCDDP. By 1975, over 280,000 women nationwide had enrolled in the program [48].

In 1976, motivated by a lack of clarity among BCDDP researchers regarding what constituted a normal or abnormal thermogram, the NCI formed an *ad hoc* committee, led by William Pomerance, MD. The committee established for the first time objective criteria for assessing thermograms as normal or abnormal [31,32].

In 1977, after receiving 2 annual screenings' worth of data, the ACS/NCI BCDDP formally discontinued the use of thermography as a breast cancer screening technique [48,49]. This decision came at the recommendation of an NCI-established working group of 19 physicians and professionals, led by Oliver H. Beahrs, MD, based on the conclusion that thermography was not a suitable substitute for mammography due to its lower sensitivity (45% versus 43%) and high false positive rate when compared to initial mammographic and physical exam findings [49]. As a result, thermography lost a significant amount of credibility and research interest within the medical community.

Later, in 1984, two physicians who led BCDDP centers–Haberman (Oklahoma City, OK, BCDDP) and Margaret Abernathy, MD, (Washington, DC, BCDDP)–retrospectively commented that most BCDDP centers were ill-prepared for thermography, stating that only 5 centers nationwide had personnel experienced in thermography and provided excellent data while the remaining centers had poor quality

Table 1
Summary of thermography studies surveyed.

+/−	Study	Year	No. patients	No. years	Static/ dynamic	IR/liquid crystal	IR system	Sensitivity	Specificity	Conclusions	Ref.
+	Williams	1969	300	5	Static	–	–	–	–	Prognosis (+)	[10]
+	Isard et al.	1972	10,055	4	Static	IR	AGA Thermovision	61%	–	Adjunct (+) Screening (+) Risk (+) Diagnosis (–)	[6]
–	Nathan et al.	1972	359	–	Static	IR	(1) Bofors (2) EMI Thermoscan	79%	50%	Screening (–) Diagnosis (–)	[19]
+	Jones et al.	1975	12,000	5	Static	IR	(1) Smith's Pyroscan Mark IIb (2) Rank Thermographic System	–	–	Adjunct (+) Prognosis (+)	[11]
–	Moskowitz et al.	1976	97	–	Static	IR	Spectrotherm	24%	56%	Adjunct (–) Screening (–)	[17]
–	Feig et al.	1977	16,000	–	Static	IR	Unspecified	39%	–	Screening (–)	[16]
+	Gautherie and Gros	1980	57,581	12	Static	IR & liquid crystal	Philips Thermograph	–	–	Adjunct (+) Screening (+) Prognosis (+) Risk (+)	[5]
+	Haberman et al.	1980	39,802	3	Static	IR	Spectrotherm 2000	76%	–	Adjunct (+)	[12]
+	Nyirjesy and Billingsley	1984	8,757	9	Static	IR	AGA Thermovision 680	76%	–	Adjunct (+)	[13]
+	Stark	1985	11,240	16	Static	IR	AGA Thermovision	86%	98%	Screening (+) Risk (+) Diagnosis (–)	[8]
+	Isard et al.	1988	5,040	13	Static	IR	AGA Thermovision 680	–	–	Adjunct (+) Prognosis (+)	[7]
–	Williams et al.	1990	10,229	5	Static	IR	(1) AWRE/Barr and Stroud (2) Rank Precision Industries	61%	74%	Screening (–) Risk (–)	[15]
–	Sterns and Zee	1991	3,768	13	–	Liquid crystal	–	57%	–	Prognosis (–) Risk (–)	[18]
+	Head et al.	1993	326	–	Static	IR	Unspecified	65%	72%	Risk (+) Prognosis (+)	[9]
+	Keyserlingk et al.	1998	100	–	Static	IR	Bales Scientific	83%	81%	Adjunct (+)	[14]
+	Parisky et al.	2003	769	4	Dynamic	IR	BCS2100 (Computerized Thermal Imaging)	97%	14%	Adjunct (+) Screening (–)	[20]
+	Arora et al.	2008	92	2	Dynamic	IR	Sentinel BreastScan (Infrared Sciences Corp.)	97%	44%	Adjunct (+)	[21]
+	Delgado et al.	2010	911	2	Static	IR	DL-700 (Zhejiang Dali Technology Co.)	94%	–	Screening (+)	[23]
+	Wang et al.	2010	276	–	Static	IR	ATIR-M301 (Associated Technology Corp.)	72%	77%	Adjunct (+)	[24]
–	Kontos et al.	2011	63	1	Static	IR	med2000 (Meditherm)	25%	85%	Screening (–)	[25]
–	Collett et al.	2014	99	1	Dynamic	IR	NoTouch BreastScan	79%	89%	Adjunct (–) Screening (–) Diagnosis (–)	[22]
+	Rassiwala et al.	2014	1,008	–	Static	IR	Unspecified	98%	99%	Adjunct (+) Screening (+)	[26]
+	Wu et al.	2016	143	2	Static	IR	ATIR-M301 (Associated Technology Corp.)	–	–	Prognosis (+)	[27]

thermograms and data; as a result, combining these data at the national level led to poor conclusions regarding thermography [50].

Nevertheless, in 1982, the United States Food and Drug Administration (FDA) approved thermography only as an adjunct to mammography [35]. Today, the FDA strongly admonishes that thermography is not a substitute for mammography [51]. In fact, major health insurance providers generally do not cover infrared thermography services for breast cancer screening, typically citing a lack of supporting evidence for thermography or deeming it a medically-unnecessary procedure.

4. Clinical studies in infrared thermography

Seminal studies that evaluated infrared thermography as a breast cancer screening technique are objectively summarized (see Table 1); this review includes studies whose conclusions both favored and disfavored the use of thermography. For all studies surveyed, researchers pointed out that thermography was never solely used to formally diagnose a patient with breast cancer; rather, conventional methods such as biopsy were used. Furthermore, for all studies surveyed, patients were female.

4.1. Studies favoring infrared thermography

Lawson's initial observation (1956): Lawson first quantified the local temperature rise of a breast tumor to be 0.7–1.9°C (originally reported in Fahrenheit) using a thermocouple probe for 26 breast cancer patients, with an average local temperature rise of 1.3°C [40]. In 1957, Lawson proposed infrared thermography as a way to measure the physiological effects of cancer as a complement to conventional methods [41]. Later, in 1964, in a more thorough study of 36 breast cancer patients, Lawson and Gaston observed the local temperature rise due to a breast tumor to be 0–2.5°C (average of 0.8°C) using a thermistor fine needle probe [52]. Lawson and Gaston also observed the venous return temperature of a breast tumor to be hotter than its arterial supply, indicating the increased metabolic heat generation in the tumor.

Gautherie's 57,581-patient, 12-year study (1980): Michel Gautherie and Charles M. Gros published a study of 57,581 symptomatic patients over 12 years in France [4,5]. This study focused on the 1,527 patients with suspicious thermograms (< 3% of entire population)–that is, those patients whose thermograms were neither normal

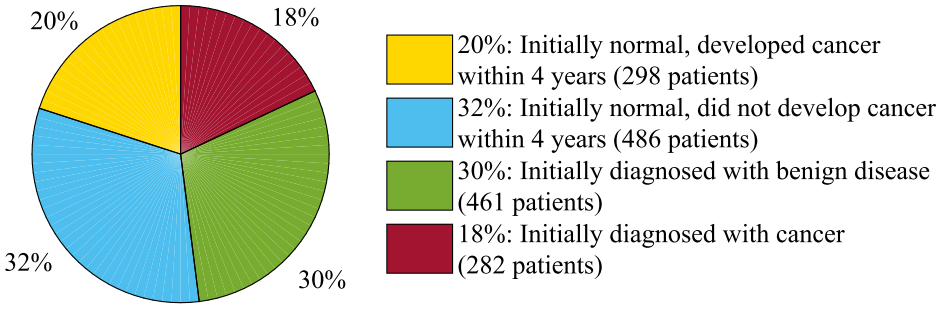

Fig. 4. Distribution of the 1527 patients studied with suspicious thermograms (neither normal nor abnormal) in Gautherie and Gros' 58,000-patient study [4]. At presentation, 18% were diagnosed with cancer whereas 30% were diagnosed with a benign breast disease. The remaining approximately 52% (784 patients) were initially considered normal; of them, 298 patients (20% of total) developed breast cancer within 4 years, whereas 486 patients (32% of total) had not. The conclusion was that suspicious thermograms provided an early warning signal for the 20% of normal patients who subsequently developed breast cancer within 4 years [44].

(92%) nor abnormal (5%); see Fig. 4 for the patient distribution. In the 1,527 patient group, 784 patients were initially considered normal at presentation, but of them, 298 patients (38%) subsequently developed breast cancer within 4 years, at an average of 1.5 years [5]. Similarly, 461 patients were initially diagnosed with benign breast diseases at presentation, but 44% developed breast cancer within 4 years. These observed cancer diagnosis rates (38% and 44%) contrasted the < 1% of 52,952 patients with normal thermograms that subsequently developed breast cancer within 4 years.

Results of this study led Gautherie and Gros to advocate the use of thermography in conjunction with other techniques for the preliminary screening of patients, particularly those with suspicious thermograms [4,5]. Gautherie later reported that an abnormal thermogram was a significant risk factor for breast cancer development, even more important than family history [4,44].

Key takeaways from Gautherie and Gros' 57,581-patient, 12-year study [4]:

- Abnormal thermograms were associated with cancer patients, whereas normal thermograms were associated with non-cancer patients.
- The vast majority (approximately 90%) of the 3,066 patients with abnormal thermograms at presentation were initially diagnosed with breast cancer.
- Breast cancer development rates over 5 years were remarkably higher for non-cancer patients with suspicious thermograms (38%–44%) than non-cancer patients with normal thermograms (< 1%).
- Gautherie and Gros' study was later criticized by other researchers for their inability to reproduce Gautherie and Gros' results [46].
- Gautherie and Gros' findings supported the role of thermography in breast cancer screening, risk assessment of breast cancer development, and prognosis of breast cancer patients [5,44].

Isard's 10,055-patient, 4-year study (1972): Isard et al. published a study of 10,055 symptomatic and asymptomatic patients over 4 years in the United States [6]. 5,662 patients were symptomatic, of which 36% had abnormal thermograms; 4,393 patients were asymptomatic, of which 23% had normal thermograms. From this, Isard et al. observed that symptomatic patients had a greater incidence of abnormal thermograms than asymptomatic patients.

Further, Isard et al. observed that of the 270 histologically-confirmed symptomatic cancer patients, 196 patients (73%) had abnormal thermograms. Similarly, of 36 histologically-confirmed asymptomatic cancer patients (i.e., clinically occult cancers), 22 patients (61%) had abnormal thermograms. From this, Isard et al. concluded that thermography was useful as an adjunct to mammography and clinical breast exam in breast cancer screening of symptomatic patients, and more importantly, in the preliminary screening of asymptomatic patients in order to identify occult cancers–that is, those patients with a high risk of breast cancer.

Key takeaways of Isard's 10,055-patient, 4-year study [6]:

- The majority of cancers (71% of 306 cancers)–including both symptomatic and asymptomatic patients–had abnormal thermograms.
- Greater percentages of abnormal thermograms were observed in symptomatic patients than asymptomatic patients (36% vs. 23%).
- 73% of 270 cancers from symptomatic patients and 61% of 36 cancers from asymptomatic patients had abnormal thermograms.
- Thermal patterns in normal patients were remarkably consistent over time and uniquely identifying of an individual, analogous to a heat signature or fingerprint.
- Isard et al.'s findings supported the role of thermography in the breast cancer screening of symptomatic and asymptomatic patients in conjunction with other techniques and in the risk assessment of breast cancer, but not as a diagnostic exam.

Stark's 11,240-patient, 16-year study (1985): Stark published a study of 11,240 asymptomatic patients over 16 years in Britain [8]. 1,499 patients had an abnormal thermogram, of which 346 patients (23%) were diagnosed with breast cancer within 10 years, at an average time of 6.4 years. In Stark's study, an abnormal thermogram was considered a risk factor with other conventional risk factors (e.g., nulliparity, family history, previous pathology, etc.). Of the 414 cancers diagnosed in the study, 356 cancers (86%) had an abnormal thermogram.

Stark concluded that thermography had a definite role in the preliminary screening of asymptomatic patients, particularly given its inexpensiveness. Stark emphasized that the value of thermography was as a risk factor for breast cancer, as important as conventional risk factors, and as an early warning sign (given sequential thermograms over time). However, Stark did not support thermography as a diagnostic test.

Key takeaways from Stark's 11,240-patient, 16-year study [8]:

- 23% of 1,499 patients with an abnormal thermogram were diagnosed with breast cancer within 10 years (average time of 6.4 years).
- 86% of all cancers diagnosed (356 of 414 cancers) had an abnormal thermogram (sensitivity).
- Stark's findings supported the role of thermography in breast cancer screening and risk assessment of breast cancer development, but not as a diagnostic exam.

Isard's 5,040-patient, 13-year study (1988): Isard et al. published another study of 5,040 patients screened over 13 years in the United States [7]. For the 70 patients diagnosed with breast cancer, survival rates were compared to thermogram result. Isard et al. found that survival rates were remarkably lower for patients with abnormal thermograms: Breast cancer patients with normal or only slightly abnormal thermograms had 5-year survival rates of 88%–89%, in contrast to 30% for those with abnormal thermograms. Similarly, 10-year survival rates

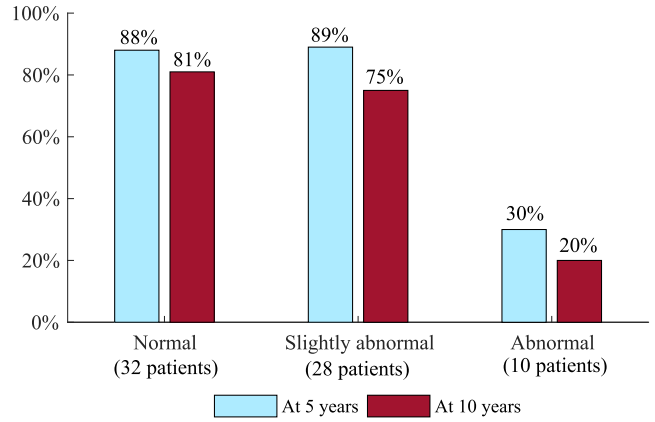

Fig. 5. Survival rates of 70 breast cancer patients over 13 years per thermogram assessment in Isard et al.'s 5000-patient study [7]. Of the 70 breast cancer patients, 32 patients had normal thermograms, 28 patients had "equivocal" or slightly abnormal thermograms, and 10 patients had clearly abnormal thermograms. Isard et al. observed that breast cancer patients with normal thermograms and even slightly abnormal thermograms had remarkably higher survival rates than breast cancer patients with abnormal thermograms.

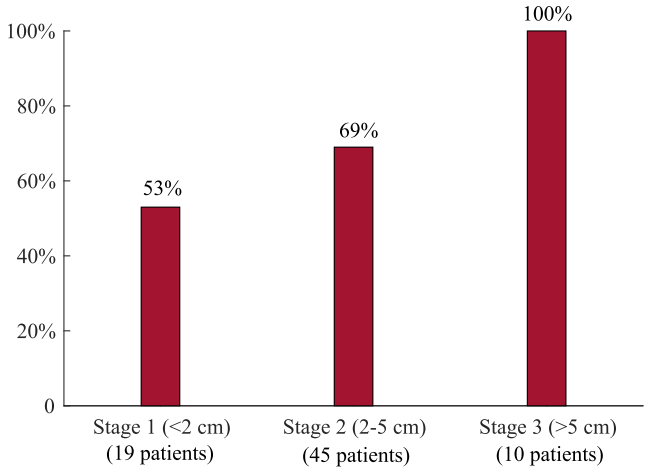

Fig. 7. Incidence of abnormal thermograms per clinical tumor size for 74 breast cancer patients in Head et al.'s study [9]. Of 19 patients with tumors less than 2 cm in clinical size, 53% had abnormal thermograms; of 45 patients with tumors measuring 2–5 cm, 69% had abnormal thermograms; and of 10 patients with tumors greater than 5 cm, 100% had abnormal thermograms.

were 75%–81% versus 20%, respectively. See Fig. 5. Based on these findings, Isard et al. concluded that thermography was useful as a prognostic indicator for breast cancer patients.

Key takeaways from Isard et al.'s 5,040-patient, 13-year study [7]:

- 5- and 10-year survival rates (20%–30%) were drastically lower for breast cancer patients with abnormal thermograms than those without abnormal thermograms (70%–80%).
- Isard et al.'s findings supported the role of thermography in the prognosis of breast cancer patients.

Head's 326-patient study (1993): Jonathan F. Head et al. published a study of 326 patients in the United States [9,53,54]. Of the 100 patients without breast cancer, only 28% had abnormal thermograms. In contrast, of the 100 patients with breast cancer, 65% had abnormal thermograms, whereas of the 126 patients who died of breast cancer, 88% had abnormal thermograms. See Fig. 6. Based on these findings, Head et al. concluded that abnormal thermograms were associated with a higher risk of breast cancer and poorer prognosis for the patient.

Further, Head et al. observed that of 74 breast cancer patients with varying tumor sizes, 53% of patients with tumor sizes < 2 cm had abnormal thermograms, in contrast to the 69% of patients with tumors between 2–5 cm and the 100% of patients with tumors > 5 cm (see Fig. 7). It was also observed that patients with abnormal thermograms had higher tumor ferritin concentrations, along with 3 tumor growth-related prognostic indicators: DNA synthesis, proliferative index, and Ki-67 expression. From this, Head et al. concluded that patients with abnormal thermograms had clinically larger tumors, faster-growing tumors, and more proliferative tumors.

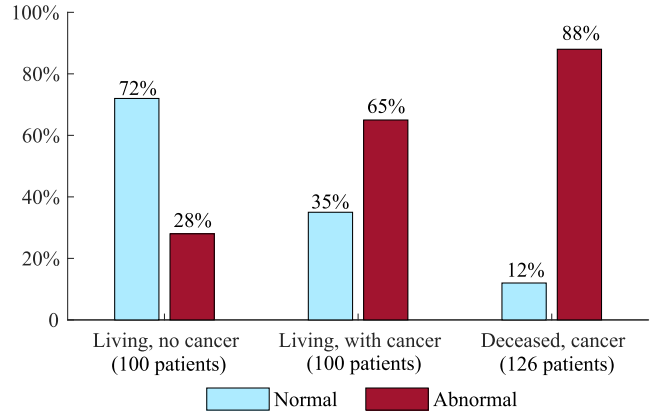

Fig. 6. Incidence of normal and abnormal thermograms for 326 patients in Head et al.'s study [9]. The study consisted of 100 living patients without cancer (i.e., normal or with a benign breast disease), 100 living breast cancer patients, and 126 deceased breast cancer patients. Head et al. observed that abnormal thermograms were more prevalent in breast cancer patients than non-cancer patients.

Later in 2000, Head et al. published another study of 220 non-cancer patients that improved the quality of thermograms by comparing IR images taken with a first-generation IR scanner to those taken by a then-state-of-the-art IR system [53]. Thermogram results were observed to be statistically independent of other established risk factors such as family history and past breast biopsy. Head et al. also observed the general consistency in thermogram result in 85% of 20 living breast cancer patients at diagnosis and 1 year prior to diagnosis, whether normal or abnormal. From all this, Head et al. concluded that thermogram results were an independent risk factor in breast cancer.

Key takeaways from Head et al.'s 326-patient study [9]:

- Of 326 patients studied, abnormal thermograms were observed in 28% of non-cancer patients, in contrast to the 65% of living breast cancer patients and the 88% of deceased breast cancer patients [53,54].
- Abnormal thermograms were associated with an increased risk of breast cancer and a poorer prognosis for the patient.
- Abnormal thermograms indicated clinically larger tumors and faster-growing tumors.
- 85% of 20 breast cancer patients had consistent thermogram results for at least 1 year prior to diagnosis.
- Head et al.'s findings supported the role of thermography as an independent risk factor for breast cancer, a prognostic indicator, and a better risk assessment than other factors such as having children and first-degree relative family history [53,54].

Williams' 300-patient, 5-year study (1969): K. Lloyd Williams, MD, published a study of 300 symptomatic patients over 5 years in Britain [10]. Of 167 breast cancer patients, 92% had a local tumor temperature rise of 1°C or more (as high as 7°C), which corroborated Lawson's findings a decade earlier [40]. In contrast, of the 133 patients with a benign breast disease, only 20% similarly had a 1°C or more local tumor temperature rise.

Then, Williams followed up with breast cancer patients at regular

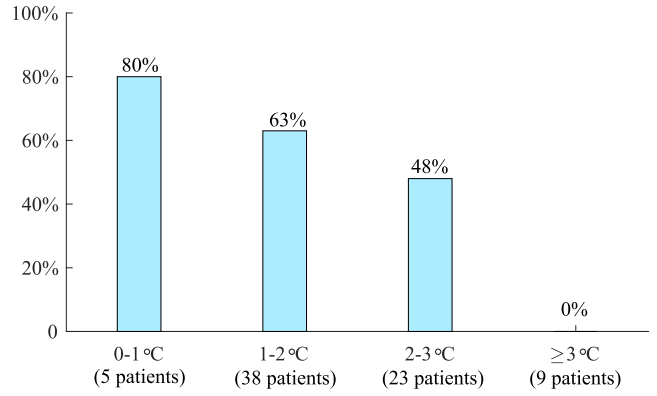

Fig. 8. 5-year survival rates for 75 breast cancer patients per local tumor temperature rise in Williams' 300-patient study [10]. Lower survival rates were observed based on the magnitude of the local tumor temperature rise in the cancerous breast.

intervals over a 5-year period. Williams observed a statistically-significant correlation between the local tumor temperature rise and survival rates at each follow-up interval (see Fig. 8), leading Williams to conclude that the magnitude of local tumor temperature rise was a prognostic indicator for the breast cancer patient. From these findings, Williams concluded that thermography was useful in the prognosis of breast cancer patients.

Key takeaways from Williams' 300-patient, 5-year study [10]:

- Breast cancer patients with the largest tumor temperature rises had the worst prognoses (i.e., survival rates).
- 92% of 167 breast cancer patients had a 1°C local tumor temperature rise over surrounding healthy tissue.
- Williams' findings supported the role of thermography in the prognosis of breast cancer patients.

Other notable foundational studies: Other seminal, large-population studies that favored the role of thermography in breast cancer screening included the following:

- Jones et al.'s 12,000-patient, 5-year study (1975) in Britain that supported thermography as an adjunctive screening technique for breast cancer [11].
- Haberman et al.'s 39,802-patient, 3-year study (1980) in the United States that supported the use of thermography in conjunction with other screening techniques [12].
- Nyirjesy and Billingsley's 8,757-patient, 9-year study (1984) in the United States that also supported thermography in a multimodal screening approach [13].
- Keyserlingk et al.'s 100-patient study (1998) in Canada that concluded thermography was useful as an adjunct to mammography and clinical breast exam [14].

4.2. Studies disfavoring infrared thermography

Nevertheless, contrary to the evidence demonstrated by preceding studies, several studies concluded that thermography was neither useful nor reliable in breast cancer screening. Several researchers, most notably Moskowitz, conducted studies that led them to strongly disfavor the use of thermography in any capacity as a screening technique.

Williams' 10,229-patient, 5-year study (1990): Williams et al. published another study of 10,229 patients over 5 years in Britain [15]. 59 patients (< 1%) were diagnosed with breast cancer by mammography, of which 61% (36 patients) had an abnormal thermogram as assessed by the examining physician. Of the remaining 10,170 patients (> 99%) without any evidence of breast cancer, 26% had abnormal thermograms. These results indicated a 61% sensitivity (true positive rate) and 74% specificity (true negative rate) for thermography, respectively. Because the observed sensitivity and specificity of thermography were lower than that reported of mammography, Williams et al. concluded that thermography was not sufficiently sensitive as a breast cancer screening technique.

Williams et al. also followed up with 9,819 patients at 5 years to determine breast cancer development rates based on patients' initial thermogram assessments. The vast majority of patients (> 99%) had not developed breast cancer, of which 74% initially had a normal thermogram. However, of the 60 patients who had subsequently developed breast cancer, only 28% initially had an abnormal thermogram. These results contrasted Gautherie and Gros' findings [4]. Therefore, Williams et al. also concluded that thermography was neither useful as an indicator of risk of developing breast cancer.

Key takeaways from Williams et al.'s 10,229-patient, 5-year study [15]:

- At initial screening, thermography had a sensitivity of 61% (based on 59 breast cancer patients) and specificity of 74% (based on 10,170 non-cancer patients).
- At 5 years, although 74% of 9,759 patients who initially had normal thermograms did not develop breast cancer, only 28% of 60 patients who initially had abnormal thermograms developed cancer.
- Williams et al.'s 5-year breast cancer development rates contrasted Gautherie and Gros' 4-year breast cancer development rates based on thermogram result [4].
- Williams et al.'s findings did not support the role of thermography in breast cancer screening nor in the risk assessment of breast cancer development.

Feig's 16,000-patient study (1977): Stephen A. Feig, MD, et al. published a study of exactly 16,000 patients screened in the United States [16]. This study compared detection rates (sensitivity) among mammography, clinical breast exam, and infrared thermography. Trained thermographers assessed thermograms both with and without objective criteria established by the NCI [31].

Of 16,000 patients, 406 patients were biopsied. Of the 139 patients diagnosed with breast cancer (< 1% of total), mammography had the highest sensitivity of 78%, followed by clinical breast exam with 55% and thermography with 39%. However, when NCI-established criteria were used, the sensitivity of thermography increased from 39% to 50% but was still inferior to the other screening techniques.

Feig et al. also compared detection rates based on tumor size. Mammography had the highest detection rate for all tumor sizes. However, thermography had a higher detection rate than clinical breast exam for small tumor sizes (< 0.5 cm) and large tumor sizes (> 3 cm). See Fig. 9.

Although Feig et al.'s study only evaluated initial screenings, cases were observed of patients who initially had abnormal thermograms without any mammographic or clinical abnormalities and subsequently developed breast cancer during the study. As a result, Feig et al. acknowledged the possibility of patients with abnormal thermograms having an increased risk of developing breast cancer.

Feig et al. also commented on the increased likelihood of breast cancer patients producing an abnormal thermogram whose non-cancerous breast had moderate vascularity. In contrast, breast cancer patients whose non-cancerous breast was highly vascular were least likely to produce an abnormal thermogram, thereby eluding detection.

Key takeaways of Feig's 16,000-patient study [16]:

- IR thermography generally had the lowest sensitivity (39%) compared to mammography (78%) and clinical breast exam (55%) for 139 breast cancer patients considering all tumor sizes.
- The sensitivity of thermography increased from 39% to 50% when NCI-established criteria were used to assess thermograms.

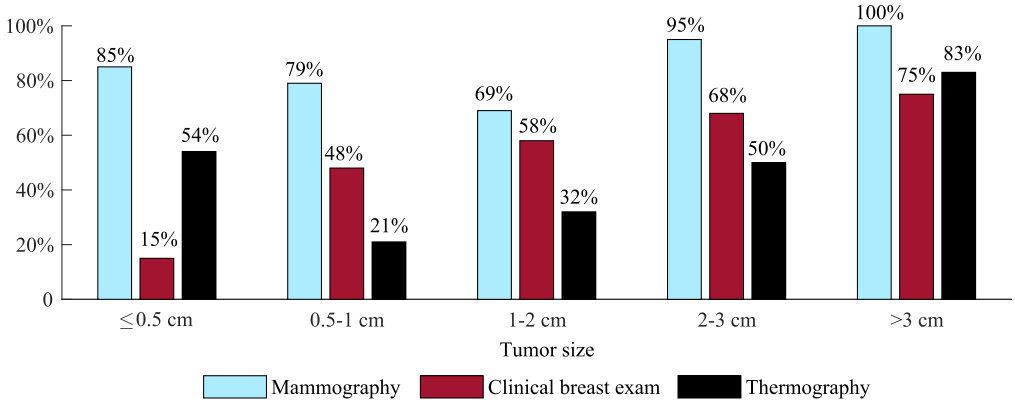

Fig. 9. Detection rates of screening techniques per tumor size for 139 breast cancer patients in Feig et al.'s 16,000-patient study [16]. Feig et al. observed that mammography generally had the highest detection rates independent of tumor size. Thermography's detection rate peaked for tumor sizes greater than 3 cm. These rates reflected thermogram assessments without NCI-established criteria [31]. (Note: Data shown amounted to 141 breast cancer patients for an unspecified reason.)

- For small tumors (< 0.5 cm), thermography had a higher sensitivity (54%) than clinical breast exam (15%).
- For large tumors (> 3 cm), thermography had a sensitivity of 83%, lower than mammography (100%) but higher than clinical breast exam (75%).
- IR thermography's highest sensitivity was 83% for larger-sized tumors (> 3 cm).
- Breast cancer patients whose normal breast was highly vascular were least likely to produce an abnormal thermogram, thereby eluding thermographic detection.
- Feig et al.'s findings indicated that thermography had the lowest sensitivity but was most effective in detecting larger tumors and node-positive tumors.
- According to Feig et al., thermography showed "theoretical promise" in "selecting high risk groups for follow-up screening."

Moskowitz's 97-patient study (1976): Moskowitz et al. published a study of 97 patients in the United States [17]. Sensitivity and specificity rates were determined based on 42 breast cancer patients and 55 non-cancer patients, respectively. Thermograms were obtained using an infrared spectrometer and assessed by both experienced and inexperienced thermographers.

Moskowitz et al. observed a sensitivity for thermography of 24% as assessed by experienced thermographers, given that thermography accurately identified the cancerous breast side (left or right); however, retrospective analysis by the present authors showed that the sensitivity of thermography increased slightly to 43% if thermography merely identified a cancerous patient. Further, Moskowitz et al. observed a specificity of 56% for thermography.

As a result, Moskowitz et al. concluded that thermography was unable to identify early stage breast cancer patients from those without cancer and was therefore of no value. Moskowitz et al.'s findings did not support the use of thermography as a stand-alone screening technique nor as an adjunctive technique, claiming that thermography was as useful as a random selection process.

On a relevant note, this particular study drew criticism on multiple levels from several researchers–proponents and opponents alike–most notably Feig and Nyirjesy [47]. These researchers questioned Moskowitz' methodology and results, specifically regarding the experienced thermographers used in the study and the quality of thermograms, and concluded that the diagnostic efficacy of thermography was not truly evaluated by Moskowitz et al.'s study.

Key takeaways from Moskowitz et al.'s 97-patient study [17]:

- IR thermography had a sensitivity of 24% for 42 early stage breast cancer patients and specificity of 56%.
- Expert thermographers did not assess thermograms any better than inexperienced readers.
- IR thermography was unable to identify early breast cancer stage patients from normal patients and was claimed to be as accurate as a random screening process.
- The validity of Moskowitz et al.'s study was questioned by several other prominent researchers [47].
- Moskowitz et al.'s findings did not support the role of thermography as an adjunctive screening technique, but in a later 36-patient study suggested that liquid crystal thermography could detect large tumors [45].

Other notable unfavorable studies: Other large-population studies disfavoring the use of thermography included the following:

- Sterns and Zee's 3,768-patient, 13-year study (1991) in Canada that concluded that thermography was not useful for prognosis nor risk assessment, but agreed that abnormal thermograms indicated larger tumors and node-positive tumors [18].
- Nathan et al.'s 359-patient study (1972) in Britain that concluded that thermography had no role in the preliminary screening for breast cancer nor in differential diagnosis [19].

4.3. Recent studies

Clinical research in infrared thermography generally declined after the year 2000. Possible reasons for this include the negative findings from the ACS/NCI BCDDP regarding thermography [49], the general clinical finding that thermography had a lower sensitivity than mammography (see preceding sections), and most importantly, the FDA's and ACS's formal positions on thermography, limiting thermography as an adjunct and citing clinical evidence demonstrating its ineffectiveness in screening [51,55].

Nevertheless, clinical studies continued after 2000 with mostly favorable findings and conclusions regarding the technique. IR thermography has been recently termed "digital infrared thermal imaging," or DITI. Recent studies have largely focused on evaluating the diagnostic efficacy of IR thermography. Also, IR systems in medical diagnostics have evolved to incorporate intelligence (artificial neural networks) in assessing IR images, eliminating the subjectivity in thermogram assessments. Notable recent studies with both favorable and unfavorable findings are summarized.

Parisky et al.'s 769-patient, 4-year study (2003): Yuri R. Parisky, MD, et al. published a study of 769 patients over 4 years in the United States [20]. 769 patients across 5 institutions nationwide who had been recommended for biopsy based on mammographic or clinical abnormalities provided 875 biopsies, of which 187 were malignant (21%). Each of the 875 lesions were evaluated by three experienced radiologists with subjects' mammograms and original case reports in hand; these two sets of information included lesion size and location. Evaluators determined an IR index-of-suspicion between 0–100 indicating the likelihood of malignancy; the index-of-suspicion threshold between a positive or negative result used in the study was not specified and was

determined based on a training subset of 54 malignant lesions that maximized sensitivity.

By design, the study required that IR assessments accurately locate lesions on IR thermograms based on mammogram and case report data in order to be included in the final analysis. IR assessments wherein a discrepancy existed between the region of interest on IR thermograms located by evaluators and the location of the lesion outlined in the subject's case report were excluded from the final analysis; this, in effect, insured that IR assessments were in agreement with case reports and therefore that IR thermography was used adjunctively. A total of 2,299 IR indices-of-suspicion were valid in the end (rather than $875 \times 3 = 2625$). The IR camera system used in the study was a BCS2100 (Computerized Thermal Imaging Inc.). This dynamic IR system blew cold air onto patients' breasts and collected a series of IR images. Parisky et al. noted that the IR system's proprietary algorithm was developed using 2,400 patients' data (IR thermograms and corresponding biopsy diagnoses) in the same study.

The 2,299 IR assessments from the 875 biopsies resulted in a sensitivity of 97% (482/495) and specificity of 14% (260/1,804). The high number of false positives owing to the low specificity were attributed to microcalcifications. Interestingly, patients with very dense breast tissue were reported to yield fewer false positives. In the end, Parisky et al. concluded that while IR thermography had value as an adjunct to further evaluate mammographic abnormalities, IR thermography was not designed as a screening technique identifying malignancy.

Key takeaways from Parisky et al.'s 769-patient study [20]:

- IR thermography had a 97% sensitivity and 14% specificity based on 769 patients.
- 2,400 patients' data (IR thermograms and diagnosis) were inputs to software algorithm.
- IR thermography was most efficacious with lesions that were masses.
- Lesion size correlated with IR index-of-suspicion (i.e., likelihood of malignancy).
- Parisky et al.'s findings supported the role of thermography as an adjunct to mammography for diagnosis, but not in screening for malignancy.

Arora et al.'s 92-patient, 2-year study (2008): Nimmi S. Arora, MD, et al. published a study of 92 patients over 2 years in the United States [21]. 92 patients who had been recommended for biopsy based on mammogram or ultrasound abnormalities provided 94 biopsies, of which 60 were malignant (64%). The IR system used in the study was a Sentinel BreastScan (Infrared Sciences Corp.), which outputted a risk score between 0–7 in three different modes: screening mode, clinical mode, and neural network mode. The IR camera had an uncooled LWIR detector of 320×240 resolution and 0.08°C sensitivity. A non-zero score in all modes was considered positive (suspicious). The IR system blew cold air onto patients' breasts and recorded a series of IR images for automated scoring.

In screening mode, Arora et al. observed a sensitivity of 97% (58/60) and specificity of 12% (4/34). In clinical mode, a 90% sensitivity (54/60) and 44% specificity (15/34) were observed. Finally, in neural network mode, a 97% sensitivity (58/60) and 27% specificity (9/34) were observed. The low specificity was attributed to the patient population selected (i.e., patients with radiologic exam abnormalities). Interestingly, the four cases of ductal carcinoma in situ were accurately identified. In the end, Arora et al. concluded that IR thermography was a valuable adjunct to mammography and ultrasound.

Key takeaways from Arora et al.'s 92-patient study [20]:

- IR thermography had a maximum sensitivity of 97% and specificity of 44% based on 92 patients (in different modes).
- A trend of higher risk scores correlating with more advanced cancer stages was observed.
- A risk score of 3 or greater had a statistically-significant greater likelihood of indicating a cancer diagnosis in screening mode.
- Arora et al.'s findings supported the role of thermography as an adjunct to mammography and ultrasound in breast cancer detection.

Collett et al.'s 99-patient, 1-year study (2014): Collett et al. published a study of 99 patients over 1 year in the United States [22]. 99 patients who had been recommended for biopsy based on imaging abnormalities provided 105 biopsies, of which 33 were malignant (31%). The IR system used was a NoTouch Breast Scan (UE LifeSciences Inc.). Similar to the IR system used in Parisky et al.'s and Arora et al.'s studies, the NoTouch BreastScan was a dynamic system that blew cold air onto patients' breasts and collected a series of images. The IR system had two modes: screening mode (i.e., high specificity mode, or NTBS1) and diagnostic mode (i.e., high sensitivity mode, or NTBS2). In each mode, the IR system provided a risk score between 0–10 for three parameters: nipple (individual breast), full breast (individual breast), and iMeasure (overall score considering both breasts); a score of 4 or greater in either parameter was considered abnormal. Patients were imaged in screening mode prospectively and in diagnostic mode retrospectively (i.e., no longer blinded).

Collett et al. reported the sensitivity and specificity of each mode. In screening mode, a 45% sensitivity (15/33) and 89% specificity (64/72) were observed; in diagnostic mode, a 79% sensitivity (26/33) and 49% specificity (35/72) were observed. However, due to the retrospective nature of the diagnostic mode results, it was claimed that results may have been biased, though it was unclear how. In the end, Collett et al. concluded that because neither mode had a sufficiently high combined sensitivity and specificity, IR thermography was unacceptable as an adjunctive diagnostic technique and as a screening technique for breast cancer.

Key takeaways from Collett et al.'s 99-patient study [22]:

- IR thermography had a maximum sensitivity of 79% and specificity of 89% based on 99 patients (in different modes).
- Because IR thermography had an insufficiently high sensitivity and specificity in a single mode, IR thermography was not recommended as an adjunct to mammography.
- Collett et al.'s findings did not support the role of thermography in the screening nor in the diagnosis of breast cancer.

Other notable recent studies: Other recent clinical studies (with favorable and unfavorable findings) included the following. Studies whose researchers held conflicts of interest were excluded [56,57].

- Delgado et al.'s 911-patient, 2-year study (2010) in Mexico that concluded thermography was useful as a screening tool [23].
- Wang et al.'s 276-patient study (2010) in Taiwan whose findings inconclusively indicated that thermography may be useful as an adjunct to mammography and ultrasound [24].
- Kontos et al.'s 63-patient, 1-year study (2011) in Britain that concluded that thermography should not be used in breast cancer screening [25].
- Rassiwala et al.'s 1,008-patient study (2014) in India that concluded that thermography was useful as an adjunctive screening technique [26].
- Wu et al.'s 143-patient, 2-year study (2016) in Taiwan that found thermography to indicate prognosis in breast cancer patients [27].

Finally, the reviews of Ng (2009) [33], Kennedy et al. [35], Vreugdenburg et al. [58], and Etehadtavakol and Ng [59,60] surveyed various thermography studies and arrived to favorable conclusions regarding infrared thermography. In contrast, the reviews of Kerr [61], Fitzgerald and Berentson-Shaw [62], and Brennan and Houssami [63] surveyed select thermography studies and arrived to unfavorable conclusions regarding infrared thermography.

5. Infrared thermography in breast cancer screening

5.1. Criteria of an abnormal thermogram

Based on the foundational studies surveyed, the following criteria and characteristics were generally identified by thermography researchers to constitute an abnormal thermogram:

1. Thermal asymmetry in vascular patterns between breasts [5,6,8,15,31,32]; it should be noted that thermal symmetry did not mean that thermovascular patterns are identical [6,16,32].
2. Localized hyperthermia (hotspot) [5,6,15,32]; an increase of +1.5–3.0°C or more over the opposite healthy breast [8,31] or +2.0–2.5°C over the mean temperature of the same breast was reported [5,32].
3. Areolar or periareolar hyperthermia (hotspot) [5,6,8,15,31,32]; an increase of +0.5°C over the opposite healthy breast was reported [5].
4. Generalized or diffuse hyperthermia [5,6,15,31,32]; an increase of approximately +1.5°C–3.0°C over the opposite healthy breast was reported [5,8].

While most studies surveyed relied on trained thermography experts to assess thermograms as normal or abnormal [4,6,16,64], some studies relied on the examining physicians to assess thermograms [15]. Some researchers noted the degree of subjectivity and variability in assessing thermograms and called for more objectivity [16,17,53]. More recently, however, artificial intelligence algorithms incorporated into the IR systems have assessed thermograms [20–22].

5.2. Key points of thermogram assessments

Based on the studies reviewed, the following conclusions from a thermogram assessment were observed.

A normal thermogram (negative result):

1. Was generally present in normal patients (i.e., those without a malignant or benign breast disease), but not all [4,6].
2. Generally indicated a lower risk of developing breast cancer in the future [4,7,8,10].
3. Did not necessarily indicate the absence of cancer in the present nor preclude the development of cancer in the future (i.e., nonzero false negative rate) [15–19,25].

In contrast, an abnormal thermogram (positive result):

1. Simply indicated a thermal abnormality in the breast (malignant or not) warranting further investigation and prolonged surveillance [6–8].
2. Was present in most breast cancer patients, but not all [4,8,9,12–14,19–23,26].
3. Generally indicated a higher risk of developing breast cancer in the future and a poorer prognosis [4,6–10,16].
4. Indicated at times a benign condition (e.g., fibrocystic disease) or superficial feature (e.g., veins, scar) [5,16].
5. Did not necessarily indicate cancer in the present nor denote the development of cancer in the future (i.e., nonzero false positive rate) [9,15,17,19].

5.3. Limitations to infrared thermography

The limitations of infrared thermography in breast cancer screening are well-documented. Both proponents and opponents of thermography acknowledged the limitations, shortcomings, and obstacles inherent in thermography. In fact, these limitations have precluded the widespread adoption of thermography by the medical community as a routine, adjunctive screening technique [53].

5.3.1. Thermal transport in breast tissue

Because infrared thermography is inherently a surface measurement, thermal transport between the tumor and the skin surface is a critical factor in thermographic detection. Tumors that are small, deep, and/or diffuse may consequently be undetectable on the skin surface, thereby eluding detection. As such, the ability of thermography to detect breast cancer is highly dependent on the following factors: Tumor size, tumor depth, tumor growth rate (related to metabolic heat generation), tumor concentration, and tissue thermal properties [5].

Relevant to the discussion are (1) thermal properties of breast tissue surrounding the tumor that either inhibit or facilitate heat transfer between the tumor and skin surface, and (2) the presence of biological features or processes that interfere with thermographic observations.

First, breast tissue with a higher thermal conductivity will, from a thermal standpoint, diffuse heat generated by a tumor more effectively throughout breast tissue than it would with a lower thermal conductivity, resulting in a lower surface temperature increase and a more generalized hyperthermia. In contrast, breast tissue with a lower thermal conductivity will feature a higher surface temperature increase and a more localized hyperthermia (hotspot), *ceteris paribus*. Moreover, any tissue properties or internal conditions that facilitate thermal transport from the tumor to the skin surface will improve thermographic detection, which primarily includes blood vessel convection through veins [5].

Second, superficial features (e.g., veins, scars, skin lesions) and benign diseases (e.g., fibroadenomata, abscesses, cysts, papillomas) can appear as thermal abnormalities on infrared images, and thus false positives, by causing localized or generalized hyperthermia. In contrast, processes such as inflammation, edemas, and skin thickening can hide legitimate cancers as false negatives [5,6,8].

5.3.2. Sensitivity, specificity

Sensitivity and specificity are two separate but related statistical parameters that quantify the accuracy of a positive/negative test–here, infrared thermography for breast cancer screening (see Table 2). Sensitivity quantifies how accurately a test detects true positives, whereas specificity quantifies how accurately a test detects true negatives.

Sensitivity is defined as a test's detection rate of true positives from the sick (or positive) population (see Eq. (1)). Mathematically, it is the ratio of true positives (TP) to the sum of true positives and false negatives (FN). This quantity is equivalent to unity less the false negative rate. Hence, one caveat is that sensitivity is calculated based on only the sick population, not the entire population.

$$\text{Sensitivity} = \frac{\sum TP}{\text{Sick population}} = \frac{\sum TP}{\sum TP + \sum FN} = 1 - R_{FN} \tag{1}$$

Specificity is defined as a test's detection rate of true negatives from the normal (or negative) population (see Eq. (2)). Mathematically, it is the ratio of true negatives (TN) to the sum of true negatives and false positives (FP). This quantity is equivalent to unity less the false positive rate. Similarly, one caveat is that specificity is calculated based on only the normal population, not the entire population.

Table 2
Sensitivity and specificity definitions.

Population	Test result: Positive	Test result: Negative	Parameter
Positive (sick; with cancer)	True positive	False negative	Sensitivity
Negative (normal; without cancer)	False positive	True negative	Specificity

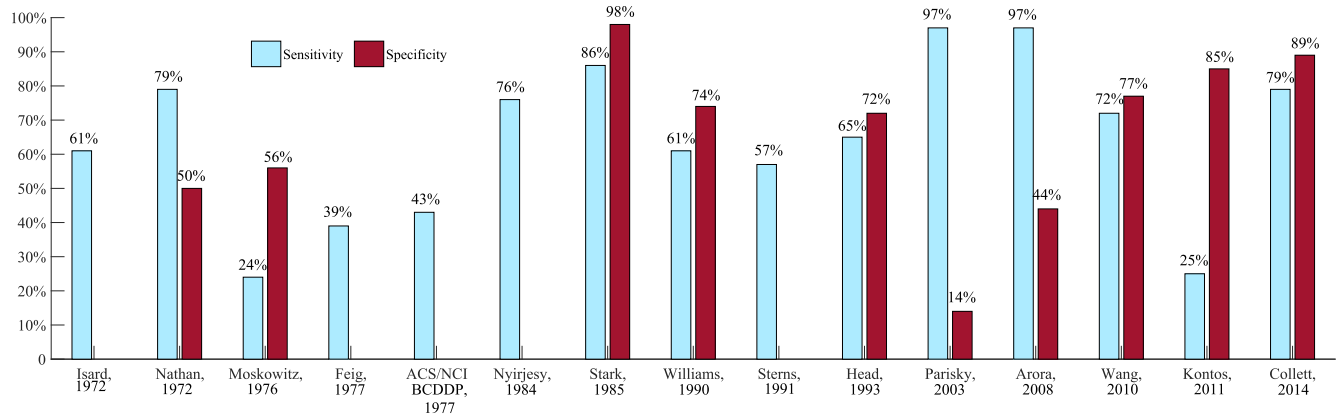

Fig. 10. Sensitivity and specificity rates of infrared thermography as observed by the studies surveyed [6,8,9,12,13,15–19,49]. A median sensitivity of 65% and specificity of 73% were observed among the studies shown.

$$\text{Specificity} = \frac{\sum TN}{\text{Normal population}} = \frac{\sum TN}{\sum TN + \sum FP} = 1 - R_{FP} \quad (2)$$

Of the studies surveyed with favorable conclusions, the following sensitivity and specificity values were reported (see Fig. 10 and Table 1):

- Isard et al. (1972) reported sensitivity values of 73% based on 270 cancers in symptomatic patients and 61% based on 36 clinically occult cancers in asymptomatic patients, which were both lower than values reported for mammography of 85% and 83%, respectively; however, when thermography was used in conjunction with mammography, the sensitivity increased to 92% and 89%, respectively [6].
- Haberman et al. (1980) observed a sensitivity of 76% based on 66 cancers [12].
- Nyirjesy and Billingsley (1984) reported a sensitivity of 76% [13].
- Stark (1985) observed an 86% sensitivity based on 414 cancers (reported as a 14% false negative rate) and 98% specificity based on a 10-year screening period (reported as a 1.7% false positive rate) [8].
- Head et al.'s data (1993) suggested a 65% sensitivity based on 100 cancer patients (per the reported 35% false negative rate); further, Head et al. observed a specificity of 72% based on 100 normal patients (reported as a 28% false positive rate) [9].
- Keyserlingk et al. (1998) observed an 83% sensitivity based on 100 cancer patients (reported as a 17% false negative rate) and an 81% specificity based on 100 benign biopsies (reported as a 19% false positive rate) [14].
- Parisky et al. (2003) observed a 97% sensitivity and 14% specificity based on 769 patients [20].
- Arora et al. (2008) observed a maximum sensitivity of 97% and specificity of 44% based on 92 patients (in different IR system modes) [21].
- Delgado et al. (2010) reported a 94% sensitivity based on 17 cancer patients [23].
- Wang et al. (2010) reported an optimal 72% sensitivity and 77% specificity based on 276 patients [24].
- Rassiwala et al. (2014) observed an 98% sensitivity and 99% specificity based on 1,008 patients [26].

Regrettably, Gautherie and Gros did not report sensitivity or specificity and did not provide tabulated data for retrospective calculation [4,5]. However, Gautherie attributed false negative cases to slow tumor growth rates, carcinomas in situ (i.e., carcinomas that have not yet become cancer and spread), and poor internal thermal transport within the breast; similarly, false positive cases were attributed to inflammatory processes [5]. Additionally, Isard et al. proposed sequential screening as a solution to false negative cases [6].

Of the studies surveyed with unfavorable conclusions, the following were reported (see Fig. 10 and Table 1):

- Nathan et al.'s data (1972) suggested a sensitivity of 79% based on 27 breast cancer patients and specificity of 50% based on 231 normal patients [19].
- Moskowitz et al. (1976) reported a 24% sensitivity based on 42 early cancer stage patients and a 56% specificity based on 55 normal patients [17].
- Feig et al. (1977) reported a sensitivity of 39% based on 139 cancer patients, which was retrospectively increased to 50% in the study [16].
- Williams et al. (1990) reported a 61% sensitivity based on 59 cancer patients and 74% specificity based on 10,170 normal patients [15].
- Sterns and Zee (1991) observed a sensitivity of 57% based on 214 breast cancer patients [18].
- Kontos et al. (2011) reported a 25% sensitivity and 85% specificity based on 63 patients [25].
- Collett et al. (2014) observed a maximum sensitivity of 79% and specificity of 89% based on 99 patients (in different IR system modes) [22].

Moreover, other reviews have indicated the following:

- Kennedy et al. (2009) provided an excellent survey of several thermography studies, observing a reported sensitivity of thermography generally in the range of 83%–97% [35].
- Vreugdenburg et al. (2013) pulled together several newer thermography studies within the past 20 years and observed that thermography has been generally reported to have a high sensitivity of 71%–96% but moderate specificity of 44%–85% [58].
- Brennan and Houssami's survey (2013) of thermography studies observed a median sensitivity of 47% as a screening test and 59% as a diagnostic test [63].

Finally, in order to increase the overall detection rate in a multimodal screening environment, most researchers supported the use of thermography as an adjunct to other conventional screening techniques [4–7,11–14,20,21,24,26,43]. This, in turn, would result in the early detection of breast cancer for more patients, allowing for earlier treatment.

5.3.3. Inconclusiveness and insufficiency

A recurring concession among thermography researchers was the inconclusiveness and insufficiency of infrared thermography as a standalone breast cancer screening technique [8,17,19]. Proponents and

critics both acknowledged that thermography alone was inconclusive and insufficient in diagnosing breast cancer. Therefore, thermography was generally considered to be non-diagnostic and non-specific, unable to neither formally diagnose breast cancer nor precisely locate a tumor [5,6,8,19,20,42,44]. This was attributed to the fact that thermography was only able to inherently provide thermophysiological information of the skin resulting from underlying breast abnormalities [6,8,20,21]. As a result, thermography was generally regarded as an adjunct to mammography, ultrasound, and clinical breast exam for screening, leaning on diagnostic exams (e.g., biopsy) for formal cancer diagnosis.

6. The proper role of infrared thermography

Infrared thermography's full potential is realized when its proper role is considered. The primary motivation for using IR thermography is its lack of ionizing radiation exposure to the patient, similar to ultrasound and contrary to mammography. This is bolstered by the fact that it is non-invasive and does not require contact during imaging.

The following assessments of IR thermography as a screening technique and as a diagnostic technique are based on the studies surveyed as a whole.

6.1. Breast cancer diagnostics

All studies considered, the general consensus among researchers was that IR thermography should not be used for the following purposes and applications:

1. Diagnose cancer solely by means of thermography, absent of other techniques [6,8,19,22].
2. Isolated, stand-alone screening exam providing any definitive conclusions regarding cancer (i.e., as a replacement or substitute for mammography) [6,8,17,19,42,44,65].
3. Identify tumor location [8,19,20,42,53].

In breast cancer diagnostics, there is no real need for thermography except to further confirm other techniques' results, e.g., mammography and ultrasound. Because the goal of IR thermography is to avoid unnecessary radiation exposure (mammography), IR thermography's only role is as an adjunctive diagnostic technique confirming existing results. However, since histological results provide far more confidence than any imaging modality, and since non-thermography techniques are sufficient to warrant biopsy, IR thermography's necessity is therefore severely limited in the realm of diagnostics.

6.2. Breast cancer screening

In breast cancer screening, however, IR thermography plays a larger role. Despite its low specificity (high false positives) when used alone to detect breast malignancies, IR thermography's benefit is maximized when used as an adjunct to other screening techniques (i.e., mammography, clinical breast exam, ultrasound).

All studies considered, researchers mostly agreed that IR thermography was best used for the following specific purposes and applications:

1. Adjunctive imaging technique in the preliminary screening of breast cancer that identified patients warranting follow-up with other screening techniques, supported by the fact that IR imaging procedures were inexpensive, safe, non-invasive, and increased the overall sensitivity in a multimodal screening environment [4–8,11–14,20,21,31,42,43,54,65].
2. Detection of thermal abnormalities in the breast possibly indicating early stages of cancer, prior to detection by conventional screening techniques, but not necessarily signifying malignancy [5,6,8,16,42].
3. Risk assessment and risk factor for future breast cancer development [8,9,44,53,54]; accordingly, for identifying patients warranting subsequent monitoring for breast cancer development [4,6,8,16,42].
4. Indication of prognosis of breast cancer patients (i.e., survival rates) based on the degree of thermographic abnormality [4,7,9–11,27,53,54].
5. Detection of large tumors and/or fast-growing tumors [4,16]; as an indication of tumor growth rate, which is related to prognosis [5,9].
6. Sequential screening to detect physiological changes in thermal patterns over time and to possibly identify occult cancers or to correct past false negatives [6,8,42,44,65].

Finally, and most importantly, the following two populations stand to benefit the most from IR thermography:

Younger women (under 40). Women in this population are the ideal candidates for IR breast imaging, as originally speculated by Dodd [65], Arora et al. [21], and Ng and Kee [66]. Sequential screening (e.g., annually) in order to establish a baseline thermal pattern in a woman's breasts over time for future reference, at an age too young to absorb the inherent risks of mammography [34], is the most appropriate niche for infrared thermography in breast cancer screening. Then, in the future, any deviations in thermal patterns from earlier IR thermograms would subsequently warrant further clinical investigation, particularly when the woman is of age for routine mammograms.

Rural populations. Those without quick access to healthcare facilities stand to benefit greatly from IR thermography. This is supported by the technique's inexpensiveness per imaging procedure (despite high initial capital costs), ease of portability (by design of IR equipment), safety, and non-invasive nature. The most successful IR thermography studies screened rural populations or those without immediate access to healthcare [12,23,26].

7. Conclusions

Infrared breast thermography is a medical imaging technique in which IR images of a patient's breasts are used to detect physiological abnormalities associated with breast cancer. Early studies throughout the 1960s–1990s evaluated infrared thermography as a screening technique and arrived to favorable conclusions when it was used as an adjunct to mammography and clinical breast exam due to the increased combined sensitivity. Studies also suggested that abnormal thermograms were an indication of a patient's risk and prognosis. However, based on mixed findings from researchers, and exacerbated by the degree of subjectivity in assessing thermograms, infrared thermography lost considerable research interest and credibility within the medical community.

Nevertheless, clinical studies continued after 2000, with a focus on its adjunctive diagnostic capability. These recent studies have generally had favorable conclusions regarding infrared thermography and have supported its role as an adjunct to current imaging techniques like mammography and ultrasound. Infrared systems have also evolved from static to dynamic systems that recorded a series of IR images and implemented artificial intelligence for image assessment.

Together, these findings pointed to the proper role of infrared thermography: An adjunctive technique in the preliminary screening for breast cancer that, at a minimum, identified patients warranting follow-up by other screening techniques. Younger women are the ideal candidates for IR breast imaging; until the benefits of routine mammograms outweigh the risks of exposure to ionizing radiation, routine thermograms can establish a baseline thermal pattern in patients' breasts that could later be used as a reference upon future deviations. Given the technological improvements in infrared metrology, infrared thermography is better suited to assist breast cancer screening and diagnostics today than it was 50 years ago when first investigated.

To the scientist or engineer, the infrared thermography of a system

provides valuable information that is otherwise not readily available. Therefore, if its limitations and caveats are kept in mind, and if used appropriately, infrared thermography can also be of value to the medical community.

Conflict of interest

Declarations of interest: None.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Raytheon Space and Airborne Systems financially supported Lozano's graduate study as an employee but did not provide any funds for this research.

Acknowledgements

The authors acknowledge the financial support from the National Science Foundation Grant No. 1454334 and the Excellence in Education Doctoral Fellowship by UT Dallas. The authors also acknowledge Stephen P. Lozano, PharmD, and Hayaa F. Hashemi, PhD, for their medical and scientific counsel.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.infrared.2018.12.017.

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