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# Non-Invasive Devices for Early Detection of Breast Tissue Oncological Abnormalities Using Microwave Radio Thermometry

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## 1. Introduction

Breast cancer is the most common cancer in women worldwide, comprising 16% of all female cancers and is the leading cause of cancer-related deaths in women ages 40-55. Each year in the U.S.A. over 180,000 women are diagnosed with breast cancer and 46,000 women die of this disease. One in twelve women in the United Kingdom develops breast cancer and the annual death toll stands at around 14,000. Over 33,000 new cases are being monitored year on year basis in the UK. In all, 10%-11% of all women can expect to be affected by breast cancer at some time during their lives. The causes of most breast cancers are not yet fully understood. Sixty years ago, MacDonald proposed that the biological behaviour of a neoplasm is established during its preclinical growth phase (MacDonald, 1951). This view is supported by some data on the behaviour of metastatic lesions such as poor cytological differentiation, lymphatic permeation, blood vessel invasion and the invasion of the surrounding soft tissue by the tumour (Nealon et al, 1979). Screening and early diagnosis are currently the most effective ways to reduce mortality from this disease. Early diagnosis and treatment are the keys to surviving breast cancer. Breast cancer survival rates vary greatly worldwide, ranging from over 80% in North America, Sweden and Japan to around 60% in middle-income countries and below 40% in low-income countries. It is believed that the low survival rates in less developed countries are mainly due to the lack of early detection programmes, resulting in a high proportion of women presenting with late-stage disease, as well as by the lack of adequate diagnosis and treatment facilities. Studies from the American National Cancer Institute show that 96 percent of women whose breast cancer is detected early live five or more years after treatment. Early diagnosis remains an important detection strategy, particularly in low- and middle-income countries where the disease is diagnosed in late stages and resources are very limited. There is some evidence that this strategy can produce "down staging" of the disease to stages that are more amenable to less aggressive treatment. Therefore, thousands of lives and considerable healthcare costs could be saved each year with treatment if early symptoms of breast cancer are detected. Taking full advantage of early diagnosis and treatment means that screening technology should have the characteristics that have high detection success rate, speed of procedure, comfort to the subject and very low health risk.

The principal aim of early breast cancer detection is to identify the disease at a more curable stage and thus improve the prognosis and other vital clinical outcomes. Currently breast cancer detection is a three part procedure. The first part is identification of the abnormality in the breast tissue either by physical examination or by an imaging technique. Secondly, the abnormality is diagnosed as a benign or a malignant condition by using additional diagnostic methods or by biopsy and microscopic examination of the tissue morphology. The third part is concerned with biochemical characterisation of the malignant tissue in order to stage the cancer according to the size of the tumour and extent of invasion and metastasis. Of particular importance is the ability to clearly distinguish between malignant and benign tumours and early detection. This then determines the prognosis and appropriate course of treatment. A review of the published literature shows that all current breast cancer detection techniques have limited capability and surgery is often required to establish the true nature of the tumour.

Currently, the frontline strategies for breast cancer detection still depend essentially on clinical and self-examination and mammograms. The limitations of mammography, with its reported sensitivity rate often below 70% are recognized (Sickles, 1984) and the proposed value of self-breast examination is being queried (Thomas et al, 1997). Mammography is accepted as the most reliable and cost-effective imaging technique, however, its contribution continues to be challenged with persistent false-negative results - ranging up to 30% (Moskowitz, 1983 & Elmore et al, 1884). However, most of the research and development activity related to cancer detection and diagnosis is focussed on the analysis of the existing condition and is costly, time-consuming and requires trained personnel to use the equipment. Furthermore, the incidence of the earliest form of breast cancer, Ductal Carcinoma in Situ (DCIS), has increased significantly over the last few years in the United States and this seems to be directly related to successful screening programmes. This clearly shows that there is a need and scope for developing early breast cancer detection techniques that are simple, quick and can be used by women by themselves.

In this chapter a review of some of the most promising techniques that are being developed for breast cancer detection is presented. A comparison of the various breast cancer detection techniques that are in the developmental stages with the established procedures has been carried out and a state-of-the-art in all the areas is briefly described and the concept of a wearable breast cancer detection device - the 'smart bra'- is also discussed. Particular emphasis has been placed on the non-invasive thermometry based methodologies for early detection of the oncological condition. When infrared thermography was first introduced in medicine, the instrumentation was not sensitive enough to detect the subtle changes in temperature that are involved in diseases such as breast cancer. However, more recently the sensitivity of infrared instrumentation has greatly improved and the IR thermography imaging is being developed and used to monitor the health of the breast and detection of cancerous tumours. Recent literature shows that the technique has the ability to detect tumours that are 3cm in size and are located deeper than 7 cm from the skin surface and tumours smaller than 0.5 cm can be detected if they are close to the surface of the skin. Non-invasive techniques based on profiling of the breast tissue using microwave radiometry are also being developed and investigated as early warning systems for breast cancer. These techniques involve the measurement of the passive electromagnetic thermal radiation emitted from human body using suitable combination of microwave antenna internal temperature sensor and infrared surface temperature sensor, with an appropriate configuration to determine the temperature profile of the concerned area of the body.

Microwave radiometry principles can be employed to obtain sensor information from subcutaneous tissues up to a few centimetres in depth. The device based on these principles can provide an early breast cancer detection/warning technique that is simple, quick and may also be used for diagnosis of other types of cancers such as prostate cancer in men.
The evidence indicates that screening mammography, when correctly performed at recommended intervals and combined with appropriate interventions, can reduce, but not eliminate, breast cancer mortality. This conclusion is based on evidence of efficacy in clinical trials and evidence of effectiveness in the general population. The "ideal" breast cancer screening tool has not yet been developed. All of the tests available for the screening and diagnosis of breast cancer have different strengths and limitations. The ideal test would combine the following characteristics:

- The test should present a low risk of harm from screening
- The test should have high degrees of specificity and sensitivity (low rates of false-positive and false-negative results).
- The test results should have uniform high quality and repeatability.
- Interpretation of test results should be straightforward (objective).
- The test should be simple to perform.
- The test should be non-invasive.
- The test should be able to detect breast cancer at a stage that is curable with available treatments.
- The test should have the ability to distinguish life-threatening lesions from those that are not likely to progress.
- The test should be cost-effective (usually considered <$50,000 per quality-adjusted life year saved).
- The test should be widely available.
- The test should be acceptable to women.

Each modality has different strengths and limitations therefore it seems to be feasible to adopt a multi modality approach in order to achieve the optimum methodology for the detection and diagnosis of the breast tissue oncological abnormalities.

### 1.1 Anatomy and physiology of female breast

It is important to consider the physiology of the breast, as the changes seen in the breast during a woman's life will have an effect on the properties of the tissues. The female breast is a complex and sensitive organ, which is composed of a mass of glandular, fatty, and fibrous tissues positioned over the pectoral muscles of the chest wall and attached to the chest wall by fibrous strands called Cooper's ligaments (Figure 1). A layer of fatty tissue surrounds the breast glands and extends throughout the breast. The fatty tissue gives the breast a soft consistency. The glandular tissues of the breast house the lobules and the ducts.
The female breast has a network of arteries and capillaries that carry oxygen- and nutrient-rich blood to the breasts. The axillary artery extends from the armpit and supplies blood to the outer half of the breast. The internal mammary artery, which extends down from the neck, supplies blood to the inner part of the breast. The breast also contains lymph vessels. The lymphatic system is part of the immune system and is composed of blood vessels, lymph ducts and lymph nodes. Clusters of lymph nodes are located under the arm, above the collarbone, behind the breastbone and in various other parts of the body.

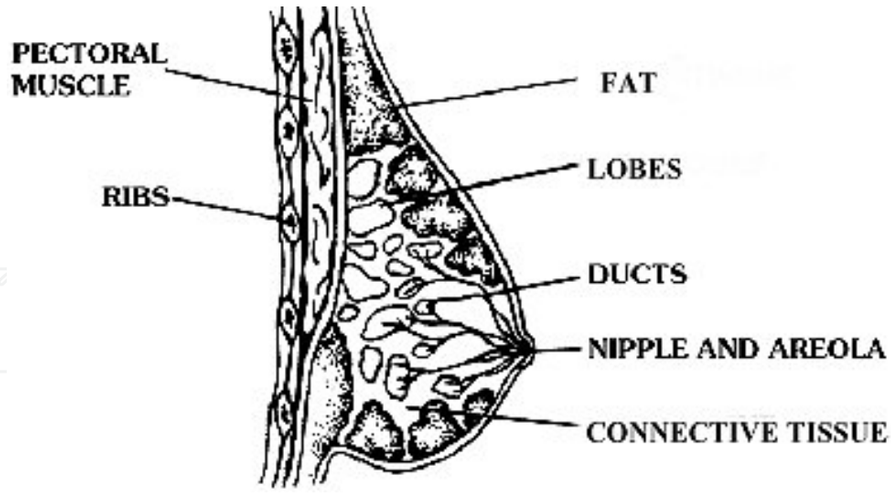


Fig. 1. The anatomical structure of the female breast

The shape and appearance of female breast undergo a number of changes as a woman ages. In young women, the breast skin stretches and expands as the breasts grow, creating a rounded appearance. Young women tend to have denser breasts, due to the presence of more glandular tissue, than older women. The denser breasts lead to poorer contrast between healthy and diseased tissue in x-ray mammography. However the occurrence of breast cancer in younger women is low, with 80 % of breast cancers occurring in women over the age of 50. The growth of breast tissue is mainly influenced by the relative concentrations of progesterone and oestrogen in the body. During each menstrual cycle, breast tissue tends to swell due to variation in the oestrogen and progesterone levels. The milk glands and ducts enlarge resulting in retention of water by the breast. During menstruation, breasts may temporarily appear swollen and this can give rise to breast pain, tenderness, or they may feel lumpy. At menopause, a woman's body stops producing oestrogen and progesterone, which causes a variety of symptoms in many women including hot flushes, night sweats, mood changes and vaginal dryness. During this period breasts also undergo many changes, such as mentioned earlier for the menstrual cycle, and sometimes appearance of cysts may be observed. The glandular tissue tends to shrink after menopause and is replaced with fatty tissue. The breasts also tend to increase in size and droop because the fibrous tissue loses its strength. The breasts become less dense after menopause, which makes the detection of breast cancer often easier in older women. A woman's risk of breast cancer increases with age thus all women are recommended for breast cancer screening at regular interval beyond the age of 40.

### 1.2 Main types of breast cancer

Treatment of cancer depends on the type and stage of the cancer along with other issues such as the individual circumstances of the patient. Mostly breast cancer develops in the glandular tissue and is classified as adenocarcinoma, which is a cancer of the epithelium that originates in the glandular tissue. The common types of breast cancers are:

*Carcinoma in situ:* This term is used for early stage cancer, when it is confined to the place where it started. In breast cancer, it means that the cancer is confined to the ducts or the lobules, depending on where it started. It has not gone into the fatty tissues in the breast nor spread to other organs in the body.

*Ductal carcinoma in situ (DCIS):* This is the most common type of non-invasive breast cancer. DCIS means that the cancer is confined to the ducts. It has not spread through the walls of the ducts into the fatty tissue of the breast. Over 70% of breast cancers are ductal carcinomas, which are associated with the milk ducts. Nearly all women with cancer at this stage can be cured.
*Infiltrating (invasive) ductal carcinoma (IDC):* This type of cancer starts in a duct and breaks through the wall of the duct, and invades the fatty tissue of the breast (Figure 2), then spreading to other parts of the body. IDC is the most common type of breast cancer. It accounts for about 80% of invasive breast cancers.

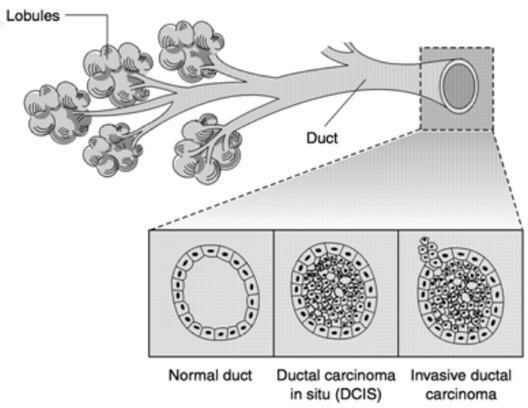


Fig. 2. Growth of ductal carcinoma

Lobular carcinoma in situ (LCIS): This condition begins in the milk-making glands but does not go through the wall of the lobules. Although not a true cancer, having LCIS increases a woman's risk of getting cancer later. For this reason, it is important that women with LCIS follow the screening guidelines for breast cancer. 10% - 15% are lobular carcinomas associated with the lobes, and the rest are relatively rare forms of cancer such as of the connective tissue.
*Infiltrating (invasive) lobular carcinoma (ILC):* This type of cancer starts in the lobules and can spread to other parts of the body (Figure 3). About 10% of invasive breast cancers are of this type.

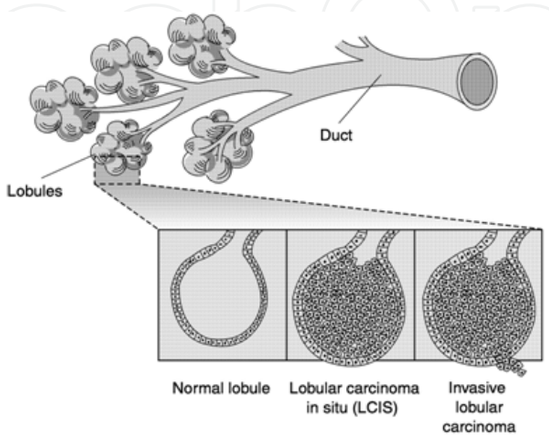


Fig. 3. Growth of lobular carcinoma

*Benign conditions:* There are many lesions and conditions that are non-cancerous but still affect the health of the breast and could be mistaken for cancer. These include fibroadenomas, cysts, mastalgia, breast calcifications, duct ectasia and periductal mastitis, fat necrosis, hyperplasia, intraductal papilloma, phyllodes tumour and sclerosing adenosis.

## 2. Current breast cancer detection modalities and their limitations

Breast is susceptible to a range of pathologic conditions. The most serious of these is breast cancer, which is widely recognised as the most common cancer in women. Other breast conditions include mastalgia, which is referred to a variety of conditions that cause breast pain, and benign lesions such as fibroadenomas and cysts. These conditions are not fatal but they are a source of undesirable symptoms and considerable anxiety for the patients. Improved methods for early detection and diagnosis of breast disease are essential to decrease mortality rates due to cancer. In addition a greater understanding of the physiology of the breast is needed to aid in the diagnosis of disease and in improving treatments.

The breast cancer detection is a three part procedure. The first part is the identification of the abnormality in the breast tissue either by physical examination or by an imaging technique. Secondly the abnormality is diagnosed as a benign or malignant condition by using additional diagnostic methods or by biopsy and microscopic examination of the tissue morphology. The third part is concerned with biochemical characterisation of the malignant tissue in order to stage the cancer according to the size of the tumour and extent of invasion and metastasis. This then determines the prognosis and appropriate course of treatment. The most commonly used imaging modalities are described in the following sections.

The main strategy of breast cancer detection is based on clinical examination and mammography. Mammography is considered to be the 'gold standard' test for breast cancer detection and diagnosis and is accepted as the most cost-effective imaging modality. The performance of a screening test is evaluated by three related measurements: sensitivity, specificity, and a positive predictive value. The sensitivity of a screening test is the proportion of people with the disease who test positive. Specificity is the proportion of people without the disease who test negative. The positive predictive value is the proportion of individuals with a positive screening test result who actually have the disease. In the development of optimum detection modality, there is often a trade-off between sensitivity and specificity, with an increase in one leading to a decrease in the other. The contribution of mammography continues to be challenged with persistent false-negative rates ranging up to 30%.The clinical examination has been challenged with reported sensitivity rates often below 65%. There is also variability in radiologists' interpretation of mammograms with decreasing sensitivity in younger patients and those on oestrogen replacement therapy. In addition, recent data suggests that denser and less informative mammography images are precisely those associated with an increased cancer risk (Boyd et al, 1995). It has also been suggested that mammography procedure cannot be performed by an inexperienced technician or radiologist. With the current emphasis on earlier detection, there is now renewed interest in the development of complimentary imaging techniques that can also exploit the metabolic, immunological, and vascular changes associated with early tumour growth. While promising, techniques such as Doppler ultrasound and MRI are associated with a number of disadvantages, which include the following:

- Duration of the test,

- Limited accessibility,
- Need of intravenous access,
- Patient discomfort,
- Restricted imaging area,
- Difficult interpretation
- Limited availability of the technology

These modalities are in fact more suited as the second-line options to pursue the already abnormal screening evaluations. This stepwise approach currently results in the non-recognition, and thus delayed utilization of any second-line technology in approximately 10% of established breast cancers (Moskowitz, 1995). This view is supported by another study of infrared screening of breast cancer [Keyserlignk & Ahlgren, 1998). A list of the established breast cancer detection modalities approved by FDA is given in Table 1.

| Modality | Description |
|---|---|
| Full-field digital mammography | Detector responds to X-ray exposure, sends electronic signal to computer to be digitized and processed. Separates detector and image display. |
| Computer-assisted detection | Computer programs to aid in identification of suspicious mammograms and classification as benign or malignant. |
| Ultrasound : Compound imaging and Three-dimensional ultrasound imaging | Uses high-frequency sound waves to generate an image. |
| Magnetic resonance imaging (MRI) | Makes use of the property of nuclear magnetic resonance (NMR) to image nuclei of atoms inside the body. Image generated by signals from excitation of nuclear particles in a magnetic field. Breast tumours show increased uptake of contrast agent. |
| Scintimammography | Image created with radioactive tracers, which concentrate more in cancer tissues than in normal tissues. |
| Positron emission tomography (PET) | Uses tracers such as labelled glucose to identify regions in the body with altered metabolic activity. |
| Infrared Thermography | Measures heat emitted by the body. Tumours can raise skin surface temperature, which is detected by infrared cameras. Dynamic area telethermometry detects changes in blood flow. |
| Electrical impedance imaging | Measures voltage at skin surface while passing small current through breast. Changes in cancerous tissue decrease impedance of tissue. |

Table 1. FDA approved modalities for breast cancer detection

### 2.1 X-ray mammography

X-ray mammography is the most common method of imaging the breast at present. The technique involves the breast being compressed between two plates with an x-ray film placed underneath and low energy x-rays are then passed through the breast and the images are recorded. The best contrast between soft tissues is achieved at low energies and hence these are used in x-ray mammography. The x-rays are produced by an electron beam irradiating either a tungsten or molybdenum target depending on the size of the breast to be imaged. At low energies, the transmission is low causing a high dose to the patient. Thus a compromise between contrast and dose is necessary. This problem is reduced by compression of the breast. The breast is compressed to between 2 and 8 cm enabling a high contrast whilst keeping the dose within an acceptable level. Contrast is dependent on the thickness of the breast and the difference in linear attenuation coefficient ($\mu$) between the tissue types. The value of $\mu$ is dependent on the atomic number of the material. Thus tissues with higher atomic numbers will produce a higher attenuation than others (e.g. microcalcifications).

The established sensitivity of mammography is higher than 91% (Brem et al 2003), which is greater than any other imaging modality for breast cancer detection. This is the main reason for the use of mammography in screening programmes. The reported specificity of the technique is quite variable and is considered to be in the region of 72% (Bone et al 1997). This means that nearly a quarter of the benign lesions are diagnosed as suspicious, which leads to unnecessary invasive procedures, biopsies, in order to establish the true nature of the lesion. Furthermore, the sensitivity of mammography for younger women is lower than that for older women. Younger women have denser breasts and less adipose tissue. Adipose tissue provides a greater contrast to calcifications than denser fibrous tissue and so mammography is more successful in older women.

Nearly one quarter of all invasive breast cancers are not detected by x-ray mammography in women aged between 40-49 years. However, the statistics for women above the age of 50 years are significantly better (1 in 10). Treatment of women with undetected invasive cancers, because of false-negative results, may be delayed. Many mammographic abnormalities may not be cancer, but will prompt additional testing and anxiety. Approximately 10 percent of all screening mammograms are read as abnormal. This will result in additional diagnostic tests such as diagnostic mammography, ultrasound, needle aspiration, core biopsy, or surgical biopsy. Given the lower incidence of breast cancer in 40- to 49-year-old women compared with that in older women, false-positive examinations are more common in younger women and the proportion of true-positive examinations increases with increasing age. There is concern that women having abnormal mammograms, both true-positive and false-positive, experience psychosocial stresses, including anxiety, fear, and inconvenience. There is the concern that experiencing a false-positive mammogram may affect subsequent willingness of the patient to undergo future screening mammography at ages when it is of greatest benefit.

The main advantages of x-ray mammography are that the technique has good resolution and microcalcifications can easily be observed. Furthermore, the relatively fast imaging time allows many women to be scanned in one screening session. The major drawbacks of the modality are the use of ionising radiation, which is potentially harmful for the patient and the operator, and interpreting mammograms can be difficult due to differences in the appearance of the normal breast for each woman. The sensitivity is high (91.4% (Brem et al, 2003) but is not 100% and also the specificity is relatively low for some types of tumours.

Particularly, the sensitivity is lower for women with dense breast tissue (e.g. younger women) and breast implants can affect the accuracy of mammography, as silicone implants are not transparent to X-rays. The disadvantages of compressing the breast are that it is, at best, uncomfortable and for many women with sensitive breasts it can be very painful. This limits the maximum time feasible for the imaging process. Also the spatial accuracy of the image can be distorted so that it is difficult to exactly locate an identified lesion.
The risk of radiation-induced breast cancer has long been a concern and has driven the efforts to reduce the radiation dose per examination. Radiation has been shown to cause breast cancer in women, and the risk is proportional to the dose. Especially the younger women are at a greater risk for breast cancer due to the exposure to radiation. Radiation related breast cancers occur at least 10 years after exposure. However, breast cancer as a result of the radiation dose associated with mammography has not been established. Radiation from yearly mammograms during ages 40-49 has been estimated as possibly causing one additional breast cancer death per 10,000 women.

### 2.2 Magnetic resonance imaging (MRI)

The principal imaging modality used for the detection of breast tissue abnormalities is x-ray mammography, which has a high sensitivity, but suffers from a relatively poor specificity for some tumours and breast types, leading to unnecessary biopsies. Thus there is a need for an imaging technique that can non-invasively distinguish between malignant and benign lesions. At the present, magnetic resonance imaging (MRI) and ultrasound (US) can provide additional diagnostic information for this purpose.
The theory of MRI is based on the fact that the nuclei of some atoms have a property known as spin. Such nuclei act like tiny current loops and consequently generate a magnetic field (or magnetic moment), along the spin axis. Under normal circumstances these moments have no fixed orientation so there is no overall magnetic field. When an external magnetic field is applied, the moments will align in certain directions. In the case of hydrogen nuclei, which are the most abundant nuclei in the human body, two discrete energy levels are created. An MRI detection system consists of a magnet, magnetic gradient coils, a radio frequency transmitter and receiver, and a computer that controls the acquisition of signals and computes the MR images obtained. When an atomic nucleus is exposed to a static magnetic field, it resonates when a varying electromagnetic field is applied at an appropriate frequency and an image is computed from the resonance signals.
The signal in MRI arises from the rotating magnetisation, but it decays due to two different relaxation processes. The first process is the spin-lattice relaxation. The second relaxation process is the spin-spin relaxation. During spin-spin relaxation, the detected signal decays over a period of time. However, the spins are also subject to inhomogeneities in the magnetic field causing the signal to decay faster than the natural time period. Part of the signal can be obtained due to the spin-echo effect. This involves the application of a further RF pulse which causes the spins to be flipped by 180°. This means that the phase-position of each spin has been inverted and so nuclei that were precessing faster are now behind spins that were precessing at a slower rate. At the echo time *TE*, the spins will catch each other up and a peak in the signal will be detected. An MRI exam of the breast typically takes between 30 and 60 minutes. Diffusion and perfusion MRI are relatively new procedures. Diffusion MRI measures the mobility of water protons whereas perfusion MRI measures the rate at which blood is delivered to tissue. Both of these factors vary in malignant tissues as compared with benign tissue and therefore can be used as indicators for cancer.

The injection of a contrast agent can enhance the ability of MRI to detect specific features or in the case of dynamic contrast-enhancement MRI the functionality of the tissue can be investigated. The contrast agents used are paramagnetic agents with gadolinium (Gd-DTPA) being the most common. The increased vascularity of tumours produces a preferential uptake of contrast agent and the technique can be used to improve their contrast from surrounding normal tissue. In dynamic contrast-enhancement MRI, scans are repeatedly acquired following the contrast injection and the dynamic nature of contrast uptake can be examined, which may improve the differentiation of benign and malignant disease.

The main advantages of MRI are that the modality is suitable for women with denser breasts and the technique is non-ionising. It is possible to take images in any orientation and determine multi-focal cancers. The technique can also show breast implants and ruptures. The disadvantages of MRI are that a contrast agent is required to provide adequate specificity and that it is immobile, expensive, and unsuitable for some women. The modality cannot image calcifications and can induce feelings of claustrophobia, and require long scan times in comparison to x-ray mammography.

### 2.3 Ultrasound

Ultrasound is defined as a frequency of sound above the threshold of human hearing (i.e. > 20 kHz). The frequency range used in medical ultrasound imaging is 1 – 15 MHz. This allows wavelengths less than 1 mm to be measured and thus produces good spatial resolution. Ultrasound waves interact with tissue in a variety of ways but it is the reflection and transmission at interfaces between tissues of different acoustic impedance that is utilised in medical imaging. If there is a large acoustic mismatch between two tissues then a large fraction of the ultrasound intensity will be reflected. If there is a small difference in the acoustic impedance then most of the intensity will be transmitted. The time between pulse generation and the detection of an echo provides the depth of the reflecting interface, and thus images can be generated. Measuring the magnitude and time difference between different reflected signals can be used to determine the type, depth and size of different tissues.

Ultrasound pulses are generated and detected by a hand-held transducer, based on an array of small piezoelectric crystals. The very low acoustic impedance of air means that any boundary between air and tissue results in a near 100% reflection, so to ensure that the ultrasound waves are coupled into the body an impedance matching gel is used between the breast and the transducer. As there is a large difference between the acoustic impedance of a liquid filled cyst and normal breast tissue, around 23% of the ultrasound wave is reflected at such a boundary, making this technique particularly useful for the diagnosis of such a lesion. The small differences in acoustic impedance between adipose tissue and glandular tissue mean that this technique is of particular use for younger women with denser breasts, where x-ray mammography is often unsuitable. Doppler ultrasound utilises Doppler shifts from Rayleigh backscattered ultrasound waves to determine the velocity at which red blood cells are moving. Doppler ultrasound can be used to monitor blood flow and as a result can be used as an indicator of vascularisation of a malignant tumour in the breast.

Ultrasound is relatively inexpensive and a versatile technique. It can provide excellent contrast resolution, which means suspicious areas are easy to differentiate from normal tissue. X-ray mammograms are frequently followed up with ultrasound imaging to determine whether a lesion that appeared on a mammogram is a cyst or a solid mass. Since

a fluid-filled cyst has a different sound signature than a solid mass, radiologists can reliably use ultrasound to identify cysts, which are commonly found in breasts. The technique can be used for younger women and women with breast implants and is entirely safe, and can be used repeatedly. The main disadvantages of the modality are the lack of fine detail, difficulty in detection of microcalcifications, poor ability to see deep lesions and inability to differentiate between certain types of solid breast masses.

### 2.4 Scintimammography

Scintimammography or nuclear medicine imaging is sometimes used alongside x-ray mammography in the diagnosis of breast disease since this technique is able to determine if a located lesion is malignant. The technique involves injection of a radioactive tracer into the patient. The tracer emits radiation, which is detected using a gamma camera. Appropriate image reconstruction algorithms enable the distribution of the tracer within the body to be mapped. Since the tracer accumulates differently in malignant and benign tissues it can be used to distinguish between the two conditions. Several radioactive compounds have been investigated, although only one, technetium-99m sestamibi (MIBI), is approved by FDA for use in breast imaging. A nuclear medicine investigation of the breast usually takes between 45 and 60 minutes. In a typical examination, the radioactive tracer (Tc-99m sestamibi) is injected into the patient's arm. The patient lies face down on a special table with her breast suspended through a hole. The images of the breast are taken from several angles using a gamma camera.

The advantages of scintimammography are that it can be used on patients with dense breasts and it can image large palpable lesions that do not appear with other imaging modalities. The modality involves the use of ionising substance that is injected into a patient (invasive) and is time consuming. Whilst it is 90% accurate for abnormalities over 1cm it is only 40- 60% accurate for smaller size abnormalities. The technique can be used to test tissue remaining from a mastectomy and can also be used to check for metastases in the auxiliary lymph nodes.

## 3. Techniques under development for breast cancer detection

There are several modalities that are at early stages of development but have a considerable potential as breast cancer detection devices. Majority of the imaging technologies for the breast are based on physical, mechanical, electrical, chemical and biological characteristics of the breast tissue. These detection techniques are based on their response to various tissue properties as listed in Table 2.

In an article about controversy over breast cancer screening, Reidy argued that death from malignancy rather than detection of malignancy should be a point of reference in evaluating any screening modality, since fast growing tumours, although detected while small, may have already metastasised. As a result, the number of malignancy related deaths have not altered regardless of their detection stage (Reidy, 1988). This has led to the view that the development of any new breast cancer detection modality must recognise the existence of three biologically distinct breast cancer patient subgroups. Firstly, there is a group of patients, which have slow-growing population of malignant cells that show ability to metastasise until very late. The second group comprises of patients with rapidly growing tumours that can lead to the development of micrometastases long before the tumour is detectable using the current modalities. Finally, there is the group of patients that have

moderately fast growing tumours that may or may not be metastatic at the time of detection. The current breast cancer detection modalities are more valuable for the last group of patients. Some of the more likely modalities that can be developed as breast cancer diagnostic tools, which appear to be based on the recognition of the above points, are described in Table 3 and briefly discussed in the following sections.

| Mode of Imaging | Tissue Property |
|---|---|
| Physical | Photon attenuation<br>Temperature |
| Electrical | Conductivity<br>Dielectric coefficient<br>Impedance |
| Mechanical | Architecture<br>Elasticity |
| Biological | Protein (expression/function)<br>Perfusion |

Table 2. Properties of breast tissue exploited by different modes of imaging

| Modality | Description |
|---|---|
| Magnetic resonance spectroscopy | Use of magnetic resonance spectra and "functional" molecular markers to measure biochemical components of cells and tissues. |
| Optical imaging | Use of fibre-optic probes to obtain spectral measurements of elastically scattered light from tissue. Generates spectral signatures that reflect architectural changes at cellular and sub-cellular levels. |
| Optical tomography | Use of light to image the breast |
| Electrical potential measurements | Measurement of electrical potential at the skin surface. Proliferation of epithelial tissue disrupts normal polarization |
| Electronic palpation | Quantitative palpation of breast using pressure sensors. |
| Thermo acoustic computed tomography | Breast is irradiated with radio waves, causing different thermal expansion of tissue and generating sound waves, from which a three-dimensional image is constructed. |
| Microwave imaging | Transmits low-power microwaves into tissue and collects backscattered energy to create three-dimensional image. Higher water content in malignant tissues causes more scatter |
| Hall effect imaging | Induces vibrations by passing electric pulse through tissue while exposed to a magnetic field. |
| Magneto mammography | Tags cancerous tissue with magnetic agents that are imaged with SQUID magnetometers. |

Table 3. Modalities under development for breast cancer detection

### 3.1 Optical imaging

Near infrared imaging is a simple method to determine the optical properties of tissues. It involves placing a light source onto the surface of the tissue and detecting the diffusely reflected light via a fibre/ detector placed some distance from the source. Measurements made in this manner can be used to determine the concentration of different chromophores such as oxy (HbO2) and de-oxy (Hb) haemoglobin within tissue. Optical imaging provides a potential alternative modality to the current breast cancer detection techniques. Diffuse optical tomography (DOT) and spectroscopy (DOS) are non-invasive techniques used to measure the optical properties of tissues. In the near-infrared (NIR) spectral window of 600 - 1000 nm, photon propagation in tissues is dominated by scattering rather than absorption. Photons experience multiple scattering events as they propagate deeply into tissue (up to 10 cm). The technique is based on the study of functional processes and provides several unique measurable parameters with potential to enhance breast tumour sensitivity and specificity. Optical tomography provides a distinction between different tissues based on their optical properties obtained from measurements of transmitted light. The presence of various substances in biological tissues contributes to the absorption of light. Tissue optical absorption coefficients provide access to blood dynamics, total haemoglobin concentration, blood oxygen saturation, water concentration and lipid content. These tissue properties are often substantially different in rapidly growing tumours; for example, high concentrations of haemoglobin with low oxygen saturation are suggestive of rapidly growing tumours due to their high metabolic demand. (Vaupel et al, 1991, 1998 & Weidner, et al 1992). The main substances of interest in optical imaging of breast tissue are water, lipids, haemoglobin and melanin. Of particular interest is the facility to exploit the differences between the absorption spectra of oxy-haemoglobin and deoxy-haemoglobin at near infrared wavelengths to produce images of blood volume and oxygen saturation (Cheng et al, 2003 & Jiang et al, 2003).

Optical tomography involves transillumination of the breast using near infrared (NIR) light. Characteristic absorption by oxy- and deoxy- haemoglobin at NIR wavelengths can be exploited to yield oxygen saturation and blood volume information. This information can provide a distinction between the high vascularisation often associated with malignant lesions and benign or normal breast tissue. Cutler demonstrated the first use of light for breast imaging in 1929 (Cutler, 1929), but it was not until the mid 1980s that interest in the subject became widespread due to the emergence of new source and detector technologies (Hebden et al, 1997). The research activity in this field was further enhanced by the developments in computing technology, which allowed the use of algorithms to reconstruct images representing the optical properties contained within a three-dimensional volume. The constant improvement in processing speeds and detectors has made optical tomography a potential safe alternative imaging technique that, in combination with conventional imaging techniques, can provide greater specificity for breast cancer diagnosis.

In a recent study, a 32 channel time-correlated single photon counting system has been utilised to perform the test (Yates, 2005). Specific data extracted from a histogram of the times of flight of photons across the breast is used to reconstruct images of the optical properties. The reconstruction is performed using a non-linear, finite element based algorithm. One system is based on two rings of different diameters to which source and detector bundles are attached. Images displaying heterogeneous features that are unique to specific healthy tissues and reproducible are presented. Pre-diagnosed benign lesions can be identified but they are not always the most dominant feature. A single tumour is identified

as a dominant increase in absorption. The second system based on a hemisphere filled with a coupling fluid can also be used. Preliminary findings suggest second method provides superior information to the ring system due to its three dimensional capability and its ability to provide consistent coupling.

### 3.2 Electrical impedance based modalities

Trans-scan (T-scan) and electrical impedance tomography (EIT) modalities are based on the principle that tissues have different conductivities depending on their cell structure and pathology. Cancerous tissue causes alterations in the intracellular and extracellular fluid compartments, cell membrane surface area, ionic permeability, and membrane associated water layers. These histological biochemical changes within the cancerous tissue give rise to measurable changes in tissue electrical impedance. When a small alternating current is placed across the breast, the increase in electrical conductance and capacitance of the cancer tissue distorts the electric field within the breast and the resulting impedance map can be used to highlight a malignant area.

#### 3.2.1 Trans-scan (T-scan)

T-scan is an imaging technique that utilises the inherent differences in electrical impedance between neoplastic and normal tissue and maps noninvasively the distribution of the breast tissue electrical impedance and capacitance. It is a simple device that utilises measurements of electric impedance to distinguish between benign and malignant lesions. The methodology measures low-level bioelectric currents to produce real-time images of the electric impedance properties of the breast. It is considered that a T-scan used in addition to x-ray mammography can increase the specificity of breast cancer diagnosis. During a T-scan 1.0 to 2.5 mA of AC electrical current are generated by the system and conducted through the body via a metallic wand held by the patient. The scanning probe is then moved over the breast, and the current at the surface is measured. This information is then used to construct an image, which is immediately displayed on a computer screen. A gel is used between the skin and the scanning probe to improve the conductivity.

The technique employs relatively small and inexpensive devices and can detect small cancers down to 1 mm. The limitations of the method are that depth information is not available and microcalcifications cannot be detected. Furthermore T-scan cannot be used on patients with pacemakers and is less sensitive to larger tumours. The sensitivity and specificity of the T-scan have not yet been fully investigated, although values of 78% and 53 % respectively have been reported (Tetlow & Hubbard, 2000). T-scan has also been evaluated for symptomatic patients and women with screen-detected abnormalities. Patients undergoing both mammographic and T-scan examinations, which subsequently underwent excision or core biopsy, were retrospectively analysed. The results suggested that the T-scan is a useful addition to the assessment of patients, increasing diagnostic accuracy in terms of both sensitivity and specificity (Barter & Hicks, 2000).

#### 3.2.2 Electrical impedance tomography (EIT)

EIT uses the same principles as a T-scan but utilises a number of measurements obtained by applying different current distributions to reconstruct an image of the electric impedance of the whole breast. The quantities measured by EIT are related to the electric impedance at low frequencies via the Laplace equation. The solution of the Laplace equation is very

sensitive to noise in the measurements and so normalisation techniques are used. Most in-vivo images use linear approximating techniques which attempt to find a solution for a small change in resistivity from a known starting value. Until recently, this change in resistivity was measured over time, and so EIT images displayed physiological function. More recently anatomical images have been produced using the same reconstruction technique, but by imaging changes with frequency (Osterman, et al, 2000).
The advantages of using electric impedance devices are that they are much smaller and cheaper than other imaging modalities and use non-ionising radiation. Also in principle it is possible for EIT to produce thousands of images per second. Its main limitations are low resolution and large variation of images between subjects. The EIT technique still requires further research and development before it is approved for the detection of breast cancer.

### 3.3 Modalities based on histological examination and biomarkers

#### 3.3.1 Fine needle biopsy

If a breast lesion appears to be suspicious or is undefined following examination using the imaging methods described then the patient will undergo a biopsy. There are two degrees of biopsy: fine needle aspiration cytology and core biopsy. In the first biopsy technique a fine needle and syringe are used to obtain a small sample of cells from the suspicious area. If this sample is insufficient or the diagnosis remains inconclusive a core biopsy may be needed which requires a larger needle to remove a larger sample of cells. In both cases the procedure is painful and involves the extraction of potentially diseased tissue through healthy tissue. This is one of the main reasons for a considerable research activity for the development of non-invasive imaging techniques with greater specificity that can reduce the need for biopsy.

#### 3.3.2 Ductal lavage

Ductal lavage is a relatively newer technique used to detect pre-cancerous and cancerous breast cell changes in women who are at high risk for developing breast cancer. It is estimated that over 95% of breast cancers begin in the cells lining the breast ducts. Ductal lavage involves analysing cells that have effectively been washed out from the breast ducts using a breast pump or aspirator. The cells are studied under a microscope to determine whether they have malignant characteristics before they develop into breast cancer. This technique is still in its early stages of development and is a similar idea to the Pap smear used to test for cervical cancer.

#### 3.3.3 Tumour markers

These are substances produced by cancer cells and sometimes normal cells. They can be found in large amounts in the blood or urine of some patients with cancer. Less often, they can also be found in large amounts in the blood or urine of people who do not have cancer. There are many different kinds of tumour markers. Some are produced only by a single type of cancer. Others can be produced by several types of cancer. Most tumour markers used today are proteins or parts of proteins. They are detected by combining the patient's blood or urine with antibodies made to react with that specific protein. The results of any tumour marker test are considered with other laboratory test results and a thorough medical history and physical examination. The American Society of Clinical Oncology first published evidence-based clinical practice guidelines for the use of tumour markers in breast cancer in

1996, which are updated at regular intervals. Thirteen categories of breast tumour markers have been considered that showed evidence of clinical utility and were recommended for use in practice. These include: CA 15-3, CA 27.29, carcinoembryonic antigen, oestrogen receptor, progesterone receptor, human epidermal growth factor receptor 2, urokinase plasminogen activator, plasminogen activator inhibitor 1, and certain multiparameter gene expression assays. Not all applications for these markers were supported, however. The following categories demonstrated insufficient evidence to support routine use in clinical practice: DNA/ploidy by flow cytometry, p53, cathepsin D, cyclin E, proteomics, certain multiparameter assays, detection of bone marrow micrometastases, and circulating tumour cells (Harris et.al, 2007). However, as yet, there are no tumour markers that are useful for diagnosis of early stage breast cancer.

### 3.4 Thermal imaging techniques (TITs) for breast cancer detection

Thermography is based on the principle that metabolism and blood vessel proliferation in both pre-cancerous tissue and the area surrounding a developing breast cancer is almost always higher than in normal breast tissue. Developing tumours increase circulation to their cells by enlarging existing blood vessels and creating new ones in a process called neovascularisation or angiogenesis. This uncontrolled proliferation is considered to be of critical importance in the development of neoplastic condition. The tumour mass is unable to grow to a detectable size (2 $mm^3$) without the establishment of a new blood supply, since passive diffusion of nutrients and waste products is not sufficient for the growing tumour's metabolic requirements. Angiogenesis is induced as a result of the release of a variety of angiogenic peptides that may be produced by the neoplastic cells. These newly developed blood vessels are quite porous and provide easy access to the circulating immediately adjacent tumour cells. For this reason the propensity to metastasise has been related to the number of micro vessels found in a growing mass of tumour. (Nathanson et al, 2000; Wade & Kozolowski, 2007). This process frequently results in an increase in regional temperature of the breast and forms the basis of the thermal modalities for the detection of breast cancer.

The first recorded use of thermo-biological diagnostics can be found in the writings of Hippocrates around 480 B.C. Mud slurry was spread over the patient and allowed to dry. The body areas that dried first were thought to indicate underlying organ pathology. Since then continued research and clinical observations proved that certain temperatures related to the human body were indeed indicative of normal and abnormal physiological processes. There are two thermal based modalities that could have a very significant impact on the detection and diagnosis of breast cancer. These are named as infrared thermography and microwave radiometry. Both techniques detect the changes in the physiology of the tissue rather than evaluating the changes in the tissue anatomical and dielectric features. Figure 4 illustrates that the physiological changes (preclinical phase) in the tissue begin nearly eight years earlier before they become apparent in the form of mass of malignant tumour (Lundgren, 1981).

Although thermography is an appealing method of screening for breast cancer, research over the past 20 years has failed to produce a system that is reliable for such a purpose and therefore thermography is not a widely used modality. However, it is expected that advances such as computerised thermal imaging will provide significant improvement in the cancer detection rate but this remains to be seen. Furthermore, attenuation of infrared radiation in tissue is high. For this reason thermography will only ever be able to provide information on the surface temperature variations and so no depth information is available. This is a severe limitation of infrared thermography in detecting breast cancer.

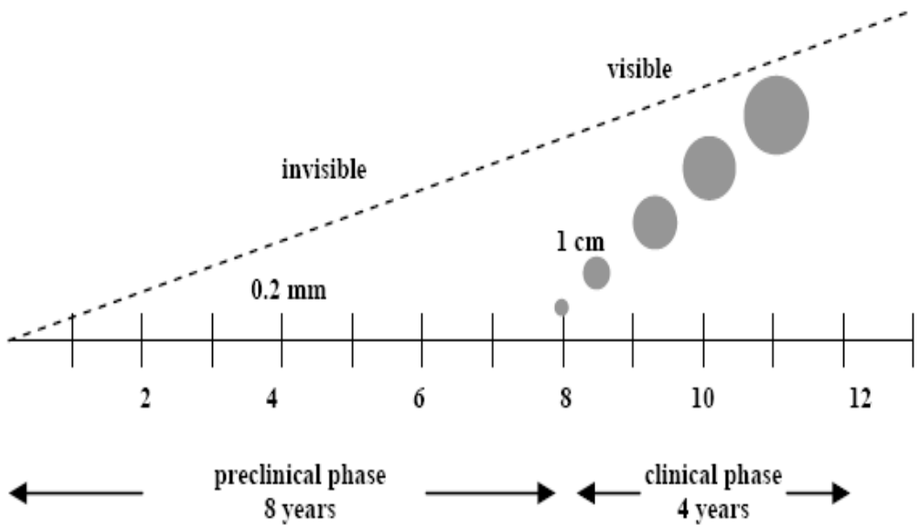


Fig. 4. Kinetics of tumour growth ((Lundgren, 1981)

### 3.4.1 Infrared thermography

Infrared thermal imaging has been used for several decades to monitor the temperature distribution over human skin. Abnormalities such as malignancies, inflammation, and infection cause localized increases in temperature that appear as hot spots or asymmetrical patterns in an infrared thermogram. Thermography, alternatively termed thermometry has been pursued for many years as a technique for breast cancer detection. Studies of thermography have focused on a range of potential uses, including diagnosis, prognosis, and risk indication and as an adjunct to existing technologies; however, the results have been inconsistent and scientific consensus has been difficult to achieve. The research activity in infrared thermography as cancer detection technique was diminished in the 1970s, but the recent technological advances have renewed the interest in the modality. Digital infrared cameras have much-improved spatial and thermal resolutions, and libraries of image processing routines are available to analyze images captured both statically and dynamically.

As an addition to the breast health screening process, infrared imaging has a significant role to play. Due to the technique's unique ability to image the metabolic aspects of the breast, very early warning signals have been observed in long-term studies. A breast tumour can raise the temperature of the skin surface by as much as 3 $^0$C compared with the temperature of the skin surface of a woman with normal tissue probably due to the elevated rates of tumour metabolism and elevated levels of vascularity and perfusion. It is for this reason that an abnormal infrared image may be the single most important marker of high risk for the existence of or future development of breast cancer. Furthermore, the proven sensitivity, specificity, and prognostic value of the modality, makes infrared imaging one of the frontline methods for breast cancer screening. The diagnosis of cancer is based on the difference in temperature relative to that for the contralateral breast, which serves as a built-in control. The procedure is non-invasive and does not require compression of the breast or radiation exposure.

### 3.4.2 Microwave radio thermometry (MRT)

The National Cancer Institute (NCI) in the United States of America has funded numerous research projects to improve conventional and develop new technologies to detect, diagnose, and characterize breast cancer. According to the U.S. Institute of Medicine, an ideal breast screening tool is a low risk device that is sensitive to tumours, detects breast cancer at a curable stage, non-invasive, simple to use, cost effective and widely available. The device should also involve minimal discomfort to the user and provides easy to interpret, objective and consistent results. Of particular importance is the ability to clearly distinguish between malignant and benign tumours and early detection. A brief review of the published literature shows that all techniques have limited capability in these respects and surgery is required to establish the nature of the tumour. The research in this area is time consuming since the ultimate test of a technique beyond the proof of concept stage must be clinical trials.

Microwave radio thermometry (MRT) is a modality that uses non ionising electromagnetic radiation for cancer detection in humans. The technique has attracted a great deal of research in the last three decades. An electromagnetic imaging method can be active or passive. In an active system, one or more antennas radiate onto the body, where the electromagnetic field is scattered by tissue dielectric inhomogeneities and then received by the same or other antennas. In multi-frequency active imaging, data is collected at various frequencies and for various locations of the antennas outside the body [Liu et al, 2002; Meaney et al, 2000]. Field data are known terms in the inverse scattering problem, whose solution attempts a retrieval of the contrast of an eventual dielectric anomaly with respect to the background permittivity of healthy tissues. On the other hand time-domain systems exploit higher frequencies and wide-band antennas showing some similarity to ground penetrating radar [Fear & Stuchly, 2000; Li et al, 2004].

Thermal imaging methods include both infrared and microwave radiometry modalities. Both methods detect physiological tissue response, rather than evaluating anatomic dielectric features. Heat is released from the body on the whole electromagnetic spectrum with a maximum at infrared frequencies. There are several physiological features that are related to malignant tissue, which may contribute to the infrared signal. These include increased blood flow in the area surrounding a malignancy, angiogenesis, and the release of vasoactive mediators. The infrared imaging system uses a camera that is highly sensitive to infrared radiation in the appropriate spectrum. Microwave radiometry is based on the measurement of the electromagnetic field spontaneously emitted by a body in the microwave frequency range [Bardati & Solimini, 1983; Edrich, 1979; Leroy et al, 1998; Meyer et al, 1979]. Charged particles in motion are primary sources of incoherent thermal radiation propagating inside the body, where it is partially absorbed and partially radiated externally. Antennas located in the vicinity of the body collect and changes the radiation to an electrical current that fluctuates in the receiver's input unit. Assuming that the body is in a thermodynamic equilibrium, the spectral content of the radiometric signal can be related to the local temperature distribution in the body, allowing its retrieval to be attempted from radiometric data collected at different frequencies and for various antenna positions. A thermal anomaly may be a significant indicator of a malignancy.

The fundamental basis for developing a microwave imaging technique for detecting breast cancer is the significant contrast in the dielectric properties, at microwave frequencies, of normal and malignant breast tissue, as evidenced by experimentally measured data [Li et al, 2005; Bardati et al 2002]. The estimated malignant-to-normal breast tissue contrast is

between 2:1 and 10:1, depending on the density and water content of the different tissues. Therefore, microwave modality does not offer the potential for the high spatial resolution provided by X-rays, but it does permit exceptionally high contrast with respect to physical or physiological factors of clinical interest, such as water content, vascularisation or angiogenesis, blood-flow rate, and temperature. Microwave imaging techniques result in a three-dimensional (3-D) volumetric mapping of the relevant tissue properties, and thus offer in situ 3-D positioning of the tissue abnormalities. Furthermore, microwave attenuation in normal breast tissue is low enough to make signal propagation through even large breast volumes quite feasible (~ 4 cm). For these reasons, microwave breast imaging has the potential to overcome some of the limitations of conventional breast cancer screening modalities.

Microwave systems in use or under development may be categorised into three types: passive, active or hybrid. However, the passive technique has been investigated for many years, with clinical trials undertaken with the availability of commercial units that are currently used mainly in conjunction with mammography. The passive method detects regions of increased temperature due to the tumour from the very small "natural" microwave signal from the breast (black body radiation as given by Planck's law). The signals detected are very low and require sensitive electronic systems. Temperature differentials between adjacent areas on the breast are taken as an indication of an abnormality, using a similar area on the other breast as a reference – the approach is somewhat empirical. The increased tumour temperature is thought to arise from "vascularisation" (angiogenesis). There is a great deal of ongoing research, which is related to the development of thermal models of the breast to relate the measured temperature differentials with temperature rises located in the tissue. There is also a considerable focus for the last few years in the USA on the development of detecting antennas. There is evidence that the passive MRT technique can detect malignant tissue abnormality at an early stage, but as yet this cannot be taken as an established fact.

Current understandings of the underlying pathological mechanisms for increased temperature in breast cancer are that breast cancer cells produce nitric oxide, which interferes with the normal neuronal (nervous system) control of breast tissue blood vessel flow by causing regional vasodilation in the early stages of cancerous cell growth, and enhancing angiogenesis in the later stages. The subsequent increased blood flow in the area causes a temperature increase relative to the normal breast temperature, and even deep breast lesions may also contribute to the detectable increase in the heat evolved. These changes relate to physiological breast processes. It is believed that in healthy individuals, temperature is generally symmetrical across the midline of the body. Subjective interpretation of many diagnostic imaging modalities, including microwave thermometry and infrared thermography, rely on the normal contralateral images are relatively symmetrical, and the likelihood that small asymmetries may indicate a tissue abnormalities. Therefore, in breast cancer, thermography/thermometry detects disease by identifying areas of asymmetric temperature distribution on the breast surface.

Microwave radiometry is used for diagnosis of diseases by measuring small changes of internal tissue temperature. The detection and diagnosis is conducted by measuring the intensity of natural electromagnetic radiation of patient's internal tissues at microwave frequencies. The intensity of radiation is proportional to the temperature of the tissues. Cancerous tumours have a significantly different index of refraction and the internal tissue temperature often changes due to inflammation changes in the blood supply or with

increased metabolism of cells during oncological transformation of tissues. Microwave radiometry measures the emission of natural radiation from the body in the microwave, or centrimetric, region of the electromagnetic spectrum. All materials above absolute zero emit natural, thermally generated electromagnetic radiation. At body temperature of 37°C the maximum intensity of radiation occurs in the infrared part of the spectrum at wavelengths close to 10 μmeters (Fraseri et al, 1987).

Microwave thermometry may be envisioned as the microwave analogue of infrared thermography (Barrett, et al, 1980). Whereas infrared thermography uses wavelengths of 10 mm (typical), microwave thermometry makes use of much longer wavelengths, typically 1 - 20 cm; this leads to important and fundamental differences between the two techniques as described in the literature(Barrett & Myers, 1975a, 1975b; Barrett et al, 1977, 1980). Microwave radiation is capable of penetrating human tissue and therefore the emission provides information related to subcutaneous conditions within the body. The intensity of microwave emission is linearly proportional to the temperature of the emitter. Therefore, microwave thermometry provides information related to internal body temperatures. The depth of penetration, and hence the depth from which microwave radiation may escape from the body, depends on the wavelength, the dielectric properties of the tissue and the water content of the tissue. Furthermore, the frequency used for microwave breast imaging needs to be low enough to provide adequate depth of penetration, but high enough to allow the use of small antenna array elements. The final resolution of the image depends on both the number of antenna array elements and the frequency. In general, resolution increases with frequency and the number of antenna array elements. In order to obtain useful images, there must be significant contrast between normal and malignant tissue and the greatest contrast in breast tissue occurs in the frequency range 600 MHz-1 GHz.

The distinctive feature of microwave radiometry is an extremely low signal strength entering input of the antenna from the biological tissues. This signal strength is approximately $10^{-13}$ Watt. While conducting the measurement it is necessary to distinguish temperatures differing on a tenth part of degree, which corresponds to signal strength to be $10^{-16}$ Watt. Therefore the special circuits are required for receipt, amplification and treatment of signals. So far, the application of microwave radiometry has been directed at the early detection and diagnosis of breast cancer. Present breast cancer detection techniques, other than radiometry, require that the tumour must have significant mass and contrast with respect to the surrounding tissue (i.e., palpation physical examination, mammography and ultrasound). This results in approximately 85 percent of all determinations of breast disease undergoing extensive surgical procedures. Early detection could lead to a more conservative treatment and a positive attitude toward detection. The diagnosis of breast cancer at a smaller size or earlier stage will allow a woman more choice in selecting among various treatment options.

The passive MRT method is a non-invasive, non-ionizing procedure that determines the thermal activity of the tissue rather than mass and therefore when used in conjunction with one or more other detection modalities, could provide early indication of breast with good accuracy. The determination of thermal activity is a measurement of tumour activity, or growth rate, providing data beyond the physical parameters (i.e., size and depth determined by mammography). Suspicious results found by screening using microwave radiometry could then be referred for further investigation by mammography and other appropriate techniques. Medical microwave radiometry has a number of positive characteristics as follows:

- Early diagnosis of diseases;
- Possibility of non-invasive detection of disease in internal organs before the appearance of structural changes that can be detected by X rays or ultrasound;
- Completely harmless for the patients of all age and with any diseases as well as for medical staff;
- Possibility to conduct the investigation repeatedly (control of treatment):
- Depth of anomaly detection is from 3 to 10 cm;
- Accuracy of measuring the internal averaged temperature ± 0,2 $^{O}$C
- Simplicity of the device handling, the procedure may be conducted by the secondary medical staff.
- Time measuring of one point: 5 – 15 sec.

### 3.5 The concept of the smart bra as an early warning system for breast cancer

The concept of wearable early warning system for breast cancer is under investigation at the Institute of Materials Research and Innovation (IMRI), University of Bolton. The researchers are working on the development of a wearable system that integrates the passive microwave antennae with textile structures. The basic concept of this approach is to present the microwave antennas to the breast in the form of a 'Smart Bra'. Work on developing antenna systems and microelectronics is being carried out. Miniaturisation of the radiometer, antennae and electronics and there integration with appropriate textile structures are the main thrusts of the research and development programmes in progress. It remains to be established how much of the electronics would be mounted on the bra and how critical accurate positioning of the sensors would be. The incorporation of the electronics is the critical part of the research and development programme. Work is also in progress on the development of wearable breast cancer device at De Montfort University, Leicester, UK. This is a low frequency active electrical impedance tomography (EIT) based system, which utilises the differences in electrical properties between healthy and malignant breast tissues and the researchers have introduced the concept of a "Smart Bra" which allows the impedance tomography to be carried out conveniently and rapidly. However, the microwave radio thermometry modality being adopted by the Bolton team is non-contact and passive whereas the EIT is an active modality albeit at low power levels. In the following sections the concept of MRT based wearable early warning system for breast cancer is described.

The microwave radiometer is a device which measures the intensity of electromagnetic radiation from human body in microwave wave length. The noise power at the input of the microwave receiver is proportional to the internal temperature of human body. An array of receivers can resolve the local temperature inside the breast in 3-D and hence provide a signature of local temperature differences inside the breast. The geometrical resolution is determined by the element number and the bandwidth and frequency of operation. Tumour detection relies on temperature difference resolution, which is a function of the noise figure of the receiver, its stability and the bandwidth as well as the test integration time (Skou, 2006).

Traditional microwave radiometers for breast cancer detection known from literature and available on the market are rather large and heavy in weight. Today, only one relatively compact model of microwave radiometer (RTM-01-RES) is available in the market. The radiometer receives energy-emissions from the human body using an infrared sensor and a

microwave sensor. The weight of internal temperature sensor is rather high and consequently it is not possible to incorporate such a device in a self-powered wearable system. It is therefore necessary to design miniature balance zero Microwave Radiometer and the Microwave Multi-Channel Electron Switch (MMCES). Miniaturization is essential for both technical reasons, achieving direct coupling to antenna and good stability, as well as for integration into textiles for maximum comfort. In traditional microwave systems antennae are fabricated on rigid substrates, as wires or as hollow structures. Antennae on textiles have been demonstrated earlier but only with limited design variations, mainly as microstrip patch or slot antennae (Klemm et al, 2004, 2005; Locher, 2006; Klemm & Troester, 2005, 2006; Behdad, 2004; & Alomainy et al, 2005). There is a need to explore different structures especially in view of multi-frequency or wideband operation.

The relevant accuracy of measuring the noise power at the input of the receiver is ~ $10^{-3.}$ The dielectric constant of a person may change dramatically from 5.5 for fat breast to 50 for muscle. Therefore, the reflection coefficient between antenna and human body tissue may change significantly and as a result about 10% of energy may be reflected from the antenna. However, the accuracy of noise power measurement should remain unchanged. In order to solve this problem it is necessary to use zero balance radiometer with compensation of reflections between antenna and human body tissue. This principle is used in most modern microwave radiometers (Leroy et al, 1998, Hand et al, 2001 & Lee et al, 2002). An overview of microwave radiometry is given in a recent publication (Hand et al, 2001). The balance multi-frequency microwave radiometer has also been described (Leroy et al, 1998). These researchers used 5 frequencies in calculating the temperature profile in the brain. It is very important to use multi-frequency radiometer in order to visualize the temperature inside body. But the increase in the number of frequencies increases the sizes and the weight of the radiometer and decreases the noise imperviousness of the device. The radiation from human body is very small therefore the noise immunity is one of the critical parameters of the microwave radiometer.

It is expected that the multi frequency radiometer will have better accuracy for breast cancer detection in comparison with a single channel radiometer, but it is not evident that the sensitivity will increase greatly. Thousands of measurements during 10 years with the microwave radiometer (RTM-01-RES) have shown that there are about 10 % of breast cancer patients who have no skin temperature increase or brightness temperature increase (Burdina et al, 2005). Thus the probability that these patients will have temperature increase at another frequency is not very high. Due to the weight and sizes limitations for a wearable system, there is no reason to use more than two frequencies. Furthermore, skin temperature information is very important for breast cancer detection.

The fluctuation error of radiometer is dependent on time of integration, the bandwidth and losses of the microwave part of the receiver. Usually for the receiver's bandwidth of 500-600 MHz the measurement time is 5 seconds and fluctuation error is 0.1°C. The increase of bandwidth may decrease the fluctuation error. Another possibility to decrease the fluctuation error is to increase the integration time. Monolithic microwave integrated circuit (MMIC) provides the opportunity to increase the bandwidth of microwave device greatly. Furthermore, for wearable, self-examination devices the time of measurement is not a very important factor, therefore, the fluctuation error may be minimized by choosing the proper value of integration time.

It may be possible to combine a single channel microwave radiometer and a MMCES. In this case, the results of brightness temperature measurement will highly depend on the environment temperature, due to the losses in the MMCES. To overcome this problem, it is necessary to use balance zero radiometer and balance the losses of MMCES and losses of reference noise source. In this situation the losses of MMCES do not decrease the performance of radiometer. Furthermore, it is possible to minimise the losses in MMCES by the utilization of integrated radiometer front-ends. The integration requires the design and fabrication of microwave monolithic integrated circuits with ultra low-noise performance. This can be achieved using state-of-the-art MMIC fabrication processes. Such components are very compact (few square millimetres) and therefore minimize losses and temperature variations. The employed fabrication processes can achieve amplifiers with noise figure below NF<0.5 dB with high gain resulting in excellent radiometer performance (Dabrowski et al, 2004). However, these devices are either large and operate at cryogenic temperatures or are relatively narrowband. There is a need to especially focus on the development of wideband for multi-frequency receiver in order to improve the overall system performance. Yet, another possibility is the introduction of multi-receiver system alleviating the need for an MMCES. This however requires identical channel operation, which can only be fabricated using identical components. In the development of MMIC for the radiometer front-end such a technique becomes feasible.

Introduction of microelectronic microwave components close to the antenna requires appropriate textile integration technologies. This aspect has been dealt within various publications both with woven and nonwoven materials (Catrysse et al, 2004; Coosemans et al, 2005; Hermans et al, 2005; Van Langenhove et al, 2003a, 2003b; Scilingo et al, 2005 & Paradiso et al, 2005). However, only little data is available on the microwave properties of different woven and nonwoven materials (Locher, 2006). Interconnection to the microwave monolithic integrated circuit is an important area of research and development. One possible approach is the implementation of ribbon type interconnects, which can efficiently be used for power supply and low frequency output signals. The active components need to be developed with MMIC operating over a wide range. Low-noise amplifiers determine the overall noise performance of the receivers. Very wideband performance has been demonstrated in GaAs and CMOS technologies, respectively (Nosal, 2001; Jung et al, 2006; Xu et al, 2005 & Wang et al, 2005). However, in most cases a noise figure NF>1.0 dB over a frequency range of DC – 10 GHz has been achieved. There is a need to design amplifiers complying with the frequency range of DC – 10 GHz, but exhibiting a noise figure NF < 1.0 dB with an associated gain of G > 30 dB. These parameters are well beyond the state-of-the-art today. There is a need to develop MMIC components that can be used for the assembly of the microwave radiometer system. Figure 5 shows one possible functional scheme of Multi-Channel Microwave Radiometer.

Multi-Channel Microwave Radiometer's development consists of the following stages.

- Designing of Multi-Channel switch.
- Designing of Radiometer's microwave parts
- Designing of radiometer's digital part and analog low-frequency part of feedback circuit.
- Software design for visualization of the measurements and for the radiometer's microcontrollers.

Microwave radiometer consists of an electronic switch, circulator, isolator, low-noise amplifier, filter, amplitude detector and miniature reference noise source with the temperature sensor. All of these components parts must be designed in miniature sizes using MMIC and plastic materials.
There are two critical parameters which define Radiometer's quality:

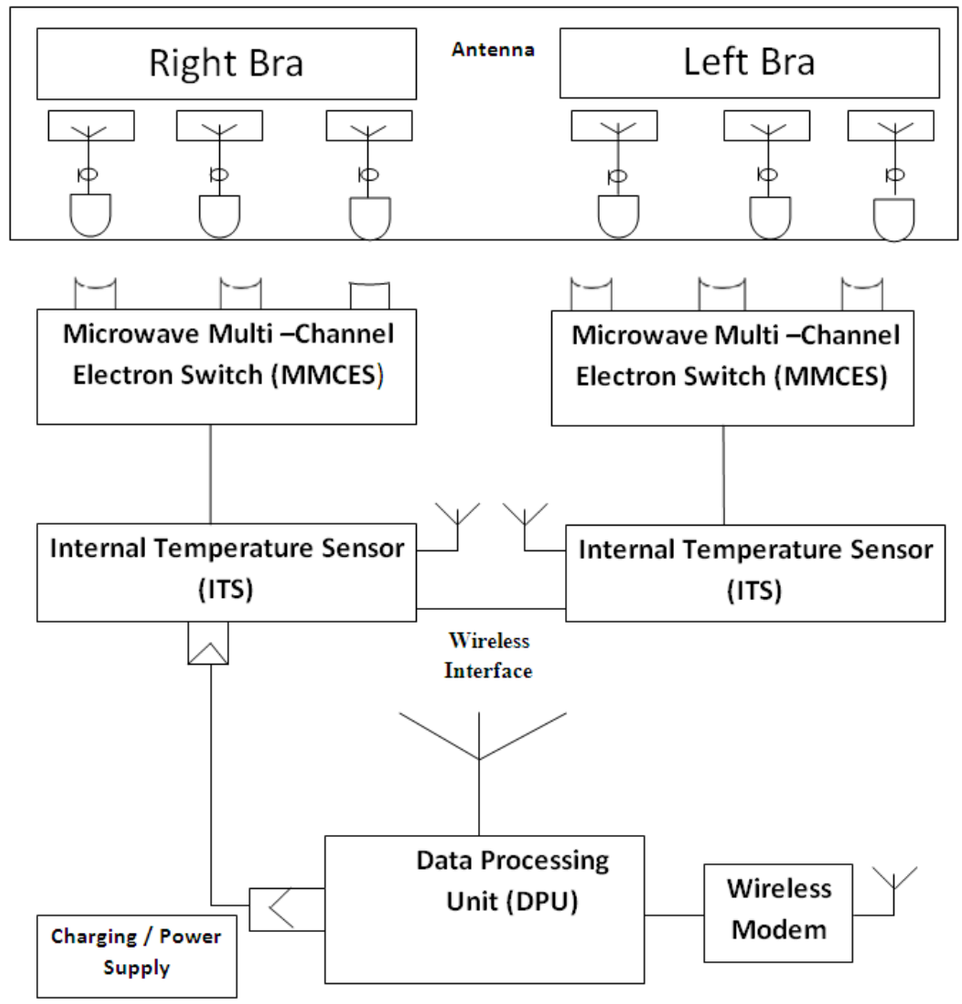


Fig. 5. The functional scheme of Multi-Channel Microwave Radiometer

1. Brightness temperature error when the reflection's coefficient of antenna changes.
2. Brightness temperature error when the environment's temperature changes.

The over arching aim of the research in progress on the development of wearable breast cancer detection system is to deliver a miniaturized microwave technology, Multi-frequency Microwave Radiometry (MFMWR), which is a totally non-invasive and passive method for cancer detection. It is proposed to use microwave radiometry (MWR) to detect the "hot spots" (the cancerous regions) in the breast tissue. This technology was initially used in the field of astrophysics, measuring the minute amounts of microwave energy emitted by stars and planets. The same principle can be used for medical diagnostics (Chaudhary, 1984), as anything that can absorb radiation also emits radiation. In MWR, the power in the

microwave region of the natural thermal radiation from body tissues is measured to obtain the brightness temperature of the tissue under observation. The brightness temperature at an antenna centre frequency $f_i$ is,

$$T_{B,i} = \frac{P_i}{k\,df_i} = \frac{(1-R_i)\,P_{tissue,i}}{k\,df_i} = (1-R_i)T_{B,tissue,i} \tag{1}$$

Where $P_{tissue,i}$ is the thermal radiation power emitted by the tissue, $P_i$ is the power received by the antenna in a bandwidth $df_i$ around $f_i$, $R_i$ is the power reflection coefficient at the skin-antenna interface at $f_i$ and $k$ is Boltzmann's constant.
According to the Rayleigh-Jeans law, at microwave frequency $f_i$, the thermal radiation intensity is proportional to the absolute temperature, so that

$$T_{B,i} = \int_{\Omega} W_i\,T(r)\,dv \tag{2}$$

where $T(r)$ is the absolute temperature in a tissue volume of $dv$ located at $r$, $W_i(r)$ is the receiving antenna's weighting function and the integration is over the antenna's field of view Ω.
It can be seen that (equation 1) that the brightness temperature $T_{B,i}$ is dependent upon the temperature in the tissue $T_{B,tissue,i}$ and the reflection coefficient R. For balance zero radiometer with the compensation of the reflection on the border antenna and tissue the reflection from the tissue is compensated by thermal radiation of the radiometer and the brightness temperature is independent of reflection coefficient R. Therefore, for non-invasive detection of temperature abnormalities it is possible measure the power radiation P from the tissue.
Thus the measured brightness temperature at frequency $f_i$,

$$T_{B,i} = \frac{\int_{\Omega} W_i\,T(r)\,dv}{1-R_i} \tag{3}$$

The receiving antenna's weighting function depends upon its operating frequency and microwave attenuating properties of the tissues, as well as antenna characteristics. Microwave reflections occur at interfaces between different tissue regions and between these regions and the measuring equipment. Since the attenuation of microwaves in tissue and the antenna characteristics are frequency dependent, the temperature-depth profile within the tissue beneath the antenna can be found using a multi-frequency radiometer and a stable solution to the inverse problem of retrieving the temperature-depth dependence from a set of measured brightness temperatures. The human body's tissues have different permittivities therefore the reflection coefficient of the antenna for diverse people or in different tissues can reach 10%. This fact can decrease noise power at the input on the radiometer. But brightness temperature cannot change in spite of the fact that the brightness temperature is proportional to noise power at the input on the radiometer. This problem can be overcome by balance zero radiometer with sliding scheme of the reflections compensation.
Evidently the temperature of microwave part of the radiometer may change greatly. This leads to noise power change at the input of the radiometer. If the front-end loss of

radiometer is about 1 dB, one degree change in the environment temperature will lead to brightness temperature change in 0.4 degree. This is why the radiometer input circuits temperature is usually stabilized. But this is not feasible for the wearable self-powered detection system because of the power demand. For balanced radiometer it is possible to optimize parameters of input circuit including Multi-Channel Switch and the reference noise source circuit to minimize error due to environment temperature changes. However, if the losses of microwave part of radiometer do not change in time, the error due to environment temperature change can be compensated. For this purpose it is necessary to measure the front-end temperature. This principle was successfully used in industrial single-channel radiometer (RTM-01-RES) and can be applied to the multi-channel radiometer. For this purpose it is important to measure antenna array temperature and to transmit this information to the radiometer. Software is a need for visualisation of the results of the measurements and the database storage in the control centre. It is vital that radiometer should monitor the function of its various components appropriately, estimate the measurement error and transmit this information to the central database by wireless connection. This allows the estimation of the radiometer's accuracy automatically. Fabrication of the breast cancer microwave screening system also requires the development of the hardware for the system.

Microwave thermometry is the detection of microwave radiation from the human body and may be considered as the microwave equivalent of infrared thermography. Infrared thermography typically uses wavelengths of 10 μmetre, whereas in microwave thermometry much longer wavelengths are employed (1 -20 cm). The other major differences between the two modalities can be summarised as following:

- Microwave radiation is capable of penetrating human tissue and therefore the emissions can provide useful thermal signals related to the subcutaneous conditions within the body. On the other hand, infrared radiation is not able to penetrate such depths and therefore is able to detect conditions close to the surface i.e. skin.
- The intensity of microwave emission is linearly proportional to the temperature of the emitter. Therefore a measurement of the emission may be easily related to the temperature of the emitter. Infrared intensity measurements may also be related to the body temperature but this relationship is somewhat nonlinear.
- Microwave emission gives coarser spatial resolution (~ 1cm) than infrared because of its longer wavelength than infrared (~1mm). This supposes that microwave thermography provides information about internal body temperatures. The depth of penetration, and hence the depth from which microwave radiation may escape from the body, depends on the wavelength, the dielectric properties of the tissue, and, most importantly, on the water content of the tissue.

Development of a wearable, self-powered early warning system for breast cancer will also require the production of textile structures that are flexible, comfortable, breathable, light and suitable for integration with the materials developed to perform various functions to operate the cancer detecting devices produced. Conducting fibres and filaments are needed to produce fabrics using a range of mechanical conversion methods, particularly knitting, crochet or braiding to produce the developmental materials. The structures then need to be characterised and optimised. Conducting fabrics can also be prepared using chemical methods, including coating, printing and lamination. Wet chemical methods and dry methods can be employed for this purpose. The integrated textile structures must be tested for their efficiency, durability, launderability, mechanical and comfort properties. Finally, the integrated textiles need to be converted into wearable structures to act as cancer detection devices.

## 4. Conclusions

At present x-ray mammography is the most commonly used breast imaging technique and is the only modality used for routine screening. X-ray mammography has become the "gold standard" for breast imaging. The technique has a high sensitivity and is able to detect very small tumours and calcifications. The main limitations of x-ray mammography are that it has a poor specificity for some tumour types and that it is unsuitable for use on women with dense breasts. In addition, x-ray mammography uses ionising radiation and usually causes considerable discomfort to the patient. Thus there is potential for an alternative technique to replace x-ray mammography or to be used as an additional resource to improve the overall specificity of the diagnosis. As discussed MRI, ultrasound and Nuclear medicine are currently used to provide additional diagnostic information, but all have their limitations and are not alternatives to mammography. Other techniques are currently being investigated such as EIT and infrared thermography but as yet these have severe limitations in resolution and specificity. Thus there still remains a niche for an additional imaging modality to aid in the early detection and diagnosis of breast tissue oncological abnormalities.

Microwave radiometry (MRT) appears to be an attractive alternative modality for breast imaging. MRT can be used effectively in breast cancer investigation. The method has many advantages over the currently used breast cancer detection techniques:

- Oncological changes in tissues could be detected earlier using MRT as compared to the classical methods based on ultrasounds and ionising radiation
- Breast cancer detection is made at a curable stage
- The technique is non-invasive and non-hazardous both to the patient and the device operator.
- MRT is easy to use, cheap and fast
- Involves no risk for patients of any age
- Involves a minimum discomfort for patient, easily accepted by women - is easy to interpret and objective.

The MRT can be used repeatedly to improve cancer detection rates and monitor the progress of cancer treatment. Using microwave radiometry in conjunction with other traditional modalities can significantly improve the diagnosis, especially for the patients with fast growing tumours. Studies show that breast thermometry has the ability to warn a woman that a cancer may be forming many years before any other test can detect the condition. The major gaps in knowledge can be addressed by more robust research on the technologically advanced microwave thermometry devices and large-scale, prospective randomised trials for population screening and diagnostic testing of breast cancer. The MRT system components can be miniaturised and integrated with textiles to produce wearable early warning systems for breast cancer.

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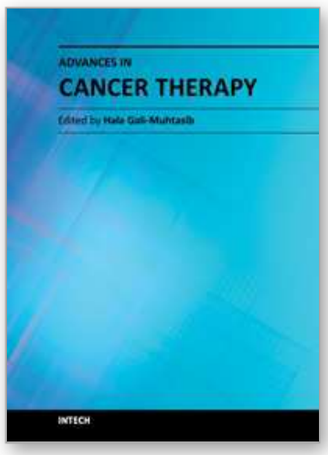


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