CHAPTER 1

INTRODUCTION AND SCOPE OF THE THESIS

1.1 INTRODUCTION: BREAST CANCER

The term “breast cancer” refers to a malignant tumor that has developed from cells in the breast. Usually, it begins in breast tissue, which is made up of glands for milk production, called lobules, and the ducts that connect the lobules to the nipple. Less commonly, it can begin in the stromal tissues, which include the fatty, fibrous connective tissues and lymphatic tissues of the breast [1, 2].

Collectively, United States of America (USA), India and China account for almost one third of the global breast cancer burden. In USA, 232,714 women were newly detected with breast cancer and 43,909 women died with the same in 2012. For every 5 or 6 women newly diagnosed with breast cancer, one lady is dying of it. In India, 144,937 women were newly detected with the disease and 70,218 women died with the same. For every 2 women newly diagnosed with the disease, one lady is dying due to the same [3]. The incidence of breast cancer had also increased from 25.9% in the year of 2008 to 27% in 2012. In the year 2012, there were about 2,32,000 breast cancer cases reported in USA, whereas in India 1,45,000 new cases were diagnosed. This implies that, though, because of India's population, the percentage of total women affected seems less, the breast cancer burden in India has almost reached about two out of thirds of that of the USA and is steadily rising. For the years 2015, there will be an estimated 1, 55,000 new cases of breast cancer and about 76,000 women in India are expected to die of the disease [3]. For decades together, cervical cancer was the most common cancer in women in India and more deaths were attributed to cervical cancer than any other cancer. But
over last ten years or so, it has been rising steadily, and for the first time in 2012, it is the most common cancer in women in India, the way ahead of cervical cancer [4].

In early stage, it usually does not cause symptoms. This is why regular breast exams are important. As the cancer grows, symptoms may include: i). breast lump or lump in the armpit that is hard, has uneven edges, and usually does not hurt; ii). change in the size, shape, or feel of the breast or nipple - for example redness, dimpling, or puckering that looks like the skin of an orange; iii). fluid coming from the nipple - may be bloody, clear to yellow, green, and look like pus; iv). men can get breast cancer, too. Symptoms include breast lump and breast pain and tenderness. Symptoms of advanced breast cancer may include: i). bone pain; ii). breast pain; or discomfort; iii). skin ulcers; iv). swelling off in the armpit (next to the breast with cancer); and v). weight loss.

Gender being a woman is the main risk factor for developing breast cancer, because of the female hormones estrogen and progesterone. The risk for the disease increases with age [5]. About 5% to 10% of breast cancer cases are thought to be hereditary. The most common cause of hereditary disease is an inherited mutation in the BRCA1 and BRCA2 genes. Other gene mutations like ATM, TP53, CHEK2, PTEN CDH1, and STK11 can also lead to inherited diseases. A woman with cancer in one breast has a 3- to 4-fold increased risk of developing a new cancer in the other breast or in another part of the same breast. Women with a family history of breast cancer also have an increased risk of breast cancer.

White women are likely to develop breast cancer than are African-American women. Breast density, age, menopausal status, the use of drugs (menopausal hormone therapy and birth control drugs), more menstrual cycles, pregnancy, usage of alcohol, obese after menopause and genetics are also some other risk factors. Woman, who had radiation therapy in the chest area as treatment for another cancer, is increased risk for breast cancer. Diet and vitamin intake, chemicals in the environment, tobacco smoke, night work are some of the unproven and unclear factors for the disease.
Obesity (BMI more than 30), overweight (BMI=25-30), meat consumption more than three times in a week, smoking, physical activity less than 5.5 h/w, first pregnancy more than 30 years old, not having live birth and education more than 12 years were the risk factors for the breast cancer in women [6] in a study carried out in EMRO population. Takalkar et al (2014) reported that strong positive association of positive family history in first degree relatives, number of abortions and past history of benign breast disease, were the major risk factors in Indian women with breast cancer [7].

Kamath et al (2013) in their study reported significant (p<0.05) unadjusted risk of breast cancer for the women with education more than 7 to 12 years, non vegetarian diet, age at menarche more than 13 years, age at first child birth more than 30 years and induced abortion [8]. Prevention strategies of breast cancer identified so far; to all women are maintenance of a healthy body weight, regular physical activity, moderation of alcohol intake and chemoprevention [9].

Therapies for breast cancer include chemotherapy, radiation therapy, hormone therapy, targeted therapy and surgery. Chemotherapy is treatment with cancer-killing drugs that may be given intravenously or by mouth. When therapy is given to patients with no evidence of cancer after surgery, it is called adjuvant therapy. Chemo given before surgery is called neoadjuvant chemotherapy. Chemo side effects depend on the type of drugs, the amount taken, and the length of treatment. Some of the most commonly used drug combinations for early breast cancer are: CAF (or FAC), 5-FU, TAC, AC → T, FEC: → T, 5-FU, TC, TCH. Platinum agents (cisplatin, carboplatin), Vinorelbine (Navelbine®), Capecitabine (Xeloda®), Liposomal doxorubicin (Doxil®), Gemcitabine (Gemzar®) etc. Some of the most common possible side effects include hair loss, mouth sores, loss of appetite or increased appetite, nausea and vomiting, and low blood cell counts [10].

Radiation therapy is treatment with high-energy rays or particles that destroy cancer cells. Radiation to the breast is often given after breast-conserving surgery to help lower the chance that the cancer will come back in the breast or nearby lymph nodes. Radiation may also be recommended after mastectomy in
patients either with a cancer larger than 5 cm, or when cancer is found in the lymph nodes. Radiation therapy can be given in two main ways. The radiation is focused from a machine outside the body on the area affected by the cancer EBRT (External Beam Radiation Therapy). Brachytherapy, also known as internal radiation, is another way to deliver radiation therapy. Instead of aiming radiation beams from outside the body, radioactive seeds or pellets are placed into the breast tissue next to the cancer. Woolf et al (2014) compared the treatability of Targeted Intraoperative radiotherapy (TARGIT-IORT) with EBRT. The TARGIT-IORT treatment is completed with a single fraction, whilst EBRT requires at least 15 fractions [11].

Hormone therapy is another form of systemic therapy. It is most often used as an adjuvant therapy helping to reduce the risk of the cancer coming back after surgery, but it can be used as neoadjuvant treatment, as well. It is also used to treat cancer who has come back after treatment or has spread. Examples are Tamoxifen, Toremifene (Fareston®), Fulvestrant (Faslodex®) [12]. Some newer drugs specifically target the gene changes. Examples are Ado-trastuzumab emtansine (TDM-1, Kadcyla™), Pertuzumab (Perjeta®), Lapatinib (Tykerb), Everolimus (Afinitor®), Bevacizumab (Avastin®) etc.

Most women with breast cancer have some type of surgery. Surgery is often needed to remove a breast tumor. Options for this include breast-conserving surgery and mastectomy. The breast can be reconstructed at the same time as surgery or later on surgery is also used to check the lymph nodes under the arm for the cancer spread. Options for this include a sentinel lymph node biopsy and an axillary (armpit) lymph node dissection. Different types are; partial (or segmental) mastectomy: removal a part of the affected breast. Lumpectomy removes only the breast lump and a surrounding margin of normal tissue. Quadrantectomy removes more breast tissue than a lumpectomy. Mastectomy (simple mastectomy, skin-sparing mastectomy, modified radical mastectomy, radical mastectomy) removes the entire breast. To determine if the breast cancer has spread to axillary (underarm) lymph nodes, one or more of these lymph nodes may be removed and looked at under the microscope. The types are Axillary lymph node dissection (ALND), Sentinel lymph node biopsy (SLNB).
Wang et al (2010) evaluated the diagnostic performance of infrared imaging of the breast using age adjusted multivariate model. In their study, the radiologists read the infrared (IR) images based only on the findings at the lesion sites of concern and scored the findings according to the five independently diagnostic IR signs modified from the Ville Marie IR grading scale. The age-adjusted multivariate model was presented as shown below: where $P$ value was the predicted probability of a lesion being malignant estimated from the regression model. Therefore, the $P/(1-P)$ ratio indicated the odds (OD), that was, the ratio of the probability of being malignant neoplasm to being benign neoplasm for a given lesion.

A total of 276 women (mean ± SD age = 50.8 ±11.8 years) with suspicious findings on mammograms or ultrasonogram were tested with IR imaging of the breast before the excisional biopsy. From the receiver operating characteristics (ROC) derived from the multivariate model, the sensitivity of the most optimal cut-off value found as 72.4% with the corresponding specificity 76.6% (Youden’s Index = 0.49), positive predictive value (PPV) 81.3% and negative predictive value (NPV) 66.4% [13]. Jiang et al (2005) discussed about the usage of thermography in the biomedical field in his review paper. IR imaging was being widely used for diagnosis and to study the progress of treatment of many disorders, mainly in the wide area of rheumatology, dermatology, orthopedics and circulatory abnormalities also in small animal model [14]. Song et al (2007) assessed tumor growth using thermography in xenografts induced nude mice model. In a xenograft induced breast tumor nude mice model using MDA-MB-231 and MCF7, the induced breast tumor had a lesser skin temperature on 6th day of tumor induction, when comparing to non-tumor parts of the mice [15].

CAD systems may aid the average radiologist by substantially improving detection of early stage malignancies using mammograms with no more than a proportionate increase in recall rate. Iacomi et al (2014) proposed a novel chaotic map clustering approach to the segmentation of mammographic digital images. The chaotic map clustering algorithm was used to group together similar subsets of image pixels resulting in a medically meaningful partition of the mammography. By this algorithm high recognition rate about 94% was achieved for small mass lesions.
while being less effective on identification of larger mass lesions [16]. Abo-Eleneen et al (2013) introduced a semi-automatic unsupervised successive segmentation technique to isolate abnormal breast tissue based on certain 1st order statistical features. The effectiveness of the segmented results by the fisher information measure is compared quantitatively with other segmentation methods such as Shannon, Reny entropy, Kapur entropy and Harvrdar and Charvat entropy based thresholding algorithms by using the uniformity measure describing the region of homogeneity. Effective features have to be extracted from the suspicious region of mammogram to characterize the suspicious region as benign or malignant neoplasms [17]. Zheng et al (2013) carried out breast mass segmentation, region by region as follows: i). breast region; ii). removal of pectoral muscle; iii). breast tumor region using the following algorithms: i). snake algorithm; ii). otu thresholding and multiple regression analysis; iii). then using upper outlier detection and texture complexity; and finally iv). random walk scheme [23].

Suganthi et al (2014) extracted Gabor wavelet transform based features such as energy and amplitude from the tissues of the breast thermogram. Anisotropy index and orientation measures were calculated from the extracted features, to quantify the difference in texture energy between normal and cancer tissues. Maximum of 6 % difference in average energy value at 150° orientation was obtained between normal and abnormal tissues. Similarly, among the different pathological conditions, maximum variation was observed at 0° orientation [18]. Elfarra et al (2012) developed computer aided diagnosis (CAD) model for mammogram image analysis. An active contour segmentation method was performed to segment the abnormal region from the selected ROI and used for feature extraction and classification. 94.6% of accuracy was achieved by this feed forward artificial neural network (FFANN) with back-propagation classification. This algorithm did not segment properly ill-defined cases. Feature selection methods have to be enhanced and further the performance of FFANN classifier has to be compared with other classifiers [19]. Meenalosini (2013) applied gray level gradient buffering algorithm to the selected preprocessed region of interest (ROI) of mammogram and its texture features were extracted by spatial gray level
dependence (SGLD) approach. Further, these features were used to classify the mammogram using support vector machine (SVM). The efficiency of classification by this method was calculated using Par test which gives 99.3% sensitivity and 98.1% specificity [20]. Iterative thresholding followed by region based active contour method was applied by Yuvaraj et al (2013) [21], for segmenting the tumor region from selected ROI of mammogram. The sensitivity and the specificity was 87.5% and 100% respectively and the overall classification accuracy obtained through adaptive neuro-fuzzy inference system (ANFIS) was 91.30%. Maitra et al (2011) applied to divide and conquer homogeneity enhancement algorithm (DCHEA) and binary homogeneity enhancement algorithms for enhancing mammograms before segmentation. Then region growing method was applied after anatomical segmentation of breast ROI and the removal of pectoral muscle. An accuracy of 99% was achieved by this segmentation method [22].

Literature review reveals that variety of algorithms was available for automated sequential segmentation of abnormal masses from mammograms such as statistical approaches [17], random walk scheme method [23], dual tree complex wavelet transform (DTCWT) [24], different thresholding algorithms [25, 26], adaptive median filtering followed by texture analysis [27], unsupervised segmentation using statistical features [28] and texture approach [29] etc., Most of the segmentation methods were carried out on the selected suspicious breast mass region of interest, after manual selection. The detailed literature review related to the proposed work has been tabulated in Appendix I.

1.2 SCOPE OF THE THESIS

Thermography is non invasive, non hazardous radiation free method of imaging modality. If proven that thermography is useful in predicting the breast tumor well before, this modality can be used as a screening tool. A small animal surface temperature profile captured using the infrared camera is helpful for the assessment of physiological responses associated with the regulation of body temperature. IR imaging can be used to study vascular pattern, inflammations, tumor growth and improvements in therapy. Diagnosing breast
cancer in early stage itself has the greater effect on the prognosis. Best “treatment” of cancer is preventing its occurrence in the first place or detecting it early when it may be most treatable. Nowadays, mammography is the best way of screening breast cancer. In India experienced radiologists are not widely available. Solution for an accurate diagnosis relies on objective visual interpretation by means of readily available CAD system. By CAD system, diagnosis is possible even in the rural remote diagnosis center. The existing literature review revealed that there is no standard automated CAD system for the evaluation of breast cancer from mammogram. Thermography is also not considered as a standard screening tool for breast cancer as there is no quantitative evaluation of breast thermogram. There is no comparison study between different imaging modality with breast biopsy as standard for the evaluation of breast cancer.

Hence the present study is focusing on the following broad areas which are limited both in India and in abroad: i).evaluation of mammary cancer using thermography in small animal model; ii).comparison of the breast thermogram, digital X-ray mammogram and PET CT with breast biopsy as standard; iii).developing a complete automated CAD system for the evaluation of breast mass from a mammogram; iv).texture feature extraction and classification of segmented breast mass as normal, benign and malignant neoplasm.

1.3 ORGANISATION OF THE THESIS

Numerous diagnostic methods used in an evaluation of breast cancer are briefly covered in the Chapter 2. Chapter 3 deals with the investigation of the potential of thermography in the evaluation of induced breast cancer in wistar rat model. In Chapter 4, a comparison of mammogram, PET-CT image, and thermogram in diagnosis breast cancer with breast biopsy as a standard in human subjects was studied. The Chapter 5 focuses on segmentation of an abnormal breast mass present in mammogram automatically using combined multimodal segmentation approach. Chapter 6 explains about the extraction of
the texture features from the segmented breast mass region and manually cropped ROI of the normal breast mammogram by gray level cooccurrence matrix (GLCM) and run length matrix (RLM) and classification of an abnormal breast mass present in mammogram into normal, benign- and malignant-neoplasms using the extracted features by multi class support vector machine, Naive Bays classifier and feed forward neural network.

1.4 OBJECTIVES OF THE THESIS

- To induce breast cancer in the lower-right flank region of wistar rats (n=6) using DMBA (7,12-dimethylbenz(a)anthracene).
- To capture thermal images of rats for 60 days from the day of induction until the tumor becomes into a palpable size.
- To investigate asymmetrical distribution of skin surface temperature as well as pseudo color distribution between breast cancer induced lower right flank region and non tumor site.
- Asymmetrical RGB color histogram analysis.
- To compare the thermal study results with biomarker Carcino Embryonic Antigen (CEA) and biopsy as standard.
- To segment the abnormal mass region of the breast from thermogram, mammogram and PET-CT of the breast using color K-means clustering, multimodal segmentation and thresholding followed by region growing respectively.
- To extract statistical features of the bilateral breast from thermogram.
- To extract the texture features from the mammogram by GLCM and RLM approaches.
- To evaluate asymmetrical skin surface temperature (SST) in °C of the breast using gray intensity histogram and color histogram approaches.
- To compare the variables measured from thermogram, PET-CT, mammogram, with histopathological examination of the breast tissues using biopsy as a standard.
- To develop an automated segmentation of abnormal breast mass with
good accuracy using a combination of dual tree complex wavelet transformation, watershed segmentation and K-means clustering methods called as multimodal segmentation, when comparing to an abnormal breast mass outlined in mammogram by radiologists of ACR as standard.

- To extract texture features of the automatic segmented breast mass region as well as manually cropped normal breast region of interest in mammogram using both GLCM, RLM algorithms along four spatial orientations (0°, 90°, 45°, 135°) separately.

- To classify an abnormal breast mass present in mammogram into normal, benign- and malignant- breast neoplasm using multi class support vector machine, Naive Bays classifiers and feed forward back propagation neural network.

- To evaluate the accuracy of the classifiers mentioned above in the evaluation of breast cancer, using all extracted features of breast mass/breast region in mammogram, when compared to breast biopsy as a standard.