CHAPTER 2

BREAST AND MAMMOGRAPHY

2.1. Breast anatomy

The fundamental knowledge of breast structure and some breast pathologies is essential to understand the importance of breast cancer study. Breast cancer is a malignant neoplasia produced by a cellular division dysfunction. Mammography is a particular form of radiography, using radiation levels between specific intervals with a purpose to acquire breast images to diagnose an eventual presence of structures that indicates a disease, especially cancer. In case of mammary pathologies, their early detection is extremely important. The technological advances verified in imaging have contributed to the increase in successful detection of breast cancer cases. In this area, mammography has an important role to detect lesions in initial stages and make a favorable prognosis.

During the fetal period is created, by epidermis, a depression which forms a mammary pit on the local of mammary gland. The region where the mammary glands appear is located in left and right sides of the upper ventral region of the trunk. The breasts exist in woman and man, but the mammary glands are normally most developed in female, except in some particular circumstances related with hormonal problems. The nipple is a small conical prominence surrounded by a circular area of pigmented skin, the areola, which contains large sebaceous glands that are often invisible to the naked eye. The base of the female breast, roughly circular, extends from the second rib above to the sixth rib below. Medially, it borders the lateral edge of the body of the sternum and laterally it reaches the mid auxiliary line in Figure 3 (Moinfar, 2007 and Moore et al, 2004).
At puberty, the female breasts normally grow according to the glandular development and increase of fat deposition; furthermore, also the nipples and areolas grow. The size and shape of breast depends on genetic, racial and dietary factors. During the pregnancy, the areola color becomes dark, and after that keeps the pigmentation. This color diminishes as soon as lactation is over, but is never entirely lost throughout life (Moore et al, 2004 and Gray, 2000).

The breast consists of gland tissue, fibrous tissue, connecting its lobes and fatty tissue in the intervals between lobes. The breast contains 15 to 20 lobes of glandular tissue, which constitute the parenchyma of the mammary gland. These lobes give a shape characteristic to the breast due to a considerable amount of fat, and these are composed of lobules, connected together by areolar tissue, blood vessels and ducts. Each lobule is drained by a lactiferous duct, which opens independently on the nipple. Just deep to the areola, each duct has a dilated portion, the lactiferous sinus, which accumulates milk during lactation. The smallest lobules include also the alveoli, which open into the smallest branches of the lactiferous ducts (Dixon, 2006).
Many changes happen in the breast tissue during the menstrual cycle and pregnancy, due to hormones progesterone and estrogens. In a woman who is not pregnant or suckling, the alveoli are very small and solid, but during the pregnancy enlarge, and the cells undergo rapid multiplication. The mammary glands only produce milk when the baby is born, despite being prepared for secretion since mid-pregnancy. The first milk, colostrums, eliminates the cells in the center of the alveolus that suffered fatty degeneration. In a woman who has given birth more than twice the breast become large and pendulous, and in elderly women, they usually become small because of the decrease in fat and glandular tissue atrophy. But, normally in young women the breasts are supported and kept in their position by the cooper’s ligaments. These ligaments, particularly well developed in the upper part of the gland, help to maintain the lobes of the gland.

Cancer is a condition that affects people all over the world. Research in this area began in 1900 and cancer was considered a disease without cure. As other cancers, breast cancer arises when cells grow and multiply uncontrollably, which produces a tumor or a neoplasm. The tumors can be benign when the cancerous cells do not invade other body tissues or malignant if cells attack nearby tissues and travel through the bloodstream or lymphatic system to other parts of the body, spreading a cancer by a process known as metastasis (Seeley, 2004).

Children breast consists principally ducts with dispersed alveoli, being similar in adipose deposition and the growth of the mammary glands, as well as the initial development of lobules and alveoli of the breast. Progesterone and prolactin which cause the final growth, are responsible for the function of these structures and cause the external appearance of the mature female breast (Guyton and Hall, 2000).

During pregnancy, the concentration of estrogen increases. This phenomenon causes expansion and branching of the breast gland ducts and deposition of additional adipose tissue (Gunderman, 2006).
2.2. Breast pathologies

2.2.1. Fibroadenoma

Fibroadenomas are the most common breast tumors in pubertal females, and there are three types of fibroadenoma classified as: common, giant and juvenile. These tumors are characterized by a proliferation of both glandular and stromal elements, have well-demarcated borders and are firm, rubbery, freely mobile, solid, usually solitary breast masses. There is no pain or tenderness due to fibroadenomas and their size do not change with the menstrual cycle. Women aged in their 20s and adolescents are the most common people affected with this disease. A rapid growth sometimes occurs but usually that growth is extremely slow. A giant fibroadenoma should measure over 5 cm in diameter but the average is 2.5 cm. These tumors may return (approximately 20% recur), women should be aware of this risk and have periodic examinations (Dixon, 2006 and Moinfar, 2007).

2.2.2. Mammary dysplasia

Mammary dysplasia also can be called as fibrocystic changes (FCC), fibrocystic disease, fibrous mastopathy or fibroadenosis cystic. In reality, these alterations not indicate a disease. This pathology is defined as being a benign alteration of the breast consisting of cystic dilatation of intralobular glands with or without stromal fibrosis. The age distribution of this lesion is between 20 and 50 years. Normally, fibrocystic changes are associated to the cyclic levels of ovarian hormones, because during ovulation and before menstruation, the hormone level changes often lead the breast cells to retain fluid and develop into nodules or cysts, which feel like a lump when touched. The texture of the breast is, in these cases, similar to the breast in pre-menstrual phase. The signs of fibrocystic changes include increased engorgement and density of the breasts, excessive modularity, rapid change and fluctuation in the size of cystic areas, increased tenderness and occasionally spontaneous nipple discharge. It can be unilateral, bilateral or just affect a part of the breast (Malik et al, 2010 and Moinfar, 2007).
2.2.3. Mastitis and breast abscess

Inflammatory conditions of the breast, particularly acute mastitis and breast abscess are rare pathologies. Often these infections can happen in postpartum situations or after a lesion. There are two types of mastitis: acute and chronic. In acute mastitis, it is predominantly composed of neutrophilic granulocytes, seen mostly in lactating women. Chronic mastitis may be due to reinfection or a relapsed infection; the first case occurs sporadically and commonly is transmitted from the baby and the second case means that eradication of the pathogen failed (Jatoi and Kaufmann, 2010; Moinfar, 2007). Breast abscess arises when mastitis was treated inadequately and milk retention exists. The most common diagnostic techniques used for treatment include ultrasonography of the breast and needle aspiration under local anesthesia with a purpose of identifying collection of fluid or pus (Jatoi and Kaufmann, 2010; Moinfar, 2007).

2.3. Cancer and Breast Cancer

One in eight deaths worldwide is due to cancer (García et al., 2007). Cancer is the second leading cause of death in developed countries and the third leading cause of death in developing countries. In 2009, over the years, the incidences of breast cancer in India have steadily increased and as many as 100,000 new patients are being detected every year (Siegel et al., 2011). In the United States, cancer is the second most leading cause of death, and accounts for nearly 1 of every four deaths (American Cancer Society, 2008).

Cancer results from a series of molecular events that fundamentally alter the normal properties of cells. In cancer cells the normal control systems that prevent cell overgrowth and the invasion of other tissues are disabled. These altered cells divide and grow in the presence of signals that normally inhibit cell growth; therefore, they no longer require special signals to induce cell growth and division. As these cells grow they develop new characteristics, including changes in cell structure, decreased cell adhesion and production of new enzymes.

These heritable changes allow the cell and its progeny to divide and grow, even in the presence of normal cells that typically inhibit the growth of nearby cells. Such changes
allow the cancer cells to spread and invade other tissues. The abnormalities in cancer cells usually result from mutations in protein-encoding genes that regulate cell division. Over time more genes become mutated (Schneider, 2001). This is often because the genes that make the proteins that normally repair DNA damage are themselves not functioning normally because they are also mutated. Consequently, mutations begin to increase in the cell, causing further abnormalities in that cell and the daughter cells. Some of these mutated cells die, but other alterations may give the abnormal cell a selective advantage that allows it to multiply much more rapidly than the normal cells. This enhanced growth describes most cancer cells, which have gained functions repressed in the normal, healthy cells. As long as these cells remain in their original location, they are considered benign; if they become invasive, they are considered malignant. Cancer cells in malignant tumors can often metastasize, sending cancer cells to distant sites in the body where new tumors may form.

Cancer is a disease that begins in the cells of the body. Under normal conditions, the cells grow and divide depending on the requirement of the body. This orderly process is disturbed when new cells are formed which is not needed by the body and old cells don’t die when they should. These extra cells lump together to form a growth called tumor. There are two types of cancer, benign and malignant.

2.3.1. Types of cancer

Benign

Benign tumors are not cancerous. They can usually be removed and generally don’t grow back once they’re gone. The cells in benign tumors don’t spread and it is rare for a benign tumor to be life threatening.

Malignant

Malignant tumors, on the other hand are cancerous. The cells are abnormal and divide randomly. The cells behave aggressively and attack the tissue around them. They also can move away from malignant tumor and enter the blood stream to form new tumors in other parts of the body.
Many viruses infect humans but only a few viruses are known to promote human cancer. These include DNA viruses and retroviruses, a type of RNA virus.

2.3.2. Stages of cancer

Doctors group tumors by Stage. The Stage of a tumor refers to the way the cells look under a microscope. Different Stages of cancers are there in our body system.

Determining the cancer's stage

After your health care providers know what type of cancer you have, they will determine what "stage" the cancer is in. This means how far advanced its growth is. There are many staging systems, but a common example is the TNM. The "T" refers to the size of the tumor, the "N" to the number of lymph nodes involved and the "M" to metastases (the spread of the cancer to other organs through the lymphatic and/or circulatory system). Generally, the lower the stage, the less advanced the cancer is and the better the treatment outcome is likely to be.

- Stage 0 = precancer.
- Stage 1 = small cancer found only in the organ where it started.
- Stage 2 = larger cancer that may or may not have spread to the lymph nodes.
- Stage 3 = larger cancer that is also in the lymph nodes.
- Stage 4 = cancer in a different organ from where it started.

Table 1. Breast cancer stages in India (Source from Indian Council of Medical Research, New Delhi).

<table>
<thead>
<tr>
<th>Stage of Breast cancer at presentation at 4 major Indian cancer centers</th>
<th>Patients %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mumbai</td>
</tr>
<tr>
<td>I</td>
<td>7.8</td>
</tr>
<tr>
<td>II</td>
<td>57.4</td>
</tr>
<tr>
<td>III</td>
<td>28.9</td>
</tr>
<tr>
<td>IV</td>
<td>5.9</td>
</tr>
<tr>
<td>Unstaged</td>
<td></td>
</tr>
</tbody>
</table>
2.3.3. Breast Cancer

Breast cancer can be separated into different types based on the way the cancer cells look under the microscope. Most breast cancer is carcinomas, a type of cancer that starts in the cells that line organs and tissues like the breast. In fact, breast cancers are often a type of carcinoma called adenocarcinoma, which starts in glandular tissue.

No effective way to prevent the occurrence of breast cancer exists. Therefore, early detection is the first crucial step towards treating breast cancer. It plays a key role in breast cancer diagnosis and treatment. Data from breast cancer facts and figures tells us about estimated new female cases and deaths by age

Table 2. Estimated female cases and deaths by age.

<table>
<thead>
<tr>
<th>Age (Yrs)</th>
<th>In Situ Cases</th>
<th>Invasive Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>1,900</td>
<td>10,980</td>
<td>1,020</td>
</tr>
<tr>
<td>&lt;50</td>
<td>15,650</td>
<td>48,910</td>
<td>4,780</td>
</tr>
<tr>
<td>50-64</td>
<td>26,770</td>
<td>84,210</td>
<td>11,970</td>
</tr>
<tr>
<td>65+</td>
<td>22,220</td>
<td>99,220</td>
<td>22,870</td>
</tr>
<tr>
<td>All ages</td>
<td>64,640</td>
<td>232,340</td>
<td>39,620</td>
</tr>
</tbody>
</table>

Global cancer statistics show that breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females, accounting for 23 percent of total cancer cases and 14 percent of cancer deaths. Breast cancer is now also the leading cause of cancer death among females in economically developing countries (Ahmedin Jemal et al, 2011). Each year about 700 women are diagnosed with this cancer. American statistics classify this cancer as the second leading cause of death among women with an age between 40 and 55 years. Early detection is the key to improving breast cancer prognosis. Consequently many counties have established screening programs. These programs yield large volumes of mammograms. Cancer that originates from the breast tissue is called as breast cancer. The ability to improve diagnostic information from medical images can be further enhanced by designing computer processing algorithm, applications and software intelligently.
Figure 4. Leading causes of cancer deaths among female (Boyle and Levin, 2008).

The Indian Council of Medical Research (ICMR) and Population Based Cancer Registry (PBCR) data reported that breast cancer is the commonest cancer among women in urban registries of Delhi, Mumbai, Ahmedabad, Calcutta and Trivandrum constituting >30% of all cancers in females (Indian Council of Medical Research, New Delhi, 2001).

Figure 5. International comparisons of age adjusted cancer incidence rates for male (Source from Indian Council of Medical Research, New Delhi, 2001).
Figure 6. International comparisons of age adjusted cancer incidence rates for female (Source from Indian Council of Medical Research, New Delhi, 2001).

Figure above shows the highest and lowest AAR in all the continents, viz., Africa, Asia, Central and South America, Europe, North America and Oceania (Parkin et al, 1997). Besides, the rates of Indians in Singapore are compared with that of the registries in India.

Table 3. Calculation based on age specific rates from 0-64 years of age (Source from Indian Council of Medical Research, New Delhi, August 2012).

<table>
<thead>
<tr>
<th>Registry</th>
<th>Cumulative Rate (%)</th>
<th>Cumulative Risk (%)</th>
<th>(%) No. of persons developing Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>Bangalore</td>
<td>5.92</td>
<td>8.84</td>
<td>5.75</td>
</tr>
<tr>
<td>Barshi</td>
<td>2.68</td>
<td>4.67</td>
<td>2.64</td>
</tr>
<tr>
<td>Bhopal</td>
<td>6.57</td>
<td>7.11</td>
<td>6.36</td>
</tr>
<tr>
<td>Chennai</td>
<td>6.87</td>
<td>8.76</td>
<td>6.64</td>
</tr>
<tr>
<td>Delhi</td>
<td>7.70</td>
<td>10.09</td>
<td>7.41</td>
</tr>
<tr>
<td>Mumbai</td>
<td>6.46</td>
<td>7.92</td>
<td>6.26</td>
</tr>
</tbody>
</table>
Table 4. Calculation based on age specific rates from 0-74 years of age (Source from Indian Council of Medical Research, New Delhi, August 2012).

<table>
<thead>
<tr>
<th>Registry</th>
<th>Cumulative Rate (%)</th>
<th>Cumulative Risk (%)</th>
<th>(% No. of persons developing Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>Bangalore</td>
<td>11.60</td>
<td>14.12</td>
<td>10.95</td>
</tr>
<tr>
<td>Barshi</td>
<td>5.68</td>
<td>6.36</td>
<td>5.52</td>
</tr>
<tr>
<td>Bhopal</td>
<td>12.50</td>
<td>1044</td>
<td>11.75</td>
</tr>
<tr>
<td>Chennai</td>
<td>12.05</td>
<td>12.98</td>
<td>11.49</td>
</tr>
<tr>
<td>Delhi</td>
<td>14.34</td>
<td>15.10</td>
<td>13.36</td>
</tr>
<tr>
<td>Mumbai</td>
<td>13.89</td>
<td>13.73</td>
<td>12.97</td>
</tr>
</tbody>
</table>

Based on the above, and assuming that the age specific rates (from 0-74 years) of the 1990-1996 are sustained, and there is no other competing cause of death, one could estimate that on an average one in about nine men and one in about eight women in the urban centers could develop cancer in their lifetime.

Figure 7. Ten leading sites of cancer - females in Chennai (Source from Indian Council of Medical Research, New Delhi, August 2012).
Among females, cancer of the cervix was the leading site in Bangalore, Barshi, Bhopal and Chennai; and cancer of breast was the leading site in Delhi and Mumbai. These two sites together constituted over 40% of cancers of all sites in females in the urban registries and over 65% of cancers in the rural registry at Barshi. As in males, cancer of the oesophagus was an important leading site of cancer, in females also. In Chennai and Bangalore cancer of stomach was seen as the third and sixth leading site of cancer respectively. Cancer of the gall bladder was the fourth common site in Delhi and the eighth in Bhopal, but this was not seen among the ten leading sites of cancer in other registries.

2.3.4. Breast cancer lesions

Breast cancer has some characteristic lesions such as microcalcifications (MCs), masses, architectural distortions and bilateral asymmetry.

a) Microcalcifications

Microcalcifications are small deposits of calcium of size from 0.33 to 0.7 mm and are slightly brighter than surrounding tissues. These lesions are difficult to detect in mammography because appear with low contrast due to their small size, although have high inherent attenuation properties. Associated with extra cell activity in breast tissue, microcalcification may show up in clusters or in patterns (Kavitha and Kumaravel, 2007).

A microcalcification cluster normally is more detectable than an isolated microcalcification and contributes for the diagnosis of early stages of breast cancer. These clusters may have three or more microcalcifications present in a mammogram region with an area around 1 cm. Once microcalcification may be a sign to malignancy it is important to be able to distinguish benign and malignant microcalcification. Table 5 presents the grade, degree of suspicion and mammographic appearance (Rovere et al, 2006).
Table 5. Grading of imaging reports of microcalcifications according to risk of malignancy (Source from Rovere et al 2006).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Degree of suspicion</th>
<th>Mammographic appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>No abnormality seen</td>
</tr>
<tr>
<td>2</td>
<td>Consistent with a benign lesion</td>
<td>Popcorn, ring, micro cystic or diffuse bilateral calcification</td>
</tr>
<tr>
<td>3</td>
<td>Atypical or indeterminate but probably benign</td>
<td>Localized cluster of round, fine or punctuate calcification</td>
</tr>
<tr>
<td>4</td>
<td>Suspicious of malignancy</td>
<td>Localized cluster of granular calcification</td>
</tr>
<tr>
<td>5</td>
<td>Consistent with malignancy</td>
<td>Comedo calcification</td>
</tr>
</tbody>
</table>

Figure 8. Types of microclassifications commonly seen on mammographic images (Source from Gunderman, 2006).

b) Masses

Masses are lesions more difficult to detect in mammograms than microcalcifications because the features of a mass bear resemblance to those of the normal breast parenchyma. In general, mass shape can be round, oval, lobular or irregular, and margins can be from circumscribed to spiculated, below figure.
When a mass is detected it is difficult to distinguish if it is benign or malignant but there are differences in the features of shape and texture between them. Benign masses are typically smooth and distinct and their shapes are similar to the round. On the other hand malignant masses are irregular and their boundaries are usually blurry. A mass with regular shape has a higher probability of being benign whereas a mass with an irregular shape has a high probability of being malignant (Saki and Tahmasbi 2010).

**Differentiation between breast tumors**

Although there are many types of breast abnormalities, it is possible to have a general differentiation between benign and malignant breast tumors using their boundary shapes with the surrounding breast tissue. This differentiation can be performed by examining spiculations on the malignant tumor, which can easily be observed using mammography or ultrasound techniques. Spiculation is a stellate distortion caused by the intrusion of breast cancer into the surrounding tissue and its existence is very important for tagging the tumor as malignant. There are many successful techniques based on mammography or ultrasound to quantify the degree of spiculations for a successful decision of differentiation between the benign and malignant type of breast tumors in Figures below (Huang et al, 2004).
2.3.5. Types of breast tumors

Breast cancer can be classified according to the breast tissue where the cancer originated (glands, ducts, fat tissue or connective tissue) and according to the extent of the cancer spread (noninvasive/in situ or invasive/infiltrating) (Gunderman, 2006).

Carcinoma in situ tumor is an early form of carcinoma (invasive malignant tumor due to mutated epithelial cells) detected in an early stage and with the absence of invasion of surrounding tissues. A cancer is known as infiltrating when the cells that started in glands or ducts spread to healthy surrounding tissue. This type of cancer can have a variety of appearances (Eastman and Crosin, 2006).

Both in situ and infiltrating cancers can be ductal and lobular, depending on the breast cancer location. Ductal carcinoma in situ (DCIS) is a non-invasive cancer where abnormal cells have been found in the lining of the breast milk duct. The atypical cells have not spread outside of the ducts into the surrounding breast tissue. Ductal carcinoma in situ is very early cancer that is highly treatable, but if it’s left untreated or undetected, it can spread into the surrounding breast tissue. In the term “carcinoma in
situ”, Carcinoma means “cancer” and in situ means “in the original place” (National breast cancer foundation).

The infiltrating ductal carcinoma is the most frequent type of breast cancer, being responsible for nearly 80% of cases. A Tumor with irregular mass is characteristic in the mammography of this type of cancer.

Figure 11. Invasive Ductal Carcinoma showing microlobulated borders and microcalcifications (Kaushak, 2007).

Lobular Carcinoma begins in the milk glands and in the terminal lobules. The lobules are expanded by a uniform population of small yet atypical cells. Usually this process obliterates the lumen of the acini. These atypical cells do not penetrate through the walls of the lobules. LCIS rarely gives rise to mammographic abnormalities. It is often found in biopsies that have been done for other reasons such as removal of benign lesions. LCIS is a risk factor for developing breast cancer. The majority of patients are therefore managed by careful follow ups. Approximately, 10% of breast cancer is lobular carcinoma (Gunderman, 2006).

Difference between DCIS and IDC are DCIS means the cancer is still contained in the milk duct and has not invaded any other area and IDC is cancer that began growing in the duct and is invading the surrounding tissue. Cancer staging done by a physician, along with a physical exam and medical history can help identify the best treatment options.
When cancer spreads to other parts of the body through blood and lymph circulation, it is called metastization. When the ductal carcinoma invades the skin of the nipple it is called Paget’s disease.

Inflammatory breast cancer corresponding to an aggressive tumor that invaded the dermal lymphatic, representing about 1 to 4% of the breast cancer. This cancer usually presents breast inflammation.

Triple Negative Breast Cancer is a diagnosis of triple negative breast cancer. It means that the three most common types of receptors known to fuel most breast cancer growth—estrogen, progesterone and the HER-2/neu gene—are not present in the cancer.

This means that the breast cancer cells have tested negative for hormone epidermal growth factor receptor 2 (HER-2), estrogen receptors (ER) and progesterone receptors (PR). Since the tumor cells lack the necessary receptors, common treatments like hormone therapy and drugs that target estrogen, progesterone and HER-2 are ineffective. Using chemotherapy to treat triple negative breast cancer is still an effective option. In fact, triple negative breast cancer may respond even better to chemotherapy in the earlier stages than many other forms of cancer.

Metastatic breast cancer is also classified as Stage 4 breast cancer. The cancer has spread to other parts of the body. This usually includes the lungs, liver, bones or brain.

- Cancer cells invade nearby healthy cells. When the healthy cell is taken over, it too can replicate more abnormal cells.
- Cancer cells penetrate into the circulatory or lymph system. Cancer cells travel through the walls of nearby lymph vessels or blood vessels.
- Migration through circulation. Cancer cells are carried by the lymph system and the bloodstream to other parts of the body.
- Cancer cells lodge in capillaries. Cancer cells stop moving as they are lodged in capillaries at a distant location and divide and migrate into the surrounding tissue.
- New small tumors grow. Cancer cells from small tumors at the new location (called micro metastases).
It is possible to be diagnosed with breast cancer during pregnancy, although it is rare and the breast cancer is not caused by the pregnancy. Women who are diagnosed with breast cancer during pregnancy have tremendous additional strain due to concern for the safety of the unborn child. It can be a traumatic and extremely difficult situation, but there is still hope for both mother and child, thanks to the many treatment options available.

Risk on breast cancer

All women are at risk for breast cancer, but not all women have the same risk. Experts use a woman’s personal and family medical histories, genetic tests, lifestyle and exposures, and other factors to assess risk and make recommendations for breast screening and risk management. All women should be familiar with the look and feel of their breast so they can report any change or lumps to their doctors.

Mammograms are most often used to screen women for breast cancer.

- Breast magnetic resonance imaging (MRI) is a very sensitive tool used to screen high-risk women.
- Ultrasound is not typically recommended for screening, but it is sometimes used to see if breast changes are solid masses or fluid filled cysts, or to screen high-risk women who are pregnant for whom mammograms and MRI may not be safe.
- Experts also use these tools along with biopsies to follow up on breast changes or lumps. What is my risk of breast cancer? What techniques are used to detect breast cancer?
- Very high-risk women have a 30% or greater lifetime risk of breast cancer. This group includes women with: Known mutations in a BRCA1 or BRCA2 gene or mutations associated with other hereditary cancer syndromes including Li-Fraumeni Syndrome and Cowden Syndrome.
- Intermediate-risk women have a lifetime risk of breast cancer that is higher than the average woman but less than 30%. This group includes women with: A breast biopsy that shows changes such as atypical ductal or lobular hyperplasia or Lobular Carcinoma In Situ (LCIS)
A calculated risk of breast cancer that is 20% to 29% based upon family history, personal health history, or certain genetic markers, average-risk women with none of the above risk factors have a 10-13% lifetime risk of breast cancer.

2.3.6. Other breast pathologies

General Screening for finding breast cancer tests may be done for the purposes of research, but they have not yet been found to be helpful in diagnosing breast cancer in most women.

Nipple discharge exam

If women have nipple discharge, some of the fluid may be collected and looked at under a microscope to see if any cancer cells are in it. Most nipple discharges are secretions and not cancer. In general, if the secretion appears milky or clear green, cancer is very unlikely. If the discharge is red or red-brown, suggesting that it contains blood, it might possibly be caused by cancer, although an injury, infection or benign tumors are more likely causes. Even when no cancer cells are found in a nipple discharge it is not possible to say for certain that a breast cancer is not there. If a patient has a suspicious mass, it will be necessary to biopsy the mass, even if the nipple discharge does not contain cancer cells (American Cancer Society, 2015).

Ductal lavage and nipple aspiration

Ductal lavage is an experimental test developed for women who have no symptoms of breast cancer but are at very high risk for the disease. It is not a test to screen for or diagnose breast cancer, but it may help give a more accurate picture of a woman's risk of developing it. Ductal lavage can be done in a doctor's clinic or an outpatient facility. An anesthetic cream is applied to numb the nipple area. Gentle suction is then used to help draw tiny amounts of fluid from the milk ducts up to the nipple surface, which helps locate the ducts' natural openings. A tiny tube (called a catheter) is then inserted into a duct opening. Saline (salt water) is slowly infused into the catheter to gently rinse
the duct and collect cells. The ductal fluid is withdrawn through the catheter and sent to a lab, where the cells are scrutinized at under a microscope.

Ductal lavage is not done for women who aren't at high risk for breast cancer. It is not clear if it will ever be useful. The test has not been shown to detect cancer early. It is more likely to be helpful as a test of cancer risk rather than as a screening test for cancer. More studies are needed to better define the usefulness of this test. Nipple aspiration also looks for abnormal cells developing in the ducts, but is much simpler because nothing is inserted into the breast. The device for nipple aspiration uses small cups that are placed on the woman's breasts. The device warms the breasts, gently compresses them, and applies light suction to bring nipple fluid to the surface of the breast. The nipple fluid is then collected and sent to a lab for analysis. As with ductal lavage, the procedure may be useful as a test of cancer risk but is not an appropriate screening test for cancer. The test has not been shown to detect cancer early.

**Biopsy**

A biopsy is done when mammograms, other imaging tests, or the physical exam finds a breast change (or abnormality) that is possibly cancer. A biopsy is the only way to tell if cancer is really present. During a biopsy, a sample of the suspicious area is removed to be scrutinized at under a microscope by a specialized doctor with many years of training called a pathologist. The pathologist sends the doctor a report that gives a diagnosis for each sample taken. Information in this report will be used to help manage patient care. There are several types of biopsies, such as fine needle aspiration biopsy, core (large needle) biopsy and surgical biopsy. Each has its pros and cons. The choice of which to use depends on the specific situation. Some of the factors the doctor will consider include how suspicious the lesion appears, how large it is, where in the breast it is located how many lesions are present other medical problems the patient might have and the patient’s personal preferences. Patient might want to discuss the pros and cons of different biopsy types with their doctor.
2.4. Breast cancer detection methods

2.4.1. X-ray

Breast cancer screening is vital to detecting breast cancer. The most common screening method is mammography. A mammogram is an x-ray photograph of the breast. Imaging plays a crucial role for breast cancer screening for classifying and sampling non-palpable breast abnormalities, as well as for defining the extent of breast tumors, both locally, loco-regionally, and at distant sites. Evaluating response to therapy constitutes an additional important role of imaging. Therefore, imaging via different modalities represents an essential, life-long component for patients with breast cancer, from initial diagnosis throughout the evolution of the disease. X rays (also called radiographs) are used in cancer diagnosis and typically represent a two dimensional image. For example, chest radiographs are used for early cancer detection or to see if cancer has spread to the lungs or other areas in the chest (Nitin et al, 2013).

Diagnostic mammograms are used to diagnose breast disease in women who have breast symptoms (like a lump or nipple discharge) or an abnormal result on a screening mammogram. A diagnostic mammogram includes more images of the area of concerned. In some cases, special images known as cone or spot views with magnification are used to make a small area of abnormal breast tissue easier to evaluate.

A diagnostic mammogram can show

- That the abnormality is not worrisome at all. In these cases the woman can usually return to having routine yearly mammograms.
- That a lesion (area of abnormal tissue) has a high likelihood of being benign (not cancer). In these cases, it is common to ask the woman to come back sooner than usual for her next mammogram, usually in 4 to 6 months.
- That the lesion is more suspicious, and a biopsy is needed to tell if it is cancer. Even if the mammograms show no tumor, if the patient or the doctor can feel a lump, a biopsy is usually needed to make sure it isn't cancer. One exception would be if an ultrasound exam finds that the lump is a simple cyst (a fluid-filled sac), it is very unlikely to be cancerous.
2.4.2. Ultrasound

Ultrasound, also called Ultrasonography (US), is an imaging technique in which high-frequency sound waves that cannot be heard by humans are bounced off tissues and internal organs. Their echoes produce a picture called a sonogram (National Cancer Institute, 2006). A gel is put on the skin of the breast and a handheld instrument called a transducer is rubbed with gel and pressed against the skin. It emits sound waves and picks up the echoes as they bounce off body tissues. The echoes are converted by a computer into a black and white image on a computer screen. This test is painless and does not expose you to radiation.

Breast ultrasound is sometimes used to evaluate breast problems that are found during a screening or diagnostic mammogram or on physical exam. Breast ultrasound is not routinely used for screening. Some studies have suggested that it may be helpful to use ultrasound along with a mammogram when screening high risk women with dense breast tissue. But at this time, ultrasounds cannot replace mammograms. More studies are needed to figure out if ultrasound should be added to routine screening mammograms for some groups of women.

Ultrasound is useful for taking a closer look at some breast masses, and it’s the only way to tell if a mass is a cyst without putting a needle into it to take out (aspirate) fluid. Breast ultrasound may also be used to help doctors guide a biopsy needle into an area of concern in the breast. There is a newer system, called a 3-dimensional automated whole breast ultrasound, which can be used on the breast. The FDA has approved it to be used along with mammography. The 3-D ultrasound can be done with a handheld transducer, but more often, a larger transducer is placed over the whole breast, which can then be scanned automatically.

Ultrasound has become a valuable tool to use along with mammograms because it’s widely available, non-invasive and costs less than other options. But the value of an ultrasound test depends on the operator’s level of skill and experience though this is less important with the new automated ultrasound systems. Ultrasounds aren’t used by themselves for screening because they can miss some cancers seen on mammograms.
Ultrasound is less sensitive than MRI (that is, it detects fewer tumors) but it has the advantages of costing less and being more widely available.

Ultrasound is especially good at imaging soft tissues and distinguishing between solid tumors and fluid-filled cysts. It can help determine how far tumors of the uterus, esophagus or rectum have spread and it can help physicians learn whether cancer has spread into blood vessels, especially the liver and pancreas. Ultrasound is also used widely to guide minimally invasive therapies for liver, prostate and other cancers. Another important use of ultrasound is to evaluate lumps that are hard to see or characterize on a mammogram. Sometimes, ultrasound is used as part of other Medical Imaging Technologies.

Figure 12. Ultrasound image scanners (Source from National Cancer Institute, Cancer Imaging Program, accessed February 10, 2006 at http://imaging.cancer.gov/imaginginformation/cancerimaging/).
2.4.3. Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) shows great promise for detecting mammographically occult breast cancers and for defining the extent of malignant disease. MRI-guided needle localization and core needle biopsy techniques have been developed to complement the increased utilization of MRI for breast cancer staging (Bevers, 2008). MRI has also shown to be of value for screening in women at high risk of breast cancer.

MRI scans use radio waves and strong magnets instead of x-rays. The energy from the radio waves is absorbed and then released in a pattern formed by the type of body tissue and by certain diseases. A computer translates the pattern into a very detailed image. For breast MRI to look for cancer, a contrast liquid called gadolinium is injected into a vein before or during the scan to show details better.

MRI scans can take a long time—often up to an hour. For a breast MRI, you have to lie inside a narrow tube, face down on a platform specially designed for the procedure. The platform has openings for each breast that allow them to be imaged without compression. The platform contains the sensors needed to capture the MRI image. It is important to remain very still throughout the scan.

MRI can be used along with mammograms for screening women who have a high risk of developing breast cancer or it can be used to better examine suspicious areas found by a mammogram. MRI is also sometimes used for women who have been diagnosed with breast cancer to better determine the actual size of the cancer and to look for any other cancers in the breast. It is not yet clear how helpful this is in planning surgery in someone known to have breast cancer. In someone known to have breast cancer, it is sometimes used to look at the opposite breast; to be sure that it does not contain any tumors.
Table 6. Performance Comparison of all imaging techniques based on the image processing results (Mussarat Yasmin et al., 2013).

<table>
<thead>
<tr>
<th>Image Acquisition Technique</th>
<th>Affordable</th>
<th>Performance/ Accuracy</th>
<th>Reliable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammography</td>
<td>Yes</td>
<td>97%-98%</td>
<td>Yes but regular mammography has side effects</td>
</tr>
<tr>
<td>Thermal Infrared Imaging</td>
<td>Very less</td>
<td>85%-90%</td>
<td></td>
</tr>
<tr>
<td>Microscopic Slide Images</td>
<td>Yes</td>
<td>99%</td>
<td>Yes and no side effects</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Less</td>
<td>97.92%</td>
<td>Yes</td>
</tr>
<tr>
<td>MRI and CT Scan</td>
<td>Yes</td>
<td>97%-99%</td>
<td>Yes but has side affects</td>
</tr>
</tbody>
</table>

2.4.4. Positron Emission Mammography Detection

Mammograms are an important tool in detecting breast cancer. The main potential benefit of mammograms is that they help reduce the chance that a woman will die from breast cancer. Mammograms also have potential harms. The most serious harm is overdiagnosis. This occurs when a woman is diagnosed with a breast cancer that would not have become a threat to her health during her lifetime. Currently, it is not possible for a woman to know whether or not her cancer will progress. As a result, almost all women diagnosed with breast cancer are treated. This can lead to overtreatment, including surgery, chemotherapy and radiation that can have significant harms. Another harm, which is more common, occurs when the mammogram suggests that breast cancer may be present when there is no cancer. This is called a “false-positive” result. False-positive results can lead to follow-up tests and procedures that aren’t needed. False-positive results also cause anxiety and while some women do not mind this, others consider it harm. Because the risk of developing invasive breast cancer increases with age, the value of mammograms also increases with age.
The Task Force found that the balance of benefits and harms is different at different ages:

- Women ages 50 to 74 benefit the most from screening mammograms. The best balance of benefits and harms occurs when screening is done every 2 years.
- Women in their 40s can also benefit from screening every two years, but because their risk of developing breast cancer is lower than for older women, the benefits of screening are lower. The rate of potential harms is also higher for women in their 40s, as they are more likely to have false-positive results and follow-up procedures, such as breast biopsies.
- Women in this age group who have a mother, sister, or daughter with breast cancer are at increased risk of developing breast cancer.
- These women may benefit more from beginning screening in their 40s than women with no close relatives with breast cancer.
- For women ages 75 and older, the evidence on the potential benefits and harms of screening mammograms is limited. As a result, the Task Force was unable to make a recommendation for or against screening for this group of women.

Figure 13. Positron Emission Mammography setup (Anne Rosenberg et al 2012).
Mammography is an imaging procedure for examination of the breast that gives information about breast morphology, anatomy and pathologies. It is used for detection and diagnosis of breast cancer, as well as evaluates mass lesions in breast. The early detection of breast cancer is an important factor to treat this disease with success.

This procedure is similar to the other X-Rays, however, are used in low doses, presenting a high quality that leads to high contrast and resolution and low noise (Sivaramakrishna and Gordon, 1997). The breast is sensitive to ionizing radiation, so it is desirable to use the lowest radiation dose compatible with excellent image quality.

Mammography is more sensitive and specific in assessing fatty breasts than dense breast. Dense breast tissue is particularly difficult to assess in young women. Mammography is also used in assisting needle core biopsies and for localization of non-palpable lesions (Chianyama Catherine, 2004). In screening mammography the uniform compression of the breast is important to ensure image contrast, thus these tools have to be highly sensitive, identifying as correctly as possible.

**Positron Emission Mammography Equipment**

The Positron Emission Mammography (PEM) prototype is intended to evaluate PET technology principle in the diagnosis of malign neoplasm in the breast and of ganglion loco-regional invasion. Relative to whole body PET systems, dedicated equipment has potentially better spatial resolution, obtained with fine-grain crystal segmentation, and allows tighter coverage of the region under analysis, leading to better sensitivity.

The two main types of breast changes found with a mammogram are calcifications and masses. Calcifications are tiny mineral deposits within the breast tissue, which look like small white spots on the pictures. They may or may not be caused by cancer.

A mass, which may or may not have calcifications is another important change seen on mammograms. Masses can be many things, including cysts (fluid-filled sacs) and non-cancerous solid tumors, but they could also be cancer. Any mass that’s not clearly a simple fluid-filled cyst usually needs to be biopsied (A biopsy is taking out a piece of tissue to see if cancer cells are in it).
Having your older mammograms available for the radiologist is very important. They can help to show if a mass or calcification has changed over time, which could affect whether a biopsy is needed.

The PEM system intends to detect breast and armpit cancer with size at least of 2 mm, improving ten times the resolution of current PET systems, as an essential factor for an early detection of this type of cancer. Within PEM system, cancerous cells react with a radioactive substance (named radioactive tag), which being injected in the patient is disbursed all over the body by the blood flow. It is known that this liquid, essentially composed by glucose, is taken in more quantity by tumor cells than normal cells, due to their higher metabolism. In its natural decomposition, the liquid’s radioactive isotope emits positrons (electron’s anti-particle) which quickly recombine with electrons generating, among others, two photons in the same line and opposite directions. These photons can be detected by specific crystals (collision) that scintillate when hit. The presence of cancerous cells is detected by the intersection of those photons’ paths.

Cancer imaging by positron emission tomography (PET) with fluoro-2-deoxy-D-glucose (FDG) is based on enhanced uptake of FDG by tissues with increased metabolic demand versus their normal tissue (Smith et al, 2006). The large-scale diffusion of FDG PET imaging (and especially PET/CT) for whole-body analysis in the evaluation of the majority of tumors has raised interest in its use to diagnose primary breast cancer. The primary diagnosis of breast cancer is best achieved with the use of dedicated devices for positron emission mammography (PEM). In this regard, although whole-body FDG PET has a certain diagnostic accuracy for detecting malignant breast lesions, its sensitivity is lower than that of other standard diagnostic imaging techniques.

PEM imaging is conducted with either a dual head or ring style gamma-ray detector. Both systems are designed to detect the coincident gamma rays which are traveling approximately 180° from each other after the annihilation reaction. In PEM imaging, since there are two gamma-rays traveling 180° apart, the event location is calculated as a line of response between the location that each gamma-ray strikes the pair of opposed detectors. One advantage to PEM is that it does not have the same loss of resolution
with distance that BSGI/MBI systems experience. One limitation of the dual-head PEM detector design is that, due to the limited angle of acquisition, it has limited resolution in the Z-axis (depth). Ring detectors do not suffer from this limitation as they provide a 360° acquisition for reconstruction however there is currently no biopsy capability on the ring detector systems (Anne Rosenberget al, 2012). A needle biopsy localization device was recently introduced for the opposed dual-head detector system PET with FDG is more sensitive and specific than conventional imaging for staging patients with a high risk to develop malignant melanoma. Moreover, a number of studies have shown that the results from PET scans have been used by physicians to alter treatment decisions in a significant number of cancer patients. Changes in treatment resulted in reducing the number of surgeries and biopsies for cancer patients, and in cost savings.

The overall architecture of the PEM system is shown in Figure 14. The main modules are represented: plans of crystals matrix, Front-end electronics (FE), and Data Acquisition electronics (DAQ) and image reconstruction computer (Carlos Leong et al, 2007).

![Figure 14. PEM architecture (Source from Carlos Leong et al, 2007).](image)
The FE system is responsible for the conditioning of the electrical signal generated in APDs as the result of the scintillation crystal when hit by a photon.

The most challenging aspect of the FE is the processing of the analog signal generated in the APD. Indeed, in order to obtain a good resolution of the reconstruction image in a short period of time, it has been concluded that the signal generated by the APD should be amplified and processed.

After the FE builds the signal with the correct shape, it samples that signal and identifies the signals with greater energy. Once identified, these signals and the correspondent crystals, that information is sent to the Data Acquisition (DAQ) system, responsible for the acquisition and processing of digital signals received from the FE. An FE module consists of APDs, ASICs (responsible for conditioning and amplification of signals generated by APDs) ADCs (to convert the analog signals provided by the ASIC to digital signals) and serialization data transmission circuits that are responsible for sending digitized data to the DAQ system.

As both MRI and PEM have similar sensitivities, PEM’s role in clinical practice mirrors that of MRI. Detection and characterization of primary breast lesions in preoperative surgical planning or pre chemotherapy evaluation remain primary indications for the exam.

Disadvantage of PEM is the radiation exposure. In terms of relative risk to a 40-year-old woman, a single PEM study involving the use of a label-recommended radionuclide dose is associated with a 15-fold higher risk of cancer induction than a single screen film or digital mammogram. Overall, there is also a 25-fold higher risk of cancer-related mortality. In mammography, fibroglandular tissue is the only tissue exposed to a substantial level of ionizing radiation. In PEM, however all body organs are irradiated with radio nuclides. Therefore, the risk from mammography is essentially only that of induced breast cancer, while PEM can lead to cancer induction in any number of radiosensitive organs. This is caused primarily by a reliance on both radioactive decay (Shannon, 2013).
2.5. Digital mammography equipment

2.5.1. Introduction to mammography equipment

Mammography is the most commonly used technique to detect breast cancer at early stages, usually pre-symptomatic. When symptoms are developed, the cancer has typically become invasive and consequently the prognosis is less favorable (Oliver, 2010). This technique aim is to assist the radiologist to reduce missed breast lesion detection and consequently prevent the propagation of the cancer in to a more severe stage.

2.5.2. Working principle of mammography equipment

The Mammography is the most efficient system to detect clinically occult illness, being the only image based method recommended for breast cancer screening. An application of Hough transform to Identify Breast Cancer in Images (VIP image). Mammography can greatly reduce the breast cancer mortality in a well-organized screening program over the population, being the breast cancer detection technique that most reduces mortality (Eastman and Crossin, 2006). The performance of the mammography decreases as the density of the breast increases.

Mammography is diagnosis exam that uses low amplitude and high current X-rays to examine the human breast. X ray is an electromagnetic radiation with high energy: wavelength in the range of objects and bodies (Bronzino, 2000).

The main X-ray photons interactions with the tissue are photoelectric effect and Compton scattering (Akay, 2006). The photoelectric effect occurs when an X-ray photon of short wave length interacts with the electric field of an atom nucleus and ejects off its electrons. The free electron becomes an ionizing particle (Kima, 1995). In Compton scattering, the X-ray photon intersects with an external electron and becomes free. The incident photon transfers energy to the scattering electron, which is ejected and becomes ionized. The photon changes direction. The photoelectric effect is the primary responsible for the radiologic image contrast, while Compton scattering is the primary mechanism for the image resolution limit. Currently, Mammography
equipment has an X-ray tube which produces X-rays. This radiation crosses a metal filter and a collimator, which narrows the beam wave.

The radiation is transmitted to the breast, which transmits a portion to an anti-scatter grid, passing to the image receptor. There, the photons interact and deposit their energy locally, allowing the image formation. A fraction of x-rays passes through the receiver without interaction, reaching a sensor, which is used to activate the mechanism of automatic exposure control (Webster, 2006).

The image formation will depend on the structures’ densities when penetrated with the X-rays, as it absorption is dependent on the structures’ densities. The image must have high spatial resolution to delineate the edges of structures of reduced dimension, as microcalcifications. Usually, there are two standard image projections: craniocaudal (CC), which is a view from top, allowing a better imaging of the central and inner breast sectors; and mediolateral oblique (MLO), which is lateral view from a central angle, having an enhanced perspective of the glands (Arnau, 2007).

![Diagram of digital mammography equipment](image)

**Figure 15.** Diagram of digital mammography equipment (Bronzino, 2000).
Figure 16. Two distinct mammography projections: a) craniocaudal view and b) mediolateral oblique view (Arnau, 2007).

This permits some indication of three dimensions and an understanding of overlapping structures. High-quality mammogram with high spatial resolution and adequate contrast separation allows radiologists to observe fine structures. Studies have shown that the mortality rate could decrease by 30% if all women age 50 and older have regular mammograms.

With the widespread development of screening programs in the USA, radiologists have had to read a large number of mammograms. Reading mammograms is difficult and requires a great deal of experience. Several studies have shown that 20% to 40% of breast cancer fails to be detected at screening (Harvey et al, 1993) due to radiologist fatigue, the complex image structure of the breast tissue, and the subtlety of the cancer. Even the most experienced mammographic readers only have a correct detection rate of 85-91% (Bird et al, 1992). Moreover, a study found that there is about 2.6% to 15.9% false positive reading of negative or benign mammograms by radiologists (Elmore et al, 2002). Several studies showed that double reading by two radiologists can improve detection sensitivity up to 15% (Thurfjell et al, 1994). However, implementing double reading can be very costly, time consuming and logically difficult.

Limitations of mammography

- Normal breast structures may obscure cancerous lesions particularly in dense breast with high composition of fibro glandular tissues.
- Superimposed tissue can cause unnecessary recall after diagnosis.
- Complex structures can mask abnormality.
• Inter-intra observer variability is high.
• Low positive predictive value for biopsy recommendations.
• Chances of misinterpretation leading to high false positive and false negative.
• Wrong interpretations may sometimes lead to over diagnosis and over treatment.

2.6. Introduction of breast cancer detection

A typical Digital Mammogram application is the detection of tumors in a breast Mammogram image. Breast Mammogram system may help radiologists evaluate images and detect breast cancer. Such systems are used in addition to the human evaluation of the diagnosis. A breast mammogram system not only improves the cancer image quality, increases the image contrast and automatically determines lesion location, and it also greatly reduces the human workload associated with the diagnosis, and improves the accuracy of detection and diagnosis.

Generally, a typical digital mammogram system includes three steps:
1. Mammogram image acquisition
   a. Image segmentation
   b. Image binarization and thinning
   c. Gray scale extending
2. Mammogram image post processing
   a. Image Orientation
   b. Image triangulation
   c. Euclidean distance calculation

Figure 17. Steps of Image Processing of Mammogram Image.