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A REVIEW ON BREAST CANCER

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ABSTRACT

Breast cancer is the common disease in women worldwide, with some 5-10% of all cases due to inherited mutations of BRCA1 and BRCA2 genes. The prognosis of breast cancer is generally favorable. Ductal carcinoma in situ is regarded as non-life threatening disease. Hence early diagnosis and quick treatment is essential. Obesity, hormone therapy and use of alcohol are possible causes and over-expression of leptin in adipose tissue may also play a role for breast cancer. Normally surgery, radiation therapy and chemotherapy allow a good prognosis for breast cancer. Recent treatment measures include adjuvant therapy, neo adjuvant therapy, and introduction of mono-clonal antibodies and enzyme inhibitors.

Keywords: Breast Cancer, BRCA1, BRCA2, Chemotherapy.

INTRODUCTION

Cancer [1] is mainly caused by the mutation in genes which are present in nucleus of all cells in body. Cancer may be benign or malignant. If cancerous cells remains localized to specific organ of body, it termed as benign tumor however when these tumor cells start migrating towards other organs then it becomes malignant. Uncontrolled proliferation of cells which starts in breast cells and attains malignancy is called breast cancer. A malignant tumor is a group of cancer cells that can grow into (invade) surrounding tissues or spread (metastasize) to distant areas of the body. Survey has shown that breast cancer contributes 11 percent among all types of cancer diagnosed globally annually and it is a major cause of death in women. Breast cancer [2] mainly originates from the milking ducts or the lobules responsible for milk supply towards ducts. Depending upon the origination breast cancers may be ductal or lobular carcinomas. The variation observed in rates of incidence as well as mortality due to breast cancer, is due to a number of contributing factors like age, race, socio-economic status, life style, reproductive history, family history, etc. As a consequence of advancements in diagnostic procedures and treatments available, the rate of survival of patients has increased.

Hence, it is expected that the population susceptible to develop pain as a complication would increase. Pain [3,4] arising in advanced stage of breast cancer can cause emotional suffering and affects quality of life of patients⁵. As per the estimates of the International Association for the Study of Pain (IASP) the prevalence of pain in breast cancer ranges from 40-89 per cent. It has been found that persistent pain after surgical treatment is quite common and is higher among young patients, those undergoing radiotherapy and axillary lymph node dissection and about 20-50 per cent women are affected by persistent neuropathic pain after their surgical treatment.

The normal breast [5]

Mammary gland (glandula mammaria s. mamma) is a pair organ, which relates to the type of the apocrine glands of the skin. It mostly occurs at the base on the large breast muscle (m. pectoralis major), partially on the front of ridge-shaped muscle (m. serratus anterior) and crossing the free edge of breast muscle, adjoins by its small section to the side of breast wall. In the average the base of gland reaches the external edge of sternum. The mammary gland is usually located at the level of the III to (VI) VII ribs, and from all sides (except the nipple and areola) is surrounded

by fatty tissue. Between both mammary glands there is a deepening called cavity (sinus mammarum). Out of the period of lactation the mammary gland has in average 10-12 cm in the diameter, with the thickness of 2-3 cm. The weight of the gland varies in girls in the limits of 150-200 g, in the period of lactation 300-900 g. In the majority of the young healthy women the gland is elastic and has a form of hemisphere. Approximately in the center of the most convex part of the gland, which corresponds to the level of the 5th rib, there is a pigmented section of the skin - the field of areola (areola mammae) surrounding the nipple, with a diameter of 3-5 cm, in an oval, circular or amorphous shape, in center of which comes out the nipple of mammary gland (papilla mammae). The circumference of the pigment of the areola are vestiges of sweat and sebaceous glands (Montgomery glands, there are about 15), which function during lactation. Mammary gland is covered with soft skin. The skin, which covers the nipple and the field of nipple, is characterized by special softness and has the large number of small folds, in a form which resembles wrinkles. The color of the skin is various: it can be pink or brown depending on the general pigmentation of the skin. The intensity of the pigmentation of the field of nipple and the nipple of mammary gland is strengthened during the pregnancy. Each segment of mammary gland is divided into the lobules (lobuli mammae), which are isolated one from another by connective tissue. Each lobule consists of alveoli. The adipose tissue, which carries out all spaces nodes are small, bean-shaped collections of immune system cells (cells that are important in fighting infections) that are connected by lymphatic vessels.

Types of breast cancer [6]

Carcinoma

This is a term used to describe a cancer that begins in the lining layer (epithelial cells) of organs like the breast. Nearly all breast cancers are carcinomas (either ductal carcinomas or lobular carcinomas).

Adenocarcinoma

An adenocarcinoma is a type of carcinoma that starts in glandular tissue (tissue that makes and secretes a substance). The ducts and lobules of the breast are glandular tissues (they make breast milk), so cancers starting in these areas are often called adenocarcinomas.

Carcinoma in situ

This term is used for an early stage of cancer, when it is confined to the layer of cells where it began. In breast cancer, in situ means that the cancer cells remain confined to ducts (ductal carcinoma in situ). The cells have not grown into (invaded) deeper tissues in the breast or spread to other organs in the body. Ductal carcinoma in situ of the breast is sometimes referred to as non-invasive or pre-invasive breast cancer because it might develop into an invasive breast cancer if left untreated. When cancer cells are confined to the lobules it is called lobular carcinoma in situ.

between them, divided in the individual sections by connective-tissue grid, is located between the glandular body of gland and its external cover. In the structure the breasts consist of alveoli. Each segment has its own excretory duct (galactophore, ductus lactiferous), going towards the nipple and opening itself to the surface of the nipple in a 8-14 pin hole (pori lactiferi 0,2-0,3 mm). The nipple has a conical or cylindrical in shape. There are flat nipples and inverted. Ducts pass into the milk sinuses (milky sacs, sinus lactiferus) that serve as reservoirs that collect the milk produced by the alveoli (diameter 0.5-0.7 mm). In the milk sinuses entry numerous branching and anastomosing milk ducts that until the onset of lactation end in thin blind tubes - alveolar milk passages that during pregnancy and lactation give rise to numerous alveoli. The so-called glandular field is formed around the ducts. The greatest number of glandular elements is found in the upper-external part of the breast. From the time of puberty under the influence of hormonal ovarian function begins an intensive development of the mammary glands. Size and shape of glands, the ratio of glandular, connective and fatty tissues of an individual varies, also vary with age, during pregnancy and lactation period. Its largest size it reaches the end of pregnancy and during lactation. To understand breast cancer, it helps to have some basic knowledge about the normal structure of the breasts. The lymph system is important to understand because it is one way breast cancers can spread. This system has several parts. Lymph

Invasive (infiltrating) carcinoma

An invasive cancer is one that has already grown beyond the layer of cells where it started (as opposed to carcinoma in situ). Most breast cancers are invasive carcinomas either invasive ductal carcinoma or invasive lobular carcinoma.

Sarcoma

Sarcomas are cancers that start in connective tissues such as muscle tissue, fat tissue, or blood vessels. Sarcomas of the breast are rare. Types of breast cancers. There are several types of breast cancer, but some of them are quite rare. In some cases a single breast tumor can be a combination of these types or be a mixture of invasive and in situ cancer.

Ductal carcinoma in situ

Ductal carcinoma in situ (DCIS; also known as intraductal carcinoma) is considered noninvasive or pre-invasive breast cancer. DCIS means that cells that lined the ducts have changed to look like cancer cells. The difference between DCIS and invasive cancer is that the cells have not spread (invaded) through the walls of the ducts into the surrounding breast tissue. DCIS is considered a pre-cancer because some cases can go on to become invasive cancers. About 1 in 5 new breast cancer cases will be DCIS. Nearly all women diagnosed at this early stage of breast cancer can be cured.

Lobular carcinoma in situ

In lobular carcinoma in situ (LCIS) cells that look like cancer cells grow in the lobules of the milk-producing glands of the breast, but they do not grow through the wall of the lobules.

Invasive (or infiltrating) ductal carcinoma

This is the most common type of breast cancer. Invasive (or infiltrating) ductal carcinoma (IDC) starts in a milk duct of the breast, breaks through the wall of the duct, and grows into the fatty tissue of the breast. At this point, it may be able to spread (metastasize) to other parts of the body through the lymphatic system and bloodstream. About 8 of 10 invasive breast cancers are infiltrating ductal carcinomas.

Invasive (or infiltrating) lobular carcinoma

Invasive lobular carcinoma (ILC) starts in the milk-producing glands (lobules). Like IDC, it can spread (metastasize) to other parts of the body. About 1 invasive breast cancer in 10 is an ILC. Invasive lobular carcinoma may be harder to detect by a mammogram than invasive ductal carcinoma.

Inflammatory breast cancer

This uncommon type of invasive breast cancer accounts for about 1% to 3% of all breast cancers. Usually there is no single lump or tumor. Instead, inflammatory breast cancer (IBC) makes the skin on the breast look red and feel warm. It also may give the breast skin a thick, pitted appearance that looks a lot like an orange peel. Doctors now know that these changes are not caused by inflammation or infection, but by cancer cells blocking lymph vessels in the skin. The affected breast may become larger or firmer, tender, or itchy.

In its early stages, inflammatory breast cancer is often mistaken for an infection in the breast (called mastitis) and treated as an infection with antibiotics. If the symptoms are caused by cancer, they will not improve, and a biopsy will find cancer cells. Because there is no actual lump, it might not show up on a mammogram, which can make it even harder to find it early. This type of breast cancer tends to have a higher chance of spreading and a worse outlook (prognosis) than typical invasive ductal or lobular cancer.

Triple-negative breast cancer

This term is used to describe breast cancers (usually invasive ductal carcinomas) whose cells lack estrogen receptors and progesterone receptors, and do not have an excess of the HER2 protein on their surfaces. Breast cancers with these characteristics tend to occur more often in younger women and in African-American women. Triple-negative breast cancers tend to grow and spread more quickly than most other types of breast cancer. Because the tumor cells neither lack these certain receptors, neither hormone therapy nor drugs that target HER2 are effective treatments. Chemotherapy can still be useful, and is often

recommended even for early-stage disease as it lowers the risk of the cancer coming back later.

Paget disease of the nipple

This type of breast cancer starts in the breast ducts and spreads to the skin of the nipple and then to the areola, the dark circle around the nipple. It is rare, accounting for only about 1% of all cases of breast cancer. The skin of the nipple and areola often appears crusted, scaly, and red, with areas of bleeding or oozing. The woman may notice burning or itching. Paget disease is almost always associated with either ductal carcinoma in situ (DCIS) or infiltrating ductal carcinoma. Treatment often requires mastectomy. If no lump can be felt in the breast tissue, and the biopsy shows DCIS but no invasive cancer, the outlook (prognosis) is excellent. If invasive cancer is present, the prognosis is not as good, and the cancer will need to be staged and treated like any other invasive cancer.

Phyllodes tumor

This very rare breast tumor develops in the stroma (connective tissue) of the breast, in contrast to carcinomas, which develop in the ducts or lobules. Other names for these tumors include phylloides tumor and cystosarcoma phyllodes. These tumors are usually benign but on rare occasions may be malignant. Benign phyllodes tumors are treated by removing the tumor along with a margin of normal breast tissue. A malignant phyllodes tumor is treated by removing it along with a wider margin of normal tissue, or by mastectomy. Surgery is often all that is needed, but these cancers might not respond as well to the other treatments used for more common breast cancers. When a malignant phyllodes tumor has spread, it can be treated with the chemotherapy given for soft-tissue sarcomas (this is discussed in detail in our document,

Angiosarcoma

This form of cancer starts in cells that line blood vessels or lymph vessels. It rarely occurs in the breasts. When it does, it usually develops as a complication of previous radiation treatments. This is an extremely rare complication of breast radiation therapy that can develop about 5 to 10 years after radiation. Angiosarcoma can also occur in the arms of women who develop lymphedema as a result of lymph node surgery or radiation therapy to treat breast cancer

Classification of breast cancer [7,8]

The term "early breast cancer" refers to breast cancer in stages 0, I and II at the time of diagnosis. Tumor nodal metastasis (TNM) classification of primary tumor (T).

TX-Primary tumor cannot be assessed

T0-No evidence of primary tumor

Tis-Carcinoma in situ

• Tis (DCIS)-Intraductal carcinoma in situ

• Tis (LCIS)-Lobular carcinoma in situ

• Tis (Paget's)-Paget's disease of the nipple with no tumor; tumor-associated Paget's disease is

Classified according to the size of the primary tumor

T1-Tumor 2 cm or less in greatest dimension

- T1mic-Microinvasion 0.1 cm or less in greatest dimension
- T1a-Tumor more than 0.1 but not more than 0.5 cm in greatest dimension
- T1b-Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
- T1c-Tumor more than 1 cm but not more than 2 cm in greatest dimension

T2-Tumor more than 2 cm but not more than 5 cm in greatest dimension

T3-Tumor more than 5 cm in greatest dimension

T4-Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below:

- T4a-Extension to chest wall
- T4b-Edema (including peau d'orange) or ulceration of the breast skin, or satellite skin nodules confined to the same breast
- T4c-Both (T4a and T4b)
- T4d-Inflammatory carcinoma

Note: Dimpling of the skin, nipple retraction, or any other skin change except those described for T4b and T4d may occur in T1-3 tumors without changing the classification.

Regional lymph nodes (N): Clinical classification

NX-Regional lymph nodes cannot be assessed (eg, previously removed)

N0-No regional lymph node metastases

N1-Metastasis to movable ipsilateral axillary lymph nodes(s)

N2-Metastasis to ipsilateral axillary lymph node(s) fixed or matted, or in clinically apparent ipsilateral internal mammary nodes in the absence of evident axillary node metastases

- N2a-Metastasis to ipsilateral axillary lymph node(s) fixed to one another (matted) or to other structures
- N2b-Metastasis only in clinically apparent (as detected by imaging studies [excluding lymphoscintigraphy] or by clinical examination or grossly visible pathologically) ipsilateral internal mammary nodes in the absence of evident axillary node metastases

N3-Metastasis to ipsilateral infraclavicular lymph node(s) with or without clinically evident axillary lymph nodes, or in clinically apparent ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastases, or metastasis in ipsilateral supraclavicular lymph nodes with or without axillary or internal mammary nodal involvement

- N3a-Metastasis to ipsilateral infraclavicular lymph node(s)
- N3b-Metastasis to ipsilateral internal mammary lymph node(s) and clinically apparent axillary lymph nodes.
- N3c-Metastasis in ipsilateral supraclavicular lymph nodes with or without axillary or internal mammary nodal involvement

Regional lymph nodes: Pathologic classification (pN)

Classification is based upon axillary lymph node dissection (ALND) with or without sentinel lymph node dissection (SLND). Classification based solely on SLND without ALND should be designated (sn) [eg, pN0 (i +) (sn)].

pNX-Regional lymph nodes cannot be assessed (eg, previously removed, or not removed for pathologic study)

pN0-No regional lymph node metastasis; no additional examination for isolated tumor cells (ITCs, defined as single tumor cells or small clusters not greater than 0.2 mm, usually detected only by immunohistochemical or molecular methods but which may be verified on hematoxylin and eosin (H&E) stains. ITCs do not usually show evidence of malignant activity [eg, proliferation or stromal reaction])

• pN0 (i -)-No histologic nodal metastases and negative by immunohistochemistry (IHC)

• pN0 (i +)-No histologic nodal metastases but positive by IHC, with no cluster greater than 0.2 mm in diameter

• pN0 (mol -)-No histologic nodal metastases and negative molecular findings (by reverse transcriptase polymerase chain reaction, RT-PCR)

• pN0 (mol +)-No histologic nodal metastases, but positive molecular findings (by RT-PCR)

pN1-Metastasis in 1 to 3 ipsilateral axillary lymph node(s) and/or in internal mammary nodes with microscopic disease detected by SLND but not clinically apparent

• pN1mi-Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)

• pN1a-Metastasis in 1 to 3 axillary lymph nodes

• pN1b-Metastasis to internal mammary lymph nodes with microscopic disease detected by SLND but not clinically apparent

• pN1c-Metastasis in 1 to 3 ipsilateral axillary lymph node(s) and in internal mammary nodes with microscopic disease detected by SLND but not clinically apparent. If associated with more than 3 positive axillary nodes, the internal mammary nodes are classified as N3b to reflect increased tumor burden.

pN2-Metastasis in 4 to 9 axillary lymph nodes or in clinically apparent internal mammary lymph nodes in the absence of axillary lymph nodes

• pN2a-Metastases in 4 to 9 axillary lymph nodes (at least one tumor deposit >2 mm)

• pN2b-Metastasis in clinically apparent internal mammary lymph nodes in the absence of axillary lymph nodes

pN3-Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary nodes; or in more than three axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph node(s)

• pN3a-Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm), or metastasis to the infraclavicular lymph nodes

• pN3b-Metastasis in clinically apparent ipsilateral internal mammary lymph nodes in the presence of one or more

positive axillary nodes; or in more than three axillary lymph nodes with microscopic metastasis in internal mammary lymph nodes detected by SLND but not clinically apparent

- pN3c-Metastasis in ipsilateral supraclavicular lymph node(s)

Distant metastasis (M)

MX-Distant metastasis cannot be assessed

M0-No distant metastasis

M1-Distant metastasis

STAGE GROUPINGS

Stage 0-Tis N0 M0

Stage I-T1 N0 M0 (including T1mic)

Stage IIA-T0 N1 M0; T1 N1 M0 (including T1mic); T2 N0 M0

Stage IIB-T2 N1 M0; T3 N0 M0

Stage IIIA-T0 N2 M0; T1 N2 M0 (including T1mic); T2 N2 M0; T3 N1 M0; T3 N2 M0

Stage IIIB-T4 Any N M0

Stage IIIC-Any T N3 M0

Stage IV-Any T Any N M1

Causes of breast cancer [9]

DNA is the chemical in each of our cells that makes up our genes the instructions for how our cells function. We usually look like our parents because they are the source of our DNA. But DNA affects more than how we look. Some genes control when our cells grow, divide into new cells, and die. Genes that speed up cell division are called oncogenes. Others that slow down cell division, or cause cells to die at the right time, are called tumor suppressor genes. Certain changes (mutations) in DNA that “turn on” oncogenes or “turn off” tumor suppressor genes can cause normal breast cells to become cancerous.

Inherited gene mutations

Certain inherited DNA mutations can dramatically increase the risk for developing certain cancers and are responsible for many of the cancers that run in some families. For example, the BRCA genes (BRCA1 and BRCA2) are tumor suppressor genes. A mutation in one of these genes can be inherited from a parent. When one of these genes are mutated, it no longer suppresses abnormal growth, and cancer is more likely to develop. Women have already begun to benefit from advances in understanding the genetic basis of breast cancer. Genetic testing can identify some women who have inherited mutations in the BRCA1 or BRCA2 tumor suppressor genes (or less commonly in other genes such as PTEN or TP53). These women can then take steps to reduce their risk of developing breast cancers and to monitor changes in their breasts carefully to find cancer at an earlier, more treatable stage. These steps are discussed in later sections of this document. Mutations in tumor suppressor genes like the BRCA genes are considered “high penetrance” because they often lead to cancer. Although many of the women with high penetrance mutations develop cancer, most cases of cancer (including

breast cancer) are not caused by this kind of mutation. More often, low-penetrance mutations or gene variations are a factor in cancer development. Each of these may have a small individual effect on cancer development, but the overall effect on the population can be large because they are common, and people often are affected with more than one at the same time. The genes involved may affect things like hormone levels, metabolism or other things that interact with risk factors for breast cancer. These genes may be responsible for much of the risk of breast cancer that runs in families.

Acquired gene mutations

Most DNA mutations related to breast cancer occur in single breast cells during a woman's life rather than having been inherited. These acquired mutations of oncogenes and/or tumor suppressor genes may result from other factors, like radiation or cancer causing chemicals. But so far, the causes of most acquired mutations that could lead to breast cancer are still unknown. Most breast cancers have several acquired gene mutations. Tests to spot acquired gene changes may help doctors more accurately predict the outlook for some women with breast cancer. For example, tests can identify women whose breast cancer cells have too many copies of the HER2 oncogene. These cancers tend to be more aggressive. At the same time, drugs have been developed that specifically target these cancers and improve outcomes for patients.

Symptoms [10]

Pain usually does not occur in early breast cancer. A painless lump may be the first symptom. In later stages, pain may occur due to involvement of deeper structures like muscles, ribs, etc., resulting in severe excruciating pain which increases with chest movements. Patients undergoing mastectomy may develop chronic neuropathic pain which may be either phantom breast pain, or intercostobrachial neuralgia (including post-mastectomy pain syndrome), or neuroma pain (including scar pain) or pain due to other nerve injury. During radiotherapy, there may be active painful skin lesions at the radiation site and later cervical or brachial plexopathy may develop. Involvement of brachial plexus by tumour results in pain and Horner's syndrome, whereas sensory symptoms like paresthesia, numbness, dysesthesia and swelling and weakness of arm occur in radiation induced injury to brachial plexus. Depending upon the measurement tool used, 2-83 per cent of breast cancer survivors suffer from lymphoedema over the chest or arm¹⁰. Breast cancer metastasis commonly involves bones, lungs, brain and liver, which respectively results in bony pain, pain in hypochondrium, headache and other symptoms in areas of cancer invasion. There may be sudden exacerbations of pain, termed as breakthrough cancer pain (BTcP). A patient is supposed to have BTcP only when he/she has adequately controlled background cancer pain and is still experiencing transient exacerbations of pain. It can either occur unexpectedly (idiopathic pain) with

involuntary acts like coughing, or expectedly (volitional pain) with voluntary acts like walking. The site and pathophysiology of BTcP is usually the same site as that of background pain. It is relatively common in advanced disease, painful vertebral metastasis and pain originating from nerve plexuses.

Other possible signs of breast cancer include:

- Swelling of all or part of a breast (even if no distinct lump is felt)
- Skin irritation or dimpling
- Breast or nipple pain
- Nipple retraction (turning inward)
- Redness, scaliness, or thickening of the nipple or breast skin
- Nipple discharge (other than breast milk)

Sometimes a breast cancer can spread to lymph nodes under the arm or around the collar bone and cause a lump or swelling there, even before the original tumor in the breast tissue is large enough to be felt.

Risk factors for breast cancer [6,11,12]

A risk factor is anything that affects your chance of getting a disease, such as cancer.

Gender

Simply being a woman is the main risk factor for developing breast cancer. Men can develop breast cancer, but this disease is about 100 times more common among women than men. This is probably because men have less of the female hormones estrogen and progesterone, which can promote breast cancer cell growth.

Aging

Your risk of developing breast cancer increases as you get older. About 1 out of 8 invasive breast cancers are found in women younger than 45, while about 2 of 3 invasive breast cancers are found in women age 55 or older.

Genetic risk factors

About 5% to 10% of breast cancer cases are thought to be hereditary, meaning that they result directly from gene defects (called mutations) inherited from a parent.

BRCA1 and BRCA2

The most common cause of hereditary breast cancer is an inherited mutation in the BRCA1 and BRCA2 genes. In normal cells, these genes help prevent cancer by making proteins that keep the cells from growing abnormally. If you have inherited a mutated copy of either gene from a parent, you have a high risk of developing breast cancer during your lifetime. Although in some families with BRCA1 mutations the lifetime risk of breast cancer is as high as 80%, on average this risk seems to be in the range of 55 to 65%. For BRCA2 mutations the risk is lower, around 45%. Breast cancers linked to these mutations occur more often in younger women and more often affect

both breasts than cancers not linked to these mutations. Women with these inherited mutations also have an increased risk for developing other cancers, particularly ovarian cancer. In the United States BRCA mutations are more common in Jewish people of Ashkenazi (Eastern Europe) origin than in other racial and ethnic groups, but they can occur in anyone.

Changes in other genes

Other gene mutations can also lead to inherited breast cancers. These gene mutations are much rarer and often do not increase the risk of breast cancer as much as the BRCA genes. They are not frequent causes of inherited breast cancer.

ATM: The ATM gene normally helps repair damaged DNA. Inheriting 2 abnormal copies of this gene causes the disease ataxia-telangiectasia. Inheriting 1 mutated copy of this gene has been linked to a high rate of breast cancer in some families.

TP53: The TP53 gene gives instructions for making a protein called p53 that helps stop the growth of abnormal cells. Inherited mutations of this gene cause Li-Fraumeni syndrome (named after the 2 researchers who first described it). People with this syndrome have an increased risk of developing breast cancer, as well as several other cancers such as leukemia, brain tumors, and sarcomas (cancer of bones or connective tissue). This is a rare cause of breast cancer.

CHEK2: The Li-Fraumeni syndrome can also be caused by inherited mutations in the CHEK2 gene. Even when it does not cause this syndrome, it can increase breast cancer risk about twofold when it is mutated.

PTEN: The PTEN gene normally helps regulate cell growth. Inherited mutations in this gene can cause Cowden syndrome, a rare disorder in which people are at increased risk for both benign and malignant breast tumors, as well as growths in the digestive tract, thyroid, uterus, and ovaries. Defects in this gene can also cause a different syndrome called Bannayan-Riley-Ruvalcaba syndrome that is not thought to be linked to breast cancer risk.

CDH1: Inherited mutations in this gene cause hereditary diffuse gastric cancer, a syndrome in which people develop a rare type of stomach cancer at an early age. Women with mutations in this gene also have an increased risk of invasive lobular breast cancer.

STK11: Defects in this gene can lead to Peutz-Jeghers syndrome. People with this disorder develop pigmented spots on their lips and in their mouths, polyps in the urinary and gastrointestinal tracts, and have an increased risk of many types of cancer, including breast cancer.

Genetic testing

Genetic tests can be done to look for mutations in the BRCA1 and BRCA2 genes (or some other genes linked to breast cancer risk). Although testing may be helpful in some situations, the pros and cons need to be considered carefully.

Family history of breast cancer

Breast cancer risk is higher among women whose close blood relatives have this disease. Having one first-degree relative (mother, sister, or daughter) with breast cancer approximately doubles a woman's risk. Having 2 first-degree relatives increases her risk about 3-fold. The exact risk is not known, but women with a family history of breast cancer in a father or brother also have an increased risk of breast cancer. Altogether, less than 15% of women with breast cancer have a family member with this disease. This means that most (over 85%) women who get breast cancer do not have a family history of this disease.

Personal history of breast cancer

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. This is different from a recurrence (return) of the first cancer.

Race and ethnicity

Overall, white women are slightly more likely to develop breast cancer than are African-American women, but African-American women are more likely to die of this cancer. However, in women under 45 years of age, breast cancer is more common in African-American women. Asian, Hispanic, and Native-American women have a lower risk of developing and dying from breast cancer.

Dense breast tissue

Breasts are made up of fatty tissue, fibrous tissue, and glandular tissue. Someone is said to have dense breast tissue (as seen on a mammogram) when they have more glandular and fibrous tissue and less fatty tissue. Women with dense breasts have a higher risk of breast cancer than women with less dense breasts. Unfortunately, dense breast tissue can also make mammograms less accurate. A number of factors can affect breast density, such as age, menopausal status, the use of drugs (such as menopausal hormone therapy), pregnancy, and genetics.

Certain benign breast conditions

Women diagnosed with certain benign breast conditions might have an increased risk of breast cancer. Some of these conditions are more closely linked to breast cancer risk than others. Doctors often divide benign breast conditions into 3 general groups, depending on how they affect this risk.

Non-proliferative lesions

These conditions are not associated with overgrowth of breast tissue. They do not seem to affect breast cancer risk, or if they do, it is to a very small extent. They include: Fibrosis and/or simple cysts (this used to be called fibrocystic disease or changes), mild hyperplasia, adenosis (nonsclerosing), ductal ectasia, phyllodes tumor (benign), a single papilloma, fat necrosis, periductal fibrosis, squamous and apocrine metaplasia, epithelial-related

calcifications, other benign tumors (lipoma, hamartoma, hemangioma, neurofibroma, adenomyoepithelioma) Mastitis (infection of the breast) is not a lesion, but is a condition that can occur that does not increase the risk of breast cancer.

Proliferative lesions without atypia

These conditions show excessive growth of cells in the ducts or lobules of the breast tissue. They seem to raise a woman's risk of breast cancer slightly (1½ to 2 times normal). They include:

- Usual ductal hyperplasia (without atypia)
- Fibroadenoma
- Sclerosing adenosis
- Several papillomas (called papillomatosis)
- Radial scar

Proliferative lesions with atypia

In these conditions, there is an overgrowth of cells in the ducts or lobules of the breast tissue, with some of the cells no longer appearing normal. They have a stronger effect on breast cancer risk, raising it 3½ to 5 times higher than normal. These types of lesions include: atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH) Women with a family history of breast cancer and either hyperplasia or atypical hyperplasia have an even higher risk of developing a breast cancer.

Lobular carcinoma in situ

In lobular carcinoma in situ (LCIS) cells that look like cancer cells are growing in the lobules of the milk-producing glands of the breast, but they do not grow through the wall of the lobules. LCIS (also called lobular neoplasia) is sometimes grouped with ductal carcinoma in situ (DCIS) as a non-invasive breast cancer, but it differs from DCIS in that it doesn't seem to become an invasive cancer if it isn't treated. Women with this condition have a 7- to 11-fold increased risk of developing invasive cancer in either breast. For this reason, women with LCIS should make sure they have regular mammograms and doctor visits.

Menstrual periods

Women who have had more menstrual cycles because they started menstruating early (before age 12) and/or went through menopause later (after age 55) have a slightly higher risk of breast cancer. The increase in risk may be due to a longer lifetime exposure to the hormones estrogen and progesterone.

Previous chest radiation

Women who, as children or young adults, had radiation therapy to the chest area as treatment for another cancer (such as Hodgkin disease or non-Hodgkin lymphoma) have a significantly increased risk for breast cancer. This varies with the patient's age when they had radiation. If chemotherapy was also given, it may have

stopped ovarian hormone production for some time, lowering the risk. The risk of developing breast cancer from chest radiation is highest if the radiation was given during adolescence, when the breasts were still developing. Radiation treatment after age 40 does not seem to increase breast cancer risk.

Diethylstilbestrol exposure

From the 1940s through the 1960s some pregnant women were given the drug diethylstilbestrol (DES) because it was thought to lower their chances of miscarriage (losing the baby). These women have a slightly increased risk of developing breast cancer. Women whose mothers took DES during pregnancy may also have a slightly higher risk of breast cancer.

Having children

Women who have had no children or who had their first child after age 30 have a slightly higher breast cancer risk. Having many pregnancies and becoming pregnant at a young age reduce breast cancer risk. Pregnancy reduces a woman's total number of lifetime menstrual cycles, which may be the reason for this effect.

Birth control

Oral contraceptives

Studies have found that women using oral contraceptives (birth control pills) have a slightly greater risk of breast cancer than women who have never used them. This risk seems to go back to normal over time once the pills are stopped. Women who stopped using oral contraceptives more than 10 years ago do not appear to have any increased breast cancer risk. When thinking about using oral contraceptives, women should discuss their other risk factors for breast cancer with their health care team.

Depot-medroxyprogesterone acetate

(DMPA; Depo-Provera®) is an injectable form of progesterone that is given once every 3 months as birth control. A few studies have looked at the effect of DMPA on breast cancer risk. Women currently using DMPA seem to have an increase in risk, but the risk doesn't seem to be increased if this drug was used more than 5 years ago.

Hormone therapy after menopause

Hormone therapy with estrogen (often combined with progesterone) has been used for many years to help relieve symptoms of menopause and to help prevent osteoporosis (thinning of the bones). Earlier studies suggested it might have other health benefits as well, but these benefits have not been found in more recent, better designed studies. This treatment goes by many names, such as post-menopausal hormone therapy (PHT), hormone replacement therapy (HRT), and menopausal hormone therapy (MHT). There are 2 main types of hormone therapy. For women who still have a uterus (womb), doctors generally prescribe both estrogen and progesterone (known

as combined hormone therapy or HT). Progesterone is needed because estrogen alone can increase the risk of cancer of the uterus. For women who no longer have a uterus (those who've had a hysterectomy), estrogen alone can be prescribed. This is commonly known as estrogen replacement therapy (ERT) or just estrogen therapy (ET).

Combined hormone therapy

Using combined hormone therapy after menopause increases the risk of getting breast cancer. It may also increase the chances of dying from breast cancer. This increase in risk can be seen with as little as 2 years of use. Combined HT also increases the likelihood that the cancer may be found at a more advanced stage. The increased risk from combined hormone therapy appears to apply only to current and recent users. A woman's breast cancer risk seems to return to that of the general population within 5 years of stopping combined treatment. The word bioidentical is sometimes used to describe versions of estrogen and progesterone with the same chemical structure as those found naturally in people. The use of these hormones has been marketed as a safe way to treat the symptoms of menopause. It is important to realize that although there are few studies comparing "bioidentical" or "natural" hormones to synthetic versions of hormones, there is no evidence that they are safer or more effective. The use of these bioidentical hormones should be assumed to have the same health risks as any other type of hormone therapy.

Estrogen therapy (ET)

The use of estrogen alone after menopause does not appear to increase the risk of developing breast cancer. In fact, some research has suggested that women who have previously had their uterus removed and who take estrogen actually have a lower risk of breast cancer. Women taking estrogen seem to have more problems with strokes and other blood clots, though. Also, when used long term (for more than 10 years), ET has been found to increase the risk of ovarian cancer in some studies. At this time there appear to be few strong reasons to use post-menopausal hormone therapy (either combined HT or ET), other than possibly for the short-term relief of menopausal symptoms. Along with the increased risk of breast cancer, combined HT also appears to increase the risk of heart disease, blood clots, and strokes. It does lower the risk of colorectal cancer and osteoporosis, but this must be weighed against possible harm, especially since there are other effective ways to prevent and treat osteoporosis. Although ET does not seem to increase breast cancer risk, it does increase the risk of blood clots and stroke. The decision to use hormone therapy after menopause should be made by a woman and her doctor after weighing the possible risks and benefits, based on the severity of her menopausal symptoms and the woman's other risk factors for heart disease, breast cancer and osteoporosis. If a woman and her doctor decide to try hormones for symptoms of menopause, it is usually best to

use it at the lowest dose needed to control symptoms and for as short a time as possible.

Breast feeding

Some studies suggest that breastfeeding may slightly lower breast cancer risk, especially if it is continued for 1½ to 2 years. But this has been a difficult area to study, especially in countries such as the United States, where breastfeeding for this long is uncommon. One explanation for this possible effect may be that breastfeeding reduces a woman's total number of lifetime menstrual cycles (similar to starting menstrual periods at a later age or going through early menopause).

Drinking alcohol

The use of alcohol is clearly linked to an increased risk of developing breast cancer. The risk increases with the amount of alcohol consumed. Compared with non-drinkers, women who consume 1 alcoholic drink a day have a very small increase in risk. Those who have 2 to 5 drinks daily have about 1½ times the risk of women who don't drink alcohol. Excessive alcohol consumption is also known to increase the risk of developing several other types of cancer.

Being overweight or obese

Being overweight or obese after menopause increases breast cancer risk. Before menopause your ovaries produce most of your estrogen, and fat tissue produces a small amount of estrogen. After menopause (when the ovaries stop making estrogen), most of a woman's estrogen comes from fat tissue. Having more fat tissue after menopause can increase your chance of getting breast cancer by raising estrogen levels. Also, women who are overweight tend to have higher blood insulin levels. Higher insulin levels have also been linked to some cancers, including breast cancer. But the connection between weight and breast cancer risk is complex. For example, the risk appears to be increased for women who gained weight as an adult but may not be increased among those who have been overweight since childhood. Also, excess fat in the waist area may affect risk more than the same amount of fat in the hips and thighs. Researchers believe that fat cells in various parts of the body have subtle differences that may explain this.

Physical activity

Evidence is growing that physical activity in the form of exercise reduces breast cancer risk. The main question is how much exercise is needed. In one study from the Women's Health Initiative, as little as 1.25 to 2.5 hours per week of brisk walking reduced a woman's risk by 18%. Walking 10 hours a week reduced the risk a little more.

Diet and vitamin intake

Many studies have looked for a link between what women eat and breast cancer risk, but so far the results have been conflicting. Some studies have indicated that diet may

play a role, while others found no evidence that diet influences breast cancer risk. Studies have looked at the amount of fat in the diet, intake of fruits and vegetables, and intake of meat. No clear link to breast cancer risk was found. Studies have also looked at vitamin levels, again with inconsistent results. Some studies actually found an increased risk of breast cancer in women with higher levels of certain nutrients. So far, no study has shown that taking vitamins reduces breast cancer risk. This is not to say that there is no point in eating a healthy diet. A diet low in fat, low in red meat and processed meat, and high in fruits and vegetables might have other health benefits. Most studies have found that breast cancer is less common in countries where the typical diet is low in total fat, low in polyunsaturated fat, and low in saturated fat. But many studies of women in the United States have not linked breast cancer risk to dietary fat intake. Researchers are still not sure how to explain this apparent disagreement. It may be at least partly due to the effect of diet on body weight (see below). Also, studies comparing diet and breast cancer risk in different countries are complicated by other differences (like activity level, intake of other nutrients, and genetic factors) that might also affect breast cancer risk. More research is needed to understand the effect of the types of fat eaten on breast cancer risk. But it is clear that calories do count, and fat is a major source of calories. High-fat diets can lead to being overweight or obese, which is a breast cancer risk factor. A diet high in fat has also been shown to influence the risk of developing several other types of cancer, and intake of certain types of fat is clearly related to heart disease risk.

Chemicals in the environment

A great deal of research has been reported and more is being done to understand possible environmental influences on breast cancer risk. Compounds in the environment that have estrogen-like properties are of special interest. For example, substances found in some plastics, certain cosmetics and personal care products, pesticides (such as DDE), and PCBs (polychlorinated biphenyls) seem to have such properties. These could in theory affect breast cancer risk. This issue understandably invokes a great deal of public concern, but at this time research does not show a clear link between breast cancer risk and exposure to these substances. Unfortunately, studying such effects in humans is difficult. More research is needed to better define the possible health effects of these and similar substances.

Tobacco smoke

For a long time, studies found no link between cigarette smoking and breast cancer. In recent years though, more studies have found that long-term heavy smoking is linked to a higher risk of breast cancer. Some studies have found that the risk is highest in certain groups, such as women who started smoking when they were young. In 2009, the International Agency for Research on Cancer concluded that there is limited evidence that tobacco

smoking causes breast cancer. An active focus of research is whether secondhand smoke increases the risk of breast cancer. Both mainstream and secondhand smoke contain chemicals that, in high concentrations, cause breast cancer in rodents. Chemicals in tobacco smoke reach breast tissue and are found in breast milk.

The evidence on secondhand smoke and breast cancer risk in human studies is controversial, at least in part because the link between smoking and breast cancer hasn't been clear. One possible explanation for this is that tobacco smoke may have different effects on breast cancer risk in smokers and in those who are just exposed to smoke. A report from the California Environmental Protection Agency in 2005 concluded that the evidence about secondhand smoke and breast cancer is "consistent with a causal association" in younger, mainly premenopausal women. The 2006 US Surgeon General's report, *The Health Consequences of Involuntary Exposure to Tobacco Smoke*, concluded that there is suggestive but not sufficient evidence of a link at this point. In any case, this possible link to breast cancer is yet another reason to avoid secondhand smoke.

Night work

Several studies have suggested that women who work at night for example, nurses on a night shift may have an increased risk of developing breast cancer. This is a fairly recent finding, and more studies are looking at this issue. Some researchers think the effect may be due to changes in levels of melatonin, a hormone whose production is affected by the body's exposure to light, but other hormones are also being studied.

Antiperspirants

Internet e-mail rumors have suggested that chemicals in underarm antiperspirants are absorbed through the skin, interfere with lymph circulation, cause toxins to build up in the breast, and eventually lead to breast cancer. Based on the available evidence (including what we know about how the body works), there is little if any reason to believe that antiperspirants increase the risk of breast cancer.

Bras

Internet e-mail rumors and at least one book have suggested that bras cause breast cancer by obstructing lymph flow. There is no good scientific or clinical basis for this claim. Women who do not wear bras regularly are more likely to be thinner or have less dense breasts, which would probably contribute to any perceived difference in risk.

Induced abortion

Several studies have provided very strong data that neither induced abortions nor spontaneous abortions (miscarriages) have an overall effect on the risk of breast cancer.

Breast implants

Several studies have found that breast implants do not increase the risk of breast cancer, although silicone breast implants can cause scar tissue to form in the breast. Implants make it harder to see breast tissue on standard mammograms, but additional x-ray pictures called implant displacement views can be used to examine the breast tissue more completely. Breast implants may be linked to a rare type of lymphoma called anaplastic large cell lymphoma. This lymphoma has rarely been found in the breast tissue around the implants. So far, though, there are too few cases to know if the risk of this lymphoma is really higher in women that have implants.

Aetiology [13]

The aetiology of cancer pain is multi-factorial. It may arise due to (i) cancer itself due to release of inflammatory mediators or due to metastases to distant tissues including bones and neuronal tissue, and (ii) cancer treatment. Sensory neurons are degenerated after chemotherapy and lead to neuropathic pain. Radiotherapy induced pain arises as a result of microvascular changes and nerve compression. The main causes for surgery induced pain are damage to the intercostobrachial nerves and neuroma formation. Estrogen deficiency caused by aromatase inhibitors leads to arthralgias.

Diagnosis of breast cancer [14,15]

Diagnostic mammograms

A mammogram is an x-ray of the breast. Screening mammograms are used to look for breast disease in women who have no signs or symptoms of a breast problem. Screening mammograms usually take 2 views (x-ray pictures taken from different angles) of each breast. 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 concern. 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 you or your 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), which is very unlikely to be cancerous.

Magnetic resonance imaging (MRI) of the breast

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. If an abnormal area in the breast is found, it can often be biopsied using an MRI for guidance.

Breast ultrasound

Ultrasound, also known as sonography, uses sound waves to outline a part of the body. For this test, a small, microphone-like instrument called a transducer is placed on the skin (which is often first lubricated with ultrasound gel). 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 that is displayed on a computer screen. This test is painless and does not expose you to radiation. Ultrasound has become a valuable tool to use along with mammography because it is widely available and less expensive than other options, such as MRI. The use of ultrasound instead of mammograms for breast cancer screening is not recommended.

Usually, breast ultrasound is used to target a specific area of concern found on the mammogram. Ultrasound helps distinguish between cysts (fluid-filled sacs) and solid masses and sometimes can help tell the difference between benign and cancerous tumors. Ultrasound may be most helpful in women with very dense breasts. Clinical trials are now looking at the benefits and risks of adding breast ultrasound to screening mammograms in women with dense breasts and a higher risk of breast cancer.

Ductogram

This test, also called a galactogram, sometimes helps determine the cause of nipple discharge. In this test a very thin plastic tube is placed into the opening of the duct in the nipple that the discharge is coming from. A small amount of contrast medium is injected, which outlines the shape of the duct on an x-ray image and shows if there is a mass inside the duct.

Newer imaging tests

Newer tests like scintimammography and tomosynthesis are not used commonly and are still being studied to determine their usefulness. These 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

In nipple discharge exam 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 or secretions are 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, doctors cannot be sure breast cancer is not present. 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.

Fine needle aspiration biopsy

In a fine needle aspiration (FNA) biopsy, the doctor uses a very thin, hollow needle attached to a syringe to withdraw (aspirate) a small amount of tissue from a suspicious area, which is then looked at under a microscope. The needle used for an FNA biopsy is thinner than the one used for blood tests. If the area to be biopsied can be felt, the needle can be guided into the area of the breast change while the doctor is feeling (palpating) it. If the lump can't be felt easily, the doctor might use ultrasound to watch the needle on a screen as it moves toward and into the mass. A local anesthetic (numbing medicine) may or may not be used. Because such a thin needle is used for the biopsy, the process of getting the anesthetic may actually be more uncomfortable than the biopsy itself. Once the needle is in place, fluid is drawn out. If the fluid is clear, the lump is probably a benign cyst. Bloody or cloudy fluid can mean either a benign cyst or, very rarely, a cancer. If the lump is solid, small tissue fragments are drawn out. A pathologist will look at the biopsy tissue or fluid under a microscope to determine if it is cancerous. An FNA biopsy is the easiest type of biopsy to have, but it has some disadvantages. It can sometimes miss a cancer if the needle is not placed among the cancer cells. And even if cancer cells are found, it is usually not possible to determine if the cancer is invasive. In some cases there may not be enough cells to perform some of the other lab tests that are routinely done on breast cancer specimens. If the FNA biopsy does not provide a clear diagnosis, or your doctor is still suspicious, a second biopsy or a different type of biopsy should be done.

Core needle biopsy

A core biopsy uses a larger needle to sample breast changes felt by the doctor or pinpointed by ultrasound or mammogram. (When mammograms taken from different angles are used to pinpoint the biopsy site, this is known as a stereotactic core needle biopsy.) In some centers, the biopsy can be guided by an MRI scan. The needle used in core biopsies is larger than the one used in FNA. It removes a small cylinder (core) of tissue (about 1/16- to 1/8-inch in diameter and ½-inch long) from a breast abnormality. Several cores are often removed. The biopsy is done using local anesthesia (you are awake but the area is numbed) in

an outpatient setting. Because it removes larger pieces of tissue, a core needle biopsy is more likely than an FNA to provide a clear diagnosis, although it might still miss some cancers.

Vacuum-assisted biopsies

Vacuum-assisted biopsies can be done with systems such as the Mammotome® or ATEC® (Automated Tissue Excision and Collection). For these procedures the skin is numbed and a small incision (about ¼ inch) is made. A hollow probe is inserted through the incision into the abnormal area of breast tissue. The probe can be guided into place using x-rays or ultrasound (or MRI in the case of the ATEC system). A cylinder of tissue is then suctioned in through a hole in the side of the probe, and a rotating knife within the probe cuts the tissue sample from the rest of the breast. Several samples can be taken from the same incision. Vacuum-assisted biopsies are done as an outpatient procedure. No stitches are needed, and there is minimal scarring. This method usually removes more tissue than core biopsies.

Surgical (open) biopsy

Usually, breast cancer can be diagnosed using needle biopsy. Rarely, surgery is needed to remove all or part of the lump for microscopic examination. This is referred to as a surgical biopsy or an open biopsy. Most often, the surgeon removes the entire mass or abnormal area as well as a surrounding margin of normal-appearing breast tissue. This is called an excisional biopsy. If the mass is too large to be removed easily, only part of it may be removed. This is called an incisional biopsy. It is most often done in the hospital's outpatient department under local anesthesia, often with intravenous sedation. This type of biopsy can also be done under general anesthesia. If the breast change cannot be felt, a mammogram may be used to place a wire into the correct area to guide the surgeon. This technique is called wire localization or stereotactic wire localization. After the area is numbed with local anesthetic, a thin hollow needle is placed in the breast, and x-ray views are used to guide the needle to the suspicious area. Once the tip of the needle is in the right spot, a thin wire is inserted through the center of the needle. A small hook at the end of the wire keeps it in place. The hollow needle is then removed. The surgeon can then use the wire as a guide to the abnormal area to be removed. The surgical specimen is sent to the lab to be looked at under a microscope.

Treatment Strategies for Breast Cancer [16-19]

Surgical therapy

Breast conserving therapy (BCT) refers to surgical removal of the tumor without removing excessive amounts of normal breast tissue. The aim of BCT is to provide a cancer operation equivalent to mastectomy and a cosmetically acceptable breast, with a low rate of recurrence in the treated breast. The critical obstacle to widespread acceptance and utilization of BCT is the risk of in-breast

recurrence. Most doctors advise against BCT and instead recommend mastectomy if they estimate the risk of in breast recurrence to be >10 to 15 percent over the succeeding 5 to 10 years, even after surgery and radiation. BCT provides an acceptable alternative to mastectomy for many, but is applicable to only 60 to 75 % of newly diagnosed women. There are very few contraindications to BCT. For most women, the choice of BCT versus mastectomy can be a matter of personal preference. Absolute contraindications include pregnancy (first or second trimester), diffuse suspicious calcifications, previous radiation to the region and inability to achieve negative margins (particularly with EIC-extensive intraductal carcinoma). Relative contraindications include two or more gross tumors (multicentric disease) in different quadrants, tumor greater than 5 cm initially or after neoadjuvant chemotherapy, large tumorbreast ratio for cosmesis and collagen vascular disease. It's truth that breast conserving surgery is not an option for all women. If the tumour is ! 4cm, multifocal or if radiotherapy has to be avoided, mastectomy is the method of choice. Regardless of the method used, an axillary lymph node dissection is always mandatory.

Minimally invasive procedures

Today breast conservation therapy has become the treatment standard for early-stage breast cancer patients and sentinel lymph node biopsy allows prediction of axillary lymph node status without the need for axillary lymph node dissection. The next challenge is to treat the primary tumor without open surgery but with minimally invasive procedures. Percutaneous tumor excision, radiofrequency ablation (RFA), interstitial laser ablation, focused ultrasound ablation (FUS) and cryotherapy provide interesting alternatives to open breast surgery

Percutaneous Stereotactic Excision

Percutaneous stereotactic biopsy techniques have been used as a treatment option for excision of benign and malignant breast lesions .Stereotactic biopsy systems, including the Advanced Breast Biopsy Instrumentation (ABBI) system (U.S.Surgical, Norwalk, CT, <http://www.ussurgical.com>), other vacuum-assisted core-sampling devices such as the Mammotome (Ethicon, Cornelia, GA, <http://www.ethicon.com>) and the Minimally Invasive Breast Biopsy (MIBB; U.S. Surgical Corporation), were developed and subsequently used in a percutaneous excisional purpose; although the patients who treated with these approaches were highly selected and conclusions cannot be applied to all breast cancer patients. The procedure was well-tolerated under local anesthesia and sedation but the investigators don't proposed the RAF as an alternative to open surgery because the patients have residual disease after application of the intervention.

Focused Ultrasound Ablation

Thermal tumor ablation has also been evaluated using FUS. After localization of the tumor within the breast,

ultrasound can be focused and rapidly generate a substantial increase in local temperatures of up to 90°C by converting acoustic energy into heat. FUS ablation heats the tumor and causes cell damage and tumor death. FUS is based on a 1.5-MHz ultrasound source. Tumor ablation is monitored through temperature probes and skin monitors. Duration of FUS ablation is usually 10 minutes. The major advantage of FUS over other ablative techniques is that no skin incisions are needed. However, tumors close to the skin may be treated with less success and with such adverse effects as skin burns.

Laser Ablation

Another technique currently being investigated for local treatment of breast cancer is laser ablation. Laser ablation is a technique that generates heat and subsequently causes cell death and tumor destruction. Laser energy is delivered directly to the target tumor through a fiberoptic probe inserted under imaging guidance. Several laser types have been evaluated and used for thermal ablation: the Nd:YAG laser (1064 nm, 1, 320 nm), semiconductor diode laser (805 nm) and argon laser (488 and 514 nm). Laser type 805 nm was used more because it is a portable device and may be applied in tumors through special needles. Laser ablation consists in delivering 2-2.5 W in 500 s (>1, 000 J for each fiber) on the tumor. The size of tumor destruction can be increased with the use of several fibers. Laser treatments may be performed under imaging guidance (mammography, ultrasound, or MRI). A target temperature of 80°C-100°C is generated during 15-20 minutes to obtain tumor ablation. Laser ablation for the treatment of early-stage breast cancer has not been studied extensively, but some have shown that small tumors can be ablated with negative margins. After technical improvements, the success rate for complete tumor ablation rose to 93%.

Cryotherapy

Cryotherapy was initially developed and used in the treatment of nonoperable liver metastases from colorectal cancers. Cryotherapy uses coldness to achieve tumor destruction. Energy is produced by an external generator composed of an argon or nitrogen freezing system and a helium heating system. Cryosurgery involves the use of a freezing probe linked to the generator. Several probes (up to seven) can be used simultaneously to treat larger tumors, as thermal conduction increases the volume of cooled tissue. The probe is inserted in the center of the tumor under imaging guidance (ultrasound or MRI) through a tiny incision. Once the probe is positioned correctly, an iceball is created at the needle tip. This iceball destroys the tumor as well as 5-10 mm of additional breast tissue surrounding the lesion. During each freeze cycle, temperatures from -185°C to -70°C are obtained and constantly monitored. Currently, the U.S. Food and Drug Administration has approved cryotherapy without resection as a treatment option for core biopsy-proven fibroadenomas. For early-stage breast cancer (tumors less than 10-15mm),

cryotherapy is promising, as this technique can be realized under local anesthesia.

Radiofrequency Ablation

Radiofrequency ablation has been used successfully for the treatment of primary or metastatic tumors of numerous organs, such as liver, lungs, bones, central nervous system, pancreas, kidneys, or prostate. Radiofrequency Ablation destroys the tumor with heat. A radiofrequency probe (15-gauge) with RFA electrodes is inserted in the tumor and an alternating high frequency electric current (400-500 kHz) is administered. The heat that is generated affects the cell membrane's fluidity and the cytoskeleton proteins and finally acts on the nuclear structure, resulting in the interruption of cell replication. This finally leads to irreversible tumor destruction, as tumor cells are more susceptible to heat than are normal cells. The RFA targeted tumor volume depends on applied tension (up to 200 W). Under imaging guidance, the RFA probe is inserted into the center of the lesion and a star-like array of electrodes is deployed from the tip of the probe. At least 5 minutes are necessary to gradually reach the target temperature (95°C). This temperature is maintained for 15 minutes to achieve complete ablation and is followed by a 1-minute cool-down period. Temperature is monitored during the entire procedure by sensors. Several studies evaluated the use of RFA ablation in the treatment of breast cancer.

Hormonal Therapy

Hormones function as chemical messengers and they show their effects at different organs in body via reaching target organs through blood stream. In females, ovaries produce two major hormones estrogen and progesterone and these two hormones are responsible for development of female sex characteristics and maintenance of menstrual cycle. However enhanced levels of these hormones can also be a leading cause of hormone-sensitive breast cancer. To identify the hormone-sensitive breast cancer surgically cancerous tissues are removed and these samples are checked for the presence of hormone receptors. If hormone receptors are present it confirms the hormone-sensitive breast cancer. Hormonal therapy reduces the development of hormone-sensitive cancerous cells by inhibiting the production of estrogen and progesterone from ovaries in body and also by inhibiting the hormonal actions. Ovaries are the main source of estrogen and in case of premenopausal women; high estrogen levels can cause breast cancer. It can be reduced by ovarian ablation via radiation therapy or surgery. Radiations and surgery causes permanent blockage of ovarian function. However ovarian function can be suppressed temporarily by treatment with drugs e.g. GnRH agonists or LH-RH agonists. Two FDA approved drugs are Goserelin and Leuprolide both interfere with signals from the pituitary gland that stimulate the ovaries to produce estrogen. Selective estrogen receptor modulators are also effective in treating the breast tumors.

They show their effects by binding to estrogen receptors and prevent the actions of estrogen by functioning as antagonist of estrogen. However at the same time they also act as estrogen agonists in some other tissues. Tamoxifen is a substance which functions as selective estrogen receptor modulator. It works as antagonist in breast tissues to inhibit the tumor cells, hence also possesses agonistic potential in some other tissues e.g. in uterus and bone tissues. Aromatase is an enzyme which facilitates the formation of estrogen by ovaries and other tissues in body. In ER-positive breast cancer aromatase inhibitors are used which blocks the formation of estrogen from ovaries via blockage of aromatase enzymes. Aromatase inhibitors are more effective in postmenopausal women because the ovaries in premenopausal women produce large quantities of estrogen and blockage by aromatase inhibitors is not sufficient to block the production of estrogen. In case of premenopausal women aromatase inhibitors can be used in combination with other therapies which blocks the function of ovaries. FDA approved aromatase inhibitors are anastrozole and letrozole but they block aromatase enzymes temporarily however exemestane is also an FDA approved aromatase enzyme inhibitor which causes permanent suppression of aromatase enzymes in ovaries.

Neoadjuvant Therapy for Breast Cancer

Therapy which is given before surgery or any other main therapy is called neoadjuvant therapy. The main purpose of neoadjuvant therapy is to reduce the size of breast tumors which facilitates the surgery. Neoadjuvant therapy enhances the surgical outcomes in postmenopausal women with breast cancer. However research has shown that neoadjuvant therapy is also useful in young females with breast cancer. In earlier research studies tamoxifen was suggested as neoadjuvant therapy in postmenopausal women.

Adjuvant Therapy

Adjuvant therapy is the therapy which is given after main treatment (surgery) to enhance the prevention. It may include radiation therapy, chemotherapy and hormonal therapy. In case of premenopausal and postmenopausal females tamoxifen is used as adjuvant therapy which has approved by FDA as adjuvant therapy in early stage breast cancer. However FDA has also approved two other drugs anastrozole and letrozole as adjuvant therapy in treatment of breast cancer but they can only be used in postmenopausal females. Another aromatase inhibitor exemestane has approved as adjuvant therapy in females who already have treated with tamoxifen.

Monoclonal Antibodies

FDA have approved two drug therapies to suppress the over expression of HER-2 tyrosine kinase. Trastuzumab (monoclonal antibody) is used to target extracellular portion of HER-2 and lapatinib which is a direct HER-2 inhibitor. However the response with these therapies is reduced due to

emergence of resistance. Resistance may be inherent or may also be produced after initial treatment with these drug therapies. Another mechanism of resistance is alteration in signaling pathways and gene expressions. Resistance can be suppressed by inhibition of P-13 kinase pathways and by blockage of neoangiogenesis mechanisms. However HER-2 dimerization site targeted monoclonal antibodies and conjugate therapies can also reduce the resistance. In hormone receptor positive breast cancer a pathway known as P-13 kinase is very active. P-13 kinase pathway can be blocked by afinitor (everolimus) drug which is previously approved for kidney carcinomas. Afinitor gives synergistic effects when administered orally in combination with Aromasin (Exemestane) for the treatment of breast cancer. Afinitor also gives better effects when given in combination with tamoxifen. These combinations have reduced the chances of resistance for receptor positive breast cancers in females. T-DM1 is an experimental drug known as “super Herceptin. It is an antibody-drug conjugate cancer-killing agent combined with targeted antibody trastuzumab (Herceptin). A study has demonstrated that in 25% of breast cancer females who were victims of HER2 overexpression, T-DM1 frequently overcame the breast tumors and allowed the patients to go into remission. In 15-20% cases of breast cancer there is over expression of HER-2 which has reduced the prognosis of breast cancer. New HER-2 targeted drug therapies have been evaluated due to the emergence of resistance against trastuzumab. A study has demonstrated the efficacy of Pertuzumab against HER-2 over expression breast cancer. Results of study showed that Pertuzumab has significant antitumor activity alone and also in combination with other monoclonal antibodies. Breast cancer can metastasize towards bones which causes severe pain, bone fracture and nerve compressions which may be life threatening. The mechanism involved in breast cancer metastasis towards bones involves multiple steps and results in the disruption of bone turnover. Biphosphonates have been used from last few years for the treatment of breast cancer related bone metastasis. It has been observed that biphosphonate can delay the first skeletal event and can decrease the pain. However biphosphonates do not have any preventive effect on breast cancer related bone metastasis and can't enhance the survival rate. Denosumab which is a radionuclide is a newer treatment which can also reduce the rate of skeletal morbidity along with delay of first skeletal event and also reduces bone pain.

Immunotherapy in Treatment of Breast Cancer

Previously immunotherapies were not used for the treatment of breast cancer. However clinical data obtained from different studies have shown that immunotherapies have potential to improve the breast cancer related clinical outcomes and breast cancer can be considered a suitable target for immunotherapies. In recent clinical trials immunotherapies which have shown promising results in treatment of breast cancer include. A vaccine Nelipepimut-S is under exploration to reduce the chances of breast cancer

recurrence among patients with short to transitional levels of HER2 expression following surgery. A phase III trial has carried out in 2012 to evaluate the activity of nelipepimut-S against breast cancer. In a phase 2 clinical trial relating 600 females who were already treated with primary therapy and were without any kind of disease evidence, a vaccine was explored to target the AE37 peptide. In a meeting of American Society of Clinical Oncology (ASCO), which was conducted at the end of 2012, results of the trial showed that the treatment reduced the chances of cancer recurrence, with enhanced benefits in females with low levels of HER2 expression. GVAX is a type of vaccine which is made from linings of breast cancer cells, genetically engineered to secrete the immune molecule GM-CSF. GVAX has tested in a phase II clinical trial in women with stage IV breast cancer without any overexpression of HER-2. The wide antigen expression and the discharge of GM-CSF has made GVAX a perfect part of combination immunotherapy in treatment of breast cancer.

COX-2 Inhibitors in Treatment of Breast Cancer

A randomized double blind study was carried out to determine the anti-tumor activity of Cyclooxygenase-2 (COX-2) inhibitors. Thirty seven patients with breast cancer were used in study and celecoxib COX-2 inhibitor was used at dose rate of 400mg twice daily. Experiment was carried out for a period of two to three weeks. Quantitative PCR analysis was used to analyze the gene expressions. Results of the study revealed that celecoxib showed anti-tumor activity by significant reduction in Ki-67 positive cells via transcriptional changes in gene expressions in primary breast cancers.

Nanomedicines in Treatment of Breast Cancer

Nanomedicines can effectively utilized for avoiding all the problems associated with conventional chemotherapy. A study was carried out to evaluate the estrogen receptor targeted pH-sensitive liposomal preparation for the efficient site specific delivery of doxorubicin in the treatment of breast cancer. For intracellular delivery of doxorubicin a liposomal preparation was made by using estrone (biological ligand). Estrone was attached on the surface of liposomal preparation for intracellular delivery of doxorubicin to specific estrogen receptors. Estrone anchored liposomal preparation showed significant intracellular invading activity at acidic pH. Results of the study showed that pH-sensitive liposomal preparation showed more activity against breast cancer than non-pH-sensitive and free doxorubicin formulations. However In-vitro cytotoxic studies revealed that pH-sensitive liposomal targeted formulation is more cytotoxic than free doxorubicin and non pH-sensitive preparations via the formation of reactive oxygen species.

Enzyme Inhibitors

Radiations and chemotherapy are most commonly used therapies in the treatment of breast cancer. But now a

days resistance has been emerged against these therapies in the treatment of breast cancer. This resistance is emerged due to metabolic changes in cancer cells. A study has demonstrated that almost 40% of all and 50% of advanced breast cancer cells are metabolically hypoxic which causes altered metabolism. Due to hypoxic cancer cells resistance has emerged against conventional therapies used for the treatment of breast cancer. Due to this altered microenvironment of cancer cells focus is now diverted towards the use of other therapies for the treatment of breast cancer which include different enzymes such as carbonic anhydrase IX (CAIX).

MiR-886-5p Inhibitors

Mechanisms of miR-886-5p involved in inhibition of growth and migration of MCF-7 cells were evaluated in advanced breast cancer women. In study miR-886- 5p inhibitors and accelerators were used to increase or decrease the miR-886-5p expressions. Rate of apoptosis, expressions of caspases 3, 8, 9, VEGF-C and MCF-7 cells secreted MMP2 and MMP9 levels (ELISA) were measured to determine the roles of miR-886-5p inhibitors and accelerators in breast cancer treatment. Results of study demonstrated that there was a significant inhibition of MCF-7 cells growth as levels of miR-886-5p were reduced. It was also observed that reduced levels of miR- 886-5p also enhanced the rate of apoptosis and caused a significant reduction in migration of MCF-7 cells. The levels of VEGF MMP2 and MMP9 were also reduced by reducing the expression of miR-886-5p. From results it was concluded that miR-886-5p inhibitors can be used as therapeutic agents in treatment of breast cancer as they caused a significant reduction in growth and migration of MCF-7 cells.

Natural Products in Treatment of Breast Cancer

In connection with severe side effects of synthetic anticancer drugs, now different drugs have been derived recently from plant sources for the treatment of cancer. However in treatment of breast cancer various drugs of plant origin are in clinical development depending upon their target sites. A study was carried out to evaluate the anticancer activity of D-pinitol. D-pinitol is a drug of plant origin and it possesses different pharmacological activities. Apoptotic activity of D-pinitol was evaluated in MCF-7 cells. Different dose levels of D-pinitol were used in breast cancer patients and results were evaluated by using MTT and LDH assays. Results of study demonstrated that D-pinitol significantly reduced the MCF-7 cell proliferation in a dose dependent manner. Results also showed that D-pinitol enhanced the expression of p53 and Bax. Hence it significantly reduced the Bcl-2 and NF-kB expression. Resistance against anticancer drugs has become a main problem in treatment of cancer. Due to rapid emergence of resistance for chemotherapeutic agents focus is now diverted towards natural products for their anticancer potential. A study was carried out to demonstrate the anticancer potential of mangiferin in treatment of breast

cancer under the assumption that it may have the ability to re-sensitize MCF-7 cells in vitro in those breast cancer cells which were already treated with doxorubicin. Mechanism involved in the anticancer activity of mangiferin was may be the modulation of P-glycoprotein, MRP1 and BCRP. In study the breast cancer cells which were already treated with doxorubicin were exposed to mangiferin for a period of ten days using different concentrations of mangiferin 10, 25 and 50µM respectively. In order to evaluate the anticancer potential of mangiferin viability of breast cancer cells and expressions of P-glycoprotein, MRP1, BCRP were measured. Results of the study demonstrated that at highest concentrations mangiferin it caused a significant reduction in cell viability in combination with doxorubicin. However

at low doses it was failed to cause any significant reduction in cell viability. Results also revealed that at high concentrations mangiferin reduced the P-glycoprotein expression. However it did not showed any significant effects on MRP1, BCRP. It was concluded that mechanism involved in anticancer activity of mangiferin was may be its inhibitory effect on P-glycoproteins. Studies have shown that isoflavones present in soy possesses anticancer potential. It has been observed that enhanced consumption of soy can reduce the chances of recurrence and mortality associated with breast cancer and it binds mainly with ER α receptors. Soy has both estrogenic and antiestrogenic activity.

Figure 1(a). Anatomy of normal breast of human(female)

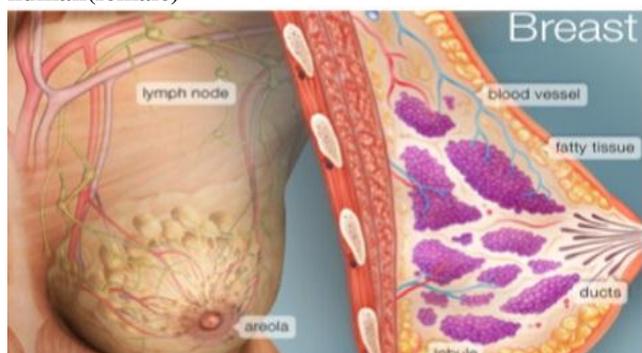


Figure 1(b). Anatomy of normal breast of human(female)

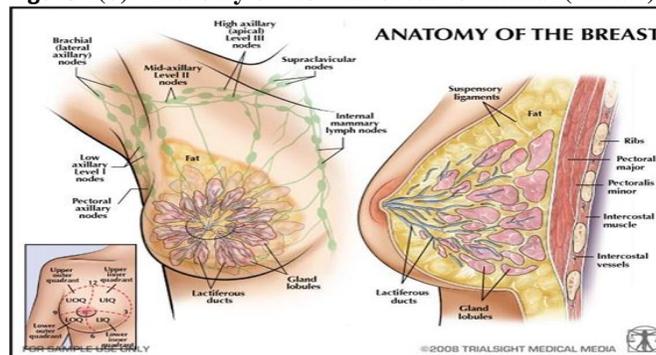


Figure 2. Description of parts normal breast of human (female)

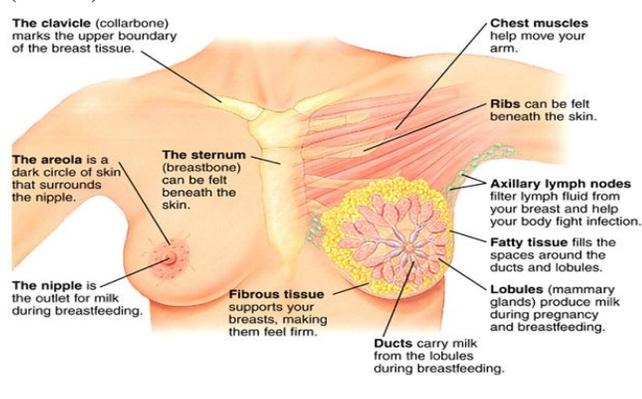
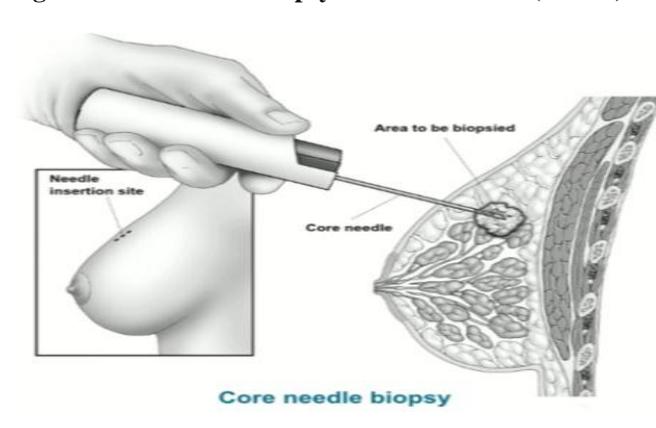


Figure 3. Core needle biopsy of human breast (female)



CONCLUSION

The life expectancy of breast cancer patients is increased due to effective treatment options available today. Nonetheless, persistent chronic pain of oncologic origin has depreciated the quality of life in advanced stage breast cancer survivors after treatment. A range of analgesics and adjuvant medications are accessible to the patients.

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