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A REVIEW ON BREAST CANCER AND ITS MANAGEMENT

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ABSTARCT

Now days, breast cancer is the most frequently diagnosed life-threatening cancer in women and the leading cause of cancer death among women. Since last two decades, researches related to the breast cancer has lead to extraordinary progress in our understanding of the disease, resulting in more efficient and less toxic treatments. Increased public awareness and improved screening have led to earlier diagnosis at stages amenable to complete surgical resection and curative therapies. Consequently, survival rates for breast cancer have improved significantly, particularly in younger women. This article addresses the types, causes, symptoms, risk factors and various approach both non-drug (such as surgery and radiation) and drug treatment (including chemotherapy, gene therapy etc.) of breast cancer.

KEYWORDS: Breast cancer, tumor, chemotherapy, gene therapy.

INTRODUCTION

Breast cancer is the most common cause of cancer in women and the second most common cause of cancer death in women in the U.S. Breast cancer refers to cancers originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk.

Worldwide, breast cancer comprises 10.4% of all cancer incidences among women, making it the second most common type of non-skin cancer (after lung cancer) and the fifth most common cause of cancer death. In 2004, breast cancer caused 519,000 deaths worldwide (7% of cancer deaths; almost 1% of all deaths). Breast cancer is about 100 times more common in women than in men, although males tend to have poorer outcomes due to delays in diagnosis.

Cancer cells are very similar to cells of the organism from which they originated and have similar (but not identical) DNA and RNA. This is the reason why they are not very often detected by the immune system.[1] Cancer cells are formed from normal cells due to a modification / mutation of DNA and / or RNA. These modifications / mutations can occur spontaneously ill Law of Thermodynamics - increase of entropy) or they may be induced by other factors such as; nuclear radiation, electromagnetic radiation (microwaves, X-rays, Gamma-rays, Ultraviolet-rays etc.), viruses, bacteria and fungi, parasites (due to tissue inflammation / irritation, heat, chemicals in the air, water and food, mechanical cell-level injury, free radicals, evolution and ageing of DNA and RNA, etc. All these can produce mutations that may start cancer. Cancer can be called therefore "Entropic Disease" since it is associated with the increase of entropy of the organism to the point where the organism cannot correct this itself External intervention is required to allow the organism to return to a stable entropic state.[2]

Cancer develops if the immune system is not working properly and / or the amount of cells produced is too great for the immune system to eliminate.[3] The rate of DNA and RNA mutations can be too high under some conditions such as; unhealthy environment (due to radiation, chemicals, etc.)[4], poor diet (unhealthy cell environment)[5], people with genetic predispositions to mutations[6] and people of advanced age (above 80).[7]

- **The cell cycle**

In cancerous cells, the process of cell division is disrupted and unregulated, resulting in cell proliferation and tumor growth. The normal cell cycle is as represented in figure 1.

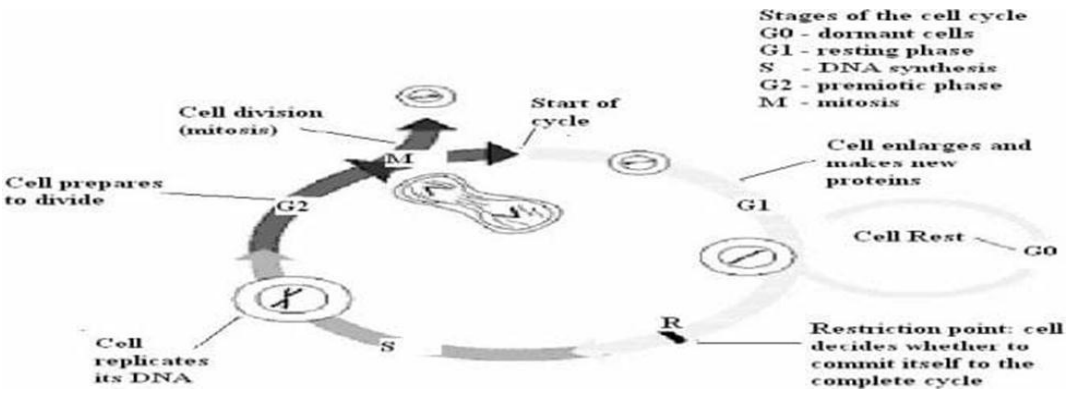


Figure 1: Stages of normal cell cycle[8]

BREAST CANCER

Breast cancer refers to the erratic growth and proliferation of cells that originate in the breast tissues[9] Cancer begins when healthy cells in the breast change and grow out of control, forming a mass or sheet of cells called tumor. A tumor can be cancerous or benign. A cancerous tumor is malignant, means it can grow and spread to other parts of the body. A benign tumor means the tumor can grow but will not spread.

The breast is composed of two main types of tissues i.e., Glandular tissues and stromal (supporting) tissues. Glandular tissues house the milk-producing glands (lobules) and the ducts (the milk passages) while stromal tissues include fatty and fibrous connective tissues of the breast. The breast is also made up of lymphatic tissue-immune system tissue that removes cellular fluids and waste[10] There are several types of tumors that may develop within different areas of the breast. Most tumors are the result of benign (non-cancerous) changes within the breast. For example, fibrocystic change is a non-cancerous condition in which women develop cysts (accumulated packets of fluid), fibrosis (formation of scar-like connective tissue), lumpiness, and areas of thickening, tenderness, or breast pain.[11]

Most breast cancers begin in the cells that line the ducts (ductal cancers). Some begin in the cells that line the lobules (lobular cancers), while a small number start in the other tissues.[12]

- **Breast**

The breast is the tissue overlying the chest (pectoral) muscles. Women's breasts are made of specialized tissue that produces milk (glandular tissue) as well as fatty tissue. The amount of fat determines the size of the breast. The milk-producing part of the breast is organized into 15 to 20 sections, called lobes. Within each lobe are smaller structures, called lobules, where milk is produced. The milk travels through a network of tiny tubes called ducts. The ducts connect and come together into larger ducts, which eventually exit the skin in the nipple. The dark area of skin surrounding the nipple is called the areola. Connective tissue and ligaments provide support to the breast and give it its shape. Nerves provide sensation to the breast. The breast also contains blood vessels, lymph vessels, and lymph nodes[13] The structure of breast in represented in Figure 2.

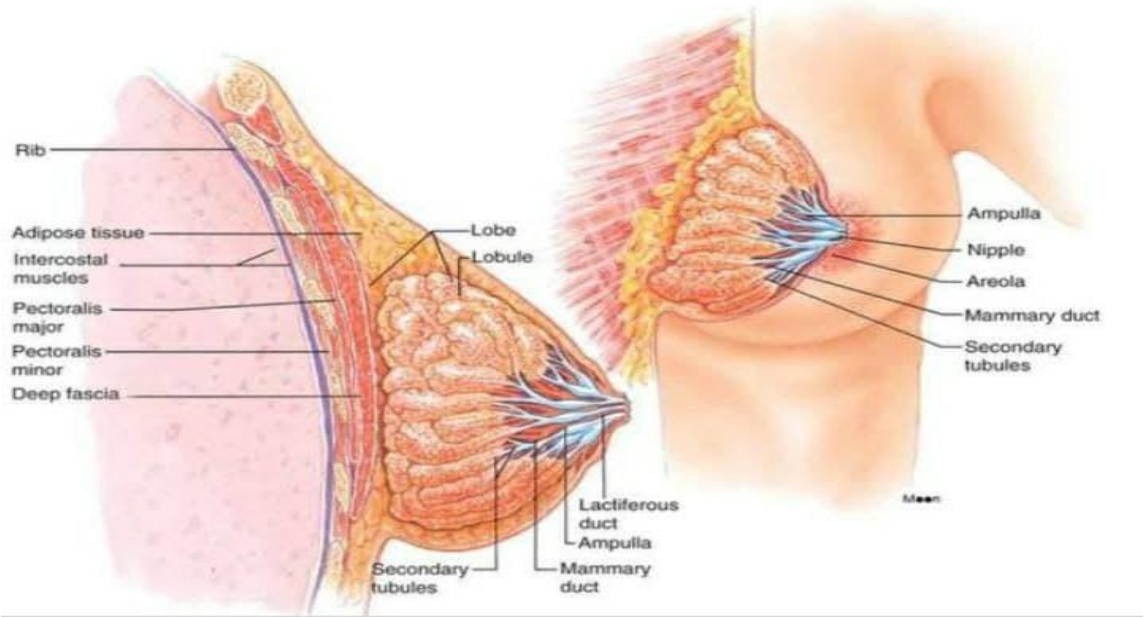


Figure 2: Structure of breast.[14]

TYPES OF BREAST CANCER

According to site, it is divided into invasive and non-invasive breast cancers.

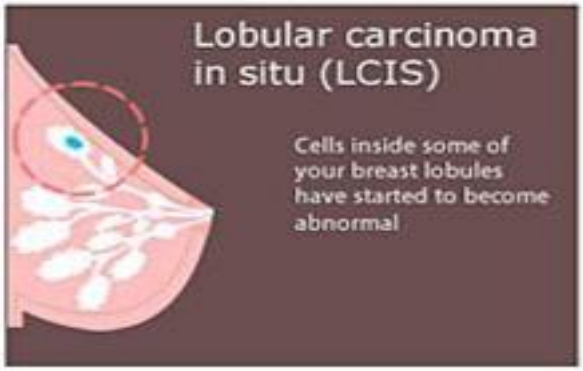
A. Non-invasive breast cancer

It is a cancer that has not extended away from the lobule or ducts where it situated.[15] An example of a kind of non-invasive breast cancer is ductal carcinoma in situ. Ductal carcinoma in situ appears when atypical cells develop within the milk ducts, however have not extended to close proximity of tissue or outside. The word “in situ” describes “in place.” Even though the atypical cells have not extended to tissues outer the lobules or ducts, they can progress and grow into invasive breast cancer. The normal background of every scientific unit is demonstrated and a biological understanding of the accessible information is presented. Lobular carcinoma in-situ is understood merely a risky sign moderately than a predecessor for the successive growth of invasive cancer, so that one time the judgment is made, additional operative involvement is avoidable and sequential follow-up only is suggested. The management of ductal carcinoma in-situ should be kept in mind that breast-preserving treatment is at the present considered best therapy of breast cancer, the illness we are attempting to stop.[16] The pitfalls of suggested management based on retrospective statistics are have been taken into account and the requirement to conduct clinical studies intended to establish the best possible beneficial treatment of non-invasive breast cancer is affirmed.[17]

Types of non-invasive cancer

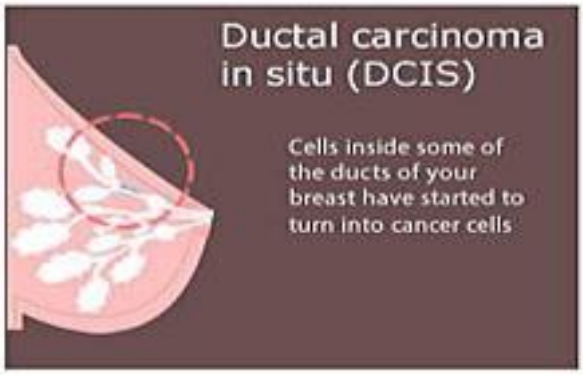
1. Lobular carcinoma in situ (LCIS)

This type of breast cancer develops into breast lobules.[18] The breast cancer has not extended exterior to the lobules into the breast tissue.[19] Lobular carcinoma in situ is usually identified as non-invasive breast cancer. In the breast are tens of thousands of tiny clusters of lobules to produce breast milk. Cells that resemble cancer cells may grow inside these lobules. LCIS tends to remain there and not spread. However, having LCIS puts you at an increased risk for invasive breast cancer.[20]



2. Ductal carcinoma in situ (DCIS)

It is the most general kind of non-invasive breast cancer, is limited to the breast duct.[21] About 20 percent of newly diagnosed breast cancers are classified as DCIS, according to the ACS. DCIS starts out as a mass that grows in a milk duct, which carries milk from the lobules, or glands, to the nipple. A DCIS hasn't spread to other parts of the body. Over time, chances increase for the mass to break through the ductal walls into the surrounding tissue and fat of the breast. With advances in diagnostics and treatments, however, most patients treated for DCIS, also called stage 0 breast cancer, have positive outcomes.[22]



B. Invasive breast cancer

It exists when abnormal cells from within the lobules or milk ducts split out into close proximity of breast tissue.[23] Cancer cells can pass through the breast to different parts of the body through immune system or the systemic circulation.[24] They may move early in the development when the tumor is a minute or afterward when the tumor is huge Invasive breast cancer is most occurring general carcinoma in females. The regions of elevated threat are the prosperous populations of Australia and Europe wherever 6% of females suffer from invasive breast cancer prior to 75 years of age. The prevalence of breast cancer enhances quickly with increasing age.[25] Invasive breast cancer that extends to different organs of the body is also recognized as metastatic breast cancer.[26] Most common organ to which these cells spread are brain, bones, lungs and liver. These cells once more segregate and expand irregularly and produce new cancers. The new forming cells are developing in different part of the body, it is still breast cancer.[27]

Types of Invasive Cancer

1. Invasive ductal carcinoma

The most common type of breast cancer—accounting for roughly 70 to 80 percent of all cases—is called invasive ductal carcinoma (IDC). IDC is a cancer that starts in a milk duct (the tubes in the breast that carry milk to the nipple) and grows into other parts of the breast. With time, it may spread further, or metastasize, to other parts of the breast.[28,29]

2. Invasive lobular carcinoma

Invasive lobular carcinoma (ILC) is the second most common type, accounting for roughly 5 to 10 percent of all breast cancers. ILC starts in lobules (where breast milk is made) and then spreads into nearby breast tissue. Like IDC, it may metastasize. However, this cancer is harder to detect on mammograms and other exams than IDC. One in five women with ILC have both breasts affected.[28,29,30]

- Other, less common types of breast cancer include.

I. Inflammatory breast cancer

Inflammatory breast cancer, which may be detected in the ducts or lobules, tends to spread faster than other types of breast cancer. This quick-growing, aggressive disease makes up about 1 to 5 percent of breast cancers in the United States, according to NCI. It gets its name from the inflammatory signs it causes, usually redness and swelling on the surface of the breast. Because of these signs, it's often misdiagnosed as a breast infection. In fact, for one out of three patients with this type of cancer, it's not diagnosed until more advanced stages of the disease when it's already metastasized to other areas of the body, according to the American Cancer Society (ACS). For these reasons, this type of cancer has a lower survival rate.[31]

II. Paget's disease of the breast

Also known as Paget's disease of the nipple, Paget's disease of the breast is a much less common type of breast cancer. It primarily affects about 1 to 4 percent of patients also

diagnosed with another breast cancer, according to NCI. It develops in the skin of the nipple and the areola, creating unique tumor cells called Paget cells.[32]

III. Angiosarcoma of the breast

Angiosarcoma is breast cancer that forms in the lining of lymph or blood vessels. It's rare and accounts for only 1 to 2 percent of all sarcomas (including those found anywhere else in the body), according to NCI. Though anyone may develop angiosarcoma, it's most common in people older than 70. It's frequently caused by complications from radiation therapy to the breast, but it may not occur until eight to 10 years later. Angiosarcoma is a type of cancer that grows quickly and often isn't diagnosed until it's already spread to other areas of the body.[33]

IV. Phyllodes tumors

Phyllodes tumors are rare and are found in the connective tissues of the breast. This type of tumor mostly affects women in their 40s, though it may develop in patients of all ages. People who have an inherited genetic condition called Li-Fraumeni are at an increased risk for this type of tumor. About 25 percent of phyllodes tumors are cancerous, according to ACS.[34]

V. Medullary carcinoma

Medullary carcinoma is an invasive breast cancer that designs a discrete margin normal tissue and medullary tissue.[35]

VI. Mucinous carcinoma

It is recognized as colloid carcinoma, mutinous carcinoma is a uncommon breast cancer created by the mucus-forming cancer cells. Females with mutinous carcinoma usually have an improved prediction than females with additional general kinds of invasive carcinoma.[36]

VII. Tubular carcinoma

Tubular carcinomas are a particular kind of invasive breast carcinoma. Females with tubular carcinoma usually have an improved prospects than women with additional general kinds of invasive carcinoma.[37]

Other, even more rare, types of invasive breast cancer include adenoid cystic carcinoma, low-grade adenosquamous carcinoma, papillary carcinoma.

- **Understanding hormone receptor status**

Genomic research has also led to a more specific classification of breast cancers, based on their genes and proteins. Sixty percent of breast cancers are estrogen-positive, for example, while 20 percent are HER2-Positive, and another 20 percent are triple-negative.[38]

1. Hormone-receptor status

Hormone receptor status refers to whether or not breast cancer cells have specific proteins that act as "receptors" for the hormones estrogen and progesterone. Hormone-receptor status is determined by testing breast cancer cells removed during a biopsy or surgery. If breast cancer cells have hormone receptors, then the cancer is hormone receptor-positive, which means the hormones estrogen ("ER-positive") and progesterone ("PR-positive") are responsible for fueling the cancer's growth. These represent 60 to 75 percent of breast cancers, according to the American Society of Clinical Oncology (ASCO).If there are no receptors, the cancer is hormone receptor-negative. These cancers tend to grow at a faster rate than hormone receptor-positive cancers. A cancer's hormone receptor status influence how it's treated because inhibiting the hormones from attaching in hormone receptor-positive cancers may help keep it from spreading. Clinical trials have resulted in many innovative drugs in this area.[39]

2. HER2 status

Breast cancers may also be HER2-positive or HER2-negative depending on the levels of a growth-promoting protein called HER2 within the cancer cells. HER2-positive breast cancers have high levels of the HER2 protein, which means they're more likely to be fast-growing than some other types of breast cancer, but they may also be treated with drugs specifically designed to target the HER2 protein. Cancers that are HER2-negative don't respond to the same drugs. Cancers that rely on human epidermal growth factor receptor 2 (HER2) to grow (HER2-positive) are found in 15 to 20 percent of invasive breast cancers. A cancer that's

hormone receptor-negative and HER2-negative is called triple-negative. These tend to grow and spread at a fast rate. This disease more often affects younger women, women of African-American descent and women with the BRCA 1 gene mutation.[40,41]

3. Triple-negative breast cancer

When a tumor doesn't express any of these three proteins, it's considered a triple-negative breast cancer. About 15 percent of all invasive breast cancers are triple-negative, according to ASCO. This cancer is more common in younger women. Women who carry the BRCA1 gene mutation also tend to have a higher chance of developing triple-negative breast cancer.[42]

Pathogenesis of breast cancer

The breast is a complex tubule-alveolar organ fixed within an asymmetrical connective tissue[43], that go through a chain of alteration from child bearing age to senility. The changes seen with every menstrual cycle and pregnancy guided us to assume the occurrence of precursor cells in the mature tissue that is able of synthesizing novel duct-lobular units.[44] The typical breast architecture contains a stratified epithelium bordered by a basement membrane and fixed in a template of blood vessels, lymphatic and stromal cells.[45] In the usual breast, the stratified epithelium comprised of two dissimilar cell populations, myoepithelial and epithelial, which can be distinguished by way of immune histochemical staining with antibodies against myosin and CK, correspondingly. It has been postulated that the creation of cellular heterogeneity in breast disorders depends on the primary developmental series of the usual breast. This heterogenicity of the breast carcinoma might happen from the neoplastic change of either myoepithelial or epithelial cell, or yet from a stem cell that has the ability to develop into myoepithelial or epithelial cells.[46] According to the oncology of breast cancer, neoplastic cells differ from the normal body cells. Normal tissues of the body have limited growth promotion and regulation which helps to keep the structure and functions of tissues usual. However, cancerous cells have prolonged and chronic proliferation without any external stimuli.[47] Cancer cells overcome the growth suppressor genes.[48] Breast cancer is a malignant disease that initiates in the breast cells. Like other malignant tumors, there are numerous causes that can increase the possibility of developing breast cancer. Injure to the deoxyribonucleic acid (DNA) and hereditary alteration can guide to breast cancer have been associated with the exposure of estrogen. Some patients inherit fault in the deoxyribonucleic acid (DNA) and genes like the P53, BRCA1 and BRCA2 among others. The patients with a family history of breast or ovarian cancer have possibility

of developing breast cancer.[49] Neoplastic cells require considerable potential to multiply and convert into a massive tumor.[50] The immune system usually tries to find out cancer cells and cells with injured deoxyribonucleic acid (DNA) and demolish them. Breast cancer might be outcome of malfunction of such an useful immune defence and surveillance. Breast cancer commonly occurs due to an association between genetic and environmental factors. RAS/MEK/ERK pathway and PI3K/AKT pathway defend normal cells from cell suicide. When mutation occurs in genes that are involved in encoding of these protective pathways, the cells become unable of committing suicide when they are no longer required which then leads to development of cancer. These mutations were confirmed to be experimentally associated with estrogen exposure.[51] It was recommended that deformity in the growth factors signaling can assist growth of malignant cells. Over expression of leptinin breast adipose tissue enhances proliferation of cell and cancer.[52] These are numerous growth factors signaling and other factors that interrelate between epithelial cells and stromal cells. Interruption in these might result in development of breast cancer. In cancer cells, enzyme telomerase turns away the chromosomal shortening and allows the extensive replication of cells.[53] Tumor cells get their nutrients and oxygen supply by angiogenesis.[54] Cancer cells break their boundaries and can enter into the blood, lymphatic tissues and other tissues of the body to produce a secondary tumor.[55]

Stages of Breast Cancer

Breast cancer can be divided into stages based on the size of the tumor(s) and how much it has spread. Cancers that are large and/or have invaded nearby tissues or organs are at a higher stage than cancers that are small and/or still contained in the breast. To stage a breast cancer, doctors need to know.

- if the cancer is invasive or noninvasive
- how large the tumor is
- whether the lymph nodes are involved
- if the cancer has spread to nearby tissue or organs.[56]

Whereas stage 0 describes the non invasive and stage 4 describes the invasive kind of tumor. Descriptions of those tumor stages are:

Stage 0

This is the non invasive stage of tumor which indicates that both cancerous and non cancerous cells are within the boundaries of that part of the breast in which the tumor begins

to grow and no evidence found of their invasion in the surrounding tissues of that part, the example of this tumor stage is ductal cell carcinoma in situ (DCIS).[57]

Stage 1

This stage describes as the invasive breast carcinoma and microscopic invasion is possible in this stage. It has two categories that are 1A and 1B stage. The category 1A describes the tumor which measures up to 2 cm and none of the lymph nodes are involved in it while stage 1B describes that small group of cancer cells larger than 0.2 mm founds in lymph node.[58]

Stage 2

Stage 2 also has two categories 2A and 2B. Stage 2A describes that the tumor is found in axillary lymph nodes or in sentinel lymph nodes but no tumor found in breast. The tumor can be smaller or larger than 2 cm but not more than 5 cm. However stage 2B describes that the tumor could be larger than 5 cm but can't reach to the axillary lymph nodes.[59]

Stage 3

It has been divided into three sub categories that are 3A, 3B and 3C. Amongst which stage 3A describes that no tumor is found in breast but it can be found in 4–9 axillary lymph nodes or in sentinel lymph nodes while stage 3B describes that the tumor can be of any size but have caused swelling or ulcer on the skin of the breast and can have spread up to 9 axillary lymph nodes or to sentinel lymph nodes stage 3B can be considered as inflammatory breast cancer which includes red, warm and swollen skin of the breast. However stage 3C describes the spread of tumor up to 10 or more than 10 axillary lymph nodes and it also have involved the lymph nodes above and below the clavicle.[60]

Stage 4

This is the advanced and metastatic stage of cancer and this stage describes the spread to other organs of the body that is lungs, bones, liver brain etc.[61]

Causes of Breast Cancer

A previous history of breast cancer

A woman who has had breast cancer has an increased risk of getting breast cancer in the other breast.[62]

Significant family history

If several members of patient's family have had particular types of cancer, patient may have an increased risk of developing breast cancer.[62,63]

Genetic causes

Family history has long been known to be a risk factor for breast cancer. Both maternal and paternal relatives are important. The risk is highest if the affected relative developed breast cancer at a young age, had cancer in both breasts, or if she is a close relative. First-degree relatives, (mother, sister, daughter) are most important in estimating risk. Several second-degree relatives (grandmother, aunt) with breast cancer may also increase risk. Breast cancer in a male increases the risk for all his close female relatives. BRCA1 and BRCA2 are abnormal genes that, when inherited, markedly increase the risk of breast cancer to a lifetime risk estimated between 40 and 8S%. Women who have the BRCA1 gene tend to develop breast cancer at an early age.[64]

Hormonal causes

Alteration in hormonal level may precipitate breast cancer. It could be attended by starting and stopping of periods (Menstrual Cycle), Pregnancy in early age, Hormonal replacement therapy, Use of oral pills etc.[65]

Life style and dietary cause

Sedentary life style, high dietary intake of fat obesity particularly in postmenopausal women may cause breast cancer. The use of alcohol is also another one cause of breast cancer. The risk increases with the amount of alcohol consumed. Women who consume two to five alcoholic beverages per day have a risk about one and a half times that of nondrinkers for the development of breast cancer.[66,67]

Environmental cause

There is known to be a slight increase in risk in ladies who work with low doses of radiation over a long period of time-for example, X-ray technicians.[66,67]

- **Risk factors for breast cancer**

There are several risk factors that increase your chances of getting breast cancer. However, having any of these doesn’t mean you will definitely develop the disease.

Some risk factors can't be avoided, such as family history. You can change other risk factors, such as quitting smoking, if you smoke. Risk factors for breast cancer include.[69,70]

- **Age.** Your risk for developing breast cancer increases as you age. Most invasive breast cancers are found in women over age 55 years.
- **Drinking alcohol.** Alcohol use disorder raises your risk.
- **Having dense breast tissue.** Dense breast tissue makes mammograms hard to read. It also increases your risk for breast cancer.
- **Gender.** White women are 100 times more likely to develop breast cancer than white men, and Black women are 70 times more likely to develop breast cancer than Black men.
- **Genes.** Women who have the BRCA1 and BRCA2 gene mutations are more likely to develop breast cancer than women who don't. Other gene mutations may also affect your risk.
- **Early menstruation.** If you had your first period before age 12 years, you have an increased risk for breast cancer.
- **Giving birth at an older age.** Women have their first child after age 35 years have an increased risk for breast cancer.
- **Hormone therapy.** Women who took or are taking postmenopausal estrogen and progesterone medications to help reduce their signs of menopause symptoms have a higher risk for breast cancer.
- **Inherited risk.** If a close female relative has had breast cancer, you have an increased risk for developing it. This includes your mother, grandmother, sister, or daughter. If you don't have a family history of breast cancer, you can still develop breast cancer. In fact, most women who develop it have no family history of the disease.
- **Late menopause start.** Women who start menopause after age 55 years are more likely to develop breast cancer.
- **Never having been pregnant.** Women who have never become pregnant or carried a pregnancy to full term are more likely to develop breast cancer.
- **Previous breast cancer.** If you have had breast cancer in one breast, you have an increased risk for developing breast cancer in your other breast or in a different area of the previously affected breast.[70,71,72,73]

Sign and symptoms

The classic symptom for breast cancer is a lump found in the breast or armpit. Doing monthly breast self-exam (BSE) is a great way to be familiar with the breasts' texture, cyclical changes, size, and skin condition. The general alerting features of breast cancer are such as swelling or lump (mass) in the breast, swelling in the armpit (lymph nodes), nipple discharge (clear or bloody), pain in the nipple, inverted (retracted) nipple, scaly or pitted skin on nipple, persistent tenderness of the breast, and unusual breast pain or discomfort. In Advanced stage (Metastatic) of disease underarm lymph nodes are present with other symptoms such as bone pain (bone metastases), shortness of breath (lung metastases), drop in appetite (liver metastases), unintentional weight loss (liver metastases), headaches, neurological pain or weakness.[68]

Screening/Diagnosis of breast cancer

Physical Breast Exam

The physical breast exam includes a self-breast exam and a clinical breast exam. A self-breast exam is an examination of own breasts and underarms for changes using own hands and mirror. Whereas, in clinical breast examination, a doctor inspects your breast and the axillary area for lumps and other changes that can be a reason for breast cancer. Physical examination includes inspection of breasts, area around neck and collarbone, and armpits (axillae) carried out by clinicians. Breasts are observed for any deformities such as lumps or other manifestations of breast cancer. Lymph nodes are also examined that are usually enlarged in patients with breast cancer.

Mammography

Mammography has been considered as an appropriate screening method for breast cancer detection for many years. Mammography is an advanced method of breast screening using an X-ray unit. Most oncologists for cancer detection in healthy people with no evident signs favor mammogram screening. In mammography, an X-ray machine generates breasts image that looks thorough breast skin and soft tissues. Your radiologist will read those images to find the existence of breast cancer.

Ultrasound

Ultrasound is next to mammography. Ultrasound technique can detect cancer with images using sound waves in those areas of the breast where mammography finds it hard to reach. It also can help to check the nature and density of a lump in the breast. Ultrasound breast

imaging shows the size and position of tumor whether it is filled with fluid or is solid and needs to be biopsied to rule out cancer. This examination is quickly becoming a routine procedure for diagnosing lumps in young women.

MRI - Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is a technique of breast scanning and generating images using radio waves and magnets. MRI and mammograms are applied together to scan breasts with greater risk of breast cancer or who have already been diagnosing and treating for breast cancer. Doctors do not apply and recommend MRI to healthy women or at a lower risk of developing cancer.

Breast biopsy

Breast biopsy is the simply best technique for diagnosing breast cancer. There are numerous different types of breast biopsies. To enhance diagnostic precision and get rid of as many false negative results as possible, breast imaging, clinical breast examination and biopsy are performed concurrently (triple test).

Fine needle aspiration

A thin prickle is employed to get cells from the abnormal area or a breast lump. Ultrasound can be used to assist direct the prickle. A restricted anesthetic might be used to anesthetize the region where the prickle will be inserted.[134]

Core biopsy

A wider prickle is to get a portion of tissue (a core) from the abnormal area or breast lump. It is typically made under restricted anesthetic, thus breast is insensitive, while patient may experience little hurt or uneasiness at what time the anesthetic is given. MRI, ultrasound and mammogram can be used to guide the prickle for the duration of core biopsy.

Vacuum-assisted stereotactic core biopsy

In this core biopsy, different tiny tissue samples are taken via single tiny incision in the skin with a prickle and a suction-type device. It is carried out using local anesthetic. MRI, ultrasound or a mammogram may be employed to direct the prickle into position. The patient may experience little uneasiness during the process.

Surgical biopsy

If the abnormal vicinity is too minute to be biopsied by another procedure or the biopsy outcome is not apparent, a surgical biopsy is carried out. Prior to the biopsy, a guide wire may be placed into the breast to assist the medical doctor locate the abnormal tissue. Local anesthetic can be used and the physician may use MRI, ultrasound and mammogram to direct the wire into position. The biopsy is after that carried out under a general anesthetic. Little area close to breast tissue and lump are detached, alongside the wire.

Digital mammography

It helps to find lumps in dense tissue. The image can also be easily stored and transmitted to another radiologist for a second opinion. Mammography may give false negative and false positive results in patients with dense breast tissues. The practice of mammography is 19% in Malaysian women as compared to other study which was 10.5%. Lack of health insurance coverage, low income and embracement were the main barriers to mammography as mentioned in earlier studies. Mammography is considered as the gold standard test for early detection of breast cancer but in case of scarce resources in some areas in breast health awareness program should be promoted for the early detection of breast cancers and the staff should also gets the training of clinical breast examination so that the patient get diagnosed at earlier stage especially in those areas where mammography is unavailable.

PEM and MRI in breast cancer patients

Hence both the positron emission mammography and magnetic resonance imaging have proven breast cancer detection sensitivity, however hormone replacement therapy, post menopausal status and breast tissue density has no influence on the sensitivity of PEM and MRI. Positron emission mammography can be used as an alternative of MRI in patients who don't want to have an MRI due to multiple reasons such as time issues, limited budgets, lack of interest, claustrophobia (fear of being kept in as small space). However, both have the similar sensitivity to detect cancerous lesions comprehending invasive and ductal carcinoma in SITU.[74,75,76,77,78]

Treatment

In the management of breast cancer, aim is to preserve quality of life with prolonged life expectancy.

Breast cancer management strategies differ depending on the step of the cancer—its mass, place, whether it has extended to other organs of the body and the physical condition of the individual. Present management for breast cancer includes targeted therapies, hormonal treatment, radiation therapy and surgery. Following approaches are to be made for the management of breast cancer. They are as follows.[79]

Surgery

Depending on the stage and type of the tumor, lumpectomy (removal of the lump only), or surgical removal of the entire breast (mastectomy) is performed. Standard practice requires the surgeon to establish that the tissue removed in the operation has margins clear of cancer, indicating that the cancer has been completely excised. If the removed tissue does not have clear margins, further operations to remove more tissue may be necessary. This may sometimes require removal of part of the pectoral is major muscle, which is the main muscle of the anterior chest wall. More recently, the technique of sentinel lymph node (SLN) dissection has become popular, as it requires the removal of far fewer lymph nodes, resulting in fewer side effects. Advances in sentinel lymph node mapping over the past decade have increased the accuracy of detecting sentinel lymph node from 80% using blue dye alone to between 92% and 98% using combined modalities.[79,80]

Surgery for breast cancer consists of two main options.

In breast-conserving surgery, only the tumor and an area of normal tissue surrounding it are removed. Breast-conserving surgery includes the following.

Lumpectomy: A small amount of surrounding normal tissue is removed.

Wide excision: Also called as partial mastectomy in which somewhat larger amount of the surrounding normal tissue is removed.

Quadrantectomy: About one fourth of the breast is removed.

In mastectomy, all breast tissue is removed.

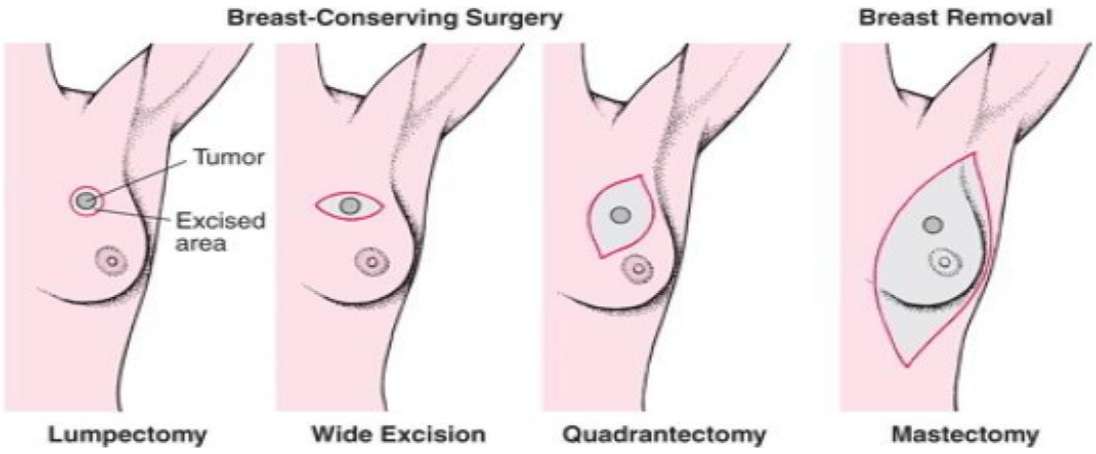


Fig 3: Various types of surgery applied for breast cancer.

Radiation Therapy

Radiation therapy involves using high-energy X-rays or gamma rays that target a tumor or post surgery tumor site. These radiations are very effective in killing cancer cells that may remain after surgery or recur where the tumor was removed. In addition to this treatment implanted radioactive catheters (brachytherapy), similar to those used in prostate cancer treatment, can be used. However this treatment option has been superseded by electron beam radiotherapy to the breast scar. Radiation therapy for breast cancer is usually performed after surgery and is an integral component of breast-conserving therapy. The dose of radiation must be strong enough to ensure the elimination of cancer cells. Treatments are typically given over a period of five to seven weeks, performed five days a week. Each treatment takes about 15 minutes.[81,82]

Brachytherapy

It is a kind of radiotherapy. It might be recognized as accelerated partial breast irradiation. It directs radiation merely to the area around the vicinity wherever the cancer was. This might replace the requirement to provide radiation to the whole breast. It also decreases the number of management sessions.[83]

Chemotherapy

Chemotherapy is the use of anti-cancer drugs to treat cancerous cells. Specific treatment for the breast cancer will be based on; overall health, medical history, age (whether menstruation is there or not), type and stage of the cancer, tolerance for specific medications and procedures etc. Chemotherapy treatments are often given in cycles; a treatment for a period of time, followed by a recovery period, then another treatment. Chemotherapy can be given

before surgery to shrink the tumor and sometimes make breast conserving surgery possible rather than a mastectomy. Many times, it is given after surgery and may be given every three weeks or every two weeks in a "dose dense" fashion.[84,85] Commonly used agents in breast cancer chemotherapy are.[86]

Chemotherapeutic agents used in management of breast cancer

S. No.	Abbreviations	Component
1	AC	Doxorubicin (Adriamycin) 60 mg/m² IV, day 1 Cyclophosphamide 400-600 mg/m² IV, day 1 (Repeat cycle every 21 days)
2	CAF (FAC)	Cyclophosphamide 100 mg/m² PO, days 1-14 Doxorubicin 25 mg/m² IV, days 1, 8, or 60 Fluorouracil 500-600 mg/m² IV, days 1, 8 (Repeat cycle every 28 days)
3	CMF(CNF,FNC)	Cyclophosphamide 500-600 mg/m² IV, day 1 Fluorouracil 500-600 mg/m² IV, day 1 Mitoxantone 10-12 mg/m² IV, day 1 (Repeat cycle every 21 days)
4	CMF	Cyclophosphamide 100 mg/m² PO, days 1-14 Methotrexate 40 mg/m² IV, day 1, 8 Fluorouracil 600 mg/m² IV, days 1, 8 (Repeat cycle every 28 days)
5	NFL	Mitoxantone 12 mg/m² IV, day 1 Fluorouracil 350 mg/m² IV, days 1-3, given after leucovorin Leucovorin 300 mg IV over 1 h, days 1-3 (Repeat cycle every 21 days)
6	Sequential DOX-CMF	Doxorubicin 75 mg/m² IV, every 21 days for 4 cycles, Followed by CMF for 8 cycles
7	VATH	Vinblastin 4.5 mg/m² IV, day 1 Doxorubicin 45 mg/m² IV, day 1 Thiotepa 12 mg/m² IV, day 1 Fluoxymesterone 10 mg PO tid (Repeat cycle every 21 days)
8	Vinorelbine & Doxorubicin	Vinorelbine 25 mg/m² IV, days 1, 8 Doxorubicin 50 mg/m² IV, day 1 Repeat cycle every 21 days
9	Single-Agent Regimens	Docetaxelv60-100 mg/m² IV, over 1h, every 21 days, and dexamethasone 8 mg PO bid for 5 days, begin 1 day before docetaxel Gemcitabine 725 mg/m² IV, over 20 min, weekly for 3 wk, followed by 1-wk rest Repeat cycle every 28 days Paclitaxel 250 mg/m² IV, over 3 or 24 h, or 175 mg/m² IV, over 3 h, every 21 days Vinorelbine 30 mg/m² IV, every 7 days

Age related approaches to chemotherapy for management of breast cancer

AGE GROUP	LYMPH NODE STATUS	ENDOCRINE RECEPTOR (ER) STATUS	TUMOR	RECOMMENDATION
Premenopausal	Positive	Any	Any	Multi drug chemotherapy + Tamoxifen if ER-positive + trastuzumab in HER-2/neu positive tumors
Premenopausal	Negative	Any	>2 cm, or 1-2 cm with other poor prognostic variables	Multi drug chemotheraphy + Tamoxifen if ER-positive + trastuzumab in HER-2/neu positive tumors
Postmenopausal	Positive	Negative	Any	Multi drug chemotherapy + trastuzumab in HER-2/neu positive tumors
Postmenopausal	Positive	Positive	Any	Aromatase inhibitors and tamoxifen with or without chemotherapy + trastuzumab in HER-2/neu positive tumors
Postmenopausal	Negative	Positive	>2 cm, or 1-2 cm with other poor prognostic variables	Aromatase inhibitors and tamoxifen + trastuzumab in HER-2/neu positive tumors
Postmenopausal	Negative	Negative	>2 cm, or 1-2 cm with other poor prognostic variables	consider Multi drug chemotherapy

- **Recent approaches in management of breast cancer**

Gene Therapy

It is generally accepted that cancer arises because of an accumulation of multiple molecular genetic defects that culminate in a cellular phenotype characterized by unregulated growth. Based on the knowledge, a variety of gene therapy strategies have been developed as potential new therapies for cancer. Current knowledge of proto-oncogene and tumor suppresser genes in the genesis of malignancy has stimulated the development of gene therapy tactics directed at ablating or restoring such genes, respectively. In other strategies, cancer cells are endowed with the ability to convert a systemically delivered pro drug to a toxic metabolite, or a target for destruction by replicating viral vectors conversely transfer of drug resistance genes into normal cells may provide chemo protection during high dose antineoplastic treatment. Finally, immune system modulation can activate anticancer drug defense mechanisms.[87]

Oncogenes Inactivation

Several oncogenic proteins have been identified and associated with various malignancies. The most commonly applied approach in clinical trials to date has been use of antisense strategies. Transcription of oncogenes also can be inhibited by using adenoviral gene E1A, which interfere with the transcription of erbB-2, a strategy useful in treating cancer that over express this oncogenic protein, such as breast and ovarian cancer.[87]

Augmentation of Tumor Suppresser Genes

More then 24 tumor suppresser genes have been identified, and mutations in these genes have been associated with a variety of neoplastic conditions. Several clinical trials are under way to deliver p53 using adenoviral vectors to a variety of cancers. Similarly, viral vectors have been utilized to introduce a retinoblastoma gene and breast cancer gene BRCA1 into bladder and ovarian cancer, respectively. In some situations, this approach will fail, because the mutant gene exhibits dominant negative effects on the normal gene. To circumvent this problem for p53 gene therapy, a genetic repair strategy rather then a gene augmentation approach could be more effective.

Cell-Target Suicide

A conversion of a pro drug to a toxic metabolite by genetically engineering tumor cells is an attractive way to create an artificial difference between normal and neoplastic tissue. This can be achieved by the expression of a gene that confers a dominant, negatively selectable phenotype to the cancer cells, such as cell death imparted by expression of a prodrug – metabolism enzyme. Greater selectively in killing malignant cells will be obtained by transferring a gene that is not normally found inhuman beings (e.g. HSV--thymidine kinase), rather then by overexpression an endogenous gene. The prototype for this approach utilizes the HSV-1 Thymidine kinase gene given to combination with produg ganciclovir in a manner distant from mammalian thymidine kinase. Phosphorylated ganciclovir is ultimately incorporated into DNA and inhibits DNA synthesis and transcription. The efficacy and safety on this approach is being tested in several clinical trials involving multiple malignancies.[88]

Immunomodulation

Various cytokines can enhance immunity against cancer cells, and this observation has stimulated the development of gene- based approaches to modulate the immune reaction in malignancy.

Ectopic Cytokine Expression: A variety of cytokine have been shown to decrease tumor growth when ectopically expressed in tumor cells or in there microenvironment. Some immune stimulatory agents do not alter the growth rate of the tumor initially, but lead to immunity against tumor growth if the animal is later challenged with wild type tumor cells.

Immune enhancement: One such approach is to express on the surface of cancer cells highly immunogenic molecule, such as all type MHC antigens. It has been long known those additional "co stimulatory" pathways distinct from the T-cell are needed to achieve T cell activation. The molecules B7-1 (CD 80) and B7-2 (CD 86) stimulate one such pathway. The B7s, whose expression normally is limited to antigen presenting cells and other specialized immune effector cells, engage specific receptors on the T cells surface in concert with antigen binding to the T-cell receptor.[89]

CONCLUSION

The occurrence of breast cancer in female can be observed in only 5% cases with a malignant mass present with breast pain. Other symptoms such as immobility, skin changes (i. e, thickening, swelling, and redness) or nipple abnormalities (i.e., ulceration, retraction, spontaneous bloody discharge) may also be present at the same time. Today there are so many approaches, which can be made for the treatment of the cancer of breast such as surgery, radiation therapy chemotherapy, hormonal therapy and recently gene therapy. With advances in screening, diagnosis, and treatment, the death rate for breast cancer has declined. In fact, about 90% of women newly diagnosed with breast cancer will survive for at least five years. Research is ongoing to develop even more effective screening and treatment programs.

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