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Review Article

A REVIEW ON CLINICAL AND DIAGNOSTIC ASPECT OF BREAST CANCER

Hazarika Iswar*,Gorge Glodiya ,ChandyVineeth

T John College of Pharmacy, Gottigere, Bannerghatta Road, Bangalore, Karnataka-560083

Corresponding author: - Hazarika Iswar

ABSTRACT
Breast cancer is one of the major problems among women which in turns have set a limitation in the medical sciences. Annually, around 1 million people are been diagnosed to have breast cancer, out of which around 40-50% dies. Breast cancer is unpredictable and can occur at any age. However, if certain cares are taken it can be prevented. Moreover, Medical science has now developed into an extent that if proper diagnosis is done on early stages, breast cancer can be prevented. Hence this article will try to review the different risk factors, its diagnosing technique and the treatment procedures.
Keywords: Breast cancer,breast cancer detection; breast cancer treatment; breast cancer pathology;.

INTRODUCTION

Breast cancer is a type of cancer that occurs due to the uncontrolled growth of the breast cells. These cells can grow into surrounding tissues or can spread to distant areas of the body.Breast Cancer is one of the major public health issuesglobally. Approximately around 1 million new cases are diagnosed annually, out of these 400,000 annual deaths. It is the main reason for the mortality among women with carcinoma.[1, 2] Breast cancer is seen 100 times more in women than men. Breast cancercases are increasing day to day especially in the developingcountries like India but the reason for itscause is unknown in many cases.[3,4].Even though breast cancer is the second leading cancer death in women,the mortality rate decreased due to the earlier detection along with chemotherapy and hormone therapy treatment.[5]

SIGNS AND SYMPTOMS:

Signs and symptoms of Breast cancer may include Lump in the breast, Sunken or inverted nipple, Change in the size and shape of the breast, Peeling of the nipple skin or breast skin, Discharge from the nipple, Pain in the armpits or nipple which is not related to woman's menstrual period, Redness of the skin of the breast, . Drastic weight loss and Swelling in one of the armpits. In those with distant spread of disease may include Bone pain, swollen lymph nodes, and shortness of breath or yellow skin.

TYPES OF BREAST CANCER:

Breast cancer is divided into different categories based on the grade of tumor,the stage of tumor,and the expression of proteins and genes and histological appearance.

Classification based on the histological appearance :

DUCTAL CARCINOMA IN SITU: It is a non-invasive type of cancer.This is actually the beginning form of cancer which has not spread.It is seen in the ductal system but that has not attacked any tissues nearby.

INVASIVE DUCTAL CARCINOMA:It is the most common type and starts in the milk duct which can affect the surrounding tissue. It has the ability to spread to other parts of the body through the lymph and the blood stream..There is a formation of lump or mass during the self-examination.

MEDULLARY CARCINOMA:It is type of invasive breast cancer.This is called medullary carcinoma because the tumor is soft, fleshy mass that is similar to the medulla of the brain. This type of carcinoma mainly starts from the milk duct and spread to the near tissues but this cannot grow quickly and does not spread out to the lymph nodes.It is easy to treat compared to other types.

LOBULAR CARCINOMA IN SITU:It is a type of cancer that occurs when there is an abnormal cell growth in the lobules.It is not cancer but it is an increased risk factor to get the breast cancer.It is also called as lobular neoplasia.

INFILTRATING LOBULAR CARCINOMA (invasive lobular carcinoma): This type of cancer begins in the milk producing lobules and invades the tissues of the breast and later it will spread to other parts of the body .Compared to the invasive ductal carcinoma invasive lobular carcinoma occurs later in life.It is the second most type of breast carcinoma.In this type of cancer there no lump formation;there will be a change in breast that feels like a thickening in one part of the breast which looks different from normal breast tissue.

TUBULAR CARCINOMA:In this type of cancer the cancer cells looks like tiny tubules.This is usually seen in women above 50 years.

MUCINOUS CARCINOMA OR COLLOID:These cells are different from the normal cells under microscope and these cells produce mucus.This mucus and the cancer cells together form a jelly like tumor.

PAGETS DISEASE: This type of breast cancer occurs at any age mainly for women above 50 years.In this type there is a eczema like changes in the nipple skin.

INFLAMMATORY BREAST CANCER:In this type of cancer the breast appear to be red; swollen and inflamed.There will be a blockage of lymph vessels in the breast skin.Over a large area of breast will be affected by the cancer.

METASTATIC BREAST CANCER:It is the stage at which the cancer spread to other organs like liver,brain ovaries etc.

TRIPLE NEGATIVE BREAST CANCER:This is a type of breast cancer that is negative for estrogen receptor,progesterone receptor and HER2/neu proteins.

Classification based on the grade:

GRADE 1: The cancer cells resemble to the normal cells,i.e well differentiated .usually slow growing cancer.

GRADE 2:The cancer cells can be moderately differentiated from the normal cells.

GRADE 3:The cancer cells doesnot look like the normal tissues i.e poorly differentiated,they are fast growing.

a. Classification based on stage of cancer:

The cancer is classified based on the TNM staging in which T is the tumor size,N is the lymph node involvement and M is the metastasis.

b. C**lassification based on the protein and gene status:**

Breast cancers are tested for their expression or detectable effect of estrogen receptor,progesterone receptors and HER2/neu protein. Therapy will be initiated and chosen based on the expression.

PATHOPHYSIOLOGY:

Some cells lose the ability to stop dividing and produce numerous cells withoutdying at proper time. This is the condition when we say that the cell became cancerous.In normal condition the P13K/AKT pathway and the RAS/MEK/ERK pathway protect the cells from the cell suicide.When these protective mechanisms get mutated, the cells lose the ability to commit suicide and keep on dividing.

Abnormal growth factor signaling can facilitate malignant cell growth .this abnormal growth factor signaling occurs in the interaction between the stromal cells and epithelial cells.

Mutation of the BRACA1 or BRACA2 which is inherited or acquired after birth may leads to breast cancer .This mutated gene interfere with the repair of DNA cross links and DNA double stand breaks, due to this uncontrolled division, lack of attachment and metastasis to distant organs take place.

The expression of the estrogen receptor is directly controlled by the GATA-3.Mutation of this gene can leads to loss of differentiation, increased cancer cell invasion and metastasis.

RISK FACTORS FOR BREAST CANCER

PREVENTABLE BREAST CANCER

OVERWEIGHT: Being overweight (BMI over 24) increases the risk of breast cancer especially in case women after menopause .During this period the estrogen level increases due to the increased fat tissue. Studies show that obese women are likely to have large tumors,along with greater lymph node andpoorer breast cancer prognosis with 30% higher risk of mortality. But the link between the overweight and breast cancer is not clearly known. [6]Obesity occurred due to poor diet and a sedentary lifestyle is seen to be the second leading cause of death in the United State.[7, 8]

LACK OF EXERCISE: People excising regularly maintain a weight and have no excess fat compare to people who don’t do exercise. The extra fat cells which is formed due to the lack of physicalactivity makemore estrogen thus increases the risk of breast cancer.[9]

DIET: Diet is considered to be another risk factor for breast cancer.A diet with low fat diet and increased fruits and vegetables is recommend more because the red meat and other animal fats contain hormones, other growth factors ,antibiotics and pesticides and even having too much cholesterol increases the risk of causing breast cancer. [10]

ALCOHOL CONSUMPTION: Alcoholconsumption will increase estrogen level in the body. It is found that women who drink 2 ounces of alcohol every day are 40% more likely to develop breast cancer when compared to women who do not drink any alcohol. [11]Alcohol sometimes damages the DNA of the cells; this can also be a factor to cause the breast cancer. [12]

SMOKING: Smoking increases the risk of breast cancer mainly in younger premenopausal women. The exposure to tobacco smoke create problems between puberty and first child birth, this is because the breast tissue during this stage is most sensitive to chemical carcinogens. [13]

HORMONE REPLACING THERAPY:women who take the HRT are at more risk of breast cancer compared to the combination therapy of estrogen and progestin.[14] HRT with high dose increases the risk of breast cancer compared to low dose HRT. The HRT only with estrogen

increases the risk of breast and ovarian cancer, but only when it is used above 10 years. [15]
ORAL CONTRACEPTIVE USE:The studies show that the women who has been using the oral contraceptives (birth control pills) before the age of 20 is at higher risk of breast cancer. [16]
ENVIRONMENTAL FACTORS:The exposure to ionizing irradiation, organic chlorines and synthetic estrogens like cosmetics and phytoestrogen will increase the risk of breast cancer. [17,18,19,20]

NON-PREVENTABLE RISK FACTORS
AGE: The risk of breast cancer increases with age and it's rarely seen below the age of 20 years.The higher risk period is between 50-59 years. [36-39]
SEX: Breast cancer is most commonly occurring in females than that in males. [21].
MENSTRAL HISTORY: Early menarche and late menopause increases the risk of breast cancer because to increased exposure to hormones. Having children above the age of 30 or not having children also increases the same risk.[45]
PREGNANCY HISTORY:The estrogen is found to be the primary stimulant for breast epithelial proliferation.Use of contraceptives, first term pregnancy at increases age increases the risk. Induced abortion and spontaneous abortion will not increase the risk.[40-44]
BREAST FEEDING HISTORY: Women who breast feed for 1 ½ to 2 decrease the risk of breast cancer this is because of decrease estrogen level during this period, production of milk reduces the misbehavior of the breast cell ,and good lifestyle. [51]
FAMILY HISTORY: Family history of breast cancer increases the risk.There is an increased risk if single or 2 first degree relatives have had breast cancer [46-47].BRACA-1 AND BRACA-2 accounts for 80% of hereditary breast cancer. [48]
PERSONAL HISTORY:The risk of breast cancer increases in people who previously had breast, ovarian,uterine or bowel cancer.3-4 times increased risk to developnew breast cancer in the other breast or the different tissue of the same breast [50]
RADIATION:Women who have had exposed to radiationto the chest before age 45 have increased risk of breast cancer, mainly during the age of 10 to 14 years. These people should undergo checkup after 10years of radiation or by age 35.[49]
RACE:White women have more risk to get have breast cancer compared to African Americans.This may be due to less quality medical care and lifestyle.[52]
BREAST CELLULAR CHANGES: Changes in the breast cells like overgrowth of cells,abnormal appearances increases the risk of breast cancer[53]
OOPHORECTOMY AND MASTECTOMY: In specific cases like people with high risk mutation of BRCA1 and BRCA2, prophylacticoopharectomy and mastectomy are done this decreases the risk of breast cancer.[54]
DES EXPOSURE:Women who have taken diethylstilbestrol(DES),which is used to prevent miscarriage have increased risk to develop breast cancer and women whose mothers taken DES during their pregnancy have high risk to develop breast cancer.[55]
EXPOSURE TO ESTOGEN: Long term exposure to estrogen increases the risk of breast cancer that is early menstruation, delayedmenopause, exposure to environmental estrogen like hormones in meat, DDT. [56]

DIAGNOISIS:
Breast self-examination, clinical breast examination: Breast self-examination and clinical breast examination can be used to find breast cancer but it cannot be taken as a conformation of

cancer but can used to identify the breast lesions.[57,58]

Mammograms: It is an important method to differentiate the benign and malignant tumor and it is even used in diagnosis of breast cancer.

Xeromammography: The method in which the image is recorded on a xerography plate. Through this method the details of entire breast and the soft tissue of chest wall can be obtained in a single exposure.

Mammary ductoscopy:It is an endoscopic technique that gives direct visualization and biopsy examination of mammary ductal epithelium.This test is mainly done when there is a nipple discharge especially in case when the fluid contains blood.[59-62]

Full-Field Digital Mammography: FFDM records the image in an electronic file. These images can be transmitted eletrically using internet so the physician as well as the radiologist can view the image sitting anywhere in the world. [63]The main disadvantage is that this requires expensive machines and files require large amount of digital storage space. [64]

Computer-Aided Detection (CAD):It is software that identifies the abnormalities on images and shows the same to the radiologist.It is more helpful in finding microcalcification than masses.[64]

Modalities using ultrasound:This test is also called as sonomammography.It is used to image the palpable masses in the breast or even used as a follow-up test for the abnormal results that are found in the mammogram.[65]

B-Mode Ultrasound: It is the most commonly used type of ultrasound. This technique uses sound wave that are bounced back from the tissues to create an image of the breast. The created image will be a two- dimensional one. This method is mainly used to find the palpable mass and to examine the women who cannot undergo mammography(young and pregnant ladies). [65]

Compound imaging:This method will give more realistic image by improving the tissue differentiation, margin visualization, internal architecture visualization and giving low contrast lesion conspicuity. [66,67]

Doppler Ultrasonography:It is a method to find malignant tumors through their neoangiogenesisby using a doppler effect to tract the blood supply.This method is of 2 type – colour and power out of this two power doppler ultrasound is a better technique. [64,68]

MRI(Magnetic Resonance Imaging): By using the magnetic field and radio waves image will created .(64,69)This is the method used for post chemotherapy imaging.[70,71]

Nuclear Medicine: Even though nuclear medicine is an expensive procedure and exposure to radiation is required, it is an efficient method.

Radioimmunoscintigraphy:Radiopharmaceutical agents are injected and identify the antigen expression in normal and cancer cell. [72,73]

^{99m}Tc-sestamibiscintimammography:It is a method used for the detection of cancer in patients with dense breast .It is also used when mammography, CBE, show no abnormalities, and also in case of cancer reoccurrence, monitoring to chemotherapy but it has low ability to detect small primary cancer. [74]

Positron Emission Tomography:Even though it takes about 40-60 minutes for imaging it is one of the good method for cancer detection [75-77] it can also be used for follow-up examination,checking the entire body for reoccurrence.[75]

BIOPSY: Three methods are used to take the suspicious breast lump.One of the methods is fine needle aspiration but it cannot be used to differentiate ductal carcinoma in situ and invasive carcinoma. [82]Core needle biopsy often preferred biopsy because it is more accurate than fine needle aspiration and this does not required surgery.[83]Senitinellymph node biopsy is done to

check the spread of cancer to axilla.[84]

TREATMENTS

Surgery: By surgical resection, breasttumors can be removed completely in the early stages. Breast conserving surgery,mastectomy,axillary lymph node sampling and removal are the some of the surgicalprocess .Surgery will help in the removal of the affected cancer tissue and some nearby tissues. [22,23]Even though breast conservation surgery requires high quality breast imaging equipment it is effective as mastectomy in stage1 or 2 of breast cancer.[27]

Radiation Therapy: This is the therapy that can be done in all stages of breast cancer. With help of high energy rays or particles the cancer cells will be destroyed.[24] One of the common methods used is beam radiation in women with breast cancer. After the breast conservation surgery, the radiation therapy will be done to the entire breast as well as an extra boost dose will be given to the area where the cancer cells were removed to prevent the reoccurrence to that area.Brachytherapy (internal radiation) is another type of radiation therapy. It is method to give an extra boost of radiation along with the external radiation, in which radioactive seeds or pellets are placed near to the cancer tissue.[25,26]

Chemotherapy: chemotherapy with two or more agents gives good result compared to single drug therapy. The most common regimen includes cyclophosphamide,methotrexate, fluorouracil,CAF,AC, and FEC.Four to six months course of treatment gives the optimalbenefit, i.e.about 3-6 months.[28]

Alkylating agents at all the stages,will directly damages the genetic material of each cell e.g.cyclophosphamide .Anti metabolites act on S phase during the duplication of genetic material egmethotrexate. Anti-tumor antibiotics cause DNA cleavage e.g. anthracyclins.Mitotic inhibitor act on M phase and have the ability to interfere other phases e.g. taxanes. [29]

Hormone Therapy: The drugs used in hormonal therapy either lower the amount of estrogen level or reduces its action on the breast cells. Selective estrogen receptor modulators (such as tamoxifen, raloxifene and toremifene) and selective estrogen receptor down regulators such as fulvestrant are theanti-estrogen therapies.SERMs will block the activity of estrogen and SERDs will cause destabilization and degradation of estrogen.Drugs like aromatase inhibitors will decrease estrogen production in peripheral tissues and within the tumor by inhibiting aromatase enzyme which is responsible for estrogen biosynthesis.[30]

Targeted Therapy:It is the therapy that is personalized to an individual patient's tumor. E.g. in PI3K mutant-Anti- PI3K, anti- AKT and m-TOR are used as targeting therapies as well as in HER2 over-expressing and HER2 positive tumor.[80,81]

Rehabilitation: In some countries rehabilitation of breast cancer patient is quiteactive,with the improved outcomes of breast cancer treatment.[33]There is a pre-operative rehabilitation program along with the physiotherapy for the patient with lymph oedema for most of the breast cancer units in Denmark.[34]

Patient follow up: Regular follow up can help to identify the early signs of reoccurrence of the diseases .It will also help in to identify the toxicity of the previous treatment. [35]

Immunotherapy:The development of vaccines against the tumor associated antigens was the first step in the development of immunotherapy.[31] The Human epithelial growth fact or receptor 2 (HER2), carbohydrate antigens, telomerase reverse transcriptase (hTERT), and mucin-1 (MUC-1) [51] are the key tumor associated antigen. Monoclonal antibodies like Trastuzumab will bind to HER2 and prevents further signal transduction that promotes cell cycle progression and inhibit apoptosis.[32]

CONCLUSION:

Even though the numbers of women that are effected by breast cancer are increasing day to day the mortality rate is decreased due to the advancement in the diagnosis i.e. even the self-examinationof breast during bathingmay help in earlier diagnosis and progression of the available therapy .Still the many studies are going on to the impure this diseases and prevent the condition.

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