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A REVIEW ARTICLE ON BREAST CANCER

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ABSTRACT

Breast cancer is the most common malignancy in women.[1] Breast cancer is the second leading cause of cancer deaths among women.[2] It is classified into few major molecular subtypes according to hormone and growth factor receptor expression.[1] Several etiological factors have been implicated in its pathogenesis and include age, genetic, family history, diet, alcohol, obesity, lifestyle, physical inactivity as well as endocrine factors. These factors act separately or together in the causation of breast cancer.[3] Early-stage cancer detection could reduce breast cancer death rates significantly in the long term. The most critical prognosis is to identify early stage cancer cells. Investigators have studied many breast diagnostic approaches, including, mammography, magnetic resonance imaging, ultrasound, computerized tomography, positron emission tomography and biopsy.[4] This article addresses the types, causes, clinical symptoms and various approaches both non-drug (such as surgery and radiation) and drug treatment (including chemotherapy, gene therapy etc.) of breast cancer.[5]

KEYWORDS: Breast cancer, mammography, surgery, chemotherapy.

INTRODUCTION

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

DEFINITION

Usually, cancer is named after the body part in which it originated; thus, breast cancer refers to the erratic growth and proliferation of cells that originate in the breast tissue. The breast is composed of two main types of tissues i.e. glandular tissues and stromal tissues. Glandular tissues house the milk producing glands (lobules) and the ducts (milk passages) while; stromal tissues include fatty and fibrous connective tissues of breast.

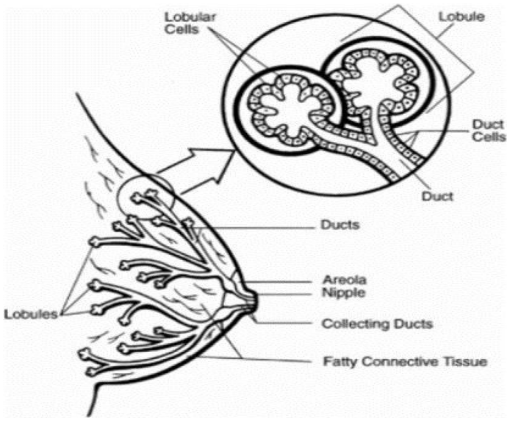

Fig.1 Structure of breast.

TYPES OF BREAST CANCER

According to site

Non-Invasive breast cancer cells that are confined to the ducts and do not invade surrounding fatty and connective tissues of the breast. Ductal carcinoma in situ (DCIS) is the most common form of non-invasive breast cancer (90%). Lobular carcinoma in situ (LCIS) is less common and considered a marker for increased breast cancer risk.

Frequently occurring breast cancer

Lobular carcinoma in situ (LCIS, lobular neoplasia)

LCIS is a sharp increase in number of cells within the milk glands (lobules) of the breast.

Ductal carcinoma in situ (DCIS)

DCIS, the most common type of non-invasive breast cancer, is confined to ducts of the breast. For example, ductal comedocarcinoma.

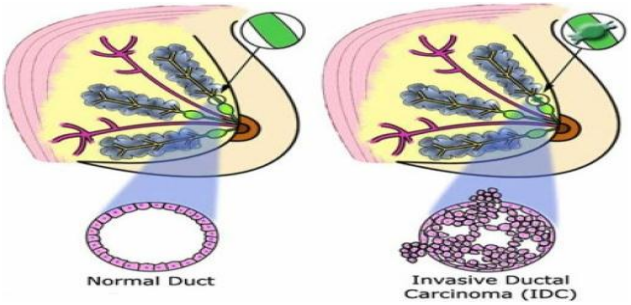

Fig.2 Typical structure associated with ductal carcinoma.

Infiltrating lobular carcinoma (ILC)

This begins in the milk glands (lobules) of the breast, but often spreads to other regions of the body. ILC accounts for 10% to 15% of breast cancers.

Infiltrating ductal carcinoma (IDC)

IDC begins in the milk ducts of the breast and penetrates the wall of the duct, invading the fatty tissue of the breast and possibly other regions of the body.

Less commonly occurring breast cancer

Medullary carcinoma: Medullary carcinoma is an invasive breast cancer that forms a distinct boundary between tumour tissue and normal tissue.

Mutinous carcinoma: Also called colloid carcinoma, mutinous carcinoma is a rare breast cancer formed by the mucus-producing cancer cells.

Tubular carcinoma: Tubular carcinomas are a special type of infiltrating (invasive) breast carcinoma. Tubular carcinomas accounts for around 2% of breast cancer diagnosis.

Inflammatory breast cancer

Inflammatory breast cancer is the appearance of inflamed breasts (red and warm) with dimples and/or thick ridges caused by cancer cells blocking the lymph vessels or channels in and over the breast.

Paget’s disease of the nipple

A rare form of breast cancer that begins in the milk ducts and spreads to the skin of the nipple and areola, Paget’s disease of the nipple only accounts for about 1% of breast cancers.

Phylloides tumour

Phylloides tumours (also spelled "phyllodes") are can be either benign (non-cancerous) or malignant (cancerous). Phylloides tumours develop in the connective tissue of the breast and may be treated by surgical removal.

CAUSES OF BREAST CANCER

A previous history of breast cancer- A women who has had breast cancer has an increased risk of getting breast cancer in the other breast.

Genetic causes- BRCA1 and BRCA2 are abnormal genes that, when inherited, markedly increase the risk of breast cancer to a lifetime risk estimated between 40 and 80%.

Hormonal causes- Alteration in hormonal level may precipitate breast cancer.

Lifestyle and dietary cause- Sedentary lifestyle, 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.[5]

EPIDEMIOLOGY

Breast cancer is the second most common cancer in the world and the most common cancer among women. In 2012, 1.67 million new cases of breast cancer were identified worldwide, accounting for 25% of all cancers. Although cancer the world, its incidence rate is higher in developed countries, and the incidence rate of breast cancer varies greatly with race and ethnicity.[6]

RISK FACTORS

Aging- Besides sex, aging is one of the most important risk factor of breast cancer, because the incidence of breast cancer is highly related to the increasing age.

Family history- Nearly a quarter of all breast cancer cases are related to family history. The inherited susceptibility of breast cancer is partially attributed to the mutations of breast cancer related genes such as BRCA1 and BRCA2.

Reproductive factors- Reproductive factors such as early menarche, late menopause, late age at first pregnancy and low parity can increase the breast cancer risk.

Estrogen- Both endogenous and exogenous estrogens are associated with the risk of breast cancer. The endogenous estrogen is usually produced by the ovary in premenopausal women and ovariectomy can reduce the risk of breast cancer. The main sources of exogenous estrogen are the oral contraceptives and the hormone replacement therapy (HRT).

Lifestyle- Modern life styles such as excessive alcohol consumption and too much dietary fat intake can increase the risk of breast cancer.[2]

SIGNS AND SYMPTOMS

The classic symptom for breast cancer is a lump found in the breast or armpit. 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), unintentional weight loss 9liver metastases), headaches, neurological pain or weakness.[5]

PATHOGENESIS

Breast tumors usually start from the ductal hyper proliferation, and then develop into benign tumors or even metastatic carcinomas after constantly stimulation by various carcinogenic factors. Tumor microenvironments such as the stromal influences or macrophages play vital roles in breast cancer initiation and progression. Macrophages can generate a mutagenic inflammatory microenvironment, which can promote angiogenesis and enable cancer cells to escape immune rejection. Different DNA methylation patterns have been observed between the normal and tumor-associated microenvironments, indicating the epigenetic modifications in the tumor microenvironment can promote the carcinogenesis. Breast cancer stem cells (bCSCs) are more likely to originate from luminal epithelial progenitors rather than from basal stem cells. Signaling pathways including Wnt, Notch, Hedgehog, p53, PI3K and HIF are involved in the self-renewal, proliferation and invasion of bCSCs.[2]

DIAGNOSIS

History and physical examination

The clinical history is directed at assessing cancer risk and establishing the presence or absence of symptoms indicative of breast disease. It should include age at menarche, menopausal status, previous pregnancies and use of oral contraceptives or post-menopausal hormone replacements. In addition, a family history of breast cancer and/or ovarian cancer in a first- degree relative should be established. Any significant prior breast history should be elucidated including previous biopsies.

Physical examination should include a careful visual inspection with the patient sitting upright. Nipple changes, asymmetry and obvious masses should be noted. The skin must be inspected for changes such as; dimpling, erythema, peaud' orange (associated with local advanced or inflammatory breast cancer). After careful inspection and the patient in the sitting position the cervical, supraclavicular and axillary lymph node basins are palpated for adenopathy. When palpable the size, number and mobility should be ascertained. Palpation of the breast parenchyma itself is performed with the patient supine and the ipsilateral arm placed over the head. The sub areolar (central quadrant of both breasts is palpated systematically. Masses are noted with respect to their size, shape, location, consistency and mobility.

DIAGNOSTIC IMAGING

The initial choice of imaging should be individualized to each patient based on the age and characteristics of the lesions. Diagnostic imaging and image guided needle biopsies play a central role in the diagnosis, treatment panning, and staging of patients with breast cancer.

Mammography

Mammography remains the main stay in breast cancer detection. Diagnostic mammograms are performed in women who have palpable mass or other symptoms of breast disease, a history of breast cancer within the preceding 5 years, or have been recalled foe additional imaging from an abnormal screening mammogram. Diagnostic mammograms include special views such as focal compression of one area of the breast tissue or magnification images. The breast imaging reporting and database system (BI-RADS) is the standardized method for reporting of mammographic findings. Carcinomas present as masses, asymmetries, and calcifications (Table 1).

Table 1: Breast imaging reporting and database system.

Category	Assessment	Follow up
0	Need additional imaging evaluation	Additional imaging needed before a category can be assigned
1	Negative	Continue annual screening mammograms (women older than 40 yr.)
2	Benign	Continue annual screening mammograms (women older than 40 yr.)
3	Probably benign	Initial short term follow- up (usually six month) mammogram (<2% chance of malignancy)
4	Suspicious abnormality	Biopsy should be considered (2%-95% chance of malignancy)
5	Highly suggestive of malignancy	Requires biopsy (>95% chance of malignancy)
6	Known cancer	Biopsy- proven malignancy

MRI

Breast MRI has become an integral part of breast cancer diagnosis and management in selected patients. Current indications for breast MRI include evaluation of patients in whom mammographic evaluation is limited by augmentation (including silicone and saline implants and silicone injections), determining the extent of disease at the time of initial diagnosis of breast cancer (including identification of invasion of pectoralis major, serratus anterior, and intercostal muscles), evaluation of inconclusive findings on clinical examination, mammography, and/or ultrasonography, screening of the contralateral breast in selected patients with newly diagnosed breast carcinoma, and asymptomatic screening of patients at very high risk of breast carcinoma (in conjunction with routine mammography). Other uses of breast MRI include evaluation of response to neoadjuvant chemotherapy with imaging before, during, and/or after treatment, and identification of residual disease in patients with positive margins after lumpectomy.

Ultrasound

The current indications for breast ultrasonography include palpable findings (including as the initial imaging test of palpable findings in patients who are younger than 30 years, pregnant, or lactating), abnormalities or suspected abnormalities on mammography or MRI, problems with breast implants, suspected underlying mass in the setting of micro calcifications or architectural distortion on mammography, supplemental screening in women at high risk for breast cancer who are not candidates for or do not have easy access to MRI, and suspected axillary lymphadenopathy. Real time imaging is also possible with ultrasonography, making it ideal for interventional procedures, Breast ultrasound imaging should be performed with a high-resolution real-time linear array transducer with a center frequency of at least 10 MHz, using the highest frequency with which adequate penetration of the tissue is feasible.[7]

Treatment

The 2 basic principles of treatment are to reduce the chance of local recurrence and the risk of metastatic spread. Surgery with or without radiotherapy achieves local control of cancer. When there is a risk for metastatic relapse, systemic therapy is indicated in the form of hormonal therapy, chemotherapy, targeted therapy, or any combination of these. In locally advanced disease, systemic therapy is used as palliative therapy with a small or no role for surgery.[8]

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 pectoralis 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.

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.

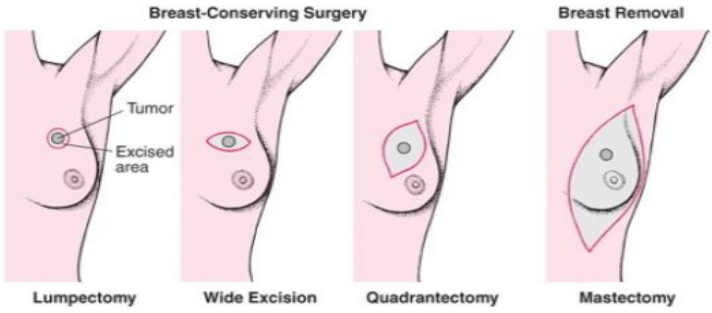

Fig.3 Various types of surgery applied for breast cancer.

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 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.[5]

Medical Oncology

Chemotherapy, hormone therapy, and targeted therapy are the systemic therapies that are used in the management of breast cancer. A 25 percent reduction in the risk of relapse over a 10 to 15- year period using a first generation chemotherapy regimen such as cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) in a 6-month cycle. Anthracyclines (doxorubicin or epirubicin) and the newer agents such as the taxanes are modern regimens used for breast cancer. Three to 6-month period is used for adjuvant and neoadjuvant chemotherapy. Adjuvant treatment of early-stage HR+ breast cancer with tamoxifen for at least 5 years has been shown to reduce the recurrence rate by about half throughout the first 10 years and reduces breast cancer mortality by about 30% throughout the first 15 years. More recently studies have shown that extended use of adjuvant tamoxifen (10 years versus 5 years) further reduces the risk of breast cancer recurrence and mortality, so clinical practice guidelines now recommend consideration of adjuvant tamoxifen therapy for 10 years. The main stay of treatment for most premenopausal women with HR+ tumors is tamoxifen. Treatment guidelines recommend aromatase inhibitors (AIs) such as anastrozole should be included in the treatment of postmenopausal women with HR+ breast cancer. Targeted therapy is usually indicated in about 17% of breast cancers that overproduce the growth-promoting protein HER2/neu. Trastuzumab, the first approved drug, is a monoclonal antibody that directly targets the HER2 protein. It reduces the risk of recurrence and death by 52% and 33% respectively if combined with chemotherapy in HER2+ early breast cancer if compared to chemotherapy alone.[8]

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., ulceration, retraction, spontaneous bloody discharge) may also be present at the same time.[5] This cancer is developed in breast tissues including ducts (tiny tubes that carry the milk) and lobules (milk-producing glands). Although the exact cause of breast cancer is unknown,

specific risk-factors have been identified.[9] There is a great refinement in breast cancer care with increased specialization and collaboration amongst surgeons, oncologists, radiation oncologists, nurses, geneticist, reconstructive surgeons and patients. The effectiveness and benefits of a multidisciplinary approach to the treatment of breast cancer has been empirically demonstrated.[7]

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