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Research Article

A REVIEW ON BREAST CANCER-AN AWARENESS NEEDED DISEASE

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A B S T R A C T

This article mainly presents a comprehensive review of breast cancer along with its prevention. Breast cancer is most frequently occurring cancer in women in both developing and developed countries in the world. After skin cancer, breast cancer is the most common cancer among women. It is also the second leading cause of cancer death in women after lung cancer. The potential adverse effects will make an impact on quality of life. The different prediction models laminate on women's risk for developing cancer and can steer recommendations of screening based on environmental, genetic, or personal risk factors. The interrogative approaches include screening methods along with pharmacological, nutritional, surgical methods. The usage and role of selective estrogen receptors, modulators such as tamoxifen and raloxifen which was using for breast cancer is well entrenched. Along with these several other agents such as aromatase inhibitors are being currently used. The various current approaches including prevention of breast cancer i.e., diet and nutrition, ionizing radiation etc., are getting drastic change in women world who are suffering with breast cancer. But along with these several future approaches are developing where breast cancer is preventable and thousands of lives can be saved from experiencing this terrible disease.

INTRODUCTION

Breast cancer is the most common cancer affecting women worldwide. It refers to a malignant tumour that has developed 40m cells in breast. The tumours may be developed either in cells of flabella which produce milk or in stroma tissue, which include fatty and fibrous tissue of breast [1]. There are different ways for origin of breast cancer. It may be by a mixture of genetic, environmental and lifestyle factors. Breast cancer was becoming most common in both developed and developing countries now days. It is estimated that 5, 08,000 women died in 2011 worldwide due to breast cancer.

Incidence rates vary greatly worldwide from 19.3 per 1, 00, 000 women in Africa to 89.7 per 1, 00,000 in Europe. In most developing areas the incidence is below 40 per 1, 00,000[2]. There are 20 million new cases registered worldwide in breast cancer and 6 million deaths are predicted. Yet only small fraction was concentrating in prevention in which most of this focused on avoiding toxins [3].The survival rates of breast cancer vary greatly in different regions due to lack of early detection programmes. Preventing breast cancer is the most important thing we can do in terms of breast cancer research. [4] By targeting on early detection treatment and quality of life of breast cancer, the national breast cancer foundation has invested 11 million dollars into 20 cancer research projects, supporting total of 73 researches finally. Research continues in developing our understanding, preventing, and managing and curing breast cancer [5].

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Pathophysiology

Like other cancers, breast cancer also can be caused due to interaction between external factors and genetical factor. Generally, cells in our body divide up to the need and stops. If the cells loose ability of stopping the division to attach to other cells, to live where they generate, and to die at proper time leads to cancer.

Programmed cell death occurs if the cells are no longer needed which are prospected by various protein clusters and pathways from death. Various protective pathways for cell are P13K/AKT pathway and RAS/MEK/ERK pathway. Sometimes the genes along with the protective pathways are mutated so that these turns them permanently 'on', and rendering the cell incapable of committing suicide when it is no longer needed. This is one of the steps that cause cancer in combination with other mutations. PTEN proteins inactivates P13K/AKT pathway when cell is ready for programmed cell death. In some breast cancers, the gene for PTEN protein is mutated so the P13K/AKT pathway is stuck in the "on" position, and the cancer cell does not commit suicide [6]

Abnormal growth factors of stromal cells and epithelial cells can make malignant cell development easier [7, 8]. In adipose tissue of breast, excessive expression of leptin leads to increased cell expansion and cancer. [9]In the United States, 10 to 20% of people with breast cancer and ovarian cancer are relative to one of these diseases. The related tendency to develop these cancers is known as 'hereditary breast-ovarian cancer syndrome'. The BRCA mutations give a lifetime risk of breast cancer of 60 to 85%. Cancer combine with some mutations such as P53, BRCAL and BRCA2 used to correct errors in DNA. These mutations may either receive or reject after birth. Thus, allow other mutations which leads to uncontrolled division, lack of attachment and metastasis of cells to faraway organs [10]. The unobserved risk factors cause residual risk variation that goes well beyond hereditary BRCA gene mutations. The results in environmental and other cause's activation of breast cancer. The received mutation in BRCA1 or BRCA2 gene combine with repair of DNA cross links and DNA double strand breaks [11]. This effects crosslinks and double strand of DNA that require pathways for repair containing BRCA1 and BRCA2 [12, 13]. However, BRCA genes account for only 2 to 3% of all breast cancer [14], half of hereditary breast-ovarian cancer disorders involve unknown genes.

Mutations that can lead to breast cancer have been experimentally linked to oestrogen exposure [15]. GATA-3 controls expression of oestrogen receptor (ER) and others which are associated with epithelial differentiation. Loss of GATA-3 leads to loss of differentiation and poor medical condition due to cancer cell occupation and, malignancy [16].

Types of Carcinoma

Non-invasive Carcinoma

This is of two types

Ductal Carcinoma in situ

In ductal carcinoma the abnormal cells are found in lining of breast milk duct. Ductal carcinoma is an invasive cancer which is highly lobular in early condition but, if it is left untreated it can spread into the surrounding breast tissue.

Lobular Carcinoma in Situ (LCIS)

In this, it looks like cancer cells are growing in the milk producing glands of the breast (lobules) but they don't grow through the wall of lobules. LCIS is an indication that the person is at higher than average risk for getting breast cancer in future so, it also termed as lobular neoplasia

Invasive Carcinoma

This is of two types

Invasive Ductal carcinoma/ Infiltrative Ductal Carcinoma

The abnormal cells formed in the milk ducts spread into the other parts of the breast tissue and also spread to other parts of the body. IDC is most common type of breast cancer which can also affects men and it makes up 80% of all cancer diseases

***Invasive Lobular Carcinoma* (ILC)**

Here, cancer begins in the milk carrying ducts and spreads beyond it. ITC refers to cancer that has broken through the wall of the lobule and begun to invade the tissue of the breast. Over time it spread to lymph nodes and to other areas of the body. ITC can also occur at any age but it is more common as a woman grows older.

Medullary Carcinoma

Medullary carcinoma cells are soft, fleshy moss that resembles medulla of the brain. It can occur at any age but usually effects women in age 40s and early 50s. It is easier to treat medullary carcinoma compared to other because it doesn't grow quickly and doesn't spread outside the breast to lymph nodes

Colloid Carcinoma

In this type of cancer, the tumour is made up of abnormal cells that flow in pools of mucin, a slippery substance known as mucus. So, it is also called as 'mucinous carcinoma'. In colloid carcinoma, mucin becomes the part of the tumour and surrounds the breast cancer cells. It is extremely seen in women. Some studies have found that the average age of women for diagnosis is in the 60s or early 70s in women. It can be treated. It accounts 5% of all invasive breast cancer

Papillary Carcinoma

An invasive papillary carcinoma usually has a well-defined border and is made up of small, finger like projection. It accounting for less than 1 to 2% of Invasive breast cancer.

Tubular Carcinoma

Tubular carcinoma is usually small (about 1cm or less) made up of tube-shaped structures called tubules. Here the tumour cells look similar to normal healthy cells and tend to grow slowly. At one time, tubular carcinomas accounted for about 1 to 4% of a breast cancer but now a day's tubular carcinoma are being diagnosed more frequently. This type of cancer is rare in man. Tubular carcinoma is an Invasive breast cancer but it is less aggressive type that is responsible to treatment.

Adenoid Cystic Carcinoma

Adenoid cystic tumours are often "triple negative" means that the cells don't express the oestrogen, progesterone receptor or HER2 receptor. When these cells are examined in microscope, they look like cancer cells more commonly found in salivary glands and saliva. It accounts 1% or less than 1% of all breast cancers and its treatment is based on the features of tumours.

Secretary Breast Cancer

Secretary carcinoma is very rare tumour that represents less than 0.15% of all breast cancer types. It appears like a honey-combed structure characterised by milk like secretion seen on the cells in 50% of the cases. This tumour mainly affects girls and women that cover around the nipple or areole.

Inflammatory Breast Cancer

Inflammatory breast cancer starts with the reddening and swelling of the breast instead of a distinct lump. IBC tends to grew more quickly and symptoms are seen within days or even hours. A 2008 study states that over- weight makes a person more likely to develop IBC.

Carcinoma of Breast with Metaplasia

Meta-plastic carcinoma of breast is a heterogeneous group of cancer that exhibits varied patterns of metaplasia and differentiation along multiple cell lines. Meta-plastic breast

cancer is a rare and histological diverse sub type of breast carcinoma. It accounts for less than 1% of all breast cancer. [18]

Stages of Carcinoma

The simple way to approach stages of breast cancer is by using TMN classification. They are mainly 5 stages.

Stage 0: In this, cancer is present only in lobules or tissue of breast. It doesn't spread to other tissue or surrounding tissue of breast. It is also called non- invasive cancer (N0, M0)

Stage I: It is classified into two types

a. **I**A – Tumour is invasive, small, not spread to lymph nodes (T1, N0, M0)
b. **I**B – Spread to lymph nodes, size will be larger than 0.2mm but less than 2mm size.

Stage II: It is classified into two types

IIa– It have 3 conditions

a. ***Condition 1*** – No evidence of tumour, but cancer spread to 1 to 3 axillary lymph nodes, but it won't spread to distant parts of body (To, N1, Mo)
b. ***Condition 2*** – 20mm or smaller, spread to axillary lymph node
c. ***Condition 3*** – > 20 mm but not > 50mm, no spread to axillary lymph node (T2, No, Mo)

IIb – It have 2 conditions

a. ***Condition 1*** – > 20mm but not > 50mm and spread to 1to 3 axillary lymph node
b. ***Condition 2*** - >50mm not spread to axillary lymph node

Stage III: It is classified into three types

IIIa – Cancer of any size will spread to 4 to 9 axillary lymph nodes. It has no spread to other parts but, it may also be a tumour >50mm

IIIb – Spread to chest wall cause swelling it is diagnosed as inflammatory breast cancer. It may or may not spread to axillary lymph node. No spread to other parts (T4; N0, N1, N3; M0)

IIIc – Any size spread to 10 or more axillary lymph nodes; internal mammary lymph node and lymph node under collar bone. No spread to other parts of body (any T, N3, M0)

Stage IV

Metastasis – Any size and spread to other organs such as heart, lungs, brain, liver etc. [17]

Breast Cancer Risk Factors

Breast Occurs Due to the Following Risk Factors like

1. Getting older, the risk increases. Mostly found in women of age 55 and older [19].
2. Occurs due to certain inherited genes and mutations in the genes like BRCA 1 and BRCA 2 and changes in some genes [22, 23, 24].
3. Having a first degree relative (mother, sister, or daughter) with breast cancer almost doubles a women's risk.[20]
4. Having a personal history of breast cancer. A woman with cancer in one breast has a higher risk of developing a new cancer in other breast or in another part of the same breast. But this risk is low.[21]
5. Certain benign breast conditions like non-proliferative lesions that includes fibrosis, hyperplasia, adenosis, papilloma etc.
6. Starting menstruation early
7. Going through menopause after age 55
8. Women who were treated with radiation therapy to the chest for another cancer when they were younger have a significantly higher risk.
9. Exposure to diethylstilbestrol (DES) during pregnancy.
10. There are also some life style related breast cancer risk factors which includes [25].

Drinking alcohol [26]

Being overweight or obese.

Having more fat tissue after menopause can raise estrogen levels and increase the chance of getting breast cancer. Still the link between weight and breast cancer is complex. Weight may also have effect on different types of cancers. Researchers suggest that being overweight before menopause might increase the risk of triple negative breast cancer. [27]

Not being physically active

Evidence is growing that regular physical activity reduces breast cancer risk, especially in women post - menopause. Even a little as a couple of hours a week might be helpful, although more is better. [28]

Not having Children

Women who have not had children or who had their first child after the age 30 have a slightly higher risk. Having many pregnancies and becoming pregnant at an early age reduces the risk. But for triple negative breast cancer, pregnancy seems to increase the risk.

Not breast Feeding

According to some studies, breast feeding may slightly lower the risk of breast cancer, especially if it is continued for 1 and half to 2 years. This effect may be because it reduces the woman's total number of life time menstrual cycles.

Birth Control

Some birth control methods use hormones, which might increase breast cancer risk. Women who use oral contraceptives have a slightly higher risk than women who never used them. Women currently using birth control shots have an increase in the risk. Birth control implants, IUD'S, skin patches, vaginal rings, which use hormones, could fuel the breast cancer growth.

Hormone Therapy after Menopause

Use of combined hormone therapy after menopause increases the risk of breast cancer. The risk can be seen with as little as 2 years of use. It may also increase the risk of dying from breast cancer. Use of bioidentical hormone therapy has considered having the same health risks as other type of hormone therapy. The use of estrogen therapy alone after menopause does not seem to increase the risk much, but when used for more than

15 years it has been found to increase the risk of ovarian and breast cancer.

Breast implants

Silicone breast implants can cause scar tissue to form in the breast. Certain types of breast implants can be linked to a rare cancer called anaplastic large cell lymphoma (ALCL). If ALCL show up after an implant, it can show up as a lump. It usually responds well to the treatment. [29]

Diagnosis

Physical examination primarily includes visual examination by observing nipple changes, irregular uneven growth of mass by allowing the patient sitting up-right and observed conditions are noted. This also includes skin changes such as thickening, formation of ridges. After this examination patient with sitting position is tested for adenopathy in clavicular and axillary lymph nodes. Irregular masses are noted considering its shape, size, location, ability to move and stability. After diagnosis the patient should be evaluated for symptoms like breast pain, uneasiness, nipple discharge, weight loss. The diagnostic tests include the following

1. Breast examination
2. Mammography (X-Ray of Breast)
3. Breast ultrasound
4. Biopsy [30]
5. MRI (Breast magnetic resonance imaging) [31, 32]
6. Scinti mammography' (molecular breast imaging)

Prevention

Natural Prevention of Breast Cancer

The scientifically documented agents provide powerful protection against breast cancer through number of mechanisms by using pomegranates, green tea, cur cumin, and vitamin-D protect the other cells from cancer cells and soya extracts can help guard against estrogen hyper proliferating actions. The scientific studies also provide nutritional cancer protective compounds that play a major role to helping to win war against breast cancer. Wide variety of colourful fruits and vegetables, foods rich in fibre, such as whole grains, beans, dark green leafy vegetables like pepper, tomatoes, egg, carrot, broccoli etc., also helps to prevent breast cancer.

Exercise appears as it improves physiological and psychological walfering in breast cancer patients. [33] Some evaluation proves that association between physical activity and breast cancer risk reduction. Consumption of tobacco and alcohol should be avoided as the breast cancer incidence was 24% higher in former smokers than non- smokers. [34]

Chemoprevention of Breast Cancer

Two selective estrogens receptor modular (SERM) medications, tamoxifen and raloxifene, are approved by the FDA to prevent breast cancer in high risk women. SERMs act as an anti – estrogen in some organ systems, and in a pro – estrogenic fashion in others. Tamoxifen was the first agent to be approved and the only one approved for use in pre and post -menopausal women. It reduced the risk of invasive breast cancer by 49% overall and in all age subgroups by over 40%. It also reduced the incidence of ductal carcinoma *insitu* (DCIS) by 50%, lobular carcinoma *insitu* (LCIS) by 56% and atypical hyperplasia by 86%. Raloxifene was approved based on the findings from a trial, done by comparing it to tamoxifen. The American society of clinical oncology suggested the use of chemo preventive medications in women at increased breast cancer risk, and the first to recommend is exemestane, an aromatase inhibitor, as an alternate to tamoxifen or raloxifene. When exemestane was compared with placebo or celecoxib with exemestane in post- menopausal women deemed to be at increased risk of breast cancer. Exemestane plus or minus celecoxib decreased the risk of ER positive but not ER negative breast cancer. DCIS incidence was lower with exemestane, but not at a significant rate. Another drug anastrozole found to decrease the risk of developing breast cancer. [35]

Immunoprevention

The prevention through immunity play a role in the usage of cancer preventing vaccines. Recently hepatitis-B virus is eradicated with immunoprevention against hepato cellular cancer which is 80% effective and also in the case of human papilloma virus which is 90-100% effective. [36]

The non -viral cancer agent's prevention through these vaccines is approaching. The HER2 vaccine estimate the prevention of HER2 positive breast cancer was also developed [37]. The premalignant humour of the breast is eradicated by developing immunity to multiple antigens that shows high action than the single immune dose. [38]

Surgical approach to prevent breast cancer

Various genetic mutations can impart a risk of breast cancer including BRCA1 & BRCA2; TP53; PTEN; STK11; CDH1; PALB2; CHECK2; NBN; and NFI [39]. Each genetic action has its specific impact on breast cancer risk. According to current study, American society of breast cancer recommends risk reducing bilateral mastectomy approach for women without breast cancer who have deleterious mutation in BRCA1, BRCA2, PALB2, and TPS3[40]. Mastectomy is of many types.

Simple or total mastectomy: It mainly concentrates on breast tissue but sometimes lymph nodes are occasionally removed it they locate near breast tissue taken during surgery.

***Modified radical mastectomy*:** It involves removal of both breast tissue and lymph nodes i.e., axillary lymph nodes are dissected.

Radical mastectomy: In this entire breast removed along with chest wall muscle under the breast.

Partial mastectomy: It mainly includes removal of cancerous part and along with normal tissue around it mastectomy in this tissue is removed than partial mastectomy.

Nipple discharge mastectomy: In all breast tissue removed but nipple is remains.

Treatment

Adjuvant Therapy

A multi-disciplinary approach to the treatment of breast cancer has been fundamental for the recent advances in the management of this disease. The purpose of adjuvant systemic therapy is to improve the disease – free survival (DFS) and overall survival (OS) rates associated with the treatment of BC by local therapies alone. The high rates of recurrence are probably related to the presence of micro metastatic disease in 10% to 30% of LN-negative and in 35% to 90% of LN positive

patients at the time of diagnosis [41, 42]. Adjuvant chemotherapy helps eradicate residual local or distant residual microscopic metastatic disease.

Current guidelines for adjuvant hormonal and chemotherapy after surgical treatment for invasive breast cancer vary depending on hormone receptor positivity or negativity and expression of HER-2/neu. The applicable practice guidelines are below [43]:

Hormone Receptor – Positive

HER-2 positive disease: pT1, pT2, orpT3; and pN0 or pN1mi

1. Tumour less than or equal to 0.5cm or micro invasive (pN0, consider adjuvant endocrine therapy or adjuvant chemotherapy with trastuzumab followed by endocrine therapy.
2. Tumour 0.6-1.0 cm, adjuvant endocrine therapy +or-adjuvant chemotherapy with trastuzumab.
3. Tumour >1cm, adjuvant endocrine therapy +adjuvant chemotherapy with trastuzumab.
4. Node positive, adjuvant endocrine therapy +adjuvant chemotherapy with trastuzumab.

Hormone Receptor-Negative

HER-2 negative diseases: pT1, pT2 or pT3; and pT0 or pN1mi

Tumour less than or equal to 0.5cm or micro invasive (pN0, consider adjuvant endocrine therapy; pN1mi, adjuvant endocrine therapy with trastuzumab; 2) Tumour >0.5cm, consider 21-gene RT-PCR assay.

Most recently, the development of genomic profiling techniques has identified gene expression patterns in breast tumours with distinct molecular profiles, pathologic features, and clinical outcomes [44, 45]. Expression patterns have defined 4 different subtypes: luminal A and B, HER-2 enriched, and basal like tumours.

Adjuvant hormone therapy is considered standard in all patients with endocrine sensitive tumours defined by the expression of ER and PR by IHC. Approximately 70% of BC's have positive expression of the ER and are considered hormone sensitive. Treatment with tamoxifen for 5 years reduces the risk of recurrence by 41% and BC mortality by 34%. [46]

In post -menopausal women, an aromatase inhibitor may be substituted because of the proven efficacy and the low risk for development of endometrial cancer with this drug. The arimidex, tamoxifen, alone or in combination trial (ATAC), is a pivotal trial in adjuvant hormone therapy [47].

Approximately 15% to 20% of all BCs present with amplification of the HER-2 gene [48]. This gene over expression is reported to be an independent predictor of poor prognosis. This can be addressed by the incorporation of anti-HER2 therapy with trastuzumab, which in the adjuvant setting has shown significant improvement in clinical outcomes from adjuvant chemotherapy plus trastuzumab compared with chemotherapy alone. Based on the results from randomized clinical trials, a trastuzumab containing regimen for up to 1 year is now considered standard for all patients with HER-2 positive tumours larger than 1cm [49, 50].

There are rapid advances being made with respect to systematic therapy targeting specific molecular targets like phosphatidylinositol 3-kinase vascular endothelial growth factor receptor, epidermal growth factor receptor and poly polymerase.

Locoregional Treatment

Lumpectomy with surgical Axillary Staging

Negative axillary nodes: Radiation therapy to whole breast with or without photons, brachy therapy, or electron beam for consideration of partial breast irradiation (PBI) in some patients. Radiations therapy should follow chemotherapy when it is necessary.

One-three positive axillary nodes: In this the radiation is treated to whole breast with or without boost (by photons, brachytherapy, or electron beam) to tumour bed following chemotherapy when chemotherapy is indicated. Strongly consider radiation therapy to infraclavicular region and supraclavicular area and to internal mammary nodes. Radiation therapy should follow chemotherapy if indicated.

Four-positive axillary nodes: In this the radiation is treated to whole breast or without boast in some PBI patients. The radiation therapy to infraclavicular region and supraclavicular area

Total Mastectomy with Surgical Axillary staging

i. ***No radiation therapy:*** Negative axillary nodes and tumour </= 5cm and margins >1mm.
ii. ***Consider post chemotherapy radiation therapy to chest wall***: negative axillary nodes and tumour </= 5cm and close margins (<1mm).
iii. ***Strongly consider radiation therapy to internal mammalian nodes:*** negative axillary nodes and tumour >5cm or margins positive.
iv. ***One three positive axillary nodes:*** strong post chemotherapy to chest wall, infraclavicular and supraclavicular areas. The radiation therapy given is internal mammary node therapy [51].

CONCLUSION

Various experiments are improved to understand the breast cancer based on patient condition and accuracy based for the breast cancer treatment. These developmental investigations show future of breast Cancer prevention. The multi-disciplinary approaches for effective and beneficiary treatment of breast cancer have been empirically demonstrated. Improvements in screening increase earlier detection of breast cancer. The earlier detection of breast cancer provides more effective treatment options and decrease mortality rates and greater chance of cure. Along with this, women with moderate risk profile for developing breast cancer allow for better benefits and limitation of annual screening MRI. Besides this, a proper awareness raising components, to educate patients, family and community members about cancer risk factors and need to take preventive measures to avoid developing cancer. In future, there will be great value in genomic sequencing and proto- identification of women risk against a breast cancer.

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