BREAST CANCER: AN OVERVIEW

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Abstract: Breast cancer accounts for the second largest cause of death in women in Western countries. The incidence of breast cancer in Asian populations is indeed 6 to 7 fold lower as compared to Western populations. Globally more than 7,00,000 women are diagnosed with breast cancer every year. In USA, approximately 1,82,460 new cases of invasive and 67,770 new cases of non-invasive (in-situ) breast cancers were diagnosed in women. In India 70,000 new cases of breast cancer and 35,000 deaths due to this cancer are reported every year. Though genetic factor accounts for 10–15% of all breast cancer case, life style and environmental factors play a significant role in predisposing women to this form of cancer. The present review discuss about the epidemiology, etiology, pathogenesis, biomarkers and chemoprevention of breast cancer.

Key words: Breast cancer, Etiology, Diagnosis, Chemoprevention, Biomarkers

INTRODUCTION

Cancer arises from genetic changes in one single cell, which may be started by external agents (Radiation, chemical carcinogens and viruses) and inherited genetic factors. It comprises a large group of diseases and has a sizable contribution in the total number of deaths. Cancer is the second largest non-communicable disease and can affect any part of the body. Worldwide, around 12.7 million new cancer cases and 7.6 million deaths were reported in 2008 and the most commonly diagnosed cancers include lung, breast, and colorectal cancers [1]. The most common cause of cancer death is due to lung, stomach and liver cancers [2]. More than 70% of all cancer deaths occurred in low- and middle-income countries. The deaths from cancer worldwide are projected to continue rising, with an estimated 12 million deaths in 2030 [3]. It has been reported that half of all men and one-third of all women in the United States will develop some form of cancer during their lifetime. It has been reported that newly diagnosed cancer cases are more in Asia due to the fact that 45% of world population are in Asia. The incidence of cancer rises dramatically with age and about 80 percent of all cancers occur in people over the age of fifty-five.

Cancer is emerging as major public health problems in India. Cancer prevalence in India is estimated to be around 2.5 million, with over 800,000 new cases and 550,000 deaths occurring each year due to this disease [4]. More than 70% of the cancer cases in the advanced stages at the time of diagnosis, this has lead to a poor survival and high mortality rate.

Approximately 30 percent of all cancers worldwide are due to tobacco use. Dietary practices, reproductive and sexual practices etc, accounts for 20-30% of cancers. Tobacco use, including cigarettes, cigars, chewing tobacco, and snuff, can cause cancers of the lung, mouth, throat, larynx, bladder, kidney, esophagus, and pancreas. Tobacco related cancers account for about 52% of all cancers in males and 25% of all cancers in females. In India alone, 5500 youths succumb to tobacco addiction each day, thus making tobacco a source of growing concern not only for the government but also for society. While tobacco use increases rapidly, studies indicate that by the year 2025, the overall increase in
Chemical carcinogenesis: Chemical carcinogenesis begins when cells are exposed, usually to complex mixtures of chemicals that are found in the human environment. Carcinogenesis is a multistep process and can be conceptually divided into four stages: tumor initiation, tumor promotion, malignant conversion, and tumor progression [7]. Tumor initiation results from irreversible genetic change that occurs as the result of chemical–DNA interaction, and thus, initiated cells are at greater risk of malignant conversion than are normal cells. Tumor promotion comprises the selective clonal expansion of initiated cells. Tumor promoters reduce the latency period for tumor formation after exposure of a tissue to a tumor initiator. The transformation of a pre-neoplastic cell into one that expresses the malignant phenotype is known as malignant conversion, which requires further genetic changes. Tumor progression, the stepwise evolution of cancer cells into higher degree of malignancy, comprises the expression of the malignant phenotype and the tendency of already malignant cells to acquire more aggressive characteristics such as metastasis with time.

Breast cancer: Breast cancer starts in the tissues of the breast. Ductal carcinoma starts in the tubes (ducts) that move milk from the breast to the nipple. Ductal carcinoma accounts for 75% of all invasive breast cancers. Ductal carcinoma in situ, also known as intraductal carcinoma or non-invasive ductal carcinoma contains breast duct cells that have malignant characteristics when viewed under a microscope. Lobular carcinoma starts in the parts of the breast, called lobules that produce milk. Lobular carcinoma in situ, also known as non-invasive lobular carcinoma usually occurs in women who have not undergone menopause. Lobular carcinomas accounts for 5% to 10% of all invasive breast cancers [8]. If breast cancer penetrates the membrane that surrounds the lobules or ducts, it is called an infiltrating or invasive carcinoma. Inflammatory carcinoma is a very serious, rapidly spreading type of tumor that accounts for about 1% of all breast cancers. Although most breast cancers are epithelial carcinomas, a very small number of breast cancers may arise from the muscle, fat, or connective tissues of breast. Breast cancer is the most common form of cancer among women and the second most common cancer in the world. Breast cancer incidence is rapidly increasing in developing countries including India, due to the fact that developing countries adopt Western culture and their habits. Recent studies suggest that breast cancer is not a single homogenous disease but consists of at least 5 distinct molecular subtypes with different treatment options and prognoses [9].

Epidemiology: Breast cancer is the second leading cause of deaths in women and is the most common cancer among women, excluding non melanoma skin cancers. Breast cancer incidence varies widely within regions and countries, and has been increasing in the general population all over the world likely due to differences in racial and ethnic make-up, health resources, and lifestyle patterns. Worldwide, the incidence of breast cancer varies from 3.9/100,000 in Mozambique to as high as 101.1/100,000 in the U.S. Geographic variation in breast cancer incidence can be attributed to racial and genetic differences, cultural differences, as well as environmental exposures that vary throughout the world [10].

Breast cancer is the most common cancer of women in the United States and affluent European countries. According to the American Cancer Society, in general, breast cancer rates have risen about 30% in the past 25 years in western countries, due in part to
increased screening which detects the cancer in earlier stages. Approximately 2.4 million women living in the U.S. have been diagnosed with and treated for breast cancer. Breast cancer continues to be the most commonly diagnosed cancer in women in the United States, accounting for 26% of all female cancers. In 2009, around 192,370 newly diagnosed invasive and 62,280 non invasive breast cancer cases were reported in USA. Also, about 40,170 women were died due to breast cancer in USA in 2009 [11].

The life time probability of developing breast cancer is about 4.8% in developed countries whereas 1.8% in developing countries. The lowest breast incidence is reported from far Eastern and South-East Asian countries [12]. In the developing countries of Asia, the health care burden on account of breast cancer has been steadily mounting. Breast cancer is the most common neoplastic disease amongst women in the UK and Wales, accounting for more than 12,000 deaths each year [13]. 36 women in Australia diagnosed with breast cancer every day [14]. In Nigeria, about two-thirds of women with breast cancer are diagnosed at advanced stage of cancer [15]. In Greece, the annual incidence is more than 3000 per year and the annual incidence is increased over the last 20 years has been 1.3%. An increase in incidence rate was reported every year in Japan, Singapore and Korea [16]. Reports from Pakistan showed increasing incidence of ER, PR negative breast cancer among women populations [17].

Breast cancer is the commonest cancer of urban Indian women and the second commonest in the rural women [18]. In India, 75,000 new cases of breast cancer are reported every year and increase in incidence has been reported in metropolitan cities [19]. Breast cancer is the most common cancer among Indian women in urban registries of Delhi, Mumbai, Ahmadabad, Calcutta, and Trivandrum where it constitutes 30% of all cancers in females. It has been reported that the age standardized incidence rates for breast cancer range varies from 6.2 to 39.5 per 100,000 in Indian women. The highest incidence was however reported in the Parsi community of Mumbai women [20]. Owing to the lack of awareness of this cancer and in absence of a breast cancer screening program, the majority of breast cancers are diagnosed at a relatively advanced stage.

**Age and sex distribution:** Breast cancer is about 100 times more common in women than in men, but survival rates are equal in both sexes. All women are at risk for developing breast cancer. The older a woman is, the greater her chances of developing breast cancer. Approximately 77% of breast cancer cases occur in women over 50 years of age. Annual breast cancer rates are 8-fold higher in women who are at 50 years old, in comparison with women who are at 30 [21]. If a woman has already had breast cancer, she has a greater chance of developing a new cancer in the other breast.

**Risk Factors:** The established risk factors for breast cancer may enhance chances of getting the cancer. Breast cancer as it is a complex disease with often many different contributing causes. The greatest risk factor for developing breast cancer is gender (female) and the second is age. Women who begin menstruating before age 12 are at increased risk of developing breast cancer [22]. In more recent years, research has indicated the impact of diet and other behaviors on breast cancer. These additional risk factors include a high-fat diet, obesity, and environmental factors such as tobacco use, endocrine disruptors and shift work.

**Reproductive factors:** Reproductive factors that increase breast cancer risk include a long menstrual history (early menarche and late menopause), never having children, having one’s first child after age 30, never breastfeeding, being overweight or obese after menopause and use of postmenopausal hormone therapy (specifically, combined estrogen and progestin therapy). Nulliparity and late age at first childbirth are consistently observed reproductive risk factors. A case control study in Mumbai indicated that compared to married women, single women had a 4-5-fold higher risk for developing breast cancer in the age group of 40-54 and above. In another study, nulliparous women had a 2.2-fold higher risk than parous women [23].

**Radiation exposure:** A significantly increased risk of breast cancer has been found in women who received radiation therapy in the chest area during childhood or young adulthood. Although the radiation from mammography is a low dose, the cumulative effect can cause cancer [24].

**Alcohol consumption:** Women who consume one alcoholic beverage a day have a slightly increased risk of breast cancer. By contrast, breast cancer risk is nearly doubled in women who have more than three drinks daily. A positive association between the consumption of more than two drinks a day and an
increased level of estrogen in the blood has been reported [25].

**Genetic factor:** Risk is increased by a personal or family history of breast cancer and inherited genetic mutations in the breast cancer susceptibility genes BRCA1 and BRCA2. It has been estimated that 5 to 10 percent of breast cancer cases result from inherited mutations or alterations in BRCA1 and BRCA2 [26].

**Other risk factors of breast cancer:** The other factors are i) high breast tissue density, ii) high bone mineral density, iii) biopsy-confirmed hyperplasia and iv) Viruses are considered to be one of the high-risk factors closely related to human breast cancer. DNA viruses, such as specific types of human papillomavirus (HPV), Epstein–Barr virus (EBV), human cytomegalovirus (HCMV), herpes simplex virus (HSV), and human herpes virus type 8 (HHV-8) [27].

**Sign and Symptoms:** The most common symptom of breast cancer is a mass or lump in the breast. In early stages, breast cancer usually has no symptoms. The earliest sign of breast cancer is often an abnormality detected on a mammogram, before it can be felt by the woman or a health care professional. Larger tumors may become evident as a painless mass [28].

In advanced stage cancer, the symptoms include, bone pain, weight loss, swelling of an arm, and skin ulceration. Other signs of breast cancer include 1) Swelling of part of the breast, 2) Skin irritation or dimpling, 3) Nipple pain or the nipple turning inward, 4) Redness or scaliness of the nipple or breast skin, 5) A nipple discharge other than breast milk, 6) A lump in the underarm area, 7) Pain or tenderness in the breast. 8) Change in the contour, texture or temperature of the breast, 9) abnormal modifications in the appearance or sensation of the nipple area including, 10) the retraction/ enlargement of the nipple, 11) a purulent appearance , 12) a bloody, clear-to-yellow, or green fluid secretion that weeps from the nipple and 14) itching sensations.

**Screening and diagnosis:** Breast cancer screening refers to screen healthy women for breast cancer, in an attempt to achieve an earlier diagnosis. The assumption is that early detection will improve outcomes. A number of screening test have been employed, which include clinical and self breast examinations, mammography, genetic screening, ultrasound, and magnetic resonance imaging [29, 30].

**Mammogram:** The first diagnostic tool to identify breast cancer is Mammogram. It is an X-ray of the breast that can show the presence of abnormal growth lumps in the breast area. On average, mammography will detect about 80%-90% of breast cancers in women without symptoms.

**Ultra-Sonography:** Use of high frequency sound waves often identifies whether the lump is filled with liquid or solid for further investigation. Ultrasonographic evaluation in addition to mammography can help to distinguish between solid and cystic lesions, accurately determine the size of a spiculated lesion and guide accurate biopsy of a suspicious area.

**Aspiration:** Fine needle is inserted in the lump to take the tissue or liquid out from the lump and then a biopsy is performed to test for carcinoma.

**Surgical biopsy:** Removes a small part of lump by surgery and then the lump is tested for further diagnosis.

**Biopsy:** Pathologic diagnosis of a breast lesion can be achieved using a number of biopsy techniques.

**MRI:** MRI, in addition to mammography is recommended for women at high lifetime risk of breast cancer starting at age 30. MRI is a particularly useful modality for detailing architectural abnormalities in the breast and can help detect lesions as small as 2-3 mm. In cancers, it is useful in defining the precise size of the tumor and in detecting multifocal disease.

**Dynamic imaging:** Dynamic imaging is the most specific sequence and can help to distinguish between benign and malignant lesions, and is particularly useful in the assessment of the scarred breast when looking for tumor recurrence. Dynamic imaging relies on the shape of the time-signal curves using gadolinium-diethylenetriamine penta-acetic acid enhancement; malignancies typically show rapid, strong enhancement because of high vascularity.

**Positron Emission Tomography (PET):** PET is the most sensitive and specific of all the imaging modalities for breast disease, but it is also one of the most expensive and least widely available. Using a
A wide range of labeled metabolites (e.g., fluorinated glucose), changes in metabolic activity, vascularization, oxygen consumption, and tumor receptor status can be detected. At present, its main use may be for helping to detect recurrences in scarred breasts, but it is also useful in multifocal disease, detecting axillary involvement and in equivocal cases of systemic metastases.

**Staging:** Staging is a method that has been developed to describe the extent of cancer growth. Breast cancer is ‘staged’ by information that is obtained from surgical and other findings. In addition, staging is based upon findings from imaging studies—such as chest x-ray, abdominal ultrasound (images produced by high-frequency sound waves) computed tomography (CT or CAT scan; computer-assisted technique that produces cross-sectional images of the body), and bone scans.

Pathologists (disease specialists) use a specific system to stage breast cancer. This method—known as the TNM system—was devised by the American Joint Committee on Cancer (AJCC) in collaboration with the National Cancer Institute (NCI) [31]. Within the TNM system, “T” refers to tumor size, “N” refers to lymph node involvement, and “M” refers to the extent of metastasis. To simplify this information, the TNM classifications are grouped within four basic stages, labeled stage 0 through stage IV (0-4).

**Stage 0:** It is an early stage of breast cancer refers to lobular carcinoma in situ (LCIS) or ductal carcinoma in situ (DCIS)

**Stage I:** It is an early stage of invasive breast cancer. The tumour is no more than 2 centimetres (three-quarters of an inch) across. Cancer cells have not spread beyond the breast.

**Stage II:** The tumour in the breast is no more than 2 centimetres. The cancer has spread to the lymph nodes under the arm. The tumour is between 2 and 5 centimetres. The cancer may have spread to the lymph nodes under the arm. The tumour is larger than 5 centimetres (2 inches). The cancer has not spread to the lymph nodes under the arm.

**Stage III:** The tumour in the breast is smaller than 5 centimetres (2 inches). The cancer has spread to underarm lymph nodes or the cancer may have spread to lymph nodes behind the breastbone. The tumour is more than 5 centimetres across. The cancer has spread to the underarm lymph nodes or to other structures or the cancer may have spread to lymph nodes behind the breastbone.

**Stage IV:** It is a distant metastatic cancer. The cancer has spread to other parts of the body.

**Treatment:** The treatment of breast cancer is determined by many factors, and depends on tumor stage, tumor type, tumor characteristics, the person’s general health and medical conditions that may influence treatment [32].

**Surgery:** The primary goal of breast cancer surgery is to remove the cancer from the breast and lymph nodes. Once the tumor is identified as malignant, surgery becomes one safe option to surgically remove the malignant lump. Surgery could involve removing whole of the breast or just the area where lump has formed. In a lumpectomy, only cancerous tissue plus a rim of normal tissue is removed. Lumpectomy is almost always followed by six to seven weeks of radiation therapy. Simple or total mastectomy includes removal of the entire breast. Both lumpectomy and mastectomy are often accompanied by removal of regional (axillary) lymph nodes to determine if the disease has spread beyond the breast. Surgery is often combined with other treatments such as radiation therapy, chemotherapy, hormone therapy and/or monoclonal antibody therapy.

**Radiation Therapy:** Radiation may be used to destroy cancer cells remaining in the breast, chest wall, or underarm area after surgery, or to reduce the size of a tumor before surgery.

**Hormone Blocking Therapy:** Some breast cancers require estrogen to continue growing. They can be identified by the presence of estrogen receptors (ER+) and progesterone receptors (PR+) on their surface. These ER+ cancers can be treated with drugs that block the production of estrogen or block the receptors, such as tamoxifen or an aromatase inhibitor. Women whose breast cancers test positive for estrogen or progesterone receptors can be given hormone therapy to block the effects of estrogens on the growth of breast cancer cells. Tamoxifen, the most commonly used antiestrogen drug, has been shown to provide a 26% annual reduction in recurrence and a 14% annual reduction in deaths. Hormone therapy is effective in both postmenopausal
Table 1: Reported chemopreventive agents in experimental mammary carcinogenesis

<table>
<thead>
<tr>
<th>Medicinal Plants/ Bioactive Constituents</th>
<th>Mechanism of Action</th>
<th>References</th>
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<tr>
<td>Siamese Cassia</td>
<td>Phase II detoxification cascade inducing capacity as well as phase I detoxification cascade inhibitory activity.</td>
<td>Tepsuwann et al.[36]</td>
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<tr>
<td>Dietary dibenzoyl methane</td>
<td>Inhibited the formation of DMBA-DNA adducts.</td>
<td>Lin et al. [37]</td>
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<td>Green tea</td>
<td>Suppressed cell proliferation.</td>
<td>Kavanagh et al. [38]</td>
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<tr>
<td>Neem flowers</td>
<td>Modulating effect on detoxification cascade.</td>
<td>Tepsuwann et al. [39]</td>
</tr>
<tr>
<td>Jasminium grandiflorum</td>
<td>Antilipidperoxidative and antioxidants properties.</td>
<td>Kolanjiappan and Manoharan. [40]</td>
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<tr>
<td>Resveratrol</td>
<td>Modulating mammary gland architecture, cell proliferation and apoptosis.</td>
<td>Whitsett et al. [41]</td>
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<td>Propolis</td>
<td>Stimulating phase I and phase II detoxification enzymes.</td>
<td>Padmanavathi et al. [42]</td>
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<tr>
<td>Vanadium</td>
<td>Suppression of cell proliferation, induction of apoptosis and cell cycle arrest.</td>
<td>Ray et al. [43]</td>
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<tr>
<td>Black tea polyphenols</td>
<td>Modulating effect on xenobiotics metabolizing enzymes, oxidative stress, cell proliferation, apoptosis and angiogenesis.</td>
<td>Kumaraguruparan et al. [44]</td>
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<tr>
<td>Operculina turpethum</td>
<td>Antioxidant activity.</td>
<td>Anbuselvam et al. [45]</td>
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<tr>
<td>Dietary beta-ionone</td>
<td>Antiproliferative and apoptotic potential.</td>
<td>Liu et al. [46]</td>
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<tr>
<td>Dietary fish oil</td>
<td>Induction of apoptosis and modulating expression of Bax and Bcl-2</td>
<td>Manna et al. [47]</td>
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<tr>
<td>Purple corn color</td>
<td>Induction of apoptosis.</td>
<td>Fukamachi et al. [48]</td>
</tr>
<tr>
<td>Dietary acetyl salicylic acid</td>
<td>Positive modulation of the hepatic antioxidant systems.</td>
<td>Girolami et al. [49]</td>
</tr>
<tr>
<td>Lycopene</td>
<td>Antioxidant potential.</td>
<td>Moselby and Al Mslmani, [50]</td>
</tr>
<tr>
<td>Fresh apples</td>
<td>Down regulating the expression of proliferating cell nuclear antigen, cyclin D1 and bcl-2 and up regulating the expression of Bax and by apoptosis induction.</td>
<td>Liu et al. [51]</td>
</tr>
<tr>
<td>Semecarpus anacardium Linn. nut extract</td>
<td>Antilipid peroxidative and antioxidants properties. Stimulating phase I and phase II detoxification enzymes.</td>
<td>Mathivadhani et al. [52]</td>
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<tr>
<td>Ferulic acid</td>
<td>Antigenotoxic and antioxidant potential as well as modulatory effect on phase II detoxification cascade</td>
<td>Baskaran et al. [53]</td>
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<tr>
<td>Genistein</td>
<td>Decreased incidence of DMBA-induced mammary tumors</td>
<td>Fritz et al. [54]</td>
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<tr>
<td>Daidzein</td>
<td>Antioxidant potential.</td>
<td>Mathivadhani et al. [52]</td>
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<td>Daidzein</td>
<td>Induction of hepatic CYP1A1, B1, and AhR</td>
<td>Choi and Kim, [58]</td>
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<tr>
<td>Daidzein and Daidzein</td>
<td>Suppressed NFKB activation in TNFα-stimulated mouse fibroblasts and in ER-negative breast cancer cells by a mechanism that involved abrogation of MEK1 and ERK activity</td>
<td>Vanden Berge et al. [59]</td>
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<tr>
<td>Baicalein</td>
<td>Decrease xenobiotox-induced Cyp1A1 and Cyp1B1 mRNA expression by interfering with activation of the XRE by AhR</td>
<td>Chan et al. [60]</td>
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<tr>
<td>Resveratrol and Quercetin</td>
<td>Inhibit N-methyl-N-nitrosourea (NNMU) and DMBA-induced mammary carcinogenesis in rats</td>
<td>Baneerje et al. [62]</td>
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<tr>
<td>Biochanin-A</td>
<td>Chemomodulation of the antioxidative enzymes and peroxidative damage</td>
<td>Mishra et al. [64]</td>
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and premenopausal patients whose cancers are positive for steroid hormone receptors.

Estrogen replacement therapy (ERT), also known as hormone replacement therapy (HRT), is used by many older women to relieve the symptoms of menopause. Certain studies indicate that ERT may increase the risk of breast cancer after long-term use (10+ years).

**Systemic Therapy:** Systemic therapy includes chemotherapy and hormone therapy. Adjuvant systemic therapy is used after all visible cancer has been surgically removed in order to kill any undetected tumor cells that may have migrated to other parts of the body.

**Chemotherapy:** Chemotherapeutic drugs are given with the hope that micrometastases will be eliminated before they spread to other tissues. Many chemotherapeutic drugs interfere with cell division or other metabolic processes. Therefore, they are most harmful to rapidly dividing cancer cells, although normal cells also may be damaged.

Chemotherapy typically is delivered in the form of shots or pills. It may be the only treatment used if breast cancer has spread to other parts of the body. Commonly, chemotherapy is given as an adjuvant (assisting therapy) to reduce the chance of cancer recurring after surgery, radiation therapy, or both. Research has established that combinations of several drugs are more effective than just one drug alone. Chemotherapy medications for breast cancer include, Paclitaxel, Doxorubicin, Paraplatin, Cyclophosphamide, Epirubicin, Gemcitabine, and Vincriistine. In early stage breast cancer, standard chemotherapy regimens lower the risk of the cancer coming back. In advanced breast cancer, chemotherapy regimens make the cancer shrink or disappear in about 30-60% of people treated.

Targeted therapy, also called as biologic therapy, is a newer type of cancer treatment. This therapy uses...
special anticancer drugs that target certain changes in a cell that can lead to cancer. One such drug is trastuzumab (Herceptin). It may be used for women with HER2-positive breast cancer.

Treatment for various stages of breast cancers including

- Stage 0 and DCIS - Lumpectomy plus radiation or mastectomy is the standard treatment. There is some controversy on how best to treat DCIS.
- Stage I and II - Lumpectomy plus radiation or mastectomy with some sort of lymph node removal is standard treatment. Hormone therapy, chemotherapy, and biologic therapy may also be recommended following surgery.
- Stage III - Treatment involves surgery possibly followed by chemotherapy, hormone therapy, and biologic therapy.
- Stage IV - Treatment may involve surgery, radiation, chemotherapy, hormonal therapy, or a combination of such treatments.

Prevention of Breast Cancer: Modifiable factors that are associated with a lower risk of breast cancer include breastfeeding, moderate or vigorous physical activity, and maintaining a healthy body weight. Two medications tamoxifen and raloxifene, have been approved to reduce breast cancer risk in women at high risk [33]. Raloxifene appears to have a lower risk of side effects, such as uterine cancer and blood clots. In women with estrogen-receptor positive breast cancer, additional treatment with tamoxifen reduces the risk of second breast cancers by about half.

Chemoprevention: Cancer chemoprevention is defined as the use of natural or synthetic agents to reverse, suppress or prevent carcinogenic progression. Chemopreventive agents that are derived from natural resource are considered pharmacologically safe [34]. Primary chemoprevention strategies seek to prevent malignancies (cancers) in an otherwise healthy population. Primary chemoprevention mainly focuses on the prevention of cancer in populations who are at higher risk of cancer development. Secondary chemoprevention mainly involves the prevention of cancer in populations with premalignant or pre-cancerous condition. Tertiary chemoprevention deals with the prevention of secondary cancers in patients treated for primary cancer or individuals who have been treated for premalignant lesions. Chemopreventive agents can be placed into three broad categories [35]. Blocking agents prevent carcinogenic agents from reaching or reacting with critical target site, thus act by exerting a barrier function. Resisting agents decrease the vulnerability of target tissue to carcinogenic stimuli. Suppressing agents prevents the evolution of neoplastic process in tissue that otherwise would become malignant. Chemopreventive agents reported so far against breast carcinogenesis is given in table.1

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Blood/other Body fluids / Tissues</th>
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<tr>
<td>17-β estradiol (E2)</td>
<td>Plasma</td>
<td>Mady, [65] Dunbier et al. [66]</td>
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<tr>
<td>TBARS</td>
<td>Plasma and mammary tissue.</td>
<td>Kolanjiappan and Manoharan, [40] Kumaraguruparan et al. [67]</td>
</tr>
<tr>
<td>Enzymatic antioxidants (SOD, CAT, GPx)</td>
<td>Plasma, liver and mammary tissue.</td>
<td>Singh et al. [68] Mishra et al. [57] Perumal et al. [69]</td>
</tr>
<tr>
<td>Non-enzymatic antioxidants - GSH</td>
<td>Plasma, liver and mammary tissue.</td>
<td>Kolanjiappan and Manoharan, [40]</td>
</tr>
<tr>
<td>Phase I detoxification enzymes</td>
<td>Liver and mammary tissue</td>
<td>Girolami et al. [70] Kumaraguruparan et al. [44]</td>
</tr>
<tr>
<td>Phase II detoxification enzymes</td>
<td>Liver and mammary tissue</td>
<td>Malejka-Giganti et al. [71]</td>
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<tr>
<td>Total sialic acid</td>
<td>Plasma, erythrocytes and mammary tissue</td>
<td>el-Aziz et al. [72]</td>
</tr>
<tr>
<td>Fucose</td>
<td>Plasma</td>
<td>Turner et al. [73]</td>
</tr>
<tr>
<td>Protein bound hexose</td>
<td>Plasma, erythrocytes and mammary tissue</td>
<td>Rosato et al. [74]</td>
</tr>
<tr>
<td>Protein bound hexosamine</td>
<td>Plasma, erythrocytes and mammary tissue</td>
<td>Spiers and Malone, [75]</td>
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Biomarkers: Biomarkers are biochemical facets or substances that can be used to measure different aspects of a disease, like the risk to develop it, its progress or the effects of particular treatments. The status of such markers in the blood, other body fluids or tissues may reveal the sign of normal or pathological conditions. Disease markers can be studied at many molecular levels, ranged from genomic, epigenomic, proteomics, cellular and morphologic, to genetic factors. These factors predispose patients to the disease or indicate its occurrence. The biochemical markers associated with mammary cancer are given in the table.2
Biomarkers of mammary cancer are of several types. Risk biomarker are those associated with increased cancer risk and include mammographic abnormalities, proliferative breast disease with or without atypia, family clustering, and inherited germ-line abnormalities. Surrogate end-point biomarkers are tissue, cellular, or molecular alterations that occur between cancer initiation and progression. These biomarkers are used as end points in short-term chemoprevention trials. Prognostic biomarkers provide information regarding outcome irrespective of therapy, whereas predictive biomarkers provide information regarding response to therapy.

Oxidative stress has been implicated in the pathogenesis of several cancers including mammary carcinoma. The status of plasma lipid peroxidation by-products serves as an index to assess the extent of tissue damage. Enzymatic and non-enzymatic antioxidants form the first line of defense mechanism to scavenge excessively generated ROS in the system. Abnormalities in the status of antioxidants lead to several disorders including cancer. Increased level of lipid peroxidation by-products in plasma and tumors tissues has been well documented in both human and experimental carcinogenesis. Over production of oxygen free radicals and decreased activities of antioxidants in mammary cancer tissues have been demonstrated.

Glycosylation of proteins has been shown to have significant impact on protein function and confirmation. Hexoses, fucose and sialic acid form the monosaccharide units of the oligosaccharides that are attached to proteins. More than half of all proteins in human serum are glycosylated. Measurement of serum glycoconjugates serve as a potential source of disease biomarkers and provides insights into disease pathogenesis. Altered glycoconjugates levels were reported in many pathological conditions including mammary cancer [72-75].

Approximately 2/3 of breast cancers (both hereditary and sporadic) are estrogen sensitive. Lifetime exposure of estrogen has been implicated in the pathogenesis of initiation and promotion of breast cancer. The most active estrogen, 17-â-estradiol (E2) regulates the growth, differentiation, and physiology of the reproductive process through the estrogen receptor [65, 66]. The estrogen receptors (ER) are nuclear receptors that modulate the transcription of target genes responsible for the proliferation of mammary cells. Increased ER status plays a major role in the progression and metastatic potential of breast cancer. Breast epithelial cell proliferation is not only related to estrogen levels but also to progesterone, which acts through its own receptor, progesterone receptor (PR). The PR status was significantly elevated during mammary carcinogenesis [85].

Human Epidermal Growth Factor Receptor-2 (HER-2), also known as c-erbB-2 or neu have substantial homology with the epidermal growth factor receptor (EGFR). HER family includes four structurally related members, HER-1 (erbB1, also known as EGFR), HER-2 (erbB2), HER-3 (erbB3) and HER-4 (erbB4). HER-2 plays an important role in cell growth, survival, and differentiation of normal cells. Over expression of HER-2 was reported in mammary carcinogenesis and its metastasis [86]. The status of ER, PR and HER2/neu has been used as routine markers for diagnosis, prognosis and response to treatment of breast cancer.

Breast cancer occurs as the result of a progressive accumulation of genetic aberrations in the cells of mammary gland and it can be curable if diagnosed at an early stage. Detection of biochemical or molecular markers in tumors could have repercussion on prognosis and monitoring. Investigations of tumor cell proliferative activity, invasive capacity, angiogenesis, and apoptosis could help to detect tumor stage as well as therapeutic response. Currently, molecular markers such as p53, PCNA, VEGF, iNOS, Bcl-2, and Bax are used routinely as prognostic and predictive markers for breast cancer [76-81]. The candidate prognostic biomarkers for breast cancer is shown in table 3.

<table>
<thead>
<tr>
<th>Markers</th>
<th>Type</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53, p63, p73, RB</td>
<td>Tumor suppressor proteins</td>
<td>Levrero et al. [76]</td>
</tr>
<tr>
<td>PCNA, Ki67, Cyclin</td>
<td>Cell proliferation protein</td>
<td>Muskhelishvili et al. [77]</td>
</tr>
<tr>
<td>VEGF, iNOS</td>
<td>Angiogenesis factor</td>
<td>Foekens et al. [78], Coskun et al. [79]</td>
</tr>
<tr>
<td>Becl2, Bcx-L2</td>
<td>Anti-apoptotic protein</td>
<td>Callagy et al. [80]</td>
</tr>
<tr>
<td>Bax, Bad</td>
<td>Pro-apoptotic protein</td>
<td>Hollager et al. [81]</td>
</tr>
<tr>
<td>NFкB, COX2</td>
<td>Anti-inflammatory</td>
<td>Aggarwal et al. [82]</td>
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<tr>
<td>Caspases</td>
<td>Apoptotic proteins</td>
<td>Philchenkov et al. [83]</td>
</tr>
<tr>
<td>MMP, E-Cadherin</td>
<td>Metastatic proteins</td>
<td>Hujal et al. [84]</td>
</tr>
<tr>
<td>ER/PR</td>
<td>Steroid hormone receptor</td>
<td>Lee et al. [85]</td>
</tr>
<tr>
<td>HER2/neu</td>
<td>Epidermal growth factor receptor</td>
<td>Pegram et al. [86]</td>
</tr>
</tbody>
</table>

Table 3: Molecular biomarkers in breast cancer
CONCLUSION
Cancer continues to be a leading cause of death around the world. In the spectrum of cancer, breast cancer is the major health concern and the second leading cause of cancer mortality in women, with approximately one in eight being affected over their lifetime. Established risk factors and environmental pollutant may increase a woman’s chances of developing breast cancer. The key to successful management of breast cancer is awareness, screening and early detection. This review presented essential facts regarding breast cancer, which could help for its management and treatment.

REFERENCES