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Review article

The Epidemiology of Human Breast Cancer

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ABSTRACT

Breast cancer is the most common cancer among women and is the second leading cause of cancer related death. In India 70,000 new cases of breast cancer and 35,000 deaths due to this cancer are reported every year. The etiology of breast cancer is multifactorial. Hormonal, genetic and environmental factors appear to inter play in the pathogenesis of breast cancer. Hence, an attempt has been made in this review in order to discuss about the epidemiology, etiology, pathogenesis, diagnostic and treatment measures of breast cancer.

KEY WORDS: Breast cancer, Epidemiology, Risk factors, Diagnostic and Treatment.

INTRODUCTION

Cancer is a multi-factorial diseases, which is characterized by varying degree of morphological disorientation, uncontrolled over growth, invasive and metastasis [1]. This uncontrolled division can compromise the function of the host and ultimately may cause death. Cancer can appear as a result of different causes which can be both external factors such as tobacco, infectious organisms, chemicals, radiation and also internal factors like hormones, immune conditions and mutations which occur from metabolism in a variety of sites within the body and that each type of cancer displays its own growth rate, prognosis and treatability[2]. Breast cancer is a malignant growth which begins in the tissues of the breast primarily from the epithelial component of the gland where it proliferates at high rate, causing necrosis of surrounding tissues [3].

As they infiltrate at high rate, the malignant cells metastasize to regions like lungs, bone, liver and brain. An accumulation of genetic and epigenetic alternations convert normal breast cells to cancer cells. The interior segment of the female breast consists mostly of fatty and fibrous connective tissues. Breast tissue is a complex network of lobules (small round sacs that produce milk) and ducts (canals that carry milk from the lobules to the nipple openings during breastfeeding) in a pattern that looks like bunches of grapes. These "bunches" are called lobes. Adult women have 15 to 20 lobes in each breast and each lobe has 20 to 40 lobules [4]. Small ducts are attached to the lobules. These ducts join together like branches of grape stems into increasingly larger ducts. There are about ten duct systems in each breast, each with its own opening at the nipple [5].

The ducts carry the milk through the breast and converge in a collecting chamber located just below the nipple. It is reported that 15% to 20% of breast cancers fall into the category of non-invasive cancer or carcinoma *in situ*- tiny growth that have not spread across the wall of the milk ducts or lobules. More advanced cancers are called "invasive" which have spread beyond the ducts and lobules. Breast cancer grows at different rates but according to an estimation of oncologists that the average tumour doubles in size every 100 days.

Since cancer start with one irregular cell, even with this doubling time, they may not be palpable for years. Mammography can find tumours that are too small to be felt, but even the tumours have probably been growing for years they are large enough to be visible on a Mammogram. Breast cancer cells migrate to the lymph nodes under the arm (axillary), in the neck (cervical), or those just below the

collarbone (supra-clavicular). The most common sites of breast cancer metastasis are skin, distant lymph nodes, bone, lung and liver[6].

TYPES OF BREAST CANCER

Ductal carcinoma IN SITU

Ductal carcinoma *in situ* (DCIS) is an early stage of cancer. It is non-invasive, generally not spread beyond the milk ducts to other parts of the breast and to the lymph nodes in the under arm, or to other parts of the body. In addition, several types of DCIS are also exist. If not removed, it develops into an invasive cancer. Others may never progress to this stage and DCIS is highly curable [7].

Lobular carcinoma IN SITU

Lobular carcinoma *in situ* (LCIS) is a non-invasive growth limited to the milk lobules of the breast. According to the National Cancer Institute, women with LCIS have about a 1% risk of developing invasive breast cancer per year. At 20 years, this risk is about 18%[8].

Invasive ductal carcinoma

In more advanced stages, breast cancer cells cross the lining of the milk duct or lobule and begin to invade or infiltrate adjacent tissues. In this stage, the cancer is called "infiltrating cancer". Invasive ductal carcinoma (also known as infiltrating ductal carcinoma) is most common kind of invasive breast cancer. More than half of all cases are of this type[9].

OTHER TYPES OF BREAST CANCER

Medullary Carcinoma

This is the type of invasive ductal carcinoma which appears well confined, but often has infiltrated the lymph nodes. Medullary carcinoma may grow large but has a better than average prognosis[10].

Mucinous Carcinoma

This is a type of invasive ductal carcinoma which produces a gelatinous-like tumour. These cancers have a very good prognosis[11].

Tubular Carcinoma

Tubular carcinomas are a special type of infiltrating (invasive) breast carcinoma. Women with tubular carcinoma generally have a better prognosis than women with more common types of invasive carcinoma. Tubular carcinomas account for around 2% of breast cancer diagnoses[12].

Invasive Lobular Carcinoma

This cancer arises at the ends of the ducts or in the lobules and may cause widespread breast thickening rather than a specific lump. The prognosis is better than average[13].

Paget's disease

This is very rare type of cancer. It appears as an itchy rash around the nipple and areola. It should not be mistaken for a benign skin conditions such as eczema or contact dermatitis[14].

Inflammatory Carcinoma

Inflammatory Carcinoma is the most serious breast cancer. The skin over the breast becomes very inflamed and swollen because the skin lymph vessels are blocked by cancer. While the prognosis has improved considerably with new treatments, this cancer still has the least favourable prognosis[15].

EPIDEMIOLOGY

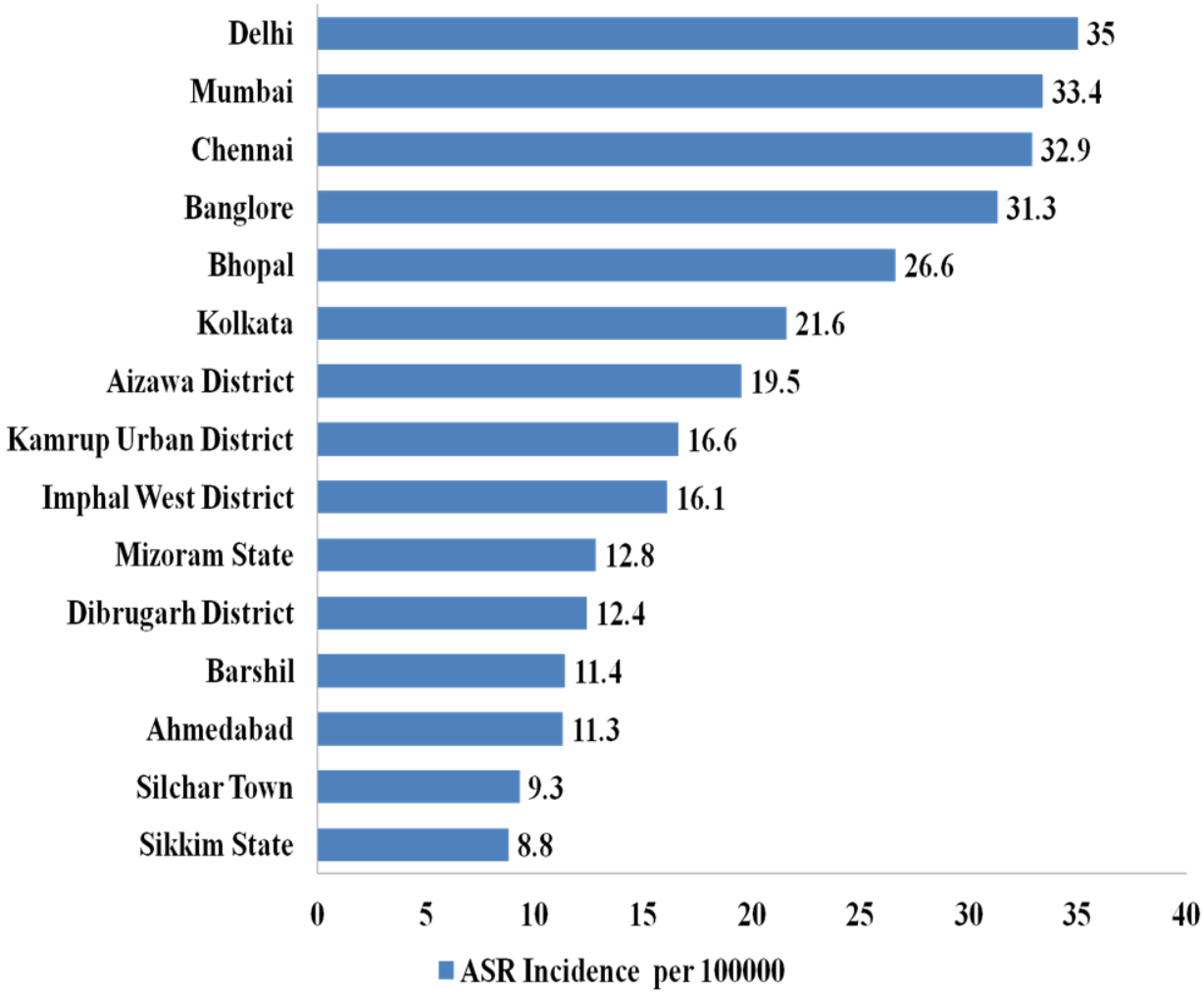
Breast cancer is the second leading cause of deaths in women and is the most common cancer among women, excluding non melanoma skin cancers. Breast cancer incidence varies widely within regions and countries which has been increasing in the general population all over the world due to differences in racial and ethnic make-up, health resources and lifestyle patterns[16,17]. Breast cancer is the most common cancer of women in the United States and European countries. According to the American Cancer Society, 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 2013, an estimated 232,340 new cases of invasive breast cancer are expected to be diagnosed among women, as well as an estimated 64,640 additional cases of *in situ* breast cancer. Of these, approximately 85% will be ductal carcinoma *in situ* (DCIS).

The incidence rate of the *in situ* breast cancer increased 2.8% per year from 2005 to 2009. An estimated 40,030 breast cancer deaths (39,620 women, 410 men) are expected in 2013[18]. Breast cancer is the commonest cancer of urban Indian women and the second commonest in the rural women. [19] In India, 75,000 new cases of breast cancer are reported every year and the incidence has been increased gradually in metropolitan cities [20]. 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. However, the highest incidence was reported in the Parsi community of Mumbai women[17,21] (Fig.1). 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.

Figure 1:Age Standardised incidence rates(ASR)for breast cancer in India



RISK FACTORS

Recently number of factors has been identified that play a major role in the etiology of breast cancer and increase the risk of breast cancer development. The factors include endogenous factors, such as inherited mutations, hormones, immunity conditions and exogenous factors like, tobacco, radiations, and chemicals such as heavy metals, pesticides, and polycyclic aromatic hydrocarbons[22].These factors introduced commercially in the last forty years have proven to be carcinogenic both in animals and in human systems[23]. The risk factors involved in the development of breast cancer include age, environmental factors, early menarche, late menopause, family history, older age child birth, prolonged hormone replacement therapy, alcohol consumption, and genetic mutations[24] (fig.2).

Age

The incidence of breast cancer increases with age, doubling about every 10 years after menopause. Women who live up to the age of 90 have about 14.3% or one in seven have a chance of developing breast cancer[25]. In this context Pike *et al.*, (1993) [26] are of the opinion that the incidence of the breast cancer around age group of 45-55 years may be due to the reproductive hormones, since non- hormone dependent cancer do not show these changes in incidence rate around the time of menopause. Breast cancer incidence increases about 2.17% per year of age in the post-menopausal period. This rise can be attributed solely to endogenous estrogen[27].

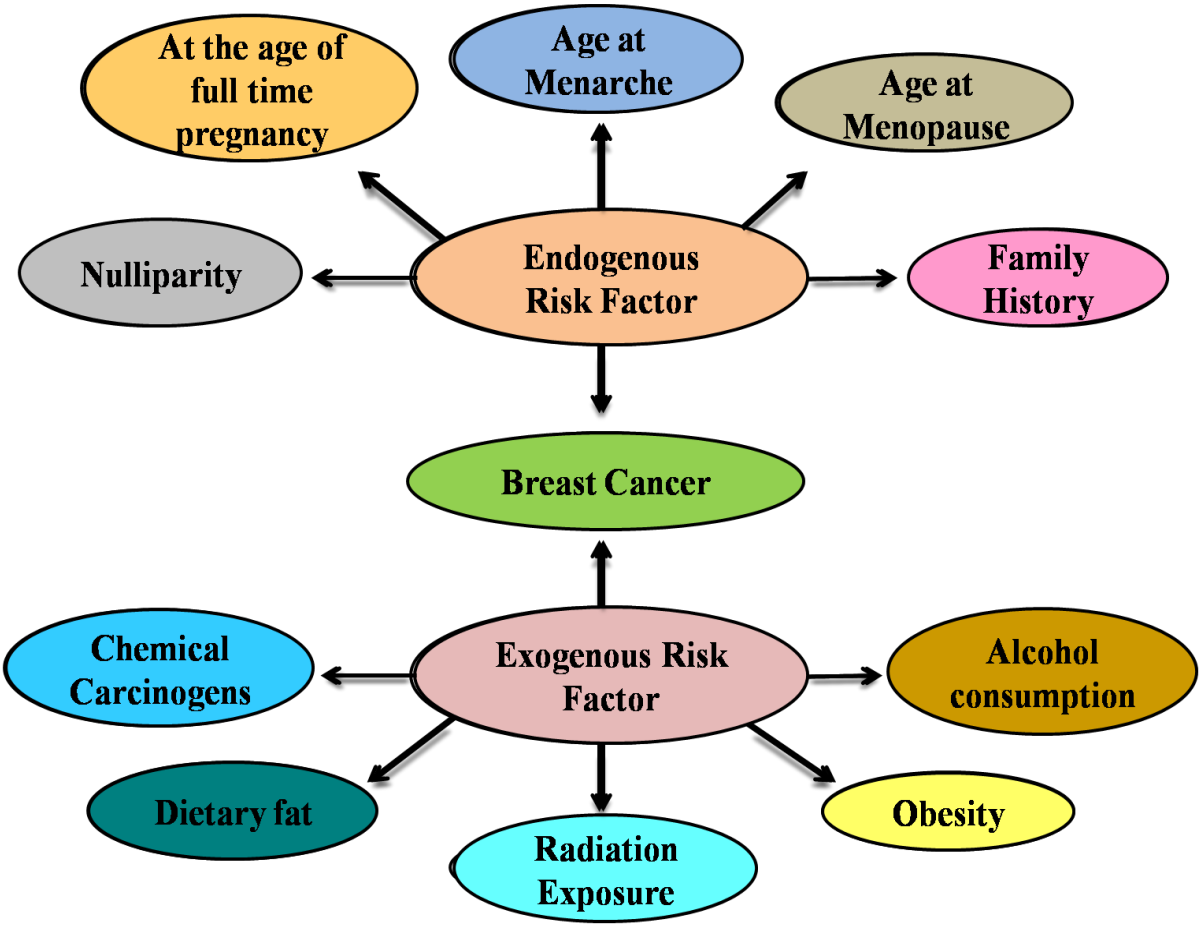
Age at menarche and menopause

The menstrual factors have an important role in the genesis of breast cancer. Women's with early menstruation or who have a late menopause have an increased risk of developing breast cancer. Nulliparity and late first birth both increase the risk of breast cancer[28]. The younger a women's age at menarche, the higher the risk of breast cancer[29]. A number of reports have established that women with early menarche have higher estrogen level for several years after menarche and probably throughout their reproductive lives[30].

In this connection, Hsieb *et al.*, (1990) [31] have reported that for each 2 years delay in the onset of menstruation breast cancer risk was reduced by 10%. In addition, Brinton *et al.*, (1988) [32] also reported that women with onset of menstruation at or after the age of 15 years had a 23% lower risk than those with an age at menarche of 12 years or younger. The later a women's age at menopause, the higher, the risk of breast cancer[33].

The increased risk is associated with early age of menarche and late age menopause suggested that the longer the exposure to sex hormones during the reproductive years, results in the higher risk of breast cancer[34]. Nulliparous women are at increased risk for breast cancer in comparison with parous women[35]. The protective effect of multiparity has been mostly in women aged between 40-50 years or more.

Figure 2: Multifactorial risk factors of breast cancer



Family history

It is reported that about 10% incidence of breast cancer in western countries is due to genetic predisposition. Breast cancer susceptibility is generally inherited as an autosomal dominant trait with limited penetrance. Two breast cancer susceptibility genes, BRCA1 and BRCA2, account for a substantial proportion of very high risk families. Women with severe atypical epithelial hyperplasia have a 4-5 times higher risk of developing breast cancer. Women with palpable cysts, complex fibro adenomas, duct papillomas, etc. have a slightly higher risk of breast cancer[36,37].

Diet

The diet plays an important role in the etiology of breast cancer. The types of fat are important, although there is a close relationship between the incidence of breast cancer and dietary fat intake in populations, the true relationship does not appear strong or consistent[38].

Obesity

It is well established that obesity is a major problem not only for cancer but also for other diseases such as cardiovascular, diabetes, atherosclerosis etc. The relationship of breast cancer to obesity is more complex but associated with a two-fold increase in the risk of breast cancer in postmenopausal women[39]. According to an estimate by the American cancer society, over weighted women (BMI>25) are have a risk of 1.3 to 2.1 times to die from breast cancer compared to normal women (BMI- 18.5-24.9).

Hormone replacement therapy (HRT)

The current users of HRT and those who have ceased using HRT for 1- 4 years have the relative risk of breast cancer and it is diagnosed to increases for each year of HRT use[40]. In this connection, Li *et al.*, (2003) [41] have reported that taking oestrogen and progestrogen for longer than 10 years may lead to an increase risk of developing breast cancer. In addition, most breast cancer risk factors are related to gynaecological or endocrinological events in a women's life[30].

Alcohol consumption

Alcohol is consistently associated with increased breast cancer by elevating the oestrogen and androgen levels [42] and is a risk factor for breast cancer[43]. The national institute on alcohol abuse and alcoholism concluded that chronic alcohol consumption is associated with 10% increase in breast cancer [44].

Genes and breast cancer

It is reported that the genes such as BRCA1 and BRCA2, which are breast cancer susceptibility genes, have been mapped to chromosomes 17q21 and 13q12, respectively[45]. Both the genes are very large and mutations can occur at almost any position. The BRCA1 and BRCA2 proteins are essential for recombination but dispensable for end-joining. In individual cells deficient in either protein, breaks in double stranded DNA are repaired predominantly through error-prone mechanisms, leading to chromosomal aberrations and increased rates of mutation[46]. Several genes (ATM, CHEK2, BRCA1, and BRCA2) whose inactivation predisposes people to breast and other cancers participate in the error-free repair of breaks in double-stranded DNA. In sporadic breast cancer, abnormalities have been identified in genes, including p53, bcl-2, c-myc, and c-myb[47].

Mutations in the cell- cycle- checkpoint kinase gene (CHEK2) account for about 5% of all cases of familial breast cancer (defined by the diagnosis of breast cancer in two or more family members before the age of 60 years), but the risk for individual mutation carriers is probably less than 20%[48]. All other cases of breast cancer are presumed to be due to an undefined number of additional susceptibility genes with various degrees of penetrance to hormonal, environmental and genetic events[49].

Radiation

A doubling of breast cancer risk was observed among teenage girls exposed to radiation during the Second World War. Ionizing radiation also increased risk later in life, particularly when exposed rapidly during rapid breast cancer formation stage[50].

STAGES OF BREAST CANCER

Cancer of the breast occurs more often in left breast than the right and it is bilateral in about 4% of cases. In an anatomical perspective, upper-outer quadrant is the site of tumor in half of the breast cancers, followed in frequency by the central portion, and equally in the remaining both lower and the upper inner quadrants. Breast cancer can be presented in four stages depending on the duration and severity of the disease. The American Joint Committee (AJC) is suggesting that Tumor Node Metastasis (TNM) staging is the most widely used system in order to recognize the stages of breast cancer. The stages of breast cancer were briefed below according to the 6th revised edition of the TNM classification of breast cancer [51].

In stage-I the size of tumor may be 2 cm or less in diameter with no nodal spread and in Stage-II the size of tumor is greater than 2 cm in diameter with the involvement of regional lymph nodes, in stage- III A the size of tumor is greater than or equal to 5 cm in diameter with involvement of regional lymph nodes on same side. Whereas in stage-III B the size of the tumor is greater than or equal to 5 cm in diameter with the superaclavicular and intraclavicular lymph nodes involvement. In stage-IV the tumor is any size, with or without regional spread, but with distant metastasis.The differentiations is essential for clinical diagnosis since the choice of treatment between surgery, radiotherapy and chemotherapy depends on the lesion whether it is benign or malignant and whether the particular histological subtype is sensitive to radiotherapy or chemotherapy. There is a great variation in the sensitivity of different breast tumors to several cytotoxic drugs. Therefore appropriate therapy can be prescribed only when the tumor tissue has been accurately classified[52].

SYMPTOMS OF BREAST CANCER

The early stages of breast cancer may not have any symptoms. For this reason it is important to follow screening recommendations. When the tumor grows in size, it can produce a variety of symptoms which including, swelling of part of the breast, skin irritation or dimpling, nipple pain or the nipple turning inward, redness or scaliness of the nipple or breast skin, a nipple discharge other than breast milk, a lump in the underarm area, pain or tenderness in the breast, change in the contour and texture or temperature of the breast, abnormal modifications in the appearance or sensation of the nipple area including-the retraction/ enlargement of the nipple, a purulent appearance, a bloody clear to yellow or green fluid secretion that weeps from the nipple and itching sensations[53].

DIOGNOSTIC METHODS OF BREAST CANCER

Carcinoma of the breast is the second most common malignancy in the female population and is the cause of morbidity in women all over the world. The recent developments in medical diagnostic techniques such as mammography, ultrasonsography, positron emission tomograpghy and magnetic resonance (MRI) [54] are used to detect small cancers, visible circumscribed lesion or palpable masses where a cyst is in the differential diagnosis[55] and to evaluate solid breast masses[56], breast carcinoma and ductal carcinoma[57]. Mammography may help to identify the breast masses, ultrasonography can find out whether the lump is solid or fluid[58].

In addition to this other methods are available to diagnose the breast cancer which include, needle aspiration in which the biopsies of the mass are examined for cyst, whereas in needle biopsy the cells are directly removed from mass for evaluation and in surgical biopsy a portion of mass is removed for further evaluation. On the other hand in incisional biopsy surgical removal of a portion of the mass is performed for evaluation [59] and it enables one to decrease 30% in breast cancer mortality[60]. It improved imaging, enables the detection of small cancer[61].

TREATMENT STRATEGY FOR BREAST CANCER

The treatment of breast cancer is determined by many factors, and depends on stages of tumor, type and characteristics (table.1). Further the person's general health and medical conditions that may influence treatment[62].

Table 1: Treatment of breast cancer based on type

Type	Possible Treatments
Ductal carcinoma in situ	Mastectomy Wide excision with or without radiation therapy
Lobular carcinoma in situ	Observation plus regular examinations and mammograms Tamoxifen or, for some post menopausal women, raloxifene to reduce the risk of invasive cancer Bilateral mastectomy (rarely) to prevent invasive cancers
Stages I and II (early-stage)cancer	Chemotherapy before surgery if the tumor is larger than 2 inches (5 centimeters) Breast-conserving surgery to remove the tumor and some surrounding tissue, usually followed by radiation therapy Sometimes mastectomy with breast reconstruction After surgery, chemotherapy, hormonal therapy, trastuzumab, or a combination, except in some postmenopausal women with tumors smaller than 0.4 inches (1 centimeter)
Stage III (locally advanced) cancer (including inflammatory breast cancer)	Chemotherapy or sometimes hormonal therapy before surgery to reduce the tumor's size Breast-conserving surgery or mastectomy if the tumor is small enough to be completely removed Mastectomy for inflammatory breast cancer Usually, radiation therapy after surgery Sometimes chemotherapy, hormonal therapy, or both after surgery
Stage IV (metastatic) cancer	If cancer causes symptoms and occurs in several sites, hormone therapy or chemotherapy If the cancer cells have too many HER2 receptors, trastuzumab. Radiation therapy for the following: Metastases to the brain, Metastases that recur in the skin, Metastases that occur in one area of bone and that cause symptoms,For metastases to bone, IV bisphosphonates,(such aszoledronate or pamidronate) to reduce bone pain and bone loss
Paget's disease of the nipple	Usually, the same as for other types of breast cancer Occasionally, local excision only
Breast cancer that recurs in the breast or nearby structures	Radical or modified radical mastectomy sometimes recede by chemotherapy or hormone therapy
Phyllodes tumors if they are cancerous	Wide excision Mastectomy if the tumor is large

Surgery

Almost all women with breast cancer will have some type of surgery in the course of their treatment. The purpose of surgery is to remove as much of the cancer as possible from breast and lymph nodes, and there are many different ways that the surgery can be carried out. It depends upon the stage and type of the tumor. In lumpectomy, only cancerous tissue and some of normal tissues is removed. In contrast the surgical removal of entire breast is called mastectomy. In this connection, Veronesi *et al.,* (2002) [63] are of the opinion that the removal of entire breast and lymph nodes under the arm is called modified radical mastectomy. Unfortunately as a consequence of surgery a serious swelling of the arm by retention of lymph fluid ultimately lead to lymphedema in the axillary nodes were reported as side effects[64].

Radiation therapy

Radiation (X-rays or γ rays) therapies are used to destroy cancer cells ramainging in the breast, chest wall, or underarm after surgery. Radiation injures or destroys the cancerous cell by damaging the genetic material and inhibits cell division. In addition, it also cuts off the blood supply to cancer cells leading to necrosis[65]. Though the radiation therapy damages the cancer cells, it also has some adverse effect on normal cells[66].

Hormonal therapy

It is important that the examination of the tumor whether they express estrogen and progesterone receptors. Patients whose tumor expresses estrogen receptors are candidates for therapy with an estrogen-blocking drug called Tamoxifen[67]. This drug has been shown to drastically reduce the risk of recurrence if the tumor expresses estrogen receptors. It may also directly induce programmed cell death[68]. However, there are side effects commonly associated with Tamoxifen including weight gain, hot flashes and vaginal discharge that may bother patients. There are also very uncommon side effects like blood clots, strokes and uterine cancer. Besides, irregular menstrual cycles, ocular toxicity, thromboembolic events, gynaecological complications such as endometrial cancer-low grade, endometrial hyperplasia and polyps, and ovarian cysts were reported[69]. In addition, some of the new agents used for the treatment of breast cancer are Raloxifene, Toremifene (anti-oestrogen), formestane, letrozole, exemestane (aromatase inhibitors), gemcitabine (purine analogue), which reduces the risk of cancer development[70].

Biological therapy

The examination of tumor for the presence of HER-2/neu over expressions is very useful in the breast cancer treatment. HER-2/neu is a receptor that some breast cancer expresses. Its expression shows a higher chance of having the tumor recurrence after surgery. A compound called Herceptin or Trastuzumab is a substance that blocks their receptor and helps to stop the breast cancer from growing. It is a humanized monoclonal antibody that directly targets the HER-2/neu protein of breast cancer patients and slows down the cell growth[71]. This drug is used for treatment of patient with metastatic disease and is also associated with significant cardiac toxicity[72].

Chemotherapy

Chemotherapy is the use of anti-cancer drugs that go throughout the body. In combination chemotherapy, multiple drugs have been used, which is more effective than administering a drug alone. There are several different chemotherapy regimens that may be used. The determination of the appropriate regimen depends on many factors including the character of the tumor, lymph node status, and the age and health of the patient[73]. Possible chemotherapy regimens include, (CMF) cyclophosphamide, methotrexate and 5-fluorouracil, (FAC) 5-fluorouracil, doxorubicin and cyclophosphamide, (AC) doxorubicin and cyclophosphamide (AC) with pacitaxel administered after the (AC), (TAC)docetaxel, doxorubicin and cyclophosphamide, (FEC) 5-fluorouracil, epirubucin and cyclophosphamide for 6 cycles (FEC) for three cycles followed by docetaxel for three cycles dose dense, (AC) doxorubicin and cyclophosphamide followed by paclitaxel, (TC) Taxotere (docetaxel) and cyclophosphamide.

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[74]. 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 pre-malignant 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 pre-malignant lesions[75]. Chemopreventive agents can be placed into three broad categories. Blocking agents which prevent carcinogenic agents from reaching or reacting with critical target site, thus act by exerting a barrier function. Resisting agents which decrease the vulnerability of target tissue to carcinogenic stimuli. Suppressing agents prevents the evolution of neoplastic process in tissues or otherwise it would become malignant[76]. Several compounds from plant origin have been reported to have chemopreventive property such as Plumbagin, Zerumbone, Garcinol, Mangiferrin,T hymoquinone, Piperin, Quercetin, Emodin, Naringin , Gossypol, Curcumin, Ursolic acid, Epigenin, Galic acid etc.,

CONCLUSION

As elaborated in detail, 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 life time. The key to successful management of breast cancer is awareness, screening and early detection. In fact, about 90% of women newly diagnosed with breast cancer will survive for at least five years. Recently cancer chemopreventive potential of naturally occurring compounds is of great interest for its less or no side effects in living systems. Therefore, considering the above factors, extensive research will be required in order to find out an alternative treatment strategy to combat against breast cancer effectively and in addition even more effective screening methods will be required to find out in the early stages of breast cancer.

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