

# Breast cancer overview: Epidemiology, tumor heterogeneity, diagnosis, treatment, and risk factors

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## ABSTRACT

Cancer is a global burden. Cancer is a disease characterized by morphological and molecular change resulting in uncontrolled proliferation and spread. In females, breast cancer is the leading cancer in incidence and mortality. Next to the lung cancer, breast cancer is the most common cancer when considering both the sexes. Breast cancer which stood second is moving toward the first position in cancers of females due to lack of preventive strategies. The high incidence and the high mortality combined with differences in the incidence and mortality rates worldwide make breast cancer a major area of concern in both developing and developed countries. The mortality to incidence rates is rapidly increasing in Asian countries than Western countries this may be due to the available health-care system that parallels the socioeconomic development of the country. Breast cancer presents tumor heterogeneity; different subtypes exist based on histology and molecular subtypes. This review summarizes the epidemiology of breast cancer worldwide, Asian countries and also in India. It also presents an overview on the modifiable and non-modifiable risk factors, leading to breast cancer, methods of diagnosis, different treatment modalities such as surgery, combination therapy, radiation chemotherapy, and targeted therapy; the interplay of genetic factors in diagnosis, treatment, and prevention strategy has been presented.

**KEYWORDS:** Breast cancer, Diagnosis, Epidemiology, Risk factors, Treatment

## INTRODUCTION

Lung cancer ranks first for the highest incidence and mortality in males, followed by prostate and colorectal cancer in terms of incidence and liver and stomach cancer in terms of mortality. When both the sexes are considered, lung cancer is the most frequently diagnosed cancer and leading cause of mortality followed by breast cancer.<sup>[1]</sup> Breast cancer is the most common form of cancer in developed and developing countries and ranks second among cancers worldwide.<sup>[2]</sup> By 2020, 1.7 million new breast cancer cases will be presented with 70% deaths occurring in the developing countries presents a huge difference in survival chances. Due to the lack of appropriate preventative strategies, breast cancer poses serious public health issues. Among the Indian population, breast cancer, which previously stood second, has moved to the first position and has become the most

common cancer.<sup>[3]</sup> Cancer is a disease characterized by morphological and molecular change resulting in uncontrolled proliferation and spread, leading to the formation of a mass or lump in the body called tumor and named depending on the site of origin. Breast cancer arises from the tissue called lobules consist of glands involved in the secretion of milk or in the organ that connects the lobes to the nipple called ducts.<sup>[4,5]</sup>

## EPIDEMIOLOGY

### Breast Cancer Incidence Worldwide

Globally, non-communicable diseases are the major cause of death.<sup>[6]</sup> Worldwide, incidence and mortality of cancer are increasing due to the increase in population, increase in the distribution and prevalence of risk factors and socioeconomic status of the countries. According to the World Health Organization estimation in 2015 in 91 countries out of 172 countries assessed, cancer ranked first or second among the cause of death.<sup>[7]</sup> Worldwide, there were 14.9 million new breast cancer cases and in two decades, it is predicted to hike up to 22 million new breast cancer

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cases, this includes per year 1.7 million new breast cancer cases, topping as the second most common cancer and contributing to about 25% of all cancers.<sup>[8]</sup> The incidence rate of breast cancer varies widely from 19.4/100,000 in East Africa to 89.7/100,000 in West Europe.<sup>[9]</sup> The high incidence combined with its high mortality makes breast cancer a major cause for concern in developing countries.<sup>[10]</sup> Worldwide, breast cancer presented a huge difference in the age-standardized incidence and mortality rates [Figure 1].

Recently, the incidence of breast cancer is increasing strongly in Asia, Africa, and South America.<sup>[11]</sup> By 2020, it is estimated that in developing countries, 1.7 million new breast cancer cases will be diagnosed with wide variation in survival chance. In the US for the year 2008, 182,460 new breast cancer occurrence was estimated, for 2018, 266,120 new breast cancer cases were estimated to occur.<sup>[12]</sup> Belgium ranks first and Samoa ranks last on top 25 countries ranking in the incidence of breast cancer in 2018 [Figure 2].

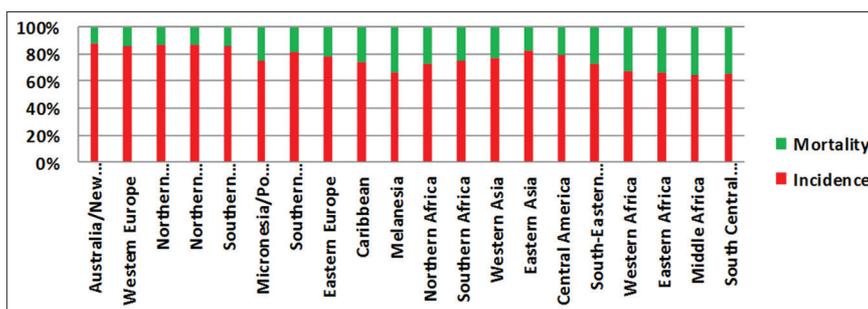
**Burden of Breast Cancer in Asian Population**

The largest continent, Asia, is home to three-fifths of the world’s population and is for 39% of all diagnosed breast cancer cases. Breast cancer is the second leading cause of death due to cancer in Asia. Although the incidence of breast cancer varies among different regions in Asia, it is still lower than the incidence reported by Western countries. The contribution of

Asia, in terms of the proportion of cases, to the global rates of breast cancer incidence is rising rapidly. This parallels the socioeconomic development seen in Asia. Mortality-to-incidence ratio, however, is significantly higher in Asia when compared with Western countries. The reason for this could be the wide variation in health-care systems seen across such a large landmass as Asia. Even within Asia, due to this, there exists a difference in the incidence and mortality of breast cancer.

**Incidence of Breast Cancer in India**

Cervical cancer was seen most often in Indian women in the past; however, currently, it has been surpassed by breast cancer, in rural areas.<sup>[13]</sup> The mortality rate due to breast cancer in India is 12.7/100,000 women. Although the age-adjusted rate of breast cancer in India is lower than that seen in some other countries, for example, the United Kingdom (95/100,000), there seem to be no differences regarding the mortality rate (12.7 vs. 17.1/100,000).<sup>[14]</sup> Thus, a significant increase has been observed in breast cancer incidence and cancer-related morbidity and mortality in the Indian subcontinent.<sup>[15]</sup> Within India, the highest incidence rate (age adjusted) of breast cancer of 41/100,000 was seen in Delhi, followed by Chennai with an incidence rate of 37.9, Bangalore with 34.4, and Thiruvananthapuram district with 33.7. The breast cancer incidence adjusted according to the age was found to increase significantly with time (1982–2014)



**Figure 1:** Worldwide incidence and mortality rates of breast cancer. Region-specific incidence and mortality, age-standardized rates for cancers of the female breast in 2018<sup>[1]</sup>



**Figure 2:** The countries ranking in top 25 places for the highest rates of breast cancer in 2018. Countries arranged rank wise for breast cancer incidence. Belgium ranks first and Samoa ranks least. The top 25 countries are presented<sup>[1]</sup>

in all the population based cancer registries, that is, Bangalore (annual percentage change: 2.84%), Mumbai (1.42%), Barshi (1.87%), Delhi (1.44%), Bhopal (2.00%), and Chennai (2.44%).<sup>[16]</sup> Regional and global epidemiological studies have demonstrated that breast cancer occurs in both Asian and Indian women at younger premenopausal stage in comparison to the Western countries where the breast cancer occurs at later age.

## HETEROGENEITY OF BREAST TUMOR

The hallmark of malignant transformation is tumor heterogeneity. Effective treatment becomes a challenge due to genetic heterogeneity. Identifying the genome of each patient is vital for the development of therapies that overcome obstacles raised due to molecular heterogeneity. The heterogeneity of breast cancer determines the shift from standard classification based on pathology to more personal approach before treatment.<sup>[17]</sup>

Intratumor heterogeneity is noted in breast cancer of different individuals. Intratumor heterogeneity is due to the heterogeneous nature within the individual tumor.<sup>[18]</sup> Earlier tumor heterogeneity was defined by the characteristics of the tumor such as the metastatic ability of the tumor, the resistance exhibited by the tumor to treatment. By the 19<sup>th</sup> century, the heterogeneity at cellular level was recognized and estrogen receptor testing was introduced due to the clinical significance 30 years ago. Currently, the knowledge of cellular and molecular heterogeneity of relevance to diagnosis, management, prognosis, and treatment of breast cancer is the subject of interest for research.

## TYPES OF BREAST CANCER

Breast cancer is not a single disease entity but is of various subtypes, each with its own distinctive biological and histological characteristics, clinical symptoms, and therapy responses. Invasive carcinomas are also classified into various types such as infiltrating ductal, ductal/lobular, invasive lobular, tubular, mucinous, papillary carcinomas and medullary, and stages.<sup>[19]</sup>

### Histological Classification of Breast Tumors

Breast tumors can be broadly categorized histologically into two types, *in situ* carcinomas and invasive (infiltrating) carcinomas, the former is a kind of pre-invasive cancer with the malignant cells blocked at the site of origin, it is this cancer which can then transform and become invasive over the course of few years or decades. Thus, *in situ* carcinoma is considered an obligate precursor of invasive carcinoma of the breast.

Approximately 20% of all cases of breast cancer that are diagnosed are *in situ* carcinomas also, these can be of two types ductal and lobular, classified based on the origin of the cancer cells.<sup>[20-24]</sup>

## BREAST CANCER DIAGNOSIS

The diagnosis of breast cancer on the basis of tissue biopsy depends on several factors such as the location, patient characteristics, available resources, and preferences.

### Physical Examination

Breast cancer detection is either during physical screening or when the woman notices a mass or lump in the breast.

### Breast Cancer Screening

The American Cancer Society recommends that screening for early breast cancer detection can vary based on a woman's age and includes screening methods such as mammography and magnetic resonance imaging (MRI) for high-risk women. It has been recommended that those aged 40–44 years can begin undergoing annual mammography tests; for those aged 45–54 years, it is mandatory to undergo annual mammography screening; while for those aged 55 years or older, biennial mammography is advised, or they can continue with annual mammogram scanning. Screening should be continued for as long as overall health is good and for as long as life expectancy is for another 10 years or more. For high-risk women (~20%–25% or greater), annual MRI screening is recommended along with mammography starting from the age of 30.<sup>[25]</sup>

### Breast Ultrasound

An ultrasound can be used to evaluate abnormal findings as a follow-up on from a mammogram or physical examination as ultrasound has been shown to detect more cancer than mammography alone, especially when screening mammographically dense breast tissue in certain women; however, there is also a high chance of false-positive results in this case.<sup>[26]</sup>

### Confirmation – Tissue Biopsy

Mammogram detection of breast lumps and masses mostly turns out to be benign. Hence, microscopic analysis of breast tissue by biopsy is needed for accurate diagnosis and characterization of the type and extent of the migration of the disease.

### Staging and Grading

Intertumor heterogeneity is attributed by the clinical staging based on imaging and physical examination, the TNM system of staging recommended by the American Joint Committee on Cancer. The TNM

classification of tumors uses information on tumor size and how far it has spread within the breast and to adjacent tissues (T), the extent of spread to the nearby lymph nodes (N), and the presence or absence of distant metastases (spread to distant organs) (M). Once the T, N, and M are determined, a Stage of 0, I, II, III, or IV is assigned, with Stage 0 being *in situ* (abnormal cells have not penetrated the ducts or glands from which they originated), Stage I being early-stage invasive cancer, and Stage IV being the most advanced disease. Breast cancers can be low grade – Grade 1 (slow growing), intermediate grade – Grade 2, and high grade – Grade 3 (faster growing).<sup>[27]</sup>

## BREAST CANCER TREATMENT

On consideration of the stage and biological characteristics of the cancer, the patient's age, menopausal status, and preferences, the risks and benefits associated with each option, treatment decision is made on an individual basis.

Surgery is combined with other treatment methodologies to reduce the risk of recurrence in women with early stage of breast cancer. Treatment methodologies combined with surgery in these cases include radiation therapy, chemotherapy, hormone therapy, and/or targeted therapy. In case of metastatic disease, systemic therapies are the treatment of choice, and these are chemotherapy, targeted therapy, and/or hormonal therapy.

### Surgery

The main aim of surgery in breast cancer patients is to remove the cancer and help in determining its stage. Surgery for breast cancer treatment is of two types, breast-conserving surgery (BCS) and mastectomy. BCS has the aim of removing only the cancerous tissue, along with a rim of normal tissue (tumor margin). Hence, this is not an option in women with a high tumor-to-breast ratio, in patients with multicentric cancers, or in those with inflammatory or locally advanced cancers.<sup>[27]</sup>

### Radiation Therapy

This technique involves the use of high-energy beams or particles to kill cancer cells. It is generally used following surgery to destroy the remnant cancer cells in the breast, chest wall, or underarm area. Radiation therapy to the breast is almost always performed to reduce the risk of cancer recurrence by about 50% at 10 years. It also reduces the risk of breast cancer death by almost 20% at 15 years. External beam radiation, brachytherapy, or a combination of both are usually used for breast cancer cases. The type of radiation therapy depends on the type, stage, and location of the tumor and also takes into account individual patient characteristics.

### Systemic Therapy

Systemic therapy is used in metastatic disease. In this case, the therapy moves through the bloodstream and reaches almost all parts of the body. Chemotherapy, hormone therapy, and targeted therapy are some kinds of systemic therapy, and all of these work by different mechanisms. In chemotherapy, drugs are administered which work by attacking the cells that grow quickly, such as cancer cells. In hormone therapy, the natural body hormones are blocked or their effects are lowered, as high levels of certain hormones can sometimes lead to tumor growth. Targeted drugs work on specific molecules or on cells, i.e., a target, that are generally seen more often in cancer cells than normal ones.

### Chemotherapy

Chemotherapy is usually taken as the choice of treatment depending on various factors. The success of therapy is based on the tumor size, lymph nodes number involved, the presence of progesterone or estrogen receptors, and the Her2 overexpression on the cancer cells. Her2+ and triple-negative breast cancers are usually highly sensitive to chemotherapy compared with HR+ tumors.<sup>[24]</sup>

### Targeted Therapy

The growth-promoting protein Her2/neu is overexpressed by 17% of breast tumors and so there are many drugs currently approved for the treatment of this subtype. Trastuzumab was the first drug to be approved and it is a monoclonal antibody targeting the Her2 protein directly. Two large trials have shown when trastuzumab was added to standard chemotherapy for early-stage Her2+ breast cancer, the risk of recurrence and death was reduced by 52% and 33%, respectively, compared to treatment with chemotherapy alone.<sup>[24]</sup>

### Hormonal Therapy

Two major antiestrogen drug classes used are the aromatase inhibitors and selective estrogen receptor modulators (SERMs) and SERMs are compounds that act in an agonistic or antagonistic manner on estrogen receptors. The most well-known example of a SERM is the drug tamoxifen (TAM), used for over 30 years in breast cancer treatment.<sup>[28]</sup>

## RISK FACTORS FOR BREAST CANCER

About one-third of breast cancer cases are due to modifiable factors such as alcohol consumption, lack of breastfeeds, less physical activity, obesity, use of hormones, lifetime exposure to estrogen hormone, and the age of the mother at the first childbirth. The increased occurrence of breast cancer in individuals with a family history of cancer, the condition of multiple family members being affected with breast

cancer, and other cancer and an autosomal dominant pattern of inheritance of breast cancer from both male and female suggest genetic contribution to breast cancer. Genetic component coupled with additional risk factors such as radiation exposure, reproductive history, hormone replacement therapy, oral contraceptive usage, obesity, less physical activity, and diet influence the risk of developing breast cancer for an individual.<sup>[29-32]</sup> The characteristics of familial breast cancer include diagnosis at young age, increased risk for the development of bilateral breast cancer, increased chance for multiple members in family to be affected, and an association with ovarian cancer. Striking familial occurrence of breast cancer has been produced by high penetrant gene mutations *BRCA1*, *BRCA2*, *p53*, and Cowden disease genes and contributes to 5%–6% of sporadic breast cancer. Specific founder mutations of *BRCA1* and *BRCA2* are identified for certain populations such as Ashkenazi Jews. Mutation in *HRAS1* and *ATM* is rare but does have substantial contribution to breast cancer.<sup>[33]</sup>

## CONCLUSION

Breast cancer was previously and even now continue to be the most dreadful common malignant disease. The exact cause of the disease is unknown. However, genetic, modifiable, and non-modifiable factors also increase the risk of breast cancer. The epidemiology of breast cancer worldwide, Asian and in India, shows an increase in incidence of breast cancer. The molecular, histopathological genetic heterogeneity attributes to the complexity in diagnosis and treatment options. Breast cancer remains the most common and dreadful malignancy that puts the women in depression and it has to detect at the earliest to unplug the root to save the lives of many.

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