BREAST CANCER: TYPES, EPIDEMIOLOGY & AETIOLOGY – A REVIEW

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ABSTRACT
Breast carcinoma is the most widespread cancer in women worldwide. Breast cancer is the most common cancer among women and is the second leading cause of cancer related death. According to the American Cancer Society, about 249,100 women will be diagnosed with breast cancer and more than 39,840 women are expected to die from breast cancer in 2011. The average women’s lifetime risk of developing breast cancer is approximately 12%. The risk factors involved in the development of breast cancer include: older age, environmental factors, early menarche, late menopause, family history, prolonged hormone replacement therapy and alcohol consumption. A number of genes including BRCA1, BRCA2, HER-2 are also identified as causative agents. Hence this review highlights the types, epidemiology and causes of breast cancer briefly.

Key words: breast cancer; epidemiology (world and Indian scenario), etiology, types

INTRODUCTION
Breast cancer begins in breast tissue, which is made up of glands for milk production, called lobules, and the ducts that connect the lobules to the nipple. The remainder of the breast is made up of fatty, connective, and lymphatic tissue. The breast cancer is one of the most challenging health problems that the medical science is facing. It is not restricted to developed nations only but it has very high impact in developing nations also.

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In United States statistical analysis showed that about one woman out of eight suffering invasive breast cancer in her lifetime according to the Breast cancer.org. At the same time rate of suffering breast cancer among women in China, India and Malaysia is 1 in out of 14, 15 and 24 respectively. It has been found that around ten percent of all women suffer breast cancer whereas nearly twenty five percent of all cancers detected in female are breast cancers.

Types of breast cancer
There are several types of breast cancer, but some of them are quite rare. In some cases a single breast tumor can be a combination of these types or be a mixture of invasive and in situ cancer.
Ductal carcinoma in situ

Ductal carcinoma in situ (DCIS also known as intra ductal carcinoma) is considered noninvasive or pre-invasive breast cancer. DCIS means that cells those lined the ducts have changed to look like cancer cells. The difference between DCIS and invasive cancer is that the cells have not spread (invaded) through the walls of the ducts into the surrounding breast tissue. DCIS is considered a pre-cancer because some cases can go on to become invasive cancers. About 1 in 5 new breast cancer cases will be DCIS. Nearly all women diagnosed at this early stage of breast cancer can be cured.

Lobular carcinoma in situ

Invasive (or infiltrating) ductal carcinoma

This is the most common type of breast cancer. Invasive (or infiltrating) ductal carcinoma (IDC) starts in a milk duct of the breast, breaks through the wall of the duct, and grows into the fatty tissue of the breast. At this point, it may be able to spread (metastasize) to other parts of the body through the lymphatic system and bloodstream. About 8 of 10 invasive breast cancers are infiltrating ductal carcinomas.

Invasive (Or Infiltrating) Lobular Carcinoma

Invasive lobular carcinoma (ILC) starts in the milk-producing glands (lobules). Like IDC, it can spread (metastasize) to other parts of the body. About 1 invasive breast cancer in 10 is an ILC. Invasive lobular carcinoma may be harder to detect by a mammogram than invasive ductal carcinoma.

Less common types of breast cancer

Inflammatory breast cancer

This uncommon type of invasive breast cancer accounts for about 1% to 3% of all breast cancers. Usually there is no single lump or tumor. Instead, inflammatory breast cancer (IBC) makes the skin on the breast look red and feels warm. It also may give the breast skin a thick, pitted appearance that looks a lot like an orange peel. Doctors now know that these changes are not caused by inflammation or infection, but by cancer cells blocking lymph vessels in the skin. The affected breast may become larger or firmer, tender, or itchy. In its early stages, inflammatory breast cancer is often mistaken for an infection in the breast (called mastitis) and treated as an infection with antibiotics.

If the symptoms are caused by cancer, they will not improve, and a biopsy will find cancer cells. Because there is no actual lump, it might not show up on a mammogram, which can make it even harder to find it early. This type of breast cancer tends to have a higher chance of spreading and a worse outlook (prognosis) than typical invasive ductal or lobular cancer.

Triple-negative breast cancer

This term is used to describe breast cancers (usually invasive ductal carcinomas) whose cells lack estrogen receptors and progesterone receptors, and do not have an excess of the HER2 protein on their surfaces.
Triple-negative breast cancers tend to grow and spread more quickly than most other types of breast cancer.

**Paget disease of the nipple**
This type of breast cancer starts in the breast ducts and spreads to the skin of the nipple and then to the areola, the dark circle around the nipple. It is rare, accounting for only about 1% of all cases of breast cancer. The skin of the nipple and areola often appears crusted, scaly and red with areas of bleeding or oozing. The woman may notice burning or itching. Paget disease is almost always associated with either ductal carcinoma in situ (DCIS) or infiltrating ductal carcinoma.

**Phyllodes tumor**
This very rare breast tumor develops in the stroma (connective tissue) of the breast, in contrast to carcinomas, which develop in the ducts or lobules. Other names for these tumors include phylloides tumor and cystosarcomaphyllodes. These tumors are usually benign but on rare occasions may be malignant. Benign phyllodes tumors are treated by removing the tumor along with a margin of normal breast tissue.

**Angiosarcoma**
This form of cancer starts in cells that line blood vessels or lymph vessels. It rarely occurs in the breasts. When it does, it usually develops as a complication of previous radiation treatments. This is an extremely rare complication of breast radiation therapy that can develop about 5 to 10 years after radiation. Angiosarcoma can also occur in the arms of women who develop lymph edema as a result of lymph node surgery or radiation therapy to treat breast cancer. These cancers tend to grow and spread quickly.

**Special types of invasive breast carcinoma**
There are some special types of breast cancer that are sub-types of invasive carcinoma.
- Adenoid cystic (or adenocystic) carcinoma
- Low-grade adenosquamous carcinoma (metaplastic carcinoma)
- Medullary carcinoma
- Mucinous (or colloid) carcinoma
- Papillary carcinoma
- Tubular carcinoma
- Metaplastic carcinoma (most types, including spindle cell and squamous)
- Micropapillary carcinoma
- Mixed carcinoma (has features of both invasive ductal and lobular)

In general, all of these sub-types are still treated like standard infiltrating ductal carcinoma.

**Epidemiology of breast cancer**

**World scenario**
Breast cancer is the most common cancer in women worldwide, comprising 16% of all female cancers. Although breast cancer is thought to be a disease of the developed world, a majority (69%) of all breast cancer deaths occurs in developing countries. Incidence rates vary greatly worldwide, with
Breast cancer is the most common cancer and the leading cause of cancer deaths in women worldwide, accounting for >1.6% of deaths and case fatality rates are highest in low-resource countries. In 2012, 1.7 million women were diagnosed with breast cancer and there were 6.3 million women alive who had been diagnosed with breast cancer in the previous five years. Since the 2008 estimates, breast cancer incidence has increased by more than 20%, while mortality has increased by 14%. Breast cancer is also the most common cause of cancer death among women (522,000 deaths in 2012) and the most frequently diagnosed cancer among women in 140 of 184 countries worldwide. It now represents one in four of all cancers in women.

According to GLOBOCAN-generated data of 2008, more than 146,660 new cases of breast cancer have been diagnosed in women less than 40 years of age worldwide, with an age-standardized rate per 100,000 (ASR) of 6. Early onset breast cancer trends vary among populations and areas of the world. Although 77% of the cases occurred in developing countries, the ASR for women below the age of 40 was marginally higher in developed countries (8.8 vs. 5.4). Overall, GLOBOCAN-generated rates of breast cancer in women less than 40 years in different countries have shown relatively stable annual rates around the world, ranging from an ASR of 1.1 to 17. This is in contrast to the overall breast cancer population rates, which vary from 8 to 109. The lowest rates come from countries in Eastern and Southern Africa, while the highest rates are recorded in Europe and North America. In the USA, the Surveillance, Epidemiology and End Results (SEER) program is a principal source for cancer statistics in the country and extensive analysis of these data are periodically published in the literature. SEER data between 1988 and 2003 showed an incidence of breast cancer below the age of 40 of 6.4% (15,548 patients) out of the total breast cancer population in that period (243,012 patients).

Indian scenario

In India, cancer of the breast is the most common cancer among women in many regions and has overtaken cervix cancer, which was the most frequent cancer a decade ago. A recent study of breast cancer risk in India revealed that 1 in 28 women develop breast cancer during her lifetime. This is higher in urban areas being 1 in 22 in a lifetime compared to rural areas, where this risk is relatively much lower being 1 in 60. Incidence rates (age-standardized to the world-standard population as well as age specific) for breast cancer between 1968 and 2002 were obtained from volumes III-IX of Cancer Incidence in Five Continents (CI5) individual registries and publications of the National Cancer Institute.
Cancer Registry Programme. The CI5 included incidence data for 5-year time periods reported by the Indian Population-Based Cancer Registries covering areas Ahmedabad, Bangalore, Chennai, Delhi, Mumbai, Nagpur and Pune. The data for Ahmedabad, Bangalore and Chennai, Mumbai, Nagpur, Pune and Delhi relate to the periods 1983-87 to 1993-97, 1983-87 to 1998-02, 1968-72 to 1998-2002, 1978-82 to 1998-02, 1973-77 to 1998-02 and 1988-92 to 1998-02 respectively. The measure of trend over the period has been estimated as the overall or mean annual percentage change (MAPC%) in age standardized (AAR) and age-specific incidence rates (ASIR) using the relative difference in the incidence rates between the latest and furthest time periods. The AAR of breast cancer during 1998-2002 in the six registries ranged from 24.4 (Pune) to 29.2 per 100,000 women (New Delhi). Trend analysis by period revealed that incidence rates (AARs) rose among women in all the registries, with the exception of Ahmedabad, which showed a decreasing trend. The AAR increased from 18.2 to 25.2, 19.9 to 26.6, 20.2 to 26.9, 19.2 to 27.4, 23.3 to 24.4, and 26.6 to 29.4 with the corresponding MAPC% of 1.05, 1.33, 0.96, 1.86, 0.16 and 0.7 in Bangalore, Chennai, Mumbai, Nagpur, Pune and Delhi respectively.

The ASIR for age intervals (viz.15-34, 35-44, 45-54, 55-64 and 65+ years) by period revealed an increase in the incidence of the disease in various age groups in all the registries except in Ahmedabad. Increase in MAPC% was noted in all the age-intervals in most of the registries. The MAPC% in the youngest age group of 15-34 years were 2.28, 1.42, and 5.89 while for the oldest age interval of 65+ years, it ranged from 0.97% to 2.35% in Chennai, Mumbai and Nagpur respectively.

In Bangalore and Delhi, except in the first and the first two age intervals, increases were noted in other age groups. India is rapidly stepping towards industrialization vis-à-vis urbanization resulting in change of lifestyle factors. These factors possibly contributed to a gradual increase in the incidence of breast cancer in the country.

**Breast cancer etiology**

The precise cause of the breast cancer is not known. Certain risk factors which are not causal in nature have been linked. A variety of risk factors for breast cancer have been well-established by epidemiologic studies carried out to date, in addition to increasing age and female sex. These risk factors include non-modifiable factors such as race, ethnicity, and genetics, as well as modifiable exposures related to diet, physical inactivity, exogenous hormones, and certain female reproductive factors.

Circulating levels of endogenous sex steroid hormones such as estradiol has been associated with increased risk of breast cancer among postmenopausal women. Sex hormone levels are strongly associated with some risk factors for breast cancer (for example, obesity and higher alcohol consumption) and may mediate the effects of these factors on breast cancer risk.
Socio-economic status

Socio-economic status (SES) is highly correlated with cancer risk. Persons with lower SES are more likely to engage in behaviors that increase cancer risk, such as tobacco use and physical inactivity, in part because of marketing strategies that target these populations and in part because of environmental and community factors, such as fewer opportunities for physical activity and less access to fresh fruits and vegetables. Lower SES is also associated with financial, structural, and personal barriers to health care, including lack of or inadequate health insurance, reduced access to recommended preventive care and treatment services and lower literacy levels.

Race

Several factors may account for racial differences in breast cancer mortality including socio-economic factors, access to screening mammography and timely treatment, and biological factors. In the United States, Hispanic ethnicity and black race have been associated with later stage at breast cancer diagnosis compared with white women in the United States, black women tend to have more aggressive breast cancers that present more frequently as estrogen receptor negative tumors. Among premenopausal women, tumors that are estrogen receptor negative, progesterone receptor negative, and HER2 negative (“triple negative” tumors) are more common among black women than among white women.

Age at menarche, parity, and age at first live birth

Younger age at menarche, parity, and older age at first full-term pregnancy are well-established risk factors for breast cancer. These risk factors may influence breast cancer risk through long-term effects on sex hormone levels in premenopausal women, through long-lasting changes in breast tissue, or by other biological mechanisms. Null parity increases breast cancer risk in older women. Pregnancy may reduce breast cancer risk by bringing about persistent changes in the mammary gland that make the breast less susceptible to carcinogenic factors. Younger age at first live birth is protective.

Menopausal Status and Age at Menopause

Older age at menopause is also a well-recognized risk factor for breast cancer. Both early menarche and older age at menopause increase lifetime exposure of breast tissue to hormones.

Breast feeding

Breast feeding reduces women risk of breast cancer and is an important modifiable preventive behavior. Longer duration of breast feeding has been associated with a greater reduction in breast cancer risk.

Oral contraceptives

Epidemiologic studies of oral contraceptive use and breast cancer risk have generally shown little or no increased risk. Recent use of oral contraceptives may slightly increase the risk of breast cancer.
Hormone therapy

Results from observational studies and the Women’s Health Initiative Randomized Trial indicate that hormone replacement therapy after menopause increases breast cancer risk. Use of a regimen that includes both estrogen and progesterone has been associated with a higher risk of breast cancer than the use of estrogen.

Clinical factors

High bone mineral density in postmenopausal women also has been recognized as a risk factor for breast cancer in most studies. Bone density is routinely measured to identify women at increased risk for osteoporosis (high bone density indicates absence of osteoporosis) and may help determine a woman’s risk for developing breast cancer. The association between bone density and breast cancer is probably mediated by hormonal factors.

Women with breast cancer also are at risk for developing a second primary cancer. There is a strong relationship between younger age at diagnosis of the primary breast cancer and risk of subsequent cancer. Women diagnosed with early onset breast cancer (age <40) have almost a 3-fold increased risk of any subsequent cancer, with a 4-5 fold increased risk of subsequent breast cancer.

Nutrition and diet

There is strong scientific evidence that healthy dietary patterns, in combination with regular physical activity, are needed to maintain a healthy body weight and to reduce cancer risk.

Physical activity

There is considerable evidence from epidemiologic studies that high level of physical activity reduces breast cancer risk in women. The possible biological mechanisms include the influences of physical activity on body composition, insulin resistance, and circulating levels of sex steroid hormones.

Genetic risk factors

BRCA1 and BRCA2

The most common cause of hereditary breast cancer is an inherited mutation in the BRCA1 and BRCA2 genes. In normal cells, these genes help prevent cancer by making proteins that keep the cells from growing abnormally. If a person has inherited a mutated copy of either gene from a parent, she has a high risk of developing breast cancer during her lifetime. Although in some families with BRCA1 mutations the lifetime risk of breast cancer is as high as 80%, on average this risk seems to be in the range of 55 to 65%. For BRCA2 mutations the risk is lower, around 45%. Breast cancers linked to these mutations occur more often in younger women and more often affect both breasts than cancers not linked to these mutations. Women with these inherited mutations also have an increased risk for developing other cancers, particularly ovarian cancer.

Changes in other genes
Other gene mutations can also lead to inherited breast cancers. These gene mutations are much rarer and often do not increase the risk of breast cancer as much as the BRCA genes. They are not frequent causes of inherited breast cancer.

**TP53**

The TP53 gene gives instructions for making a protein called p53 that helps stop the growth of abnormal cells. Inherited mutations of this gene cause Li-Fraumeni syndrome (named after the 2 researchers who first described it). People with this syndrome have an increased risk of developing breast cancer, as well as several other cancers such as leukemia, brain tumors, and sarcomas. This is a rare cause of breast cancer.

**CHEK2**

The Li-Fraumeni syndrome can also be caused by inherited mutations in the CHEK2 gene. Even when it does not cause this syndrome, it can increase breast cancer risk about two fold when it is mutated.

**PTEN**

The PTEN gene normally helps regulate cell growth. Inherited mutations in this gene can cause Cowden syndrome, a rare disorder in which people are at increased risk for both benign and malignant breast tumors, as well as growths in the digestive tract, thyroid, uterus and ovaries. Defects in this gene can also cause a different syndrome called Bannayan-Riley-Ruvalcaba syndrome that is not thought to be linked to breast cancer risk.

**CDH1**

Inherited mutations in this gene cause hereditary diffuse gastric cancer, a syndrome in which people develop a rare type of stomach cancer at an early age. Women with mutations in this gene also have an increased risk of invasive lobular breast cancer.

**STK11**

Defects in this gene can lead to Peutz-Jeghers syndrome. People with this disorder develop pigmented spots on their lips and in their mouths, polyps in the urinary and gastrointestinal tracts, and have an increased risk of many types of cancer, including breast cancer.

**Family history of breast cancer**

Breast cancer risk is higher among women whose close blood relatives have this disease. Having one first-degree relative (mother, sister or daughter) with breast cancer approximately doubles a woman’s risk.

**Personal history of breast cancer**

A woman with cancer in one breast has a 3 to 4 fold increased risk of developing a new cancer in the other breast or in another part of the same breast. This is different from a recurrence (return) of the first cancer.

**CONCLUSION**
Thus the present review summarizes the types, causes and risk factors of breast carcinoma. Hence familiarity about the advances in breast cancer will pave way for the new discoveries of treatment drugs against breast cancer.

REFERENCES


