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THE CURRENT STATUS OF BREAST CANCER IN INDIA AND ASSOCIATED RISK FACTORS: A REVIEW

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ABSTRACT

Breast cancer is one the most common health challenge faced by women all around the world. It is the most frequently occurred malignancy in women and is the leading cause of cancer related death. The risk of developing breast cancer of a women in her lifetime is higher in urbanized countries, like the women in western countries than the Asian women. However, over the last few years, a declined rate of incidence could be seen so far in most of the western countries due to the growing awareness among women and also because of the advancement or modernization in screening technologies, advanced treatment therapy etc. Our country is also moving forward to make all the possible advancement in the screening facilities and treatments, spreading awareness among people so that India also sees a declined rate of breast cancer incidence. However, this review article aims to assess the risk factors of breast cancer as a thorough understanding of the same can create awareness among women and help to increase the rate of surveillance.

Keywords: Breast cancer, Invasive lobular carcinoma, Non-invasive carcinoma, genetic susceptibility, Ionizing radiation

INTRODUCTION

Breast cancer is the most common form of malignancy in women all over the world and also the second leading cause of cancer related death in women. Breast cancer accounts for 22% of all female cancers and 15% of cancer related deaths in women of age between 50 – 75 years. Particularly white people in western countries and the people in industrialized area are more susceptible to breast cancer development than women in Africa and Asia

[1]. The United States alone accounts for more than 20% of the one million cases occurring all over the world. The rate of incidence has increased by 50% in UK over the past 25 years **[2]**. However, death rate from breast carcinoma has seen to be stabilized over the past few decades in USA and UK which may be due to better screening techniques, advanced treatment therapy**,** and decrease in hormone replacement therapy prescription **[3, 4]**. In the last decade, India has also seen a steady rise in incidence rate of breast cancer, particularly in the urban areas of the sub-continent are more so. 2018 statistical studies reported 87,090 deaths while 1,62,468 new cases were registered. A recent report tells that an Indian woman is diagnosed with breast cancer in every four minutes. Breast cancer accounts for approx. 14% of cancers in Indian women which makes it the most common type of cancer in women. Decades ago, cervical cancer was the leading cause of cancer related death in women in India. But in 2012 for the first time, Breast Cancer became the most common cancer in Indian women surpassing cervical cancer. The reason for this rise has been mostly attributed to the uncontrolled increase in the cases of Breast Cancer among women and due to the decrease in the incidence rate of cervical cancer to some extent. The incidence of Breast Cancer cases has been consistently increasing and has reached a percentage change in the incidence rate in ranged from 0.46 to 2.56 annually **[5]**. Extensive Research have shown that in India, young age group <50 years is mostly affected by Breast Cancer. Although the survival rate in breast cancer has been showing an outstanding growth in USA because of increased awareness and availability of advanced screening techniques but it is still a matter of growing concern in other developing countries like India, where mortality is still higher. Early detection of breast carcinoma leads to high rate of curability. Survival becomes more difficult if only diagnosed at its higher stage. More than 50% of Indian women are diagnosed with stage 3 or 4 of breast cancer whereas the rate of post cancer survival is 60% of Indian women compared to 80% in women in US. Lack of awareness and inadequate screening techniques and diagnosis rates being the very reason for the low survival rate among Indian women **[6]**.

BREAST CANCER BURDEN ACROSS THE STATES OF INDIA

The Indian states with highest rate of breast cancer includes Mizoram, Haryana, Delhi Karnataka, and Kerala being listed at the top with the highest rate of cancer amongst all. Whereas Mizoram, Kerala and Haryana are the top 3 states with the highest death rate due to breast cancer, respectively. Women are more vulnerable to the development of breast cancer in their early thirties till fifties and it reaches its peak between the age of 50 to 64 years. Every woman in the world is affected by cancer either by literal diagnosis or by a

lifelong worry of getting cancer. In India, every 1 in 28 women is in risk of developing breast cancer during her lifetime. It is more so in urban areas (1 in 22) than the rural group (1in 60) **[7, 8]**.

THE RISE OF BREAST CANCER IN INDIA

New statistical data spell an alarming future – before the situation gets worse, it is time we take preventive actions.

Breast cancer is the most common form of cancer in the country, having surpassed cervical cancer. In the major industrialized cities like Delhi, Mumbai, Bangalore, Chennai, Ahmedabad, Bhopal, Kolkata etc breast cancer only accounts for 25% to 32% of all female cancers. The young women aged between 25-50 are more commonly affected than the elder women and 70% of the cases are diagnosed in advanced stages and therefore had a poor survival rate with high mortality.

The numbers of cases are shockingly on rise **(Table 1)**. According to a report published by ICMR estimated that in 2016 the total number of new cancers was approx. 14.5 lakhs and by 2020 the figure was estimated to have increased to 17.3 lakhs.

Table 1: No of new cases and deaths due to different types of cancers

Cancer site	No of new cases (%of all sites)	No of deaths (% of all sites)
Lung	2.09 million cases	1.76 million
Breast	2.09 million cases	627 000
Colorectal	1.80 million cases	862 000
Prostate	1.28 million cases	358 989
Skin cancer (non-melanoma)	1.04 million cases	65,155
Stomach	1.03 million cases	783 000
Liver	841,080	782 000

The survival rate depends on the stage of breast cancer and how quickly we detect it and start necessary treatment. But in India due to vast population, less medical facilities per capita, lack of awareness, high-cost medical expense etc affects the survival and rate of mortality. Prevention of the above given factors along with increase awareness can help us in reducing the number of cases in our society. In this matter people who are susceptible to breast cancer e.g., people with Positive family history can prevent breast cancer by early detection by regular breast self-examination and prevention can be done by elective mammography surgery **[9-11]**. The graph in figure 1 is a rough representation of the current scenario of Breast Cancer in different age group compared to the data 25years back. The age group has been represented by X axis and the Y axis represents the percentage of cases. The red and green colour represents the incidence 25years back and current situation, respectively **[12, 13]**.

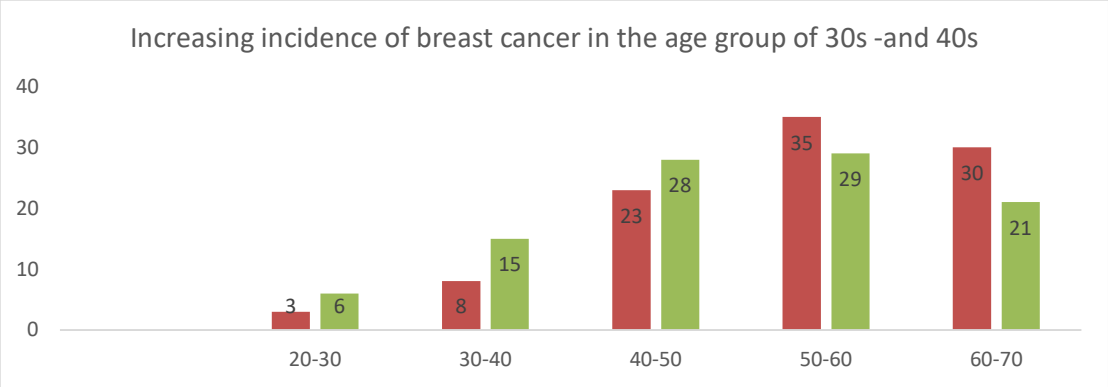

Figure 1: Increase in the number of cases of breast cancer in the age group of 30s and 40s

INCIDENCE OF BREAST CANCER IN INDIA:

Before 2008, the statistical data shows that cervical cancer was the commonest cancer in Indian women followed by breast cancer. But according to the statistical data in 2008, breast cancer become the most common cancer in urban areas leaving behind cervical cancer. But cancer of cervix was still widely spread in rural areas being at the top. The 2012 statistical data showed a completely different scenario. The report shows that there has been more than double number of cases in women than 2008 and became the most common cancer in women in India both in cities and rural areas and it is still in the rising form. The bar graph in figure 2 represents the percentage distribution of top ten carcinogen in females in Mumbai, for the year 2001 – 2004. It clearly shows how the number of cases has been rising constantly since then and is still growing in an uncontrollable manner.

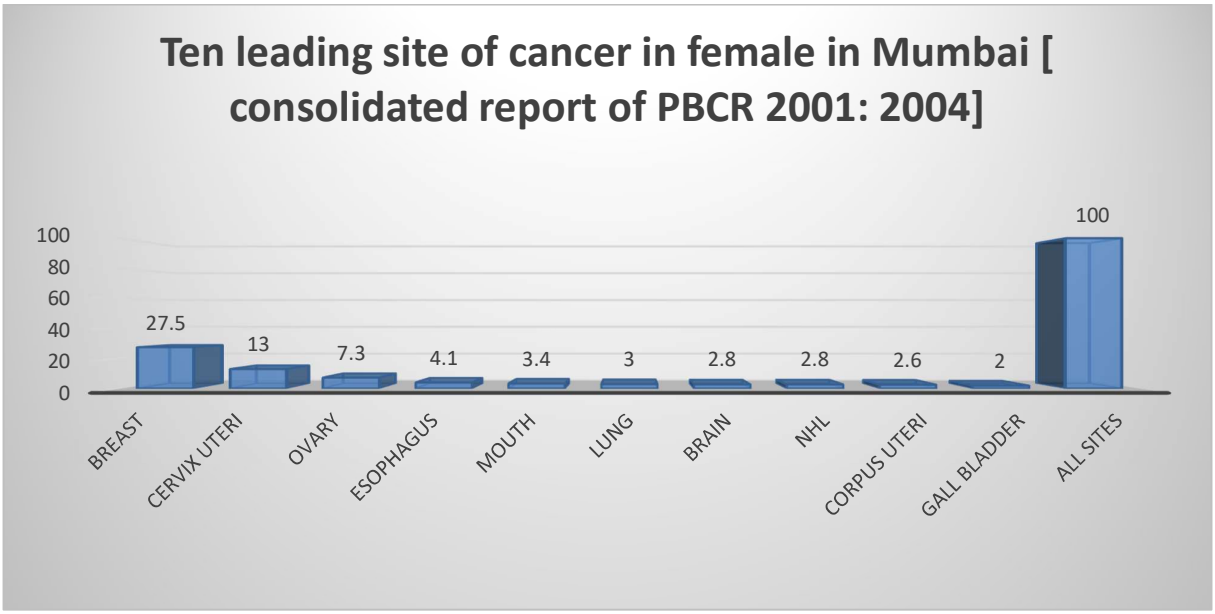

Figure 2: Ten leading site of cancer occurrence in female in Mumbai in the year between 2001 and 2004

THE SURVIVAL RATE FROM BREAST CANCER IN INDIA :

In 2009, American Society of Clinical Oncology (ASCO) published a data which shows an overall improvement in five-year survival for various cancers in US **(Table 2)**. For Breast Cancer, if we speak particularly the survival rate jumped up from 75% in 1970's to almost 89% in 2005 which has been estimated to be 95% (current) according to a recent US SEER data. But this is barely relatable with the statistics of India. According to a roughly estimated report by PBCR and HBCCR, the five years survival for breast cancer in women in India is even less than 60%. This is because the disease is detected at an advanced stage. The main reason why India is lagging because of the lack of awareness among Indian women particularly in rural areas. Although most women notice the symptoms for example - a painless lump in the breast but they do not know that it might be cancerous due to lack of awareness, which then spreads and reaches the advanced stage.

Table2: Overall improvement in five-year survival for various cancers in us

Five-year survival rates of various cancers in USA in the year: 1975-2004			
Cancer type	**1975-1977**	**1984-1986**	**1996-2004**
All cancers	**50.2**	**54.5**	**66.3**
Prostate	**69.3**	**75.8**	**99.4**
Thyroid	**93.4**	**93.9**	**97.3**
Testis	**83.2**	**92.7**	**96.2**
Breast	**74.9**	**79.3**	**89.4**
Hodgkin's lymphoma	**74**	**79**	**80**
Endometrial	**88.3**	**84.4**	**84.3**
Bladder	**74**	**78**	**81**
Cervical	**70**	**68**	**73**
Kidney	**51.2**	**55.8**	**66.7**
	49.3	**56.8**	**67**

Although the risk of developing breast cancer is extremely low in males, still few incidences of male breast cancer can also be seen in North America and Europe, but the rate is very low among Asian population. It represents even less than 1% of the cancers affecting men worldwide. Although the developed countries have come up with various advanced techniques to stabilize the disease progression but still countries like Africa, struggling with the low survival rate which may be because of the delay in seeking diagnosis of and treatment for breast cancer. The rate of incidence is also low in African women as compared to American or European people. Several studies have also reported that the epidemiological factor of breast cancer also differs in Europe and Africa. Different Factors like smoking, lifestyle, hormonal therapy, history of breast cancer have different relation to the people in Africa and Europe **[4, 5]**.

RISK FACTORS:

Research over the past decades have elucidated several different risk factors, in

particular the discovery of cancer susceptible genes (BRCA-1 and BRCA- 2) and the use of contraceptive hormone therapy. Its etiology involves both behavioural and genetic factors **[16, 17, 28]**. However, the various risk factors have been discussed as follows…

Sex: Breast cancer has always been almost 100 % unique to Women**.** Although men are also susceptible to develope **[1, 9]**.

Age: Increasing age is a major risk factor in women between the age of 35 to 75 years. It is rarely seen in female below 20 years of age. However, breast tumors in younger women appear in larger size, advanced stages, positive lymph nodes, and weaker survival **[1,4, 16]**.

Race: A wide range of variation in the rate of incidence can be seen among women worldwide. White Women in western countries like USA, New Zealand, are more susceptible to breast cancer development (incidence over 80/100,000) than women living in Asia and Africa (around or below 30/100,000) **[28]**.

Genetic susceptibility:

a. Genetic susceptibility is one of the most established risk factors of breast carcinoma. Large scale studies on genetic mutations have been carried out in the last few years. Various genes such as BRCA I and BRCA II, PTEN, STK11, CDH1, TP53 have been identified to be responsible for increased susceptibility to cancer to various degree. BRCA I and BRCA II mutations are more common in Ashkenazi Jews. The people with a family history of breast cancer are more prone to thrive ovarian cancer as BRCA II increases the risk **[1, 9, 18]**.

b. **Cowden's disease (multiple hamartoma syndromes)** In Cowden's disease there is decreased tumour suppressor gene PTEN count. In 30-50% of the patients, the disease progresses to breast cancer by the age of 50 years **[1]**.

d. **Li-Fraumeni syndrome** is a rare autosomal dominant disorder and is associated with inherited mutation of tumour suppressor P53 gene .90% of carrier's progresses to breast cancer by the age of 50.

History of breast cancer: About 0.5 to 0.7% women with a history of invasive breast cancer develope very high Risk of recurring breast cancer. The risk increases by 3 to 4 folds in women with a 1st degree relative who had breast cancer or incidence of premenopausal and bilateral cancer. Women with ductal carcinoma in situ (DCIS) are at an increased risk of developing ipsilateral and contra lateral breast cancers (4.1 % after 5 years). Proliferative breast lesions are more vulnerable for malignancy than non-proliferative lesions such as cysts and duct ectasia **[18]**. Diet, body size, and physical activity: The evidence of the effects of diet, physical activity and body size in relation to the development of breast cancer, has been extensively analyzed by the World Cancer Research Fund (WCRF). IARC Handbooks of Cancer Prevention has also published similar studies. However, the studies have suggested

that no such dietary factors can be linked to breast cancer risk. However, there is only limited evidence suggesting the correlation of intake of saturated fats and reduced intake of phyto-oestrogens with increased risk of breast cancer **[9, 18]**.

Evidence of dose –response relationship indicates that high body fat probably protects obese women from developing breast cancer in premenopausal phase. Whether, in contrast, another epidemiological evidence states a clear dose response relationship, which with a number of concrete evidence indicates that accumulation of body fat is associated with postmenopausal breast cancer risk. Abdominal adiposity also increases postmenopausal breast cancer risk **[18, 19]**.

Endocrinal causes:

a. Menarch at early age (≤ 11 years) and late age at menopause (≥ 55 years) and also nulliparity have been found to be associated with increased **[20]** female breast cancer risk by 1-to-2-fold. Full time pregnancy at the age above 30 is also presents high risk. However, on the other hand, breastfeeding provide protection against breast cancer in both premenopausal and postmenopausal women to certain extent. (more children, each child breastfed longer **[18]**.

b. Multiple abortion is also one of the major risk factors.

d. **Hormone replacement therapy (HRT):** Use of oestrogen-progesterone contraceptives, consumption of contraceptives in the peri or postmenopausal period, or women who takes contraceptives at an early age i.e. In less than 20 years and/or before their first full-term pregnancy particularly in postmenopausal women, have been consistently shown to increase the incidence of breast cancer. Estrogen-progestogen hormone replacement therapy at an age above 60 years or taking it in very high dose increase breast cancer risk to several folds. while hormone replacement therapy with estrogen alone (without progestogen) is also associated with an increased risk of developing female breast carcinoma. Frequent exposure to diethylstilbestrol during pregnancy increases a female child's risk of developing breast cancer.

e. **Chest wall radiation:** exposure to mantle radiation in young age, for Hodgkin's disease increases risk (19%) by the age of 50 **[21]**.

Geographical: Breast Carcinoma is particularly seen in western countries which can be contributed to its geographical configuration to some extent. The cases are rarely seen in Asian countries like Japan and Taiwan. Genetic predisposition also exists in a few cases, especially in bilateral breast carcinoma **[22]**.

Ionizing radiation: Frequent exposure to ionizing radiation eg. x-ray and gamma ray has been proved to be as dangerous as carcinogenic in humans in relation with female breast carcinoma. The risk is even higher when exposure occurs during the period of

breast tissue prolifiration) [4, 22]. Although A recent study from Korea does not suggest an increase in breast cancer risk among women with occupational exposure to ionizing radiation **[29]**.

Ethylene oxide: Ethylene oxide is a substance with several various applications such as for the production of certain chemicals in chemical industry and also for sterilization of medical equipment. Although there is only limited epidemiological evidence onto the fact, based on a study on the mechanism of carcinogenicity and studies in animal model, IARC Working Group has classified ethylene oxide as group I carcinogen **[17, 30]**.

Shift work involving circadian disruption:

Very limited studies (only 9, 6 of which found relevant) on female breast cancer are available in relation to the effects of occupational hazards. The study included mainly three occupational categories which are female flight attendants, female nurses and those working as marine telephone operators. The study was carried out only in Caucasian postmenopausal women. The IARC also evaluated the breast cancer evidence based on these relatively few studies in human. These studies used very different definitions of shift work, and different methodologies as well among which three were nested case-control studies, two were prospective cohort studies, one was a nationwide census-based cohort study and two were retrospective case-control studies [31, 32]. But several studies have reported that there were several methodological errors in these studies, particularly relating to the definition of shift work. There is a need of many more human studies to have a thorough understanding of the correlation between shift work and breast cancer risk, and to assess the details of a possible relationship, which could lead to preventive measures. These studies should have strong methodological planning and execution and should include different ethnic groups as well as premenopausal women. Moreover, they should include several industry groups that use shift work and pay particular attention to the classification and measurement of patterns of shift work.

Several studies have reported that in UK the 4.6% incidence rate of female breast could be attributed to shift work**.** It was further estimated that out of all the registered cases of female breast cancer (~ 2,000**)**, 54.0% of occupation-related female cancer cases were due to shift work. There is only very limited research that has been done in human to have a very established association between shift work and breast cancer, as well as to answer the questions related to the patterns of the association. Indeed, there is much more to be explored to have a fair knowledge in relation to the occurrence of breast cancer due to occupational hazard. Future research investigation should also include different prospects; if women who does shift work should be screened more frequently than the general population; if patterns of shift work

can also be equally harmful; if exposure to shift work before first full-term pregnancy is especially harmful; if there are any interactions between shift work with other lifestyle factors, physical activity physical activity, such as alcohol consumption, or body size and shape; if women who does shift work should be screened more frequently than the general population; and breast cancer risk, and, if so, if policy makers should regulate the maximum amount of years women are allowed to work in shifts **[17, 33, 34]**.

Other risk factors: [9, 35, 36]

Analysis of the evidence of several study report established a relationship between the incidence rate of breast cancer in postmenopausal European women and air pollution **[37]**. These studies state that female breast cancer is more common in highly polluted areas and urban areas.

Socioeconomic status

Recently the studies have been emphasized on how the socioeconomic status affects the incidence rate of female breast cancer. From various studies it has been established that there is a relationship between socioeconomic status and breast cancer **[17, 39]**. The rate of incidence of breast cancer is higher in women with higher socioeconomic status. The contributory factor may be linked to the lifestyle related risk factors such as older age at the first childbirth and during menopause, and paralysis. In addition, food habit with high fat content, alcohol consumption, cigarette smoking in this social class can directly and indirectly affect the menstrual cycle of women. On the other hand, the rate of recovery is also higher in this class due to access to care, diagnosis, treatment and prevention. Among the other important factors that affect the incidence rate of breast cancer are educational level, and employment status. Studies have found that employed women generally have higher income and are more likely to use health insurance. The economic status also takes care about the health and investment on medical care. Due to differences in lifestyle, diet, and environmental factors, women living in rural areas comparatively lower risk of developing breast cancer. lower levels of vitamin C, retinol and beta carotene, and high level of fat intake are found to have association with hormonal changes as in the levels of oestrogen and prolactin hormones in the incidence of breast cancer.

Diabetes: Hyperglycaemia may double the risk of breast cancer by several mechanism like interfering with biological mechanisms or through its effects on screening and treatment. Studies have shown that diabetes associated risk of breast cancer increases to many folds among postmenopausal women and those with higher BMI **[17]**. Women with type II diabetes are at 20% increased risk of developing female breast cancer. Women, whose BMI is greater than 26 kg/m^2at and in postmenopausal women as well, the elevated

blood glucose levels, insulin, and IGF-1 patterns increases the risk of progressive breast cancer **[40]**. In people with breast cancer and II diabetes, metformin treatment can improve the survival rate **[41]**. According to EPIC, the risk is significantly increasing in women with elevated levels of IGF-1 and insulin-like growth factor binding protein-3 (IGFBP-3). The risk is even higher in women in whom tumors are detected after the age of 50 years. The control of HbA1C below 7% can improve the outcome of women with breast cancer **[42]**.

CONCLUSION: Incidence of breast cancer in India is rising at a higher rate. According to a statistical data after 2008 it has even surpassed cervical cancer in the country. Not only the urban or industrialized region but the remote areas are equally affected. It may be likely due to lack of awareness among women, late diagnosis and inadequate health service system. Today with the availability of advanced screening, diagnostic and treatment technique, a steep rise in the improvement graph can be observed though the susceptibility remains the same for the women of rural area. However, knowledge about the risk factors could help the women to assess their condition and seek for help at an early stage. Thus, it may help to lower the prevalence rate of the disease to some extent.

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