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Epidemiology and Vaticination of Breast Cancer in Young Women

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ABSTRACT

The risk of developing breast cancer increases with age. But in India, the average age at which breast cancer is detected is about 10 years lesser compared to other developed countries. Almost 6.6% of cases diagnosed in young women with breast cancer are below the age of 40. Review of modifiable risk factors shows that long-term use of oral contraceptives, low body mass index (BMI) and high animal fat diet consumption are associated with increased risk of premenopausal breast cancer. Decreased physical activity and obesity increase risks of breast cancer in postmenopausal women, Non-modifiable risk factors such as family history and genetic mutations do account for increased risks of breast cancer in premenopausal women. Breast cancer in young women is associated with adverse pathological factors, including high grade tumors, hormone receptor negativity, and HER2 over expression. Moreover, younger women often tend to present with breast cancer at a later stage than their older counterparts, which further explains worse outcome. Despite these factors, age per se is still being advocated as an independent role player in the prognosis. This entails more aggressive treatment modalities and the need for closer monitoring and follow-up.

INTRODUCTION

Breast cancer constitutes a major public health issue globally with over 1 million new cases diagnosed annually, resulting in over 400,000 annual deaths and about 4.4 million women living with the disease. It is the commonest site specific malignancy affecting women and the most common cause of cancer mortality in women worldwide (**1,2**).

India is going through epidemiologic transition. It is reported that the prevalence of breast cancer is rising rapidly in India as a result of changes in reproductive risk factors, dietary habits and increasing life expectancy **(3).** The available estimates suggest that approximately 75,000 new cases occur in Indian women every year **(4).** This might be a gross underestimate given that there is paucity of information available on incidence, prevalence and other epidemiologic correlates of breast cancer in India.

Around 6.6% of all breast cancer cases are diagnosed in women less than 40 of age, 2.4% in women less than 35, and 0.65% in women less than 30 (**5,6**); if plotted on a curve, the cumulative incidence of breast cancer seems to follows an exponential function below the age of 40 after which it seems to rise linearly (**5**). The overall worldwide burden of breast cancer has doubled between 1975 and 2000, and this is thought to be attributable to the increasing life expectancy and widespread adoption of westernized lifestyle with all its risk factors (**7**). However, these trends are not seen in early onset breast cancer, as the rates have been more or less stable in most countries in the past 20 years **(8**). As for death rates, they have been steadily decreasing, especially in younger women, owing to the improved treatment and early detection (**9**); however, breast cancer in young women remains a great challenge to patients, families and health care providers. Although the diagnosis of breast cancer is much less common in women under the age of 40 years, it can have a greater impact than in older counterparts, as it tends to present at a later stage, be more aggressive and have a poorer prognosis (**10, 11).**

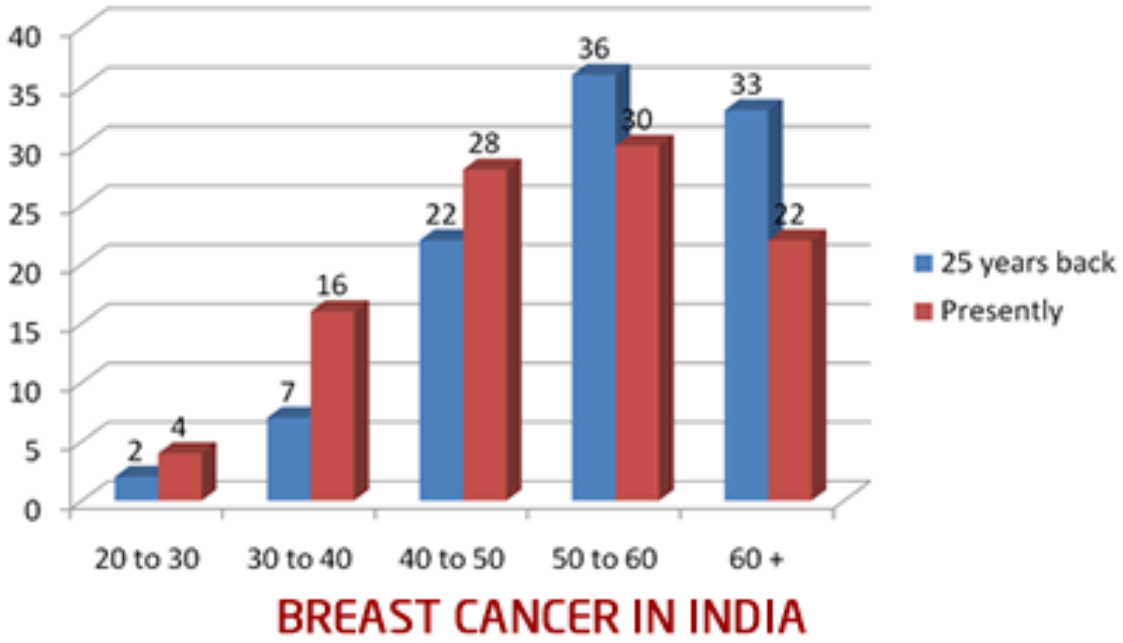
Many studies have suggested that age is an independent prognostic factor; however, this issue is now considered controversial. Breast cancer in young women is more likely to be of a more aggressive subtype, such as triple negative or HER2-positive breast cancer, and is more likely to present at an advanced stage, either because of its biological aggressive subtype or because of a low index of suspicion and delayed diagnosis. This may translate into more loco-regional

recurrences and distant metastases, which contributes to the poorer outcome of young women with breast cancer.

In this review article, a review of the epidemiology, pathology, as well as prognosis and anticipation of young women with breast cancer is presented.

EPIDEMIOLOGY

Early onset breast cancer trends vary among populations and areas of the world. In India, the average age of developing a breast cancer has undergone a significant shift over last few decades. Please consider the below graph (This is only a rough representation of the data).



As per the PBCR (Population Based Cancer Registry, Website):

The horizontal line lower down represents the age groups: 20 to 30 years, 30 to 40 yrs and so on. And the vertical line represents the percentage of cases. The blue color represents the incidence 25 years back, and maroon color represents the situation today. 25 years back, out of every 100 breast cancer patients, 2% were in 20 to 30 years age group, 7% were in 30 to 40 and so on. 69% of the patients were above 50 years of age. Presently, 4% are in 20 to 30 yrs age group, 16% are in 30 to 40, 28% are in 40 to 50 age group. So, almost 48% patients are below 50. An increasing numbers of patients are in the 25 to 40 years of age, and this is definitely a very disturbing trend.

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 (12).

Table 1. ASR (Age Standardized Incidence Rates per 100,000 women per year) and Cumulative Risk (Cum Risk) of Breast Cancer in selected countries [Adapted from GLOBOCAN 2008 Reference (10)].

Country	Age <40		All ages	
	ASR	Cum Risk (%)	ASR	Cum Risk (%)
Italy	13.2	0.6	86.3	9.19
France	12.8	0.59	99.7	10.74
UK	11	0.5	89.1	9.49
Lebanon	9.9	0.45	55.4	5.81
US	9.8	0.45	76	8.26
Argentina	9	0.41	74	7.76
Nigeria	8.8	0.4	38.7	4.05
Japan	7.4	0.34	42.7	4.38
Egypt	7	0.32	37.3	3.65
Brazil	6.3	0.29	42.3	4.51
Turkey	5.8	0.26	28.3	2.94
Russia	5.3	0.24	43.2	4.78
China	4.4	0.2	21.6	2.24

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) (12). 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 (12). The lowest rates come from countries in Eastern and Southern Africa, while the highest rates are recorded in Europe and North America. Rates of breast cancer below and above 40 years from selected countries are presented in the above Table. These differences are less likely related to screening

practices, since screening recommendation is not offered before the age of 40, nor to the use of HRT, since patients are premenopausal (8). It is important to note that not all countries have sufficient data and statistics on cancer rates. Most data come from high-income industrialized countries and tend to be the most accurate, precise, and up-to-date. 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. Pertaining to our topic, 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) (13).

RISK FACTORS

Much of the increase of breast cancer in India has been associated with greater urbanization and changing life styles. In a study on risk factors for breast cancer among women attending a tertiary care hospital in southern India, the population was predominantly from a rural background which sustained on agriculture. This revealed the fact that this disease is no longer confined to an urban setting. However, despite the rural status, women were literate and nearly 25% were employed which probably explains the increased risk (14). Higher education level and income are shown to be significant reasons for an increased risk (15, 16). This is because economic independence may encourage women to remain single or marry late thereby increasing their risk of getting the disease (15.9%).

Genetic factors may play a role in affecting rates of early onset breast cancer in different areas, though their role cannot by itself account for international variation in risk. In the UK, approximately 3% of all breast cancers are attributable to mutations in BRCA1 or BRCA2 (17), whereas this number increases in Ashkenazi Jews to up to 40% (18). TP53 mutation, although vary rare, is the causative agent of breast cancer in Li-Fraumeni syndrome, which tends to affect women between 20 and 40 years of age (19). Some populations such as in Southern Brazil have relatively high mutation frequency of TP53 mutation, reaching one in 300 women (20, 21).

Hormonal factors also vary in different populations, races, and ethnicities. In a study by Lund et al. (22), in Atlanta, USA, incidence rates of triple-negative tumors differed by race, with an incidence of 36.3 per 100,000 for black women, and 19.4 per 100,000 for white women.

Nevertheless, most of the variation in risk is believed to be due to differential environmental exposure to certain risk factors. Studies of migrants further emphasize this hypothesis; incidence of cancers tend to rise following migration from low to high incidence countries, especially if it occurs early in life (23). Many risk factors for breast cancer have been well-established by case-control and cohort studies. However, there have been few efforts to quantify the magnitude of risk disparities between countries that might be explained by such factors.

The role of risk factors in early-onset breast cancer is even less clear. Studies involving this category of breast cancer patients are usually hindered by small sample sizes (8). Moreover, factors such as intrauterine exposures would be of utmost difficult to follow in cohort studies. Nevertheless, case-control studies have shown that birth weight, growth rate in childhood, and attained height are all risk factors for premenopausal breast cancer (24, 25). It has been postulated that prenatal influences, including hormones and growth factors, may alter the risk of breast cancer, but such correlations would be very difficult to measure (26).

Sex

Breast Cancer is 100 times more common in women than in men with male breast cancer accounting for <1% of all breast cancer cases in the United States and 0.1% of cancer mortality in men (27-29). The risk of developing breast cancer increases with age. But in India, the average age at which breast cancer is detected is about 10 years lesser compared to other developed countries. So, more number of young women between the age of 20 and 30 years are also affected but the risk is especially higher after the age of 45 years.

Hormones/Pregnancy related factors

The role of estrogen in the causation of breast cancer has been extensively studied and the general opinion is that estrogen is the primary stimulant for breast epithelial proliferation. Factors that increase exposure to high or prolonged level of estrogen are therefore associated with an increased risk of developing breast cancer (30-34). These include early menarche, late menopause, use of contraceptives and exogenous estrogen, nulliparity and increased age at first term pregnancy. Induced abortion and spontaneous abortion do not increase the risk. Prolonged lactation and breast feeding reduce the risk. The demands for education and a career may

increase the number of women who delay childbearing, have fewer children, use contraceptives and breast feed for a shorter time.

Previous Breast Disease

Individuals who have a prior history of invasive carcinoma or ductal carcinoma *in situ* have a 0.5%-1% per year risk of developing a new invasive breast carcinoma. Women with atypical ductal or lobular hyperplasia have a four to five times higher risk of developing breast cancer. Proliferative lesions without atypia, such as moderate hyperplasia and sclerosing adenosis, are associated with a slightly increased risk (1.5-2%). Other common non-proliferative changes such as palpable cysts, fibro adenomas and duct papillomas are not associated with a significantly increased risk. (35).

Environmental factors

Exposure to ionizing irradiation increases the risk of developing breast cancer. Excess breast cancer has been observed in patients given multiple fluoroscopies, radiotherapy for ankylosing spondylitis, Hodgkin‘s disease, or enlargement of the thymus gland and in survivors of the atomic bombings, painters of radium watch faces and X-ray technicians (36).

LIFESTYLE RISKS

Anthropometric indices and physical activity

Height, obesity and high body mass index are risk factors especially in post menopausal women. In pre-menopausal women, obesity and high body mass index has an insignificant but inverse relationship to breast cancer risk that is reduced by physical activity (37-39).

Diet, Alcohol and Smoking: Alcohol and Diets rich in fat especially saturated fat raises the risk while smoking does not appear to affect the risk (40-42).

FAMILY HISTORY AND GENETICS

A family history of breast cancer increases a woman's risk of developing the disease.

A woman is considered to be at increased risk if the family member is a first degree relation with early age of onset (< age 50), if both breasts are involved, or if she has multiple primary cancers

(such as breast and ovarian cancer). Women with one, two, and three or more first-degree affected relatives have an increased breast cancer risk when compared with women who do not have an affected relative (risk ratios 1.8, 2.9 and 3.9, respectively) (43). Such women are recommended to begin breast cancer screening at an age 10 years younger than the age at which the affected relative was diagnosed.

Hereditary breast cancer caused by an underlying inherited gene mutation accounts for a small proportion (5-10%) of all breast cancers. The majority is accounted for by 2 germline mutations BRCA-1 (50%) and BRCA-2 (32%), which are inherited in an autosomal dominant fashion with varying penetrance. These tumor suppressor genes are important in the processing of DNA damage and preservation of genomic integrity. BRCA-1 is located on chromosome 17q while BRCA-2 is located on chromosome 13q. (44).

Up to 50-87% of women carrying a mutated BRCA1 gene develop breast cancer during their lifetime. Risks for ovarian and prostate cancers are also increased in carriers of this mutation. BRCA2 mutations are identified in 10-20% of families at high risk for breast and ovarian cancers and in only 2.7% of women with early-onset breast cancer. The lifetime risk of developing breast cancer in female carriers is 25-30%. BRCA2 is also a risk factor for male breast cancer; male carriers have a lifetime risk of 6% for developing the cancer. BRCA2 mutations are associated with other types of cancers, such as prostate, pancreatic, fallopian tube, bladder, non-Hodgkin lymphoma, and basal cell carcinoma.

PATHOLOGY AND TYPES OF BREAST CANCER

Breast cancers are derived from the epithelial cells that line the terminal duct lobular unit. Cancer cells that remain within the basement membrane of the elements of the terminal duct lobular unit and the draining duct are classified as *in situ* or non-invasive. An invasive breast cancer is one in which there is dissemination of cancer cells outside the basement membrane of the ducts and lobules into the surrounding adjacent normal tissue.

Classification of Primary Breast Cancer

Noninvasive Epithelial Cancers

-Lobular Carcinoma *in situ* (LCIS)

-Ductal Carcinoma *in situ* (DCIS) or intraductal carcinoma: Papillary, cribriform, solid and comedo types

Invasive Epithelial Cancers (percentage of total)

-Invasive lobular carcinoma (10-15%)
-Invasive ductal carcinoma
-Invasive ductal carcinoma, (NOS) Not Otherwise Specified (50-70%)
-Tubular carcinoma (2-3%)
-Mucinous or colloid carcinoma (2-3%)
-Medullary carcinoma (5%)
-Invasive cribriform (1-3%)
-Invasive papillary (1-2%)
-Adenoid cystic carcinoma (1%)
-Metaplastic carcinoma (1%)
-Pagets disease (<1%)

Mixed Connective and Epithelial Tumors

-Phylloides tumors, benign and malignant
-Carcinosarcoma
-Angiosarcoma

LCIS

This originates from the terminal duct lobular units and only develops in the female breast. It is 12 times more frequent in white women than in African American women. Invasive breast cancer subsequently may develop in 25 to 35% of women with LCIS over their lifetime, and may develop in either breast, regardless of which breast harbored the initial focus of LCIS.

DCIS

This predominantly seen in the female breast, it accounts for 5% of male breast cancers. The risk for invasive breast cancer is increased nearly fivefold in women with DCIS. The invasive

cancers are observed in the ipsilateral breast, usually in the same quadrant as the DCIS that was originally detected, suggesting that DCIS is an anatomic precursor of invasive ductal carcinoma.

Paget's disease

This disease of the breast is a rare manifestation of breast cancer characterized by neoplastic cells in the epidermis of the nipple areolar complex. It most commonly presents with eczema of the areola, bleeding, ulceration, and itching of the nipple. The diagnosis is often delayed because of the rare nature of the condition and confusion with other dermatologic conditions. Because of this, it is recommended that any ulcerated or irritated lesion on the nipple areolar complex undergo a punch biopsy under local anesthesia. There is an associated cancer elsewhere in the breast up to 80% of cases.

PROGNOSIS

It has been generally accepted that young age at diagnosis correlates with a worse clinical outcome compared to their older counterparts based on various prospective and retrospective studies performed in the past two decades (5,45-50). This holds true irrespective of menopausal status, as age is still a risk factor among premenopausal women (51). In addition, breast cancer survival rates are comparatively lower for women less than 40 years of age than for older women across all histological subtypes and stages (5).

However, the controversy lies in the question of whether age per se is an independent risk factor for worse prognosis. Many studies have refuted this hypothesis; they rather propose that the effect of young age on outcome is merely a reflection of over-representation of other known prognostic pathological factors, such as higher grade of differentiation, presence of lymphovascular invasion, higher mitotic rate, lower ER/PR expression, and higher HER2 expression (52-55).Yet other studies have attributed the inferior outcome of young age to the more advanced presentation at diagnosis, including higher rates of axillary lymph node positivity and larger tumor size (49,56-58).

Others have postulated that the effect of differential gene expression between different age groups might play a role (59, 60). In any case, knowing the true impact of age on prognosis may have an effect on our management. If it is indeed an independent factor, then young women

might get benefit from more aggressive treatment than their older counterparts with the same clinical and pathological scenario.

CONCLUSION

Age during the period of diagnosis remains an important factor for anticipating and making treatment decisions in patients with breast cancer. Although, breast cancer in women below 40 years of age constitutes a small proportion of the total incidence, it has a significant burden on women and society. Incidence rates and cumulative risk rates in women below 40 years vary little between populations, but generally remain low and do not justify screening in average risk women. Risk factors in breast cancer do not necessarily have the same effect in young and older patients. While a high BMI seems to have a protective effect against development of breast cancer in premenopausal women, controversy still surrounds the influence of diet and physical activity in this population.

Breast cancer in young women is associated with a poorer outcome, partly because of over-representation of more aggressive subtypes, such as triple negative or HER2-positive breast cancer. In addition, they are more likely to present at an advanced stage or have a delayed diagnosis because of a low index of suspicion by the patient and the primary physician. Many studies have shown a worse prognosis even after controlling for pathological factors and staging. However, the discovery of more prognostic markers and factors might weaken the correlation between age and outcome.

Management of young women with breast cancer still requires particular attention to surgical negative margins, long term follow-up after breast-conserving therapy, more aggressive adjuvant therapy because of poorly differentiated histologies, receptor negative and/or HER2-positive tumors, or poor gene signatures, and improvement of access to care worldwide.

REVIEW CRITERIA

The articles that were reviewed for this manuscript were based on a keyword search using the word string “breast cancer” AND “Epidemiology” OR “Age”. Only articles published in English were considered. All titles were reviewed but only those articles that were considered to be the

most relevant to our topic were included in the review. Additional pertinent articles were included if these were deemed to be relevant by the author.

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