

Risk factors in breast cancer: can we change something

Abstract

Breast cancer is the commonest cancer of urban Indian women and the second commonest in the rural women. Age incidence rates in India suggest that the disease peaks at a younger age (eg, 40-50 years) than in Western countries. Owing to the lack of awareness of this disease and in absence of a breast cancer screening program, the majority of breast cancers are diagnosed at a relatively advanced stage. That lifestyle changes can change the risk of developing breast cancer is supported by several lines of evidence. The rates of breast cancer vary widely by the geographic areas around the world and only a small part of these differences is due to genetics. Over a period of time within-country changes in breast cancer incidence has been seen to be paralleled by lifestyle and behavior changes. The risk of breast cancer may be lowered to the extent that one can make lifestyle changes consistent with modifiable risk factors. In addition, healthy lifestyle choices such as limiting alcohol intake, maintaining a healthy body weight, high dietary soy intake and engaging in regular physical activity may help lower one's risk.

Keywords: breast cancer, risk, life style, countries, rising, cancer, awareness, deaths, ethnic, cultural

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Introduction

Breast cancer is the commonest cancer in women worldwide with a widely variable incidence between countries and regions. The developed countries with a small proportion of the world population account for almost 50% of breast cancers diagnosed worldwide.¹ The incidence of breast cancer is low in India, but rising. Breast cancer is the commonest cancer of urban Indian women and the second commonest in the rural women.² Owing to the lack of awareness of this disease and in absence of a breast cancer screening program, the majority of breast cancers are diagnosed at a relatively advanced stage. India is a sub-continent with wide ethnic, cultural, religious, and economic diversity and variation in the health care infrastructure. The health care facility pattern is heterogeneous, with numerous regions where the benefits of the awareness, early diagnosis, and multidisciplinary treatment programs have not reached. As per the ICMR-PBCR data, breast cancer is the commonest cancer among women in urban registries of Delhi, Mumbai, Ahmedabad, Calcutta, and Trivandrum where it constitutes >30% of all cancers in females.² In India, breast cancer is the second most common cancer (after cervical cancer) with an estimated 115,251 new diagnoses and the second most common cause of cancer-related deaths with 53,592 breast cancer deaths in 2008.³ The age-standardized incidence rate for breast cancer in India is 22.9 per 100,000, one-third that of Western countries, and the mortality rates are disproportionately higher.³ Breast cancer accounts for 22.2% of all new cancer diagnoses and 17.2% of all cancer deaths among women in India. Breast cancer in urban areas of India is three times higher than in rural parts of the country.⁴

Studies have shown a rising trend in the incidence of breast cancer in India with steadily increasing rates since the mid-1980's with the largest increases observed in Mumbai.^{5,6} The increasing burden of disease may be associated with lifestyle factors such as later age at marriage, age at first birth, reduced breastfeeding and westernization of diet and physical activity patterns.^{7,8} Marriage at an early age, early and multiple childbirths, and breastfeeding of all children for a long period of time is the norm in most Indian societies. However,

the urban educated class is moving away from this trend, with late-age childbirth and little or no breastfeeding due to changing social values and the demands of jobs on working women. Breast cancer rates tend to be higher in women of higher education and in specific communities that have adopted a more westernized lifestyle, such as the Christians and the Parsis. These changes may be partly responsible for the increasing trend of breast cancer incidence.

It has been established that one of the strongest predictors of women risk of breast cancer are: increasing age, geographic region, family history of this disease and genetic factors such as mutations in BRCA1 and BRCA2 genes and in other high-penetrance genes (e.g., p53).^{9,10} The next well established factors that increase breast cancer risk included exposure on ionizing radiation in childhood, lifetime exposure to endogenous sex hormones determined by reproductive factors. Over the past two decades numerous investigations have focused on the possible role of lifestyle factors. Strong evidence exists that oral contraceptives (OCP) recent use, hormonal replacement therapy (HRT), smoking, physical inactivity, increased alcohol consumption (about 1 drink/day, \approx 10g alcohol), obesity (in postmenopausal women), diet rich in high saturated fatty acids and red meat are associated with increased breast cancer risk. Studies have also found a positive association between experience of psychological stress and breast cancer risk.¹¹ Recognized breast cancer risks contribute to a better understanding of etiology of the disease but they only explain a small proportion of cancer patients. It is known that physical activity, diet, energy intake and body weight exert effect on breast cancer risk independently as well as these determinants of lifestyle undergo complex interaction.¹² Similarly, reproductive factors are also interrelated. Furthermore, mechanisms responsible for developing breast cancer may be different among subgroups of women, e.g. in pre- and post-menopausal women. Some of behavioral risk factors may be easily modified; thereby their modification may play an important role in the prevention of breast cancer.¹³

The most important modifiable and non-modifiable risk factors are as follows

Non-modifiable risk factors

Age, height, Personal history of benign breast or other breast disease, family history, BRCA1/BRCA2 mutations, menstrual history, Breast density on mammogram, exposure to radiation

Modifiable risk factors

Age at first child, hormone replacement therapy, breast feeding

Lifestyle and dietary factors

Socioeconomic status: Women of higher socioeconomic status are at greater risk for breast cancer, with as much as a twofold increase in incidence from lowest to the highest strata. This is thought to reflect differing reproductive patterns with respect to parity, age at first birth, age at menarche, smoking, and utilization of screening mammography.¹⁴

Weight: Weight and body mass index (BMI) have opposite influences on postmenopausal as compared to premenopausal breast cancer. Higher weight/BMI and postmenopausal weight gain have been associated with a higher risk of breast cancer in multiple studies.¹⁵⁻¹⁷ Expressed in terms of BMI, women with a BMI >33 kg/m² had a 27 percent increased breast cancer risk compared to those with a BMI <21 kg/m². Prospective cohort studies have found an inverse association between obesity and premenopausal breast cancer. Premenopausal women with a BMI ≥ 31 kg/m² were 46 percent less likely to develop breast cancer than those with a BMI <21 kg/m².¹⁵ The biologic mechanisms underlying this association are unclear.

Height: In the majority of studies, increased height has been associated with a higher risk of both premenopausal and postmenopausal breast cancer.^{15,16} Women who were at least 175 cm (69 inches) tall were 20 percent more likely to develop breast cancer than those less than 160 cm (63 inches) tall.¹⁵

Physical activity: Regular physical exercise appears to provide modest protection against breast cancer.^{18,19} Some studies have shown a decreased risk of premenopausal breast cancer in women who exercise more, particularly during adolescence but others have shown no difference.^{18,20} In premenopausal women, even moderate physical activity can be associated with an ovulatory cycles, which are associated with decreased risk. Among postmenopausal women, the data more consistently show a protective effect of regular strenuous activity on breast cancer incidence. The benefit of physical activity was most pronounced in women who performed strenuous exercise at age 35 compared to a younger (age 18) or older (age 55) age and in women who currently engaged in the equivalent of 10 hours or more per week of brisk walking.²¹

Smoking: Accumulating evidence supports an association between active and passive tobacco smoking and increased breast cancer risk, particularly in premenopausal women.²² Increased risks are most consistent in studies for early initiation, longer duration and/or higher pack-years of smoking.²³

Dietary factors

- a. **Alcohol:** Intake of alcohol is associated with an increased risk of hormone receptor-positive breast cancer, and the effect appears to be additive with hormone therapy. There is evidence of a dose-response relationship for example as little as one to two drinks per day can increase risk. One combined analysis of data from

53 studies around the world estimated that the relative risk for breast cancer increased 7% for each additional 10 g of alcohol consumed daily.²⁴

- b. **Fat intake:** Animal and ecologic studies have shown a positive correlation between fat consumption and increased breast cancer risk. However, the results of case-control and prospective cohort studies have been mixed. In a prospective Diet and Health Study, women with fat intake of 90 g/day (40 percent of total calories from fat) had rates of invasive breast cancer that were 11 to 22 percent higher than those of women with median fat intake of 24.2 g/day (20 percent of calories from fat).²⁵ While intake of dietary fat per se has not been established as associated with risk for breast cancer, increased dietary fat typically increases caloric intake. This results in obesity which is risk factor for breast cancer.
- c. **Red meat:** An association between intake of red meat (>5 servings per week) and ER/PR-positive premenopausal breast cancer has been observed.^{26,27}
- d. **Calcium/vitamin D:** Several studies suggest that intake of low-fat dairy products may protect against breast cancer, mainly in premenopausal women.^{28,29} However studies in postmenopausal women did not find a strong association between dairy intake and breast cancer risk.³⁰ Calcium (1000 mg daily) plus vitamin D (400 international units daily) did not report any significant influence of supplementation on breast cancer risk in postmenopausal women.³¹
- e. **Phytoestrogens:** Phytoestrogens are naturally occurring plant substances with a chemical structure similar to 17-beta estradiol. They consist mainly of isoflavones (found in high concentrations in soy beans and other legumes) and lignins (found in a variety of fruits, vegetables, and cereal products). The high soy intake and low rates of breast cancer in Asian populations led to the hypothesis that soy consumption might decrease breast cancer risk by displacing estradiol and functioning as a relative anti-estrogen. Meta-analysis showed that higher intake of isoflavones (≥ 20 mg per day as compared to lower intake of about 5 mg per day) was associated with a 29 percent reduction in breast cancer risk.³²
- f. **Antioxidants:** There is no strong evidence for an effect of intake of vitamin E, or C or beta-carotene on breast cancer risk. Some studies on selenium suggest that the lowest levels may be associated with an increased risk, but higher levels are not protective.³³
- g. **Caffeine:** There is no association between caffeine intake and breast cancer risk.³⁴

Reproductive/hormonal risk factors

Prolonged exposure and higher concentrations of endogenous estrogen increases the risk of breast cancer.

Age at menarche and menopause: Younger age at menarche is associated with a higher risk of breast cancer.^{35,36} In one study, for every two-year delay in the onset of menarche, there was a 10 percent reduction in cancer risk.³⁶ Later menopause increases breast cancer risk. The relative risk increases by 1.03 percent for each year older at menopause, which is comparable to the increase with HT use.^{35,37} Bilateral oophorectomy before the age of 40 reduces lifetime risk by 50 percent.³⁸

Menstrual patterns/infertility: Several epidemiologic studies suggest a link between infertility due to an ovulatory disorders and a decreased risk of breast cancer, but the results are inconsistent.^{39,40}

Parity: Nulliparous women are at increased risk for breast cancer compared with parous women; the relative risk ranges from 1.2 to 1.7.^{35,41} The protective effect of pregnancy is seen after 10 years following delivery.⁴² Majority of studies suggest a decreased risk with increasing number of pregnancies.

Age at first birth: The younger a woman is at her first full-term pregnancy, the lower her breast cancer risk. The cumulative incidence of breast cancer up to age 70 for parous versus nulliparous women was 20 percent lower if the first birth was at age 20, 10 percent lower for first birth at age 25, and 5 percent higher if the first birth was at age 35.⁴¹ The risk for a woman with a first full term birth at age 30 is similar to that of a nulliparous woman. The effect of early first live birth is that full cellular differentiation, which occurs in the gland during and after pregnancy, protects the breast from breast cancer development.³⁵

Abortion: Since abortion disrupts the maturation process of the breast, it has been hypothesized to increase breast cancer risk. Both a large pooled analysis and population-based cohort studies do not support an association between abortion (induced or spontaneous) and breast cancer risk.^{43,44}

Breastfeeding: A protective effect of breastfeeding has been shown in multiple case-control and cohort studies, the magnitude of which may be dependent on the duration of breastfeeding and on parity. Data from 47 epidemiologic studies including 50,302 women with invasive breast cancer and 96,973 controls estimated that the relative risk of breast cancer was reduced by 4.3% for every 12 months of breastfeeding, in addition to a decrease of 7 percent for each birth.⁴⁵ Breastfeeding delays the reestablishment of ovulatory cycles and increases prolactin secretion with a concomitant decrease in estrogen production.

Endogenous hormone levels: Obese postmenopausal women have higher estrogen levels than non-obese postmenopausal women, due to the conversion of adrenal androgens to estrogens in fatty tissue. Obese postmenopausal women have a higher risk of breast cancer and reducing estrogen levels (by suppressing ovarian function in premenopausal women or use of drugs such as aromatase inhibitors in postmenopausal women) lowers breast cancer risk. In a study of 7705 postmenopausal women, those with highest tertile of serum estradiol levels (>12pmol/L) had a two-fold higher risk of invasive breast cancer than women with lower levels.⁴⁶ The data in premenopausal women are less clear, in part due to the inter-individual and intra-individual variability of hormone concentrations during menstrual cycles. A significant association between serum estrogen levels during the follicular phase of the menstrual cycle and breast cancer risk was shown in a case control study.⁴⁷

Bone density: Because bone contains estrogen receptors and is highly sensitive to circulating estrogen levels, bone mineral density (BMD) may be a surrogate marker for long-term exposure to endogenous estrogen. In multiple studies, women with higher bone density had a higher breast cancer risk.⁴⁸

Breast density: The extent of dense tissue within the breast is variable within the population. Although largely an inherited trait, there appears to be a potentially modifiable component.⁴⁹ Hormone therapy increases breast density while tamoxifen decreases it.

Exogenous hormone factors: Much of the available evidence supports a causal relationship between exogenous hormone therapy and breast cancer. Long-term use has been associated with the highest risk. On the other hand, short-term use of combined estrogen-progestin therapy appears not to increase the risk of breast cancer significantly. Multiple observational studies have shown an increased risk of breast cancer with postmenopausal hormone therapy, which includes unopposed estrogen therapy and combined estrogen-progestin therapy.^{50,51} Furthermore, a reanalysis of original data from 51 epidemiologic studies comprising 52,705 women with and 108,411 women without breast cancer found that for each year a woman uses postmenopausal hormones, her risk of breast cancer increases by 2.3 percent.⁵⁰ The relative risk of developing cancer was 1.35 for women who were current hormone users and had taken hormones for five years or longer compared with never users. Greater breast cancer risk was observed with initiation of estrogen-progestin therapy close to menopause, earlier the therapy started higher the risk.⁵² Epidemiologic studies have generally not demonstrated an association between OC use and the risk of breast cancer later in life. Nocturnal light exposure/Night shift work. At least three studies and a meta-analysis support an association between exposure to light at night and the risk of breast cancer.^{53,54} A meta-analysis exploring the relationship between night work and breast cancer risk included 13 reported studies of airline cabin attendants and nighttime shift workers. The relative risk for all studies combined was 1.48.⁵⁵ Exposure to light at night suppresses the normal nocturnal production of melatonin by the pineal gland but the primary mechanisms for the association between melatonin and breast cancer risk are unknown. Shift work is now recognized by IARC/WHO as a probable carcinogen.⁵⁶ For women who are already at higher than average risk, their risk of developing breast cancer can be reduced by at least 50 percent or more by taking tamoxifen or raloxifene for five years. Tamoxifen and raloxifene are both approved by the United States Food and Drug Administration (FDA) for the prevention of breast cancer.

Conclusion

Men are more than one hundred times less likely to get breast cancer than women. There are several approaches that women can take to decrease their risk of breast cancer. These include lifestyle changes (eg, minimize use of postmenopausal hormones, childbearing at a younger age, breastfeeding for at least six months, avoidance of adult weight gain, limiting alcohol consumption, avoidance of smoking, regular physical activity), chemoprevention with tamoxifen or raloxifene, and early detection through adherence to recommendations for screening mammography.

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Conflicts of interest

Author declares that there are no conflicts of interest.

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