

INTRODUCTION

Breast cancer is amongst the commonest cancers among women in India¹⁻³. An analysis of breast cancer cases among women in Delhi, Mumbai, Chennai and Bangalore between 1982 to 2005 performed by the Indian Council of Medical Education and Research, revealed that the number of breast cancer cases have more than doubled in the last 10 years³. Although the incidence of breast cancer among women in India is low, the number of women with breast cancer is quite high (In a report by the Globocan Project in 2012, it was estimated that 144,937 women were diagnosed with breast cancer and 70,218 died of breast cancer in 2012². In 2012, cancer statistics showed 226,870 women will be diagnosed with breast cancer in the US compared to nearly 145,000 in India; 39,510 will

die of breast cancer in the US compared to almost 71,0000 India^{1,4}. Mortality rates are higher likely due to multiple factors related to lack of awareness, screening, early diagnosis and treatment options.

The cause for the increase in breast cancer risk is likely multifactorial due to known associations of multiple risk factors with breast cancer. Reports have suggested that the increase in incidence of breast cancer in urban Indian women may be related to lifestyle changes such as the adoption of a western diet, higher alcohol use and increased obesity. Moreover, rapid urbanization and improvements in the Indian economy have led the working woman to postpone childbearing, have fewer children and decreased breast feeding practices; practices that may increase breast cancer risk by prolonged exposure to estrogen³. Population based studies are needed to determine if specific risk factors are more relevant to the population in India. In this report, we discuss known and potential factors that influence risk and strategies that can reduce breast cancer risk.

BREAST CANCER RISK FACTORS

While there is evidence that some known risk factors for breast cancer such as age, family history, age at menarche, age at menopause, age at first live birth, and proliferative breast biopsy findings, others such as lifestyle may modify risk but research is still ongoing to understand them⁵⁻⁷. Some of these risk factors are non-modifiable such as age and family history. However, other suspected risk factors such as diet rich in fat, excess use of alcohol, prolonged use of post-menopausal hormone therapy and smoking also increase risk (risk factors known and potential are listed in Table 1.

Several reports demonstrate that the risk of breast cancer increases with increasing age^{4,5}. While breast cancer is rare in women younger than age 20 years, the probability of breast cancer increases as women age⁴. Family history of breast cancer puts a woman at increased risk, but the number, degree and age of affected relatives influences the extent of risk^{6,7}. Hereditary breast cancer occurs in association with gene mutations such as BRCA 1 and 2, and with evolving research, other genes such as TP53, CHD1 and PTEN are also now being associated with breast cancer risk⁸⁻¹². Reproductive factors such as early menarche and late menopause results in prolonged estrogen exposure and are associated with a small increase in risk¹³. Early child birth and prolonged lactation on the other hand, reduces breast cancer risk^{7,14}. Postmenopausal hormone therapy with combined estrogen and progesterone has

Table 1: Factors that Influence Breast Cancer Risk

Risk Factors	Effect on breast cancer risk
Age	Increase with increasing age
Family History	Increases based on number and degree of relationship, and age of affected relative
Benign Breast disease	Atypical hyperplasia increases risk
Breast density	Dense breasts increases risk
Genetics	Hereditary breast cancer: BRCA 1 and 2, TP53, CDH1, PTEN
Chest wall radiation for Hodgkin's disease	Increases risk
Exercise*	Lowers risk
BMI*	High BMI increases risk
Alcohol*	Excess use increases risk
Diet*	High fat diet increases risk
Post-menopausal hormone use*	Prolonged use of estrogen and progesterone increases risk
Smoking*	Increased risk
Reproductive factors such as breast feeding, age at first childbirth*	Lactation lowers risk; early age at first parity reduces risk

* Modifiable or potentially modifiable risk factor

Table 2: Strategies to Reduce Breast Cancer Risk

Strategies	Specific Measures/ Agents
Lifestyle interventions	Exercise, maintain a healthy weight/ BMI, low fat diet, avoid or minimize alcohol use
Medications	Tamoxifen, Raloxifene, Exemestane
Surgical Options	Bilateral mastectomies; Bilateral Salpingo-oophorectomies

been shown to increase breast cancer risk (HR: 1.27; 95%CI, 0.91-1.78)¹⁵. Women who have benign breast biopsies showing atypical hyperplasia are also at elevated risk (RR 4.2; 95% CI: 3.26-5.41) and the risk persists for at least 25 years after the biopsy¹⁶. Women who receive chest wall radiation therapy for Hodgkin's lymphoma are at 3-fold increased risk of breast cancer (standardized morbidity ratio 8.5% for women younger than 30 years to 1.2% for those 30 and older at radiation therapy)¹⁷. With increasing use of screening mammography, studies demonstrated that the finding of dense breasts on mammogram increases breast cancer risk. Women with dense tissue comprising over 60-75% of the mammogram have a four to six fold increased risk than women with non-dense breasts¹⁸⁻²⁰. Gathering accurate risk factor information from the patient can facilitate risk stratification efforts so that resources for breast cancer screening and risk reduction can be appropriately directed.

STRATEGIES FOR REDUCING BREAST CANCER RISK

Research studies on breast cancer risk reduction have been directed at reducing the known risk factors for breast cancer. In general, these strategies can be classified into lifestyle modifications to reduce breast cancer risk, use of risk reducing medications and risk reducing surgeries (Table 2).

LIFESTYLE MODIFICATIONS

Several lifestyle factors have been described that are associated with reduced breast cancer risk and can be incorporated into an individual's lifestyle. These include regular exercise, healthy diet, maintaining a healthy weight, limiting alcohol and avoidance of prolonged postmenopausal combined hormone therapy.

Physical activity has been associated with reduced breast cancer risk in multiple prior reports especially in postmenopausal women²¹⁻²³. Moreover, physical activity in adolescence and young adulthood is associated with reduced breast cancer risk (RR 0.81 95% CI 0.73-0.89)²⁴. General recommendations include at least 150 minutes of moderate intensity or 75 minutes of vigorous intensity activity each week for adults, and limiting sedentary behavior such as sitting or lying down²⁵.

Studies to assess the relationship between dietary factors and breast cancer risk showed positive associations with

excess intake of calories, high saturated fat, and excess alcohol while inconclusive findings were noted on the association between dietary fiber, fruits and vegetables, soy and vitamin supplements²⁶. A healthy low fat diet that is rich in fiber, fruits and vegetables is encouraged for breast cancer risk reduction.

Increased body weight/ body mass index is a known risk factor for breast cancer²⁷. In a meta-analysis study, obesity increased the risk of estrogen receptor positive postmenopausal breast cancer (relative risk 1.39) especially in women who did not use postmenopausal hormone therapy²⁷. The Nurses' Health Study showed that postmenopausal women who lost 10kg or more of their weight reduced their breast cancer risk by 56% (95% CI 0.21-0.86; p=0.01)²⁸. Moreover, studies have also shown that weight gain after age 18 associated with increased postmenopausal breast cancer incidence²⁹. Hence, we recommend that regular exercise, healthy diet and a healthy body weight should be strongly encouraged when aiming for breast cancer risk reduction.

Several prior studies have demonstrated a consistent association between alcohol and breast cancer risk³⁰⁻³³. A meta-analysis study showed that women consuming >45 gm (>3 drinks) daily had 1.5 times increased risk than non-drinkers³¹. Moreover, the risk has been shown to be dose-dependent³¹. Limiting alcohol to less than a serving a day is a practical approach²⁵.

Post-menopausal hormone therapy with estrogen and progesterone over 5 years was found to be associated with increase in incident breast cancers³⁴. However, the risk was not increased in women who only received estrogen without progesterone following hysterectomy. Therefore, women need to be informed of benefits and the risks of these medications when used to manage menopausal symptoms. In addition, this information should be reassessed on a yearly basis while she is on the medication with a plan to avoid long term use.

MEDICATIONS TO REDUCE RISK

Studies with anti-estrogen therapy have consistently demonstrated reduction in breast cancer risk³⁵⁻³⁸. These agents including the selective estrogen receptor modulators (SERM), tamoxifen and raloxifene, as well as the aromatase inhibitors exemestane and anastrozole, have demonstrated definite benefits but also side-effects from therapy and are options for the high-risk population. Additionally, factors such as the cost and availability of the medication are also important when making a choice of taking the medication. Tamoxifen is the only agent that can be used for pre-menopausal women whereas all three agents can be used for post-menopausal women.

Tamoxifen is a SERM that continues to be used for adjuvant therapy of estrogen receptor positive breast cancer. Subsequently, tamoxifen was studied for breast cancer prevention showing reduction in the risk after 5 years of use³⁵. A meta-analysis of tamoxifen trials showed that after 5 years of use, tamoxifen reduced invasive breast cancer risk by 33% (relative risk reduction 0.67; 95%CI

1056 0.52 to 0.86)²³. Side-effects of the medication include hot flashes, vaginal concerns, and weight gain similar to all anti-estrogens, but also the risk, albeit small, of deep vein thrombosis, pulmonary embolism, stroke and uterine cancer.

Raloxifene is a SERM that has been used for osteoporosis treatment for many years³⁹. In the second breast cancer prevention trial, the STAR trial, raloxifene was demonstrated to reduce breast cancer risk similar to tamoxifen in postmenopausal women³⁶. In a meta-analysis of raloxifene trials, the medication taken for 4 to 8 years, reduced estrogen receptor positive breast cancer by 59% (relative risk reduction 0.41; 95% CI, 0.27 to 0.62)²³. While the side-effects of hot flashes, vaginal concerns, and weight gain were similar to tamoxifen, there were fewer events in terms of deep vein thrombosis, pulmonary embolism, stroke and uterine cancer.

Exemestane, an aromatase inhibitor, is an option for reducing risk for postmenopausal women at elevated breast cancer risk. In an international, randomized, placebo-controlled trial of exemestane for breast cancer prevention in post-menopausal women, this agent resulted in 65% reduction in risk of invasive breast cancer (risk ratio 0.35; 95% CI 0.18 to 0.7; p<0.002) at a median follow up of 35 months³⁷. Side effects include menopausal symptoms of hot flashes, insomnia and arthralgias, and reduced bone mineral density.

Anastrozole is another aromatase inhibitor that more recently was shown to reduce breast cancer risk when used in postmenopausal women. In an international, randomized, double blind, placebo controlled trial of high risk women from 18 countries, anastrozole taken for 5 years was associated with reduced risk ((hazard ratio 0.47, 95% CI 0.32–0.68, p<0.0001)³⁸.

RISK REDUCING SURGERY

In women who are at very high risk of breast cancer such as BRCA 1 or 2 mutation carriers, prophylactic surgeries may be performed to reduce their breast cancer risk. However, these are patient-driven decisions that should be undertaken following extensive education and counseling to ensure that the patient understands the pros and cons of each decision. Risk reducing mastectomies have shown breast cancer risk reduction by 90% to 95%^{40,41}. Risk reducing salpingo-oophorectomies (RRSO) have also been shown to reduce risk of ovarian as well as breast cancer and is an option for women at very high risk such as BRCA 1 and 2 mutation carriers⁴². Additional benefits of risk reducing procedures include reduction in anxiety and detection of occult malignancies but the side effects include menopausal symptoms (with RRSO), body image and sexuality issues, and the risks of surgical intervention.

SUMMARY

Prior reports have shown the association between variety of factors and development of breast cancer. Lifestyle modifications can be recommended to women to reduce breast cancer risk. These measures have multiple health

advantages and can be safely recommended to women irrespective of their risk status. Chemoprevention with agents such as tamoxifen or raloxifene, exemestane or anastrozole may be considered in select situations for women at high risk. Risk reducing surgery is an option for women at highest risk.

The above discussions detail several measures that can reduce breast cancer risk based on the current known information. Additionally, educating the population about breast awareness and advice to seek medical attention earlier for breast concerns, can potentially impact the growing problem of breast cancer in India.

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