Chapter 174
Strategies to Reduce the Risk of Breast Cancer

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INTRODUCTION
It has been estimated that, by 2020, 14% of the world’s cancer cases will be in India. An analysis of breast cancer cases among women in Delhi, Mumbai, Chennai and Bangalore between 1982 and 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 years. Currently, 23 per 100,000 women in India get breast cancer. It is estimated that by 2020 the number of breast cancer cases will exceed cases of cervical cancer in India. Although women in India are less likely than women in Western countries to develop breast cancer, they are more likely to die of it due to paucity of screening, early diagnosis and treatment options.

The cause for the increase in breast cancer risk is likely multifactorial. 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 women to postpone childbearing, have fewer children and decreased breast-feeding practices; practices that may increase breast cancer risk by prolonged exposure to estrogen.

In this review, authors have discussed (1) the emerging body of evidence that have identified modifiable risk factors for breast cancer and (2) studies on breast cancer risk-reduction strategies and present recommendations to reduce the risk of breast cancer.

BREAST CANCER RISK FACTORS
Some risk factors for breast cancer are not modifiable such as age and family history. There are, however, several known or suspected risk factors that are modifiable such as weight, high fat diet, alcohol intake, smoking and prolonged use of postmenopausal hormone therapy (Table 1). Several studies have been done that demonstrate the association between these risk factors and breast cancer. Age is one of the strongest risk factors for breast cancer. Breast cancer is uncommon before age 25, but the risk continues to increase until age 75 years. Early menarche and late menopause are associated with slight increase in risk likely related to prolonged estrogen exposure. Prolonged breast-feeding reduces risk by 4% for each year of breast-feeding. Benign breast disease such as atypical hyperplasia increases risk fourfold (RR 4.2; 95% CI: 3.26–5.41) and the risk persists for at least 25 years from the time of benign breast biopsy. Mammographic breast density is also a known risk factor for breast cancer. Women with over 60–75% dense tissue on mammograms have a fourfold to sixfold increased risk than women with little or no density. Postmenopausal hormone use with estrogen and progesterone increases breast cancer risk (HR 1.26; 95% CI: 1.0–1.59). Chest wall radiation therapy for Hodgkin’s lymphoma is associated with threefold increased risk of breast cancer with risk being greatest for children younger than 15 years at treatment (standardized morbidity ratio 8.5% for women younger than 30 years to 1.2% for those 30 and older at radiation therapy). Understanding risk associations and the degree of risk and whether they are modifiable can help focus attention on strategies to reduce risk of breast cancer in the future.

STRATEGIES FOR REDUCING BREAST CANCER RISK
Several research studies have assessed options aimed at reducing breast cancer risk. These have been directed at addressing the known and modifiable risk factors for breast cancer. In general, these strategies can be classified as lifestyle modifications, chemoprevention and prophylactic surgeries (Table 2).

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Risk factors for breast cancer</th>
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<tbody>
<tr>
<td><strong>Modifiable risk factors</strong></td>
<td><strong>Nonmodifiable risk factors</strong></td>
</tr>
<tr>
<td>Exercise</td>
<td>Age</td>
</tr>
<tr>
<td>Body mass index</td>
<td>Family history</td>
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<tr>
<td>Alcohol</td>
<td>Benign breast disease</td>
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<tr>
<td>Diet</td>
<td>Breast density</td>
</tr>
<tr>
<td>Postmenopausal hormone use</td>
<td>Genetics</td>
</tr>
<tr>
<td>Smoking</td>
<td>Chest wall radiation for Hodgkin's disease</td>
</tr>
<tr>
<td>Reproductive factors* such as breast-feeding, age at first childbirth</td>
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*Potentially modifiable risk factor

Lifestyle Modifications
Physical Activity
Regular physical activity can assist with maintaining a healthy weight that has been associated with reduced breast cancer risk. Exercise reduces body fat and increases insulin sensitivity. Studies have shown that physical activity in adolescence and young adulthood is associated with reduced breast cancer risk (RR 0.81; 95% CI: 0.73–0.89). The data are strong in postmenopausal population of women but not as consistent among premenopausal women. The American Cancer Society (ACS) guidelines on physical activity for cancer prevention encourages being physically active. This includes
at least 150 minutes of moderate intensity or 75 minutes of vigorous intensity activity each week for adults; at least 1 hour of moderate of vigorous activity each day for children. In addition, limit sedentary behavior such as sitting, lying down or watching television.15

**Alcohol Consumption**

Numerous studies have demonstrated consistent association between alcohol and breast cancer risk.16-18 In one study, postmenopausal women who consumed alcohol were at 22% (95% CI: 9–37%) greater risk of breast cancer than nondrinkers.17 Moreover, the risk has been shown to be dose-dependent. The mechanism of action is thought to be related to elevated levels of tissue estrogen, folate deficiency in these individuals causing DNA hypomethylation and compromising DNA repair mechanisms, as well as the metabolite acetaldehyde that can behave as a carcinogen.16,19,19 Hence, the recommendation is to avoid excess alcohol intake. Limiting alcohol to less than a serving of alcohol a day with a serving being 5 ounces wine, 12 ounces beer or 1.5 ounces of 80-proof distilled spirits, or even avoiding alcohol is a reasonable approach.15

**Weight**

Mechanism of increased risk with increased weight/body mass index (BMI) is that androgens are converted, via aromatase pathway, to estrogen in the fat tissue. The Nurses’ Health Study showed that postmenopausal women who lost 10 kg or more of their weight had a 10% lower risk of breast cancer (RR 0.90; 95% CI: 0.88–0.93; p = 0.01).20 Moreover, studies have also shown that weight gain after age 18 associated with increased postmenopausal breast cancer incidence.21 Physical exercise combined with a healthy diet can facilitate attainment of a healthy body weight.

**Diet**

Extensive research has been done to study the association between dietary factors and breast cancer risk.22 Some of the known associations include the increased risk with excess caloric intake, high saturated fat and excess alcohol while data on association between dietary fiber, fruits and vegetables, soy and vitamin supplements are inconclusive. A balanced diet where caloric intake is commensurate with physical activity energy expense, diet rich in fiber, fruits and vegetables, and avoidance of or at least reducing to less than a serving a day could reduce breast cancer risk while also ensuring overall health benefits.

**Postmenopausal Hormone Therapy**

Postmenopausal hormone therapy with estrogen and progesterone over 5 years was found to be associated with increase in incident breast cancers and those diagnosed at a more advanced stage.23 Decision to use postmenopausal hormones to manage menopausal symptoms should include a discussion of benefits and risks and should be reassessed on a yearly basis while on the medication with a plan to discontinue the medication when symptoms improve.

Lifestyle choices such as exercise, maintaining healthy weight, low fat diet and reduced alcohol intake have been shown to reduce breast cancer risk.14 These changes are safe and have multiple positive effects on health and should be included in programs aimed to reduce breast cancer risk for women of any risk category.

### Chemoprevention

Chemoprevention studies with antiestrogens agents, done in the United States, Canada and Europe, have consistently demonstrated reduction in breast cancer risk.24-26 These agents including the selective estrogen receptor modulators, tamoxifen and raloxifene, as well as the aromatase inhibitor exemestane, have benefits but also side effects and may be options for the high-risk population. Cost and availability of the medication is also a factor that is an integral part of the informed decision-making process. Of note, tamoxifen is the only agent that can be used for premenopausal women whereas all three agents can be used for postmenopausal women.

**Tamoxifen**

A meta-analysis of tamoxifen trials showed that after 5 years of use, tamoxifen reduced invasive breast cancer risk by 33% (RR 0.67; 95% CI: 0.52–0.86).14 Side effects of the medication include hot flashes, vaginal dryness and weight gain similar to all antiestrogens, but also the risk, albeit small, of deep vein thrombosis, pulmonary embolism, stroke and uterine cancer.

**Raloxifene**

In a meta-analysis of raloxifene trials, the medication taken for 4–8 years, reduced estrogen receptor-positive breast cancer by 59% (RR 0.41; 95% CI: 0.27–0.62).14

**Exemestane**

In an international randomized, placebo-controlled trial of exemestane for breast cancer prevention in postmenopausal women, this agent resulted in 65% reduction in the annual incidence of invasive breast cancer (RR 0.35; 95% CI: 0.18–0.7; p = 0.002) at a median follow-up of 35 months.26 Side effects include menopausal symptoms of hot flashes, insomnia and arthralgias, and the risk of reduction in bone mineral density.

### Risk-Reducing Surgery

In women, who are at very high-risk of breast cancer such as BRCA1 or BRCA2 mutation carriers, prophylactic surgeries have been options to reduce their breast cancer risk. However, these are patient-centered and patient-driven decisions that should be undertaken following extensive education and counseling to ensure thorough patient understanding of the pros and cons and thus, optimal patient satisfaction and outcomes. Risk-reducing mastectomies have shown breast cancer risk reduction by 90–95%.27,28 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 BRCA1 and BRCA2 mutation carriers.28 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

Studies have shown the association between several risk factors and development of breast cancer. Lifestyle modifications can be recommended to women to facilitate breast cancer risk reduction. These measures have multiple health advantages and can be safely recommended to women irrespective of their risk status. Chemoprevention with agents such as tamoxifen, raloxifene or exemestane may be considered in select situations for women at high-risk. Risk-reducing surgery is an option for women at the highest risk category.

Going forward, educating the population about breast self-awareness and advice to seek medical attention earlier for breast concerns, as well as ensuring healthy lifestyle choices to reduce risk

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**TABLE 2 | Breast cancer risk-reduction strategies**

<table>
<thead>
<tr>
<th>Strategies</th>
<th>Type of intervention</th>
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<tbody>
<tr>
<td><strong>Lifestyle changes</strong></td>
<td>Exercise, healthy weight, low fat diet, avoid or minimize alcohol use</td>
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<tr>
<td><strong>Chemoprevention</strong></td>
<td>Tamoxifen, raloxifene, exemestane</td>
</tr>
<tr>
<td><strong>Risk-reducing surgery</strong></td>
<td>Bilateral mastectomies, salpingo-oophorectomies</td>
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</table>
can potentially have a significant impact in managing the problem of breast cancer in India.

REFERENCES