

## Guidelines for International Breast Health and Cancer Control–Implementation

*Supplement to Cancer*

# Breast Cancer Prevention in Countries With Diverse Resources

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Breast cancer is the most common invasive cancer in women globally, and it affects more than 1 million women worldwide each year. It is a preventable disease in part, and primary care providers and public health programs play a key role in providing cancer preventive care. There are several health behaviors that may reduce the risk of breast cancer, including prolonged lactation; regular physical activity; avoiding overweight, obesity, and lifetime weight gain; avoiding excess alcohol intake; avoiding prolonged use of exogenous hormone therapy; and avoiding excessive radiation. These behaviors, although they have not been proven in clinical trials to reduce risk, are likely to be beneficial; information on them can be provided as a prevention strategy in countries of diverse means, although the methods of information delivery and follow-up will depend on financial and personnel resources. Many of these health behaviors can reduce the risk for other chronic diseases and, thus, may be of great interest for general public health. In high resource level countries, additional prevention methods are available for high-risk women, including selective estrogen response modulators and, for women at very high risk, bilateral prophylactic mastectomy and bilateral oophorectomy. Most women can benefit from advice and preventive care for reducing their risk for breast cancer. *Cancer* 2008;113(8 suppl):2325–30. © 2008 American Cancer Society.

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**T**here are several modifiable health behaviors that may reduce the risk of breast cancer without placing an undue burden on a woman's economic or social well being, including prolonged lactation; regular physical activity; avoiding overweight, obesity, and lifetime weight gain; avoiding excess alcohol intake; avoiding prolonged use of exogenous hormone therapy; and avoiding excessive radiation. These health factors, although they have not been proven in clinical trials to reduce risk, are likely to be beneficial.

Prevention options for women at very high risk of breast cancer are available in countries with high levels of financial and relevant personnel resources that have established and extensive healthcare systems, including selective estrogen response modulator medications (tamoxifen, raloxifene), which have been shown to decrease risk of breast cancer in women with elevated risk.<sup>1,2</sup> Where there are resources for genetic testing and counseling, preventive measures,

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such as prophylactic mastectomy and bilateral oophorectomy, might be available to women with inherited risk for breast and ovarian cancers. However, in lower resource countries, these modalities are unlikely to be widely available.

In this article, we review several lifestyle factors and interventions that have been shown or are postulated to reduce breast cancer risk, with emphasis on interventions, including lactation, physical activity, weight control, diet, alcohol use, and avoidance of specific carcinogens, that could be implemented in countries with low or moderate levels of health-care resources. These potential prevention strategies have evolved in Western cultures and may not have applicability in some other populations because of cultural and possible biologic differences that may exist between populations. It is important to note that prevention strategies that have been developed in Western countries will need to be tested in other settings to define applicability in non-Western settings. Cost-intensive medication and surgery options for high-risk women are not covered in detail. This is not a comprehensive review. Rather, studies were included to illustrate particular issues. Where possible, meta-analyses or combined analyses of large datasets were referenced as the best estimates of the level of risk associated with particular breast cancer risk factors.

### Lactation

Studies around the world have demonstrated that early childbearing and increased numbers of full-term pregnancies reduce the risk for breast cancer.<sup>3</sup> However, promoting early or more pregnancies as a breast cancer risk-reduction strategy is not feasible or acceptable either culturally or economically for most women. For those women who do experience pregnancy and childbirth, lactation is associated with a significant reduction in the risk of breast cancer and has additional health benefits for babies and children beyond benefits for the mother. In a collaborative study that data from >50,300 patients with breast cancer and almost 97,000 control women from 30 countries around the world, the relative risk of developing invasive breast cancer decreased by 4.3% for every 12 months of breastfeeding (in addition to a decrease of 7% for each birth).<sup>4</sup>

The global strategy of the World Health Organization (WHO) for infant and young child feeding promotes breastfeeding as the optimal source of nutrition for babies and young children,<sup>5</sup> because breastfeeding is associated with improved nutritional status, immune function, and growth and develop-

ment compared with artificial infant feeding. The WHO estimates that, as of 2002, <35% of infants worldwide are breastfed exclusively during the first 4 months of life. The reduced risk of breast cancer is an additional incentive for women to breastfeed each baby and to increase the number of months they breastfeed each child. It may be important to promote breastfeeding in areas where there is considerable promotion of formula feeding from commercial interests.

### Physical Activity

Over 20 large epidemiologic cohort studies have investigated the association between physical activity and the risk of breast cancer, and the majority provided clear evidence of a reduced risk for breast cancer in women who were classified at the highest levels of physical activity.<sup>6-8</sup> On average, the reduction in risk was 30% to 40% for women who exercised for 3 to 4 hours per week at moderate to vigorous levels, and the reduction was evident for women with and without a family history of breast cancer and for women at every level of risk. These data suggest that women should be encouraged to perform aerobic activity for 30 to 60 minutes on most days of the week. For most women, moderate-intensity activity, such as heavy housework, brisk walking, or dancing, would provide a level of activity that would be protective. The inclusion of purposive recreational or transportation physical activity into each day, including the provision of workplace facilities, will become more important as women in developing countries increasingly enter a more sedentary workforce.

In young and teenage girls, physical activity affects menstrual patterns and the production of ovarian hormones in ways that likely are protective against cancer. Physical activity in girls of these ages delays the onset of menstruation, increases duration of menstrual cycles, and reduces circulating levels of estrogen and progesterone,<sup>9,10</sup> menstrual factors that are associated with reduced risk for breast cancer.<sup>3</sup> In postmenopausal women, physical activity reduces several hormones and peptides that may promote breast cancer development, including estrogen, androgens, insulin, inflammatory cytokines, and other products of adipose tissue.<sup>10</sup>

### Weight Control

The WHO defines several categories of weight corrected for height. For most women, a body mass index (BMI) <25 kg/m<sup>2</sup> is considered normal weight, a BMI from 25 to 29.9 kg/m<sup>2</sup> is overweight, and a BMI ≥30 kg/m<sup>2</sup> is classified as obese.<sup>11</sup> For Asian

women, the categories of overweight and obese may be lower given the increased risk for obesity-related disease in Asians at lower levels of adiposity compared with individuals from other racial backgrounds.<sup>12</sup> The WHO estimates that, in 2005, approximately 1.6 billion adults (aged  $\geq 15$  years) were overweight, and at least 400 million adults were obese. The WHO also estimates that, by 2015,  $>30\%$  of adult women will be obese in various countries with low- or middle-level healthcare resources, including the Middle East, Central and South America, Eastern Europe, and Africa.

More than 100 studies have examined the association of weight or BMI, central fat distribution, or adult weight gain and the risk of breast cancer incidence.<sup>8,10</sup> Taken together, the studies revealed that women who are overweight or obese have a 30% to 50% increased risk of developing postmenopausal breast cancer compared with leaner women.<sup>8</sup> Women who are overweight or obese should be encouraged strongly to lose weight. Many years of clinical research point to a combination of behavioral counseling, calorie reduction, and increased physical activity as the key to successful weight loss and maintenance. For the physician, appropriate management includes following weight and BMI in 1 area of the medical chart, regular follow-up visits, and appropriate referral to a nutritionist or weight-loss program. For the patient, keeping diet and activity logs as well as regular weighings (at least weekly) are key to successful weight loss. In countries with low resources, weight loss can be achieved through encouraging increased intake of vegetables and fruits and avoidance of high-calorie, low-nutrition foods, such as sugared sodas and high-fat goods, as well as encouraging increased physical activity, such as biking or walking for transportation.

### **Adult Weight Gain**

Adult weight gain has been associated consistently with an increased risk for postmenopausal breast cancer.<sup>13,14</sup> Findings from 2 of the largest cohort studies suggest that the doubling of risk that was associated with a gain in BMI from age 18 years or a weight gain  $>20$  kg was limited to women who had never used postmenopausal hormone replacement therapy. In those studies, a 20% increase in risk was observed for BMI gains between  $3.5 \text{ kg/m}^2$  and  $6.2 \text{ kg/m}^2$ <sup>13</sup> or weight gains between 2 kg and 20 kg,<sup>14</sup> although the confidence intervals around these gains were not statistically significant. Physicians or other healthcare workers should monitor patients' weights, and evidence of yearly gains of  $\geq 2$  pounds (1 kg) should trigger a discussion regarding methods of life-

time weight maintenance (eg, increased physical activity; eating a diet high in nonstarchy vegetables and fresh fruit, low in fat, and low in refined carbohydrates; and avoidance of high-calorie drinks, such as sodas sweetened with sugar or high fructose corn syrup). Although lifetime maintenance of optimal weight may be difficult in many cultures and areas of the world, the increasing prevalence of obesity throughout all economic levels around the world underscores the need for countries to address this public health problem.

### **Diet**

#### ***Vegetables and fruits***

Early epidemiologic studies suggested a role of increased intake of vegetables and fruits and decreased risk for breast cancer.<sup>15</sup> Nonetheless, a combined analysis of 8 cohort studies representing 351,825 women (including 7377 women who had breast cancer) reported no association between intake of vegetable and fruits and the risk of breast cancer.<sup>16</sup> However, a diet high in nonstarchy vegetables is key to weight loss and maintenance and should be encouraged for all individuals.

#### ***Soy, isoflavones, and lignans***

Epidemiologic data suggest that consumption of soy products is associated with a reduced risk of breast cancer.<sup>17</sup> Evidence suggests that 1 component of soy, genistein (a phytoestrogen), may promote the growth of some estrogen-sensitive tumors and reduce the efficacy of tamoxifen, which emphasizes the need for additional studies to determine whether soy is safe for women with breast cancer or who are at increased risk for breast cancer, and the different biologic effects at different life periods. Phytoestrogens can act as weak estrogens and as estrogen antagonists, depending on the hormonal milieu of the host. Thus, increased phytoestrogen intake can compete with endogenous estrogens in premenopausal women and reduce overall estrogen exposure to target tissue. Conversely, phytoestrogens can increase estrogen activities in women with low endogenous levels of estrogens (eg, postmenopausal women). These findings have been confirmed in animal experiments and in a small number of human experimental studies.<sup>15</sup>

#### ***Meat and dairy***

Some studies have pointed to increased intake of meats as a risk factor for breast cancer, but other studies have not supported that finding.<sup>15</sup> Part of the discrepancy in findings may be the different levels of carcinogens and mutagens found in meat (including

those that are the result of cooking practices) in different parts of the world. Intake of dairy foods has not been associated with risk for breast cancer. The fat content of dairy products may promote increased risk for breast cancer through increasing energy intake. Conversely, the high calcium and vitamin D content of many dairy products may be protective against breast cancer.<sup>15</sup>

#### ***Vitamins and minerals***

Several epidemiologic studies have investigated the association between dietary and supplement intake of various vitamins and minerals and the risk of breast cancer. Specific micronutrients that have been associated with decreased risk include carotenoids, folate, calcium, vitamin D, lycopene, and vitamin C.<sup>15</sup> The studies have produced mixed results, however and, because they have all been observational, are not conclusive. At this time, there is no evidence that taking any 1 supplement or combination of supplements will reduce breast cancer risk.

#### **Avoiding Excess Alcohol**

In several countries, alcohol use is highly prevalent. Several meta-analyses and major reviews of epidemiologic data confirm a moderate, but statistically significant association between moderate-to-heavy alcohol intake and the subsequent risk of developing breast cancer.<sup>18,19</sup> There is evidence of a dose-response relation, because as few as 1 to 2 drinks (14-28 g of alcohol) 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 10 g increase in daily alcohol consumed.<sup>19</sup> The association between alcohol intake and increased breast cancer risk has been observed regardless of the type of alcohol consumed and has been shown to increase risk for both premenopausal and postmenopausal breast cancer. Alcohol consumption may be particularly deleterious for individuals with suboptimal intake of some nutrients, such as folate, beta-carotene, lutein/zeaxanthin, and vitamin C. In many countries and in particular cultures, alcohol use is not allowed or available; thus, a focus on minimizing alcohol use may not be relevant in such parts of the world. However, clinicians and public health professionals should be aware of the link between alcohol use and breast cancer risk for those populations in which alcohol use may occur.

#### **Avoiding Long-term Exogenous Hormone Therapy**

The International Agency for Research on Cancer estimates that, worldwide, over 100 million women

(approximately 10%) of reproductive age currently use combined hormone contraceptives, and 300 million women have ever used these medications.<sup>20</sup> Taken as a whole, oral contraceptive use does not appear to increase the risk for breast cancer,<sup>21,22</sup> although some preparations may increase the risk for women who have a family history of breast cancer.<sup>23</sup>

Although the prevalence of menopausal hormone therapy use is lower in low- and middle-income countries, it is available in most countries and is being prescribed to an increasing number of women.<sup>20</sup> Yet, worldwide, the use of hormone therapy is associated with an increased risk of breast cancer, with an estimated 35% increased risk among women who used hormone therapy for  $\geq 5$  years compared with never users.<sup>24</sup> The United States Women's Health Initiative clinical trial, with over 27,000 postmenopausal women enrolled, demonstrated that women who were assigned randomly to receive conjugated equine estrogens 0.625 mg daily plus medroxyprogesterone acetate 2.5 mg daily had a statistically significant 24% increased risk of breast cancer after a mean 5.2 years follow-up compared with women who were assigned to receive placebo.<sup>25</sup> In contrast, unopposed conjugated equine estrogens 0.625 mg daily did not increase breast cancer risk.<sup>26</sup> In addition, menopausal hormone therapy increases mammographic density, potentially reducing screening efficacy, which is relevant to those countries that implement mammographic screening.<sup>27</sup>

#### **Conclusions**

Several strategies in the West have been associated with reducing breast cancer risk, although few of them have completed rigorous testing in clinical trials. Whether these strategies have general applicability to low-income countries remains to be studied adequately. Strategies to increase the prevalence and length of lactation may reduce the risk for breast cancer in mothers in addition to providing nutritional benefits for infants and small children. Increased adiposity, a sedentary lifestyle, and moderate to high levels of alcohol use are associated with increased risk of breast cancer. The evidence for a role for specific dietary components is less clear. For individual women, counseling ideally would include increasing physical activity and balancing energy such that weight remains stable over lifetime, and, preferably, with BMI remaining below 25 kg/m<sup>2</sup>. Provision of public transport and community-level and workplace facilities to enable these activities is to be encouraged. Counseling

should include limiting alcohol intake to no more than 1 drink per day on average. The use of combined estrogen/progesterone menopause hormone therapy should be limited to women with refractory menopausal symptoms and for as short a period of time as possible. Lower income countries should place a priority on the development of prevention strategies (within the context of their own environments).<sup>28</sup>

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