Priorities for the Primary Prevention of Breast Cancer

Graham A. Colditz, MD, DrPH1; Kari Bohlke, ScD2

Despite recent calls to intensify the search for new risk factors for breast cancer, acting on information that we already have could prevent thousands of cases each year. This article reviews breast cancer primary prevention strategies that are applicable to all women, discusses the underutilization of chemoprevention in high-risk women, highlights the additional advances that could be made by including young women in prevention efforts, and comments on how the molecular heterogeneity of breast cancer affects prevention research and strategies. CA Cancer J Clin 2014;64:186-194. © 2014 American Cancer Society

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Introduction

The Case for Prevention

With more than 234,000 new breast cancer diagnoses in the United States each year,1 efforts to improve treatment and early detection resonate strongly with clinicians and patients alike. Breast cancer prevention has received far less attention but holds tremendous promise.2 In a discussion of cancer genomics published in Science, Vogelstein et al note, “When we think of cardiovascular or infectious diseases, we first consider ways to prevent them rather than drugs to cure their most advanced forms.”3 A similar approach offers substantial hope for reducing the global burden of breast cancer. In 2012, nearly 1.7 million new cases of breast cancer were diagnosed worldwide, accounting for 25% of all new cancer cases in women.4

Breast cancer incidence rates differ by more than a factor of 13 when comparing the lowest risk and highest risk countries.5 Although some of this variability may be because of differences among countries in screening and reporting, international variability in breast cancer incidence and documented changes in incidence among populations that migrate from low-risk to high-risk countries provide powerful evidence supporting the potential for reducing the burden of breast cancer in our society.6 Migrant studies of Asian women moving to Hawaii and California, for example, convincingly showed that risk increases among the daughters of the women who migrated.7 And, in traditionally low-incidence countries in Asia, breast cancer incidence has increased steadily over time as reproductive and lifestyle patterns have changed.8,9 For example, in Korea, age at menarche has decreased from 16.9 years, on average, among women born in between 1920 and 1924 to 13.8 years among women born between 1980 and 1985.10 Fertility has decreased over the past 50 years from an average of 6 births to 1.23 births per woman in 2010.11 Age-specific breast cancer incidence has increased 3-fold to 140 cases per 100,000 women ages 45 to 49 years.9 Reverting to previous levels of these reproductive factors is neither possible nor desirable, but the potential for breast cancer prevention remains high. Furthermore, the prevalence of modifiable risk factors such as postmenopausal obesity, for example, has increased markedly in many countries around the world, including the United States.12

Established modifiable causes of breast cancer include radiation exposure,13 alcoholic beverage consumption,14 postmenopausal obesity,15 lack of physical activity,15 and postmenopausal hormone therapy with estrogen plus progestins16 (Table 1). For both premenopausal and postmenopausal women who are at high risk of breast cancer as a result of family history or other characteristics (such as a history of atypical hyperplasia of the breast29), the use of selective estrogen receptor modulators (SERMS) greatly reduces the risk of both invasive breast cancer and noninvasive lesions.30,34 Aromatase inhibitors also reduce risk among high-risk women,32 although they are not US Food and Drug Administration (FDA)-approved

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1Niess-Gain Professor of Surgery, Alvin J. Siteman Cancer Center and Department of Surgery, Washington University School of Medicine and Barnes-Jewish Hospital, St. Louis, MO; 2Consulting Epidemiologist, Alvin J. Siteman Cancer Center and Department of Surgery, Washington University School of Medicine and Barnes-Jewish Hospital, St. Louis, MO.

Corresponding author: Graham A Colditz, MD, DrPH, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, Campus Box 8109, 660 S. Euclid Avenue, St. Louis, MO 63110; colditzg@wudosis.wustl.edu

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for prevention. Randomized trials of tamoxifen and raloxifene show a roughly 50% reduction in the incidence of invasive breast cancer and an even greater reduction in hormone receptor-positive breast cancer.30,31 Furthermore, protection persists for several years after treatment cessation.33,34

Breast cancer incidence models and age incidence plots show that risk accumulates rapidly from menarche to first birth.35 The rate of increase then slows after each additional birth, and early menopause reduces subsequent breast cancer risk. Childhood and early adult exposures play an important role in driving breast cancer risk. Risk accumulation through premenopausal years and the burden of disease diagnosed among women aged <50 years both point to the importance of timing for prevention.

Overall, we estimate that more than half of all breast cancers could be prevented through healthy behaviors and chemoprevention (see Table 1 and Fig. 1, in which potential benefits of primary prevention are presented by age range at intervention). This is a substantial reduction in the annual burden of breast cancer by applying lessons learned from

### Table 1. Preventing Breast Cancer: What We Know Works Now

| Health Messages | Risk Group | Approximate Percentage of US Female Population Aged <50 Years Affected, % | Possible Reduction in Risk, % | Time Until Benefit, y | References for Magnitude of Risk Reduction |
|-----------------|------------|--------------------------------------------------------------------------|-------------------------------|-----------------------|--------------------------------------------|
| **Premenopausal women** | | | | | |
| Alcohol intake: None | Youth (ages 12-17 y), drinking at least one drink in past 30 d | 13 | 20-30 | 10-20 | Liu 2012, 201317,18 |
| Alcohol intake: ≤1 serving/d | Young adults (ages 18-24 y) drinking ≥4 drinks/wk | 15 | 20-30 | 10-20 | Liu 201318 |
| | Adults (aged ≥18 y) drinking ≥4 drinks/wk | 13 | 35 | 10-20 | Chen 2011,19 Smith-Warner 199820 |
| Healthy weight: Avoid weight gain | All women | 100 | 50 (after menopause) | 10-30 | Eliassen 200621 |
| Physical activity: ≥30 min/d | Women not meeting physical activity guidelines | 54 | 20 | 10-30 | Bernstein 200522 |
| Healthy diet: Fruits, vegetables, and whole grains | Youth eating very few fruits and vegetables | 5-11 | 20-50 | 5-20 | Korde 2009,23 Jung 201324 |
| Breastfeed: One y total across all children | Women who have given birth | 81 | 18 | 5 | Collaborative Group on Hormonal Factors in Breast Cancer 200225 |
| Prophylactic bilateral oophorectomy | BRCA1 and 2 carriers | <1 | 50 | ≥2 | Rebeck 200926 |
| Tamoxifen | High-risk women aged ≥35 y (greater than or equal to the risk for average woman aged 60 y) | 3 | 50 | 2 | Fisher 199827 |
| **Postmenopausal women** | | | | | |
| Alcohol intake: Serving/d | Adults drinking ≥4 drinks/wk | 13 | 35 | 5-10 | Smith-Warner 199820 |
| Healthy weight: Weight loss | Overweight and obese (eg 5’4” and >145 lbs) | 64 | 50 | 2-5 | Eliassen 200621 |
| Physical activity: ≥30 min/d | Women not meeting physical activity guidelines | 54 | 20 | 10-20 | Bernstein 200522 |
| Estrogen-plus-progestin postmenopausal hormones: Avoid | Current users | 1.7 | 10 | 1 | International Agency for Research on Cancer 200816 |
| | Long-term current users | 1 | 50 | 2 | International Agency for Research on Cancer 200816 |
| Tamoxifen and raloxifeneb | High-risk women (greater than or equal to the risk for an average woman aged 60 y) | 30 | 50 | 2 | Visvanathan 201328 |

*Estimates are from nationally representative samples of US women. Exemestane is not listed for prevention, because the US Food and Drug Administration has not approved this agent for primary breast cancer risk reduction.52
existing research. Breast cancer risk factors such as obesity and physical inactivity will never be eliminated completely; but, even if we fall well short of 50% of cases prevented, we could still prevent thousands of cases of breast cancer each year.

Priorities for Prevention

Of the primary prevention strategies that have been identified thus far, we focus on those that are applicable to all women (maintenance of a healthy body weight, regular physical activity, and moderation of alcohol intake), as well as chemoprevention—a strategy that has a large effect in high-risk women and is currently underused. We also discuss the additional benefit that could be obtained by expanding prevention efforts to include young women, noting that some 22% of cases in the US are diagnosed before age 50 years.36

Promote Regular Physical Activity and a Healthy Body Weight Throughout Life

Regular physical activity and maintenance of a healthy body weight are key components of cancer prevention efforts.37 More than two-thirds of US adults are

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**FIGURE 1. Breast Cancer Risk Reduction Achievable by Life Stage.** Risk is illustrated (a) starting in midlife (with 22% missed because it is diagnosed before age 50 years) and (b) starting in early life. In figure a (midlife), the factors that are illustrated for nulliparous women (body weight, physical activity, and alcohol intake) also affect the risk in parous women.
overweight (body mass index [BMI], 25.0–29.9 kg/m²) or obese (BMI, ≥30.0 kg/m²), and more than half do not engage in recommended levels of aerobic physical activity. In addition to breast cancer, cancers that are associated with excess body weight and insufficient physical activity include cancers of the esophagus (adenocarcinoma), colon and rectum, pancreas, kidney, and endometrium.

In the case of breast cancer, the effect of excess weight varies by age. Body fatness at young ages reduces the risk of breast cancer. After menopause, adipose conversion of androgens to estrogens contributes to circulating estrogen levels, such that excess body fat increases risk. In a 2008 meta-analysis by Renihan et al, each 5-kg/m² increase in BMI increased the risk of postmenopausal breast cancer by 12%. In the Nurses’ Health Study, for example, weight gain from age 18 years showed a strong and significant trend toward increasing risk of postmenopausal breast cancer directly related to the amount of weight gained. A strong association of sustained postmenopausal weight loss on breast cancer risk was also reported in the Nurses’ Health Study. Among postmenopausal women who had never used postmenopausal hormones, those who lost 10 kg or more and kept it off had a greater than 50% reduction in breast cancer risk compared with women who had steady weight after menopause. Consistent with these findings, a small pilot study of overweight or obese postmenopausal women suggests that weight loss produces favorable changes in breast tissue and serum risk markers. An important message for midlife women, therefore, is that it is not too late to reduce their risk of breast cancer through behavior change. Avoiding weight gain through adult years is a top prevention priority.

Regular physical activity reduces the risk of premenopausal and postmenopausal breast cancer, and elimination of physical inactivity could prevent an estimated 10% of breast cancers worldwide. Vigorous physical activity provides the greatest reduction in breast cancer risk, but even moderate activity such as brisk walking provides a benefit. In the American Cancer Society Cancer Prevention Study II Nutrition Cohort, for example, women who walked at least 7 hours per week had a 14% reduction in the risk of postmenopausal breast cancer relative to women who walked ≤3 hours per week. The most active women had a 25% reduction in risk relative to the least active women. In the Nurses’ Health Study, postmenopausal women who did the equivalent of roughly an hour per day of walking had a 15% reduction in breast cancer risk relative to women who had the lowest levels of physical activity. Physical activity at each stage of life from adolescence onward provides a benefit, but sustained activity throughout life may provide the greatest benefit. In the Nurses’ Health Study II, for example, a reduced risk of premenopausal breast cancer was most apparent among women who engaged in high levels of activity during both youth (ages 12-22 years) and adulthood, consistent with earlier studies.

Consume Alcoholic Beverages in Moderation (at Most)

Alcoholic beverage consumption causes cancers of the female breast, oral cavity, pharynx, larynx, esophagus, liver, and colon and rectum. In the case of breast cancer, each 10-g-per-day increase in alcohol intake results in a 7% to 10% increase in the risk of breast cancer (a typical US drink contains roughly 14 g of alcohol). Even low levels of alcohol intake modestly increase risk; in the Nurses’ Health Study, women who consumed an average of three to six drinks per week were 15% more likely than women who never drank to be diagnosed with breast cancer. Women with the highest level of alcohol intake (at least two drinks per day) were 51% more likely than nondrinkers to be diagnosed with breast cancer.

Timing matters for alcohol intake, too. Prospective data from the Nurses’ Health Study II show that alcohol intake during adolescence increases the risk of proliferative benign breast lesions, which are markers of risk for breast cancer. Intake from menarche to first birth is directly related to increased risk of both proliferative benign lesions and invasive breast cancer among premenopausal women.

Complete avoidance of alcohol intake for the purposes of breast cancer prevention is not an option that all women will choose. Furthermore, the risks of alcohol must be balanced against the potential benefits of moderate alcohol intake on cardiovascular health. However, because many alternative prevention strategies are available for cardiovascular disease, women who are concerned about their breast cancer risk should limit consumption of alcoholic beverages as a reasonable strategy to reduce risk.

When these lifestyle guidelines are evaluated in the context of reported behaviors among postmenopausal women who are followed for up to 12 years, significant benefits are observed. Women who had the closest adherence to the American Cancer Society guidelines for weight, diet, alcohol consumption, and physical activity had a significantly 22% lower risk of breast cancer during follow-up compared with women who had the lowest adherence. Although starting earlier in life can give added prevention, as shown in Figure 1, these recent US data support a reduction in the risk of breast cancer through lifestyle changes.

Consider Chemoprevention

In 2013, both the United States Preventive Services Task Force (USPSTF) and the American Society of Clinical Oncology (ASCO) issued new guidelines regarding breast cancer chemoprevention. For asymptomatic women aged ≥35 years without a prior diagnosis of invasive or in situ
breast cancer, the USPSTF issued a Grade B recommendation that “clinicians engage in shared, informed decision making with women who are at increased risk for breast cancer about medications to reduce their risk. For women who are at increased risk for breast cancer and at low risk for adverse medication effects, clinicians should offer to prescribe risk-reducing medications, such as tamoxifen or raloxifene.” A Grade B recommendation indicates that “the USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.”

For women who are not at increased risk of breast cancer, the USPSTF recommended against routine chemoprevention (Grade D recommendation). In its 2013 clinical practice guidelines on pharmacologic interventions for breast cancer risk reduction, ASCO strengthened the wording of its 2009 guideline from “may be offered” to “should be discussed as an option” for women aged ≥35 years who are at increased risk of breast cancer. The ASCO clinical practice guideline also recommended a discussion of exemestane (an aromatase inhibitor) with postmenopausal women who are at increased risk of breast cancer, or who have a history of atypical hyperplasia or lobular carcinoma in situ on breast biopsy. The guideline notes that the FDA has not approved this drug for primary prevention.

The balance of risks and benefits for chemoprevention depends on several factors, including a woman’s age, race, and risk of breast cancer; whether she has a uterus; and type of medication (tamoxifen or raloxifene). Tamoxifen increases the risk of endometrial cancer, stroke, pulmonary embolism, deep vein thrombosis, and cataracts but decreases the risk of bone fractures. Compared with tamoxifen, raloxifene (which is only approved for postmenopausal women) has a lower risk of endometrial cancer, cataracts, and thromboembolic events. In white women aged <50 years, the benefits of tamoxifen are likely to outweigh the risks when the 5-year risk of breast cancer is at least 1.5%. Younger black women at high risk of breast cancer also benefit from tamoxifen, although black women in their 40s may need a higher level of breast cancer risk to derive a net benefit. In women aged ≥50 years, the benefit/risk ratio tends to be better for raloxifene than for tamoxifen among women with a uterus, and it is similar for both drugs among women without a uterus. The level of breast cancer risk that is required to derive a net benefit increases with age and also tends to be higher for black women than for white women.

Estimates vary regarding the number of women who would derive a net benefit from chemoprevention. Considering tamoxifen alone, Freedman et al weighted several potential outcomes and estimated that more than 2 million US women between ages 35 and 79 years would derive a net benefit from chemoprevention. In the case of raloxifene, Chen et al weighed the number of breast cancers prevented against the number of thromboembolic events caused and estimated that 7.8 million women between ages 50 and 69 years would derive a net benefit from chemoprevention, preventing over 20,000 new cases each year. Both of these estimates contrast sharply with the number of women who are currently receiving chemoprevention. In an analysis of 2010 National Health Interview Survey data, Waters et al estimated that 20,598 US women between ages 35 and 79 years were using tamoxifen for primary prevention of breast cancer, and 96,890 women between ages 50 and 79 years were using raloxifene for primary prevention of breast cancer. The reasons for this underutilization are complex and involve both clinician and patient factors. At the patient level, awareness alone is not sufficient to increase acceptance; in fact, women who know the most about the risks and benefits of chemoprevention may be the least likely to accept treatment. The possibility of a negative side effect may be sufficient to deter women from using proven preventive strategies, even when the benefits are likely to outweigh the risks. Research into communication strategies that address this side effect aversion could increase the use of chemoprevention in high-risk women; these strategies, of course, must respect a woman’s autonomy, values, and preferences.

At the provider level, primary care providers are frequently limited by a lack of time and insufficient information about chemoprevention options. Because provider recommendations play an important role in women’s decisions, addressing these barriers will be necessary to increase appropriate use of chemoprevention. Easy-to-use breast cancer risk assessment tools, coupled with benefit/risk indices, provide important starting points.

**Start at a Young Age**

Although the benefits of breast cancer prevention in adult women are notable, expanding prevention efforts to include young women would further decrease breast cancer incidence. In the United States, greater than 20% of breast cancers are diagnosed before age 50 years, and greater than 4% are diagnosed before age 40 years. The incidence of breast cancer increases sharply during the third decade of life, and prevention of early cases must begin before this period—during or before adolescence. Ongoing research addressing early life, childhood, and adolescent exposures points to the importance of this period when the breast has not yet passed through terminal differentiation of cells. Based on incidence rates for breast cancer and increasing risk with age, together with evidence from atomic bomb survivors, Colditz and Frazier argued in 1995 that childhood and adolescent exposures should have a large impact on adult breast cancer risk. The Institute of Medicine report on breast cancer and the environment calls for...
priority research to include childhood and the critical window from menarche to first pregnancy to better guide future primary prevention strategies.  

The importance of the preadult period on later risk of breast cancer is illustrated by factors such as peak height growth velocity and age at menarche. Higher peak height growth velocity and early age at menarche each increase the risk of premenopausal and postmenopausal breast cancer. Behavioral factors such as adolescent physical activity, diet, and alcohol intake also are important. Women who are active during both youth and adulthood may have a lower risk of premenopausal and postmenopausal breast cancer than women who are inactive or active during only one of these phases of life. In a 2011 review by Lynch et al, the average reduction in breast cancer risk associated with physical activity at different ages was 16% for adolescence, 8% for early adulthood, 15% for middle adulthood, and 17% for women aged ≥50 years. As noted above, adolescent alcohol is directly related to risk of premalignant and invasive breast cancer in prospective cohort studies. The contribution to breast cancer risk of childhood and adolescent dietary exposures remains somewhat less certain. In a study of Asian migrants to Hawaii and the US mainland, mothers recalled their children’s diets for differing age periods. Strong protection against breast cancer was observed for higher soy intake in childhood, and protection was weaker from soy intake in adolescence and adult years. Prospective cohort data from China confirm this finding, and prospective data from US cohorts show that higher vegetable protein and fiber intake are inversely related to the risk of benign breast lesions.  

In addition to reducing the risk of early cancers, prevention efforts that begin in early life may also provide important benefits much later in life by shifting the long-term trajectory of risk accumulation. This means that, among women who engage in similar healthy behaviors at midlife, subsequent breast cancer risk will be lower among women who also engaged in healthy behaviors earlier in life. Additional high-quality studies would refine our understanding of how to maximize breast health in girls and young women.

How Will Ongoing Research Into the Biology of Breast Cancer Affect Prevention?  
As research has now clearly demonstrated, breast cancer is not a single disease. Several molecularly defined subtypes of breast cancer have been identified, and these subtypes differ greatly in their prognosis. The effects of some breast cancer risk factors also vary by breast cancer subtype, and a comprehensive prevention strategy will ideally include prevention of all of these subtypes. If studies of modifiable risk factors do not take breast cancer subtype into account, then potentially important effects may be missed or underestimated. For example, breastfeeding appears to provide an especially large reduction in the risk of breast cancer that is triple-negative (estrogen receptor [ER]-negative, progesterone receptor [PR]-negative, and human epidermal growth factor 2 [HER2]-negative) or basal-like (triple-negative cancers that are positive for epidermal growth factor receptor [EGFR] and/or cytokertatin 5/6 [CK5/6]). Triple-negative breast cancers account for only 10% to 20% of all breast cancer diagnoses but are an important target for prevention, because they currently have fewer treatment options than other types of breast cancer. In the prospective Nurses’ Health Study, breastfeeding for 4 months or longer reduced the risk of basal-like breast cancer by 40% (relative risk, 0.6; 95% confidence interval, 0.4-0.9) compared with never breastfeeding. Associations between breastfeeding and other types of breast cancer were weaker, although the test for heterogeneity by tumor subtype was not statistically significant. An inverse association between breastfeeding and triple-negative breast cancer (and a lack of association with luminal A or ER-positive breast cancer) was also observed in the Carolina Breast Cancer Study and in a case-control study among young women (ages 20-44) in Washington State. In the Women’s Circle of Health Study (a case-control study among African American women), the effect of breastfeeding on the risk of breast cancer was not statistically significant, but breastfeeding did appear to mitigate an adverse effect of parity on the risk of triple-negative breast cancer.

A second important example is the emerging evidence from combined analysis of 20 prospective cohort studies of diet and breast cancer that included follow up of 11 to 20 years and 34,526 incident invasive breast cancers. Total fruit and vegetable intake was significantly inversely associated with ER-negative breast cancer, although not with total breast cancer (ER-negative cases represented 18.8% of patients for whom receptor status was known). The inverse association was clearest for vegetable consumption, where the results were significantly inverse for higher intake and reduced risk for ER-negative/PR-negative and ER-negative/PR-positive tumors. This inverse relation is supported by pooled analysis of circulating blood carotenoid levels from eight cohorts that demonstrated a reduced risk of breast cancer with the suggestion of stronger results for a reduced risk of ER-negative tumors. Both the broader view and the subtype-specific view are important when considering the impact of a prevention strategy. How a strategy will affect the likelihood of any breast cancer captures the effect on the overall burden of breast cancer and is also the measure that will be most salient to many women (as opposed to prevention of only a
single subtype). Information about variability in effect by subtype, however, can highlight a benefit that would otherwise be overlooked and may help to guide prevention efforts. African American women, for example, have high rates of triple-negative breast cancer and relatively low rates of breastfeeding.\textsuperscript{80} Breastfeeding, therefore, may prove to be a particularly important prevention strategy for African American women,\textsuperscript{80,83} as would increasing fruit and vegetable consumption to meet nutrition guidelines of eating 2.5 cups of vegetables and fruits each day.\textsuperscript{46}

A separate but related issue is the problem of overdiagnosis, which refers to the identification of tumors that will not affect a woman’s health during her lifetime.\textsuperscript{87} Some of the breast cancers detected by routine screening mammography are likely to be indolent and clinically unimportant, but it is not currently possible to distinguish these cancers from those that would be lethal if untreated. Learning how to identify the subset of breast cancers that requires treatment is an important research priority, and when this becomes possible it will be necessary to assess the effect of prevention strategies on these cancers. Until that time, prevention strategies that reduce the incidence of any type of breast cancer are important.

**Discussing Behavior Change With Patients**

Problems such as obesity and physical inactivity are daunting, but recent examples of community-wide shifts toward healthier lifestyles demonstrate that behavior change is possible. In Australia, long-term sun protection programs have changed tanning norms and behaviors.\textsuperscript{88} In New Zealand, a primary care provider-based randomized trial of counseling showed significant increases in minutes walked and the proportion of patients attaining the goal of 2.5 hours per week of leisure exercise.\textsuperscript{89} In the United States, adolescent alcohol intake has increased,\textsuperscript{90} smoking has decreased, condom use at most recent intercourse by sexually active females ages 15 to 19 years has increased from 39% in 1995 to 51% in 2006 to 2010, and high school physical activity for at least 60 minutes per day on 5 of 7 days was reported by 50% in 2011\textsuperscript{91} compared with only 36% in 2005.\textsuperscript{92}

Adolescent behaviors can change in a relatively short time frame. The principles of clinical practice guidelines outline five major steps to intervention (the “5 As”: Ask, Advise, Assess, Assist, Arrange.\textsuperscript{93} Ask about the behaviors of interest; advise, using a clear, strong, and personalized message; assess the patient’s willingness to change their behavior; assist the behavior change via counseling or other approaches; and arrange follow-up. Health care providers are an essential source of prevention messages and are fundamental to a social strategy\textsuperscript{94} to promote systematic integration of evidence-based messages and behavioral strategies into women’s everyday lives. In addition to health care providers, regulatory changes, including taxation on alcohol, and action by community leaders, policy makers, schools, families, and by individuals are needed to implement and sustain prevention strategies that will reduce the burden of breast cancer.

**Conclusions**

True progress against breast cancer—progress that is measured not only by months of survival but also by the frequency of cancer-free lifetimes—requires that prevention become a much greater priority. We each have a role to play, whether as clinicians, researchers, funders, community planners, educators, parents, or individuals. New cancer treatments are rightfully cheered at medical meetings and in the press, but the cure of advanced breast cancer continues to be an elusive goal. Furthermore, access to expensive tests and treatments may be limited in low-income and middle-income countries that are experiencing increasing rates of breast cancer. As Vogelstein et al point out, “Plan A” must involve prevention and early detection, with “Plan B” (treatment of advanced cancer) being necessary only when Plan A fails.\textsuperscript{3}

Prevention is possible. It is true that we do not yet have all the answers, but that should not stop us from acting on what we do know. Prevention strategies such as weight control may be more difficult to adhere to than screening strategies such as mammography, but the added benefit is substantial and extends well beyond breast cancer.

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