Simplifying the Energy Balance Message for Breast Cancer Prevention

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Abstract

Simple prevention messages based on understandable biologic principles are likely to be adopted. The long-held premise that postmenopausal obesity elevates, but premenopausal obesity reduces, risk for breast cancer is confusing to the public. Furthermore, decades of positive energy balance may be difficult to suddenly reverse at the time of the menopause. In this issue (beginning on page 583), Cecchini et al. suggest that obesity may also be a risk factor for pre-menopausal women 35 and older who have additional risk factors for breast cancer. Although the relative impact of dysregulated energy metabolism depends on many factors including age, hormonal milieu, and competing risk factors, as well as how it is measured, avoiding weight gain after age 30 is increasingly being recognized as a simple way to reduce risk of breast cancer.

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In this issue of the journal, Cecchini and colleagues report that overweight and obese premenopausal women 35 and older from the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trial had a greater chance of developing breast cancer than did their more slender counterparts (1). However, overweight and obese postmenopausal women who were in P-1 or the NSABP Study of Tamoxifen and Raloxifene (STAR) were reported as not having a significantly increased risk of breast cancer. These results fly in the face of everything we thought we knew. How can they be explained?

Eight-seven percent of the group of postmenopausal women enrolled in P-1 or STAR were randomized to receive the selective estrogen receptor modulator (SERM) tamoxifen or raloxifene, and for these women, no increase in breast cancer risk was observed with increasing category of body mass index (BMI). This finding is not surprising, as the moderately elevated estrogen levels often observed in overweight or obese postmenopausal women could be expected to be easily overcome by SERMs, and the majority of obesity-related tumors in postmenopausal women are hormone receptor positive (2). Furthermore, both tamoxifen and raloxifene reduce the insulin-like growth factor 1 (IGF-1):IGF-binding protein 3 (IGFBP3) molar ratio and increase sex hormone-binding globulin, favorably modulating these additional risk biomarkers for breast cancer (3–5). Thus, it seems logical that the excess risk normally associated with postmenopausal obesity should be largely abrogated by SERM treatment in the NSABP trials.

But what about the lack of significant effect of BMI on risk for breast cancer in postmenopausal women in P-1 randomized to placebo? Although the P value for trend with increasing BMI was nonsignificant for the entire group of postmenopausal women, overweight women with a BMI of 25 to 30 kg/m² exhibited hazard ratio (HR) of 1.77 with a 95% confidence interval (CI) of 1.05 to 2.97, consistent with an effect for this subgroup. Lack of significance for increasing BMI for the postmenopausal placebo group as a whole could potentially be explained by the relatively small numbers per subgroup and prior use of hormone replacement therapy (HRT) by approximately 50% of postmenopausal women in P-1 and STAR. Current and prior HRT use have been reported to attenuate the excess risk normally observed in postmenopausal obese women; current use perhaps more so than past use (6–8). It is not clear why hormone replacement in postmenopausal women reduces the impact of obesity on risk of breast cancer. One potential explanation is that the risk of exogenous hormones is offset by estrogen’s favorable effects on adiponectin, proinflammatory cytokines, and insulin resistance in obese women (9, 10).

BMI was positively associated with risk in premenopausal women, who were all age 35 and older. Although the authors indicated no significant interaction between BMI and treatment, HRs for premenopausal obese women randomized to tamoxifen were elevated at 2.33 (95% CI, 1.10–4.90) compared with women with a normal BMI; and P for trend overall was significant at 0.02. Thus, the risk of breast cancer appeared higher for obese compared with normal weight women randomized to tamoxifen. The HR for obese premenopausal women randomized to placebo was elevated at 1.41, but the 95% CI
included one. Why would tamoxifen be less effective in obese premenopausal women than in their normal weight counterparts? Tamoxifen reduces insulin sensitivity and increases estradiol by 3- to 10-fold in premenopausal women (11–13), which may offset the favorable small decreases in IGF-1 (3, 14). It is conceivable that tamoxifen- and obesity-induced hyperinsulinemia, added to the substantial tamoxifen-induced elevations in estrogen levels, could explain a reduced effectiveness.

Thus, the obesity–breast cancer findings from the 2 NSABP prevention trials reported by Cecchini and colleagues likely are not at odds with what has been reported in the literature, but rather are the result of the complex interplay of energy balance, endogenous hormones and growth factors, prior exogenous hormones, current SERM use, and competing major risk factors.

Large cohort studies have suggested that adult weight gain and postmenopausal obesity as measured by BMI increase the risk of postmenopausal breast cancer in women not using HRT (6, 8, 15–19). This appears to be the case both for average-to-moderate risk and for very high–risk populations (20). Adult weight gain after age 18, particularly after age 30, may be a more important predictor than is BMI for postmenopausal breast cancer (8, 21). A weight gain of 10 kg has been reported to be associated with a 30% increase, a 20 to 30 kg gain with a doubling, and a 50-kg gain with a 3-fold increase in the risk for breast cancer in postmenopausal women who do not use HRT (15–17). Other studies report that the pattern of fat deposition may be more predictive for breast cancer risk than is BMI or weight gain alone (22–24).

The observation that obesity as measured by BMI does not universally correlate with postmenopausal breast cancer (25) suggests that BMI and adult weight gain are surrogate markers for the impact of a dysregulated energy metabolism on breast epithelium. In postmenopausal women, the likely molecular effectors of risk from obesity and accompanying dysregulated energy metabolism include elevated levels of free estrogen resulting from increased levels of proinflammatory cytokines and enhanced aromatase activity and/or from lowered sex hormone-binding globulin resulting from insulin resistance (26, 27).

Conversely, obesity in otherwise average-risk premenopausal women has been previously reported to decrease the risk of premenopausal breast cancer by 40% to 70%, with obesity at age 18 being strongly protective (28). Anovulatory cycles in young obese premenopausal women, with reductions in mid-cycle progesterone and free estradiol, have been offered as explanations for this phenomenon (29–31). The observation that the protective effect of obesity on breast cancer risk is limited to women who were obese before age 35 (32) supports this hypothesis.

Hormonal alterations are likely only part of the complex formula of how energy balance relates to breast cancer risk (33). Obesity at a very young age may be protective in part due to lower systemic levels of IGF-1 in later adulthood (34). Hyperglycemia and insulin resistance are likely factors for obesity-related elevated risk (35–39). It is increasingly recognized that the proinflammatory state and insulin resistance often associated with obesity may result in nonhormonal direct paracrine effects on breast epithelium through the activation of pathways important in breast cancer promotion and progression such as NF-kB, phosphoinositide 3-kinase (PI3K), and Akt/mTOR (26, 40–44). The ability to produce and/or secrete the protective adipokine adiponectin and the amount of adiponectin relative to leptin (45–48) are likely to modulate the effects of positive energy balance on these pathways. Systemic levels of adiponectin, which are lowered in insulin resistance and obesity, are inversely related to risk of breast cancer and breast cancer progression (49–52). However, obese women with high levels of adiponectin seem to be protected both from several metabolic consequences of obesity (53) and from breast cancer (54, 55).

Although there is clear evidence that adult weight gain increases risk, the evidence is less clear that, once obese, weight loss abrogates that risk. Available studies suggest that reduction in risk is likely only if women achieve at least a 5% to 10% weight loss maintained over several years (56). A 10% or greater loss is also needed to increase adiponectin and improve other inflammatory markers in obese women (57). Unfortunately, only 20% of women are able to achieve such a loss and maintain it for 2 or more years (21, 58).

Endocrine therapies, including tamoxifen, raloxifene, and aromatase inhibitors, have been shown in randomized trials to reduce risk of breast cancer by 40% to 60% (59). Survival is not improved when any of these agents is given as primary prevention to a general high-risk cohort irrespective of weight (59, 60). Uptake of endocrine therapies for primary prevention is low (61, 62).

Women at increased risk for breast cancer because of family history or a precancerous biopsy are often eager for nonprescription, nonendocrine interventions to reduce their risk. A growing body of evidence, including data from the NSABP trials, suggests that adult weight gain and obesity, particularly after the ages of 30 to 35 years old, are risk factors for breast cancer regardless of menopause status. This conclusion simplifies the message about energy balance and breast cancer risk. Avoidance of adult weight gain through diet and exercise should be a standard component of breast cancer risk counseling (63).

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