Soy and Mammographic Breast Density: Plausible Hypothesis but Limited Evidence in Humans

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The hypothesis that consumption of soy-containing foods may lower breast cancer risk comes from the observation that breast cancer incidence rates are substantially lower in Asian countries where soy consumption is high, compared with Western countries where soy consumption is low (1,2). The biological premise to support these observations is that soy foods are rich sources of isoflavones. These plant compounds are structurally similar to mammalian estrogens, which enable them to bind, albeit weakly, to estrogen receptors-α and -β (3). Frequent consumption of isoflavones may competitively inhibit 17β-estradiol at the estrogen receptor binding sites, thereby decreasing the availability of 17β-estradiol and its metabolites in hormone-sensitive tissues (3). In addition to their potential role as estrogen receptor modulators, in vitro and animal model studies suggest that isoflavones may down-regulate the synthesis of aromatase (CYP19) and other enzymes in the estrogen and testosterone biosynthetic pathways, inhibit tyrosine kinase, promote apoptosis, and modulate cell cycle progression (4,5). It is in these contexts that soy foods and isoflavones are of particular interest in relation to the prevention of hormone-dependent cancers, such as breast cancer.

Despite the strong biological rationale to support a protective effect for soy in relation to breast cancer, data from human observational studies are inconclusive. For example, in a cohort study of postmenopausal women in Japan and a case-control study in Germany, women in the highest quartile of isoflavone consumption had a 54% reduced risk of breast cancer compared with those in the lowest quartile of consumption (6,7). However, other recent case-control and cohort studies reported no association of soy or isoflavone consumption with breast cancer risk (8,9). In addition to the inconsistencies in human observational studies, some laboratory evidence suggests that the isoflavones genistein and daidzein increase cell proliferation and promote the growth of estrogen-dependent mammary tumors in animal models (10,11), results that are contradictory to the evidence noted above. These conflicting data leave nutrition scientists, physicians, and consumers confused about whether soy foods and their constituents are beneficial, harmful, or have no effect in relation to breast health.

This issue of The Journal of Nutrition contains results from a dietary intervention study, one that addresses these important issues (12). Maskarinec and colleagues investigated whether a 2-y randomized trial of supplementing the diet with 2 servings of soy foods/d vs. the usual diet would decrease mammographic density among 220 healthy premenopausal women (12). The strengths of the study included the randomized intervention design, and frequent individual and group instruction in the intervention group, a strategy that allowed participants to self-select soy foods in quantities typically observed in countries in which soy intake is high, the collection of objective nutritional biomarkers (urinary isoflavones) to assess adherence to the study protocol, use of a validated questionnaire to collect data on lifetime soy exposure, and an outcome (mammographic density) that is both responsive to dietary manipulation (13,14) and is a risk factor for breast cancer (15). Because randomized trials are considered to be the gold standard for investigating diet-disease hypotheses, this study by Maskarinec et al. (12) has the potential to provide definitive information about the association of soy intake with breast mammographic density.

Women randomized to the intervention group consumed a mean of 58 mg isoflavones/d, approximating the average daily intake of isoflavones among women in Asian countries (16,17). Women randomized to the control group consumed ~5 mg isoflavones/d. Compliance with the intervention protocol was excellent as evidenced by both self-reported dietary intake from unannounced 24-h dietary recalls and urinary isoflavone concentrations, which are reliable biomarkers of isoflavone intake (17,18). Mammograms were obtained at baseline and follow-up; computer-assisted density assessment was used for all measures.

At the end of the 2-y intervention period, there were no significant differences in any mammographic characteristics that could be attributed to the dietary intervention. However, there were modest changes in total area, dense area, and the percentage density in both the intervention and control groups. These time-related changes tended to be slightly stronger in the control group. Self-reported data on soy intake during 3 life periods were used to conduct subgroup analyses. In general, breast density was greater among women with at least some soy consumption at all phases of life compared with women with no or minimal soy intake, but the results were significant only among Caucasian women. Caucasian women who consumed ≥36 servings of soy/y during adulthood or ≥27 servings of soy/y throughout their lives had breasts that were of 28 and 23% greater density, respectively, compared with women who consumed less soy during those time periods.

What do the findings by Maskarinec et al. tell us about the...
association of soy intake with mammographic density, a strong risk factor for breast cancer? It might be tempting to draw the conclusion that soy consumption throughout the life cycle had a greater influence on mammographic density than a short-term (2-y) focused exposure to soy during middle age. Two case-control studies reported that soy intake during specific periods of life was associated with a reduced risk of breast cancer (19,20), which is consistent with the data in the Maskarinec report (although the magnitude and directions of association differ across the studies). However, this interpretation would assume that the weight of observational data supersedes that of experimental data, a view not shared by most nutritional epidemiologists. Self-reported dietary intake information used in observational studies does provide important information for generating diet-disease hypotheses, but such information is constrained by measurement error, and the analyses can be limited by residual confounding (21). Further, although it is becoming increasingly apparent that exposures (including diet) early in life affect chronic disease risk, we do not yet have the tools for the appropriate measurement of self-reported dietary intake in the remote past. Future studies that collect and archive biological specimens throughout the life cycle may help address questions of this nature.

The ultimate test of whether diet is associated with disease end points or intermediate outcomes, such as mammographic density, is the randomized trial. The report by Maskarinec et al., a randomized trial with sufficient follow-up time to allow biological response in the target tissue of interest, is an example of a reliable test. Despite a plausible biological hypothesis, the study results do not support the hypothesis that soy intake reduces mammographic breast density, a known risk factor for breast cancer. One important caveat is that the study was conducted in healthy premenopausal women. The association of soy intake with breast density may be different in postmenopausal women, among those with a strong family history of breast cancer, or among women with polymorphisms in genes that encode estrogen-metabolizing enzymes. Future studies should address these important issues to ensure formulation of the most appropriate dietary recommendations for breast cancer prevention.

LITERATURE CITED