Soy and Breast Cancer: The Controversy Continues

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Given that there are few modifiable risk factors for breast cancer, identifying cost-effective, acceptable dietary changes that can reduce breast cancer risk is of tremendous importance. In this issue of the Journal, Trock and colleagues *(1)* took on the remarkable challenge of quantifying the association between soy intake and breast cancer risk from the published literature. We commend the authors for tackling this complex and controversial, yet highly important, issue.

Although there is much interest in gaining a better understanding of the relationship between soy consumption and the risk of breast cancer, Trock et al. highlight the potential limitations that occur in summarizing published results of diet–disease associations. Studies examining these associations can assess nutrients, food groups, specific foods, or even biomarkers of exposure for a specific dietary constituent. Which exposure is reported by a study will depend on the hypothesis tested in each study, the characteristics of the dietary assessment method (i.e., whether it was designed to estimate overall nutrient intake or was targeted to measure the consumption of a specific food or nutrient), the availability of food composition data for a specific nutrient [i.e., isoflavone food composition data only recently became available *(2)*], and/or the availability of an appropriate biomarker. Another important consideration that is applicable to all dietary studies pertains to measurement error of dietary intake and its impact on risk estimates *(3,4)*. Although the authors standardized their exposure of "soy measures", additional variability is introduced by issues such as fermented versus nonfermented soy foods, total soy versus soy protein, or soy versus urinary isoflavone estimates. As a result, summarizing the published literature for a complex exposure such as soy consumption poses remarkable challenges.

In the present meta-analyses, in addition to calculating summary estimates for the original soy exposures, the authors converted the different measures of exposure into one factor (i.e., soy protein) to achieve some standardization across studies. However, this exercise had to involve multiple assumptions. Also, the quantity and type of soy consumed varied greatly across the studies, such that the contrasts in intake levels for the reported risk estimates differed widely. In a separate analysis, the authors attempted to achieve standardization in the contrasts across studies by converting the estimated odds ratios for the categorical analyses to odds ratios for continuous terms. This method also

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involved multiple assumptions, including that the association between soy consumption and breast cancer risk is linear, which may or may not be appropriate.

Because of differences in the exposures evaluated, the contrasts compared, and other differences among studies, statistically significant heterogeneity was evident in the results for the total sample as well as among study subgroups (i.e., studies conducted in Asia and those in postmenopausal women). In addressing heterogeneity across studies, an important consideration in the analysis performed by Trock et al. *(1)* is that they explored the potential impact of differences in study characteristics, dietary exposures, choice of confounding variables, study quality, study weight, and other factors in sensitivity analyses. However, others have proposed *(5)* that statistically significant heterogeneity among studies hinders attempts to calculate summary estimates.

The relevance of the findings presented by Trock et al. *(1)* relate to an important issue for U.S. women: Can increased consumption of soy foods reduce risk for breast cancer? Given that one in seven U.S. women will develop breast cancer in their lifetime *(6)*, any low-cost, adoptable lifestyle change that could reduce the burden of this disease is relevant. Further, these findings can directly affect policy. The United States Food and Drug Administration (FDA) currently allows food manufacturers to make a health claim for the effect of soy protein on lowering risk of coronary heart disease *(7)*. In 2004, the American Soybean Association also petitioned the FDA in support of a health claim for the association between soy protein intake and risk of certain cancers, including breast cancer *(8)*. This claim was based on the industry's own analyses of the data. The industry has since withdrawn their petition.

Although results of this meta-analysis suggest that soy intake is associated with a modest reduction in breast cancer risk, heterogeneity across studies limits the ability to interpret the findings. As a result, the authors were careful not to overinterpret their findings by noting that translation of these findings into clinical recommendations would be premature.

Where does this leave us? Certainly, the results of this meta-analysis do not help to elucidate the role of soy in the etiology of breast cancer. In future studies, identifying ways to reduce the heterogeneity in the published literature for the soy exposures evaluated will be extremely beneficial to better quantify the association between soy consumption and breast cancer risk. Reducing heterogeneity across studies will reduce the need for investigators conducting meta-analyses to apply many assumptions to the published results, as was necessary for Trock et al. *(1)* in their meta-analysis. For example, it would be useful for future studies to report associations for both soy foods and nutrients concentrated in soy products, such as soy protein and isoflavones, to make the data more comparable in the published literature. Also, a better understanding is needed of the role of lifetime soy exposure along with exposure during mammary gland development and exposure among women previously treated for breast cancer, particularly those with estrogen receptor–positive tumors. Only with a clearer understanding of the association between soy consumption and breast cancer risk can recommendations for soy food consumption be considered to reduce the risk of breast cancer.

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