

Phytoestrogens and breast cancer^{1,2}

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Phytoestrogens, which are widely distributed in plants, are structurally similar to mammalian estrogens and can thus bind weakly to estrogen receptors (1). The 3 major classes of phytoestrogens are isoflavones, which are concentrated in soybeans and soy products but are also found in other legumes; lignans, which are distributed in seeds, whole grains, berries, fruit, vegetables, and nuts; and coumestans, which are found in broccoli and sprouts. Although their medical importance has been less extensively studied, lignans occur in higher concentrations in US and European diets than do isoflavones. The daily dietary intake of phytoestrogens in white US women has been estimated to be <1 mg, with \approx 80% from lignans, 20% from isoflavones, and <0.1% from coumestans (2).

Estrogen is increasingly recognized as a cause of breast cancer. Both elevated concentrations of endogenous estrogen and hormonal therapy with estrogen for menopause are associated with an increased risk of breast cancer (3). However, the role of phytoestrogens is ambiguous. In animal models and in vitro studies, phytoestrogens bind weakly to estrogen receptors and can either produce or inhibit estrogen effects (4). The activity of a phytoestrogen depends on its structure and metabolism, its concentration relative to that of endogenous estrogen, and the biological function being assessed. The assumption that plant estrogens are protective derived, in part, from comparisons between international studies (5). Historically, breast cancer rates in the United States have been 4–7 times those in Asia, whereas isoflavone intake in the United States is <1% that in Asian populations, which reportedly ranges from 20 to 80 mg/d (2). However, high soy consumption is only one of many potentially protective lifestyle factors that distinguish Asian and Western women (6).

In this issue of the Journal, Keinan-Boker et al (7) present the results of an epidemiologic study comparing the usual adult intake of lignans and isoflavones with the subsequent risk of breast cancer. Approximately 15 000 Dutch women were recruited for a breast cancer screening program at 49–70 y of age and were followed for 4–8 y (median: 5.2 y), during which 280 incident cases of breast cancer were identified. The strengths of the study include the use of a detailed, validated semiquantitative food-frequency questionnaire; careful development of a database for the lignan and isoflavone content of various foods; prospectively collected dietary data; and comprehensive ascertainment of cases. No association between isoflavone intake and breast cancer incidence was observed. However, a modest 30% reduction in breast cancer risk, which was nearly significant (95% CI: 0.5, 1.1; *P* for trend = 0.6), was seen for women

in the highest quartile of lignan intake (median: 0.8 mg/d). In this Dutch population, approximately two-thirds of the total phytoestrogen intake was estimated to come from lignans.

Despite this study's strengths, limitations are also apparent and highlight the challenges and frustrations in this field of research. The food-frequency questionnaire had not been designed to assess phytoestrogen intake and, therefore, did not include questions on the intake of soy and flaxseed, foods that are consumed infrequently in the Netherlands but are rich in isoflavones and lignans, respectively. The authors originally decided to calculate lignan intake on the basis of its bioactive forms (enterolactone and enterodiol, which are referred to as mammalian lignans and are synthesized from plant lignans by gut microflora). Conversion factors were derived from an in vitro model for colonic fermentation. When the authors reanalyzed their data by using the absolute quantity of plant lignans (matairesinol and secoisolariciresinol), the modest protective effect disappeared, and breast cancer risk increased slightly but nonsignificantly with increased lignan intake. Following up on this inconsistency, they compared the intakes of plant lignans with estimates of bioavailable lignans and found that only one-third of the women in the cohort were assigned to comparable quartiles for both variables. Part of the problem was that food-composition data had not been calculated for several recently identified plant lignans (8), which provide sizable quantities of bioactive lignans.

Surprisingly, the results of a study in another Dutch cohort that measured enterolactone in prediagnostic urine as a biomarker of lignan intake do not concur with the results of the study by Keinan-Boker et al. In that study, higher enterolactone excretion was associated with a nonsignificant 40% increase in breast cancer risk (9). Plausible reasons for this discrepancy exist and reveal the complexity of this research. Urinary measures take into account individual variation in colonic metabolism and bioavailability, whereas dietary measures integrate exposure over a longer period of time. Finally, the study by Keinan-Boker et al was limited by the range of exposure in the population. Neither lignan intake (interquartile range: 0.5–0.8

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mg/d) nor isoflavone intake (interquartile range: 0.3–0.5 mg/d) was especially high, and phytoestrogen intakes comparable with those of Asian populations could not be evaluated.

Epidemiologic research on lignans and breast cancer is limited. Only 1 of the 3 published US studies that estimated dietary lignan intake found a protective effect (10). Of the 2 breast cancer studies that measured circulating enterolactone, only 1, which was conducted in Finland, reported a persuasive inverse relation (11). Of the 3 studies that assayed urinary lignans, only 2, which were carried out in Australia and China, reported a protective effect (12, 13). Explanations for these inconsistencies include the methodologic challenges mentioned above. Results from epidemiologic studies of isoflavones and breast cancer are similarly mixed, even from studies in Asian populations with high soy consumption (14). Current research that attempts to reconcile these different results focuses on phytoestrogen exposure early in life, the influence of phytoestrogens before and after menopause, and interactions with genetic polymorphisms.

Women, especially those at high risk, want to know whether phytoestrogens decrease or increase breast cancer risk. If phytoestrogens are indeed protective, are soy and isoflavone nutraceuticals that are designed to supply phytoestrogens at \approx 50 mg/d, an intake comparable with that of an Asian diet, required to guarantee sufficiently high dosages? Breast cancer survivors relying on tamoxifen to inhibit endogenous estrogen or on aromatase inhibitors to prevent its production question how phytoestrogens will interact with their treatment. Perimenopausal and postmenopausal women searching for an alternative to synthetic hormone therapy wonder whether phytoestrogens might increase breast cancer risk and not substantially improve cardiovascular or bone health. The relevant research is complicated, inconsistent, and inconclusive. At present, scientific research does not support increasing phytoestrogen intake

among US women to Asian levels, nor does it suggest that the typical US phytoestrogen intake is problematic for healthy women. 

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