Soy, soy phytoestrogens (isoflavones), and breast cancer

Dear Sir:

McMichael-Phillips et al (1) found that daily consumption (60 g) of a soy-protein product containing 45 mg isoflavones for 2 wk stimulated DNA synthesis in breast cells taken from biopsies of premenopausal women with benign and malignant breast disease. These findings suggest that soy may actually exert estrogenic rather than antiestrogenic effects on breast tissue. This is not the first human study to suggest such an effect. Petrakis et al (2) found that in premenopausal women, daily soy consumption for 4 mo was associated with an increase in breast nipple fluid aspirate secretion and breast cell hyperplasia. However, this study did not include a control group and fluid secretion increased in women even after soy feeding was discontinued. Nevertheless, both studies raise important questions about the effect of soy isoflavones on breast tissue.

The study by McMichael-Phillips et al is particularly noteworthy, assuming that the increased DNA synthesis reflects an increase in cell proliferation. Increased cell proliferation has traditionally been considered a marker for increased cancer risk. However, this notion was challenged recently, at least with regard to the colon (3). In addition, as discussed below, there is reason to question whether the increased breast cell proliferation in response to soy consumption should be interpreted in an unfavorable light.

In the assessment of cancer risk, cell proliferation is only one side of the equation, the other being apoptosis. Illustrative of the need to look at both sides of the equation is the finding that the nonsteroidal antiinflammatory drug sulindac enhances cell proliferation in 1,2-dimethylhydrazine-treated mouse colonic mucosa, but inhibits 1,2-dimethylhydrazine-induced colon tumors (4). Moorghen et al (4) suggest that sulindac inhibits carcinogenesis despite the increase in cell proliferation because proliferation in this case is a compensatory response to an even larger increase in apoptosis. Because genistein, the primary isoflavone in soybeans, causes apoptosis in breast cancer cells in vitro, perhaps a similar phenomenon occurs with soy in vivo as it does with sulindac. Consistent with this suggestion is recent research showing that soy isoflavones markedly inhibited transplantable murine bladder cancer; however, although cell proliferation decreased slightly, apoptosis increased as much as 2–3-fold (5).

As pointed out by McMichael-Phillips et al, the short-term nature of their study is an important consideration, especially because of a report showing that tamoxifen increased pS2 expression (suggesting an estrogenic effect) in the breast tissue of breast cancer patients after 6 wk of administration but that this effect was reversed after 6 mo of treatment (6). Related to this finding is the finding that chronic exposure to isoflavones in vitro down-regulates the estrogen receptor. If down-regulation takes >2 wk to occur in people eating soyfoods, any effect on cell proliferation would not have been detected by McMichael-Phillips et al. Similarly, the increase in follicular phase length in response to soy consumption that has been observed by some investigators would not be apparent after only 2 wk of soy feeding. Increasing follicular phase length could decrease breast cancer risk in the long term.

Although 2 recent studies failed to show an effect of soy on cycle length, soy was found recently to favorably affect estrogen metabolism in premenopausal women—increasing the urinary ratio of 2- to 16α-hydroxylated estrogens and of 2- to 4-hydroxylated estrogens (7). Again, this change in estrogen metabolism would likely not occur rapidly enough to affect cell proliferation after only 2 wk of soy feeding.

Overall, there are inconsistent data regarding the likely estrogenic and antiestrogenic effects of soy on breast tissue. In vitro studies suggest that the isoflavones are estrogenic, not antiestrogenic. Although partial and pure antiestrogens demonstrate antiestrogenic effects in vitro, in vitro systems are incomplete and may not permit an antiestrogenic effect of isoflavones to be observed. Studies involving intact adult animals have not shown that soy feeding increases chemically induced mammary cancer, rather, most show substantial cancer inhibition—generally a 50% reduction in tumor number has been observed.

On a more cautionary note, Hsieh et al (8) found that dietary genistein stimulated the growth of MCF-7 cells implanted subcutaneously into ovariectomized nude mice, although growth stimulation was considerably less than that observed for 17β-estradiol (8). However, there are concerns about whether results from this model can be extrapolated to either premenopausal or postmenopausal women. In contrast with the results of Hsieh et al, Shao et al (9), in a short-term study, found that in intact mice given 17β-estradiol subcutaneously, genistein markedly inhibited breast cancer cell growth in vivo.

The complexity of the findings for isoflavones, as shown by these studies (8, 9), was also illustrated by the findings of Foth and Cline (10) in ovariectomized cynomolgus monkeys. They found that in animals not given estradiol, soy feeding produced a nonsignificant increase in mammary cell proliferation but significantly antagonized the stimulatory effects of estradiol on mammary cell proliferation.

Finally, genistein exposure for just a few days during the neonatal and prepubertal periods has been shown to reduce chemically induced mammary cancer in rodents later in life. The proposed mechanism of action seems to involve an estrogenic effect of genistein on mammary tissue, resulting in enhanced mammary tissue development and differentiation. Thus, in young animals, an estrogenic effect of soy on breast tissue may result in a decreased breast cancer risk.

In conclusion, there are insufficient data on which to draw definitive conclusions about the effects of soy consumption on breast tissue in either pre- or postmenopausal women. Epidemiologic data show some support for a protective effect of soy against breast cancer (primarily premenopausal breast cancer) and, importantly, no epidemiologic studies found an increased breast cancer risk associated with soy consumption. However, it is not clear whether these epidemiologic data, which involved primarily Asian women, can be used to assess the effect of adult soy consumption on breast cancer risk in Western populations. The recent findings by McMichael-Phillips et al should serve as a stimulus for much needed research into the effects of soy on breast tissue.

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LETTERS TO THE EDITOR 575

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REFERENCE


Reply to EH Harrison and JC Smith

Dear Sir:

The remark by Harrison and Smith that there was no significant difference in serum retinol response between the vegetable and fruit groups is correct. However, analysis of duplicate portions showed that the vegetable group had received more provitamin A than the fruit group [684 compared with 535 retinol equivalents (RE)/d]. When corrected for this difference of intake, the difference in the change in serum retinol concentration between the fruit group and the vegetable group was 0.064 μmol/L, which is similar to the difference found between the vegetable group and the control group (0.07 μmol/L).

Accounting for the difference in the amount of carotenoids provided, we derived the following retinol conversion factors (μg β-carotene equivalent to 1 RE) for fruit and for leafy vegetables and carrots: 12 (95% CI: 6, 29) and 26 (95% CI: 13, 76), respectively. The factor for vegetables is more than twice as high as that for fruit, but the ranges overlap. The ranges were based on the 95% CIs of the serum retinol responses and on the average amounts of retinol and provitamin A carotenoids provided. If we had accounted for the precise variation in carotene content of the foods provided, the differences in the amounts eaten by individual children, and other factors that affect carotene bioavailability and bioconversion, the ranges would have been even larger.

However, when factors are used for converting provitamin A intake to vitamin A, an average value is required. We are confident that the conversion factors we derived represent the general difference between fruit and vegetables. However, as also mentioned in our article, the real conversion factor for specific foods under specific circumstances depends on many factors. Our confidence is based not only on the results of our study. Another study, conducted in breast-feeding women in Vietnam, found similar conversion factors: 12 for fruit and 28 for vegetables (1). The fact that the serum β-carotene response was better for fruit than for vegetables (5.7 times higher when corrected for the amount of β-carotene provided) means that the bioavailability of the most important provitamin A carotenoid was better from fruit. Thus, for fruit, bioconversion rather than bioavailability did not seem to have been optimal. Perhaps the conversion rates would be more efficient if the vitamin A status is lower, when the same amount of fruit is consumed in smaller portions throughout the day, or if both conditions exist. Thus, although we agree that serum β-carotene is not an indicator of vitamin A status, it indicates the potential for increasing vitamin A status when bioconversion could be optimized.

Earl H Harrison

J Cecil Smith

Provitamin A food sources and serum retinol

Dear Sir:

We are writing in regard to the paper by de Pee et al, “Orange Fruit is More Effective than are Dark-green, Leafy Vegetables in Increasing Serum Concentrations of Retinol and β-Carotene in Schoolchildren in Indonesia” (1). Although the data presented appear sound, we caution readers that the conclusion stated in the title with respect to retinol is not supported. The remark by Harrison and Smith that there was no significant difference in serum retinol response between the vegetable and fruit groups is correct. However, analysis of duplicate portions showed that the vegetable group had received more provitamin A than the fruit group [684 compared with 535 retinol equivalents (RE)/d]. When corrected for this difference of intake, the difference in the change in serum retinol concentration between the fruit group and the vegetable group was 0.064 μmol/L, which is similar to the difference found between the vegetable group and the control group (0.07 μmol/L).

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