

# Letter to the Editor



Mark Messina

## Conclusion that isoflavones exert estrogenic effects on breast tissue and may raise breast cancer risk unfounded

The article by Eisenbrand [1], which presented in abbreviated form the opinion of the Senate Commission on Food Safety (SKLM) of the German Research Foundation on the safety of isoflavones as dietary supplements or dietary foods for special medical purposes nicely highlighted some of the important research needs in this area. In my opinion, however, one of the two primary conclusions reached by the SKLM is not supported by the literature. According to the SKLM, "... a conclusion that can be drawn from the available data is that isoflavones, particularly at high dosage, can exert an estrogenic stimulus on the mammary gland tissue in women." Three clinical studies are cited in support of this conclusion [2–4]. However, the study by McMichael-Phillips *et al.* [3] should be ignored since it was actually a preliminary analysis and the final results involving the entire cohort, which were cited by Eisenbrand [1], were published one year later [4]. In that study premenopausal women were randomly assigned to a soy or control group [4]. The soy group was requested to consume daily 60 g textured vegetable (soy) protein (TVP) that provided 45 mg isoflavones whereas the control group consumed their usual diet only. Breast biopsies were taken at baseline and two weeks later. Of the 28 subjects in the soy group, 20 consumed the TVP for 13 or 14 days, four for 10 to 12 days, and four for 8 or 9 days. Results indicated that breast nipple aspirate pS2 levels ( $n = 20$ ), an estrogen-regulated protein, significantly increased subsequent to soy consumption. However, in contrast, breast biopsies indicated that there were no effects of soy on breast cell proliferation (as measured by tritiated thymidine and Ki67), estrogen receptor

(ER) expression, progesterone receptor (PR) expression, Bcl-expression, and apoptosis and mitosis. The short intervention period combined with the lack of effects on most measures of estrogenicity limit the implications of these findings.

In the other cited study, pre- and postmenopausal women consumed daily for 5 months 37.5 g isolated soy protein that provided 75 mg isoflavones. In comparison to the baseline values, breast nipple aspirate fluid (NAF) volume in premenopausal women ( $n = 14$ ) significantly increased ( $p = 0.001$ ) during and after discontinuation of soy consumption, whereas no increase was noted in postmenopausal women ( $n = 10$ ) overall, although in the four postmenopausal women on hormone therapy, NAF volume was said to significantly increase. In addition, epithelial hyperplasia occurred in four premenopausal and three postmenopausal (7 of 24, 29.2%;  $p = 0.021$ ) women while consuming soy whereas prior to soy consumption, this was true for only one woman (4.2%). Petrakis *et al.* [2] concluded that their findings suggest that soybean isoflavones exert an estrogenic stimulus on breast tissue. However, this study lacked a control group and the authors emphasized that it was a pilot study.

In contrast to the results by Petrakis *et al.* [2] are those from Cheng *et al.* [5], who conducted a 12-week study involving healthy postmenopausal women randomly assigned to consume daily either a placebo ( $n = 25$ ) or supplement ( $n = 26$ ) derived from soy that provided 36 mg isoflavones [5]. Mammography and a middle-needle biopsy of breast tissue were performed at baseline and at study conclusion, using ultrasound to identify glandular tissue. Biopsies indicated that there was no effect of isoflavones on breast cell proliferation or on the expression of ER $\alpha$ , ER $\beta$ , PR- $\alpha$ , PR- $\beta$  and  $\beta$ cx. Two other pilot studies, both involving breast cancer patients, also failed to find that isoflavone supplements affect breast cell proliferation; the intervention period in one was on average 23 days [6] and the other one year [7]. In both studies subjects were exposed to  $\geq 100$  mg isoflavones *per day*; however, the one-year study included only nine women/group and is published only as an abstract.

In addition to the lack of effect on cell proliferation, none of the four studies conducted (three in premenopausal [8–11] and one in postmenopausal women [10]) have found that isoflavone exposure from soyfoods, isolated soy protein, or soybean- or red clover-derived supplements affect breast tissue density. Also, the only epidemiologic study to involve breast cancer patients found that soyfood intake was unrelated to survival over the 5.2 year follow-up period [12]. In this study, of the 1001 (total cohort included 1459 subjects) Chinese breast cancer patients for whom data on receptor status was available, approximately 52.8% were ER+/PR+, 10.8% ER+/PR-, 10.5% ER-/PR+, and 25.9% ER-/PR-.

**Correspondence:** Dr. Mark Messina, Nutrition Matters, Inc., 439 Calhoun Street, Port Townsend, Washington 98368, USA

**E-mail:** markm@olympus.net

**Fax:** +1-360-379-9614

Finally, and importantly, in contrast to the lack of effect of isoflavones on breast cell proliferation and breast tissue density, exposure to estrogen and estrogen in combination with a progestin produces increases in both of these measures within the same time period to which subjects were exposed to isoflavones in the previously described studies [13–16]. Thus, while it is reasonable to argue that longer and larger studies are needed before definitive conclusions about the effects of isoflavones on breast tissue can be made, the evidence clearly does not warrant the conclusion reached by the SKLM that isoflavones exert estrogenic effects on breast tissue in women, and especially not in a way that increases breast cancer risk.

*Conflict of interest statement: Mark Messina owns his own consulting company and some of his clients include those in the soyfood and isoflavone supplement business.*

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