Letter to the Editor

Cancer Prevention Research

Soy Isoflavones for Breast Cancer Risk Reduction—Letter

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Khan and colleagues' (1) recently reported results from their phase II placebo-controlled randomized trial of the effects of soy (mixed isoflavone compound) on breast cell proliferation (Ki67), and nipple aspirate fluid (NAF) steroid levels are difficult to understand.

They studied healthy, high-risk women: 49 in the soy group (28 premenopausal, 21 postmenopausal) and 49 in the placebo group (25 premenopausal, 24 postmenopausal). Baseline and on-treatment NAF were obtained from 26 women in the soy group and from 20 women in the placebo group. The median baseline NAF estradiol levels (Supplementary Table S1) were considerably higher in postmenopausal (276.5 pg/mL) than in premenopausal (116.4 pg/mL) women in the soy group, whereas these levels were similar in postmenopausal (110.8 pg/mL) and premenopausal (104.2 pg/mL) women in the placebo group. This difference between the soy and placebo postmenopausal groups is of concern because it would appear to show a failure of randomization between the 2 groups.

In addition, it should be noted that these NAF estradiol results—higher levels in postmenopausal women in the soy group and no difference in levels between postmenopausal and premenopausal levels in the placebo group—are not compatible with the results of their previous studies. The study by Khan and colleagues (1) aimed at collecting the premenopausal NAF samples in the mid-luteal phase of the cycle and this was achieved in a high proportion of the women. In their most recent previous study (2), geometric mean NAF estradiol levels were considerably higher in premenopausal women in the luteal phase of the menstrual cycle (2,130 pg/mL) than in postmenopausal women (1,213 pg/mL). (Note: although the units are given as pg/mL in this 2010 report, this is likely to be a typographical error and the values should be reduced by a factor of 10.) Similarly, in another earlier study (3), they found a geometric mean NAF estradiol level of 86 pg/mL (316 pmol/L; Table 1 of ref. 3) in premenopausal women compared with 33 pg/mL (120 pmol/L; Table 1 of ref. 3) in postmenopausal women.

The plasma genistein and NAF genistein levels also appear incongruous. In the soy group at 6 months, the median plasma genistein levels were 156 ng/mL in postmenopausal women and 205 ng/mL in premenopausal women. This was not reflected in the median NAF genistein levels, which were 88.25 ng/mL in postmenopausal women and 35.20 ng/mL in premenopausal women.

In the soy group, the median Ki67 labeling index increased from 1.71% at entry to 2.18% at 6 months ($P = 0.04$) in premenopausal women and to a lesser extent in postmenopausal women (0.63% at entry to 0.77% at 6 months, $P = 0.56$). The corresponding levels remained unchanged in the placebo group for both premenopausal (1.90%–1.94%, $p = 0.56$) and postmenopausal (0.70%–0.63%, $P = 0.22$) women (see Table 3). Table 3 also shows that the Ki67 labeling index for premenopausal and postmenopausal women combined in the soy group was 1.17% at entry and 1.09% at 6 months. It is unclear how the overall 6-month soy group results can be lower when the values at 6 months were higher in both premenopausal and postmenopausal women. Furthermore, in their discussion (paragraph 2), the authors state that there was "a median decrease (of Ki67) of 0.13% in the postmenopausal-treated group, whereas in premenopausal women, it increased by 0.19%." This statement does not agree with the results presented in Table 3.

Finally, it should be noted that the Ki67 results of the soy group were both obtained in the luteal phase of the cycle in 25 of the 28 women in the group (89%) whereas this was only obtained in 18 of the 25 women (72%) in the placebo group. Because Ki67 is increased in the luteal phase of the cycle, this also raises concerns about the legitimacy of comparing the soy and placebo group Ki67 results.

The data reported in the article are potentially very important because the use of soy isoflavone supplements has become common place and an increasing number of food products contain soy ingredients. However, we contend that our questions raise concerns about the results presented from this study.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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