Letter to the Editor

Cancer Prevention Research

Soy Isoflavones for Breast Cancer Risk Reduction—Response

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We thank Dr. Wu and colleagues for their careful reading of our manuscript and regret that they find our results difficult to understand. We have addressed each of their concerns below.

Wu and colleagues point out that the median baseline nipple aspirate fluid (NAF) estradiol levels we reported in Supplementary Table S1 were considerably higher in treated postmenopausal women than in premenopausal (276.5 vs. 116.4 pg/mL), but not in control women (110.8 vs. 104.2 pg/mL). They worry that this difference in NAF estradiol values between the soy and placebo postmenopausal groups may show a failure of randomization between the 2 groups. Although it is true that the value of 276.5 pg/mL is higher-than-expected for NAF estradiol in postmenopausal women, we do not agree that this indicates a failure of randomization. The general expectation that a randomly allocated population will be balanced in all characteristics is likely to fail in at least some characteristics when smaller subsets are examined. *NAF data were available on approximately half the study population* and therefore are not relevant to the issue of balanced randomization for the entire study. In fact, when we examine other parameters where data are available on the whole population, we find no differences between treated and placebo groups as indicated by the Wilcoxon rank-sum test and are shown in Table 1.

Table 1. Plasma hormone concentrations in soy-treated and placebo participants

Parameter	*N*	Soy group (*n* = 49) Entry	Placebo group (*n* = 49) Entry	*P*
Median plasma estradiol (median and interquartile range)				
All patients	97	26.12 (12.73–54.59)	17.01 (10.18–38.52)	0.30
Postmenopausal	44	11.54 (6.61–16.62)	10.31 (9.33–16.62)	0.60
Premenopausal	53	45.29 (28.71–72.35)	36.32 (20.38–70.43)	0.42
Median SHBG (median and interquartile range)				
All patients	97	61.25 (45.52,104.35)	85.84 (55.26,118.71)	0.07
Postmenopausal	44	78.01 (54.98,100.97)	103.37 (58.27,122.09)	0.11
Premenopausal	53	55.13 (39.56,105.54)	77.28 (51.79,118.71)	0.23
Median ratio of estradiol to SHBG (median and interquartile range)				
All patients	97	0.32 (0.18–0.83)	0.24 (0.12–0.51)	0.13
Postmenopausal	44	0.16 (0.10–0.21)	0.14 (0.08–0.19)	0.43
Premenopausal	53	0.73 (0.37–1.31)	0.46 (0.30–0.77)	0.10
Median follicle-stimulating hormone (median and interquartile range)				
All patients	97	10.90 (5.53–69.76)	34.78 (4.24–72.62)	0.45
Postmenopausal	44	71.72 (48.73–90.67)	70.85 (50.23–96.13)	0.87
Premenopausal	53	5.73 (2.46–8.30)	4.24 (1.50–12.92)	0.80

Abbreviation: SHBG, sex hormone–binding globulin.

Wu and colleagues also point out that we report postmenopausal NAF estradiol levels that are unexpectedly higher than premenopausal levels. When results in the present study are compared with our previous publications, it is true that estradiol concentrations in NAF have been consistently, but not significantly, lower in postmenopausal women than in premenopausal women. The number of postmenopausal subjects in our 2010 and 2004 publications was 18 in each (1, 2). The higher postmenopausal NAF estradiol concentrations in the present study (3), although unexpected, can be attributed to chance when the sample size is small, as it was here, with 8 NAF-yielding postmenopausal subjects in the soy group.

With regard to the difference in NAF genistein values, it should again be noted that the summary values are based on 15 premenopausal and 8 postmenopausal observations; although the medians appear different between pre- and postmenopausal women, the major point of interest is that

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doi: 10.1158/1940-6207.CAPR-12-0189

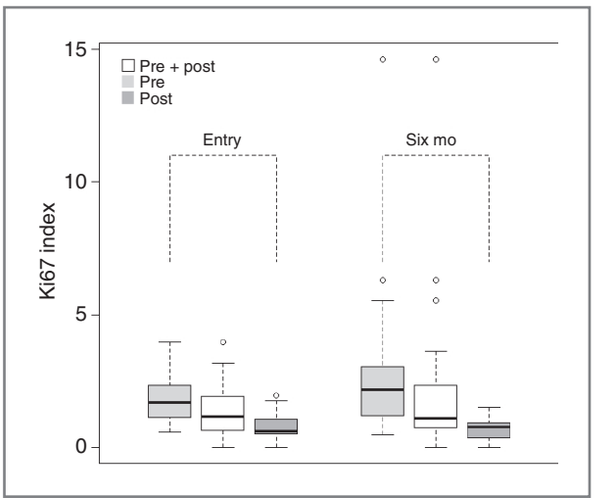

Figure 1. Ki67 labeling indices at entry and 6 months, in premenopausal women, all women, and postmenopausal women.

they are significantly different between baseline and post-intervention samples. The absence of a constant relationship between NAF and serum values is not surprising, as the determinants of NAF concentrations of dietary components are unknown. Therefore, in this context of an exploratory analysis of a small number of women, we did not expect NAF values to align with serum values.

The authors of the letter also wonder how the overall 6-month soy group Ki67 results can be lower when the values at 6 month were higher in both premenopausal and postmenopausal women. As is evident from the box plot showing the distribution of Ki67 values in the soy group (Fig. 1), the median values of the combined groups lie between the median values of the pre- and postmenopausal groups at both baseline (BL) and month 6 (M6), as would be expected.

Wu and colleagues also take issue with our statement 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%." Our statement is based on results presented in Table 3, in the last column, where the median between-group differences are shown, with their confidence intervals and *P* values. For postmenopausal women, this between-group change is −0.13 (–0.42 to 0.08), and for premenopausal women, this difference is +0.19 (–0.46 to 1.07).

Finally, Wu and colleagues note that 89% of the soy group was sampled in the luteal phase, compared with 72% of the placebo group, raising a concern about the legitimacy of comparing the soy and placebo group Ki67 results. We gave significant thought to the presentation of the study findings when it became apparent that luteal phase sampling had not been achieved in all premenopausal women and decided that it would be more appropriate to present intent-to-treat data on all premenopausal women, rather than focusing on the women who were sampled in luteal phase at both time points. In fact, the within-group difference was more apparent for premenopausal women when we look only at luteal phase subjects: 1.71 (1.12–2.35) versus 2.18 (1.18–3.04), $P = 0.04$ for all premenopausal women, and 1.87 (1.20–2.46) versus 2.33 (1.73–3.10), $P = 0.02$ for women in luteal phase at both time points. However, the between-group difference remained nonsignificant ($P = 0.40$).

We agree with Wu and colleagues that the safety of soy supplements is an important public health concern; our conclusions about the use of purified soy isoflavones (as distinct from whole soy foods) are that the effect on the breast appears to be largely neutral, but with a hint of an adverse effect on the premenopausal breast (the between-group change in Ki67, labeling indix was the planned major endpoint and was not significantly different). We have carefully focused on prespecified main endpoints in our publication; we disagree that the expected variability in secondary endpoints on small subsets of the study population raises questions about our results.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received May 3, 2012; accepted May 3, 2012; published OnlineFirst June 12, 2012.

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