

**Author's response to reviews**

**Title:** Soy Isoflavones, Estrogen Therapy, and Breast Cancer Risk: Analysis and Commentary

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**Version:** 2 **Date:** 11 May 2008

**Author's response to reviews:** see over

# **Soy Isoflavones, Estrogen Therapy, and Breast Cancer Risk: Analysis and Commentary**

Mark Messina and Charles E. Wood

## **Response to Reviewers**

### **Reviewer 1**

#### Comment

1.(Discretionary revision) The authors insist that it seems unlikely that isoflavone consumption at dietary levels elicits adverse breast cancer-promoting effects in healthy women or breast cancer survivors. Their logic seems reasonable but their way of presentation may not be balanced. First, they showed the evidence of worse effect of isoflavone and then they tried to reject the evidence by indicating the flaw of the studies. This is not like a systematic review, but rather a commentary. How about changing the title to directly represent the contents of the paper ?

#### **Response**

The title has been changed to “**Soy Isoflavones, Estrogen Therapy, and Breast Cancer Risk: Analysis and Commentary.**” The word review is no longer in the title.

2.(Discretionary revision) The authors indicated the flaw of the studies or limits of the evidences showing the worse effects of isoflavone. No attempts, however, were done to criticize the evidences supporting no effect of isoflavones on the breast cancer. It seems unbalanced. The authors are recommended to criticize the evidence of the latter in the same way.

#### **Response**

The following text has been added before discussing the epidemiologic data:

While the available trials examining breast proliferation and density have found no statistically significant effects of isoflavone-containing products it is important to recognize that many of these studies involved small sample sizes or were relative short in duration.

3.(Discretionary revision) The readers cannot evaluate if the studies which the authors demonstrated were exhaustive or systematic. If it is a commentary, the review is not necessarily exhaustive, otherwise the authors are recommended to show how exhaustive they are, especially for clinical studies.

## **Response**

The title has been changed to indicate the manuscript is more of a commentary and not a systematic review.

4.(Minor essential revision) The table 3 does not exist although the text refers. The contents are included in the table 2.

## **Response**

The text now refers to table 1 as there is now only one table in the manuscript.

## **Reviewer 2**

1. Main comments:

Table 1 is not as informative as I would have liked. I think it will be more informative to show the range of increases in association with E2 or CEE and the ranges of effect (increase, decrease, or no change) in association with soy isoflavones. Since many of the studies on soy were not adequately powered, the lack of statistical significance is not surprising. It is important to summarize the direction of the effects and the range of effects in association with soy isoflavones. Through out the paper, the authors stated that soy had effect on various outcomes of interest. The authors should clarify that soy had no 'statistically significant' effect. In addition, I like it is helpful to insert the actual % change in the text (see specific examples below).

Table 2: "Results" column- I would like to see the % changes.

Table 1 has been removed.

Table 2: Condensed results have been added.

2. Comment

~line 80, Introduction: Is there any update of the position of the American Dietetic Association- this was a 1999 reference.

## **Response**

The ADA updated their position paper on women's health in 2004. In that paper, the only mention of soy and breast cancer is in a table which indicates there is insufficient evidence to conclude whether soy increases or decreases breast cancer risk. In contrast, in the 1999 paper, there are two paragraphs on soy and isoflavones which discuss the possibility that breast cancer risk may be increased by soy/isoflavones. Also included is a statement that isoflavone supplements should be discouraged. Since the point of this reference is simply to reflect various statements made about isoflavones and breast cancer by professional groups no change to the manuscript will be made.

3. Comment

~line 150: What was the dose used in the B6C3F1 study. Did this study also use a much higher dose?

**Response**

The dose was 20 ppm (20 mg/kg bw) was relatively low. This information has been added to the manuscript.

4. Comment

~line 165: “In Japan.. adults consume about 15-20 mg genistein daily... “ Are we talking about genistein or isoflavones? If you do mean to say ‘genistein’, then I think it is also helpful to include the amount of isoflavones.

**Response**

To the manuscript has been added the following information: (total mean isoflavone intake is approximately 40 mg)

5. Comment

~line 215: “The 12 week Swedish study: ... No effect of isoflavone”... I assume you mean no statistically significant effect.

**Response**

The manuscript now indicates the effect was not statistically significant. The text reads as follows “No statistically significant effects of isoflavone treatment were seen on cell proliferation or several other indicators of estrogenicity effect (table 1).”

6. Comment

~line 225: “In addition to the lack of effect on cell proliferation”.. see my comment above.

**Response**

The manuscript now indicates the effect was not statistically significant.

7. Comment

~line 235: “Three additional ... (Table 3)- there is no Table 3.

**Response**

There is now only one table in the manuscript so the text has been changed accordingly.

8. Comment

~line 258: I am not sure about the finding for reference 104. Is this the correct reference?

**Response**

Yes, this is the correct reference. No change made.

9. Comment

~line 310: “In this study, ET was associated with modestly higher percent..” What is the % change?

**Response**

Information on percent change has been added to the text along with p values as follows:

“In one of the few clinical studies to assess breast proliferation following ET and EPT, postmenopausal women taking EPT but not ET had significantly greater breast epithelial Ki67 expression in terminal ductal lobular areas [82]. In this study, ET was associated with modestly higher percent breast epithelial area (~15%) compared to the control group (~7%;  $p = 0.01$ ), while EPT resulted in greater density beyond that seen with ET (~24%;  $p = 0.02$  compared to ET).”

10. Comment

~lines 309 and 328- I would not use the ‘attributable risk’ in this context.

**Response**

Attributable has been deleted from attributable risk.

11. Comment

~lines 350: Please consider removing the results of Reference 73 in the summary- it may be more suitable elsewhere in the paper.

**Response**

This reference is cited elsewhere in the paper and has been removed from the summary.