Author's response to reviews

Title: Green tea and urinary estrogens and estrogen metabolites in Japanese-American women

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Author's response to reviews:

Monday, December 03, 2012

To the Nutrition Journal Editorial Team;

Thank you for your review of our manuscript, titled ‘Green tea and urinary estrogens and estrogen metabolites in Japanese-American women'. We appreciate the constructive comments of the reviewers and have responded to each (see attached).

We believe that the manuscript has been improved with the changes, which are highlighted in yellow in the revised manuscript.

On behalf of the authors, thank you and we hope that the paper is now acceptable for publication as an Original Research Article in the Nutrition Journal.

Sincerely,

Barbara Fuhrman

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Reviewer: Qi Dai
Reviewer's report:

In the manuscript, the authors examined the associations between green tea drinking and urinary excretion of estrogens and metabolites in a cross-sectional study of Japanese American women. The findings are interesting. The comments are as follows.

Major Compulsory Revisions

1) In the current study, the authors found green tea drinking was associated with reduced EM in premenopausal women and was associated with reduced urinary excretions of estrone and estradiol among postmenopausal women. If these findings are real, green tea drinking should be consistently related to a reduced risk of postmenopausal breast cancer because high estrogen concentrations are an established risk factor for postmenopausal breast cancer. However, as the authors mention, previous findings on green tea drinking and breast cancer risk are not consistent. The meta-analysis from cohort studies did not show a significant association. The authors need to directly discuss this and provide a possible interpretation.

In response we have added the following text to page 16, paragraph 2: It should be noted, however, that there are a limited number of studies of green tea intake and risk of breast cancer, and that the evidence from these studies does not consistently support such an association. In particular, of three prospective studies, all conducted in Asia, two had null findings [40, 41] while the most recent found reduced premenopausal breast cancer risk in association with regular intake of green tea before the age of 26, and increased breast cancer risk in postmenopausal women with the same exposure [42]. Most studies of green tea have not considered pre- and postmenopausal women separately, or considered menopausal status as a potential modifier of the association [43]. While adjustment for other measures of acculturation did not lessen the observed associations, it remains possible that green tea intake observed in our study was associated with estrogen profiles as a very sensitive marker of acculturation rather than a causal factor. More prospective studies, with careful assessments of menopausal status and of green tea intake at susceptible times of life, are needed to establish whether green tea is associated with reduced breast cancer risk.

2) The authors mentioned that in a previous clinical trial, EGCG supplementation did not significantly reduce levels of estradiol, estrone or testosterone. Based on these findings, “green tea might modify cancer risk through other pathways”. However, this interpretation is in contrast to the major finding in the current study that green tea drinking was associated with reduced levels of estrone and estradiol. Thus, there are two possibilities 1) the findings from the current study are confounded by other underlying factors, such as cruciferous vegetables
intake; or 2) EGCG may not be the components of green tea affecting estrone and estradiol and, in turn, risk of breast cancer although EGCG may change LDL and glucose. The authors should provide a reasonable interpretation.

In response we have added the following to our discussion (highlighted text is new) to page 13, paragraph 1: Based upon these findings, the authors suggest that green tea might modify cancer risk through other pathways. It should be considered that differences between the findings of the present study and the randomized feeding trial could reflect differences in the study design or the exposure. While the present study design is more prone than the feeding trial to confounding by unmeasured covariates, it is also possible that a true effect of green tea drinking on estrogen levels is mediated by a component not present in the EGCG isolate used in the trial.

Minor Essential Revisions
1) On page 5, line 4: “The research was approved by X.” The authors need to clarify what “X” is.

We apologize for this omission and clarify this in the text on page 5, paragraph 2, as follows: The research was approved by the responsible Institutional Review Board at the National Cancer Institute.

Discretionary Revisions
1) Some sentences are too long and the authors need to consider dividing them into two sentences.

Thanks for this suggestion. We have made some minor changes to improve readability.

Quality of written English: Needs some language corrections before being published

Reviewer: Chisato Nagata
Reviewer's report:

This study examined the associations between green tea intake and urinary estrogens and estrogen metabolites. I found the present data to be of interest. The design of the study is thorough and the paper is well-written. I have only minor comments.

Discretionary Revisions
1. I would like to know that adjustment for years of education or dietary factors such as alcohol and fat intake would not alter the results.

While education was not available for our analysis, we did adjust for parity/age at first birth, which is often the presumed mechanism underlying associations of education and breast cancer risk. While we did adjust for soy intake, we did not have access to measures of alcohol intake and dietary fats. We have listed this
as a limitation of the study on page 17, paragraph 1, as follows: While we did adjust for regular intake of soy foods, we were not able to adjust for some other dietary factors such as alcohol intake.

2. Page 9: The statistical comparison of characteristics between pre- and postmenopausal women is not so important.

We felt that it was important to describe these differences because of the different associations seen between tea intake and estrogen metabolite profiles.

3. Page 11, para 2: This paragraph could be deleted or included into the section of introduction.

We have made the suggested deletion.

4. Page 11, lines 12-14: I am puzzled by the difference in the results between pre- and postmenopausal women. Please add more explanation.

We have added the following to our discussion: ... the observed associations differed by menopausal status, which could occur because of the marked differences in these two groups of women in levels and sources of systemic estrogens. It is recognized, for example, that aromatase inhibitors will have different impacts on circulating estrogens in premenopausal women with intact ovaries compared to their postmenopausal counterparts.

5. Page 13, para.2: Does this paragraph have relevancy to your finding of no association between green tea intake and urinary estrogens in premenopausal women?

We have moved this paragraph to the end of the discussion, where we use it to frame and interpret our findings. It now reads as follows:

Estrogens are recognized as important causal factors in the pathogenesis of breast cancer. Prospective studies of postmenopausal women have consistently found increased risk of breast cancer in association with higher circulating [34] and urinary estrogens [35, 36]. Recent studies suggest that elevated endogenous estrogens are associated with increased risk of both estrogen receptor positive and negative breast cancers in postmenopausal women [37]. For premenopausal women the association of circulating estrogens with breast cancer risk has not been well supported by the literature, perhaps due to methodologic challenges posed by variability in estrogen levels across the menstrual cycle. Of two studies that carefully accounted for menstrual phase [38, 39], one found increased breast cancer risk with higher plasma estradiol during the follicular but not the luteal phase of the menstrual cycle [39]. Thus our findings of differences in premenopausal estrogen metabolite profiles by green tea intake have uncertain implications for breast cancer risk.

How about the association of 16-pathway EM with the risk of breast cancer in premenopausal women?
We have added the following to our discussion of this finding:

In a recent study of urinary estrogens and estrogen metabolites in association with premenopausal breast cancer risk, most 16-hydroxylated estrogen metabolites were not associated with increased risk; however, urinary 17-epiestriol, which in our study shows a significant, inverse trend with green tea intake, was found to be associated with increased risk [27]. To date, the data on this metabolite and its association with breast cancer risk is very limited however, and so the implications of this finding are not clear.

Thank you for your careful review of our work!