Author’s response to reviews

Title: Ratio of n-3/n-6 PUFAs and risk of breast cancer: a meta-analysis of 274135 adult females from 11 independent prospective studies

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Author’s response to reviews: see over
Dear Lin,

Re: Revised manuscript 1888363717107339R2

I am pleased to submit revised version of manuscript 1888363717107339R2

We have worked through the details in the comments of the Editors and reviewers. These comments are all valuable and very helpful for further revising and improving our paper. We have revised the paper accordingly. We have addressed the each point made by editors and reviewers below:

Editors:

Question: please could you also ensure that you expand upon, in your discussion, the clinical/medical implications of your results?
Response: We have expanded the medical implications of results in our discussion (see P13, line 14-25).

Reviewer #1:

Question 1: I am still not happy with the “Intake ratio of n-3/n-6 PUFAs” which is not meaningful, in my opinion. It is better to say: “Ratio of n-3/n-6 PUFAs and the risk of breast cancer: …” which better reflects what is studied: data from dietary questionnaire in one side and data from blood samples in the other side.
Response: As suggested, we have changed the title.

Question 2: Once the authors have understood that serum phospholipids do not provide the same information as the dietary questionnaire, the lack of significant relationship between serum PL ratio and BC risk is easier to explain. Thus part of the discussion (in particular, about heterogeneity) should be rewritten.
Response: As suggested, we have rewritten relevant paragraph in the discussion section (see P10, line 12-25).

Reviewer #2:
**Question 1:** The main point is the association being apparently stronger in USA and Asian females: the authors have used meta-regression to test if there is a statistically significant difference and duly found no strong evidence for this; and yet the main conclusion states “Higher intake ratio of n-3/n-6 PUFAs is associated with lower risk of BC, particularly among Asian and USA females” and there is no mention that the difference is not unlikely to be due to chance – from reading the abstract the casual reader might assume that they had obtained a significant result.

**Response:** As suggested, we have revised the abstract accordingly.

**Question 2:** In the discussion there is a caveat about “study numbers”, but it is more urging “caution” than admitting they have no firm evidence. I think that the authors should state that they do not have conclusive evidence in the abstract, and quote the p-value for this result; and also mention this in the discussion if they are going to speculate about this particular facet of the study.

**Response:** As suggested, we have corrected the study numbers in the discussion section. We have also added the p-value for the result, and revised the discussion and conclusion accordingly. (see P2, line 19, 20 & 22; P8, line 24-26; P13, line 8-13; P14, line 9-11).

**Question 3:** I must still object to the phrase “which is a validated scale for observational studies.” (P5, line 19), which in my opinion, should be removed.

**Response:** As suggested, we have removed the sentence (see P5, line 17-19).

**Question 4:** “The explicit evidence for BC prevention” – this should perhaps be “implicit”, but either way I am not certain this makes sense. Please rephrase this sentence so it has a clear meaning – as far as I can tell, the meaning is “interpretation of the evidence”

**Response:** As suggested, we have rephrased the sentence in the abstract and conclusion section (see P2, line 24; P14, line 2).

**Question 5:** Please rephrase or omit this in some way, as it otherwise sounds as if the results are controlled for confounding – apart from “unknown or residual” – this is not really true.
Response: As suggested, we have rephrased the sentence (see P12, line 25-26; P13, line 1-2).

**Question 6:** Please note also that there is a minor error in the forest plot: the Saadatian paper has data on 91 cases and 91 controls for pre-menopausal (=182) and 106 cases and controls for post-menopausal (=212) – not 197 for pre- and post.

**Response:** Done (see revised figure 2).

**Discretionary Revisions:** There is still a lot of rather discussion about omitting one study at a time (p9, line23), in which the summary estimate ranges from 0.88 to 0.92. This does not really show anything that useful, and could be cut back substantially – the only point of interest really is that the serum results are largely influence by one study.

**Response:** We agree with reviewer, we have deleted the sentence (p9, line21).

We have improved the manuscript based on reviewer’s comments and made some changes in the manuscript. These changes will not alter the framework of the paper. We did not list the detailed changes but highlighted them in yellow in the revised paper.

We would like to thank the editors and reviewers for their advice and feedback again; we hope that the reviewed version will meet the requirements for approval. We look forward to hearing from you.

Yours sincerely,

Duo Li