Reviewer's report

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

Version: 3 Date: 22 October 2013

Reviewer: Ross Harris

Reviewer's report:

Minor Essential Revisions:

I thank the authors for their responses, which have mostly been addressed satisfactorily. However, in some cases it appears to be more to the letter than to the spirit: additions have been made, but with little change in interpretation. 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. 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.

I approve that the Newcastle Ottowa scale is not used for formal analysis, but 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. The reference is NOT a peer reviewed paper and any claims of validation must be taken with a pinch of salt. The authors cite other publications where it has been used in their response, but this also does not lend any credibility to the method – there are plenty of examples of widely-used bad practice in the literature. In addition, the authors say they have used Cochrane methodology, but nowhere is the NOS recommended, and there are specific criticisms of summary scores in the Cochrane documentation. Anyway, as perhaps you can tell, I am not keen on the method myself, but I understand its appeal.

“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”.

P17, line 24 “we performed stratified analysis by adjusting for known covariates” – analysis is either stratified (subgroups) OR it is adjusted (metaregression) – not
both. This would not help to reduce residual confounding apart from at a very
general level, as adjustment cannot be done at the individual level and it is only
“ecological” effects (averages at the group level), which are well known to be
potentially misleading. It is more that the studies themselves may have residual
confounding rather than anything the authors could possibly have done. 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
ture.

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.

Discretionary Revisions:

There is still a lot of rather discussion about omitting one study at a time (p9, line
23), 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.
I think this is the only thing that needs to be said really – in general, omitting one
study at a time doesn’t tell you anything good, just that a single study has a
strong influence (and indeed, the approach would not really tell you if two studies
were doing something unusual, as one will still be retained at each iteration). I
would tend to just examine the forest plot in order to get a feel for this sort of
thing – influential results can be spotted quite easily if they have extreme results
and/or high study weight.

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

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests