Reviewer's report

Title: Dietary and serum 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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Reviewer: Michel de Lorgeril

Reviewer's report:

This is an excellent manuscript.

The conclusion that "per 1/10 increment in dietary ratio of n-3/n-6 PUFAs was associated with 6% reduction of BC risk among study populations (USA, Europe and Asia)" and that "per 1/10 increment in serum ratio of n-3/n-6 PUFAs was associated with 27% reduction of BC risk among USA females" is impressive and confirms that dietary fatty acids and the way they are metabolized are critically important in breast cancers.

Question 1: did the authors make some efforts to contact investigators of previous studies which were not included in the present meta-analysis?

As an example, I understand from the supplementary file number 4 that the data from The Singapore Chinese Health Study were not included because the n-6/n-3 ratio was not indicated although the n-6 and n-3 were given separately (article by gago-Dominguez Br J cancer 2003).

Through a short contact, the Singapore investigators could provide the data.

I think it is an important issue and, for each excluded study, the authors should better justify why they did or did not contact the investigators.

Question 2: it is not clear (despite careful review of supplemental files) what is the exact content of the n-6/n-3 ratio in each study.

A table with precise data of the 11 selected studies would be useful.

Regarding the dietary ratio, the main n-3 are 18:3 (from plant) and then 20:5, 22:5 and 22:6 all from animal sources, mostly but not only fish. The main n-6 are 18:2 (from plant) and 20:4 (from animals). By mixing the plant and animals n-6 and n-3, authors may introduce a major bias; and apparently no adjustment has been done for some major dietary factors.

It would have been, maybe, more astute to simply use the ratio 18:2n-6/18:3n-3. Do you have such data?

Regarding the blood ratio, it is important to indicate whether they are phospholipids or total plasma (or serum) as the concentrations of each fatty acid are very different. For instance in phospholipids, 20:4 and 20:5 are more important (compared with plasma) and their weight could considerably influence the ratios. 20:5 is essentially from fish (dietary source) whereas 20:4 is very
dependent of endogenous metabolism with for instance hormonal effects.
Once again, it would be more astute to use only 18:2 and 18:3 as they are essential fatty acids and their concentrations less dependent of endogenous metabolism. In that case, of course, it is the relation of dietary fatty acids with breast cancers that is studied.
I understand that it would be very difficult to get very homogeneous data from more than 10 studies but it would be nice to know the relation (with breast cancer) of the ratio 18:2/18:3 from either the diet or the blood.

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests