Reviewer's report

Title: Effect of omega-3 fatty acid supplementation on cancer incidence, non-vascular death, and total mortality: a meta-analysis of randomized controlled trials

Version: 1 Date: 23 October 2013

Reviewer: Dennis Nilsen

Reviewer’s report:

This is an interesting and clinical relevant meta-analysis, evaluating the effect of omega-3 supplementation on: 1. cancer incidence, 2. non-vascular death and 3. total mortality. The authors have based their report on 20 randomized, controlled studies after scrutinizing the literature for clinical omega-3 studies. The selected trials are frequently cited and include 69,954 subjects, receiving treatment for either primary or secondary prevention. Follow-up time and dosages differ between studies.

The authors have also evaluated the effect of omega-3 supplementation in subgroups from the studies included; 1. those published before and those after 2000, 2. those with >1000 and those with <1000 included subjects, 3. those with more than 80% and those with less than 80% males, 4. those with a mean age >64 and those with a mean age <64 years, 5. those with primary and secondary prevention, respectively, 6. those with a duration >36 and those < 36 months, and finally 7. according to Jadad score >4 and < 4.

Their data would suggest that omega-3 fatty acids have no significant effects on cancer incidence, non-vascular mortality, or total mortality. Their subgroup analyses would suggest that omega-3 supplementation might play an important role in total mortality in men and if the duration of follow-up is less than 36 months.

Major compulsory revisions: The authors correctly state in their limitations that the trials included were designed to evaluate the effects of omega-3 on cardiovascular outcomes, and not cancer-outcomes. In the total patient population they found a 6%, statistically non-significant reduction in total mortality, and refer to a review paper by Leon et al. (BMJ 2009; 338:a2931) in which the authors conclude that omega-3 supplementation might play an important role in reducing the risk of total mortality due to the improved effects on cardiac death. Other reviews in which this opinion is not shared, should also be mentioned, and the reason for this difference in opinion should be stated. As several of the included studies have an open, controlled design, this may have introduced behavioral differences which may have had an impact on the development of cancer. Were there overall differences in smoking habits between the groups?

In the Introduction and Discussion sections the authors claim that cardiac death was reduced in numerous large-scale, randomized, controlled trials for primary
and secondary prevention of cardiovascular outcomes. This would not apply to ORIGIN and Alpha Omega Trial which are large randomized, placebo-controlled trials. This issue should be discussed and referenced, as the authors suggest that omega-3 supplementation may play an important role if the duration of follow-up is less than 36 months, claiming that these findings may be related to the early occurrence of sudden cardiac death.

In Table 2 the authors should also state the number of patients in each subgroup.

Minor Essential Revisions: The third sentence in the second paragraph of the Introduction section lacks fluency and should be revised.

**Level of interest:** An article of importance in its field

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

**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.