Author's response to reviews

Title: Arachidonic acid and cancer risk: a systematic review of observational studies

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Author's response to reviews: see over
Dear Editor,

We appreciate the helpful and insightful comments on our manuscript (MS: 1457178702715181). We carefully considered the referees’ comments and prepared this revised manuscript. Our point-by-point responses to the referees’ comments are summarized as below.

We greatly appreciate the time and effort of each referee in evaluating our manuscript, and hope that you will find the revised manuscript suitable for publication in the BMC Cancer.

Sincerely yours,

Saki Kakutani
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Responses to referee 1:

Major compulsory revisions –

Background:

It is not clear in this section that why a meta-analyses or a review is necessary in this topic. The authors have cited some studies with inconsistent results, but have not discussed why the results were inconsistent and how a meta-analyses or a review will improve the current knowledge on this topic.

Thank you for your valuable suggestion. According to your comment, we revised the Background section as shown below.

[Lines 82-87] In animal models, ARA administration did not affect tumour extension [26, 27]. Some observational studies also suggested no relationship between ARA exposure and cancer risk [28, 29]. However, there are the inconsistent observational studies that ARA exposure was positively correlated with the risk of colorectal cancer [30, 31]. ARA is one of the major polyunsaturated fatty acid, and this inconsistency is not negligible.

Methods:

As the authors stated and commented in their articles that they only searched for ‘specific words that stands for “arachidonic acid”’ and additional articles could be identified by other terms such as “fatty” or “fatty acid”. There is strong concern that the review may not be completed.

The concern of the referee is understandable. Essentially the term “arachidonic” should be suitable for our purpose, but it is difficult to search for the information of the nutrients with many similar compounds in a group, such as fatty acid, amino acid, vitamin and so on; it is often the case that information of a fatty acid is shown as one of many other fatty acids in a table, but the name of the fatty acid is not indicated either in title, abstract or mesh term. Such articles can never be selected by the PubMed search. To cover these articles, we designed the reference search to use additionally the term “fatty” or “fatty acid” which shows the wide concept close to “arachidonic” and is usually used in such articles.

Ideally, we should have identified the articles by the term “fatty” or “fatty acid” in the PubMed search as well as in the reference search. However, we did not take this strategy because we considered it unrealistic and inefficient. In fact, the number of articles hit by additional use of “fatty” is approximately six times larger than that by “arachidonic.” However, more than 95% of these articles must be excluded, because only 22 articles lacking “arachidonic” in title, abstract or mesh term were selected by the reference search. As the referee mentioned, our search method has the possibility that the review may not be completed, but is realistic and effective.

We revised the method section, and added this concern in the limitation.

[Lines 101-102] ...whereas terms for exposure were selected from specific words that stand for “arachidonic acid” (see Appendix).
Third, the search term “fatty” or “fatty acid” was not used in the PubMed search. It led to the efficient search but may cause the possibility that the review may not be completed. Fourth, quality assessment…

In the “quality assessment and data extraction section”,
1. It is not clear how the authors scored the data quality. For example, how much score did a publication obtain if it is a cohort study vs. a case-control study?
2. What is the theoretical range of the quality score?

The reporting quality score is the number of items to meet the STROBE checklist, and is applied to the observational studies regardless of study design. The score range is 0-34. To make the description clear, we revised the manuscript as shown below.

[Lines 126-129] The reporting quality shows whether the necessary information for observational studies is well indicated. It is the number of fulfilled items from the Strengthening the Reporting of Observational Studies in Epidemiology Statement (STROBE) checklist and varied 0 to 34 [33].
[Line 131-132] The methodological quality, a level of suitability of methods used in a study, was assessed by two authors (SK and MS)...

3. How did the author define high/medium/low quality studies?

Thank you for your valuable suggestion. We qualitatively assessed the studies by the reporting quality, temporal information and the other items. To make the process clear, we added the description as shown below.

[Lines 147-149] Our qualitative definition of the study quality was as below: the reporting quality score under 13 or the insufficient temporal information, low; the other studies were qualitatively divided into high/medium/low according to their strength and weakness.

4. How did the author score the “methods for controlling confounders”? The publication got a score as long as it adjusted for a confounder or the publication got scores when it adequately adjusted for a set of confounders? If the later, what are the minimal sets of confounders for each cancer site?

We considered confounders as one of the strength or weakness when we qualitatively assess the studies as described above. So, we did not make a set of confounders or the minimal sets for each cancer site.

Results:
The authors mentioned “the temporal relationship is not clear” in several places. The authors should have it in mind that the ability to assess temporal relationship depends on the study design. Only trials could provide information on temporal relations, but trials were not reviewed in the current study; other observational epidemiological studies, including cohort studies, have limitations on cause-effect inferences. Case-control, cross-sectional, and surveys are not suitable to evaluate the temporal relationship.

Thank you very much for your important advice. We intended to use “temporal relationship” specifically to distinguish two types of case-control studies, but have used the term in the other sections to lead the confusion. Of course we understand the referees’ comments. To avoid the confusion, we revised the manuscript as described below.

[Lines 181-182] …were a case-control study with little temporal information between exposure and outcome or a cross-sectional study.
[Lines 183-184] One case-control study with little temporal information between exposure and outcome and two cross-sectional studies investigated tissue ARA levels.
however, they were a case-control study with little temporal information between exposure and outcome or a cross-sectional study. 

Furthermore, most studies had one or more critical limitations, such as the obscurity of temporal information about exposure and outcome...

[Lines 177, 200 and 220 in the previous manuscript was deleted] Texts including “temporal”

Discussion:

1. What are the associations between diet, blood, and tissue ARA? If the correlations are low, which one would be the best indicator for ARA status? How is the association between this marker and cancer risks?

As shown in the Discussion, the correlations between dietary ARA and the ARA contents of blood or tissue are low in observational studies. However, the blood ARA was increased ARA-dose-dependently in a clinical trial. These data suggest the relationship between ARA intake and the ARA contents of blood or tissue, but the situation is complicated. Anyhow, the relationship may not be so high compared to the case in EPA or DHA. It is uncertain which indicator is the best at this time. While we saw the cancer risk according to the type of ARA exposure, there are no indicators which have the specific correlation with the cancer risk.

2. Line 286, discussion on selection bias: there is selection bias in case-control studies, how about the results from cohort studies?

As you mentioned, there may be a selection bias also in cohort studies. However, the effect of the bias is thought to be smaller than that in case-control studies.

3. How the authors assessed the publication bias? How publication bias affected your review results on breast and prostate cancers? The conclusion was that “ARA exposure is not associated with increased breast and prostate cancer risk”.

Thank you for your valuable suggestion. It is difficult to estimate the effect size and to quantify the publication bias in the observational studies, because they are so heterogeneous in the design, exposure/outcome assessment, etc. Therefore we assessed the publication bias qualitatively by the reporting quality and the significance of the result. As for breast and prostate cancers, most of the significant results were found in the studies with low reporting quality. They may be affected by the publication bias, because these studies may be conducted under insufficient consideration and an accidental significance may be advantageous for publication. Our review result should be affected by the publication bias partially, but not so intensively, since we did not give importance to these studies with low reporting quality. To make the manuscript clear, we revised the Discussion about the publication bias as shown below.

Fourth, publication bias based on findings of a significant association could exist, especially in breast and prostate cancer. Most of the significant results were found in the studies with low reporting quality. They may be affected by the publication bias, because these studies may be conducted under insufficient consideration and an accidental significance may be advantageous for publication. This suggests that publication bias may affect our review result on breast and prostate cancer, but the effect should be small, because we did not give importance to these studies with low reporting quality.

4. Line 262: Nevertheless, how big the studies were? Was there adequate power to detect a statistical significance? Would a meta-analyses be helpful to address the question?

Thank you very much for your insightful advice. It is very important. Although the most of articles are relatively small studies, the size of the participants reaches from several thousand to the tens of thousands in some studies. We think that we can ensure the power of each study to detect a statistical significance to some extent.
A meta-analysis is a useful tool, but we did not apply the approach to the present study because it may mislead the readers. Unfortunately, the observational studies identified here are too heterogeneous in the design, exposure/outcome assessment, etc. to integrate and analyze.

5. Is there any difference by publication year? Is there any change in ARA definition over years, e.g., calculation from the FFQ or the assay to measure the concentrations in blood or tissue? Would the changes influence the observed results?

Thank you for your important suggestion. We think that we do not have to consider the change in ARA definition over years in the present study. As for the diet, the FFQ method had been improved over years, but the reliability of estimation of ARA intake must depend on the quality of the food composition table for fatty acids. The quality varies by countries. The effect of publication year may have a small contribution.

As for measurement of blood or tissue ARA, the quantitative analysis by gas-liquid chromatography had developed by 1970’s. Of course the method has been improved but the basic principle is unchanged. We do not have to consider the change of the reliability of values of blood or tissue ARA.

6. Is there any difference by population, e.g., western or Asian populations?

It is very interesting, but we did not find the difference by population (the western countries, African, American African, Japanese, Chinese, etc.) in the present review.

Tables:
1. What are the statistical analyses for each study?

The statistical analyses for each study are one of the important information. However, we did not indicate it in the tables because of the limited space. We think that the information of statistical analyses is not usually shown in the summary table in general review studies. We would like to show the other important information in the table.

2. For case-control studies, were the cases and controls matched? What are the matching criteria? How the authors treated the matching variables in their analyses?

Thank you very much for your insightful advice. It was insufficient that we did not indicate the information "matching not indicated". Matching criteria differs by articles, and is not shown in the tables. We considered matching as one of the strength or weakness in the same manner as confounders, when we qualitatively assess the studies. According to the referees’ comment, we added information in Table 1, Table 3 and Table 4. In the same way, "precision not indicated" was added in Exposure Assessment in Tables 1-4. "Blinded to case-control status” was also added in Table 4.

Discretionary revisions –

Methods:
Line 108: How many studies were excluded for each exclusion criteria?

It is interesting, but we do not have the information. A lot of articles met more than two exclusion criteria. Unfortunately we did not keep a record in detail in these cases.

Responses to referee 2:

MAJOR COMPULSORY REVISIONS
1. Methods, Study selection, lines 113-114: why didn’t the authors assess the articles independently? Independent articles selection is a key step in a systematic literary review process, therefore the choice of a different kind of selection should be strongly motivated.

Thank you very much for your insightful advice. We agree that independent article selection is a key step, and recognize that our process causes an important limitation. Therefore, we changed the Discussion
section, and described this limitation at first. However, we think that it may not cause fatal bias in the present study, because there were few differences which depended on who was in charge due to the clear inclusion/exclusion criteria. The revised discussion is as below.

[Lines 338-342] First, studies for inclusion could not be selected independently by two or more reviewers. Our inclusion/exclusion criteria were clear and there were few differences which depended on who was in charge; however that may have introduced a potential selection bias. Second, our search was restricted to English publications and...

MINOR ESSENTIAL REVISIONS
1. Methods, Quality assessment and data extraction, lines 122-129: what is the difference between reporting quality and methodological quality? This should be shortly explained in the text.

   According to the referee’s comment, we added the explanation about the reporting quality and the methodological quality.

   [Lines 126-129] The reporting quality shows whether the necessary information for observational studies is well indicated. It is the number of fulfilled items from the Strengthening the Reporting of Observational Studies in Epidemiology Statement (STROBE) checklist and varied 0 to 34 [33].
   [Line 131-132] The methodological quality, a level of suitability of methods used in a study, was assessed by two authors (SK and MS)...

2. Methods, Quality assessment and data extraction, lines 141-143: the authors should specify what is the minimal number of studies to perform a meta-analysis taking into account the study design.

   Thank you for your important suggestion. A meta-analysis is a useful tool, but we did not apply the approach to the present study because it may mislead the readers. Unfortunately, the observational studies identified here are too heterogeneous in the design, exposure/outcome assessment, etc. to integrate and analyze.

3. Discussion, lines 230-251: in this section of the discussion the authors in part re-explain the methodology used for the systematic literature review. I suggest to shorten this part.

   According to the referee’s comment, we deleted the redundant explanation as indicated below.

   [Lines 230-235 in the previous manuscript was deleted] To effectively identify articles that corresponded to the objective of this review, our search strategy was designed as follows: first, a PubMed search formula was constructed specifically for ARA exposure, target cancer, and study type (see Appendix), and then bibliographies of retrieved articles were reviewed to conduct comprehensive literature identification (Figure 1). Finally,
   [Lines 237 in the previous manuscript was deleted] search strategy

4. Discussion, lines 296-301: the link between low reporting quality and publication bias is not clear and should be rewrite in a clearer manner.

   Thank you for your valuable suggestion. We assessed the publication bias qualitatively by the reporting quality and the significance of the result. As for breast and prostate cancers, most of the significant results were found in the studies with low reporting quality. They may be affected by the publication bias, because these studies may be conducted under insufficient consideration and an accidental significance may be advantageous for publication. Our review result should be affected by the publication bias partially, but not so intensively, since we did not give importance to these studies with low reporting quality. The previous manuscript was indeed unclear, and we rewrote the Discussion about the publication bias as shown below.
Fourth, publication bias based on findings of a significant association could exist, especially in breast and prostate cancer. Most of the significant results were found in the studies with low reporting quality. They may be affected by the publication bias, because these studies may be conducted under insufficient consideration and an accidental significance may be advantageous for publication. This suggests that publication bias may affect our review result on breast and prostate cancer, but the effect should be small, because we did not give importance to these studies with low reporting quality.

5. Discussion, line 339: the authors wrote that they did not use search terms for ARA levels of tissue in PubMed searching. What did they mean? It is not clear from the text.

Thank you very much for your important advice. Our previous text was not clear. We were not able to set the search terms suitable for ARA levels of tissue before the PubMed search, because there are so many terms related to tissues. Therefore, we identified the articles related to ARA levels of tissues in the reference searches.

Furthermore, articles that investigated tissue levels of ARA as an exposure assessment could not be identified comprehensively. We did not set the search terms for ARA levels of tissue before the PubMed search, and identified the articles in the reference search.