Reviewer's report

Title: Association of Fascin-1 with Cancer-Specific Mortality, Disease-free Survival and Metastasis in Carcinomas: a Systematic Review and Meta-analysis

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Reviewer: sarah donegan

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Comments by Sarah Donegan

Major compulsory revisions

1. Risk of bias
There is no assessment of risk of bias or quality of these studies. This is an essential part of a systematic review. Cohort studies can be assessed using the Newcastle-Ottawa scale or other appropriate methods. The methods and results of the assessment should be presented.

Risk ratios and hazard ratios can’t be combined together in meta-analysis. Hazard ratios should be combined together using the generic inverse variance method to give a pooled hazard ratio. Risk ratios can be combined together using the generic inverse variance approach (or event rates can be combined can be combined using the Mantel-Haenszel method) to give a pooled risk ratio. Rephrase the methods text and correct the analyses.

3. Choosing data for the meta-analysis (in ‘Statistical analysis’ section).
Please rephrase the following as the method is not clear 'The order of preference for choosing the data to be pooled was: i) fully adjusted HRs or risk ratios and their 95% CIs from multivariable analyses; ii) crude log risk ratios and standard errors reported in the results or obtained by contacting the authors; iii) data extracted from Kaplan-Meier curves by the method of Tierney et al [23].' Data from each study should be pooled in the primary analysis, rather than choosing data. After doing the primary analysis, sensitivity analyses can be performed, such that studies for which data were estimated from curves would be excluded, to see if the conclusions change.

Clarify whether crude estimates or adjusted estimates were used. Meta-analysis of data from cohort studies is controversial. If the hazard ratios from different studies have been adjusted for different confounders, interpretation of the pooled hazard ratios is difficult. Yet, adjusting for confounders is important in
non-randomised study designs. Decide whether to present adjusted hazard ratios, crude hazard ratios or both types of estimates. Clearly label the results as adjusted or unadjusted.

4. Forest plots
The comparison ‘positive versus negative’ and the comparison ‘high versus low’ should be on separate plots. Data from the two comparisons should not be combined.

5. Assessment of heterogeneity (in ‘Statistical analysis’ section).
In addition to the I square statistic, test for heterogeneity by comparing the overlap of confidence intervals of the study specific estimates and using the chi-square test. Describe these methods in the statistical analysis section.

6. Subgroup analyses, sensitivity analyses or publication bias (in ‘Statistical analysis’ section).
In the methods, describe how possible causes of heterogeneity were explored using sub-group analyses or meta-regression? Which covariates were considered? Also, how was the robustness of the results explored with regard to biases etc? Was publication bias explored using funnel plots or other methods?

7. Choice of carcinomas (in ‘Data sources’ section)
I think that the decision regarding which carcinomas to include should be based on whether the question is of interest rather than the number of available studies. One large kidney study may provide valuable information but it is excluded from this review because a previous review included less than two kidney studies. Previous reviews may be outdated. The review authors could change the inclusion criteria or provide alterative justification.

8. Clarity of the eligibility criteria (page 6)
I think the criteria needs to more clearly stated. Specifically, eligible study designs (e.g. randomised controlled trials, non-randomised studies) should be stated with a brief summary of the study design if it is a non-conventional design.

Furthermore, the comparison of interest needs to be made clear i.e. low versus high and negative versus positive. It would also be helpful to define ‘high’, ‘low’, ‘negative’ and ‘positive’ with regard to staining. Perhaps an explanation why are these comparisons of interest could be given in the background.

Minor essential revision
9. In the abstract, I disagree with the statement that the PRISMA guidelines have been followed.

10. In the data sources section, describe whether organisations were contacted to obtain unpublished results; whether authors of conference abstracts and on-going studies were contacted for the published or unpublished report.

11. Also, in the data sources section, describe whether the study authors were written to if eligibility was unclear; clarify whether two review authors
independently assess the titles and abstracts; and state whether the full report was assessed when eligibility was unclear based on the abstract.

12. Lastly, in the data sources section, I would rephrase ‘For multiple study publications from the same research group with the same outcomes, we chose the study with the largest number of cases.’ The same research group may publish similar studies that are different; on the other hand, different research groups may publish the same study as separate articles (e.g. if it is a collaborative project).

13. Regarding the eligible outcomes (page 6), please clarify whether: ‘lymph-node or distal metastasis’ are one or two outcomes. Also, choose either ‘survival’ or ‘mortality’ as an outcome rather than both because I think that they are the same. Clarify whether mortality is this ‘cancer-specific mortality’, ‘all cause mortality’ or whether you looked at both separately.

14. Also, with respect to the outcomes, if only time to event data will be extracted, I would rephrase the outcomes, such as, ‘time to lymph-node metastasis’, ‘time to distal metastasis’, ‘time to mortality’, ‘time to disease free’. If dichotomous data, at different time points will also be extracted, I would state ‘lymph-node metastasis, ‘distal metastasis, ‘mortality’, ‘disease-free’.

15. Refer to figure 1 in the results, rather than the methods.

16. In data extraction section, describe whether hazard ratios were extracted that were unadjusted for confounders, or adjusted hazard ratios, or both.

17. In data extraction section, if the analysis is a time to event analysis, replace ‘relative risk’ with ‘hazard ratio’.

18. Was a sensitivity analysis done excluding the studies that did not clearly define mortality? Rather than assuming that the outcome is cancer mortality, my preference would be to write to authors to ask for the definition of mortality. If no reply is received, I would treat these studies separately using the outcome ‘mortality’.

19. In data extraction section, please clarify the disease-free survival analysis. To my understanding, initially the patients were diseased. If interest is in the time from surgery to date of disease progression, this is an analysis of ‘time to disease progression’, rather than ‘time to disease free’.

20. In data extraction section, please clarify which ‘results’ were extracted for metastases outcomes and for the mortality outcomes. Were dichotomous data (i.e. number of people with a particular event and the total number of people, or risk ratios and confidence intervals) extracted? Were time to event data (i.e. hazard ratios and confidence intervals) extracted? Were measures of effect extracted that were adjusted for confounders or just the unadjusted measures of effect?

21. Relative risks and risk ratios are different names for the same measure of effect. Use one name consistently.

22. In the statistical analysis section, simply state that the analyses were stratified by comparison (i.e. low versus high, positive versus negative) and by type of cancer (i.e. lung, gastric,…)’. Delete ‘We stratified the results according to
method of scoring fascin-1 staining’ and ‘For our meta-analysis, we stratified the results by method of scoring to determine if the different scoring methodologies might lead to heterogeneity in our effect-estimates.’

23. I would move the description of staining from the statistical analysis section (lines 5-7) to the eligibility section.

24. Numbers in the results text and figure 1 are inconsistent (e.g. 48/49 full papers for review).

25. In the results section, describe how many studies reported each outcome. If no studies reported the outcome, state this.

Discretionary revisions

26. I would describe the inclusion/exclusion criteria before describing the search strategy (i.e. ‘data sources’).

27. In the data sources section, consider rephrasing ‘A systematic review of all published literature, including papers, conference abstracts and reviews’ because it is not clear whether this is a review of studies or a review of reviews or a combination of both. In any case, this sentence seems redundant to me and could be moved to the background.

28. In the data sources section, I would describe the selection of studies under a different heading i.e. from ‘The title and abstracts of all ....’ . Then the data sources section will describe the search strategy alone.

29. I found the eligibility criteria on page 6 difficult to follow. To clarify the criteria, I suggest that: sub-headings (i.e. study design, participants, interventions, outcomes) could be used; or sentences could be shortened.

30. It would be useful to have the number of studies that were excluded for each individual reason in the flow diagram (fig 1).

31. I think that the results text should have three distinct sections: description of the characteristics of the included studies; risk of bias results; results of the analysis in this review.

32. Avoid describing the included studies in the methods, that is, delete the first four lines of the statistical analysis section. Also, I would avoid providing references to specific included studies in the data extraction section. Instead, I would write ‘When studies did not ...’.

Quality of written English: Acceptable

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

Declaration of competing interests:

I declare that I have no competing interests