Reviewer's report

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

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Reviewer: sarah donegan

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Association of Fascin-1 with Mortality, Disease Progression and Metastasis in Carcinomas: a Systematic Review and Meta-analysis

Sarah Donegan
26th October 2012

The review authors have adequately addressed most of my previous comments. Previous comments that have not been fully addressed are below. Some additional comments are also given.

Major comments:

1. 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. This applies to the analysis within each carcinoma type and the analysis across carcinomas.

2. 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. The review authors could provide alternative justification.

3. In the last paragraph of the background, I disagree with the comment that the meta-analysis identifies potential sources of heterogeneity. A forest plot displays differences in results that can help to understand the causes of the difference. However, potential causes of heterogeneity should be considered prior to see the data and are therefore identified by consulting experts in the clinical area and searching published literature for proven effect modifiers. I actually think the last sentence in the background should be deleted.

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

5. Inclusion/exclusion criteria. The eligibility criteria should be written as though you have not seen the included studies and therefore do not say what some included studies did or didn’t do. For example, ‘Studies had to meet the following inclusion criteria: (1) either randomised controlled trials, cohort or case-control studies; (2) in humans with carcinomas of the breast, colorectal, gastric, lung and oesophageal; (3) detected fascin-1 by immunohistochemistry and compared high versus low....’; and (4) reported outcome data for at least one of the following
outcomes lymph-node or distal metastasis, time-to-disease progression, or mortality.’

6. The second paragraph of the inclusion/exclusion criteria is not about criteria and therefore should be under a different heading e.g. ‘selection of studies’.

7. Data extraction section is quite long and could be condensed. For example the section could be ‘Data were extracted onto standardized pro forma by one assessor (VYT) and then double checked by two others (RMM and SJL). For dichotomous outcomes (i.e. mortality, ..., Lymph Node Metastasis, Distant Metastasis) the number of patients with the event of interest and the total number of patients in each category group (i.e. high, low, positive or negative) were extracted. For time to event outcomes (i.e. time-to-Disease progression), a hazard ratio was extracted from the study report where possible, otherwise a hazard ratio was estimated from Kaplan Meier curves using the method described by Tierney et al (ref). When a measure of effect (e.g. relative risk or hazard ratio) was adjusted for covariates, it was also extracted along with details of the corresponding covariates.’

8. In the statistical analysis section, describe whether hazard ratios were analysed that were unadjusted for confounders, or adjusted hazard ratios, or both.

9. Avoid describing the included studies in the methods. Methods of systematic reviews should be pre-specified.

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

11. Some of the cells in the quality assessment table are blank. Please provide a reason for the missing information e.g. ‘unclear information’ or ‘not reported’.

12. A short summary of the quality of the studies should be given after the description of included studies and results of the search. Refer to the quality results table in the summary. Delete the text and quality from page 16. Move the information about the quality of the studies to the summary. Results of your analyses regarding quality should be presented in the subgroup analysis section instead.

13. The quality of all 26 included studies should be assessed.

14. The ‘sensitivity analysis’ for ‘definition of mortality’ is a subgroup analysis. If you delete the results for the subgroup without the definition, the analysis becomes a sensitivity analysis.

15. When there is significant heterogeneity (chi-square p-value <0.1), use the random effects model i.e. figures 2, and 3 (overall). The result from the random effects model is equivalent to the result from the fixed effects model when there is no heterogeneity, so if there is a difference between the results from each model, you could use the random effects model.

16. When there is significant heterogeneity, do not report the fixed effects meta-analysis in the forest plot because the confidence intervals are artificially narrow.
17. I don’t understand the need to ‘recalibrate’ some scoring systems for these studies. By doing this, do all the studies have the same cut-offs for high, low, positive, negative. Can you clarify the reasoning in the additional file?

18. The cutoffs of studies seem to be very different, is a meta-analysis across these studies giving a meaningful result? I suggest that this should be a discussion point in the discussion.

19. I am confused by the method used to derive hazard ratios from the KM curve. The additional file says that the method by Tierney et al gives a summary hazard ratio. But then the text says the method was applied it to get a relative risk. If the method gives a hazard ratio it should not be combined with relative risks. Rewrite the text in the additional file to clarify how a relative risk was derived. If you actually derived hazard ratios, they should be called hazard ratios and should not be combined with true relative risks.

20. Can you confirm that hazard ratios and relative risks have not been combined?

21. If you are presenting relative risks, rephrase ‘time to disease progression’ to ‘disease progressed’; or if you present hazard ratios keep ‘time to disease progression’. This will help avoid confusion.

22. Also, I do not understand the assumption that was made to derive the hazard ratio i.e. the proportion of positive versus negative patients was the same in the 75 patients as in the 100 patients. Can you clarify?

23. Can the discussion be reduced in length? What are the main limitations?

Minor essential comments:

24. 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.

25. Search terms are in file 2 not 1 as mentioned in the text?

26. Additional table 1. ‘M’ has two meanings in the footnotes.

Minor discretionary comments:

27. Change ‘systematic evaluation’ to ‘systematic review’ in the last paragraph of the background.

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