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Markers of systemic inflammation and colorectal adenoma risk: meta-analysis of observational studies

Point to point response

Major comments 1. There are a multitude of subgroup and stratified analyses presented (at least 12, across 3 different inflammatory markers, meaning the likelihood of at least 2 false positive results). The review does not appear to have had a protocol published prior to this draft, therefore it is difficult to justify that all of these analyses were considered a priori. Many appear to be arbitrary and at least two should be removed entirely from the review – namely subgroup analysis by sample size (why 200 as a cut-off?) and NOS quality score (8 as a cut-off, despite all studies being considered high quality?). All others require further justification in the methods for why these are being performed.

Author response: Most of the subgroup analyses were based on existing literature. However, exploring sample size and NOS quality score were arbitrary choices of the authors and we agreed with the reviewer to not perform such subgroup analyses (which however demonstrated to be not relevant) We deleted them from Table2 and methods/results sections. Other subgroup analyses are justified in Method section as reasons for testing heterogeneity or possible effect of confounding factors.

2. The results text reporting the subgroup/stratified results needs to be more reflective of the many non-significant findings, rather than just highlighting the significant ones – for example through the addition of concise sentences summarising 'no significant associations were observed for IL-6 and adenoma risk in other stratified analyses including by....etc'. This would help to give a more balanced tone for results.

Author response: the non-significant results have been better described in Results section.

3. There is no justification for why analysis by advanced adenoma status is considered more important than the others, aside from that this resulted in a statistically significant finding. Although clinically more important, due to the points made above, this subgroup analysis should be moved to the table of subgroup/stratified analyses, rather than presented in the main Forest plot figure for CRP results.

Author response: while results in table are subgroup analyses (same risk estimates grouped according various criteria), data on advanced and non-advanced adenomas are provided by various studies as separate risk estimates, thus represent separate individual analyses.

4. The definition of ‘advanced’ adenoma does not seem consistent with international criteria – usually an adenoma >10mm, not >5mm, is considered to be advanced. Moreover, the inclusion of HGD and tubulovillous/villous features in advanced adenoma definitions is only applicable to US studies. I am unsure if Japanese guidelines include these as features of advanced adenomas, but certainly the UK study would not have applied these criteria. Furthermore, the authors acknowledge that multiplicity and size was only addressed by two studies, and both of these are key features of ‘advanced’ adenomas. Therefore, there is a risk of misclassification bias in other adenoma studies that have not denoted ‘advanced’ adenomas. Overall, I have concerns about the definition of non-advanced adenomas and advanced adenomas used throughout, and the lack of generalisability of this definition between regions. These results should also be toned down considerably within the review (including removal from the Forest plot, as above), and discussion of these limitations emphasised instead. The abstract and conclusions/core tips should certainly not focus on these findings.

Author response: we double checked the definitions provided by the four studies providing data on advanced adenomas and all fit with the definition we considered in the methods section: “advanced adenoma was defined as having diameter >1 cm or containing villous/tubulovillous characteristics, or severe dysplasia”. However we added in the limitations paragraph the possibility of differences in definitions among studies.

5. Discussion of differences in results for CRP (and IL-6 to a lesser extent) where confounders such as smoking have been adjusted are well outlined in terms of being potential mediators of the association and the potential issue of uncontrolled confounding. Could the authors also please comment on the timing of measurements and the potential bias of reverse causation?

Author response: authors commented on reverse causation in the Discussion section.

Minor comments 6. Please add dates searched to the abstract and methods

Author response: We added date of systematic search in the abstract. The date of systematic search was in Methods section in “Literature search and study selection”.