Response to Reviewers

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Red meat intake and the risk of endometrial cancer: Meta-analysis of observational studies

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Reviewer 00742250

This review article is well written and will contribute to the clinical practice of the readers. As a minor criticism, a few grammatical errors are found in the text. For example, "Observational studies have showed" is more appropriate than "Observational studies have reported" of line 1 in Abstract.

➔ We thank you for taking time to provide us with advice in detail. We thoroughly went through the manuscript and corrected grammatical errors.

Reviewer 00503176

1. There are several spelling/typing errors scattered throughout the manuscript – the text should be carefully checked and corrected.

➔ We thank you for taking time to provide us with advice in detail. We thoroughly went through the manuscript and corrected grammatical errors.

2. In Introduction – HRT is a risk factor for EC if based on unopposed estrogen. Hence, any unopposed estrogen is a risk factor: in the "form" of "estrogen-only" HRT or, as mentioned, chronic anovulation.

➔ We agree to your suggestion. We added 'estrogen-only HRT' as another risk factor for EC in the text.

3. Figure legends should be more informative. For example, Fig. 2 shows forest plot for conventional random-effects meta-analysis of case-control studies and indicates individual

study ES, pooled estimate, I2 value and a p-value. What does this p-value refer to? Is it p-value from Q-test (heterogeneity), or for the overall effect. Z-value for the overall effect should also be depicted. The same goes for Fig. 4 (forest plot – RE meta for prospective studies).

➔ We made figure legends more informative as you pointed out. We clarified z-value and p-value for overall test as well in the text for Fig2 and Fig 4.

Figure 3 shows funnel plot for case-control studies to illustrate a lack of publication bias. What about prospective studies? If you want to display the funnel plots, OK, but then show both (e.g., Fig 3 a and b)

➔ We agree with your point and added the funnel plot for prospective studies as Fig 3B.

4. Publication bias (apart from funnel plots): the text mentions p-values from Egger's regression test. There is a limited number of studies in this review, 11 and 5. With this number, Egger's test is known to have a limited power. More informative than the p-values would be to present intercepts with 95% CI.

➔ We showed the intercept and 95% CI for Egger's test as well.

5. Meta-regression was performed to explore heterogeneity regarding case-control studies. a) In the "Methods", what is the meaning of the following: "The quality of respective studies was evaluated by performing meta-regression in relation to proper definition of exclusion criteria, types of controls, use of…." ? Did you mean to say that elements of the primary study quality were used as pre-defined covariates for heterogeneity exploration in meta-regression? This should be clarified;

b) How was heterogeneity explored – by using a single covariate in each run, or? With 11 studies, a meta-regression model could well "sustain" 2-3 covariates. Any meta-regression model with 2-3 covariates tested? Any change in residual I2or reduction in tau2? Many of the mentioned covariates are actually indicators of the primary study quality. It would be informative and useful to display results of individual study quality assessment by assigning "quality scores", for example – by using Newcastle-Ottawa instruments for case-control and cohort studies. Such scores could then be used in meta-regression. One item in particular was not addressed regarding case-control studies which is addressed by these instruments –

"length of exposure". Many of the case-control studies referred to a period of around 1 year (before the diagnosis) as an "exposure period". This might be too short of a period to assess a risk factor for a malignant disease (and, if we were to disregard for a while epidemiological knowledge, associations found under such circumstances could indicate a "reverse effect" (– that "bearing" a growing EC influences our "hunger" for red meat). The Newcastle-Ottawa instruments would acknowledge this property of a primary study by assigning appropriate score.

➔ We appreciate that you took your time and suggested a better directionality of our manuscript.

a) As there was a substantial heterogeneity we tried to find out its source. We performed a meta-regression to explore whether there was a significant correlation pattern or not. We used the elements of the primary study quality as pre-defined covariates. However we could not find any significant pattern that could explain the heterogeneity. Hence we did not describe it in detail.

b) We assessed the quality of the included studies based on the study design. We classified prospective cohort studies as high quality whereas case-control studies as low quality. One of our main algorithms was to display discrepancy between prospective studies and retrospective study, which could be achieved without further assessing the qualities individual studies.

As for the reverse causation issue, we addressed it in the discussion section as following.

Second, difference in reference year for exposure measurement relates to differential assumption regarding etiologic window of red meat intake in affecting EC risk, which could lead to inconsistent results. In case-control studies, participants were asked to recall red meat intake during 1-5 years before the assessment. This inherently assumes that recent red meat intake is relevant to current EC risk. In cohort studies, baseline assessment of red meat intake is usually assumed to represent a long-term diet and participants were followed-up for 7 to 21 years. Thus, long-term red meat intake was assumed to modulate EC risk. Thus, it is possible that case-control studies and prospective observational studies addressed different questions regarding the red meat intake-EC

relationship and thus, reached different conclusions.

6. Dose-response meta-analysis method should be described in more detail. In particular, methods to consider correlation between exposure categories should be declared, because disregarding correlation yields biased estimates (Orsini et al. Am J Epid 2012;175:66). Declare the computational method for dose-response analysis (Generalized least squares in STATA? Or?)

➔ We accept that our initial description for methods was not enough. We added following to methods section

In dose-response meta-analysis we used 'Generalized Least Squares' in STATA, which considers the correlation among exposure categories by approximating covariance with GL method.

7. The discrepancy between the estimates derived from case-control and prospective cohort studies is more or less adequately addressed. Still, an addition would be welcomed – authors' opinion on the quality of evidence from case-control vs. cohort studies and their preference about which of the two findings is more likely to represent the "true population situation".

➔ We agree with your point and revised our manuscript. To address your point, we added following to discussion section

When the implication of the current study is addressed, however, it should be considered that the quality of evidence from cohort studies be higher because it is more likely to represent the real world situation.

Reviewer 02493079

Thanks for the opportunity to review this manuscript entitled: "Red Meat Intake and the Risk of Endometrial Cancer: Meta-Analysis of Observational Studies". The manuscript is nicely written. The authors performed a meta-analysis to evaluate whether red meat intake is

related to the risk of (EC).The authors found that a significant linear association between red meat intake and EC risk based on case-control studies but this was not confirmed in prospective studies. I have a few comments for the authors: 1)This work needs to be reviewed by a statistician so that it can be considered for publication. 2)In the manuscript, there are 16 studies were included in the final analyses. The quality of studies need to assess.

➔ Thank you for taking time and insightful suggestions.

1) We think other reviewer of this manuscript, for example, Reviewer 00503176 already gave us high-level of statistical comments. We revised our manuscript point by point to address the reviewer's statistical comments.

2) We assessed the quality of the included studies based on the study design. We classified prospective cohort studies as high quality whereas case-control studies as low quality. One of our main algorithms was to display discrepancy between prospective studies and retrospective study, which could be achieved without further assessing the qualities individual studies.

Reviewer 00227488

This manuscript has been written well. It gives a comprehensive overview of the association between red meat intake and the increase in risk of endometrial cancer based on a meta-analysis. The following comment is provided to improve this paper. Specific comment: 1. The authors showed that the intake of red meat of 100 g/day was associated with an increased risk of endometrial cancer based on a review of case-control studies. However, the basis for the cutoff point of red meat intake was not stated clearly. I suggest that the authors discuss more about the amount of red meat intake and the risk of endometrial cancer in the discussion section.

➔ We fully agree with you that the basis for the cutoff point of red meat intake be very important in terms of public health implication. However it should be extremely complicated and careful process to state cutoff or amount of average recommendation because red meat intake is associated with other disease rather than endometrial cancer such as colon cancer, cardiovascular disease, etc.

In addition, the present study does not show a significant association between red meat

intake and EC risk in the analysis with prospective studies, which hardly justify the basis for cutoff point of red meat intake.