Author's response to reviews

Title: Colorectal cancer among persons with HIV: protocol for a systematic review and meta-analysis.

Authors:

Joseph Nguemo Djiometio (NguemoDjiomJ@smh.ca)
Tyler O’Neill (t.oneill@mail.utoronto.ca)
Yang Kou (KouY@smh.ca)
Anne-Marie Tynan (Tynanma@smh.ca)
Ayda Agha (AghaA@smh.ca)
Ann N. Burchell (aburchell@ohtn.on.ca)
Tony Antoniou (ttoniou@smh.ca)

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Author's response to reviews: see over
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David Moher, PhD
Editor-in-Chief, Systematic Reviews
Ottawa Hospital Research Institute
The Ottawa Hospital, General Campus
501 Smyth Road
PO BOX 201B
Ottawa, Ontario, K1H 8L6

Re: MS 187596719155460 Colorectal cancer among persons with HIV: protocol for a systematic review and meta-analysis.

Dear Dr. Moher:

Thank you for forwarding the comments of the reviewers regarding our manuscript. We appreciate their efforts in reviewing our paper, and thank them for their time. We have outlined the points below, followed by a response to each.

Changes or responses to Reviewer# 1:

Comment #1: “Abstract (P2): Trial registration should read “Systematic review registration”.

Response: We have made the requested change.

Comment #2: “Inclusion criteria (P5): The criteria state that studies of colorectal cancer identified by self-report or questionnaire will be excluded; however there is no statement of what will be considered eligible – presumably cancer identified through cancer registries? This needs to be clarified.”

Response: We have added that colorectal cancers will be identified through review of disease registries to page 5 of the protocol.

Comment #3: “Please clarify whether prospective and retrospective cohort studies will be included or prospective only.”
Response: We have clarified that both prospective and retrospective cohort studies will be eligible for inclusion (page 4).

Comment #4: “Search strategy (P5): Please state how far back the database searches will go. If the search strategy for one of the databases is available please insert as a Table.”

Response: We have elected to maintain keep the sentence from ‘inception onwards’, since the search dates have not been fixed and will be determined when we begin the review. We have added a preliminary Medline search strategy (new Table 1, page 15).

Comment #5: “Study selection (P 5): Stage 1 – please clarify whether or not the two researchers will do this in duplicate or are splitting the database between them.”

Response: We have clarified that the two reviewers will be independently reviewing all titles and abstracts independently (page 6).

Comment #6: “Background (P3): Would be helpful to state the search end date of the two earlier relevant reviews.”

Response: We have added these data to page 3 of the protocol.

Changes or responses to Reviewer #2:

Comment #1: “It seems to me that standardized incidence ratios (SIRs) could represent very different quantities depending on the similarity of the HIV-infected and HIV-uninfected individuals. If the two groups are matched, or suitable adjustment is done, then SIRs may represent different disease risks according to presence of HIV; if not then they represent differences in the demographics of individuals with and without HIV, which we know to be substantial. The distinction is important. In the latter case, better estimates might be obtained by applying generic cancer risks to demographics of the HIV population. If the former, then the results provide important information about interaction with HIV status in cancer risk. It is possible that results will reflect a mixture of the two, and great care will be required in interpretation. The study critiques and analysis strategy have nothing to say about this issue, so currently seem destined to produce rather meaningless results, and the first sentence of the discussion appears to be misguided.

Response: We thank the reviewer for highlighting this point, and agree that this could be an important source of methodological heterogeneity for our study. We have updated the protocol to include capturing information regarding the nature of confounding control, the specific confounders used for multivariable adjustment of SIRs, and if applicable, subgroup analyses comparing adjusted and unadjusted SIRs and comparisons of adjusted estimates according to the type and degree of confounding control. We have noted these changes on pages 7 and 8 of the protocol. We believe that these analyses and the ensuing interpretation of SIRs will provide a more fulsome interpretation of our effect estimates, and have therefore not made changes to the first sentence of the discussion.
Comment #2: “Inclusion criteria: "Included studies will report standardized incidence ratios and 95% confidence intervals" ought to say "Included studies will report information sufficient to obtain standardized incidence ratios and 95% confidence intervals."

Response: We have made the suggested change.

Comment #3: “Why search the Cochrane Database? It does not seem relevant for the types of studies sought.”

Response: We agree that the Cochrane Database is unlikely to yield relevant articles, and have decided to not include it as part of our search strategy.

Comment #4: “Statistical analysis: You cannot "assess publication bias using a funnel plot" – see major texts about funnel plot asymmetry by Egger et al, Sterne et al. The authors need to demonstrate more sophistication in considering what sorts of results (in this particular field) might be suppressed from the literature, and why.”

Response: We agree, and will explore the potential for publication bias qualitatively and quantitatively (page 8).

Comment #5: “A point value of I-squared is not sufficient to make decisions about heterogeneity. It is subject to considerable uncertainty, and of course does NOT measure "extent of heterogeneity" as indicated by the authors.

Response: We agree with the reviewer, and have added a section highlighting our evaluation of clinical, methodological and statistical heterogeneity (page 7).

Comment #6: “Otherwise the statistical analysis strategy would seem reasonable for sufficiently similar results - however I am not confident that the review will identify sufficiently comparable results (see major point above).”

Response: We hope that we have addressed this concern adequately (see response to comment #1), but would welcome further guidance from the Editors if additional clarity is required.

Comment #7: “Please provide more detail of what is planned in relation to the objectives to examine stage at diagnosis and site of disease, as it is not at all clear what will be done for these.”

Response: We have added additional detail regarding the secondary objectives to page 8 of the manuscript.

We hope that we have addressed all of the concerns, and that the manuscript is now suitable for publication. On behalf of my colleagues, I would like to thank you for your continued interest in our manuscript. Please do not hesitate to contact us if you have any questions or comments.
Sincerely,

Tony Antoniou, PhD
St. Michael’s Hospital