Author's response to reviews

Title: Physical Activity is Associated with Reduced Risk of Esophageal Cancer, Particularly Esophageal Adenocarcinoma: A Systematic Review and Meta-Analysis

Authors:

Siddharth Singh (singh.siddharth2@mayo.edu)
Swapna Devanna (Devanna.Swapna@mayo.edu)
Jithinraj Edakkanambeth Varayil (EdakkanambethVarayil.Jithinraj@mayo.edu)
Mohammad H. Murad (Murad.Mohammad@mayo.edu)
Prasad G. Iyer (Iyer.Prasad@mayo.edu)

Version: 3
Date: 11 May 2014

Author's response to reviews: see over
May 11, 2014

Subject: Submission of revised manuscript (BMC Gastroenterology 670667720184480.R1)

Dear Dr. Morawska

We greatly appreciate the enthusiasm and positive critique of the reviewers' and the Editorial Board in response to our manuscript titled "Physical Activity is Associated with Reduced Risk of Esophageal Cancer, Particularly Esophageal Adenocarcinoma: A Systematic Review and Meta-Analysis" (BMC Gastroenterology 670667720184480.R1).

On behalf of my co-investigators, I wish to submit a thoroughly revised manuscript addressing key concerns raised by the reviewers and the Editorial Board. We have addressed all of the reviewers' comments systematically.

I hope this revised version of the manuscript is found worthy of consideration for publication in the Journal.

With best regards,

Prasad G. Iyer, M.D., M.S.
Associate Professor of Medicine
Mayo Clinic, Rochester
RESPONSE TO REVIEWER #1

Minor Essential Revisions

Comment 1. Abstract page, Results section, second-to-last sentence: should read “There were only two studies” instead of “There was only two studies”

- Response: We thank the esteemed reviewer for taking time out to review our manuscript. We have corrected the grammatical error in the statement. Please note, that at the suggestion of reviewer #2, an updated search was conducted, and the number of studies has gone up to three.

Comment 2. Statistical Analysis section, third sentence from the end: need a “-“ in “p values.” Should read “All p-values were two tailed.”

- Response: We have corrected the error in the revised manuscript.

Comment 3. Table 1. The first study author is misspelled. It should read Huerta instead of Huarta.

- Response: We apologize for the typographical error. We have revised this throughout the manuscript.

Discretionary Revisions

Comment 4. Introduction section, first paragraph, third sentence: consider re-wording the end of this sentence starting with, “… ranging from erosive esophagitis….”

- Response: We thank the reviewer for the suggestion, and have revised the statement.

Comment 5. Introduction section, first paragraph, fourth sentence beginning with “Routine endoscopic surveillance…”: consider deleting the comma in this sentence and, as I r ead this sentence, it should say “Routine endoscopic surveillance of patients with BE and endoscopic eradication therapy for a subset of patients with high-grade dysplasia are recommended” instead of “…is recommended” since you are referring to both endoscopic surveillance and eradication therapy.

- Response: We agree with the reviewer’s comment regarding the construct of the statement and have accordingly revised the statement as suggested.

Comment 6. Methods, Data Abstraction section, first sentence: delete comma after the word “association.” Should read “… and estimates of association were independently abstracted….”

- Response: We agree with the reviewer’s comment regarding the construct of the statement and have revised the statement.

Comment 7. Results, Study Flow section. Fifth sentence. The first two commas are not needed. Consider removing these so the sentence reads: “Six studies on dietary or socioeconomic risk factors for cancer mentioned assessing physical activity as a covariate
but did not specifically measure or report association between physical activity and esophageal cancer per se;…”

- **Response:** We agree with the reviewer’s suggestion and have revised the statement.

**Comment 8.** Results, Sensitivity Analysis section, second sentence: Comma following “ESCC” is not needed. Should read “… risk of ESCC resulted in resolution….”

- **Response:** We agree with the reviewer and have revised the statement.

**Comment 9.** Discussion, Implications for Clinical Practice and Future Research section, fourth sentence: the comma following “EAC” is not needed. Should read, “…progression to EAC may help shed…”

- **Response:** We agree with the reviewer’s suggestion and have revised the statement.

**RESPONSE TO REVIEWER #2**

**Major essential revisions**

**Comment 1.** One potential concern is that the current analysis principally focusses on EAC and provides virtually no data on ESCC. Could you possibly have missed some studies on physical activity and ESCC risk? Related to this, your literature review was conducted over a year ago and may therefore not be current. For example, a study by Dar et al. on occupational physical activity and ESCC was published in September 2013 and should probably have been included in the meta-analysis.

- **Response:** We appreciate the positive critique of the esteemed reviewer. In our original search conducted in February 2013, we conducted a systematic literature review of multiple electronic databases, supplemented with a review of conference proceedings from major gastroenterology and oncology conferences as well as a review of the bibliography of comprehensive review articles on the topic. We feel it is unlikely that we missed additional studies on the association between physical activity and risk of ESCC, but that this represents paucity of data on this topic. Since our original search, an additional case-control study on the association between occupational physical activity and ESCC has been published as pointed out by the reviewer (Dar et al, Cancer Sci 2013). We have updated our analysis on ESCC risk using this study. We did not identify other unique original manuscripts on the topic on an updated literature search of PubMed.

**Comment 2.** The abstract states that physical activity may modify the effect of obesity on risk for EAC. However, the manuscript did not address that specific question, so I recommend removing that statement.

- **Response:** We agree with the reviewer that our systematic review was not able to study the interaction between physical activity and obesity and risk of esophageal cancer. We have removed this statement from the abstract.
Comment 3. The Methods section states that effect estimates were pooled using a fixed effects model if a study reported on more than one physical activity domain. Please ensure that the assumption for that model was not violated (i.e., there was no heterogeneity of effect estimates in the underlying studies).

Response: We appreciate the reviewer pointing out this important issue. In the study by Huerta et al, the investigators reported the association between occupational and recreational physical activity and risk of EAC separately, with neither association being significant. For the purposes of our study, we combined these effect estimates into a single estimate for overall physical activity and risk of EAC. On sensitivity analysis, using summary estimate from each physical activity domain separately, the overall results were unchanged (data not shown).

Comment 4. The results section states that results remained statistically significant on restricting analysis to high-quality studies. However, the upper limit of the 95% confidence interval is 1.0 and therefore lacks formal statistical significance.

Response: We agree with the reviewer that the upper limit of the 95% CI was 1.00, and hence, did not meet the pre-specified significance threshold of p<0.05. We have revised this statement in the revised manuscript.

Minor essential revisions

Comment 5. Reference number 34 contains typos in the author list.

Response: Thank you for pointing this out. We have revised the reference.

Comment 6. The name of the author Huerta et al. is misspelled in the Tables and Figures.

Response: We apologize for the typographical error, and this has been corrected in the revised manuscript.