Author's response to reviews

Title: Characterization of the association between 8q24 and colon cancer: gene-environment exploration and meta-analysis

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Author's response to reviews: see over
April 1, 2010

Bjoern Bruecher  
Associate Editor  
BMC Cancer

Dear Dr. Bruecher:

Please find enclosed a revision of our manuscript MS: 1751336102334254 which we are resubmitting in response to reviewers for publication in BMC cancer. Our original title was “Genetic variation at chromosome 8q24 and risk of colon cancer: Association study and Meta-analysis” with co-authors Carolyn M. Hutter, Martha L. Slattery, David J. Duggan, Jill Muehling, Karen Curtin, Li Hsu, Shirley A. A. Beresford, Aleksandar Rajkovic, Gloria E. Sarto, James R. Marshall, Nazik Hammad, Robert Wallace, Karen W. Makar, Ross L. Prentice, Bette J. Caan, John D. Potter and Ulrike Peters. Please note, on suggestion from one of the reviewers, we have changed our title to: Characterization of the association between 8q24 and colon cancer: gene-environment exploration and meta-analysis.

We appreciate the feedback and reviews we received from the two reviewers, as well as in the letter from your office. In response to these reviews we have made several modifications to our manuscript. We used track-changes in Word to highlight the changes:

**Referee 1**  
**Reviewer’s report:**
The study “Genetic variation at chromosome 8q24 and risk of colon cancer: Association study and Meta-analysis” by Hutter et al shows a modest association between 8q24 SNP rs6983267 and risk of colon cancer. The study is well designed, agrees with published literature, but does not add new data. Though the authors did a meta-analysis, none of the plots are shown in the results. As a review article, this manuscript needs more graphs to summarize their data as it pertains to published literature.

**Response:**
We now have several figures that show the results from our meta-analysis and summarize our data as it pertains to the published literature:
- Figures 2 and 3 show the forest plot for our meta-analysis.
- Additional file 2 shows the funnel plot for visually inspecting evidence for bias in our meta-analysis.
- Additional file 3 provides a forest plot for a sensitivity analysis, including the one study that was excluded from our meta-analysis based on pre-specified exclusion criteria.

**Referee 2**  
**Reviewer’s report:**
No major compulsory revisions necessary.  
Discretionary revisions  
The authors have restricted their analysis to Caucasian subjects, citing potential issues of population stratification. Although this might potentially influence the results, it would be worthwhile to give the data for other ethnicities, provided these data are available. (in this context, it should say “...who self-reported as white” (page six, end of first par.)
Given the interesting findings and large study cohorts, the title fails to reflect the importance of this study and should be modified accordingly.
Response:
We appreciate the reviewers comment that it would be worthwhile to give data for other ethnicities, and have expanded our results in two ways to reflect this comment:

- We have added the following text to the first paragraph of page 12 of our manuscript:
  “Results were also similar when we included subjects that did not self-report as white (126 cases and 126 controls for WHI and 139 cases and 135 controls for DALS), with an OR of 1.12 (95% CI: 0.97-1.30, p=0.14) for WHI and 1.12 (95% CI: 1.02-1.23, p=0.02) for DALS. “

- We updated our meta-analysis to reflect papers published since our last submission. In doing so we were able to include a couple more non-European/European American studies. As a result we have expanded our meta-analysis, and now report results stratified by race/ethnicity.

- We corrected the typo, so that it now says “self-reported as white” rather than “self-reported at white”

In light of the reviewer’s comment we have modified the title of our manuscript. Our new title is “Characterization of the association between 8q24 and colon cancer: gene-environment exploration and meta-analysis.”

Editor comment:
In addition to the concerns raised by the reviewers, please ensure that you expand on the description of the meta-analysis methodology in the Methods section of your manuscript. Please also ensure that your manuscript adheres to PRISMA guidelines.

Response:
We have updated our meta-analysis to be current as of March 31, 2010. We have also reviewed the PRISMA statement and have made several changes to our manuscript to ensure we adhere to PRISMA guidelines:

- We clarified the specific statement of the purpose of our meta-analysis in the full first paragraph of page 5 to now read:
  “…we performed a meta-analysis of the rs6983267 variant in relation to risk of colon and colorectal cancer.”

- We expanded the description of the meta-analysis methodology in the Methods section (pages 10-11) to specify our protocol, eligibility criteria, information sources, search terms, data collection process, description of summary measures and method for combining results, method for assessment of bias across studies, and description of pre-specified and ad-hoc sensitivity analysis.

- We expanded our presentation of the results from the meta-analysis in the Results section (page 12-13) and include additional files showing the funnel plot and ad-hoc analysis.

- We added a discussion of our meta-analysis results on page 15, and highlighted the implications for future research in the conclusions section (page 19).

Thank you for considering our manuscript for publication in your journal. We look forward to hearing your decision on this paper.

Sincerely,

Carolyn M. Hutter, PhD
Staff Scientist
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