

Dear Editor,

Re: ESPS Manuscript NO: 6022

Columns: TOPIC HIGHLIGHT

Title:

“The epidemiologic transition of colorectal cancer in developing countries: environmental factors, molecular pathways, and opportunities for prevention.”

We have revised the manuscript according to the reviewers’ comments as below:

Reviewer 1: We would like to thank this reviewer who found the manuscript acceptable and graded it as “excellent”. Reviewer 1, however, suggested to review more in depth the molecular pathways involved in colon carcinogenesis and supply the figure for molecular mechanism pathway.

In this new version we have added much on the molecular pathways of CRC that may be affected by diet/environment. Also we reviewed more extensively the association studies testing the candidate pathways with environmental risk factors at the population level.

The added sections are highlighted in yellow as requested by the editorial office.

Briefly, we expanded the section on epigenetic alterations affecting CRC, and reviewed the epigenomic effects of environmental risk factors including diet, obesity, physical activity, smoking and alcohol.

We have also added a section on Nuclear Receptors and their roles in mediating the effect of diet in colon cancer tumorigenesis. This section has been prepared by Dr. Michele Vacca, an expert in the field, who is now included among the authors.

Finally we extended our review on population-based association studies that have analyzed the associations between environmental factors including diet with the above candidate pathways.

The complexity level of interaction between several environmental factors and numerous molecular pathways in CRC, as appeared in our text, has prohibited us from depicting this in a single figure. We believe the figure that could accurately reflect the discussed molecular interactions would be too confusing and complicated to appear in the manuscript.

Reviewer 2: overall found the manuscript in an acceptable format and pointed out that “this is an interesting review which highlights the interesting problem of the CRC rise in developing countries.”

We would like to thank you for reviewing our invited highlight manuscript and the comments of your reviewers who found the manuscript interesting.