

May 1, 2022

Re: Submission of a Revised manuscript to the World Journal of Gastrointestinal Oncology

Dear Editors and Editorial Committee,

Thank you very much for giving us the opportunity to revise our invited review (Manuscript number: 76807)

We would be grateful for the consideration of our revised manuscript “Colitis and colorectal tumors should be further explored and differentiated” (by Donghui Xu, Bo Zhou, Zhipeng Li, Lianping He and Xinjuan Wang) for publication in the World Journal of Gastrointestinal Oncology. The authors have read and complied with author guidelines, and they all have seen and approved this manuscript for publication. None of the authors had a conflict of interest to disclose concerning this manuscript.

We are grateful to the editors for their precious contributions and comments. We have revised our manuscript accordingly for grammar, style, structure and we hope that you will now find it suitable for publication in the World Journal of Gastroenterology. In case of final acceptance, we agree to make this manuscript open-access.

The changes in the manuscript are identified in track change mode. Below you can find a point-by-point reply to the reviewers. We used red to denote revised or inserted text.

Thank you for your precious time.

We are looking forward to receiving your decision in due time.

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Reviewer #1: please add more reference regarding the smoking about the nicotine (mg), and the history of smoking tobacco or vaping (how long, the ingredients of nicotine, the accumulation of cigarettes smoking each day which increasing the colorectal tumours. Please add information about the gender, which one is higher on increasing colorectal tumours (women or men), how many percentages difference between women and men.

First of all, thank you for your review comments on our manuscript, here are our changes.

The Siegel RL study shows that women under 49 are about 3% more likely to die than men [8].

Research by Curtin K shows that smoking (>20 pack-years vs. non-smokers) was associated with TP53 mutations (OR = 1.4, 95% CI 1.02-2.0), BRAF mutations (OR = 4.2, 95% CI 1.3-14.2) and MSI (OR = 1.4, 95% CI 1.02-2.0) in rectal tumors = 5.7, 95% CI 1.1-29.8) associated with an increased risk. Long-term exposure to >10 hours/week of environmental tobacco smoke (ETS) was associated with an increased risk of KRAS2 mutations (OR = 1.5, 95% CI 1.04-2.2) [9].

REFERENCE

8 Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, Jemal A. Colorectal cancer statistics, 2017. *CA: a cancer journal for clinicians* 2017; 67(3): 177-193 [PMID: 28248415 DOI: 10.3322/caac.21395]

9 Curtin K, Samowitz WS, Wolff RK, Herrick J, Caan BJ, Slattery ML. Somatic alterations, metabolizing genes and smoking in rectal cancer. *International journal of cancer* 2009; 125(1): 158-164 [PMID: 19358278 PMCID: PMC2782655 DOI: 10.1002/ijc.24338]

Reviewer #2: I read with interest the letter by dr Xu in reply to the article of dr Kida (not Yuichi). I cannot disagree with most of the considerations made in this letter to the editor of WJG. However, I don't see how these considerations fit into a reply letter to a case-control study written only to explore whether the Japan Narrow-Band

Imaging Expert Team (JNET) classification and pit pattern classification are applicable for diagnosing neoplastic lesions in patients with ulcerative colitis (UC). If the authors of this letter have scientific proof or material they want to share with the scientific community, they should probably write a manuscript themselves to get credit for it. I am afraid, but I don't think this letter is a fair comment to the selected paper.

We appreciate your review comments and have corrected the citation information. We reviewed the relevant literature and made the following supplementary references to provide more substantial evidence.

We read with great interest the study by Kida Y et al. ^[1]

REFERENCE

8 Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, Jemal A. Colorectal cancer statistics, 2017. *CA: a cancer journal for clinicians* 2017; 67(3): 177-193 [PMID: 28248415 DOI: 10.3322/caac.21395]

9 Curtin K, Samowitz WS, Wolff RK, Herrick J, Caan BJ, Slattery ML. Somatic alterations, metabolizing genes and smoking in rectal cancer. *International journal of cancer* 2009; 125(1): 158-164 [PMID: 19358278 PMCID: PMC2782655 DOI: 10.1002/ijc.24338]

Reviewer #3: The authors wrote an interesting article on colitis and colorectal cancer (CRC). Following comments should be addressed. The author should discuss reproductive, environmental, dietary factors, which influence inflammation, carcinogenic mechanisms, and response to therapy. The authors should discuss these points; influence of those factors on tumor biology and clinical outcome. These factors may influence molecular pathology and response to therapy in each patient differentially. There are also influences of germline genetic variations on both immune system and cancer. Gene-by-environment interactions should be discussed. Of course, CRC is not only caused by colitis. In those lines, research on diet, environment, lifestyle, reproductive factors should be integrated with analyses of

personalized molecular biomarkers in tumor - that is needed for cancer outcome research. The authors should discuss molecular pathological epidemiology research that can investigate those factors in relation to molecular pathologies, and clinical outcomes. Molecular pathological epidemiology research can be a promising direction and should be discussed, eg, *Ann Rev Pathol* 2019.

Thank you for your recognition of our manuscript, and for your review comments on our manuscript, and for your molecular pathology perspective, which we will update in future work.