

Response to Editor and Reviewers Comments

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Beta-carotene and its protective effect of gastric cancer

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Editor comments:

Company editor-in-chief:

I recommend the manuscript to be published in the World Journal of Clinical Cases.

Responses: Yes, we gratefully appreciate for your valuable suggestion. We have revised the manuscript according to the guidelines and format of World Journal of Clinical Cases. The content of our manuscript has also been revised in accordance to the reviewers' suggestions. Revised content has been marked in blue.

Reviewer reports:

Reviewer #1: This manuscript article was well-written about beta-carotene and its beneficial effect for gastric cancer. The sections of text body were structured and contents were described in detail. However, major concerns about this manuscript are as below.

Response: Thank you very much for your careful reading of the manuscript, and thank you for your valuable comments for our manuscript. According to your comments, we made a point-to-point response, we hope to be able to meet the requirements for publication, if you are not satisfied with the revised manuscript, we will make a second revision.

Major comments:

1. First, the section of '1.3 Functions of beta-carotene' was divided into the antioxidant effect, facilitating gap-junction intercellular communication, and immune-related function. To help the readers in understanding these contents, some illustrations are needed.

Response: Yes, we gratefully thanks for your recommendation, we have add some illustrations about these contents, the new contents are marked in blue.

2. Second, Figures 2-4 were not cited in the manuscript body.

Response: Yes, thank you for your careful reading, we apologize for our negligence. We have

cited the Figures 2-4 in the appropriate site of our manuscript. The added contents have marked in blue.

3. Third, H. pylori was not described despite an important risk factor of gastric carcinogenesis in the first paragraph of '2. Gastric cancer'.

Response: Yes, thank you for your nice suggestion, we have searched more literature online and stressed H.pylori as an important risk factor.

4. Fourth, there were wrong descriptions in the second paragraph of '2. Gastric cancer'. The 'late gastric cancer' and 'site of tumor invasion' should be corrected to 'advanced gastric cancer' and 'depth of tumor invasion', respectively. The 'depressed adenoma' is not appropriate to be a type of early gastric cancer. Paris classification for gastric cancer is recommended. For example, type I, IIa, IIb, IIc, and III are useful. The 'stomach type' seems to be wrongly written. Please check the Lauren's classification including intestinal and diffuse type gastric cancer on the pathology.

Response: Yes, thank you for your valuable comments, we are sorry for the wrong description of gastric cancer. We have corrected the 'late gastric cancer' and 'site of tumor invasion' to 'advanced gastric cancer' and 'depth of tumor invasion', respectively in accordance to your suggestion. Besides, we have revised the contents about the classification of gastric cancer. We added some contents about Paris classification and Lauren's classification. All changes have been marked in blue.

5. Fifth, recent advance of gastrointestinal endoscopic techniques and equipment allows the endoscopic treatment in the selected patients with early gastric cancer. Endoscopic treatment should be added to surgery in the third paragraph of '2. Gastric cancer'. The authors mentioned the diet and lifestyle control for gastric cancer. However, there was no reference about it.

Response: Yes, thank you for underlining this deficiency. We have checked some literature about the endoscopic treatment in the selected patients with early gastric cancer so that we can enrich the treatment of gastric cancer part in our manuscript. In terms of the diet and lifestyle control for gastric cancer, we are sorry for the less rigorous summary. So we delete the content, and we add the target therapies about gastric cancers. The revised contents are marked in blue.

6. Sixth, 'special gastritis' was not understood in the fourth paragraph of '2. Gastric cancer'. Please check whether 'special gastritis' is one of official classification in the reference.

Response: Yes, thanks for your careful reading. We checked about 'special gastritis' on online database. It was indeed not an official classification, we confused the classification of gastritis. So we delete it.

7. Seventh, the authors mentioned 'animal experiments' as the subsection of '3. The mechanism by which of beta-carotene modulates gastric cancer'. However, there was no description about it.

Response: Yes, we gratefully appreciate for your valuable suggestion, its our negligence for it. At first, we thought there would be some literature about animal experiments. But when we search related literature, we didn't find useful literature about it, we forgot to delete the aspect of 'animal experiments'.

8. Eighth, the abbreviation such as AGS should be explained as full form in the section of '3.1.1 Beta-carotene and the cell cycle'.

Response: Yes, we gratefully thanks for the precious time the reviewer spent making valuable comments, we have explained the abbreviation of AGS as human gastric adenocarcinoma AGS cells in the section of '3.1.1 Beta-carotene and the cell cycle'.

9. Ninth, 'caneration' was misspelled in the footnote of Figure 4.

Response: Yes, we gratefully thanks for your careful reading, we have correct the spelling 'caneration' to 'cancerization' in the footnote of Figure 4. And they are marked in blue.

10. Lastly, I hope that author can summarize the description of '3.2 Human epidemiological studies' using table. A summary using table may be helpful because many studies were described in the section.

Response: Yes, thank you for your valuable comments. We supplement a table which summarizes the description of '3.2 Human epidemiological studies' as suggested. It is called Table 1 at the end of our manuscript.

Author	Region	Study Type	Result	reference
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Kim JH, Lee J, Choi IJ, Kim YI, Kwon O, Kim H, Kim J	South Korea	Case-control study	Higher dietary lycopene intake might be inversely associated with the risk of gastric cancer, especially in <i>H. pylori</i> -positive subjects and participants who had ever smoked.	[101]
Gonzalez CA, Riboli E	European countries	Prospective Investigation	Gastric cancer risk was related to high plasma vitamin C levels, some carotenoids, retinol and α -tocopherol, high intake of cereal fiber and strong adhesion to a Mediterranean diet.	[102]
Qiao YL, Dawsey SM, Kamangar F, Fan JH, Abnet CC, Sun XD, Johnson LL, Gail MH, Dong ZW, Yu B, Mark SD, Taylor PR	Linxian, China	follow-up study	The cumulative gastric cancer-related mortality of participants receiving "factor treatment, a combination of 50 μ g of selenium, 30 mg of vitamin E, and 15 mg of beta-carotene, decreased from 4.28% to 3.84%, which was lower than participants who did not receive factor D treatment.	[103]
Persson C, Sasazuki S, Inoue M, Kurahashi N, Iwasaki M, Miura T, Ye W, Tsugane S, Group JS	Japan	nested case-control study	The plasma level of beta-carotene was inversely associated with the risk of gastric cancer.	[104]
Larsson SC, Bergkvist L, Naslund I, Rutegard J, A	Sweden	prospective cohort study	Intake of vitamin A, retinol, and the provitamin A carotenoids α -carotene and beta-carotene was inversely associated with the risk of gastric cancer, approximately 40% to 60% lower risk of gastric cancer than participants in the lowest quartile of intake of the nutrients.	[105]
Yuan JM, Ross RK, Gao YT, Qu YH, Chu XD, Yu	Shanghai, China	Cohort Study	High serum levels of alpha-carotene, beta-carotene, and lycopene were inversely	[106]

MC				associated with the risk of developing gastric cancer.	
Harvie M	--	meta-analysis		Dietary intake of vitamins C and E, beta-carotene and alpha-carotene was inversely associated with the risk of stomach cancer, but blood levels of these antioxidant vitamins did not display this association.	[107]
Druesne-Pecollo N, Latino-Martel P, Norat T, Barrandon E, Bertrais S, Galan P, Hercberg S	--	systematic review and meta-analysis		Beta-carotene supplementation does not exert any beneficial effect on cancer prevention. In smokers and asbestos workers, a daily dose of 20 to 30 milligrams increased the risk of lung cancer and stomach cancer	[108]
Abnet CC, Qiao YL, Dawsey SM, Buckman DW, Yang CS, Blot WJ, Dong ZW, Taylor PR, Mark SD	Linxian, China	prospective study		low retinol and high lutein/zeaxanthin concentrations increased the risk of cardia cancer and non-cardia cancer, respectively.	[109]
Zhou Y, Wang T, Meng Q, Zhai S	--	meta-analysis		Data from the case-control study suggested that β -carotene and α -carotene were inversely associated with the risk of gastric cancer, while results from the cohort study were inconsistent.	[110]

11. Reviewer #2: The description of the introduction was appropriate, but if the sources are more up-to-date, please use them. Tables and figures usually come at the end of the manuscript, but in this study this was not the case.

Response: Yes, thank you very much for your careful reading of the manuscript, and thank you for your valuable comments on our manuscript. According to your comments, we made a point-to-point response, we hope to be able to meet the requirements for publication, if you are not satisfied with the revised manuscript, we will make a second revision. We have updated some new content in our manuscript and put the figures and tables in the end according to your suggestions.

Minor comments:

12. The description of the introduction was appropriate, but if the sources are more up-to-date, please use them.

Response: Yes, thank you so much for your careful check, we searched literature again and added some literature such as number 44, 45, 46, 69, 73, 74, 78, 80. The revised contents are marked blue in our manuscript.

13. Tables and figures usually come at the end of the manuscript, but in this study this was not the case.

Response: Yes, thank you for your serious check, we have put all the tables and figures at the end of the manuscript.

We gratefully thanks for the precious time the editor and reviewers spent reviewing the manuscript and making constructive comments, which greatly improves the quality of the manuscript. We hope this manuscript can meet the strict requirements of the magazine for publication.

Yours Sincerely,

Li-Xuan Sang