

June 3, 2016

Editor-in-Chief of *World Journal of Gastroenterology*

Title: The Effect of Dietary Vitamin C on Gastric Cancer Risk in the Korean Population (ESPS Manuscript NO: 25703)

Dear Editor-in-Chief:

Thank you very much for your invitation to submit a revised manuscript in your letter dated May 16. The authors appreciate the editor and reviewers' valuable suggestions for improving the manuscript.

We have made changes to the manuscript based on these suggestions, and we provide detailed information regarding these revisions in the attached document.

We hope that we have adequately addressed the editors and reviewers' concerns and that the revised manuscript is now acceptable for publication in *World Journal of Gastroenterology*. We look forward to hearing good news from you regarding the journal's decision.

Sincerely,

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Major comments

Comment 1: In the introduction section: Previous reports on epidemiological studies should be cited and explained in more detail.

Authors' response: The results from previous epidemiological studies regarding the protective effect of vitamin C against gastric cancer risk can be stratified into 2 groups: those that support the protective effect of vitamin C and those that do not. After stratification, the related articles in each group were cited.

*In the manuscript: **Introduction section, page 5, line 101-106:** "Additionally, the protective effect of vitamin C is supported by many observational studies and meta-analyses^[6-15]. However, some observational studies did not successfully demonstrate a significant association between vitamin C intake and gastric cancer^[16-18]. To date, the association between vitamin C intake and gastric cancer risk has been inconsistent."*

Comment 2: In the introduction section at the end, the authors refer to a previous study in which vitamin C supplementation might be associated with lowered gastric cancer risk. In this study, were the patients infected with H. pylori? This should be clarified. If this is not the case, this information is misleading and does not belong there.

Authors' response: The studies mentioned in the previous manuscript did not clearly report the protective effect of vitamin C against gastric cancer risk in participants with H. pylori infection. Correa's study showed the association between H. pylori infection and lower concentrations of vitamin C in the gastric juice. Besides, the other study reported that dietary vitamin C inversely associated with severity of gastritis. We deleted this sentence because it was misleading.

*In the manuscript: **Introduction section, page 6, line 113:** "Supplementation with vitamin C is associated with reduced gastric cancer risk in some human studies^[9, 13]" was deleted.*

Comment 3: In the case of H. pylori-infected patients, could the dose of vitamin C ingested be a relevant issue to discuss? If such data or other studies are available, adding more information about the doses of vitamin C where relevant would be valuable.

Authors' response: In the beginning of the research, our main result in table 2 was weakened from a significance in model II (0.64 (0.46-0.88)) to a borderline significance in model III (0.71 (0.50-1.00)). After the analysis, we wondered whether H. pylori infection played a role in the association between vitamin C and gastric cancer risk. Therefore, we made an analysis to detect the association between vitamin C and gastric cancer stratified by H. pylori infection status in the table below.

	<i>H.pylori</i> negative				<i>H.pylori</i> positive			
	Range (mg/day)	Controls/ Cases	Model I OR (95% CI)	Model II OR (95% CI)	Controls/ Cases	Model I OR (95% CI)	Model II OR (95% CI)	
Vitamin C		<80.14	108/15	1.00	1.00	175/173	1	1
	Total (n=1,245)	80.14-120.67	107/12	0.78(0.34-1.79)	1.14(0.44-2.94)	163/118	0.73(0.50-1.01)	0.79(0.56-1.12)
		≥120.67	105/6	0.46(0.18-1.16)	0.56(0.20-1.55)	148/91	0.62(0.45-0.87)	0.74(0.51-1.08)
		P for trend ^a		0.099	0.230		0.006	0.116
	Male (n=810)	<73.18	58/6	1.00	1.00	118/101	1.00	1.00
		73.18-110.59	60/5	0.81(0.23-2.79)	1.23(0.29-5.28)	113/88	0.91(0.62-1.34)	1.04(0.67-1.61)
		≥110.59	69/7	0.98(0.31-3.08)	1.08(0.27-4.27)	102/63	0.72(0.48-1.09)	0.88(0.55-1.40)
	Female (n=435)	P for trend		0.820	0.940		0.120	0.584
		<91.70	37/9	1.00	1.00	57/60	1.00	1.00
		91.70-139.52	46/3	0.27(0.07-1.06)	0.37(0.07-1.98)	50/42	0.80(0.46-1.38)	1.06(0.58-1.96)
		≥139.52	50/3	0.25(0.06-0.98)	0.34(0.05-2.27)	46/28	0.58(0.32-1.05)	0.73(0.38-1.40)
	P for trend		0.057	0.287		0.071	0.322	

^aTrends were calculated using the median intake for each dietary vitamin C category as a continuous variable: Model I: unadjusted; Model II: adjusted by first-degree family history of gastric cancer, education level, job, household income, smoking status, regular exercise.

We did not add this table in the manuscript because of some reasons below:

- 1. The results from this table are not statistically significant due to some mentioned reasons in the discussion section.*
- 2. The main purpose of our study is identifying the association between vitamin C intake and gastric cancer risk. H. pylori infection status is one of confounder factors in our adjusted model.*
- 3. We want to reduce the number of tables in the manuscript to focus on the main purpose of the research.*

However, the dose of vitamin C consumed is a relevant issue should be considered to explain why we were failed to detect the protective effect of vitamin C in participants with H. pylori infection. Therefore, in the discussion section, we additionally compared the dose of vitamin C used in our analysis with that used in another study to prove our hypothesis that “the dose of vitamin C may be relevant to the non-protective effect of vitamin C intake on people with H. pylori infection”.

In the manuscript: Discussion section, page 12, line 317-323: “Finally, the amount of vitamin C consumed by the participants with H. pylori infection could explain this finding. A Korean case-control study reported that consuming over 170

mg/day of vitamin C could protect people with H. pylori infection against the risk of gastric cancer (0.10 (0.02-0.63))^[10]. Hence, in our analysis, vitamin C doses of 120 mg/day may not be high enough to show protective effect of vitamin C in participants infected with H. pylori"

Minor comments

Comment 1: In the abstract, under the methods, results and core tip sections as well as under the introduction section, "Helicobacter pylori" and "H. pylori" should be written in italic text.

Authors' response: We have re-written Helicobacter pylori and H. pylori in italic text throughout the manuscript.

Comment 2: In the abstract, under the results section, could the authors provide the amount of vitamin C for the respective intake categories?

Authors' response: We provided the amounts of vitamin C for the respective intake categories.

In the manuscript: Abstract, under the results section, page 3, line 62-63: "the highest (≥ 120.67 mg/day) vs. the lowest (< 80.14 mg/day)".

Typo comments in the manuscript

Comment 1: Author contributions: family name should be put first in full, followed by middle names and first name in abbreviation with first letter in capital.

Authors' response: We have put full family names in the first location, followed by abbreviated middle and first names.

*In the manuscript: Title page, author contributions section, page 1, line 21-24:
“Hoang VB and Lee J contributed equally to this work; Hoang VB and Lee J analyzed
and interpreted the data; Hoang VB and Kim J wrote the manuscript; Choi IJ, Kim
YW, and Ryu KW contributed to data collection; and Kim J had primary
responsibility for the final content.”*

Comment 2: Methods in Abstract: no less than 80 words

*Authors’ response: We have described the collecting data methods in greater detail in
the abstract.*

*In the manuscript: Abstract, under the methods section, page 3, line 53-55:
“Dietary intake information was collected from the participants using a food
frequency questionnaire that has been previously reported as reliable and valid.”*

Comment 3: Key words: 5~10 words.

Authors’ response: We have added key words to the manuscript.

*In the manuscript: Abstract, under the key words section, page 3, line 77:
“Korean Population”*

Comment 4: References: Add PubMed citation numbers and DOI citation to the
reference list and **list all authors**. Please revise throughout. The author should
provide the first page of the paper without PMID and DOI.

*Authors’ response: We have checked to ensure that there are no duplicated references
in this section. We have also added the DOI citations of the articles for which that
information was available.*

In the manuscript: References section, page 15-21.

Comment 5: Figure: provide the decomposable figure of Figures, whose parts are
movable and can be edited. So please put the original picture as PPT so that we can
edit them easily.

Authors' response: I have provided decomposable figures whose parts are movable and can be edited in addition to the original PPT file.

*In the manuscript: **Figure legends section, page 23.***

Other minor comments:

Authors' response: We have responded to your comments to improve the manuscript.