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March 25, 2019

Dr. Jia-Ping Yan

Science Editor, Editorial Office

Baishideng Publishing Group Inc.

E-mail: j.p.yan@wjgnet.com

Dear Doctor and Editor Yan:

Thank you very much for your email with encouraging news regarding our manuscript. We also thank the reviewers for their positive/constructive comments and suggestions, which truly help us to improve our manuscript. After incorporating their comments and the suggestions in the edited manuscript downloaded on the WJG submission website into the revised manuscript, I would like to re-submit it for your consideration for publishing in World Journal of Gastroenterology. The amendments are highlighted in red in the specific point-by-point replies to each of the reviewers' comments, which are attached below.

Thank you again, and I hope that the revision is acceptable. I am looking forward to hearing from you soon.

Sincerely,

Dr. Ji-Han Wang

Honghui Hospital, Xi'an Jiaotong University

E-mail: 513837742@qq.com

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 46401

Title: Alteration of the esophageal microbiota in Barrett's esophagus and esophageal adenocarcinoma

Reviewer's code: 02440843

Reviewer's country: United States

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-02-19 18:22

Reviewer performed review: 2019-02-24 22:28

Review time: 5 Days and 4 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This is a very well written and extremely informative state of the art review on a topic that has not received much attention in the medical literature.



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Thank you so much for your positive remarks.

My suggestions are as follows: The information is very well presented. Since it is narrative form only, the reader may find it hard to remember the important details. I would advise the addition of several tables, such as important organisms as mentioned in the text as well as listing mechanisms as listed in the text. In conjunction with these, I advise the addition of figures that demonstrate some of the important mechanisms that are outlined in the text. These will greatly enhance the quality and future importance of the manuscript.

Thank you for your advice. That's a very good suggestion. We totally agree with your advisements, and have already added one table and one figure in the manuscript. We listed notable findings and related information from important esophageal microbiota studies on Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC) in Table 1. And the hypothetical mechanisms by which the esophageal microbiota participates in the pathogenesis of BE and EAC were shown in Figure 1. Please refer to the revised manuscript for details. Thanks for your suggestions. We appreciate it very much.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

BPG Search:

- ☐ The same title



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☐ Duplicate publication

☐ Plagiarism

☐ No

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 46401

Title: Alteration of the esophageal microbiota in Barrett's esophagus and esophageal adenocarcinoma

Reviewer's code: 02549032

Reviewer's country: Greece

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-03-06 11:37

Reviewer performed review: 2019-03-14 18:16

Review time: 8 Days and 6 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input checked="" type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This is an interesting review opinion on esophageal microbiota in barrett esophagus (BE) and esophageal adenocarcinoma (EAC). The authors reviewed large number of articles (90 articles) and concluded that esophageal microbiota <<might play a causative role in

the pathogenesis of BE/EAC>>.

Thank you for your positive remarks. After searching related publications on the topic of esophageal microbiota and BE/EAC, we've got limited studies and could only suggested that the esophageal microbiota may be altered in the patients with BE/EAC. It is quite difficult to draw the conclusion that esophageal microbiota plays a causative role in the pathogenesis of BE/EAC. Therefore, we've rewrite the sentence "which might play a causative role in the pathogenesis" into "which might provide some evidence of their relations".

Some issues to be answered:

1. No detailed methodology for this review is described. Particularly how they have chosen the relative articles, (pubmed research? Only fullpapers? Etc).

Thank you for your question. In this traditional narrative review, we conducted the systematic search in the PubMed database, using these four key words which were "Barrett's esophagus AND microbiota", "Barrett's esophagus AND microbiome", "esophageal adenocarcinoma AND microbiota" and "esophageal adenocarcinoma AND microbiome".

2. The authors stated that <<Esophageal adenocarcinoma (EAC) is a common malignancy>>. I don't agree because in Asian countries squamous esophageal carcinoma is more common. EAC is generally not common but increasing in incidence.

Thank you for your question. It is well recognized that esophageal cancer (EC) is one of the most common malignancies in the world, and most of ECs are proved to be esophageal squamous cell carcinoma. Many studies have indicated that the incidence of EAC in Western countries is higher than that in Asian countries. However, the incidence of EAC has markedly increased in recent decades all over the world. We agree with your

point. In this review, we've searched the related publications on PubMed and the studies were conducted not only in Asian countries, but also in Western countries. Now we've rewrite the sentence "Esophageal adenocarcinoma (EAC) is a common malignancy" into "Esophageal adenocarcinoma (EAC) is a malignancy with poor prognosis". Thank you.

3. The authors stated that based on their review: << ..microbiota, and dysbiosis may be related to BE/EAC.>>. However, this conclusion is not absolutely correct. The <<cause/effect>> relation of microbiota and cancer, which is multifactorial disease, is difficult to be proved and cannot be based on weak, questionable studies. It is not clear if alterations in microbiota is a cause of BE or a result of BE, which resembles to intestinal mucosa (metaplasia).

Thank you for your question. We agree with you that BE and EAC are multifactorial diseases. In this review, we mainly focused on the changes of esophageal microbiota in BE/EAC patients. After the systematic search for related studies published on PubMed, we found that there are some associations between esophageal microbial alteration and BE/EAC. We've added Table 1 to summarize the related studies and important findings. However, whether the altered microbiota is one of the causes responsible for the pathogenesis of BE/EAC has not been proved. We've discussed this point in this review. Therefore, more work and studies are needed in order to draw any definite conclusions. We hope that more researchers will focus on this field to give more clues or suggestions. We will continue to work on this area for sure. Thank you.

4. It is generalized and not specific for BE or EAC to say that inflammatory parameters might be implicated in carcinogenesis. Why in BE and not in other organs?

Thank you for your question. It's true that it is generalized and not specific for BE or EAC to say that inflammatory parameters might be implicated in carcinogenesis. Many

studies indicated that inflammation is associated with carcinogenesis in many different tissues. However, we could not draw the definite conclusion that all cancers are related to inflammation. In this review, we mainly focused on the abnormal esophagus of which are BE and EAC, and explored the relations between esophageal microbiota and BE/EAC. We've added Figure 1 to show the hypothetical mechanisms by which the esophageal microbiota might participate in the pathogenesis of BE and EAC after the systematic search. Thank you.

5. In any way alterations in microbiota in BE, EAC, cannot prove the cause-relation to BE or EAC. More data on this issue is necessary and is too difficult because of large heterogeneity of such kind of studies.

Thank you for your question. Yes, we couldn't agree more. It is absolutely right that we could not draw any definite conclusions about the cause-relation between microbiota and BE/EAC. We've added Table 1 to summarize the related studies and important findings. Without doubt, the heterogeneity of different studies exists and we can't neglect it. More studies are needed and more data is required before discussing whether the cause-relation between microbiota and BE/EAC exists or not. We've made some discussions about this point in the review as well. We will focus on this area and try our best to reveal their relations. Moreover, multi-center studies in different areas could provide more evidence. Thank you.

6. The most important issue in BE/Esophageal adenocarcinoma is the low incidence of BE/EAC in Asia v/s high incidence in West. Is this difference related to differences in esophageal microbiota?

Thank you for your question. That's quite a good point. We've taken this into consideration. Due to limited studies about esophageal microbiota in BE/EAC, we could



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not discuss the differences respectively in different areas. To our knowledge, many factors could influence the gut microbiota, such as different regions, different races, different diets and different adipose distribution. Therefore, these differences you mentioned among different races might exist and be an important factor. However, this is just a prediction and studies are needed to provide relevant evidence. Therefore, among the searched studies on Pubmed, we could only discuss the existing data. And we are looking forward to such a large-scale joint research with large samples in multi-centers and multi-regions with multi-races, which could provide more evidence. Thank you.

7. There is no clear evidence that features of esophageal microbial communities in BE and EAC patients, may promote the development of BE and EAC.>> So please re-write this conclusion in more accurate way.

Thank you for your suggestion. We agree with you. There is no clear evidence that alteration of esophageal microbiota could promote the development of BE/EAC. This review is mainly focused on the relations between alteration of esophageal microbiota and BE/EAC. Then we rewrite the sentence "which may promote the development of BE and EAC" into "which may provide some evidence of the relations between altered esophageal microbiota and BE/EAC". Thank you for your suggestion. Moreover, We've added Table 1 to summarize the related studies and important findings on BE/EAC, and added Figure 1 to show the hypothetical mechanisms by which the esophageal microbiota might participate in the pathogenesis of BE and EAC after the systematic search. Thank you for your suggestion and we appreciate it very much.

8. The authors reported on isolated studies << Macfarlane S et al. found that Campylobacter species colonized esophagus in the majority of BE patients and could not be identified in other groups>>. << Amir I et al. strongly suggested that the family



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Enterobacteriaceae (mainly the genus *Escherichia*) is associated with esophageal abnormalities, such as esophagitis and BE, ..>> However the <<cause and effect>> relationship cannot be proved. It is questionable to make definite conclusions based on isolated studies. It should be rewritten the message.

Thank you for your question. We totally agree with you. These two studies showed different results compared to the studies we discussed above. As a review, we exhibit the different conclusions in their studies in order to deliver more messages to the readers. Thus we could discuss the searched studies and their results from an objective point of view. And no definite conclusions about the "cause and effect" relationship was drawn in this review. It's true that we could not draw any definite conclusions based on limited studies. We are looking forward to such a large-scale joint research with large samples in multi-centers and multi-regions with multi-races, which could provide more evidence. Moreover, we've added the sentence "Therefore, a large-scale joint research about the alteration of the esophageal microbiota in BE/EAC are needed to provide more evidence, which is in multi-centers and multi-regions with multi-races." in this paragraph. Thank you.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

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- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

BPG Search:

- ☐ The same title



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