November 6, 2017

To,

The Editor,

World Journal of Gastrointestinal Oncology.

Dear Editor,

Thank you for reviewing our manuscript entitled: “Vitamin D in Esophageal Cancer: Is there a role for chemoprevention?”

Editor’s comments to Author:

Thank you for reviewing our manuscript and for providing us with valuable comments. We have adjusted the following in our manuscript as per your suggestions:

- The Journal name, Manuscript number and type have been added at the top of our manuscript.
- The ORCID number of each author was added to the Title page.
- “Financial Support: No funding sources” has been specified.
- A Core Tip paragraph was added.
- References have been reviewed to make sure there are no repeated ones.

Please provide the decomposable figure of Figures, whose parts are movable and editable. So please put the original picture as PPT so that we can edit them easily.

Thank you for your comment. We have asked the Art & Photography department at Cleveland Clinic to provide us with a decomposable figure of Figure 1. Unfortunately, they could not provide us with a decomposable figure, as they copyright all visual “Intellectual Properties” per their policy.
We have uploaded Figure 1 in both PDF/TIF and PPT forms as requested.
We have also uploaded, under image files, the copyright form provided to us by the Art & Photography Center. We apologize for the inconvenience and thank you for your understanding.

Please find below our point-by-point responses to the reviewers’ comments. Thank you very much for reviewing our manuscript and considering it for publication in the World Journal of Gastrointestinal Oncology.

Response to Reviewer 1 (03086186) comments:

Dr. Rouphael and the other authors made a comprehensive review of the effects of vitamin D on esophageal cancer and the precursor lesions. Despite solid conclusions regarding the chemopreventive role of vitamin D in esophageal cancer cannot be made, and problems remained regarding quantification of dietary vitamin D intake and sunlight, this review can still provide readers a deep insight into the topic. In addition, authors proposed future studies in the field, including prospective studies with accurate measurement of vitamin D status before chemoprevention with vitamin D, studies looking at the incidence of esophageal cancer in patients with pre-cancerous lesions with vitamin D supplementation. I think the review is suitable for publication in the Journal.

Thank you for reviewing our manuscript. We thank you for your time and for your positive feedback.

Response to Reviewer 2 (00052339) comments:

Vitamin D in Esophageal Cancer: Is there a role for Chemoprevention? Carol Rouphael et al. This review is not meta-analysis but just summary of the papers. The paper presented here showed the results of the correlation between Vitamin D and esophageal cancer analyzed by different methods. The 4 papers analyzed the correlation by using serum Vitamin D level, other 3 papers adopted the dietary intake, other 2 papers showed the results of ultraviolet B radiation. In addition, with genetic analysis there were two approaches such as Vitamin D receptor expression (3 papers) and Vitamin D receptor gene polymorphisms (2 papers). Thus, the different analytical methods were reviewed, and it was uncertain that the results obtained by these different methods were chemo-preventive or suppressive of development of esophageal cancer. If this manuscript may be acceptable for publication the author should review much more papers to obtain the conclusion about chemo-preventive effects of Vitamin D signaling because of many different approaches adopted by the authors

Thank you for reviewing our manuscript and providing us with valuable comments and suggestions. Our paper is a Review Article looking at the role of vitamin D as a chemopreventive agent in esophageal cancer.

In order to review the literature about our topic and collect all the articles of interest, we performed a PubMed search about our topic of interest using the following Mesh terms:

Vitamin D"[Mesh]) AND "Barrett Esophagus"[Mesh]
Esophageal Neoplasms"[Mesh]) AND "Adenocarcinoma"[Mesh])) AND "Vitamin D"[Mesh]
("oesophageal adenocarcinoma" OR "esophageal adenocarcinoma*") AND ("vitamin D" OR sun OR sunlight)*
("barrett metaplasia" OR "barrett* syndrome" OR "barrett* esophagus" OR "barrett* oesophagus" OR "barrett* epithelium") AND ("vitamin D" OR sun OR sunlight)*

((("barrett metaplasia" OR "barrett* syndrome" OR "barrett* esophagus" OR "barrett* oesophagus" OR "barrett* epithelium"))) AND ("Receptors, Calcitriol"[Mesh] OR "calcitrol receptor*")*
("oesophageal adenocarcinoma" OR "esophageal adenocarcinoma*") AND "calcitrol receptor*"*

All of the articles brought back by the search engine were reviewed and relevant articles were discussed in our manuscript. We went back to the literature but could not find additional manuscripts. We hence concluded that additional well-powered prospective studies with accurate measurement of vitamin D status are needed, before chemoprevention with vitamin D is recommended, since current evidence does not support a chemopreventive role of vitamin D against esophageal cancer.

Response to Reviewer 3 (00182114) comments:

Thank you for reviewing our manuscript. We thank you for your time and for the positive feedback.

1.I think SCC is due to tobacco and alcohol, ADC is due to GERD. There is an etiological difference between ADC and SCC. But author found serum 25(OH)D3 levels appear to be associated with higher risk of ESCC and EAC. Please comment serum 25(OH)D3 levels appear to be associated with higher risk of ESCC and EAC.

Thank you for your comment. We agree that there is an etiological difference between EAC and ESCC.

When looking at ESCC, only one population-based study from China looked at the relationship between 25(OH)D_3 serum levels and ESCC[28]. A direct association was noted. In our manuscript, we specified that those results could not be extrapolated to other populations due to overall low vitamin D levels and high rate of exposure to polycyclic aromatic hydrocarbons in this study population, with the latter factor placing them at higher risk for neoplasia [28]. We also noted that pre-neoplastic lesions with squamous cell dysplasia were also found to have an E-cadherin/osteopontin disequilibrium, with E-cadherin suppression and osteopontin up-regulation leading to increased risk of cell growth, proliferation and subsequently malignant transformation with higher calcitriol levels [14].

When looking at EAC, two studies [36,38] evaluated the association of serum 25(OH) D_3 concentrations and EAC. Both studies did not show any association between serum vitamin D levels and EAC.

We apologize for the mistake in the conclusion. Appropriate changes in the conclusion and abstract have been made and highlighted.

2. Author concluded VDR expression is increased in BE as compared to EAC or normal squamous epithelium. Please tell me the reason why VDR expression is increased in BE as compared to EAC or normal squamous epithelium.

Thank you for your comment. As mentioned in our manuscript, three studies assessed VDR expression in BE [25,34,35]. Trowbridge et al. compared VDR expression in normal esophagus, BE and normal gastric tissue, by immunofluorescent staining [34]. No VDR expression was detected in normal squamous mucosa in contrast to normal gastric mucosa and BE mucosa. This suggests a restriction of VDR expression to columnar epithelium and glandular structures, as well as potential chemopreventive effects of vitamin D in patients with BE. Those findings were reproducible in a Dutch study where VDR mRNA had a 2-fold higher expression in BE epithelium compared to squamous epithelium [25]. In another study comprising 37 patients with BE and 107 with EAC, VDR expression was found to be increased in both BE (95%) and EAC (79%), but significantly higher in BE [35]. This implies that VDR might be involved early on in EAC development.