

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The Effect of Metabolic Syndrome on Incidence of Oral Potentially Malignant Disorder: A Prospective Cohort Study in Taiwan
AUTHORS	Siewchaisakul, Pallop; Wang, Sen-Te; Peng, Szu-Min; Sarakarn, Pongdech; Chen, Li-Sheng; Chen, Tony Hsiu-Hsi; Yeh, Yen-Po; Yen, Amy Ming-Fang

VERSION 1 – REVIEW

REVIEWER	Prof Saman Warnakulasuriya King's College London, UK
REVIEW RETURNED	28-Jun-2020

GENERAL COMMENTS	<p>This is a valuable study. The authors have studied a large cohort to obtain meaningful data.</p> <ol style="list-style-type: none">1) It is not clear why epithelial dysplasia was included as one of OPMDs. This is a pathology diagnosis, not visible clinically while others are clinical conditions. I would recommend that whatever number that was included as dysplasia (last column in Table 1) should be excluded and the data reanalysed.2) Verrucous hyperplasia is an interesting, unique condition found in Taiwan and should stand alone as a separate variable (even if the numbers are low).3) Inflammatory diet could be a common risk factor. This should be discussed.4) In Table 1, there are 39 never betel quid chewers with a diagnosis of OSF. This is a surprising result as OSF is found only among BQ chewers. This suggests false reporting by BQ users or miscoding. Please explain in the discussion.5) The two conditions (OPMDs and MS) have common risk factors, particularly areca nut chewing. Unadjusted data along with adjusted data should be shown in a supplementary data table to demonstrate the effect of adjustments.6) Requires English Grammar revision in many places
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REVIEWER	Ping-Ting Lin Chung Shan Medical University, Taiwan
REVIEW RETURNED	08-Jul-2020

GENERAL COMMENTS	<p>Review comments: The manuscript was aimed to assess the effect of Metabolic Syndrome (MetS) on incident Oral Potentially Malignant Disorder (OPMD) and the authors found that MetS may significantly increase the risk of OPMD. The rationales of the present study are reasonable and interesting. However, there some criticisms may rise and need further clarification.</p> <p>Major comments:</p>
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	<ul style="list-style-type: none"> - I suggest that authors should explain the possible relationships or mechanisms between MetS and OPMD. The motivation of the present study was not clear. - The authors tried to explain that the results showed a significant correlation between the MetS and OPMD might be due to inflammation or immune response, however, the data did not provide the participants with MetS suffer from higher inflammatory status. - The demographic data in the participants are not clear, I suggest that authors should provide the data with regard to anthropometric data (BMI, waist circumference), hematologic data (blood glucose or lipid profiles) according to the states (OPMD, OSF, Leukoplakia). - It is well known that the habits of betel nut chewing, cigarette smoking, and alcohol drinking are significantly increased the risk of oral malignant disorders; however, In Table 2, the data showed that quitting these habits still lead to the oral malignant, I suggest authors should discuss the reasons. - Please define the quit of betel nut chewing, cigarette smoking, and alcohol drinking in the methods sections and the footnote of Table 2. - The strength of this study is a population-based study, is there any exclusion criteria for the data analyses? - The lifestyle habits also included dietary habits, did authors tried to detect the dietary habits in the participates? <p>Minor comments:</p> <ul style="list-style-type: none"> - In the introduction section, page 4, line 4, the abbreviation of OPMD was repeated. - Please check the abbreviations, such as CHCIS, KCIS, BOC. What is the full name? - In the methods section, page 7, line 16, For oral habits..... ex-, ever-, current-" should revise to "the habit as ex-, never-, current-". - In the discussion section, page 13, line 2, please check the consistency for the abbreviation of OPMD or OPM.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author

1. (Q) It is not clear why epithelial dysplasia was included as one of OPMDs. This is a pathology diagnosis, not visible clinically while others are clinical conditions. I would recommend that whatever number that was included as dysplasia (last column in Table 1) should be excluded and the data reanalysed.

(A) Agreed. We have excluded 41 epithelial dysplasia cases from the analysis and re-analyzed all the results.

2. (Q) Verrucous hyperplasia is an interesting, unique condition found in Taiwan and should stand alone as a separate variable (even if the numbers are low).

(A) Agreed. We have dealt with verrucous hyperplasia as a separate variable, and performed regression analyses on this subtype. The results show that metabolic syndrome can elevate the risk of verrucous hyperplasia by 33%, but, as pointed out by the Reviewer, it was not statistically significant due to the small number (aRR=1.33, 95% CI: 0.51-3.46). The results have been added to Table 4.

3. (Q) Inflammatory diet could be a common risk factor. This should be discussed.

(A) We have re-analyzed the data with the consideration of inflammatory diet, including intake of meat, vegetable, and fruit in our model. The results of dietary factors are also elaborated in the part of discussion. (Page 15, Line 262-269)

4. (Q) In Table 1, there are 39 never betel quid chewers with a diagnosis of OSF. This is a surprising result as OSF is found only among BQ chewers. This suggests false reporting by BQ users or miscoding. Please explain in the discussion.

(A) Agreed. We have carefully checked coding and consistency of the 38 OSF cases, who reported never chewing betel quid.

We found that there were 3 cases reported inconsistency in subsequence round of attending screening program. For example, participants reported never chewed betel quid in the first round of screening, but reported quit betel quid chewing at second round. However; in our study, we took the status of betel quid chewing and others exposure at the first screen of CHCIS.

We have added more explanations as limitations in discussion section as following "Possible information bias for self-reported variables, especially oral habits, still exists. Betel nut chewing, smoking, and alcohol drinking are life style behaviors deviant from social norms and regulations, and can be possibly under-reported. Evidence on this phenomena has been shown in reporting of smoking behavior [44, 45]. This might explain all the 38 subjects of OSF reported never betel quid chewing, which contradicts the well-known association between OSF and betel quid chewing.". (Page: 17, Line: 316-321)

5. (Q) The two conditions (OPMDs and MS) have common risk factors, particularly areca nut chewing. Unadjusted data along with adjusted data should be shown in a supplementary data table to demonstrate the effect of adjustments.

(A) Agreed. We have included unadjusted and adjusted results in supplementary tables 2-3 for all OPMD, tables 4-6 for OSF, tables 7-9 for leukoplakia, table 10-12 for Verrucous hyperplasia and table 13-15 for Erythroplakia + Erythroleukoplakia.

6. (Q) Requires English Grammar revision in many places

(A) Agreed. We have checked carefully and corrected typographical/ grammatical errors throughout the manuscript.

Reviewer: 2

Comments to the Author

1. (Q) I suggest that authors should explain the possible relationships or mechanisms between MetS and OPMD. The motivation of the present study was not clear. The authors tried to explain that the results showed a significant correlation between the MetS and OPMD might be due to inflammation or immune response, however, the data did not provide the participants with MetS suffer from higher inflammatory status.

(A) Agreed. We have reviewed and proposed some possible mechanisms accounting for inflammation. We have re-written the mechanism in discussion section (Page 14, 15; Line: 229-269).

2. (Q) The demographic data in the participants are not clear, I suggest that authors should provide the data with regard to anthropometric data (BMI, waist circumference), hematologic data (blood glucose or lipid profiles) according to the states (OPMD, OSF, Leukoplakia).

(A) Agreed. We have provided distribution of anthropometric data and hematologic data in Table 1.

3. (Q) It is well known that the habits of betel nut chewing, cigarette smoking, and alcohol drinking are significantly increased the risk of oral malignant disorders; however, In Table 2, the data showed that quitting these habits still lead to the oral malignant, I suggest authors should discuss the reasons.

(A) Quitting these three habits in our study mean that participants who ever had habitual use of betel quids, cigarette, alcohol, but at the time of interview they had stopped the habits.

Our results that quitting these habits still lead to higher risk of developing OPMD compared to those never experienced these three risk factors were consistent with previous studies (Chen et al, 2017; Lee et al, 2003). We have discussed this point in the Discussion section (Page 15, Line 256-261).

Chen, P.-H., Mahmood, Q., Mariottini, G. L., Chiang, T.-A., & Lee, K.-W. (2017). Adverse Health Effects of Betel Quid and the Risk of Oral and Pharyngeal Cancers [Research article]. BioMed Research International. <https://doi.org/10.1155/2017/3904098>

Lee, C.-H., Ko, Y.-C., Huang, H.-L., Chao, Y.-Y., Tsai, C.-C., Shieh, T.-Y., & Lin, L.-M. (2003). The precancer risk of betel quid chewing, tobacco use and alcohol consumption in oral leukoplakia and oral submucous fibrosis in southern Taiwan. *British Journal of Cancer*, 88(3), 366–372. <https://doi.org/10.1038/sj.bjc.6600727>

4. (Q) Please define the quit of betel nut chewing, cigarette smoking, and alcohol drinking in the methods sections and the footnote of Table 2.

(A) Agreed. Quitting these three habits in our study mean that participants who ever had habitual use of betel quids, cigarette, alcohol, but at the time of interview they had stopped the habits. This has been defined in the Materials and Methods section, and the footnote of all table, if applicable. (Page 8, Line 121-123).

5. (Q) The strength of this study is a population-based study, is there any exclusion criteria for the data analyses?

(A) We only excluded those younger than 30 years old, and those had a prior diagnosis of oral cancer before screening. This has been described in the Materials and Methods section. (Page 7-8, Line 110-113).

6. (Q) The lifestyle habits also included dietary habits, did authors tried to detect the dietary habits in the participates?

(A) Agreed. We have re-analyzed the data by including dietary habits, including intake of meat, vegetable, and fruit in our model. The results of dietary factors are also discussed. (Page 15, Line 262-269)

Minor comments:

1. (Q) In the introduction section, page 4, line 4, the abbreviation of OPMD was repeated.

(A) Agreed. We have removed the redundant abbreviation of OPMD.

2. (Q) Please check the abbreviations, such as CHCIS, KCIS, BOC. What is the full name?

(A) Agreed. We have checked the manuscript and the supplementary materials to ensure all abbreviations were explained with full name in the first time they appeared, such as CHCIS in introduction section (Page: 5; Line: 79), KCIS in Method (Page: 7; Line: 107). We removed the abbreviations of BOC.

3. (Q) In the methods section, page 7, line 16, For oral habits..... ex-, ever-, current-" should revise to "the habit as ex-, never-, current-".

(A) Agreed. We have revised the text accordingly. (Page 8, Line 121).

4. (Q) In the discussion section, page 13, line 2, please check the consistency for the abbreviation of OPMD or OPM.

(A) Agreed. We have corrected the abbreviation for oral potentially malignant disorder as OPMD throughout the revised manuscript