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Betel quid chewing and oral potential malignant disorders and the impact of smoking and drinking: a meta-analysis

Betel quid, smoking, drinking and OPMDs

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Abstract

BACKGROUND

Oral potential malignant disorders (OPMDs) are a precancerous condition of oral disease. Several studies have found that betel quid chewing, smoking, and alcohol drinking might be the risk factors of OPMDs. But the relationships of them, especially their interaction are still inconclusive.

AIM

To evaluate the relationship between betel quid chewing and OPMDs, and to explore the interaction of smoking and alcohol drinking on the relationship.

METHODS

We searched PubMed, Web of Science, Embase and the Cochrane Library databases with items complete until January 2021 for relevant studies. The research data were extracted according to the inclusion criteria. The pooled odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate the effect size. Subgroup analyses were performed to assess interactions between exposures and OPMDs. Relative excess risk of interaction (RERI) was used to estimate the size of interaction.

RESULTS

Nine articles were selected in final meta-analysis. The results showed that betel quid chewing (pooled OR: 8.70, 95%CI: 5.18-14.61), alcohol consumption (pooled OR: 1.95, 95%CI: 1.5-2.55), and smoking (pooled OR:4.35, 95%CI: 3.06-6.2) could significantly increase the risk of OPMDs compared to individuals without these behaviors. Smoking and alcohol drinking synergistically increased the association between betel quid chewing and OPMDs (pooled $OR_{(BQ+SM)}$:14.38, 95%CI: 7.14-28.95; pooled $OR_{(BQ+DK)}$: 11.12, 95%CI:8.00-15.45, respectively). The $RERI_{(BQ+SM)}$ and $RERI_{(BQ+DK)}$ were 2.33 and 1.47, respectively.

CONCLUSION

The synergistic effects between smoking/drinking and betel quid highlights the importance of focusing on individuals with multiple exposures. Further study should be conducted to confirm these interactions.

Key Words: Oral potential malignant disorders; Betel quid chewing; Smoking; Drinking; Synergistic effect

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Core Tip: Betel quid chewing, smoking, and drinking could significantly increase the risk of oral potential malignant disorders (OPMDs). And smoking and drinking synergistically increased the association between betel quid chewing and OPMDs.

INTRODUCTION

Oral cancer is the sixth most common cancer worldwide[1], occurring predominantly in developing countries. It has a high incidence in young adults, creating a major economic burden to families and society. Diagnosis time is the most important factor affecting the prognosis; therefore, early diagnosis is crucial. Oral squamous cell carcinoma (OSCC) is the most common type of oral cancer, and the majority of OSCCs are transformed from oral potential malignant disorders (OPMDs). OPMDs are a precancerous condition of oral disease, which can be transformed and cured. Hence, controlling the disease in a precancerous state is the most effective prevention strategy. A meta-analysis found that the global prevalence of OPMDs was 4.47%, higher in Asia and South America[2]. Leukoplakia, erythroplakia, oral submucous fibrosis (OSF) and oral lichen planus are four common categories of

OPMDs, focused upon the study. Among them, OSF and leukoplakia, especially erythroleukoplakia, have a higher risk of malignant transformation[3-5].

A number of studies have shown that betel quid and areca nut chewing is associated with OSF, leukoplakia, and other premalignant disorders[6-8]. In contrast, the effects of smoking and alcohol consumption on OPMDs were mixed in studies, with some suggesting that smoking or alcohol increases the risk of diseases[9-11], while others reporting the opposite conclusion[10, 12-14]. At present, about 600 million people in the world have the habit of betel quid chewing[15], accounting for about 10% of the global population, with a younger age trend[16, 17].

On the other hand, they generally have multiple exposures, such as most areca nut chewers are smokers[18-20]. If there is a joint effect among multiple exposure factors, the incidence of disease will greatly increase when multiple exposure factors exist. Lee *et al*[12] found that when smoking and betel quid were combined, the risks of OPMDs were greater than the sum of each of them alone, indicating the potential interaction between smoking and betel quid. However, Ray *et al*[21] did not observe such an interaction. Similarly, the same situation was observed in studies of betel nut and alcohol consumption exposure. Hence, whether smoking and alcohol consumption play a role in the relationship between betel quid and OPMDs is uncertain. The purpose of this meta-analysis was to evaluate the relationship between betel quid chewing and OPMDs, and to explore the effects of smoking and alcohol drinking on this process.

MATERIALS AND METHODS

Search strategy and inclusion criteria

We systematically searched four databases: PubMed, Web of Science, Embase, and the Cochrane Library. The search terms were: (1) oral precancerous lesions OR oral premalignant lesions OR oral potentially malignant disorders OR oral leukoplakia OR oral submucous fibrosis OR oral lichen planus OR oral erythema OR erythroplakia; (2) betel nut OR betel quid OR areca nut OR pan chewing; (3) alcohol OR drinking OR alcoholic beverage OR ethanol; and (4) smoking OR cigarettes OR tobacco. The specific

search strategy is shown in Table 1. The study language was limited to English. The data retrieval process was completed in January 2021.

The study inclusion criteria were: (1) the diagnosis of oral potentially malignant disorders is confirmed by a clinician and histological biopsy; (2) the exposure factors included both betel quid chewing and smoking, or both betel quid chewing and alcohol drinking; and (3) the study provided ORs and 95% confidence intervals (CIs) or sufficient information to calculate them.

Data extraction and quality assessment

After using Endnote software and manually to remove duplicates, literature screening was carried out. Firstly, two authors (Huijun Lin and Xiaolei wang) conducted preliminary screening by reading the titles and abstracts respectively, and then carefully read the full text to select the final literatures. Finally, the third author (Mengyuan Tian) was consulted to make the decision while the conclusions between the two authors were inconsistent.

The outcome indicators were oral potential malignant disorders, including oral leukoplakia, oral erythema, OSF and OLP. Though the specific mechanism of betel quid to every precancerous lesion were different, we believed that betel quid could cause all these diseases just with inconsistent degree of damage after reading literatures. Therefore, it was reasonable to include the four precancerous lesions in the meta-analysis. Several precancerous lesions might be present in a study, or only one of them. The exposure categories were divided into five types: betel quid chewing (BQ), smoking (SM), alcohol drinking (DK), betel quid chewing and smoking (BQ+SM), betel quid chewing and alcohol drinking (BQ+DK). The presence of all three exposure is rarely mentioned in studies, this case was not considered in this meta-analysis. BQ included exposure to betel quid, betel nut, areca nut and other products containing betel quid; SM referred to exposure to cigarettes, bidi and other tobacco products; and DK stood for exposure to all alcoholic beverages, including beer, white wine, *etc.* BQ+SM means exposure to both SM and BQ. BQ+DK means exposure to both BQ and DK. All

exposures were defined as having lasted at least one year. The odds ratios (ORs) and 95% confidence intervals (CIs) were extraction because the number of cases/controls in each exposure category were not specified. In the data extraction of BQ, SM, and DK, we chose the OR and 95%CI of the single exposure category, such as smoking only. If the single exposure category data were not provided in the article, the adjusted total population exposure data were selected. Other information, such as study design and types of oral precancerous lesions, were also collected in a standardized manner.

Newcastle-Ottawa Scale (NOS) criteria was used for the quality assessment of case-control studies respectively. NOS scale is a tool for evaluating the quality of case-control study with ten questions, consisting of three main components: Selection, Comparability and Exposure. The quality of cross-sectional study was assessed using the Agency for Healthcare Research and Quality (AHRQ) guidelines (11 questions) recommended by AHRQ. Each study was evaluated independently by two authors (Huijun Lin and Xiaolei Wang), and they would make a discussion when the results inconsistent. If no agreement could be reached, a third author (Mengyuan Tian) would join to discuss and reach a consensus. The higher the score of both scales, the better the quality. And the score of <6, 6-7, and >7 indicated that the studies had low, medium and high quality, respectively. Only literatures of medium quality or above could be included in this meta-analysis.

Data analysis

The data were analyzed using Stata 12.0 (Statacorp, Cannon Creek, TX, USA). We measured the effect size with ORs and 95%CIs, and performed heterogeneity tests using I^2 statistics. If I^2 was more than 50%, indicating greater heterogeneity, a random-effects model was used to calculate pooled effects; otherwise, a fixed-effects model was used. Sensitivity analyses were performed using the trim-and-fill method, which investigated whether the pooled OR changed significantly when the studies were eliminated one by one. Publication bias was assessed using Egger's regression and funnel plots, lnOR in

the X-axis, standard error of lnOR in the Y-axis. Asymmetric funnel plots suggested the existence of bias.

Subgroup analyses were conducted to analyze the association between SM or DK and OPMDs, and preliminarily explore the interaction effect of SM/DK and BQ using stratified analyses. Relative excess risk of interaction (RERI) was used to estimate the size of interaction. A and B are denoted two exposure factors. `A and`B stand for their absence, with formula (If RERI=0, there was no interaction[22]):

$RERI_{AB} = OR_{AB} - OR_{A`B} - OR_{`AB} + 1$

RESULTS

A total of 987 studies were retrieved, of which 344 were duplicates. We excluded 499 articles when reading titles and abstracts, including 441 completely unrelated articles and 48 reviews or meta-analysis. And an additional 145 articles were excluded after reading full text. Finally, nine articles were included in the meta-analysis. The article selection process is shown in Figure 1.

Study characteristics

Table 2 presents the characteristics of the final nine studies. Only one study contained four precancerous lesions[23], the other studies only included fewer condition[7, 12, 13, 21, 24-27]. One of the studies reported leukoplakia and OSF as two separate diseases, and discussed the harm of betel quid to these two respectively[13], so the effect sizes were extracted separately. Among the studies, 9 studies reported the effect size of BQ, 9 of SM, 6 of DK, 8 of BQ+SM, 9 of BQ+DK. All studies included both males and females.

Betel quid chewing exposure and oral potential malignant disorders

Nine studies were included in our meta-analysis of the relationships between BQ exposure and OPMDs. The analysis revealed great heterogeneity (I^2 =73.5%, P<0.001) between studies, so a random-effects model was used to estimate the pooled OR and

95%CI. The results suggested BQ was associated with an increased risk of OPMDs (pooled $OR_{(BQ)}$: 8.70, 95%CI: 5.18-14.61). A forest plot of the results of the individual studies and the pooled result was shown in Figure 2.

Sensitivity analysis and publication bias

Sensitivity analysis suggested that the combined $OR_{(BQ)}$ was stable and that none of the individual studies disproportionately influenced the results. The funnel plot and Egger's regression test showed no evidence of publication bias (Figure 3).

Subgroup analysis

Separate effects of smoking or alcohol drinking

In order to better explore the role of SM or DK on the association between BQ and OPMDs, we first analyzed the separate effects of SM or DK with the disease. Nine studies were included in meta-analysis of the relationships between SM exposure and OPMDs, six of DK. Heterogeneity tests showed a lack of heterogeneity in DK (I^2 =0.0%, P=0.889), but significant heterogeneity in SM (I^2 =61.6%, P=0.008). We found both SM and DK increased the risk of OPMDs (pooled $OR_{(SM)}$: 4.35, 95%CI: 3.06-6.2; pooled $OR_{(DK)}$: 1.95, 95%CI: 1.5-2.55). There was no evidence of publication bias, and the sensitivity analysis showed that the results were stable.

Effects of combined exposure with oral potential malignant disorders

In the assessment of combined BQ and SM, or BQ and DK, there was no evidence of publication bias, and the sensitivity analysis showed the results were stable.

Effects of smoking and betel quid chewing on oral potential malignant disorders

Eight studies were included in our meta-analysis of the relationships between BQ+SM exposure and OPMDs. After the heterogeneity test, a random-effects model was used to calculate the pooled OR. The results showed that smoking and betel quid

exposure increased the incidence of OPMDs (pooled OR $_{(BQ+SM)}$: 14.38, 95%CI: 7.14-28.95), and a higher risk degree than BQ alone (Figure 4).

Effect of alcohol drinking and betel quid chewing on oral potential malignant disorders

Nine studies were included in our meta-analysis of the relationships between BQ+DK exposure and OPMDs. A fixed-effects model was used to calculate the pooled OR for the risk of both BQ and DK exposure. We discovered alcohol consumption reinforced the effect of betel nut on OPMDs (pooled OR $_{(BQ+DK)}$: 11.12, 95%CI: 8.00-15.45) (Figure 5).

Interaction between smoking or alcohol drinking and betel quid

As shown in Table 3, pooled $OR_{(BQ)}$ plus pooled $OR_{(SM)}$ was smaller than pooled $OR_{(BQ+SM)}$, and pooled $OR_{(BQ)}$ plus pooled $OR_{(DK)}$ was smaller than pooled $OR_{(BQ+DK)}$. We speculated that both SM and DK had synergistic effects with BQ. After calculation, $RERI_{(BQ+SM)}$ was 2.33, and $RERI_{(BQ+DK)}$ was 1.47, providing further evidence of an interaction.

DISCUSSION

Our study found that betel quid chewing was associated with OPMDs. There was an interaction between smoking and betel quid chewing, and alcohol drinking and betel quid chewing with respect to their association with OPMDs. The data extracted from the original study was adjusted for confounding factors such as gender, age, and education status, though varies from article to article. And the sensitivity analysis also showed that our study results were stable with no significant bias. This meta-analysis provides a new approach for the prevention of OPMDs. It revealed that individuals with multiple exposures had very high risk because of synergistic interaction, which remind us that we should pay more attention to these people.

Oral potential malignant disorders are a kind of diseases with the risk of malignant transformation. It is of great significance for the prevention of oral cancer to realize the

related risk factors and avoid them in daily life so as to reduce the occurrence of the disease. Areca nut is the fourth largest psychoactive substance in the world. The International Agency for Research on Cancer recognized that betel quid and areca nut were carcinogens in 2004[28], and studies have found that betel quid chewing is a risk factor for many diseases, including oral cancer, oropharyngeal cancer[29], and esophageal cancer[30]. And a variety of oral diseases have also been linked to betel quid chewing[31, 32]. Studies found that betel quid harms the cavity mainly in two aspects: first, arecoline, the active ingredient in betel quid, would produce a variety of nitrosamines in the acidic environment of the oral cavity and stomach. And nitrosamines could interact with DNA, protein or other biological macromolecules, and then induce oxidative stress and participate in the canceration of oral mucosa. Causes of damage to the oral mucosa include oxidative stress caused by nitrification of arecoline and mechanical stimulation of the mucosa[33]. In addition, hydrated lime in betel quid could alter intracellular calcium homeostasis, causing abnormal activation of calcium-mediated transduction cascades and leading to oral cancer. Second, the mechanical stimulation of betel quid to oral mucosa caused by repeated chewing. Moreover, the current studies found that chewing betel quid could cause the changes in oral microbiota, which might be related to oral diseases[34, 35].

We found betel quid chewing was significantly increased the risk of OPMDs, which is consistent with the majority of studies[36-38]. But the effects of betel quid varied greatly across studies, and there was a large variation of the ORs[39, 40]. It might be related to the study area and population. The production methods and ingredients of betel quid vary in different countries, and the degree of oral damage also differed. But all the countries in the literature we included chew the raw betel quid, supplemented with such auxiliary materials as betel nut leaves and flowers, and all of them do not contain tobacco. Therefore, the results of our meta-analysis were robust and reliable.

In the subgroup analysis, we found that smoking alone was also associated with an increased risk of OPMDs, which is consistent with other studies[9, 41]. there was an interaction between smoking and betel quid chewing, and tobacco enhanced the toxicity

of betel quid to the oral mucosa. And studies showed that the risk of OPMDs in betel quid with tobacco was greater than that in betel quid alone[37]. Several potential mechanisms can explain this synergistic effect. The site in the oral cavity where tobacco is placed becomes keratinized due to friction. With the prolongation of tobacco use, the degree of mucosal keratosis deepens, and plaques are formed[42]. The mechanical damage caused by betel quid chewing could accelerate this process. Alternatively, both smoking and betel quid chewing could lead to the accumulation of nitrosamines in the cavity and increase oxidative stress[33], which might exert a synergistic effect. Additionally, nicotine has been reported to have a synergistic effect on betel quid cytotoxicity[43]. And the synergistic effect has been reported in other diseases. Liu *et al* found the interactions between betel quid and cigarette or alcohol in malignant transformation of OSF[44]. Similarly, the same synergistic effects in oral cancer were suggested in the study of Petti *et al*[45].

In the relationship between alcohol consumption and OPMDs, different studies had different results[10, 41, 46]. Our subgroup analysis found that alcohol consumption alone had an association with OPMDs. It was mainly due to the direct stimulation to oral mucosa by alcohol, which could be enhanced if there is damage in the mouth. The results of our meta-analysis showed that betel quid chewing interacted with alcohol consumption. Animal experiments have shown that chronic alcohol exposure can cause atrophy of the oral mucosa, making it more sensitive to stimulation[47], such as the mechanical stimulation of betel nut chewing. The increased permeability caused by alcohol could accelerate the absorption of arecoline by the mucosa. Additionally, both betel quid chewing and alcohol drinking change the composition of the oral microbiome[48]. Betel quid chewing combined with heavy alcohol drinking has been reported to change the diversity of the oral microbiome[49]. Oral microorganisms normally maintain oral health through immune regulation[50], and microbial disorders are associated with various diseases, including OPMDs[51, 52].

There are still some limitations to our study. The selected studies had cross-sectional and case-control study design, which provide weak evidence of causality. The

number of people in each subgroup may have been inadequate because of having five exposure categories, though the direct number were not reported. Further investigation should be conducted with a large cohort study to accurately assess the impact of smoking and alcohol drinking on the association between betel quid chewing and OPMDs.

CONCLUSION

The meta-analysis suggested that betel quid chewing is associated with an increased risk of oral potential malignant disorders. There was a synergistic effect between smoking or alcohol drinking and betel quid chewing. Therefore, we should focus on high-risk groups with multiple exposure, especially individuals with smoking and betel quid exposed, and provide health education about the harmful effects of unhealthy behavior. Governments should develop policies to quit betel quid, smoking and alcohol, especially in individuals with multiple exposure, in order to control and reduce the incidence of oral potential malignant disorders.

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