Smokeless Tobacco and Non-Tobacco Products and Risk of Oral Cancer in South-Asia: a Meta-analysis

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Short title: Meta-analysis of oral cancer in smokeless tobacco users

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Abstract

Background
Smokeless tobacco products (STPs) and non-tobacco products (NTPs) are shown to cause oral cancer in men and women. Most of the studies on STPs use and oral cancer have been done on western populations and the literature lacks meta-analyses on south Asian populations that use unique types of STPs.

Objectives
The objective of this meta-analysis was to summarize the evidence related to the association between smokeless tobacco and risk of oral cavity and oropharangyeal cancer in observational epidemiological studies.

Search Methods
We conducted a systematic electronic search from the MEDLINE and Google Scholar databases and identified twelve studies relevant to our research question.

Selection Criteria
The only studies included in the analysis were cohort and case control studies that reported smokeless tobacco as exposure and oral cancer as outcomes in Asian populations were included in the analysis. Randomized clinical trials, review articles, editorials, comments, duplicate publications, letter to editors and abstracts were excluded.

Data collection and analysis
Two reviewers independently pooled data from the selected studies and the third reviewer checked the accuracy of the data. Disagreements were resolved by consensus. Twelve studies published between 1977 and 2012 were included in the meta-analysis.

Results
Based on four studies of chewing habits in men and women, the pooled random effects odds ratio [OR] for smokeless tobacco and oral cancer was 1.98 (95% confidence interval [CI] 1.14 and 3.44). The OR of oral cancer for female subjects with chewing with tobacco was 16.24 (95% CI = 3.52, 75.05) and for male subjects was 6.23 (95% CI = 4.20, 9.24). Effects were attenuated when restricting analysis to chewing without tobacco products in males (OR = 2.16, 95% CI = 1.30, 3.59).
Author’s conclusion

STPs use carries an increased risk of oral cancer in Asian populations. The risk, however, increases substantially when the STPs are chewed with tobacco for both males and females. More studies are needed to elucidate the role of specific ingredients in STPs in the causation of oral cancer in Asian populations.
Background

STPs are very popular in Asia, particularly Southeast Asia (Jayalekshmi et al, 2011). The common STPs used in this region include chewing with or without tobacco, chewing betel quid with or without areca nut, snuff inhalation and other local forms of STPs. Many epidemiological studies assessing STPs use and oral cancer are regularly published in Asia particularly in India where the consumption of STPs and rate of oral and oropharyngeal cancer is high. However, most of the meta-analyses on STPs use and risk of oral cancers have been done on western populations and have not included STPs common among south Asian populations. The current meta-analysis fills this research gap of STPs use and risk of developing oral and oropharyngeal cancer in South-asian population.

STPs use in Asian populations is different than the rest of the world. For example, betel and areca nut, both regarded as carcinogens (Secretan et al, 2009 & IARC monograph, 2012), are heavily consumed in the Asian region. Snuffing is more common in the west. Because behavioral factors, culture, and common practices are different in Asian countries than the rest of the world, we believed that restricting our inquiry to studies that focus specifically on the Asian region would provide better explanation for the association between the exposure and outcome of smokeless tobacco use in Asia.

The main purpose of this analysis is to assess the association between smokeless tobacco and oral cancer among south Asian populations. To achieve this goal we include 12 published papers on oral and oropharyngeal cancer relating to STPs use in South Asia. We further aim to clarify the inconsistent findings from previous studies about the strength of association in chewing non-tobacco products. The current analysis will provide more insight into the issues the Agency of Research on Cancer (IARC) addresses, which may lead to update on the international published review of human carcinogens (IARC 2012). The present meta-analysis hypothesizes that the use of STPs increases the risk of oral cavity and oropharyngeal cancers in men and women in Asia.
Methods:

Search Strategy

We specifically used the following MeSH terms: ‘smokeless tobacco’, ‘smokeless tobacco AND oral cancer’, ‘smokeless tobacco AND oropharyngeal cancer’, ‘smokeless tobacco AND Asia’, smokeless tobacco AND India, ‘oral cancer and Asia’, ‘betel quid and oral cancer, and ‘areca nut chewing and oral cancer’. We concentrated specifically on searching Medline database for the above MeSH terms. We also used Google Scholar to search published studies between 1977-2012. We used all of the available dates in our search. Published studies during 1977 to 2012 were included in the analysis. We found two articles after searching the reference lists of other published articles. Some of the studies that we found through Google Scholar were not included in the study as the studies were not peer-reviewed research papers. All the reviewed articles were in English and no contacts to any authors were made pertaining to the reviewed studies.

Data collection and analysis
We used 2X2 contingency tables for cross-tabulation of disease and exposure states of the study populations in the published papers. Common exposure substances were various smokeless tobacco products such as betel quid with tobacco, mishri and areca nut. The abstraction form also extracted information on matching, study type, exposure and outcome definition, case control status, source of study base, and confounding factors. The outcomes were oral cavity and oropharyngeal cancer. All the papers were assessed through Newcastle-Ottawa Scale (NOS) scale, and quality of study variables were noted.

We stratified STPs use into chewing with tobacco and chewing without tobacco. This association was further stratified by gender. The stratification for generating forest and funnel plot was a) chewing habits (with or without tobacco) in both males and females; b) chewing with tobacco in males; c) chewing with tobacco in females; d) chewing without tobacco in males. No studies assessing chewing without tobacco in females were available. These stratifications were chosen to reflect the risk associated with different pattern of smokeless tobacco consumption habits in Asia. Pooled odds ratios and heterogeneity were analyzed using the RevMan program version 5.2. We used a random effects model to generate forest plots, the Q statistic to assess the presence or absence of heterogeneity, I² index to quantify the degree of heterogeneity, Funnel plots to assess publication bias, and the Newcastle-Ottawa quality assessment scale to record study quality in the meta-analyses.

Results

The characteristics of the studies are depicted in table 1.
The included studies were generally of high quality. Only two studies were of low quality, as defined by a score lower than 5. Table 2 depicts the quality of study based on the Newcastle-Ottawa Scale (NOS) scale (Wells et al, 2013).

The selected 12 studies were further sub-categorized into four types as depicted in Table 3 and Figure 2. Based on four studies of any chewing habits in both men and women, the random effects odds ratio for the association between smokeless tobacco and oral cancer was 1.96 (95% confidence interval [CI]=1.14 and 3.44). The OR of oral cancer for female subjects who chewed tobacco was 16.24 (95% CI = 3.52, 75.05) and for male subjects was 6.23 (95% CI = 4.20, 9.24). Effects were attenuated when restricting analysis to chewing without tobacco products in males, however, chewing without tobacco was still a significant risk factor for oral cancer (OR = 2.16, 95% CI = 1.30, 3.59).

The associations in all of the subgroup analyses were heterogeneous as evident from the $I^2$ values from table 3. Only one study represented moderate heterogeneity ($I^2$=48%), while the rest showed considerable heterogeneity.

Discussion

There are very few meta-analyses and systematic reviews done on STPs use and oral cancer in South Asian populations. Two meta-analyses reviewed so far have shown an increased risk of oral cancer in men and women who consumed smokeless tobacco products (Weitkunat et al, 2007 & Thomas et al 2007) in European and North American
countries. The findings from these two studies are comparable to our study. In the present study, the OR for females who chew STPs was 16.24 (95% CI = 3.52, 75.05) and for males was 6.23 (95% CI = 4.20, 9.24). The higher OR associated with female tobacco chewers’ warrants further research. There are several possible explanations that could produce higher risk of oral cancer in women. One possible explanation might be the higher incidence of HPV-associated cervical cancer in women in developing countries. HPV has also been found to infect the oral cavity in women (Adamopoulou et al, 2013) and the high infection with HPV may synergistically increase the risk of oral cancer in women. Weitkunat et al (2007) also showed a higher estimate of oral cancer risk in females who chew tobacco products, which is also supported by our analysis. In our analysis, effects were attenuated when restricting analysis to chewing without tobacco products in males (OR = 2.16, 95% CI = 1.30, 3.59). We were not able to compare chewing without tobacco products in females as we did not find enough studies to conduct stratified analysis.

Betel quid and areca nut are viewed as safe and chewed as non-tobacco products. Our analysis showed that betel quid and areca nut chewing are also a risk factor for oral cancer, a fact which is often ignored in Asian countries. Similarly, a systematic review and meta-analysis done by Thomas et al (2006) indicated an increased risk of oral cavity cancer in betel quid chewers. Lee and Hamling in 2009 demonstrated an increased risk of oropharyngeal cancer in people who used smokeless tobacco in the past. Our results are consistent with these studies.

As most of the studies included in this meta-analysis were case control studies, the quality of information on exposure depends on how accurately both cases and controls report their STPs use. As cases may recall their past STPs use habits more vividly than controls, this may increase the reporting of exposed substance and may inflate the odds ratio. Also, all of the published studies used for the present meta-analysis showed increased risk of oral cancer in STPs users signifying possible publication bias. Publication bias occurs when only significant studies are available for analysis and non-significant
studies or negative studies are either omitted or unavailable for analysis (Ahmed et al, 2012). In our meta-analysis we tried to minimize this bias by searching for non-association studies of STPs use and oral cancer. Fixed effect funnel plots in our analyses are inconclusive to assess publication bias as we have fewer studies in the stratified analysis and some estimates are very close to the boundary line of the plot (fig 3).

We excluded studies that were conducted on populations other than Asian populations. We were not able to stratify regionally as the published studies were mostly from South Asia. Similarly, we have excluded some cancers that have been related to STPs use such as esophageal and pancreatic cancer as these are rare cancers with few published studies on Asian populations.

The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis was used (Wells et al, 2013). The studies included in the analysis were generally of high quality. Only two studies were of low quality. The studies which did not define case control status and which showed inconsistency in selection procedure were rated as low quality. Although the included studies were of high quality, there were some limitations in the included studies. Most of the studies were conducted in India populations and there is a lack of substantial research on populations of other countries. Many studies included in the analysis have not fully controlled for additional confounders such as exposure to second hand smoke, environmental exposure to carcinogens and other factors which may have influenced outcomes of interest and subsequently the final results. The biases discussed previously and any unadjusted confounders missed in the design and analysis of the studies may make our result less valid. Similarly, the ingredients of the exposure of interest reported in the reviewed papers may differ from one study to the other. The ingredients of STPs and doses of consumption differ according to the location and country. As the ingredients and doses differ, it is very difficult to assess the effects of individual component and doses of the STPs use and oral cancer. Many studies lacked this kind of analysis of looking at individual components and doses of STPs and oral cancer.
Additionally, we could not perform a subgroup analysis of non-tobacco chewing habits in females and as a result could not compare it with males. We were also not able to analyze dose response relationships of STPs use and oral cancer because there was substantial variation in reporting of STPs use among studies. It is very important to see the effects of individual ingredients in smokeless tobacco products in cancer causation. Future research should also focus on leukoplakia and oral submucous fibrosis (OSF), which are precursors to oral cancer in smokeless tobacco product users.

There are some limitations of the present study. As most of the pooled analysis was from south Asian region, the result may not be applicable to populations in other parts of Asia, where chewing habits and ingredients in smokeless tobacco are different. Some studies used in the pool analysis had not fully controlled for confounders such as smoking and alcohol and this may also affect the final result and odds ratio.

Conclusion

All the published studies on smokeless tobacco use and oral cancer show increased risk of oral cancer in Asian populations. Our meta-analysis also supports the fact that use of STPs increases cancer risk in men and women. It is plausible that the causal casual relationship exists between STPs use and oral cancer.
References:


