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Review
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Review

Association of Smokeless Tobacco Use and Oral Cancer: A Systematic Global Review and Meta-Analysis

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Abstract

Introduction: Smokeless tobacco products have been linked to precancerous and cancers of oral cavity for long. Evidence was available on the association between smokeless tobacco (SLT) products and oral cancers at regional but not at global level. Present meta-analysis is aimed to evaluate the risk of oral cancer with the use of SLT products among "ever" versus "never" users.

Method: Studies published for the period (1960–2016) are retrieved using Pubmed, Indmed, EMBASE, and Google Scholar search engines for the subject "ever" versus "never" users of SLT products and estimated the risk association with oral cancer. Summary odds ratios (relative risk) are estimated and meta-analysis was performed using random-effects model.

Results: Thirty-seven studies from four of six WHO regions, Southeast Asia region (SEAR), the Eastern Mediterranean Region (EMR), Europe, and region of Americas (North and South) are included in the analysis. Significant risk with SLT products with oral cancer was found for SEAR (4.44, 95% CI = 3.51 to 5.61) and for EMR (1.28, 95% CI = 1.04 to 1.56). Significantly higher risk ($p < .001$) was found for females (5.83, 95% CI = 2.93 to 11.58). Product wise analysis for different SLT products revealed various levels of risk viz. gutkha (8.67, 95% CI = 3.59 to 20.93), pan tobacco / betel liquid (7.18, 95% CI = 5.48 to 9.41), oral snuff (4.18, 50% CI = 2.37 to 7.38), Mainpuri tobacco (3.32, 95% CI = 1.32 to 8.36), and snus (0.86, 95% CI = 0.58 to 1.29).

Conclusion: A significant positive association was observed between SLT use and the risk of oral cancer, in SEAR, EMRs, and among women users.

Implications: The present meta-analysis demonstrates SLT product use and the risk of oral cancer at global level. Moreover, the present analysis provided data on the risk associated with individual SLT product. The results fulfil the gap in the data on independent effect of individual SLT product use on the outcome of oral cancer at global level, conclusively. Chewing SLT products was associated with higher risk of oral cancer than other types of SLT. This can serve as a useful tool for policy makers in forming strict policies in controlling SLT menace. Hence, we propose that in addition to smoking, efforts should be directed towards SLT product cessation as well in reducing oral cancer incidence.

Introduction

Cancers of lip and Oral cavity are the 11th most common cancers in the world. About 300 000 new cancer cases and 145 000 deaths were estimated to have occurred in the year 2012 with wide geographical variation. Reasons for the occurrence of oral cancers have been attributed to a complex interplay of various genetic and environmental factors including exposure to various carcinogens.[1–3] Ninety per cent of oral cancers are due to preventable causes, which include smoking, use of smokeless tobacco (SLT) products and excessive alcohol consumption.[4] Though SLT products are used globally and across 121 countries, over 80% of SLT users live in SEAR countries.[5] A meta-analysis on mortality due to all cause cited SLT use as the single most important risk factor.[6]

A spectrum of SLT products is available globally. SLT products are either chewed or snuffed orally or nasally, or applied over teeth and gums, or gargled or drunk.[4] The chewed tobacco products are betel quid with tobacco (*Mainpuri* and others) and *pan masala* with *zarda* and *gutkha*. Snuffed oral products are either wet or dry. Wet snuff is used in the Western world. Nasal snuff is a dry powder known as *nas* or *naswar* and used in the SEAR and EMR[4] WHO regions.

The association between SLT use and the incidence of cancer for various sites, including oral, has been widely studied.[7–20] Studies have documented summary effect sizes of the risk of SLT use for oral cancer both at country[7,8] and regional[9–19] levels. Both narrative[7] and systematic[8] reviews have been reported from India. Reviews for SEAR,[9–13] combined European and American regions[14–18] and the American region alone are available for SLT use and the risk of oral cancer but differ in methodology [19]. Type of reviews that were reported: (1) exclusively only systematic review, without meta-analysis,[7,13–16] (2) reviews that mixed oral with oropharyngeal cancer,[7–9,11–15] and (3) those that included fewer number of studies[10,15–19] or studies on a single SLT product (betel quid).[10–12] A previous study estimated the overall risk of oral cancer from SLT use, but did not provide individual product risk.[20]

SLT products are manufactured, stored, and consumed in many different ways. This heterogeneity among SLT products and their use is substantiated as reported by different review studies in broad categories as either chewing or other than chewing (oral snuff, nasal snuff, and snus).[13,19] Systematic reviews analyzed the risk for betel quid with or without tobacco and other chewing products as a single group,[13] whereas another study reported snuff separately and other chewing products as a single group.[19] There are differences in various SLT products that are used across various geographical region leading to differences in incidence of oral cancer and the differences are due to variations in the manufacturing and processing method. Additives such as areca nut and other flavoring agents change the carcinogenic potential of the products. However, there is no supporting evidence available at global level on the association between different SLT products and risk of oral cancer. Against this backdrop, we aim to assess the association between exposure to different SLT products and the risk of oral cancer through a systematic review and meta-analysis at the global level.

Methods

Thirty-seven studies from four of the six WHO regions are included in the analysis. Two of the WHO regions namely the African Region and Western Pacific Region were excluded due to lack of data.

The present systematic review collected primary-level studies globally by following a defined search strategy and inclusion and exclusion criteria on the use of SLT products to assess its association with oral cancer.

Search Strategy

An extensive literature search was conducted using Pubmed, Indmed, EMBASE, and reports of the WHO, Google Scholar. The following search method was adopted: smokeless tobacco OR oral tobacco OR non burn tobacco OR snus OR gutkha OR *naswar* OR chew* tobacco OR tobacco powder OR tobacco tooth powder OR tobacco paste OR creamy snuff OR *mishri* OR *masheri* OR dip tobacco OR tobacco water OR *tuibur* OR *hidakphu* OR *gul* OR gutkha OR *mawa* OR *khaini* OR snuff OR pan masala OR pan masala with tobacco OR *paan* OR pan with tobacco OR zarda OR *tambaku* OR betel quid tobacco OR betel tobacco OR tobacco flakes OR tobacco leaf OR dried tobacco OR *hogesoppu* OR *gnudi* OR *kadapa* OR Mainpuri tobacco OR qiwam OR *kimam* OR dohra OR raw tobacco AND oral cancer OR oral carcinoma* OR oral malignant *OR oral tumour OR oral growth. The above keywords or search terms were used in a variety of combinations for each outcome in each of the databases.

Inclusion criteria

This study included all primary research studies fulfilling the following criteria: (1) case–control or cohort studies from January 1960 to March 2016 that were published in English, (2) either in hospital- or community-based setting, (3) a total study sample size of at least 200, and (4) case ascertainment done through histology by hospital or registry. Exposure status in the studies included was "ever" versus "never" SLT use adjusted for at least smoking status.

The reported outcome noted from studies should be exclusively for oral cancer in any part of the oral cavity, such as the floor of the mouth, tongue, gingiva, or buccal cavity, with or without the involvement of whole oral cavity. As all primary studies did not include uniformly oropharynx in oral cancers, we excluded studies that mixed oropharyngeal cancers with oral cancer.

Exclusion criteria

Case reports, case series, earlier reviews, and studies on precancerous lesions and use of products without tobacco and published in languages other than English were excluded. Cross sectional studies were also excluded due to rare occurrence of disease.

Study Records and Data Management

Selection Process

This study has been conducted and reported in accordance with the PRISMA guidelines.[21,22] Checklist on the search items has been included and the review was represented in a flowchart (Figure 1). The quality of the study with respect to various factors was studied and presented in the tables as appendixes.

Two authors (AS and DNS) independently carried out the literature search and identified 4846 citations for SLT use and associated oral cancer risk by two independent investigators (SA and DNS). Full-text articles were identified and assessed for eligibility after applying the inclusion and exclusion criteria. Critical appraisal of each study found eligible was done by both investigators. Agreement

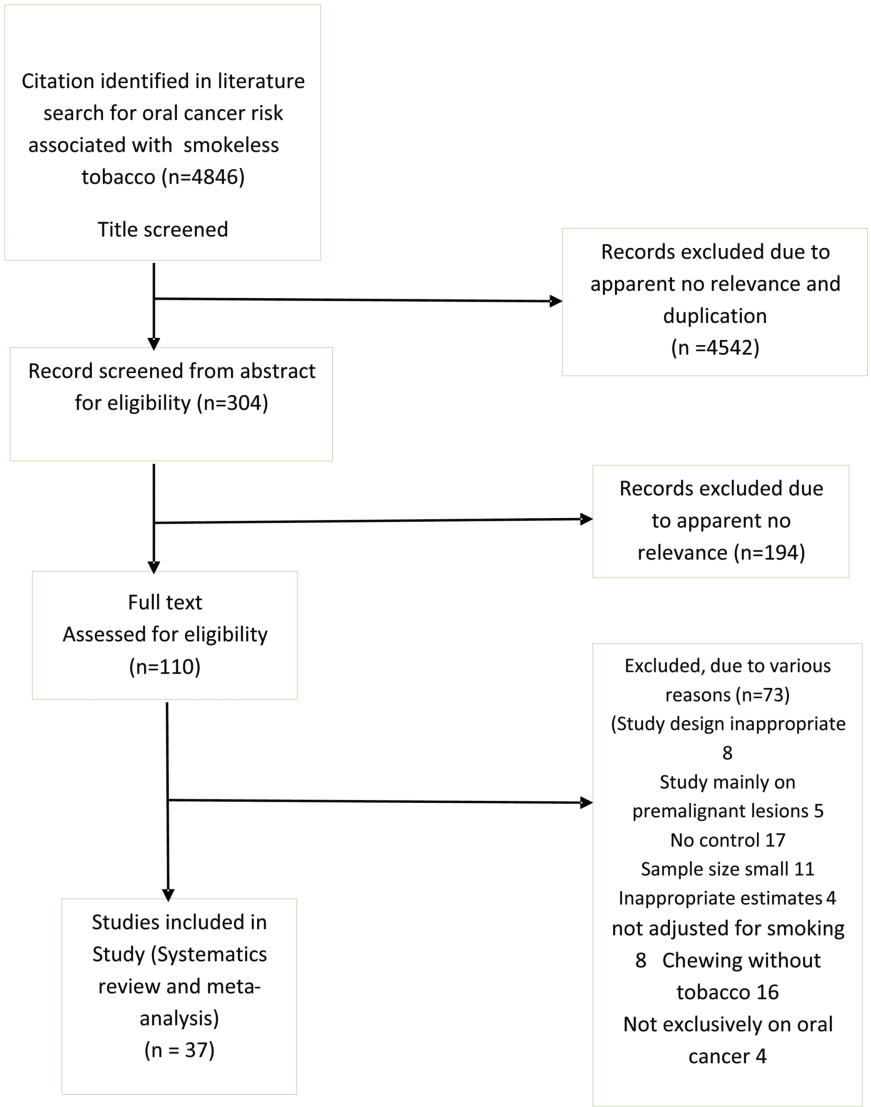

Figure 1. PRISMA flow chart for smokeless tobacco use and oral cancer risk.

of the requisite contents of the articles related to quality assessment and data extraction was performed. Any dispute in selection was resolved by third author (LS) after deliberation with SA and DNS.

The studies thus collected were segregated according to WHO regions and country following an earlier study.[20] A summary was prepared according to the WHO's regional classification of countries, and within each WHO region. The study location along with the period of study, study design, sample size, study setting, and case ascertainment for each primary study is enlisted in Supplementary Table 1. The settings for the case–control studies were mostly based in a single hospital, with a few involving multiple-hospitals. The source for the selection of controls was the patients attending the outpatients Department (OPD) of the same hospital at the same time, relatives of the patients, and other visitors. In some studies, the control selection was population based. Some studies included more than one control group. Most of the studies considered a wide age group (all ages) in their selection. Adjustments for confounding factors such as smoking, alcohol, age, body mass index (BMI), and geographical region were noted. A summary of studies included in analysis, according to the study design, SLT product used, and WHO region is presented in Supplementary Table 2. Studies are also categorized by SLT product type and year of publication such as before and after 1990.

Outcome and Associated Factors

Information given in different primary studies and their assessment report on single or multiple SLT products with oral cancer risk was noted.[23–59] Primary studies that reported on types of SLT covered pan tobacco/betel or tobacco quid,[23,25,27,31,34,38,39,42–45,48,53] gutkha,[36,37] oral snuff,[36,38,52] nasal snuff,[33,42,43,45,51] snus,[54–56] Mainpuri tobacco,[29,49,51] toombak,[52] or unspecified.[30,37,40,41,46,47,50,52,56–59]

Meta-Analysis

The meta-analysis was performed using RevMan 5.3 package. All meta-analyses were performed by using the random-effects model.[26] The effect size of interest was odds ratio (OR)/relative risk (RR) for the effect of SLT use and associated risk of oral cancer. Risk estimates of effect size along with 95% CI for overall and between factor groups

under study were tabulated. Forest plots were drawn to summarize information from individual studies and the pooled effect size for the subject under study. The variation across studies due to heterogeneity is described by a statistic called I^2. For different models, I^2 values revealed the presence of heterogeneity, and this was supported by a Q test with statistical significance. The sample size was 61 from a total of 37 studies. This was used for combining odds ratio for different groups by meta-analysis. The estimates given in the form of RR were also combined without any conversion owing to the fact that rare disease like cancer RR equates OR. A decision over selecting a model was made after assessing the level of heterogeneity. An I^2 of more than 50% was considered heterogeneous. The method of visual assessment of funnel plots was adopted to measure the bias in the meta-analysis after performing different models for various subgroups.

Statistical Analysis

IBM SPSS version 21 was used for the frequency distribution of variables and for doing cross tabulation.

Results

A total of 110 full-text articles from 4846 citations were identified and assessed for eligibility for the meta-analyses. After applying the inclusion and exclusion criteria, 37 studies were found eligible for inclusion in analysis. The distribution of these 37 studies according to WHO regions and types of study design are given in Supplementary Table 2.

Sixty-one individual estimates of the oral cancer risk with SLT use were noted from 37 studies. We have included studies that used adjustment for smoking for inclusion criteria. Most studies (70.3%) included other confounders' details given in Supplementary Table 3.

Eight studies were published before the calendar year 1990 (21.6%) and the rest there after. The SEAR, EMR, and European regions contributed a large number of studies in the post-1990 period (Supplementary Table 4). Only two studies are reported from the region of Americas and none from Europe and the EMR. The data estimates included 15 (24.6%), 21 (34.4%), and 25 (41.0%) studies for male, female, and combined sex for, respectively (Supplementary Table 5).

In the SEAR region, case determination was done through direct histological confirmation of cases and types of controls used in the studies are shown in Supplementary Tables 6 and 7.

A cursory look at the data revealed that most of the study estimates were from case–control studies (91.8%) and very few from cohort studies (8.2%). Out of 56 estimates from case–control studies, 80.3% (45) were from studies published after the year 1990. Only one out of five cohort study estimates belonged to the former study period (Supplementary Table 8).

Forty-six (75.4%) risk estimates were reported for SLT products of chewing tobacco type. Majority of SLT studies / papers reported from SEAR and EMR are on tobacco chewing whereas those from European and the American regions are on non-chewing SLT types (Supplementary Table 9).

Region-wise analysis of SLT products revealed pan tobacco/areca nut + lime + tobacco (47.8%) as the most common type in the Southeast Asia region whereas snus (100%) and oral snuff (100%) are the most common SLT types in Europe and the Americas (Supplementary Table 10). Age adjustment or the age matching was reported in 67.2% of study estimates (Supplementary Table 11).

Table 1 depicts odds ratio (95% CI) obtained from meta-analysis of studies by random-effect model. Heterogeneity between the studies was examined using I^2 statistics. As mentioned earlier, an I^2 value of >50% was considered as evidence of heterogeneity. In this analysis, the value of I^2 ranged from 0% to 98% for different subgroups and most subgroups showed more than 80% heterogeneity. Given the high heterogeneity among studies, random-effect models were preferred over fixed-effect models. In overall risk estimation, heterogeneity measured through I^2 was high with statistical significance ($p < .001$). The overall of risk estimated was more than threefold with OR 3.53 (95% CI = 2.75 to 4.51). Our study results establish the SLT use with oral cancer risk categorically.

Regional risk was found to be significantly different ($p < .001$) for different WHO regions. The OR (95% CI) of 4.44 (3.51 to 5.61) ($p < .001$) was the highest and significant for SEAR countries followed by the EMR with 1.28 (1.04 to 1.56) ($p = .02$). For the American and European regions, the OR (95% CI) were 4.72 (0.66 to 33.62) and 0.86 (0.58 to 1.29). Heterogeneity between subgroups of regions was very high ($I^2 = 96.5\%$) (Table 1). Figure 2 shows forest plots for WHO regions. Figure 3 depicts risk for females than for males and combined categories. There were 15 risk estimates for females, 22 estimates for males, and 24 for both sexes. Subgroup analysis showed a higher risk for females with the OR of 5.83 (95% CI = 2.93 to 11.58), as compared to 2.72 (1.73 to 4.27) for male and 3.35 (2.34 to 4.78) for combined sex. A significant risk was found in all subgroups ($p < .001$) (Table 1, Figure 3).

The relative risk for oral cancer with chewing types of SLT products ($n = 46$) was higher with an OR of 4.37 (95% CI = 3.27 to 5.83) ($p < .001$) than for non-chewing products with 1.56 (1.04 to 2.36) ($p = .03$) (Figure 4). Out of three studies, one study reported a non-significant result, which has contributed to over all non-significant risk. For case–control studies, the risk was higher and significant with an OR of 3.66 (95% CI = 2.83 to 4.74) ($p < .001$) than for cohort studies with 2.32 (0.91 to 5.94) and non-significant ($p = .08$). The subgroups of two types of study designs were not significantly different and were also non-heterogeneous ($p = .03$ and $I^2 = 0.0$) (Table 1, Supplementary Figure 1). Studies published before 1990 ($n = 17$) had a higher OR with 6.56 (95% CI = 5.26 to 8.17) ($p < .001$). These studies have minimum heterogeneity within the groups ($I^2 = 27.0$, $p = .18$). For studies published in the later period, the OR was 3.02 (95% CI = 2.34 to 3.91). There was significant heterogeneity in subgroups (Table 1, Supplementary Figure 2).

Results revealed the evidence of modification of the effect estimates by SLT type. For all studies/papers together, the individual products that showed the highest association of OR with 8.67 (95% CI = 3.59 to 20.95) were gutkha followed by 7.18 (95% CI = 5.48 to 9.41) for pan tobacco/areca nut + lime + tobacco, 4.18 (95% CI = 2.37 to 7.38) for oral snuff and 3.32 (95% CI = 1.32 to 8.36) for Mainpuri. Nasal snuff and snus were not associated with oral cancer risk (Table 1, Figure 3). The distribution of the use of SLT products according to consumption type (chewing/non-chewing) is shown for the different global regions in Supplementary Table 8.

Bias in Meta-Analysis

For various random-effect model estimates in different subgroups, funnel plots were observed as symmetrical and nearly inverted (Supplementary Figures 12–18) (funnel lines not shown). The meta-analysis with the random-effect model in the funnel plot, the observed effect sizes are more or less symmetrically distributed around the combined effect size inferring absence of bias. However, in the analysis of subgroups of cohort studies, in

Table 1. Results of Meta-Analysis for All Available Studies Included and Sub Group Analysis

Factors	Effect size (95%)	*p* value	Heterogeneity *p* value	I^2 (%)
All WHO Regions	3.53 (2.75, 4.51)	<.001	<.001	97.0
Region wise				
Southeast Asia (*n* = 46)	4.44 (3.51, 5.61)	<.001	<.001	87.0
Eastern Mediterranean (*n* = 9)	1.28 (1.04, 1.56)	.02	<.001	87.0
European (*n* = 3)	0.86 (0.58, 1.29)	.47	.88	0.0
American (*n* = 3)	4.72 (0.66, 33.62)	.12	<.001	88.0
Sub Group Analysis	—	<.001	—	96.3
Sex wise				
Male (*n* = 22)	2.72 (1.73, 4.27)	<.001	<.001	98.0
Female(*n* = 15)	5.83 (2.93, 11.58)	<.001	<.001	97.0
Combined sex (*n* = 24)	3.35 (2.34, 4.78)	<.001	<.001	87.0
Sub Group Analysis	—	<.001	—	97.0
Chewing (*n* = 46)	4.37 (3.27, 5.83)	<.001	<.001	98
Non-chewing (*n* = 15)	1.56 (1.04, 2.36)	.03	<.001	79
Sub Group Analysis		<.001		93.8
Case–control studies (*n* = 56)	3.66 (2.83, 4.74)	<.001	<.001	97.0
Cohort studies(*n* = 5)	2.32 (0.91, 5.94)	.08	<.001	91.0
Sub Group Analysis	—	.36	—	0.0
Studies published before 1990 (17)	6.56 (5.26,8.17)	<.001	.18	27.0
Studies published 1990 onwards (*n* = 46)	3.02 (2.34, 3.91)	<.001	<.001	97.0
Sub Group Analysis	—	<.001	—	95.0
Pan tobacco/ areca nut + lime + tobacco (*n* = 23)	7.18 (5.48, 9.41)	<.001	<.001	75.0
Oral snuff (*n* = 8)	4.18 (2.37, 7.38)	<.001	.17	44.0
Snus/ moist snuff (*n* = 3)	0.86 (0.58, 1.29)	.47	.88	0.11
Gutkha (*n* = 4)	8.67 (3.59, 20.95)	<.01	.11	62.0
Mainpuri (*n* = 5)	3.32 (1.32, 8.36)	<.01	<.001	97.0
Nasal snuff/dipping (*n* = 6)	1.20 (0.80, 1.81)	.38	.03	66.0
Unspecified/mixed (*n* = 12)	2.63 (1.73, 4.00)	<.001	<.001	96.0
Sub Group Analysis	—	<.001	<.001	94.2
Adjusted/matched for age (*n* = 41)	3.52 (2.65, 4.68)	<.001	<.001	97
Not adjusted/matched for Age (*n* = 20)	3.55 (2.41, 5.23)	<.001	<.001	80
Sub Group Analysis		.97		0.0

the regions of Europe and the Americas, before 1990 and non-chewing SLT, small sample size in the subgroups of cohort studies might introduce some asymmetry. We could not find any differences in the heterogeneity of subgroups that adjusted for age or not (I^2 = 0.0) in primary study that looked for estimates. The subgroups showed similar ORs of around 3.5 in both the groups with the absence of heterogeneity (p < .001) (Table 1, Supplementary Figure 4).

Discussion

The present study is a comprehensive systematic review consisting of strict inclusion criteria to produce a robust review of the association between exposure to SLT and oral cancer. This type of synthesis revealed various hidden trends in the strength of the association between oral cancer and SLT use from WHO regions across the globe SEAR, EMR, Europe and the Americas.

Among individual SLT products studied, "chewing" types of SLT had higher risk for oral cancer as compared with "non-chewing" types. This risk was significantly higher among females than males. This is an important finding that had not been evaluated earlier at the global level.

Regional Risk Estimations

Inclusion of large number of studies across the globe compared with earlier reported studies Sinha et al.[5] and Khan et al.[9] that were limited in detail and the information given in review justifies its global nature. This is evident in the way that the present study showed a marginally lower risk of 4.44 (95% CI = 3.51 to 5.61) for SEAR than earlier reported studies[8,9,11,12,20] due to exclusion of pharyngeal and oropharyngeal cancers.

A notable risk was observed for EMR in our study, which is much lower compared with another study[20] this may be due to the inclusion of studies having varying risks. Our result of non-significant association for Europe (p = .47) and the Americas (p = .12) was in concordance with previous studies.[20] A study which included the United States, Sweden, and India together found that the risk of oral cancer from SLT use was due to the inclusion of Indian studies, since when analyzed separately excluding India no such risk was found for US and Swedish studies.[16] Most of the studies found no or negligible risks as far as European studies are concerned. Some other studies showed an increased risk for the United States, but not for the European region.[14–17] A pooled analysis of a consortium of 11 US studies found an increased risk for the oral cavity.[19] The reason for low risk estimates from Europe and Americas might be due to difference in frequency and intensity of use and variation in SLT product type. Moist snuff used in the Swedish region was least toxic due to improved manufacturing procedure and processing.[18] A previous systematic review also suggested that the lower number of cases from studies in Europe and Americas led to insufficient power to prove SLT as a risk factor in those regions.[16]

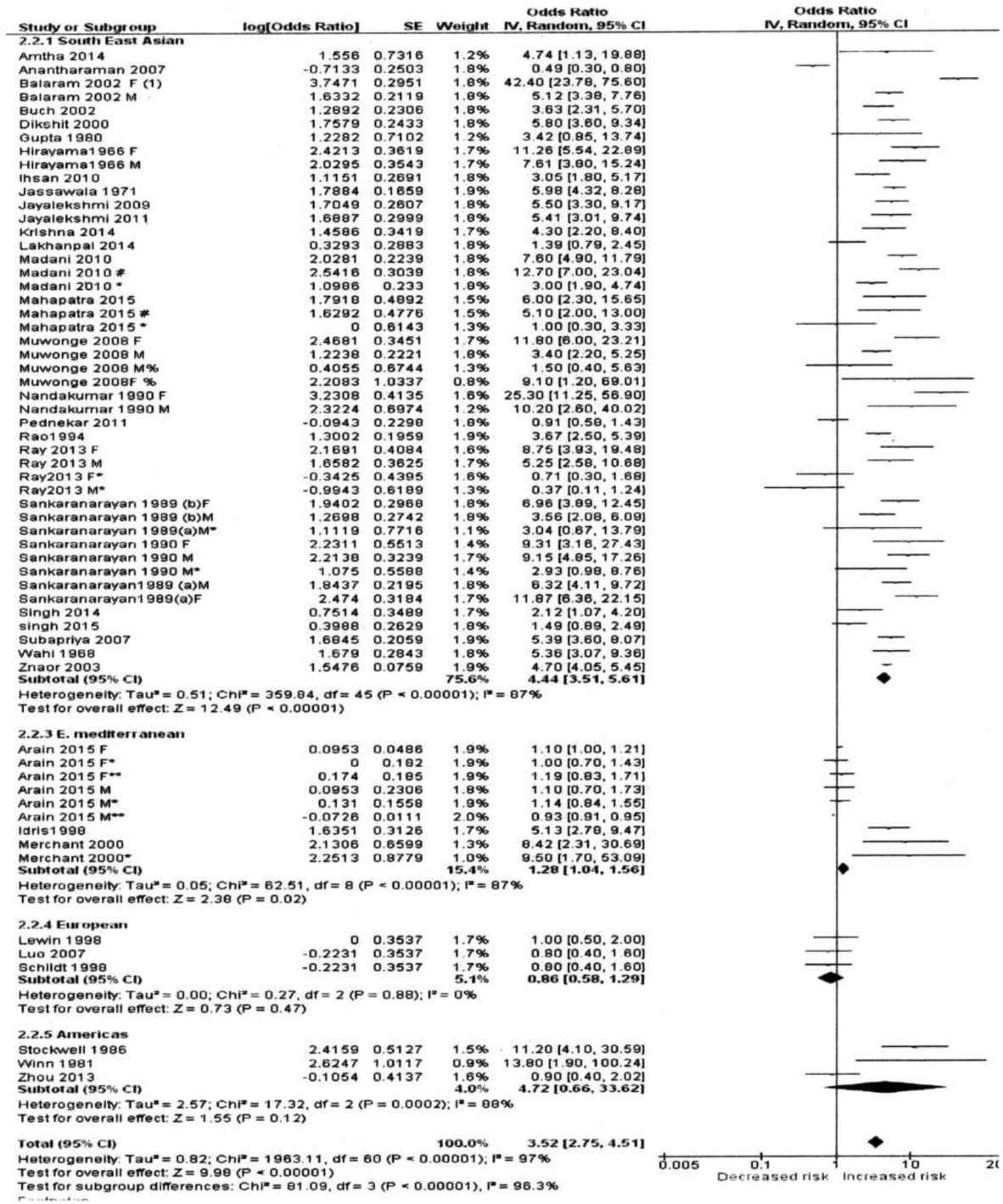

Figure 2. Forest Plot 1: odds ratio for smokeless tobacco use in the development of oral cancer by WHO region—random-effects model. F = Female, M = Male;*snuff, **Mainpuri, #gutkha, % areca nut + lime + tobacco. (a) study in gingival, (b) study in tongue and floor of mouth.

Other Differentials of Risk

Our findings in a separate analysis on gender difference in SLT use and oral cancer risk concurred with the present literature at regional or country level studies.[7–9,12,14,17,19] The reasons for this consistent high risk for women SLT users are not yet explained and need to be studied further whether they are genetic, hormonal, or environmental.

Earlier studies analyzed the study designs at global estimates.[20] Our results echoed the findings of other regional that opined that case–control studies post a higher risk result[7,9,11] compared with cohort studies.[14]

We attempted period-wise analysis of the studies published before and after 1990 to explore the risk estimates. Our results are in contradiction with the results of a study reported earlier.[14] The difference could be explained due to a greater amount of multiple risk-factor adjustments in studies published after the year 1990. In addition, subjecting the data to advanced epidemiological and

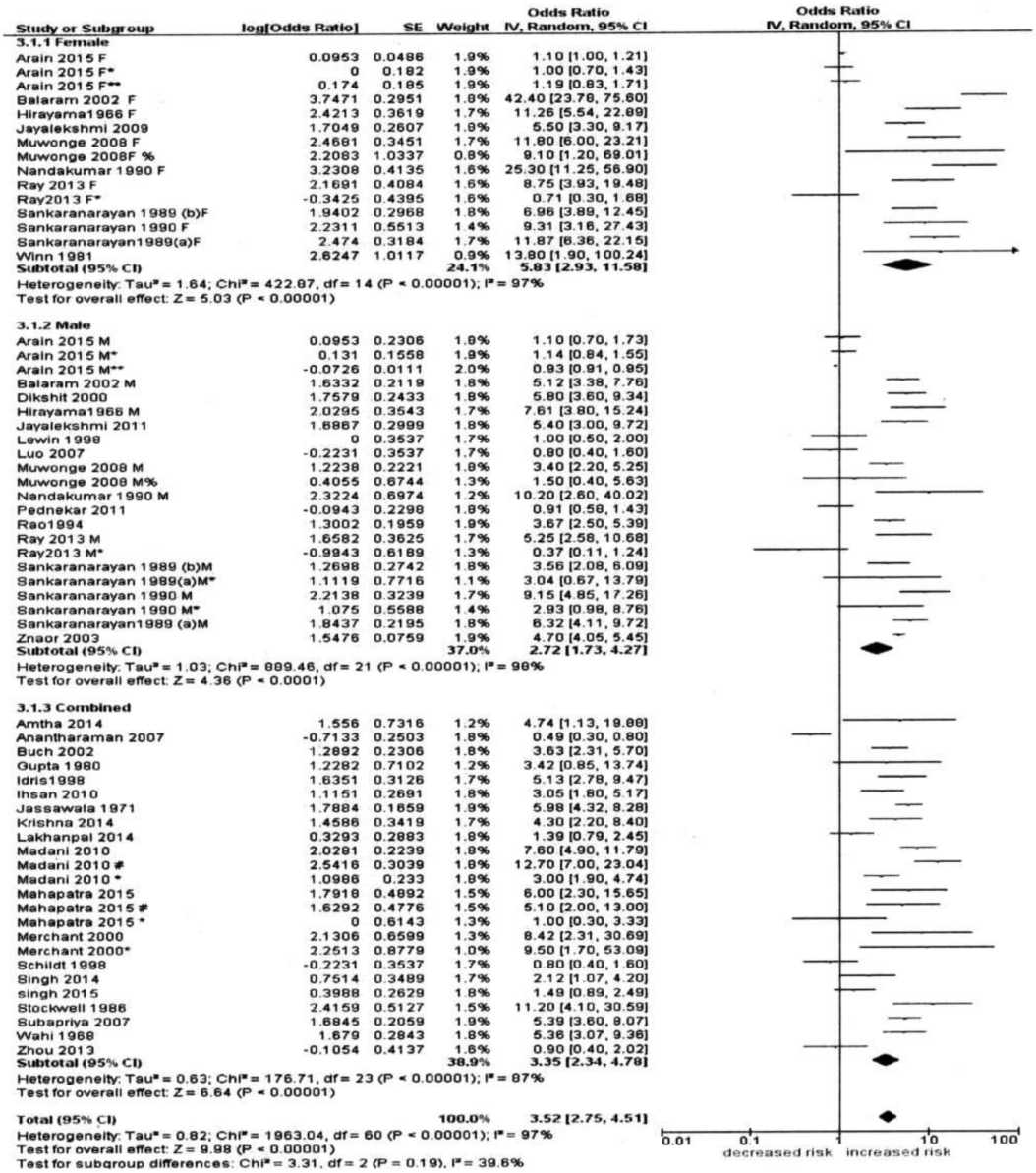

Figure 3. Forest Plot 2: random-effects model showing for smokeless tobacco use in the development of oral cancer by sex. F = Female, M = Male,*snuff, **Mainpuri, #gutkha, %, areca nut + lime + tobacco, (a) study in gingival, (b) study in tongue and floor of mouth.

statistical modeling may also be the reason for the difference in risk estimates for the post 1990 period.

Type-Specific SLT Products

Betel nut is a known carcinogen, associated with a higher risk for oral cancer either with or without tobacco.[11,12] Our results are in line with the findings and shows higher risk for chewing tobacco products containing betel nut such as betel quid and gutkha (Supplementary Table 2). However, our findings of a higher risk of oral cancer in those who chew SLT products did reflect in the findings in other WHO regions,[14,19] which reported an equal or lower risk among chewers. The reason may be attributed to the lower carcinogenic potential of chewing products in the American region.

The present study provided robust estimates at global level on the risk associated with specific SLT product. Furthermore, this study attempted both systematic review and meta-analysis and estimated global risks along with risks in subgroups. Majority of WHO global regions are covered, however, African regions are not included due to non-availability of data. As the studies from Western Pacific region countries Taiwan and Papua New Guinea did not fulfil our inclusion criteria hence could not be included in the analysis. Studies that were available from the Western Pacific region indicated that the role of chewable products was unclear due to the non-exclusion of smoking. Further studies are needed to estimate the precise risk of the association between exposure to SLT and developing cancer as recommended in the FCTC document of the WHO.[60] This study generated sufficient evidence of risk associated with various types of SLT products used. Analyzing different range of factors and the associated oral cancer risk is one of the unique features of our study. It has separate quantitative estimates that are derived into, (1) male and female, (2) type of study,

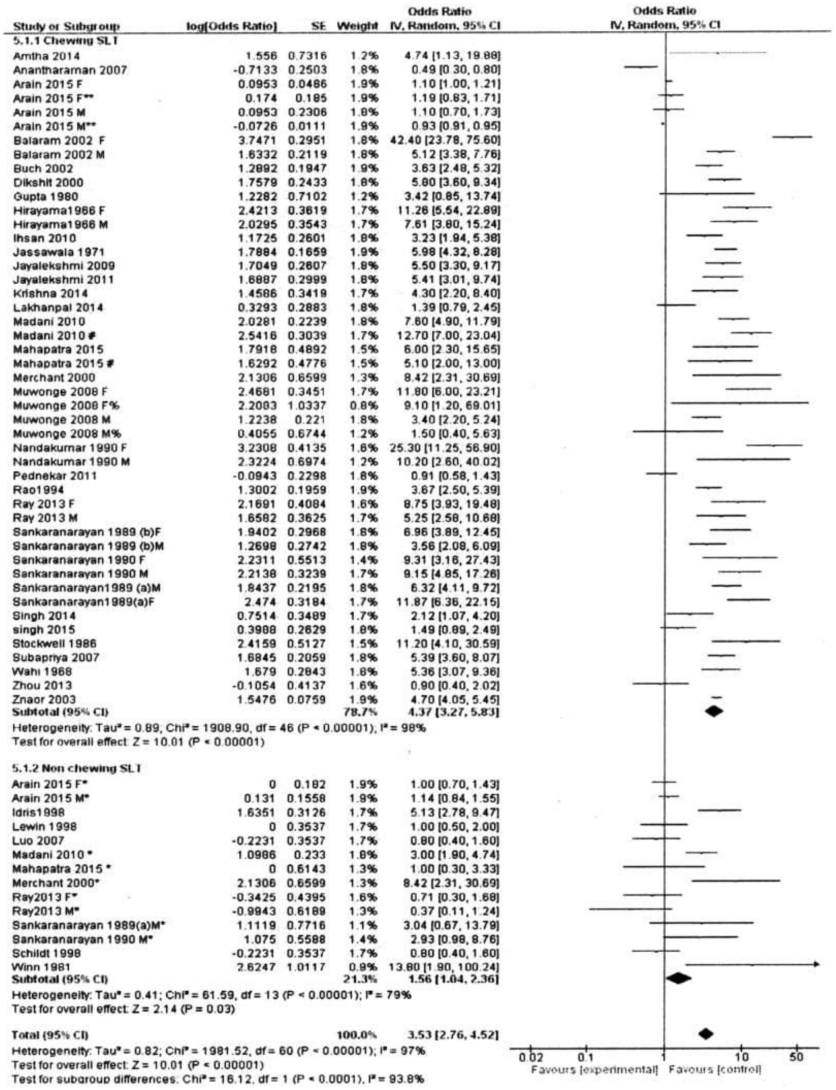

Figure 4. Forest Plot 3: random-effects model showing for smokeless tobacco use and the risk of oral cancer development by method of smokeless tobacco consumption. F = Female, M = Male, *snuff, **Mainpuri, #gutkha, %, areca nut + lime + tobacco, (a) study in gingival, (b) study in tongue and floor of mouth.

(3) studies published before and after the cut-off year of 1990, (4) various SLT types, and (5) method of SLT intake. We assessed the various quality related factors of primary studies for determining measures such as using the PBCR data rather than histology, using different populations as controls, age adjustment was not done in some studies, and no uniformity in adjustment of confounders. These are potential sources of biases, which are part of heterogeneity and may alter the estimates.

Conclusions

Oral cancer risk due to SLT use varies according to the type of tobacco used and the geographical regions. Countries in high-risk regions should formulate and implement policies stringently for the cessation of smokeless tobacco in addition to smoking. The case of banning gutkha in most of the Indian provinces/states is one of the best examples of such an application. Greater initiation at regional leadership is needed to advise policymakers for the steps towards SLT products cessation as well, for control of oral cancer.

Supplementary Material

Supplementary Table 1–11 and Supplementary Figures 1–18 can be found online at https://academic.oup.com/ntr/.

Declaration of Interests

None declared.

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