Oral Cancer Risk Assessment for Different Types of Smokeless Tobacco Products Sold Worldwide: A Review of Reviews and Meta-analyses

Alpana K. Gupta[1], Mona Kanaan[2], Kamran Siddiqi[3], Dhirendra N. Sinha[4], and Ravi Mehrotra[5,6]

ABSTRACT

Smokeless tobacco (SLT) use is a significant cause of lip and oral cavity cancers. Globally, oral cancer prevalence is strongly linked to the types of tobacco products used, their chemical composition, and their pattern of use. Except snus, all SLT products sold in different World Health Organization regions are strongly associated with oral cancer incidence. Shammah showed the highest association OR with 95% confidence intervals (CI; OR, 38.74; 95% CI, 19.50–76.96), followed by oral snuff (OR, 11.80; 95% CI, 8.45–16.49), gutkha (OR, 8.67; 95% CI, 3.59–20.93), tobacco with betel quid (OR, 7.74; 95% CI, 5.38–11.13), toombak (OR, 4.72; 95% CI, 2.88–7.73), and unspecified chewing tobacco (OR, 4.72; 95% CI, 3.13–7.11). Most SLT products containing high levels of carcinogenic tobacco-specific nitrosamines (TSNA) exhibit a high risk of oral cancer. There is an urgent need to frame and implement international policies for oral cancer prevention through legal control of the TSNA levels in all SLT product types.

Prevention Relevance: Most smokeless tobacco products sold worldwide, mainly shammah, toombak, gutkha, betel quid with tobacco, and dry snuff, are associated with a high risk of oral cancer. A high concentration of tobacco-specific nitrosamines in smokeless tobacco products is the major causative factor for oral cancer development.

Introduction

Oral cancer is a highly lethal disease and one of the most debilitating and disfiguring malignancies globally. Head and neck cancers represent the sixth most common cancer worldwide and oral cancer accounts for ∼37% of head and neck cancers with more than 500,000 cases worldwide and are predicted to rise by 62% to 856,000 cases by 2035 (1). According to global cancer statistics, Globocan 2020, cancers of the lip and oral cavity pose an enormous global challenge, with 377,713 new cases and 177,757 deaths accounting for about 3.8% of all cancer cases and 3.6% of cancer deaths globally (2).

Oral cancer is most likely caused by a combination of extrinsic and intrinsic factors acting in concert over a period of time (3, 4). Major risk factors implicated in the etiology of oral cancers are tobacco use (5), areca nut use (6), alcohol consumption (7), ultraviolet radiation, and human papillomavirus (HPV) infection (8). Other factors include poor oral hygiene, low socioeconomic status and genetic factors, occupational exposure (9), weakened immune system, deficiencies in dietary intake, or lack of healthy eating (10). Gender, age, physical activity, and environmental factors may also play a crucial role in the progression of the disease (11, 12). Tobacco and alcohol use are two of the most common risk factors for oral cavity and oropharyngeal cancers (13). As dual use of tobacco products and alcohol act synergistically, and account for 3 of 4 oral cavity cancer cases globally (14, 15).

Smokeless tobacco (SLT) includes a large variety of commercial or noncommercial tobacco preparations used orally or nasally, without combustion. Chewing tobacco, moist snuff, and dry snuff are the three most common types of SLT products used worldwide. The chewing tobacco products mainly include betel quid with tobacco, khaini, zarda, and gutkha. Nonchewing products include oral snuff, nasal snuff, and snus. Snuffed tobacco products are used in either wet or dry form. Use of wet snuff is more common in the Western world, while nasal snuff in dry powder form is used in the South East Asia and Eastern Mediterranean regions (EMR; ref. 16).

The World Health Organization (WHO) South-East Asia Region (SEAR), notably the Indian subcontinent, contains 90% of the world's 250 million SLT consumers and accounts for nearly one third of all cancers (17, 18). SLT use is culturally widely acceptable due to its association with socialization and family tradition in various parts of the world (19). SLT products

[1]Independent Research Consultant, Noida, Gautam Budh Nagar, Uttar Pradesh, India. [2]Department of Health Sciences, University of York, Heslington, York, United Kingdom. [3]Department of Health Sciences, University of York, Heslington, York, United Kingdom. [4]School of Preventive Oncology, Patna, India. [5]Centre for Health, Innovation and Policy, Noida, Gautam Budh Nagar, Uttar Pradesh, India. [6]School of Health Sciences, University of York, Heslington, York, United Kingdom.

Corresponding Author: Ravi Mehrotra, Oncology, Centre for Health Innovation and Policy Foundation, 361, Sector 15A, Noida, Gautam Budh Nagar, Uttar Pradesh 201301, India. Phone: 844-701-4176; E-mail: rmehrotra@icmr.org.in

Cancer Prev Res 2022;15:733–46

doi: 10.1158/1940-6207.CAPR-21-0567

may be premade (ready-to-use) or custom-made. Premade products range from large factory manufactured products to small cottage industry products, while custom made are assembled by the user or a vendor in market stalls or shops according to one's preferences. Due to the vast heterogeneity and lack of standardization, the chemical formulation or composition of SLT products shows great complexity. Factors for the high prevalence of SLT are its addictive properties, easy accessibility, low cost, and lack of prohibitive legislation (20). This could be the reason that the FDA nicotine reduction strategy, which greatly improved the health consequences of tobacco dependence in smokers, could not be applied to SLT products.

SLT causes cancers of all parts of the oral cavity including the lip, tongue, palate, gum, cheek, buccal gingivae, and floor of the mouth (21), along with esophageal and pancreatic cancer, etc (22). More than 180,000 cases of oral cancer occur every year in SEAR with approximately 90% of which are due to tobacco use (23). The odds of developing oral cancer in SEAR were more than 4 times higher among SLT users than non–tobacco users (24, 25). India has one of the highest incidences of oral cancer and accounts for about 30% of all new cases annually due to the high prevalence of SLT use and betel-quid chewing (26). Population-based studies from 13 countries showed that the oral cancer incidence rate is increasing, especially among the younger population (27). Other than HPV, an increased incidence of early-onset oral carcinoma in the US has been associated with SLT use, mainly chewing tobacco and snuff (28).

Due to increasing awareness about smoking-related harms and growing regulatory pressures on cigarettes, the global prevalence of smoking is showing a downward trend in the last two decades (29). A systematic analysis of the global burden of disease study results in 204 countries and territories between 1990 and 2019 indicated that the global age-standardized prevalence of smoking had decreased significantly during this period, while the use of SLT products continued unabated during this period (30). Such a trend could be one of the reasons that the incidence of nasopharyngeal cancers has decreased dramatically [estimated annual percentage change (EAPC), –1.5; 95% CI, −1.7 to −1.3) from 1990 to 2017, while the global incidence for lip and oral cavity cancers has shown a substantial increase from 1990 to 2017 (EAPC, 0.26; 95% CI, 0.16–0.37). Globally, the absolute number of lip and oral cavity cancers incidence increased from around 186,000 in 1990 to 389,800 in 2017, which is about 109% increase over 28 years (31).

Great diversity in the preparation and composition of SLT products makes their regulation a big challenge. For example, gutkha is chewing tobacco mixed with areca nut and slaked lime (32), often marketed as a mouth freshener due to added flavors (33). Shammah is a traditional form of fermented chewing tobacco popular in the Middle East (34) while toombak, a homemade oral snuff mainly used in Sudan, is prepared from the tobacco leaves of *Nicotiana rustica* species having high nicotine content (35). Weak enforcement of regulatory policies and aggressive marketing of SLT products by the tobacco industry worsens the situation (36, 37).

Broadly, reports quantifying the promotion of all types of SLT, as a harm reduction strategy and as a safer alternative to cigarettes, have shown no apparent health benefits at a population level (38). On the other hand, this has caused an increase in the sale of SLT. Because nicotine content in a cigarette stick varies from 0.8 to 13.0 mg/g, while it ranges from 0.8 to 76.0 mg/g in SLT products (39), SLT users absorb 2 to 3 times the amount of nicotine as those who smoke cigarettes (40). This is due to the high alkaline nature of most SLT products providing free nicotine at a high concentration in a short time. Excessive high nicotine concentration makes SLT products highly addictive, and nicotine is also a precursor of carcinogenic tobacco-specific N-nitrosamines (TSNA; refs. 41, 42).

Nicotine and TSNA levels

TSNAs are chemically stable compounds under physiologic conditions and are found to be associated with carcinogenicity in humans and experimental animals (43). TSNAs, mainly N'-nitrosonornicotine (NNN) and nicotine-derived nitrosamine ketone (NNK) are listed as group 1 human carcinogens by International Agency for Research on Cancer (3).They are shown to disrupt DNA repair and molecular processes and are the prime cause of oral cancer in SLT users (44–46).

Addictiveness and health hazards of SLT across the globe are largely dependent upon product's chemical composition and its use pattern (47). Globally, the magnitude of cancer risk due to SLT use shows disparity and is highly correlated with the variation in the levels of NNN and NNK present in diverse SLT products sold worldwide (48, 49). Seeing the carcinogenicity of NNN and NNK in humans, the WHO Study Group on Tobacco Product Regulation in 2010 recommended a regulatory limit for maximal total concentration of NNN and NNK as less than 2-μg/g dry weight of tobacco (48) However, the levels of NNN and NNK, per unit dose, in SLT products are much higher as compared with cigarette smoke. While on an average mainstream cigarette smoke contains NNK and NNN in the range of 0.006 to 1.74 μg/g and 0.004 to 2.83 μg/g, respectively, SLT products sold across the world showed NNK levels between 0.019 to 7,870 μg/g and NNN levels between 0.080 to 3080 μg/g against the WHO permissible limit of less than 2 μg/g.

Swedish Match, the principal manufacturer of Swedish moist snuff, adopted a voluntary standard for TSNAs levels, called the GothiaTek standard (50). **Table 1** represents comparative data on the type of SLT sold across the world, its preparation process and use, country/WHO region, levels of nicotine, total TSNAs, NNN, and NNK. SLT products viz. shammah, gutkha, toombak, betel quid with tobacco, chewing tobacco (unspecified) along with dry snuff and moist snuff (snus) were found to contain high levels of carcinogenic TSNAs, mainly NNN and NNK in them.

Table 1. Global pattern of types of SLT use and nicotine and nitrosamine levels in different SLT products.

S no	SLT type	Preparation and use	Region	Countries with major consumption	Nicotine[a] mg/g	Total TSNA[a] μg/g	NNN[a] μg/g	NNK[a] μg/g
1	Snuff	Finely cut or ground air-cured flavored tobacco dry or moist, placed in the mouth and sucked.	America	USA, Canada, Mexico,	3.9–40.1	0.3–76.5	0.37–42.6	0.38–9.9
2	Snus (Swedish)	Pasteurized finely ground moist tobacco, moisturizers, sodium carbonate, salt, sweeteners	Europe	Sweden, Denmark, Finland, Iceland, Norway,	7.8–15.2	0.6–0.7	0.42–3.28	0.13–1.1
3	Nass (Naswar)	Sun-dried and powdered tobacco; ash, oil, placed in the mouth and sucked	Parts of Europe and Eastern Mediterranean	Uzbekistan, Kyrgyzstan, Tajikistan, Afghanistan, Pakistan, Iran	8.9–14.2	0.5–1.4	0.59–1.3	0.07–0.21
4	Toombak	Fermented and grounded Tobacco, baking soda and water. Oral and nasal use	Parts of Eastern Mediterranean and Africa	Sudan, Chad	9.6–28.2	295–992	115–3085	147–7870
5	Dry Snuff	Finely ground powder, inhaled	Africa	Nigeria, Ghana, Algeria, Cameroon, Chad, South Africa	1.2–17.2	1.7–20.5	2.4–18.1	0.58–6.4
6	Gutkha (Chewing tobacco)	Commercial preparation, finely chopped tobacco with flavorings and sweeteners, Sucked and chewed	SEAR	India, Pakistan, Bangladesh, Nepal, Myanmar, Sri Lanka, UK	0.2–4.2	0.1–23.9	0.1–1.1	0.04–0.43
7	Khaini (Chewing tobacco)	Coarsely cut tobacco leaves mixed with slaked lime, Sun-dried or fermented.	South East Asia, Western Pacific and Eastern Mediterranean Europe	India, Bangladesh, Nepal, Bhutan	2.5–4.8	21.6–23.9	13.2–76.9	0.11–28.4
8	Zarda (Chewing Tobacco)	Shredded tobacco leaves are boiled with lime and saffron; often used with betel quid	SEAR	Bangladesh, India, Pakistan, Myanmar, Thailand, Indonesia, Nepal, Maldives, Sri Lanka, UK	9.5–30.4	5.5–53.7	4.79–19.9	0.22–24.1
9	Betel quid with tobacco	Mixture of betel quid with areca nut, with or without tobacco. May also be mixed with slaked lime ad f tobacco. be mixed with slaked lime, or sweeteners	SEAR	India, Pakistan, Bangladesh, Nepal, Myanmar	6.7–8.4	0.17–2.1	1.2–48.6	0–14.3
10	Shammah (Chewing tobacco)	Powdered tobacco used with slaked lime, oil, flavoring, kept in the mouth and sucked	Middle East	Saudi Arabia, Yemen, Algeria.	37.82–87.56	DNA[b]	DNA[b]	DNA[b]

Note: List of products is not exhaustive.
[a]Figures are adapted from refs (26, 37, 52, 93, and 99).
[b]DNA: Data not available.

Many research articles in the previous years have indicated the link between SLT and oral cancer but the present systematic review, for the first time, describes the levels of risk estimates of oral cancer associated with the major individual type of SLT products sold across the five WHO regions. It also reports the WHO region-wise oral cancer risk estimates associated with different SLT products and compiles data on the global pattern of different types of SLT product use and the concentration of nicotine, total TSNAs, NNN, and NNK in them.

Materials and Methods

Electronic searches

An electronic search was conducted on PubMed and Google Scholar for articles published between January 1, 2010 to August 5, 2021 using the key phrases "oral cancer", "oral squamous cell carcinoma", "smokeless tobacco", "chewing tobacco", "betel quid", "snuff", "snus", "gutkha/gutka", "toombak", and "shammah". The references of relevant articles were manually searched for additional eligible citations. This comprehensive review presents pooled data from the different studies.

Selection of studies

Author, A.K. Gupta extracted data through this literature search and identified studies. Duplicate records were removed, and the reference lists of the selected articles were screened for additional relevant articles. Titles and abstracts of papers identified through the search strategy were reviewed and relevant articles, potentially fulfilling the inclusion criteria, were retrieved in full text. A second reviewer (R. Mehrotra) screened the titles and abstracts of the retrieved articles to identify the relevance of the articles to the objectives of this review. Two authors, A.K. Gupta and M. Kanaan, independently assessed the eligibility of the selected data to assure quality and minimize biases. **Figure 1** provides the detailed strategy of the study selection process using PRISMA guidelines.

Inclusion criteria

- Oral cancer had to be one of the outcomes of SLT use in the adult population.
- Articles presented only as reviews, systematic reviews, and meta-analyses.
- Studies providing OR/risk ratio (RR) estimates with corresponding 95% confidence intervals (CI).
- Articles published in English.

Exclusion criteria

- Studies not designed to investigate SLT association with oral cancer.
- Articles published before year 2010.
- Articles published in languages other than English.

Data extraction

For articles meeting the eligibility criteria, the following information was extracted: the study authors with the date of publication, region of the study, the type of SLT, period of study, OR/RR estimates, and corresponding 95% CI. Information was extracted by one author A.K. Gupta and checked by another author, M. Kanaan (Supplementary Table S1).

The region of the study was classified as global or as one of the WHO regions, namely, the American Region (AMR), EMR including Pakistan, European Region (EUR), African Region (AFR), and South-East Asian Region (SEAR). The type of tobacco was classified as: any type of SLT, if not explicitly specified which type, shammah (Arabian chewing tobacco), toombak (Sudanese dipping tobacco), gutkha (Indian chewing tobacco), betel quid with tobacco, chewing tobacco (unspecified), dry snuff, and moist snuff (snus). If a review article had been updated, then the updated review estimates were used and if two reviews cite the same source, then the one reporting pooled estimates was used.

Data analysis

We used forest plot graphs to represent the OR/RR estimates and 95% CI. Results were stratified by WHO region and by tobacco type. No overall pooled analysis was conducted. If a previous review reported individual studies without pooling the results, these were pooled if the estimates were provided together with 95% CI or other information to enable pooling the results. All studies were systematic reviews with meta-analysis except for one study on toombak where the combined OR estimates were not reported and thus were calculated (see Supplementary Method).

Ethics statement

Article does not contain any studies involving human or animal participants.

Data availability statement

The data generated in this study are available upon request from the first author A.K. Gupta.

Results

Articles, published in the last decade, i.e., from 2010 to 2021 and reporting the oral cancer risk estimates in the association of the SLT product, were selected for the present review. After removing duplicate records, titles and abstracts of 74 records were retrieved through the selected databases. The reference lists of the included articles were screened for 4 additional articles. All 78 articles were reviewed thoroughly. After removing 52 irrelevant articles, 26 were selected for the full-text study, of which, 17 which did not meet the selection criteria, were excluded. **Figure 1** demonstrates the flowchart of the study selection process for SLT use and oral cancer risk using PRISMA guidelines. Oral potentially malignant disorders are abbreviated as OPMD in **Fig. 1**.

Nine studies fulfilling all the eligibility criteria for inclusion were finally included in the current review. Of these,

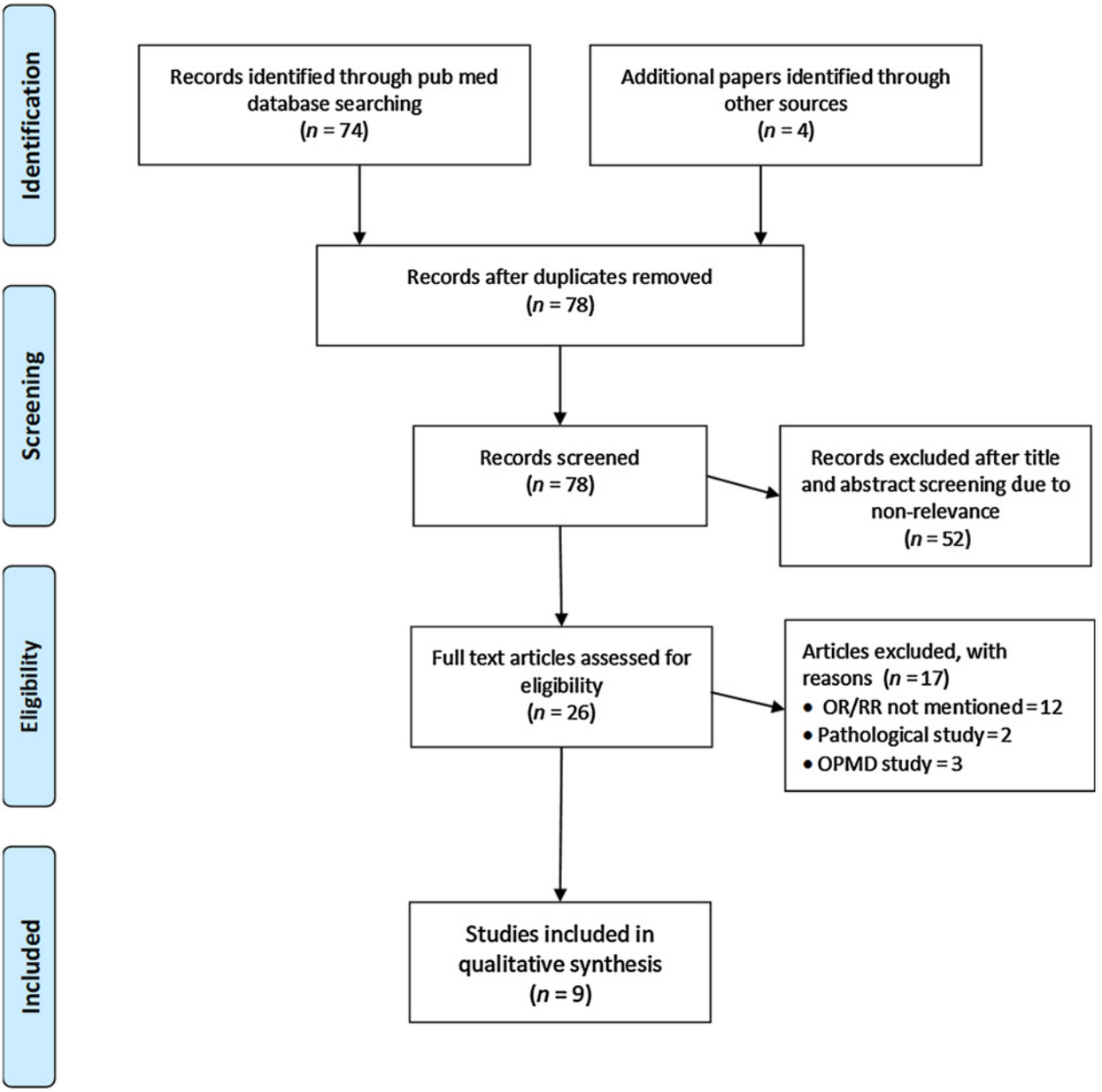


Figure 1.
Search strategy flowchart of study selection process for SLT use and oral cancer risk using PRISMA guidelines.

three reviews evaluated the risk of oral cancer with the use of all types of SLT products combined (51–53). Three reported OR estimates for betel quid with tobacco (51, 54, 55). Dry snuff was evaluated for high risk of oral cancer in three studies (51, 56, 57). Two studies mentioned chewing tobacco (without specifying the type; refs. 51, 56), while one study each was found on shammah (58), gutkha (51), toombak (59), and snus (51). All the selected studies are systematic reviews with meta-analysis and OR estimates were adjusted for confounding factors mainly smoking except for one study (ref. 59; Supplementary Table S1).

Data analysis of all included studies together indicated that the individual product that showed the highest association (OR, 38.74; 95% CI, 19.50–76.96) was shammah, followed by oral snuff (OR, 11.80; 95% CI, 8.45–16.49), gutkha (OR, 8.67; 95% CI, 3.59–20.93), tobacco with betel quid (OR, 7.74; 95% CI, 5.3–11.13), toombak (calculated OR, 4.72; 95% CI, 2.88–7.73; see Supplementary Method), and unspecified chewing tobacco (OR, 4.72; 95%

CI, 3.13–7.11). Overall, all selected SLT product types, except snus, were found to have a strong association with oral cancer incidence across the globe. **Figure 2** represents a forest plot of the included studies showing ORs and 95% CI for the association between the types of SLT products and the risk of oral cancer.

Region-wise analysis of SLT products showed that the overall global OR for oral cancer for all SLT types combined, ranged from 3.53 (95% CI, 2.76–4.52) to 3.94 (95% CI, 2.70–5.75). In general, region-wise oral cancer risk estimates, for all types combined, were highest for EMR with OR ranging from 1.28 (95% CI, 1.05–1.57) to 14.52 (95% CI, 7.69–27.41), followed by SEAR with OR 4.44 (95% CI, 3.51–5.61) to 5.67 (95% CI, 3.83–8.40) and for AMR, OR 0.95 (95% CI, 0.71–1.25) to 4.72 (95% CI, 0.66–33.69), while it was not statistically significant for EUR with OR 0.94 (95% CI, 0.71–1.25). For further details, see **Fig. 3**, which represents a forest plot of included studies by the WHO region.

A strong positive association of betel quid with tobacco and oral cancer was seen globally OR 7.18 (95% CI, 5.489.41; ref. 51) while for Asian studies risk estimates for betel quid with tobacco range from OR 7.10 (95% CI, 4.49–11.22) to 7.74 (5.38–11.13; refs. 54, 55), toombak and shammah use for EMR, showed highest oral cancer risk estimate with OR 4.72 (95% CI, 2.88–7.73; ref. 56) and OR 38.74 (95% CI, 19.50–76.96) respectively (58). Risk estimates for snuff-type products vary significantly among various WHO regions. In EUR and AMR, dry snuff and snus are more prevalent. Global oral cancer risk estimates for oral snuff showed OR 4.18 (95% CI, 2.37–7.38; ref. 51) while for AMR, OR was 3.01 (95% CI, 1.63–5.55; 56). Naswar, used in EMR was shown to have a high OR value of 11.80 (95% CI, 8.45–16.49; ref. 57). Globally, chewing tobacco, is shown to have a high oral cancer risk with OR 4.37 (95% CI, 3.27–5.84) as compared with non-chewing SLT products with OR 1.56 (95% CI, 1.04–2.35; ref. 51; **Fig. 3**).

The level of TSNAs in SLT products plays a significant role in carcinogen exposure levels. Thus, the difference in the magnitude of oral cancer risks can be correlated with the variation in the levels of NNN and NNK present in SLT products (49). TSNA levels vary from 0.08 μg/g to as high as 992 μg/g in the selected SLT products. **Figure 4** indicates that high levels of TSNAs are present in SLT products with a high RR for oral cancer. **Figure 4** (a) presents TSNAs values on the log scale while the original TSNAs levels in μg/g are presented on the right-hand side of the *y*-axis. (b) OR and corresponding 95% CIs estimates are based on review studies from the same region that the SLT product TSNAs values are based. The OR estimates for zarda and khaini are not product specific but those for all types of chewing tobacco from SEAR (54). For gutkha, dry snuff, and snus the OR estimates are based on global pooled estimates (51), whereas for naswar (a nasal snuff) these are based on EMR estimates only (57).

Discussion

Global pattern of oral cancer risk estimates for different SLT products

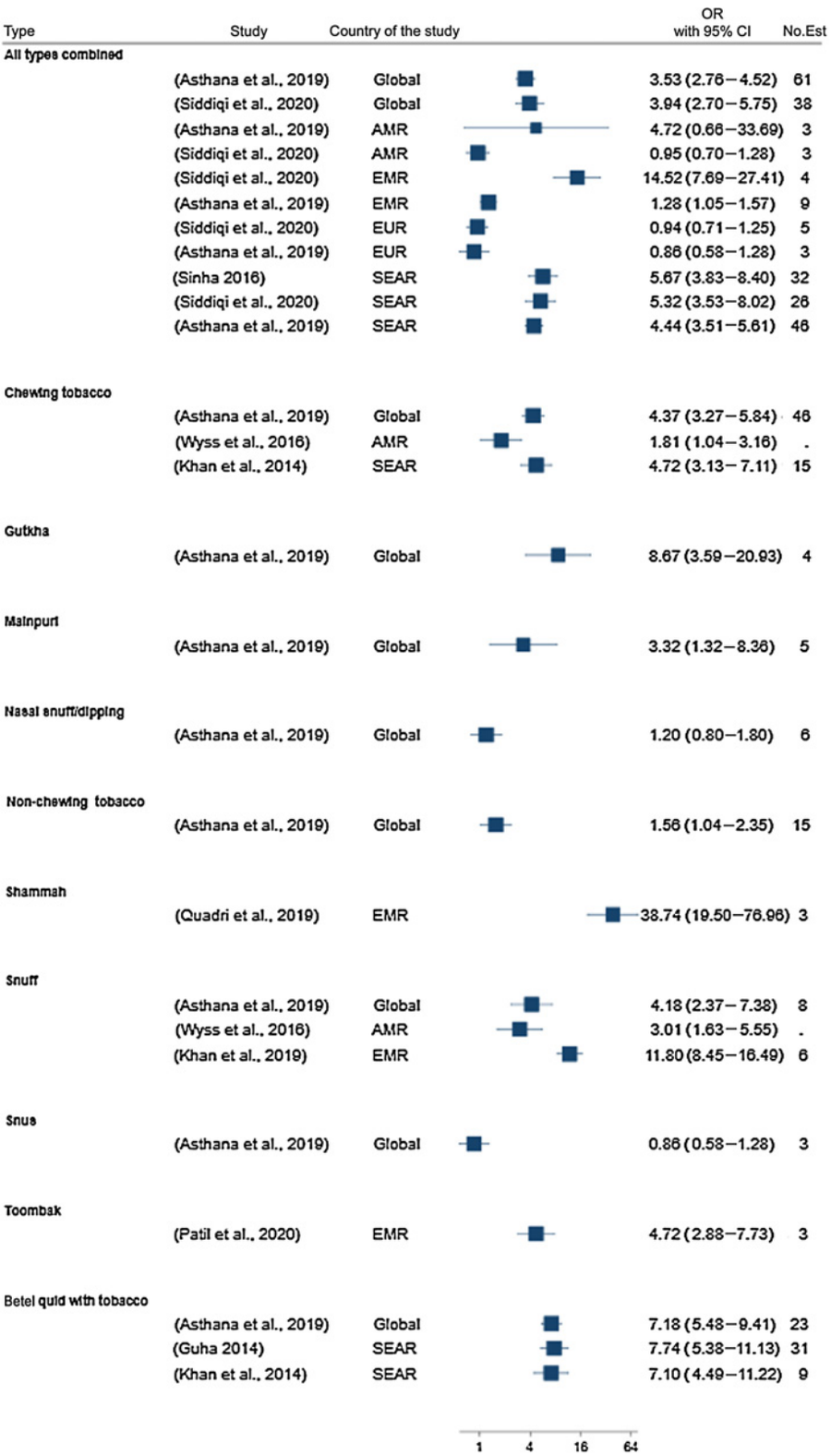
According to a recent study, published in Lancet Public Health, of the total 273·9 million tobacco chewers (age 15 and above) in the world, about 228·2 million live in SEAR (30). Over the past several decades, it has been seen that SLT use has increased by nearly 50% in low-and-middle-income countries while declining in high-income countries (60). Tobacco chewing and betel quid with tobacco are the two most prevalent forms of SLT use in Asia (61). In India, the majority of SLT users consume chewing tobacco (11.6% khaini, 8.2% gutkha preparations, 6.2% betel quid with tobacco, 4.7% oral snuff, and 4.4% other SLT products; ref. 51). Gutkha use has been gaining popularity in Europe and US in the last two decades due to its easy availability, low cost and extensive marketing (62). In the US, the sale of SLT products increased by 5.8% between 2011 and 2016, but declined by 3.9% from 2016 to 2019; however, the sale of snus consistently increased while the sale of chewing tobacco, dry snuff, and dissolvable decreased during this period (63).

A recent Centers for Disease Control and Prevention (CDC) report indicated that the incidence of cancers of the oral cavity and pharynx (all sites), not associated with HPV, increased in the US during 2007–2016 (64). In 2018, an estimated 120,000 new patients with oral cancer were diagnosed with 72,000 deaths in India alone (65). Studies revealed that a higher risk of oral cancer was observed for SLT products sold before 1990 (OR, 6.6; 95% CI, 5.3–8.2) as compared with that sold after 1990 (OR, 3.0; 95% CI, 2.3–3.9; ref. 17). Dry snuff sold in the US and Western Europe, before 2000, was shown to have higher relative risks for oral cancers (RR, 8; 95% CI, 2.7–20.0; ref. 66). This is due to improvement in the quality of manufactured tobacco products. Most SLT products sold in the US after 1990, achieved TSNAs levels below 20 ppm as compared with generally high TSNAs levels (above 100 ppm) in earlier SLT products, sold before 1990 (67). Previous studies showed that snus had an association with an increased risk of oral or pancreatic cancer as compared with non–tobacco users (68, 69). However, the current prevalence statistics and epidemiologic data on snus use, in the European population, do not indicate an increased risk of oral cancer compared with cigarettes (70).

More than 50% of oral cancers are attributable to using SLT products in Sudan and India compared with about 4% in US men (65). Literature studies show that toombak has a major role in the etiology of oral/oropharyngeal cancer in Sudan (71, 72) and sub-Saharan Africa (73). Oral cancer occurrence is about 3 to 6 times higher in North-East Nigeria than reported for the US and Europe, mainly due to the use of dry snuff (OR, 10; 95% CI, 4.1–4.3; refs. 74, 75). Oral cancer is the third most common malignancy in Saudi Arabia mainly due to the use of shammah, the traditional form of chewing tobacco prevalent in the Middle East, Yemen, and Sudan (76). A review of studies by Awan and Patil showed that in the SEAR,

Figure 2.

Forest plot of studies showing oral cancer risks associated with various types of SLT products. Data presented also include: the SLT type, the study reference, region, the OR and corresponding 95% CI, in addition, where available the number of estimates (No. Est) that the pooled estimate is based on are provided.



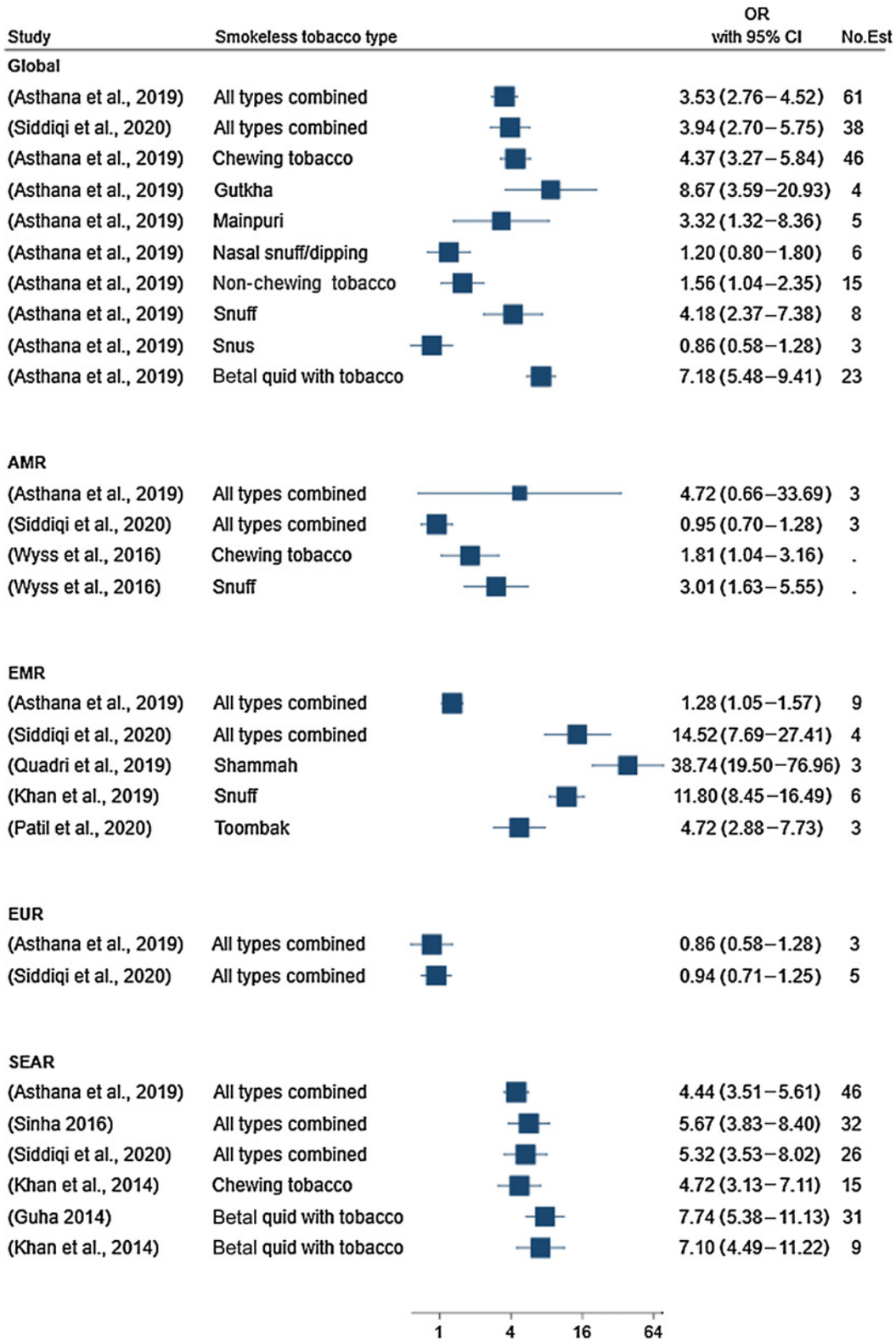


Figure 3.

Forest plot of studies showing WHO region-wise oral cancer risks associated with various SLT products. Data presented also include: the SLT type, the study reference, the OR and corresponding 95% CI, in addition, where available the number of estimates (No. Est) that the pooled estimate is based on are provided.

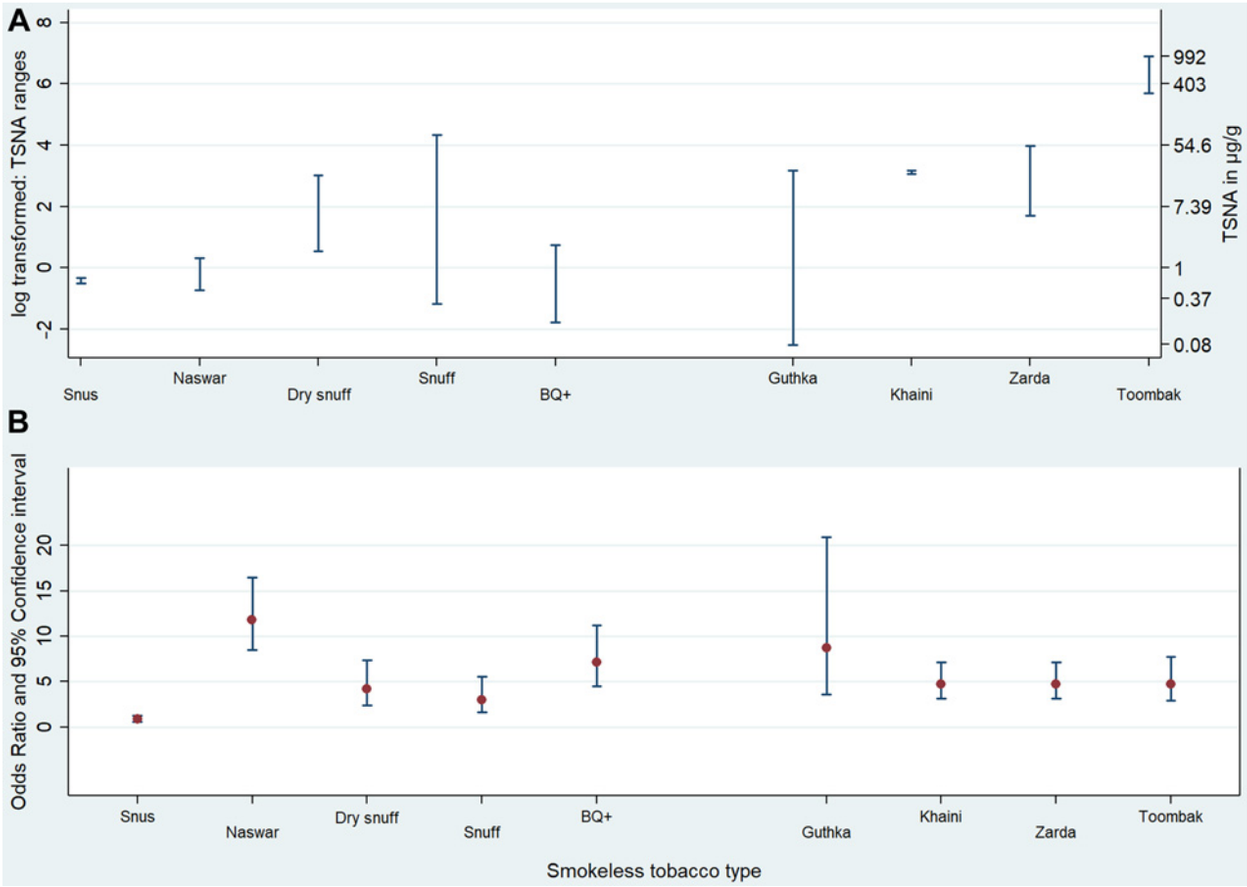


Figure 4.

TSNAs levels and OR for oral cancer in diverse SLT products. (BQ+ denotes betel quid with tobacco) (**A**) TSNA values are presented on the log scale; the original TSNAs levels in µg/g are presented on the right hand side y-axis. **B,** OR and corresponding 95% CIs estimates are based on review studies from the same region that the SLT product TSNAs values are based. The OR estimates for zarda and khaini are not product specific but those for all types of chewing tobacco from SEAR (54). For gutkha, dry snuff, and snus, the OR estimates are based on global pooled estimates (51), whereas for naswar these are based on EMR estimates only (57).

the oral cancer risk estimates (OR) for betel quid varied from 3.1 to 15.7 (95% CI, 11.0–22.1) and from 1.2 (95% CI, 1.0–1.4) to 12.9 (95% CI, 7.5–22.3) for chewing tobacco (43).

The frequency of SLT use was also seen to vary substantially across countries and by sex, age, ethnic origin, and socioeconomic characteristics within a country (77). A linear dose–response association was observed between oral cancer and chewing tobacco regarding age at initiation, duration, and frequency of chewing per day (78).

Most SLT users have limited awareness of its association with oral cancer due to a lack of knowledge of its harmful constituents and high use due to cultural traditions/ religious norms (79). According to the Global Adult Tobacco Survey in India (GATS, 2016–17), the prevalence of SLT use is very high, especially in females, which could be due to a lack of awareness and knowledge about the health hazards of the SLT product used (80). In the Indian subcontinent, betel quid chewing, with added tobacco has a much higher RR in women (OR, 14.6; 95% CI, 7.6–27.8; ref. 55). Globally, gender-wise sub-group analysis showed a higher risk for females with (OR, 5.8; 95% CI, 2.9–11.6), as compared with males (OR, 2.7; 95% CI, 1.7–4.3; ref. 51).

High levels of nicotine and TSNAs in SLT products and oral cancer

High nicotine content in SLT products is responsible for the increased levels of TSNAs, which are primarily formed during tobacco fermentation and storage, especially at elevated temperature and moisture (81). A global surveillance study across 113 countries from five WHO regions over the past 10 years, indicated that diverse SLT products sold worldwide seem to contain high levels of carcinogenic TSNAs (52). Maximum concentrations of NNN and NNK content for toombak products from Sudan were found to be 3,085 and 7,870 µg/g respectively, which were remarkably higher than most of the products sold worldwide (82). Average levels of NNN, in a brand of khaini, marketed as snus, were 22.9 and 2.6-µg/g tobacco respectively (83). Khaini, sold in South Asia, contains

alarmingly high levels of NNN (39.4–76.9 μg/g) and NNK (2.34–28.4 μg/g; ref. 84). Snuff sold in America was shown to have TSNAs levels as high as 76.5 μg/g, while NNN (0.37–42.6 μg/g) and NNK (0.38–9.9 μg/g; ref. 85). The literature did not report levels of TSNAs in shammah, showing the highest OR. On average, NNN and NNK levels showed an almost 70-fold variation with NNN concentrations ranging from 0.09 to 76.9 μg/g while NNK levels ranged from 0.04 to 28.4 μg/g in all selected SLT products (6). Fermented SLT products, like toombak, shammah, dry snuff, khaini, gutkha, have been found to contain higher levels of TSNA than pasteurized products like snus (84). Shammah, a highly fermented product with high nicotine content (86), is made under long anaerobic conditions so more nitrite is generated which increases TSNA concentration. However, no study was found reporting the TSNA levels in shammah (34). The OR of developing oral cancer, for shammah users was 38.7 (95% CI, 19.5–77.0) which was nearly 39 times higher than non-shammah users (58). Studies showed that NNN and NNK levels for toombak were about 100 folds higher than most of the products sold worldwide (87, 88). Oral cancer risk estimate for toombak use was significantly high among users in comparison with controls (OR, 3.8; 95% CI, 1.7–8.6; ref. 89). A report showed that US snus had high TSNAs with NNN and NNK as high as 42.55 and 9.95 μg/g, respectively (90). Dry snuff, the major factor for tongue carcinoma in the US, is shown to contain high TSNAs levels (91). On the other hand, Swedish snus made with improved manufacturing techniques has low oral cancer risks due to low levels of NNN and NNK (92). Thus, the levels of nicotine and TSNAs showed several hundred-fold variations across different product types and substantial vendor-to-vendor variation within some product categories (93).

Thus, SLT products with higher NNN concentration pose higher cancer risks, so reducing the levels of carcinogenic nitrosamines in finished SLT products could prove a beneficial strategy to reduce OR risk for oral cancer (94, 95).

For the protection of public health, FDA has proposed a tobacco product standard rule, which states that the mean level of NNN in any batch of finished SLT product should not exceed 1.0 μg/g of tobacco (on a dry weight basis) at any time through the product's labelled expiration date (96). However, constituent regulation and control of SLT products lag far behind cigarettes, mainly due to non-standardized production and storage methods, greater heterogeneity, and the lack of strict legal policies for SLT (39).

Conclusions

The current review is to bring attention to the prevention community to the risks of individual SLT product for risk of oral cancer. Most carcinogenic SLT types sold across the various geographic regions worldwide, mainly shammah, toombak, gutkha, betel quid with tobacco, dry snuff were found to be associated with high oral cancer risks. Data analysis indicated that the shammah showed the highest association (OR, 38.7; 95% CI, 19.5–77.0), followed by oral snuff (OR, 11.8; 95% CI, 8.4–16.4), gutkha (OR, 8.7; 95% CI, 3.6–20.9), tobacco with betel quid (OR, 7.7; 95% CI, 5.3–11.1), toombak (OR, 4.7; 95% CI, 2.9–7.7) and unspecified chewing tobacco (OR, 4.7; 95% CI, 3.0–7.1). The difference in the magnitude of oral cancer risks has been found to correlate highly with regional variation in the SLT product type which showed great diversity and heterogeneity in its composition, usage and manufacturing process. A decrease in smoking and the prevalence of lung cancer in the US shows the effectiveness of decades of public education and tobacco control policies (97). However, the rising incidence of oral cancer across the world, primarily associated with SLT use, indicates that the tobacco control policies do not have a more prominent effect on SLT usage. The huge variation in the levels of carcinogenic TSNAs, especially NNN and NNK, in diverse types of SLT products, hinders the comparability of results from evaluating the global risks estimate of SLT to human health across the globe. It is imperative to develop and effectively implement strategies for monitoring TSNA levels in SLT products. There is a critical need for systematic surveillance of all types of SLT products through legal control of the permissible TSNA levels. Global standards for testing and measuring TSNAs levels in all types of SLT products, with effective measures to minimize the levels of TSNA, can significantly help reduce oral cancer risk associated with individual SLT products.

Road ahead

The high concentration of TSNAs, mainly NNN and NNK, in diverse types of SLT products is the major causative factor for the development of oral cancer. Applying a grassroots approach to lower the levels of carcinogenic TSNAs at various stages of SLT production, right from its growth, processing, manufacturing, and storage, could prove to be a beneficial strategy. This includes the use of tobacco plant varieties having low levels of nitrate and TSNAs precursors, decreasing the use of nitrate fertilizers and chemical pesticides while growing tobacco, avoiding microbial contamination during tobacco processing, air-curing of leaves instead of fire curing under controlled conditions, use of newer technologies like heat treatment, pasteurization for tobacco processing and avoiding tobacco fermentation etc. can significantly lower the concentration of carcinogenic TSNAs in the finished SLT products (39).

As the majority of oral cancer are preventable through risk factors intervention, creating awareness about their carcinogenicity among consumers, constituent's disclosure along with their health hazard information on all SLT products may play a key factor in reducing oral cancer incidence in the future. Strict regulatory measures are to be taken for the additives and flavoring agents in SLT products, which make them palatable and more appealing especially amongst youth (98).

For the first time, the World Health Assembly, in 2007, passed a resolution on oral health and oral cancer prevention to be an integral part of national cancer control programs. The WHO global oral health program was launched to work for the capacity building in oral cancer prevention in different countries, inter-country exchange and the development of global surveillance systems for oral cancer and risk factors. With the establishment of more cancer registries across the globe and their secondary data analysis, the surveillance of SLT products should become easier.

Authors' Disclosures

K. Siddiqi reports grants from National Institute of Health Research outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

A.K. Gupta: Conceptualization, resources, data curation, investigation, methodology, writing–original draft, writing–review and editing. **M. Kanaan:** Software, formal analysis, validation, investigation, methodology, writing–review and editing. **K. Siddiqi:** Supervision, investigation, visualization, project administration. **D.N. Sinha:** Conceptualization, visualization, project administration. **R. Mehrotra:** Formal analysis, supervision, writing–original draft, project administration, writing–review and editing.

The publication costs of this article were defrayed in part by the payment of publication fees. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

Note

Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

Received November 15, 2021; revised April 28, 2022; accepted September 7, 2022; published first September 9, 2022.

References

1. Shield KD, Ferlay J, Jemal A, Sankaranarayanan R, Chaturvedi AK, Bray F, et al. The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012. CA Cancer J Clin 2017;67:51–64.
2. WHO-IARC. Globocan 2020: new global cancer data, UICC. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/1-Lip-oral-cavity-fact-sheet.pdf.
3. International Agency for Research on Cancer. Personal habits and indoor combustions. Volume 100 E. A review of human carcinogens. IARC Monogr Eval Carcinog Risks Hum 2012;100:1–585.
4. Conway DI, Purkayastha M, Chestnutt IG. The changing epidemiology of oral cancer: definitions, trends, and risk factors. Br Dent J 2018; 225:867–73.
5. Petti S. Lifestyle risk factors for oral cancer. Oral Oncol 2009;45: 340–50.
6. Gupta AK, Tulsyan S, Thakur N, Sharma V, Sinha DN, Mehrotra R. Chemistry, metabolism and pharmacology of carcinogenic alkaloids present in areca nut and factors affecting their concentration. Regul Toxicol Pharmacol 2020;110:104548.
7. Akinkugbe AA, Garcia DT, Brickhouse TH, Mosavel M. Lifestyle risk factor related disparities in oral cancer examination in the US: a population-based cross-sectional study. BMC Public Health 2020; 20:153.
8. Tanaka TI, Alawi F. Human papillomavirus and oropharyngeal cancer. Dent Clin North Am 2018;62:111–20.
9. Zini A, Czerninski R, Sgan-Cohen HD. Oral cancer over four decades: epidemiology, trends, histology, and survival by anatomical sites. J Oral Pathol Med 2009;39:299–05.
10. Freedman N, Park Y, Subar A, Hollenbeck A, Leitzmann M, Schatzkin A, et al. Fruit and vegetable intake and head and neck cancer in a large United States prospective cohort study. Cancer Res 2007;67:849.
11. Elshahat S, Treanor C, Donnelly M. Factors influencing physical activity participation among people living with or beyond cancer: a systematic scoping review. Int J Behav Nutr Phys Act 2021;18:50.
12. Curtis DC, Eckhart SC, Morrow AC, Sikes LC, Mridha T. Demographic and behavioral risk factors for oral cancer among Florida residents. J Int Soc Prev Community Dent 2020;10:255–61.
13. Goldenberg D, Lee J, Koch WM, Kim MM, Trink B, Sidransky D, et al. Habitual risk factors for head and neck cancer. Otolaryngol Head Neck Surg 2004;131986–93.
14. Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, et al. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res 1988;48:3282–7.
15. Pelucchi C, Gallus S, Garavello W, Bosetti C, La Vecchia C. Cancer risk associated with alcohol and tobacco use: focus on upper aero-digestive tract and liver. Alcohol Res Heal 2006;29:193–8.
16. National Cancer Institute and Centers for Disease Control and Prevention. Smokeless tobacco and public health: a global perspective. Bethesda, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Institutes of Health, National Cancer Institute. NIH Publication No No. 14–7983 2014;79–83.
17. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 2009;45:309–16.
18. Datta S, Chaturvedi P, Mishra A, Pawar P. A review of Indian literature for association of smokeless tobacco with malignant and premalignant diseases of head and neck region. Indian J Cancer 2014;51:200–8.
19. Mishra S, Mishra MB. Tobacco: its historical, cultural, oral, and periodontal health association. J Int Soc Prev Community Dent 2013;3:12–8.
20. Yadav A, Singh PK, Yadav N, Kaushik R, Chandan K, Chandra A, et al. Smokeless tobacco control in India: policy review and lessons for high-burden countries. BMJ Glob Heal 2020;5:2367.
21. McGuire S. World Cancer Report 2014. Geneva, Switzerland: World Health Organization, International Agency for Research on Cancer, WHO Press, 2016. Adv Nutr 2016;7:418–9.
22. Gupta S, Gupta R, Sinha DN, Mehrotra R. Relationship between type of smokeless tobacco & risk of cancer: a systematic review. Indian J Med Res 2018;14856–76.
23. Jiang X, Wu J, Wang J, Huang R. Tobacco and oral squamous cell carcinoma: a review of carcinogenic pathways. Tob Induc Dis 2019; 17:29.
24. Sinha DN, Suliankatchi RA, Gupta PC, Thamarangsi T, Agarwal N, Parascandola M, et al. Global burden of all-cause and cause-specific mortality due to smokeless tobacco use: systematic review and meta-analysis. Tob Control 2018;27:35–42.
25. Miranda-Filho A, Bray F. Global patterns and trends in cancers of the lip, tongue, and mouth. Oral Oncol 2020;102:104551.
26. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Betel-quid and areca nut chewing and some areca

nut–derived nitrosamines. IARC Monogr Eval Carcinog Risks Hum 2004;85:80–112.
27. Hussein AA, Helder MN, de Visscher JG, Leemans CR, Braakhuis BJ, de Vet HCW, et al. Global incidence of oral and oropharynx cancer in patients younger than 45 years versus older patients: a systematic review. Eur J Cancer 2017;82:115–27.
28. Campbell BR, Sanders CB, Netterville JL, Sinard RJ, Rohde SL, Langerman A, et al. Early onset oral tongue squamous cell carcinoma: associated factors and patient outcomes. Head Neck 2019;41:1952–60.
29. Wang TW, Kenemer B, Tynan MA, Singh T, King B. Consumption of combustible and smokeless tobacco—United States, 2000–2015. MMWR Morb Mortal Wkly Rep 2016;65:1357–63.
30. Kendrick PJ, Reitsma MB, Abbasi-Kangevari M, Abdoli A, Abdollahi M, Abedi A, et al. Spatial, temporal, and demographic patterns in prevalence of chewing tobacco use in 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019. Lancet Public Heal 2021;6:E482–99.
31. Du M, Nair R, Jamieson L, Liu Z, Bi P. Incidence trends of lip, oral cavity, and pharyngeal cancers: global burden of disease 1990–2017. J Dent Res 2020;99:143–51.
32. Niaz K, Maqbool F, Khan F, Bahadar H, Ismail Hassan F, Abdollahi M. Smokeless tobacco (paan and gutkha) consumption, prevalence, and contribution to oral cancer. Epidemiol Health 2017;39:e2017009.
33. Sankhla B, Kachhwaha K, Hussain SY, Saxena S, Sireesha SK, Bhargava A. Genotoxic and carcinogenic effect of gutkha: a fast-growing smokeless tobacco. Addict Heal 2018;10:52–63.
34. Alsanosy RM. Smokeless tobacco (shammah) in Saudi Arabia: a review of its pattern of use, prevalence, and potential role in oral cancer. Asian Pacific J Cancer Prev 2014;15:6477–83.
35. Idris AM, Prokopczyk B, Hoffmann D. Toombak: a major risk factor for cancer of the oral cavity in Sudan. Prev Med 1994;23:832–9.
36. Kaur J, Thamarangsi T, Rinkoo AV. Regulating smokeless tobacco and processed areca nut in South-East Asia region: the journey so far and the road ahead. Indian J Public Health 2017;61:S3–S6.
37. Kumar A, Bhartiya D, Kaur J, Kumari S, Singh H, Saraf D, et al. Regulation of toxic contents of smokeless tobacco products. Indian J Med Res 2018;148:14–24.
38. Mejia AB, Ling PM, Glantz SA. Quantifying the effects of promoting smokeless tobacco as a harm reduction strategy in the USA. Tob Control 2010;19:297–305.
39. Gupta AK, Tulsyan S, Bharadwaj M, Mehrotra R. Grass roots approach to control levels of carcinogenic nitrosamines, NNN, and NNK in smokeless tobacco products. Food Chem Toxicol 2019;124:359–66.
40. Wollina U, Verma SB, Ali FM, Patil K. Oral submucous fibrosis: an update. Clin Cosmet Investig Dermatol 2015;8:193–204.
41. Hecht SS. Tobacco carcinogens, their biomarkers and tobacco-induced cancer. Nat Rev Cancer 2003;3:733–44.
42. Hecht SS, Carmella SG, Murphy SE, Riley WT, Le C, Luo X, et al. Similar exposure to a tobacco-specific carcinogen in smokeless tobacco users and cigarette smokers. Cancer Epidemiol Biomarkers Prev 2007;16:1567–72.
43. Awan KH, Patil S. Association of smokeless tobacco with oral cancer—Evidence from the South Asian studies: a systematic review. J Coll Physicians Surg Pak 2016;26:775–80.
44. De Geu JL, Wambier L-MLM, Loguercio ADA-DAD, Reis A, de Geus J-L, Wambier L-MLM, et al. The smokeless tobacco habit and DNA damage: a systematic review and meta-analysis. Med Oral Patol Oral Cir Bucal 2019;24:e145–55.
45. Critchley JA, Unal B. Health effects associated with smokeless tobacco: a systematic review. Thorax 2003;58:435–43.
46. Xue J, Yang S, Seng S. Mechanisms of cancer induction by tobacco-specific NNK and NNN. Cancers 2014;6:1138–56.
47. Giovino GA, Mirza SA, Samet JM, Gupta PC, Jarvis MJ, Bhala N, et al. Tobacco use in 3 billion individuals from 16 countries: an analysis of nationally representative cross-sectional household surveys. Lancet 2012;380:668–79.
48. World Health Organization Study Group on Tobacco Product Regulation. WHO Study Group on Tobacco Product Regulation. Report on the scientific basic of tobacco product regulation: fourth report of a WHO study group. World Health Organ Tech Rep Ser 2012;1–83.
49. Hatsukami DK, Stepanov I, Severson H, Jensen JA, Lindgren BR, Horn K, et al. Evidence supporting product standards for carcinogens in smokeless tobacco products. Cancer Prev Res 2015;8:20–6.
50. Bates C, Fagerström K, Jarvis MJ, Kunze M, McNeill A, Ramström L. European Union policy on smokeless tobacco: a statement in favor of evidence based regulation for public health. Tob Control 2003;12:360–7.
51. Asthana S, Labani S, Kailash U, Sinha DN, Mehrotra R. Association of smokeless tobacco use and oral cancer: a systematic global review and meta-analysis. Nicotine Tob Res 2019;21:1162–71.
52. Siddiqi K, Husain S, Vidyasagaran A, Readshaw A, Mishu MP, Sheikh A. Global burden of disease due to smokeless tobacco consumption in adults: an updated analysis of data from 127 countries. BMC Med 2020;18:222.
53. Sinha DN, Abdulkader RS, Gupta PC. Smokeless tobacco-associated cancers: a systematic review and meta-analysis of Indian studies. Int J Cancer 2016;138:1368–79.
54. Khan Z, Tönnies J, Müller S. Smokeless tobacco and oral cancer in South Asia: a systematic review with meta-analysis. J Cancer Epidemiol 2014;2014:394696.
55. Guha N, Warnakulasuriya S, Vlaanderen J, Straif K. Betel quid chewing and the risk of oral and oropharyngeal cancers: a meta-analysis with implications for cancer control. Int J Cancer 2014;135:1433–43.
56. Wyss AB, Hashibe M, Lee Y-CCA, Chuang S-CC, Muscat J, Chen C, et al. Smokeless tobacco use and the risk of head and neck cancer: pooled analysis of US studies in the INHANCE consortium. Am J Epidemiol 2016;184:703–16.
57. Khan Z, Suliankatchi RA, Heise TL, Dreger S. Naswar (smokeless tobacco) use and the risk of oral cancer in Pakistan: a systematic review with meta-analysis. Nicotine Tob Res 2019;21:32–40.
58. Quadri MFA, Tadakamadla SK, John T. Smokeless tobacco and oral cancer in the Middle East and North Africa: a systematic review and meta-analysis. Tob Induc Dis 2019;17:56.
59. Patil S, Arakeri G, Alamir AWH, Patil S, Awan KH, Baeshen H, et al. Is toombak a risk factor for oral leukoplakia and oral squamous cell carcinoma? A systematic review. J Oral Pathol Med 2020;49:103–9.
60. Mummudi N, Agarwal JP, Chatterjee S, Mallick I, Ghosh-Laskar S. Oral cavity cancer in the Indian subcontinent—challenges and opportunities. Clin Oncol 2019;31:520–8.
61. Sinha DN, Bajracharya B, Khadka BB, Rinchen S, Bhattad VB, Singh PK. Smokeless tobacco use in Nepal. Indian J Cancer 2012;49:352–6.
62. Changrani J, Cruz G, Kerr R, Katz R, Gany FM. Paan and gutka use in the United States. J Immigr Refug Stud 2006;4:99–110.
63. Delnevo CD, Hrywna M, Miller Lo EJ, Wackowski OA. Examining market trends in smokeless tobacco sales in the United States: 2011–2019. Nicotine Tob Res 2021;23:1420–4.
64. Ellington TD, Henley SJ, Senkomago V, O'Neil ME, Wilson RJ, Singh S, et al. Trends in incidence of cancers of the oral cavity and

pharynx—United States 2007–2016. MMWR Morb Mortal Wkly Rep 2020;69:433–8.
65. Boffetta P, Hecht S, Gray N, Gupta P, Straif K. Smokeless tobacco and cancer. Lancet Oncol 2008;9:667–75.
66. Lee PN, Hamling J. The relation between smokeless tobacco and cancer in Northern Europe and North America. A commentary on differences between the conclusions reached by two recent reviews. BMC Cancer 2009;9:256.
67. Rodu B, Jansson C. Smokeless tobacco and oral cancer: a review of the risks and determinants. Crit Rev Oral Biol Med 2004;15: 252–63.
68. Roosaar A, Johansson ALV, Sandborgh-Englund G, Axéll T, Nyrén O. Cancer and mortality among users and nonusers of snus. Int J Cancer 2008;123:168–73.
69. Luo J, Ye W, Zendehdel K, Adami J, Adami HO, Boffetta P, et al. Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study. Lancet 2007;369:2015–20.
70. Clarke E, Thompson K, Weaver S, Thompson J, O'Connell G. Snus: a compelling harm reduction alternative to cigarettes. Harm Reduct J 2019;16:62.
71. Mustafa MB, Hassan MO, Alhussein A, Mamoun E, El Sheikh M, Suleiman AM. Oral leukoplakia in the Sudan: clinicopathological features and risk factors. Int Dent J 2019;69:428–35.
72. Ahmed HG. Etiology of oral cancer in the Sudan. J Oral Maxillofac Res 2013;4:e3.
73. Faggons CE, Mabedi C, Shores CG, Gopal S. Review: head and neck squamous cell carcinoma in sub-Saharan Africa. Malawi Med J 2015; 27:79–87.
74. Otoh EC, Johnson NW, Olasoji HO, Danfillo IS, Adeleke OA. Intra-oral carcinomas in Maiduguri, North-Eastern Nigeria. Oral Dis 2005;11:379–85.
75. Onoh I, Owopetu O, Olorukooba AA, Umeokonkwo CD, Dahiru T, Balogun MS. Prevalence, patterns, and correlates of smokeless tobacco use in Nigerian adults: an analysis of the Global Adult Tobacco Survey. PLoS One 2021;16:e0245114.
76. Subapriya R, Thangavelu A, Mathavan B, Ramachandran CR, Nagini S. Assessment of risk factors for oral squamous cell carcinoma in Chidambaram, Southern India: a case–control study. Eur J Cancer Prev 2007;16:251–6.
77. Leon ME, Lugo A, Boffetta P, Gilmore A, Ross H, Schüz J, et al., Smokeless tobacco use in Sweden and other 17 European countries. Eur J Public Health 2016;26:817–21.
78. Gupta B, Bray F, Kumar N, Johnson NW. Associations between oral hygiene habits, diet, tobacco, and alcohol, and risk of oral cancer: a case–control study from India. Cancer Epidemiol 2017;51:7–14.
79. Kakde S, Bhopal RS, Jones CM. A systematic review on the social context of smokeless tobacco use in the South Asian population: implications for public health. Public Health 2012;126:635–45.
80. Tata Institute of Social Sciences (TISS), Mumbai and Ministry of Health and Family Welfare, Government of India. Global adult tobacco survey GATS 2 India 2016–17.T | Report. 2018;161–165 SBN: 978–81–937917–0-7.
81. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Smokeless tobacco and some tobacco-specific N-nitrosamines. IARC Monogr Eval Carcinog Risks Hum 2007; 89:1–592.
82. Ahmed HG, Mahgoob RM. Impact of Toombak dipping in the etiology of oral cancer: gender-exclusive hazard in the Sudan. J Cancer Res Ther 2007;3:127–30.
83. Stepanov I, Gupta PC, Dhumal G, Yershova K, Toscano W, Hatsukami D, et al. High levels of tobacco-specific N-nitrosamines and nicotine in Chaini Khaini, a product marketed as snus. Tob Control 2015;24:e271–4.
84. Stanfill SB, Connolly GN, Zhang L, Jia LT, Henningfield JE, Richter P, et al. Global surveillance of oral tobacco products: total nicotine, un-ionized nicotine and tobacco-specific N-nitrosamines. Tob Control 2011;20:e2.
85. Mehrotra R, Sinha DN, Szilagyi T. WHO FCTC Global knowledge hub on smokeless tobacco. 2017;29–40.
86. Allard WF, DeVol EB, Te OB. Smokeless tobacco (shamma) and oral cancer in Saudi Arabia. Community Dent Oral Epidemiol 1999;27: 398–405.
87. Hassanin AA, Idris AM. Attribution of oral cancer in the Sudan to toombak dipping. Transl Res Oral Oncol 2017;2:1–5.
88. Idris AM, Nair J, Friesen M, Ohshima H, Brouet I, Faustman EM, et al. Carcinogenic tobacco-specific nitrosamines are present at unusually high levels in the saliva of oral snuff users in Sudan. Carcinogenesis 1992;13:1001–5.
89. Sami A, Stanton C, Ross P, Ryan T, Elimairi I. Ultra- structure of toombak; smokeless tobacco of Sudan and its effects on oral and systemic health. Access Microbiol 2020;2:836.
90. Richter P, Hodge K, Stanfill S, Zhang L, Watson C. Surveillance of moist snuff: total nicotine, moisture, pH, un-ionized nicotine, and tobacco-specific nitrosamines. Nicotine Tob Res 2008;10: 1645–52.
91. Stepanov I, Biener L, Yershova K, Nyman AL, Bliss R, Parascandola M, et al. Monitoring tobacco-specific N-nitrosamines and nicotine in novel smokeless tobacco products: findings from round II of the new product watch. Nicotine Tob Res 2014;16:1070–8.
92. Araghi M, Galanti MR, Lundberg M, Liu Z, Ye W, Lager A, et al. No association between moist oral snuff (snus) use and oral cancer: pooled analysis of nine prospective observational studies. Scand J Public Health 2021;49:833–40.
93. Stepanov I, Gupta PC, Parascandola M, Yershova K, Jain V, Dhumal G, et al. Constituent variations in smokeless tobacco purchased in Mumbai, India. Tob Regul Sci 2017;3:305–14.
94. Bennett JE, Fowler EA. Federal Register, FDA Proposed Rules, Tobacco Product Standard for N-Nitrosonornicotine Level in Finished Smokeless Tobacco Products. 2017;82:8004–30.
95. Appleton S, Olegario RM, Lipowicz PJ. TSNA levels in machine-generated mainstream cigarette smoke: 35 years of data. Regul Toxicol Pharmacol 2013;66:197–207.
96. Berman ML, Hatsukami DK. Reducing tobacco-related harm: FDA's proposed product standard for smokeless tobacco. Tob Control 2018; 27:352–4.
97. de Groot PM, Wu CC, Carter BW, Munden RF. The epidemiology of lung cancer. Transl Lung Cancer Res 2018;7:220–33.
98. Gupta AK, Mehrotra R. Increasing use of flavored tobacco products amongst youth. Indian J Tuberc 2021;68:S105–7.