

The effect of smokeless tobacco products in the development of head and neck cancers

A systematic review

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Advanced studies' thesis

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Abstract

Heavy alcohol use and smoking are known risk factors for head and neck cancers. Smokeless tobacco use is also thought increase the risk for head and neck cancers, and especially oral cancer, however, research results are varying. The aim of this review was to categorize research on smokeless tobacco use's risk for head and neck cancers by geographic region. Research from India, Pakistan, Bangladesh, Arabian Peninsula and Sudan showed a strong risk for head and neck cancers associated with local smokeless tobacco products, research from United States was inconclusive on the subject and research from Scandinavia didn't show a significant risk associated with local smokeless tobacco use. Most evidence were on the risk for oral cancer, but evidence for other head and neck cancers was also found.

Key words: head and neck cancer, oral cancer, smokeless tobacco, betel quid,

Table of Contents

Introduction	4
Methods	6
Eligibility criteria	6
Search strategy	6
Data extraction	6
Results	7
India	9
Scandinavia	13
Sudan	14
Arabian Peninsula	14
United States of America	15
Pakistan	16
Bangladesh	17
Others	18
Discussion	19
References	22

Introduction

Head and Neck Cancers (HNC) comprise a heterogenic group of malignant tumors that arise from the head and neck region. HNC is the eight most common type of cancer worldwide with over 850 000 new cases and over 450 000 new deaths in 2020 (1) Histologically 90 % of HNC are squamous cell carcinomas (SCC). The most common origins are, from most to least common: lip and oral cavity, larynx, nasopharynx, oropharynx, hypopharynx and salivary glands. Cancers of nasopharynx, oropharynx and hypopharynx are sometimes also categorized together as pharyngeal cancer (PC).

Most HNC are associated with heavy use of alcohol and smoking. A recent meta-analysis by Jun et al. (2024) identified the relative risk (RR) associated with heavy use of alcohol and smoking to be 36.42 for oral cancer (OC) (95% CI, 24.62–53.87) and 38.75 for laryngeal cancer (LC) (95% CI, 19.25–78.01) There is also a significant risk for oropharyngeal cancer (OPC) associated with HPV infection which is suspected to be the cause of rising incidence in OPC (3).

Another independent risk factor for OC is betel quid without tobacco. Betel quid usually contains areca nut, slaked lime, catechu, betel leaf, inflorescence of *Piper betel*, and other unspecified spices depending on the region. Betel quid contains also usually tobacco. Betel quid without tobacco has been considered group 1 carcinogenic substance for OC since 2004 (4).

Smokeless tobacco products (SLT) are tobacco products used in other ways than smoking. There are over 350 million SLT users in 121 countries of which nearly 95 % live in developing countries (5). The content of SLTs vary immensely by geographical region.

The International Agency for Research on Cancer (IARC) has concluded that SLT causes OC in humans (6) but research results also vary by region. A systematic review and meta-analysis from South-East Asia (7) demonstrated a combined odds ratio (OR) of 4.7 for OC associated with SLTs but another systematic review (8) found no statistically significant risk for OC associated with the exclusive use of Swedish snuff (snus).

The aim of this review is to compare the association between HNC and SLT use between different geographical regions.

Methods

This review was undertaken and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework.(9)

Eligibility criteria

Studies were eligible for inclusion if they were English-language papers published in peer-reviewed journal and met the following inclusion criteria: (1) being primary studies in adult subjects, (2) including subjects with HNC, (3) study population's SLT use was reported and (4) SLT use status of subjects with HNC was reported. This review also concentrates only in the SLTs that are used by chewing, holding in mouth, applying to gums and teeth or intra-nasally meaning that for example studies on bidis were excluded even though they are often categorized as SLTs.

Search strategy

The following databases were searched for relevant studies up to February 2026: PubMed and Embase. The search terms and Medical Subject Headings (MeSH) included "oral cancer" OR "oral neoplasm" OR "oropharyngeal cancer" OR "oropharyngeal neoplasm" OR "Mouth Neoplasms" OR "nasopharyngeal cancer" OR "Nasopharyngeal Neoplasms" OR "neoplasms neck" OR "cancer of head and neck" OR "head and neck cancer" OR "head cancer" OR "Head and Neck Neoplasms" OR "neck cancer*" OR "upper aerodigestive tract cancer" OR "upper aerodigestive tract neoplasms") AND "betel quid with tobacco" OR "chewing tobacco" OR "chimó" OR "gul" OR "gudhaku" OR "gutka" OR "iq'mik" OR "khaini" OR "khiwam" OR "loose leaf tobacco" OR "maras" OR "mawa" OR "mishri" OR "naswar" OR "shammah" OR "smokeless tobacco" OR "snus" OR "snuff" OR "toombak" OR "tuibur" OR "zarda."

Data extraction

Duplicates were detected using help of Rayyan AI and manually removed. Manuscripts were reviewed against the eligibility criteria. Conference abstracts, comments, case reports and reviews were excluded. Manuscripts were divided into groups based on the study population's geographical location.

Results

A total of 869 articles were identified from the electronic databases mentioned before. After screening the abstracts and full texts, 89 manuscripts that met inclusion criteria were included for analysis. The PRISMA flowchart is shown in Figure 1. The analysis was divided by manuscripts' geographical location to 7 sections: (1) studies conducted in Indian populations, (2) studies conducted in Pakistani populations, (3) studies conducted in Scandinavian populations, (4) studies conducted in Yemeni and Saudi Arabian populations, (5) studies conducted in Sudanese populations, (6) studies conducted in American populations and (7) studies conducted in Bangladeshi populations. Some included studies were the only ones from that specific area or that specific population and will be discussed in a combined chapter. The SLTs named in the studies will be presented in better detail in table 1. (10)

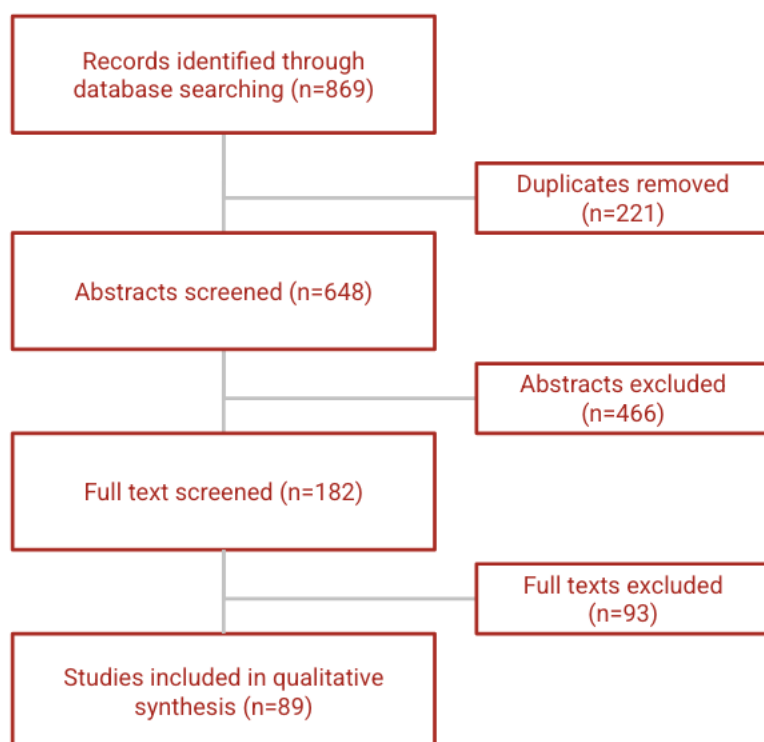


Figure 1. PRISMA flowchart

Table 1. Summary of the properties of smokeless tobacco products' (SLT) discussed in this review according to CDC.

Smokeless tobacco product	Region*	Main ingredient	Additional ingredients	Scale of production**
betel quid with tobacco	India, Pakistan, Bangladesh	tobacco, other SLTs	areca nut, slaked lime, betel leaf, catechu, other ingredients vary regionally	custom, cottage
gul	India, Bangladesh	pyrolysed tobacco leaves	sugar or molasses, alkaline modifiers	commercial
gutka	India, Pakistan, Bangladesh	tobacco	areca nut, slaked lime or other alkaline agents, catechu, sweeteners, and flavorings	commercial, cottage
khaini	India, Bangladesh	tobacco	slaked lime paste and sometimes areca nut	commercial, custom
mainpuri	India, Pakistan	tobacco	slaked lime or other alkaline agents, areca nut, camphor, and other spices	cottage, custom
mawa	India, Pakistan	tobacco	slaked lime, areca nut	cottage, custom
mishri	India	tobacco (toasted, powdered)	none	cottage, custom
naswar	Pakistan, South Africa	tobacco	slaked lime, ash, indigo (or other coloring agent), oil, water, and sometimes flavorings such as cardamom and menthol	cottage, custom
shammah	Saudi Arabia, Yemen	tobacco	slaked lime, ash, black pepper, oil, flavorings, and bombosa (sodium carbonate)	cottage, custom
snuff (creamy)	India	tobacco	clove oil, glycerin, spearmint, menthol, camphor, water	commercial
snuff (dry)	South Africa, United States, Germany	tobacco (fermented, fire-cured)	flavoring, alkaline agents	commercial

snuff (moist)	United States, South Africa	tobacco (fermented, air- or fire-cured)	flavorings (spices, essential oils, extracts), sweeteners, inorganic salts, humectants, preservatives	commercial
snus	South Africa, United States, Sweden, Norway, Denmark	tobacco (heat-treated, pasteurized)	sodium carbonate, moisturizers, salt (sodium chloride), sweeteners, flavorings, water	commercial
toombak (saffa)	Sudan	tobacco (fermented, sun-dried)	atrún (sodium bicarbonate)	cottage, custom
zarda	India, Bangladesh, Yemen	tobacco	slaked lime or other alkaline agents, spices, vegetable dyes, and sometimes areca nut, and/or silver flecks	commercial

*Only countries discussed in this review are listed

**Commercial referring to large scale production by a bigger producer, cottage to small scale or local production, custom to self-made and local vendor made products.

India

Out of the studies that met inclusion criteria 36 had an Indian study population. Out of these studies 16 were case-control studies and their results are presented in depth in table 2 (only statistically significant ORs mentioned). Also 15 different studies reported the share of subjects with HNC with a habit of SLT use and their results are summarized in table 3. Two prospective studies followed a population for several years. Parihar et al. (11) followed 300 subjects of whom 185 were SLT users for 5 years and detected 20 HNC during the follow up period, resulting in a significant hazard ratio (HR) for SLT use of 4.51 (95 % CI 2.0-10.0). Another study by Jayalekshmi et al. (12) followed 66 277 males via cancer registry for OC incidence for 15 years and found 160 OCs of which 19 occurred in former chewing tobacco users and 75 in current users, thus finding a significant relative risks (RR) of 2.1 (95 % CI 1.3-3.6) and 2.4 (95 % CI 1.7-3.3) respectively. Two cross-sectional studies on SLT using populations were also included. Jalli et al. (13) examined 1800 and Reddy et al. (14) examined 901 users of chewing tobacco and they found that of those

subjects 0.2 % and 1.2 %, respectively, had already developed OC. A cross-sectional study by Mehta et al. (15) inspected 101 761 Indian villagers and found subjects with OC of whom 66.7 % also used chewing tobacco. Nearly all case-control studies included in this review found a significant risk for HNC associated with the use of SLTs typical in Indian population, and rest of the studies found SLT use to be prevalent among Indian subjects with HNC. This suggests that the use of SLTs common in India is a risk for HNC.

Table 2. Summary of case-control studies that included an Indian study population.

Study	Site of HNC*	Type of SLT	Odds Ratio (OR) or Relative risk (RR)	95 % CI	Adjusted for
Pullat et al., 2026 (16)	buccal mucosa	Chewing tobacco (gutka, mawa, betel quid with tobacco, mishri)	21.6 (OR)	19.5–23.8	age, gender, self-reported education level maximum duration of smoking tobacco use and maximum duration of chewing tobacco use, BMI, fruit and vegetable intake and alcohol consumption
Khan et al., 2023 (17)	oral	Chewing tobacco Gutka	10.1 (OR) 0.1 (OR)	3.2–32.6 0.02–0.3	Not reported
Gholap et al., 2023 (18)	any (oral, oropharynx, hypopharynx and larynx analyzed also seperately)	Chewing (gutka, betel quid with tobacco, khaini, mishri and mawa also analyzed seperately)	11.0 (OR)	8.2–14.5	age, current region of residence, education, alcohol use, hypertension, BMI, second hand smoke exposure, lifetime vegetarian status
Kingsley et al., 2021 (19)	oral	Chewing tobacco	3.7 (OR)	1.4-9.5	age, gender, educational level, smoking, and alcohol consumption

Kadashetti et al., 2015 (20)	oral	Chewing tobacco	2.8 (OR)	1.2-7.0	age and sex
Mahapatra et al., 2015 (21)	oral	Gutka Chewing tobacco	4.8 (OR) 7.3 (OR)	2.8-8.1 3.3-16.0	age, gender, social class, education level, diet, tobacco products, oral dip products, and alcohol
Gajalakshmi et al., 2012 (22)	oral	Chewing tobacco	4.9* (OR)	3.5–6.8	age, area (rural or urban) and years of education
Madani et al., 2012 (23)	oral	Chewing tobacco Gutka Mishri	5.3 (OR) 7.3 (OR) 2.2 (OR)	3.7-7.6 4.5-12.1 1.5-3.1	other tobacco types, oral dip products, alcohol, non-vegetarian habit, education, occupation, age and gender
Subapriya et al., 2007 (24)	oral	Tobacco chewing Betel quid with tobacco	2.9 (OR) 3.2 (OR)	Not reported	age, sex, literacy, occupation, oral hygiene and alcohol drinking
Sapkota et al., 2007 (25)	hypopharynx	chewing tobacco	1.5 (OR)	1.1–2.1	age, sex, participating center, socio-economic-status and cumulative tobacco consumption
Ghosh et al., 1996 (26)	oral	Chewing tobacco (held overnight)	12.9 (OR)	Not reported	onset of the habit of chewable Indian tobacco, duration of habit, frequency of chewing, quantity chewed in 24 h and the habit of keeping the night quid
Nandakumar et al., 1990 (27)	oral	Tobacco chewing	12.9 (RR)	7.5-22.3	chewing habits, smoking habits, alcohol

					consumption, snuff habits, vegetarian diet, cereal consumed, spiciness of food, age, area of residence and sex.
Sankaranarayana n et al., 1990 (28)	buccal and labial	Pan-tobacco (males, 10+ per day) Pan-tobacco (females, 10+ per day)	16.4 (RR) 14.2 (RR)	9.7-27.7 6.9-29.5	age (and religion for men)
Sankaranarayana n et al., 1990 (29)	larynx	Pan-tobacco	NS	NS	age and religion
Sankaranarayana n et al., 1989 (30)	gingiva	Pan-tobacco (males, 10+ per day) Pan-tobacco (females, 10+ per day)	15.1 (RR) 13.7 (RR)	7.8-29.0 4.4-42.5	age
Sankaranarayana n et al., 1989 (31)	tongue and floor of the mouth	Pan-tobacco (males, 10+ per day) Pan-tobacco (females, 10+ per day)	5.5 (RR) 9.3 (RR)	2.9-10.7 3.1-27.6	age

*OR only reported for mortality, not overall cases

Table 3. Summary of prospective and retrospective studies on Indian population.

Study	Type of HNC*	Type of SLT	Number of subjects	Share of SLT users (%)
Saqib Ali et al., 2025 (32)	OC	gutka khaini	200	80.0 22.5
Begum et al., 2024 (33)	OC	chewing tobacco (gutka, snuff)	188	37.2
Shah et al., 2023 (34)	OC	not specified	58	68.9
Tandon et al., 2023 (35)	OC	chewing tobacco	200	75.5
Kumar et al., 2022 (36)	OC and OPC	khaini, gutka, paan, paan masala	109	79
Bhuyan et al., 2020 (37)	OC	gutka, gudaku, chewing, snuff	1364	20–40**

Pandey et al., 2020 (38)	any	smokeless tobacco, khaini	58	70
Sharma et al., 2019 (39)	any	chewing tobacco	362	83.7
Alam et al., 2017 (40)	any	chewing tobacco	850	39.4
Nair et al., 2016 (41)	UADT SCC	chewing tobacco	747	69.3
Addala et al., 2012 (42)	OC	chewing tobacco	5458	49.6
Aruna et al., 2011 (43)	OC	chewing tobacco (betel quid with tobacco, gutka, khaini, panmasala)	1472	25.3
Patel et al., 2009 (44)	any	chewing tobacco	111	61.2
Goud et al., 1990 (45)	OC	chewing tobacco (khaini, zarda, betel leaf with ingredients)	405	85.4
Agarwal et al., 1964 (46)	OC and PC	chewing tobacco	210	100

*HNC: head and neck cancer, OC: oral cancer, OPC: oropharyngeal cancer, UADT SCC: upper aerodigestive tract squamous cell carcinoma.

**Results reported by sex and used SLT.

Scandinavia

Out of the studies that met the inclusion criteria 7 had a Scandinavian study population. In a cohort study of 9 976 males from Sweden (47) a statistically significant HR of 3.1 (95 % CI 1.5-6.6) for OC and OPC was found in ever daily SLT users, but when adjusted for smoking no statistically significant risk was found. Also, a cohort study from Sweden of 279 897 males found no statistically significant risk when analyzing the use of snus in relation to development of OC (48). A cohort study of 10 136 Norwegians and relatives of Norwegian migrants to the United States also showed no statistically significant risk for OC in the ever, former or current snus user groups (49). Three case-control studies from Sweden were included (50), (51) and (52) and none of them found a significant risk for OC in snus users. A case-control study from Denmark reported that of the 40 subjects with HNC 8 % used snus and of the 104 subjects without HNC just 1 % used snus, yet no significant risk was reported (53). None of the studies included in this review showed a significant risk for HNC associated with snus, when adjusting for other risk factors.

Sudan

Out of the studies that met the inclusion criteria 7 had a Sudanese study population. A case-control study from Khartoum, Sudan (54) found a statistically significant risk of OC in toombak-dippers (OR 3.8, adjusted for age, smoking, and alcohol, 95 % CI 1.7–8.6). Another case-control study from Khartoum, Sudan found a statistically significant risk (RR 7.3, 95% CI 4.3-12.4 and RR 3.9, 95 % CI 2.9-5.3, both adjusted for age, sex, tribe, and residence) compared with subjects without OC and the healthy population respectively for OC deriving from lip, buccal epithelia, cavity and floor of the mouth for toombak-dippers. However no statistically significant RR was found for oral cancers deriving from tongue, palate and maxillary sinus (55). Eltohami & Suleiman (56) studied 93 subjects with OC of whom 39.9 % engaged in toombak-dipping. A descriptive case-control study of 39 subjects with OC from Khartoum, Sudan, found that 61.5 % were toombak-dippers (57), and in a descriptive study by Idris, Ahmed, Mukhtar et al. (58) the 850 recorded cases of OC in Radiation and Isotope Centre Khartoum, Sudan, were analyzed and of those 34.5 % were toombak users. Osman et al. (59) identified 261 subjects with OC of whom 28.7 % engaged in toombak-dipping and Elbeshir et al. (60) identified 60 subjects with OC of whom 81 % used saffa. Toombak use was prevalent in subjects with OC in all the studies described in this review and both case-control studies found a statistically significant risk for OC associated with toombak use.

Arabian Peninsula

Out of the studies that met the inclusion criteria 7 had a study population arising from the Arabian Peninsula (Saudi Arabia and Yemen). Out of these 4 were case-control studies. A case-control study from Riyadh, Saudi Arabia didn't find a statistically significant effect on the overall survival for subjects with OC that were shammah users (61). A case-control study in Jazan, Saudi Arabia found a statistically significant risk (OR 33.0 adjusted for age, gender, area of living and education level, 95% CI 3.2-39.9) for OC associated with the use of shammah (62) Another case-control study from Jazan, Saudi Arabia found a statistically significant risk for OC associated with shammah use (OR 29.3, 95% CI 10.3-83.1, adjusted for demographic details, khat chewing, cigarette (and pipe smoking) (63). A case-control study in Yemen found a statistically significant risk for OC in shammah users (OR 39,

adjusted for age, gender, oral habits and EBV, 95 % CI 14-105) (64). Another study from Yemen examined 200 shammah users for oral changes and found 2 subjects with OC (65). A retrospective study by El-Husseiny et al. (66) analyzed the 110 subjects with OC treated at the King Faisal Specialist Hospital and Research Centre, Saudi Arabia and found that 35 % were shammah users. In a cross-sectional study by Salem et al. (67) 671 individuals were examined for oral mucosal lesion and interviewed about shammah-habits, finding 7 subjects with OC, who were all shammah-users. All case-control studies measuring risk for developing OC found a statistically significant association with shammah use. Other studies described shammah use as common in subjects with OC, and OC was found from shammah users in cross-sectional study designs.

United States of America

Out of the studies that met the inclusion criteria 10 had an American study population. A prospective cohort study on American agricultural workers found no statistically significant HR for HNC in SLT users (68). A cross-sectional study by Sterling et al. (69) also found no statistically significant HR for OC in SLT users. However, a case-control study from Texas found a statistically significant risk for HNC associated with snuff-dipping (OR 3.4, 95 % CI 1.0-10.9) but no statistically significant risk for chewing tobacco (70). A case series of 105 subjects with verrucous carcinoma also identified that of the 77 subjects with OC 36 were tobacco chewers and 3 snuff-dippers (71). A retrospective study by Campbell et al. (72) found a significant risk associated with snuff use and early onset OC (OR 5.4, 95 % CI 1.8-15.8, adjusted for sex, race, overall clinical stage, treatment, alcohol use at diagnosis and tobacco use (never vs. ever)), yet out of the subjects with OC only 13.2 % used SLT. A retrospective study by McGuirt (73) reviewed 290 subjects with OC and found that 26.6 % had a history of heavy snuff use and 19.6 % had solely used snuff. A retrospective study by Brown et al. (74) identified 394 subjects with OC of whom 19.8 % were snuff-users. A retrospective study by Hull et al. (75) described nine subjects with verrucous OC of whom eight were snuff users. A case-control study from North Carolina and Virginia by Brinton et al. (76) found no statistically significant risk associated with chewing tobacco or snuff use for cancers of the nasal cavity and paranasal sinuses. Another case-control study in North Carolina by Winn et al. (77)

found a significant risk for cancer of gum and buccal mucosa associated with snuff use in non-smokers (RR 13.8 (95 % CI 1.9-98.0), RR 12.6 (95 % CI 2.7-58.3) and RR 47.5 (95 % CI 9.1-249.5) for users of 1-24 years, 25-49 and over 50 years respectively, adjusted for age, urban or rural residence, education, type of respondent, region of residence, source of case ascertainment, employment and smoking), however, a significant risk for cancers from other parts of mouth and pharynx was only found to be associated with snuff use of 25-49 years in non-smokers (RR 3.8, 95 % CI 1.5-9.6). Thus, literature suggests that there might be some association between snuff use and HNC in American population, but the evidence is still scarce.

Pakistan

Out of the studies that met the inclusion criteria 15 had a Pakistani study population. A case-control study by Shabir et al. (78) found a significant risk for OC associated with naswar (OR 15.8, 95 % CI 8.3-30.4, adjusted for gender, age, ethnicity, smoking status, consumption of naswar, betel quid, paan, alcohol, hot beverages, oral health indicators and medical history). A case-control study by Khan et al. (79) found a significant risk for OC associated with SLT use (OR 4.7, 95 % CI 2.5-8.7, adjusted for age and smoking). A case-control study by Amur et al. (80) found a significant risk for LC and PC associated with using mainpuri (OR 24.4, 95 % CI 3.0-525.9) but not with gutka, naswar or naas. A case-control study by Shah et al. (81) found a significant risk for HNC associated with naswar use (OR 1.6, 95 % CI not reported). A case-control study by Azhar et al. (82) found a significant risk for OC associated with SLTs (gutka, mainpuri, mawa and naswar) (OR 1.2, 95 % CI 1.0-1.3, adjusted for age and gender). A case-control study by Z. Khan et al. (83) found a significant risk for OC associated with naswar use (OR 23.7, 95 % CI 6.9-81.0, adjusted for age and sex). A case-control study by Awan et al. (84) found a significant risk for OC associated with gutka (OR 5.5, 95 % CI 2.8-10.8), naswar (OR 3.5, 95 % CI 1.2-9.8), mainpuri (OR 4.7, 95 % CI 1.3-16.9) and chewing tobacco (OR 5.3, 95 % CI 1.1-24.8), all results adjusted for age, gender, level of education, occupation and site of OC. Another case-control study by Alamgir et al. (85) found that of the 150 subjects with OC 58 % were exclusive tobacco chewers. A retrospective study by Siddique et al. (86) described that of the 543 subjects with OC in the study, 73.2 % used SLTs. A

retrospective study by Anwar et al. (87) analyzed the 186 subjects diagnosed with OC in Aga Khan University hospital in 2017 and found that 77.4 % used SLT. A retrospective study by Fatima et al. (88) described 53.4 % of subjects with OC and oral submucosal fibrosis (OSF) using betel quid with tobacco and 8.2 % using naswar, and 45.3 % of subjects with OC but without OSF using betel quid with tobacco and 22.6 % using naswar. A prospective study by Baloch et al. (89) described that of the 60 subjects diagnosed with OC 46.6 % used some combination of chewing tobacco, betel nuts, gutka, naswar, and smoking tobacco, and 8.3 %, 8.3 % and 6.7 % used solely chewing tobacco, gutka and naswar, respectively. A retrospective study by Begum et al. (90) analyzed the 628 subjects with OC registered in Institute of Radiotherapy and Nuclear Medicine in Peshawar, Pakistan, and found that 53 % used naswar. Another retrospective study by Hanif et al. (91) found that of the 129 subjects with OC, 72.1 % used SLTs. A retrospective study by Shah & Khan (92) also found that of the 186 subjects OC 91 % had a history of snuff-dipping. All case-control studies showed a risk for OC or HNC associated with at least some SLT common in Pakistan, and other studies described SLT use to be prevalent among subjects with HNC in Pakistan.

Bangladesh

Out of the studies that met the inclusion criteria 3 had a Bangladeshi study population. A case control study by Ullah et al. (93) found a significant risk for OC associated with SLT use (OR 8.8, 95 % CI 5.1-15.0). They also analyzed different SLTs and found independent associations with betel quid with zarda (OR 8.9, 95 % CI 5.2-15.3) and gul/pan masala (OR 6.4, 95 % CI 1.4-29.4), both results adjusted for age, gender, level of education, employment status and BMI. A cross-sectional study by Debnath et al. (94) described that from the 200 subjects with OC in the study 49.5 % used sadapata with betel leaf, 28 % used zarda with betel leaf, 22% used gul. A study by Ahmed et al. (95) described that of the 96 subjects with OC 1.04 % used only chewing tobacco, 36.46 % used chewing tobacco and betel quid and 35.42 % also smoked in addition to chewing tobacco and betel quid. Studies on Bangladeshi populations seem to indicate an association between HNC development and the use of SLTs typical in Bangladesh, however only one case-control study was included in this review.

Others

Out of the studies that met the inclusion criteria 4 were the sole studies on SLT use and HNC in that population. A case-control study by Motlhale et al. (96) in South Africa found no significant risk associated with snuff use for lip, oral, nasal, nasopharyngeal or pharyngeal cancer in black female population (adjusted for age group, language, education, smoking and alcohol consumption). Another study from South Africa by van Wyk et al. (97) investigated the SLT habits of Indian subjects with OC in South Africa and found that of the male subjects 9 % used snuff and of the female subjects 20 %. A case-control study in Morocco (98) found a significant risk for differentiated nasopharyngeal carcinoma in seffa using population (OR 30.2, adjusted for age, social-economic status and associated dietary factors, 95 % CI 1.7-546). A case-control study from Germany (99) found a significant risk for nasal cancer in people with more than 12.5 nasal snuff-package years (OR 2.4, adjusted for year of birth, community size, educational attainment, cigarette packyears, exposure to hardwood dust, asbestos, organic solvents, use of nasal spray/nasal lavage and ever-use of insecticides in homes, 95 % CI 1.1–5.2) and smokers with also a history of nasal snuff use (OR 2.0, same adjustments, 95 % CI 1.0–4.0).

Discussion

SLTs affect the development of HNC and increase their incidence when analyzing globally. However, the risk of developing HNC associated with SLTs vary widely between different products. According to the studies included in this review, the strongest risk for HNC was in association with the use of shammah with significant ORs around 30. The lowest risk was associated with snus, as no significant risk was found for HNC, when adjusted for smoking. Generally, most significant ORs identified by literature were between 3 and 10. However, different regions cannot be conclusively compared to each other in this review, as the study designs vary slightly from region to region and all underlying confounders can't be considered in a review setting. Also, even though discussed separately in this review, many of the same SLTs are used in India, Pakistan and Bangladesh, as they are all situated on the Indian subcontinent. This can indicate a similar risk for HNC associated with SLT use in the Bangladeshi population, even though less evidence was found in this review compared to Pakistan and India.

Most SLTs, that were associated with an increased risk in the development of HNC, included also betel leaves or areca nut, which are known risk factors associated with HNC. However, some studies on populations that used SLTs not including betel quid also showed an increased risk for HNC, suggesting also a betel-independent tobacco-induced pathway in the development of HNCs. International Agency for Cancer Research has classified Tobacco-specific nitrosamines, which most SLTs contain, as group 1 carcinogenic agents in humans (100), and some studies have also investigated the effects of SLTs in the mouth's microbiome as an explanatory factor for the development of cancer (101). Especially differences in SLTs tobacco-specific nitrosamine composition could explain the differences in the risks for HNC between different SLT products. However, as all studies described in this review did not disclose the specific SLT used by the studied population, and as many SLTs are either self-made or made by a small independent local vendor, in regions with strong culture of betel quid use, it can be difficult to evaluate whether the study population was exposed to strictly tobacco containing products or products also containing betel quid.

Most studies were also only considered in the development of OC, and the evidence about the risk for other types of HNC was scarce. A significant risk for LC and PC associated with mainpuri use was found by Amur et al., (80) in Pakistan. However, Sankaranarayanan et al. (29) didn't find a significant association with pan-tobacco chewing and LC. No significant association with snuff use and nasal, nasopharyngeal or PC was found by Motlhale et al. (96) in South Africa. Also, Gholap et al. (18) found a significant risk for OPC, LC, and hypopharyngeal cancer (HC) associated with SLT use in the Indian population. In separate analysis gutka use was associated with a risk for HC, betel quid with tobacco, khaini and only tobacco quid with OPC, HC and LC, while mishri and mawa use were not associated with other HNC than OC. Sapkota et al. (25) found a significant risk for HC associated with zarda use in all of the subjects, and with zarda, mawa, pan-tobacco and gutkha in non-smokers, but no significant risk for LC was found with any of the mentioned SLTs.

Multiple studies included in this review had also investigated the association with SLT use and stage of the HNC. Hanif et al. (91) reported that naswar use was associated with more advanced tumor stage (T4a 54.8 %), however compared to smokers, SLT use was associated with less advanced tumor size and lesser nodal involvement. AlMadan et al. (61) also reported that of the shammah users with OC around 75 % were diagnosed with stage 3 or 4 disease, however, Nasher et al. (64) didn't find a significant association with shammah use and disease stage. Saquib ali et al. (32) found that gutka use was significantly associated with a higher risk for T4 tumors. Anwar et al. (87) found a significant association between chewing tobacco use and stage 3 or 4 disease. However, Nair et al. (41) found no significant association with tumor stage and gutka, khaini or masherri. Also, Osman et al. (59) found no significant association with tumor stage and toombak use. Thus, the studies linking SLT use with late stage (3 or 4) disease were predominantly from India and Pakistan, which can mean that SLTs commonly used in those regions would be associated with more aggressive diseases. However, according to Agrawal et al. (102) in most Indian states the use of SLTs is more common in lower socio-economic classes. Lower socio-economic status can affect adversely most SLT users' abilities to get diagnosed and treated for HNC in an earlier stage, resulting in more diagnoses in later stages.

A recent review (103) listed the risk for HNC associated with smoking tobacco to be 5-25-fold compared with non-smoking population, and the risk associated with heavy alcohol use was 2.5-fold increase. A synergistic effect with heavy alcohol and tobacco use is also known and considered to raise the risk for HNC even to 40-fold (104). For OC specifically a recent meta-analysis (105) found a significant combined RR of 3.39 associated with smoking tobacco. The studies included in this review that found a significant risk show a similar or a higher risk for OC than smoking, but as there was less evidence about the risk for other subtypes of HNC, it's difficult to conclusively compare the risk for HNC associated with SLT use with alcohol and smoking tobacco.

Even though this review is only concentrated on SLTs' effect on HNC, according to the literature, SLTs have multiple other adverse effects on health. A review by Gupta et al. (106) found that SLT use had a generally negative impact on individuals' cardiovascular health. Also, multiple reviews (107), (108) have linked SLT use to elevated risk on cancers of the esophagus, stomach, and pancreas.

Use of tobacco-free nicotine pouches is also a growing trend, especially in the Nordic countries and in the Anglo-Saxon world more generally, as they're seen as a healthier option for traditional tobacco products; however, as a new and emerging product, the literature on their health risks is still scarce. As a recent review by La Rosa et al. (109) noted the absence of studies including a control group and long-term data on the effect of their use on the oral mucosa. Therefore, it is important to monitor their health effects as more data from long-term use starts to emerge.

In conclusion, SLT raises the risk for developing HNC when looking at the research globally, but the risk associated with different SLT products is not equal. Indian, Pakistani, Bangladeshi, Arabian and Sudanese SLTs were associated with stronger risk for HNCs while Scandinavian SLT did not show a similar risk to develop HNC. However, research from multiple countries with a prevalent habit of SLT use was limited, and thus more case-control studies on the risk for HNC associated with SLT use are still needed.

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