Systematic Review

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Relationship between type of smokeless tobacco & risk of cancer: A systematic review

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***Background & objectives*: Causative linkages of smokeless tobacco (SLT) use with oral potentially malignant disorders and cancers of oral cavity, oesophagus and pancreas have been reported. Published meta-analyses have provided pooled risk estimates for major cancers caused by SLT, both on global and regional levels. This systematic review was aimed at summarizing the available studies on occurrence and mortality risk of common cancers due to various SLT products.**

***Methods*: PubMed and Google Scholar databases were systematically searched from 1985 till January 2018 for observational studies on SLT and cancer. The included studies were evaluated and data were extracted and reviewed.**

***Results*: The review included 80 studies providing 121 risk estimates for various cancers. Majority of the studies from South-East Asian Region (SEAR) and Eastern Mediterranean Region (EMR) showed a significant positive association of SLT use with oral [odds ratio (OR) ranging from 1.48 to 27.4] and oesophageal cancers (OR between 2.06 and 12.8), while studies from European Region (EUR) reported a positive association with pancreatic cancer (OR between 1.6 and 2.1). Cancer-related mortality was evaluated in a few reports with higher risk of mortality for lung (OR between 2.0 and 9.1), cervical (OR 2.0) and prostate (OR 2.1) cancers. A wide variation was noted in the association of various cancers and specific SLT products based on their nature, methods of use and inherent toxicity. The majority of chewing tobacco products displayed higher risk for oral and oesophageal cancers while the same was not observed for snus.**

***Interpretation & conclusions*: This review emphasizes on the significantly positive association of SLT use with oral and oesophageal cancers in SEAR and EMR and pancreatic cancer in EUR. Mortality estimates for SLT-associated cancers need further analysis. Risk analysis for cancers of other sites in SLT users also requires multicentric well-designed studies.**

Key words Cancer - mortality - occurrence - oesophagus - oral - pancreas - pharynx - smokeless tobacco

Smokeless tobacco (SLT) consumed orally or nasally has been in use for as long as other forms of tobacco. Research studies conducted over years have shown linkage of SLT use with oral potentially malignant disorders and cancers of oral cavity, oesophagus and pancreas along with possible contributory role in

cardiovascular disease, hypertension, peptic ulcer and foetal morbidity and mortality[1].

SLT products are known to contain more than 30 carcinogens, including tobacco-specific N-nitrosamines (TSNAs), nitrite, nitrate and heavy metals such as nickel, cadmium and chromium[2]. The levels of these carcinogens vary widely among the SLT products consumed in different countries. The additives used in these products leading to changes in toxicity and associated health risks also differ in various geographic regions. This hinders the comparability of results of various studies evaluating the health effects of SLT use[3].

A conceptual model of SLT-associated carcinogenesis postulates that carcinogens present in SLT products are ingested and processed, leading to metabolic activation of carcinogens. The carcinogens cause formation of DNA adducts and subsequent mutations in *K-ras*, *p53* and other genes, leading to uncontrolled cell growth. Other changes, including chronic local inflammation, oxidative stress and formation of reactive oxygen species, may also contribute to tumour promotion[4]. Mechanisms such as activation of Akt and protein kinase A lead to reduced apoptosis and increased angiogenesis and cellular transformation. Apart from TSNAs, other compounds present in SLT products such as polycyclic aromatic hydrocarbons and areca nut may also contribute to causation of cancer in SLT users. Epigenetic pathways, such as promoter methylation of tumour-suppressor genes leading to unregulated proliferation, are also speculated to be involved in SLT-related carcinogenesis[5].

Summary risk estimates of cancer occurrence have shown a higher risk of oral cancer [risk ratio (RR) 3.43, 95% confidence interval (CI) 2.26-5.19], pharyngeal cancer (2.23, 95% CI 1.55-3.20) and oesophageal cancer (2.17, 95% CI 1.70-2.78) in SLT users[6]. However, regional variation in this risk has also been demonstrated. Risk for mortality due to cancers of upper aerodigestive tract (UADT), stomach and uterine cervix has also been shown to be significantly higher with SLT use[7]. This systematic review was undertaken to summarize the available studies (categorized into WHO-defined Regions) on cancer occurrence as well as mortality risk in users of SLT products.

Material & Methods

A systematic literature search was conducted in PubMed and Google Scholar databases for articles on SLT-associated cancers published since 1985 till January 2018 using the search terms 'smokeless tobacco,' 'chewing tobacco,' 'snus,' 'snuff,' '*khaini*,' '*gutka*,' '*toombak*,' '*shammah*,' '*tuibur'* and 'cancer' or 'neoplasm.' The PRISMA guidelines were followed[8]. The flow chart shows the search strategy used (Figure). Cross-references of all included articles were also examined for additional studies.

Inclusion criteria: (*i*) Articles published in English language or published in other languages with summary having detailed results available in English; (*ii*) Case-control or cohort studies including any age group and either or both gender and total sample size of at least 100; (*iii*) Exposure variable: SLT in one of its various forms; (*iv*) Outcome: Cancer of oral cavity, nasal cavity, pharynx, larynx, oesophagus, stomach, lung, uterine cervix, breast, prostate, urinary bladder, kidney, penis, brain, skin, colon and rectum; leukaemia/ lymphoma, multiple myeloma; sarcoma; and (*v*) Risk estimate: Estimates for combined exposure or individual SLT products were extracted. Gender-wise estimates were noted, where available.

Exclusion criteria: Case series, case reports, letters or reviews, reports of only precancerous lesions, duplicate data, and reports of chewable products without tobacco were excluded.

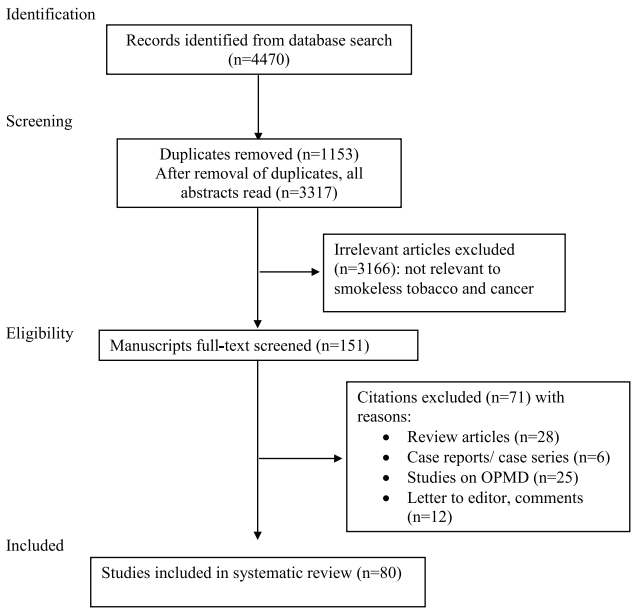

Figure. Flow chart showing search strategy for studies on association of SLT with cancer. OPMD, oral potentially malignant diseases.

Data extraction: Each article was subjected to quality assessment by two authors. Data regarding type of study, location, sample size, publication year, exposure variable, outcome definition and risk estimates with 95 per cent CIs were extracted for risk of occurrence and mortality and compared. Any disparities were resolved by deliberations and final decision was reached by mutual consensus. Risk estimates were also recorded for different SLT products, wherever available.

Results

The initial search yielded 4470 articles, of which 80 studies providing 121 risk estimates for various cancers were included in this review. Of these, 47 were conducted in WHO South-East Asian Region (SEAR, 46 in India, 1 in Indonesia), 12 in European Region (EUR), 11 in American Region (AMR), eight in Eastern Mediterranean Region (EMR) and two in African Region (AFR). No studies were retrieved from Western Pacific Region (WPR).

Smokeless tobacco (SLT) and cancer occurrence risk

Oral cancer: Risk of occurrence of oral cancer has been extensively assessed for the association with SLT; 33 studies (22 from SEAR, 5 EMR, 3 EUR, 2 AFR and 1 AMR) were retrieved in the selected time period (Table I). Majority of these studies have been case-control (28 of 33) while only five (three from SEAR and two from EUR) were cohort studies.

Cohort studies: Of the five cohort studies evaluating risk of oral cancer in SLT users, all three from SEAR[9-11] showed a significant positive association with SLT intake while both studies from EUR[12,13] did not show this positive association. Of the four studies mentioning SLT product, two studies evaluating risk of oral cancer in snus users did not find an increased risk of occurrence of oral cancer[12,13] while both the studies evaluating risk with tobacco chewing reported higher risk of oral cancer in chewers[10,11]. Four of these five studies adjusted for smoking as a confounding factor.

Case-control studies: Nineteen (19) case-control studies were retrieved from SEAR, of which 16 reported a significant positive association with the use of SLT products[17-19,24-27,29-33,37,39-41] while the remaining three did not concur with this association[22,23,28]. The single studies from EUR[35] and AMR[38] did not detect any significant positive association of oral cancer with SLT use. All five studies from EMR[15,16,20,21,34] and two from AFR[14,36] demonstrated significantly higher risk of oral cancer in SLT users.

Seven studies gave separate estimates for males and females, and found significantly higher risk of oral cancer both in male and female SLT users[14,25,27,32,39-41]. Some studies demonstrated a higher risk of cancer in female users [odds ratio (OR) ranging between 3.2 and 45.89] compared to males in the same study (OR ranging from 2.7 to 9.33).

There were 30 estimates mentioning the type of SLT product - 22 on chewing products, five on snuff, two on *toombak* and one on *naswar*. One study evaluated the risk of oral cancer with *naswar* as well as the use of *paan* with tobacco. Of the 22 studies assessing risk of oral cancer with chewing tobacco products, 15 specified the product including *gutka*, betel quid, *paan* with tobacco, *zarda*, *khaini* and *mishri*. Fourteen studies reported a significant positive association between oral cancer and SLT product while one study did not find similar association[22]. The remaining seven studies mentioned only tobacco chewing in the exposure variable without specifying the product type; of these, four demonstrated significantly higher risk of oral cancer in chewers while three did not find any similar association. Both the studies including *toombak* users and two estimates for risk of oral cancer in *naswar* users reported significant positive association[14,15,34,36]. Snuff was evaluated in five studies; two found significantly higher risk of oral cancer in users[40,41] while three studies did not report similar risk[18,35,38]. Of the 28 case-control studies, eight did not adjust for smoking as a confounding variable.

Cancer of pharynx (excluding nasopharynx): Six studies (Table I) were found for risk of occurrence of pharyngeal cancer (all from SEAR[17,30,33,42-44]) in SLT users. There was one cohort study[42] while the rest five were case-control in design[17,30,33,43,44]. All these studies evaluated this association with chewing tobacco. Three studies did not report significant association with SLT use[17,33,42] while two showed positive association[30,44]. In the study by Sapkota *et al*[43], positive association was found only with *zarda* while the same was not true for *khaini*, *mawa* and *gutka*. Six of seven studies were adjusted for smoking.

Oesophageal cancer: Risk of oesophageal cancer in SLT users has been evaluated in 15 studies (11 from SEAR[9,30,46-49,51,52,54-56], three EUR[13,45,53] and one EMR[50]). Only three were cohort[9,13,45] while the

Table I. Characteristics of studies on risk of occurrence of site-specific cancers in smokeless tobacco (SLT) users included in the review

Author/yr	Country	Study design	Gender	SLT type	OR (95% CI)	Sample size	Confounder adjusted
Oral cancer: Cohort studies							
Pednekar *et al*, 2011[9]	India	Cohort	Men	SLT	1.48 (1.03-2.13)	88,658	Age, education, religion, BMI, smoking
Jayalekshmi *et al*, 2011[10]	India	Cohort	Men	Chewing tobacco	2.4 (1.7-3.3) all 1.1 (0.7-1.9) tongue 4.7 (2.8-7.9) gum/mouth	66,277	Age, smoking, alcohol
Jayalekshmi *et al*, 2009[11]	India	Cohort	Women	Chewing tobacco	5.5 (3.3-9.0) current 9.2 (4.6-18.1) former	78,140	Age, family income
Luo *et al*, 2007[12]	Sweden	Cohort	Men	Snus	0.9 (0.4-1.8)	258	Age, BMI, smoking
Boffetta *et al*, 2005[13]	Sweden	Cohort	Men	Snus	1.13 (0.45-2.83)	10,136	Age, smoking
Oral cancer: Case-control studies							
Hassanin and Idris, 2017[14]	Sudan	Case-control	Men and women	*Toombak*	3.80 (1.70-8.59) 3.0 (1.35-6.7) males 3.2 (1.8-6.1) females	98 cases, 98 controls	Smoking, alcohol
Khan *et al*, 2017[15]	Pakistan	Case-control	Men and women	*Naswar*	27.4 (10.0-74.7)	88 cases, 179 controls	Age, sex, socio-economic status, smoking, alcohol
Awan *et al*, 2016[16]	Pakistan	Case-control	NA	*Gutka*	5.54 (2.83-10.83)	134 cases, 134 controls	Not mentioned
Nair *et al*, 2016[17]	India	Case-control	Men and Women	Chewing tobacco	3.34 (2.00-5.57)	518 cases, 83 controls	Smoking
Mahapatra *et al*, 2015[18]	India	Case-control	Men 80%	Betel quid, *gutka, supari*, snuff	5.1 (2.0-10.3) *gutka* 11.4 (3.4-38.2) supari 1.0 (0.3-3.0) snuff 6.4 (2.6-15.5) betel quid	134 cases, 268 controls	Gender, education, age, social class, diet, alcohol, other types, dip products
Kadashetti *et al*, 2015[19]	India	Case-control	NA	Tobacco quid	2.8 (1.2-7.0)	35 cases, 100 controls	Smoking, alcohol, age, gender
Merchant and Pitiphat, 2015[20]	Pakistan	Case-control	Men and women	*Paan* with tobacco	7.27 (2.15-20.43)	79 cases, 143 controls	Age, sex, education, smoking, alcohol, use of *paan* without tobacco
Quadri *et al*, 2015[21]	Saudi Arabia	Case-control	Men and women	*Shammah*	20.14 (8.23-49.25)	48 cases, 96 controls	Smoking, *khat* use
Krishna *et al*, 2014[22]	India	Case-control	Men and women	Betel quid, *gutka*, *paan* masala, *zarda*, *khaini,* etc.	0.53 (0.23-1.20)	190 cases, 189 controls	Smoking, alcohol
Lakhanpal *et al*, 2014[23]	India	Case-control	Men and women	Chewing tobacco	1.12 (0.61-2.04)	125 cases, 207 controls	Smoking, alcohol, IL-1beta

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Author/yr	Country	Study design	Gender	SLT type	OR (95% CI)	Sample size	Confounder adjusted
Amtha *et al*, 2014[24]	Indonesia	Case-control	Men and women	Betel quid with tobacco	4.59 (1.11-18.91)	81 cases, 162 controls	Alcohol, smoking, diet
Ray *et al*, 2013[25]	India	Case-control	Men and women	Chewing tobacco	2.88 (1.53-5.42) males 6.4 (3.04-13.58) females	71 cases, 187 controls	Not mentioned
Madani *et al*, 2012[26]	India	Case-control	NA	Chewing tobacco, *gutka*, *supari*, *mishri*	8.3 (5.4-13.0) chewing 12.8 (7.0-23.7) gutka 6.6 (3.0-14.8) supari 3.3 (2.1-5.4) mishri	350 cases, 350 controls	Other products, alcohol, non-veg habits, education, occupation, age, gender
Muwonge *et al*, 2008[27]	India	Nested case-control	Men and women	Chewing tobacco	4.3 (3.1-6.1) 2.7 (1.8-4.2) males 9.5 (5.0-18.0) females	282 cases, 1410 controls	Smoking, alcohol, education, religion
Anantharaman *et al*, 2007[28]	India	Case-control	Men and women	Chewing tobacco	0.49 (0.32-0.75)	283 cases, 366 controls	Age, gender, smoking, alcohol
Subapriya *et al*, 2007[29]	India	Case-control	Men and women	Betel quid with tobacco	4.10 (3.66-7.93)	388 cases, 388 controls	Age, sex, religion, diet, oral hygiene, literacy and occupation, restricted to non-smoking, non-alcohol group
Znaor *et al*, 2003[30]	India	Case-control	NA	Chewing tobacco	5.05 (4.26-5.97)	1563 cases, 3638 controls	Age, education, smoking, alcohol
Buch *et al*, 2002[31]	India	Case-control	NA	Tobacco with lime or betel quid	1.45 (0.99-2.11)	188 cases, 297 controls	Smoking
Balaram *et al*, 2002[32]	India	Case-control	Men and women	*Paan* with tobacco	6.10 (3.84-9.71) males 45.89 (25.02-84.14) females	309 males 282 females 591 controls	Age, education, smoking, alcohol
Dikshit and Kanhere, 2000[33]	India	Case-control	NA	Tobacco quid	5.8 (3.6-9.5)	148 cases, 260 controls	Age, smoking
Merchant *et al*, 2000[34]	Pakistan	Case-control	Men and women	*Paan* with tobacco *Naswar*	8.42 (2.31-30.64) paan with tobacco 9.53 (1.73-52.53) naswar	79 cases, 149 controls	Age, gender, smoking, alcohol
Schildt *et al*, 1998[35]	Sweden	Case-control	Men and women	Snuff	0.7 (0.4-1.2)	410 cases, 410 controls	Smoking, age, gender
Idris *et al*, 1995[36]	Sudan	Case-control	Men and women	*Toombak*	3.9 (2.9-5.3)	375 cases, 2820 controls	Age, sex, tribe, residence
Rao *et al*, 1994[37]	India	Case-control	Men	Chewing tobacco	3.64 (2.51-5.67)	713 cases, 635 controls	Age, residence, smoking, alcohol
Mashberg *et al*, 1993[38]	USA	Case-control	NA	Chewing tobacco and snuff	1.0 (0.7-1.4) chewing 0.8 (0.4-1.9) snuff	52 cases, 255 controls	Not mentioned

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Author/yr	Country	Study design	Gender	SLT type	OR (95% CI)	Sample size	Confounder adjusted
Sankaranarayanan *et al*, 1990[39]	India	Case-control	Men and women	*Paan* with tobacco, snuff	9.33 (5.6-15.22) males paan-tobacco 3.98 (1.53-10.34) males snuff 3.71 (1.99-6.99) females, paan-tobacco	414 cases, 895 controls	Smoking, alcohol
Nandakumar *et al*, 1990[40]	India	Case-control	Men and women	*Paan* with tobacco	4.0 (1.8-8.0) males 30.4 (12.6-73.4) females	348 cases, 348 controls	Not mentioned
Sankaranarayanan *et al*, 1989[41]	India	Case-control	Men and women	*Paan* with tobacco, nasal snuff	5.95 (2.99-11.84) males 6.62 (2.48-17.66) females 3.90 (1.19-12.70) snuff males	187 cases, 895 controls	Age
Pharyngeal cancer: Cohort studies							
Jayalekshmi *et al*, 2013[42]	India	Cohort	Men	Tobacco chewing	0.5 (0.2-1.6)	65,553	Smoking
Pharyngeal cancer: Case-control studies							
Nair *et al*, 2016[17]	India	Case-control	Men and women	Chewing tobacco	0.45 (0.23-0.85)	518 cases, 83 controls	Smoking
Sapkota *et al*, 2007[43]	India	Case-control	Men 80%	*Khaini, Zarda, Mawa, Gutka*	0.74 (0.39-1.42) *khaini* 2.23 (1.11-4.50) *zarda* 1.33 (0.61-2.89) *mawa* 1.35 (0.56-3.29) *gutka*	513 cases, 718 controls	Age, sex, socio-economic status, alcohol, snuffing, other types
Znaor *et al*, 2003[30]	India	Case-control	NA	Chewing tobacco	1.83 (1.43-2.33)	636 cases, 3638 controls	Age, education, smoking, alcohol
Dikshit and Kanhere, 2000[33]	India	Case-control	NA	Tobacco quid	1.2 (0.8-1.8)	247 cases, 260 controls	Age, smoking
Wasnik *et al*, 1998[44]	India	Case-control	Men and women	Tobacco chewing	8.01 (4.92-14.76)	123 cases, 123 non-cancer controls 123 other cancer controls	Smoking, alcohol, occupation, tobacco material for tooth cleaning
Oesophageal cancer: Cohort studies							
Pednekar *et al*, 2011[9]	India	Cohort	Men	SLT	3.65 (1.59-8.38)	88658	Age, education, religion, BMI, smoking
Zendehdel *et al*, 2008[45]	Sweden	Cohort	Men	Snuff	3.5 (1.6-7.6) SCC 0.2 (0.0-1.9) adeno	366	Smoking, age, BMI
Boffetta *et al*, 2005[13]	Sweden	Cohort	Men	Snus	1.06 (0.35-3.23)	10136	Age, smoking
Oesophageal cancer: Case-control studies							
Das *et al*, 2014[46]	India	Case-control	Men and women	Tobacco chewing	3.32 (1.21-9.14)	100 cases, 100 controls	Betel quid, smoking,

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Author/yr	Country	Study design	Gender	SLT type	OR (95% CI)	Sample size	Confounder adjusted
Talukdar *et al*, 2013[47]	India	Case-control	Men and women	Dried tobacco leaf, *zarda, khaini*	2.63 (1.53-4.5)	112 cases, 130 controls	Age, gender, betel quid, smoking, alcohol
Dar *et al*, 2012[48]	India	Case-control	Men and women	Nass *Gutka*	2.88 (2.06-4.04) *nass* 2.87 (0.87-9.46) *gutka*	702 cases, 1663 controls	Age, ethnicity, religion, residence, education, cumulative use, alcohol, fruit/veg intake
Sehgal *et al*, 2012[49]	India	Case-control		Snuff	3.86 (2.46-6.08)	200 cases, 200 controls	Alcohol, smoking, butter, sundried food, red chilli, baking soda
Akhtar *et al*, 2012[50]	Pakistan	Case-control		Betel quid with tobacco Snuff	12.8 (6.3-26.2) Betel quid 4.3 (1.6-11.7) snuff	91 cases, 364 controls	Ethnicity, areca nut, smoking
Znaor *et al*, 2003[30]	India	Case-control	NA	Chewing tobacco	2.06 (1.62-2.63)	566 cases, 3638 controls	Age, education, smoking, alcohol
Phukan *et al*, 2001[51]	India	Case-control	Men and women	Tobacco alone	4.9 (2.8-11.6) males 3.4 (1.3-5.6) females	502 cases, 1004 controls	Betel nut, smoking, alcohol
Nayar *et al*, 2000[52]	India	Case-control	Men and women	Betel leaf with tobacco	2.58 (1.24-5.37)	150 cases, 150 controls	Smoking, veg consumption
Lagergren *et al*, 2000[53]	Sweden	Case-control	NA	Snuff	1.4 (0.9-2.3) SCC 1.2 (0.7-2.0) adeno	189 cases, 820 controls	Age, gender, smoking, alcohol, education, BMI, fruit/veg, physical activity
Nandakumar *et al*, 1996[54]	India	Case-control	Men and women	*Paan* with tobacco	2.9 (1.5-5.4) males 2.2 (1.4-3.3) females	343 cases, 686 controls	Smoking, alcohol,
Sankaranarayanan *et al*, 1991[55]	India	Case-control	Men and women	Chewing tobacco	2.18 (0.71-6.70) males 0.57 (0.20-1.58) females	267 cases, 895 controls	Age, religion, smoking and alcohol among men, restricted to non-smoking non-alcohol group in women
Rao *et al*, 1989[56]	India	Case-control	Men	Chewing tobacco	5.61 (3.68-8.55)	165 cases, 295 controls	Smoking, alcohol
Gastric cancer: Cohort studies							
Zendehdel *et al*, 2008[45]	Sweden	Cohort	Men	Snuff	0.9 (0.4-2.0) cardia 1.4 (1.1-1.9) non-cardia	1385	Smoking, age, BMI
Boffetta *et al*, 2005[13]	Sweden	Cohort	Men	Snus	1.00 (0.71-1.42)	10136	Age, smoking
Gastric cancer: Case-control studies							
Al-Qadasi *et al*, 2017[57]	Republic of Yemen	Case-control	Men and women	*Shammah*	4.37 (1.92-9.95)	70 cases, 140 controls	Family history, diet, smoking

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Author/yr	Country	Study design	Gender	SLT type	OR (95% CI)	Sample size	Confounder adjusted
Malakar *et al*, 2014[58]	India	Case-control	Men and women	*Tuibur*	2.68 (1.27-5.66)	105 cases, 210 controls	Smoking, smoked fish, preserved meat
Phukan *et al*, 2005[59]	India	Case-control	Men and women	*Tuibur*, chewing tobacco	2.1 (1.3-3.1) *tuibur* 2.6 (1.1-4.2) chewing	329 cases, 665 controls	Alcohol, smoking, education, occupation, income, tuibur/chewing
Rao *et al*, 2002[60]	India	Case-control	Men and women	*Paan* with tobacco	1.03 (0.7-1.4)	170 cases, 2184 controls	Not mentioned
Lagergren *et al*, 2000[53]	Sweden	Case-control	NA	Snuff	1.2 (0.8-1.8)	262 cases, 820 controls	Age, gender, smoking, alcohol, education, BMI, fruit/veg, physical activity
Ye *et al*, 1999[61]	Sweden	Case-control	Men and women	Snuff	0.5 (0.2-1.1) cardia 0.8 (0.5-1.3) distal intestinal type 0.6 (0.3-1.2) distal diffuse type	567 cases, 1165 controls	Age, residence, BMI, socio-economic status, smoking
Gajalakshmi and Shanta, 1996[62]	India	Case-control	Men and women	Betel quid with tobacco	1.3 (0.89-1.98)	388 cases, 388 controls	Residence, education, income, alcohol
Colorectal cancer							
Araghi, 2017[63]	Sweden	Pooled cohort	Men	Snus	1.40 (1.09-1.79) rectal	71,35,504	Smoking
Nordenvall *et al*, 2011[64]	Sweden	Cohort	Men	Snus	1.08 (0.91-1.29)	40,932	Smoking
Aithal *et al*, 2017[65]	India	Case-control	Men and women	Chewing tobacco	1.53 (0.58-4.00)	100 cases, 200 controls	Age, literacy, diet, fruit consumption, physical activity, diabetes, hypertension
Pancreatic cancer: Cohort studies							
Pednekar *et al*, 2011[9]	India	Cohort	Men	SLT	1.95 (0.68-5.54)	88658	Age, education, religion, BMI, smoking
Luo *et al*, 2007[12]	Sweden	Cohort	Men	Snus	2.1 (1.2-3.6)	83 cases	Age, BMI, smoking
Boffetta *et al*, 2005[13]	Sweden	Cohort	Men	Snus	1.60 (1.00-2.55)	10136	Age, smoking
Pancreatic cancer: Case-control studies							
Hassan *et al*, 2007[66]	USA	Case-control	Men and women	Chewing tobacco and snuff	0.6 (0.3-1.4) chewing 0.5 (0.1-1.5) snuff	808 cases, 808 controls	Age, sex, race, smoking, alcohol, diabetes, education, residence, marital status

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Author/yr	Country	Study design	Gender	SLT type	OR (95% CI)	Sample size	Confounder adjusted
Alguacil and Silverman, 2004[67]	USA	Case-control	NA	Chewing tobacco and snuff	1.1 (0.4-3.1)	526 cases, 2153 controls	Race, gender, smoking, age
Laryngeal cancer							
Jayalekshmi *et al*, 2013[42]	India	Cohort	Men	Tobacco chewing	1.1 (0.5-2.4)	65,553	Smoking
Sapkota *et al*, 2007[43]	India	Case-control	Men and Women	*Khaini, Zarda, Mawa, Gutka*	0.79 (0.43-1.44) *khaini* 0.81 (0.36-1.78) *zarda* 0.59 (0.25-1.45) *mawa* 1.11 (0.45-2.74) gutka	511 cases, 718 controls	Age, sex, socio-economic status, alcohol, snuffing, other types
Lung cancer: Cohort studies							
Pednekar *et al*, 2011[9]	India	Cohort	Men	SLT	1.71 (1.08-2.73)	88658	Age, education, religion, BMI, smoking
Luo *et al*, 2007[12]	Sweden	Cohort	Men	Snus	0.8 (0.4-1.3)	154 cases	Age, BMI, smoking
Boffetta *et al*, 2005[13]	Sweden	Cohort	Men	Snus	0.80 (0.36-1.85)	10136	Age, smoking
Lung cancer: Case-control studies							
Ihsan *et al*, 2011[68]	India	Case-control	Men and women	Tobacco chewing	3.05 (1.79-5.20)	116 cases, 278 controls	Smoking, alcohol, p53
Ganesh *et al*, 2011[69]	India	Case-control	Men	Tobacco chewing	0.6 (0.3-1.2)	408 cases, 1383 controls	Smoking, alcohol
Gajalakshmi *et al*, 2003[70]	India	Case-control	NA	Tobacco chewing	0.74 (0.57-0.96)	778 cases, 1927 controls	Age, smoking
Dikshit and Kanhere, 2000[33]	India	Case-control	NA	Tobacco chewing	0.7 (0.4-1.2)	163 cases, 260 controls	Age, smoking

NA, not available; BMI, body mass index; SCC, squamous cell carcinoma; adeno, adenocarcinoma; OR, odds ratio; CI, confidence interval

rest 12 were case-control studies[30,46-56]. Of the cohort studies, one report each from SEAR and EUR showed significant positive association between SLT use and oesophageal cancer[9,45]. The third study from EUR did not find an increased risk of oesophageal cancer in snus users[13].

Nine of ten case-control studies from SEAR demonstrated a higher risk of oesophageal cancer in SLT users[30,46-49,51,52,54,56] while one study did not report any similar risk[55]. The study from EMR reported a significant positive association between SLT use and oesophageal cancer[50] while the report from EUR[53] did not find a positive association. Ten studies evaluated chewing tobacco - six specifying the product including *zarda*, *khaini*, *gutka*, betel quid, tobacco alone or *paan* with tobacco. Of these six studies, five found significantly higher risk of oesophageal cancer in tobacco users while one did not report similar association with *gutka* though this study found positive association of nass chewing and oesophageal cancer[48]. On the other hand, three studies evaluated snuff; two of these (from SEAR[49] and EMR[50]) revealed significantly higher risk of oesophageal cancer in snuff users while the study from EUR[53] did not report similarly higher risk of cancer. Smoking was adjusted as a confounding variable in 14 studies while alcohol was adjusted in only nine studies (Table I).

Gastric cancer: Of the nine studies included, four were conducted in SEAR[58-60,62], four in EUR[13,45,53,61] and one in EMR[57], as depicted in Table I. Of these, two were cohort studies[13,45] while seven were case-control in design[53,57-59,61,62]. Of the cohort studies, the report by Zendehdel *et al*[45] showed significant positive association of cancer of non-cardia part of stomach with SLT use while the same was not found for cancers in the cardia region. The other cohort study did not find increased risk of gastric cancer in snus users[13]. Among the case-control studies, report from EMR (*shammah* users)[57] and those from SEAR evaluating the effect of *tuibur* intake[58,59] reported a significantly higher risk of gastric cancer. However, the studies including users of chewing tobacco (*shammah*, *paan* with tobacco, betel quid) or snuff did not reveal significantly positive association with gastric cancer[53,60-62].

Colorectal cancer: Three studies (one pooled cohort[63] one cohort[64], and one case-control[65]) were retrieved evaluating risk of colorectal cancer in SLT users. Of these, only one study with pooled cohort reported a significantly higher risk of rectal cancer in snus users. However, risk of colon cancer was not found to be higher in SLT users in any of the studies (Table I).

Pancreatic cancer: Five studies (two EUR[12,13], two AMR[66,67] and one SEAR[9]) have assessed the risk of risk of occurrence of pancreatic cancer in SLT users (Table I). Three studies were cohort[9,12,13] while two were case-control reports[66,67]. Two cohort studies, both from EUR[12,13], reported significant positive association between snus use and pancreatic cancer. The third cohort study as well as both case-control studies did not find a similar association[9,66,67]. All the five studies were adjusted for smoking as a confounding factor.

Respiratory cancer: Two studies evaluated association of SLT with laryngeal cancer (both SEAR[42,43]) and both studies (subjects consuming chewing tobacco) reported lack of significant positive association of SLT with cancer of larynx (Table I).

Lung cancer was evaluated in three cohort[9,12,13] and four case-control studies[33,68-70]. One of the cohort (SLT type not specified[9]) and one of case-control studies (assessing chewing tobacco[68]) demonstrated significant positive association of lung cancer with SLT use. The other cohort and case-control studies failed to detect similar association between SLT use and lung cancer (Table I). All the seven studies were adjusted smoking as a confounding variable.

Other cancers: Other neoplasias including breast cancer[71,72], cervical cancer[73], lymphoma[74], genitourinary tumours[13,75,76] liver[9], and others[77-79] have also been evaluated for their association with SLT use with variable results in sporadic studies (Table II).

Smokeless tobacco (SLT) and cancer mortality

Eight studies providing 19 individual estimates for mortality due to various cancers were retrieved for this review (Table III)[80-87]. Of these, seven studies provided estimates for digestive tract cancers, three for respiratory, two for combined oral and pharyngeal cancers, two for genitourinary and one each for pharyngeal, upper aero-digestive tract (UADT), breast and cervical cancers. Significantly higher risk of mortality was found for lung (OR ranging from 2.0[81] to 9.1[86]), cervical (OR 2.0 and 2.2 for urban and rural females, respectively[84]), prostate (OR 2.1, 95% CI 1.1-4.1[87]) and UADT (OR between 1.9 and 3.8[84]). Due to small number of studies on individual cancer and mortality risk, product-specific assessment was not attempted.

Table II. Studies on association of smokeless tobacco (SLT) and risk of occurrence of cancer of other body sites

Author/yr	Country	Study design	Gender	SLT type	Site of cancer	OR (95% CI)	Sample size	Confounders adjusted
Rajbongshi *et al*, 2015[71]	India	Case-control	Women	Betel quid with tobacco	Breast	2.59 (1.34-5.01)	100 cases, 100 controls	Not mentioned
Spangler *et al*, 2001[72]	USA	Census	Women	SLT	Breast	7.79 (1.05-66.0) younger onset	1070	Not mentioned
Rajkumar *et al*, 2003[73]	India	Case-control	Women	*Paan* with tobacco	Uterine cervix	2.13 (0.78-5.86)	205 cases, 213 controls	Age, residence, education, occupation, marital status, age at marriage, pregnancies
Balasubramaniam *et al*, 2013[74]	India	Case-control	Men	Tobacco with lime	NHL	1.5 (0.7-3.2)	390 cases, 1383 controls	Smoking, milk, coffee, chicken, red meat consumption, eggs/ fish, vegetables, pesticides
Hartge *et al*, 1985[75]	USA	Case-control	Men	Chewing tobacco/snuff	Bladder	0.77 (0.38-1.56) snuff 1.02 (0.67-3.28) chew	2982 cases, 5782 controls	Age, race, residence, smoking, other type of tobacco
Hayes, 1994[76]	USA	Case-control	Men	Snuff	Prostate	5.5 (1.2-26.2)	981 cases, 1315 controls	Not mentioned
Pednekar *et al*, 2011[9]	India	Cohort	Men	SLT	Liver	2.35 (1.08-5.10)	88658	Age, education, religion, BMI, smoking
Zhou *et al*, 2013[77]	England	Case-control	Men and women	SLT	Head and neck	1.20 (0.67-2.16) 4.06 (1.31-12.64) >10 yr duration of use	1046 cases, 1239 controls	Age, gender, race, education, smoking, alcohol
Bile *et al*, 2010[78]	Pakistan	Case-control	Men and women	SLT	Oropharyngeal	4.66 (3.92-5.54)	7292	Age, sex, smoking, ethnicity
Lewin *et al*, 1998[79]	Sweden	Case-control	Men	Snuff	Head and neck	1.0 (0.6-1.6)	605 cases, 756 controls	Age, region, alcohol, smoking
Boffetta *et al*, 2005[13]	Sweden	Cohort	Men	Snus	Kidney	0.47 (0.23-0.94)	10136	Age, smoking
Boffetta *et al*, 2005[13]	Sweden	Cohort	Men	Snus	Bladder	0.72 (0.52-1.06)	10136	Age, smoking

This Table includes single studies for cancer of a particular organ or studies where the specific organ for cancer is not mentioned. NA, not available; BMI, body mass index; NHL, non-Hodgkin's lymphoma; OR, odds ratio; CI, confidence interval

Table III. Characteristics of studies on cancer-related mortality and smokeless tobacco (SLT) use included in the review

Author/yr	Country	Study design	Gender	SLT type	OR (95% CI)	Sample size	Site of cancer	Confounder adjusted
Gupta *et al*, 2005[80]	India	Cohort	Men and women	*Mishri*, betel quid	3.72 (0.46-30.26) males 2.74 (0.60-12.40) females	99570	Oral and pharyngeal combined	Age, smoking, education
Henley *et al*, 2005[81]	USA	Cohort	Men	Chewing tobacco	2.02 (0.53-7.74) CPS I 0.9 (0.12-6.71) CPS II	7745 CPS I* 3327 CPS II*	Pharyngeal	Age, race, education, BMI, exercise, alcohol, smoking, fat consumption, fruit/veg intake
Roosaar *et al*, 2008[82]	Sweden	Cohort	Men	Snus	2.3 (0.7-8.3)	9956	Oral and pharyngeal combined	Smoking, residence, alcohol
Timberlake *et al*, 2017[83]	USA	Cohort	Men and women	SLT	0.83 (0.10-7.03)	349,282	Oral	Age, gender, race, education, family income
Gajalakshmi and Kanimozhi, 2015[84]	India	Case-control	Men and women	Chewing tobacco	2.2 (1.4-3.6) urban males 1.9 (0.9-4.3) rural males 2.7 (2.0-3.7) urban females 3.8 (2.3-6.4) rural females	456 cases 429,306 controls	UADT	Smoking, alcohol, age, education
Timberlake *et al*, 2017[83]	USA	Cohort	Men and women	SLT	0.46 (0.11-2.00)	349,282	Oesophageal	Age, gender, race, education, family income
Gajalakshmi and Kanimozhi, 2015[84]	India	Case-control	Men and women	Chewing tobacco	1.9 (0.9-3.6) urban males 2.1 (1.1-4.2) rural males 1.8 (1.2-2.7) urban females 1.4 (0.9-2.2) rural females	348 cases 429,306 controls	Gastric	Smoking, alcohol, age, education
Chao *et al*, 2002[85]	USA	Cohort	Men	Chew/ snuff	1.58 (0.76-3.28)	1505	Gastric	Age, race, education, family history, high fibre foods, veg intake, citrus fruits
Timberlake *et al*, 2017[83]	USA	Cohort	Men and women	SLT	0.70 (0.34-1.43)	349,282	Pancreatic	Age, gender, race, education, family income
Accortt *et al*, 2002[86]	USA	Cohort	Men and women	SLT	0.9 (0.3-2.3) males 0.8 (0.3-2.7) females	1068	Digestive system	Age, race, poverty index ratio, residence, alcohol, exercise, fruit/veg, smoking

Contd...

Author/yr	Country	Study design	Gender	SLT type	OR (95% CI)	Sample size	Site of cancer	Confounder adjusted
Henley *et al*, 2005[81]	USA	Cohort	Men	Chewing tobacco	1.26 (1.05-1.52) CPS I 1.04 (0.77-1.38) CPS II	7745 CPS I 3327 CPS II	Digestive system	Age, race, education, BMI, exercise, alcohol, smoking, fat consumption, fruit/veg
Timberlake *et al*, 2017[83]	USA	Cohort	Men and women	SLT	0.99 (0.70-1.41)	349,282	Digestive system	Age, gender, race, education, family income
Henley *et al*, 2005[81]	USA	Cohort	Men	Chewing tobacco	1.08 (0.64-1.83) CPS I 2.00 (1.23-3.24) CPS II	7745 CPS I 3327 CPS II	Lung	Age, race, education, BMI, exercise, alcohol, smoking, fat consumption, fruit/veg
Accortt *et al*, 2002[86]	USA	Cohort	Men and women	SLT	0.0 males (no case in SLT users) 9.1 (1.1-75.4) females	1068	Lung	Age, race, poverty index ratio, residence, alcohol, exercise, fruit/veg, smoking
Gupta *et al*, 2005[80]	India	Cohort	Men and women	*Mishri*, betel quid	2.23 (0.82-6.04) males	99570	Respiratory	Age, smoking, education
Gajalakshmi and Kanimozhi, 2015[84]	India	Case-control	Men and women	Chewing tobacco	0.5 (0.3-0.8) urban females 0.9 (0.5-1.7) rural females	315 cases 429306 controls	Breast	Smoking, alcohol, age, education
Gajalakshmi and Kanimozhi, 2015[84]	India	Case-control	Men and women	Chewing tobacco	2.0 (1.5-2.7) urban females 2.2 (1.5-3.2) rural females	421 cases 429306 controls	Cervix	Smoking, alcohol, age, education
Hsing *et al*, 1990[87]	USA	Cohort	Men	SLT	2.1 (1.1-4.1)	149	Prostate	Age
Henley *et al*, 2005[81]	USA	Cohort	Men	Chewing tobacco	0.97 (0.77-1.22) CPS I 1.15 (0.85-1.56) CPS II	7745 CPS I 3327 CPS II	Genitourinary system	Age, race, education, BMI, exercise, alcohol, smoking, fat consumption, fruit/vegetable consumption

*CPS I, Cancer Prevention Study I; CPS II, Cancer Prevention Study II; BMI, body mass index; UADT, upper aerodigestive tract; OR, odds ratio; CI, confidence interval

Discussion

SLT products have a worldwide presence in various forms - chewing tobacco in the USA, snuff (snus) in Sweden and mixture of chewing tobacco with other ingredients in developing countries[1]. Reviews in the mid-1980s as well as the US Surgeon General Report in 1986 concluded that SLT products had negative health implications[88]. Recent analyses have demonstrated significant morbidity and mortality related to SLT use. One study estimated that globally, 1.7 million disability-adjusted life years (DALYs) were lost and 62,283 deaths were attributed to SLT-associated cancers based on estimated burden of disease figures available for 113 countries[6]. Another meta-analysis calculated

3.6 million DALYs and 101,004 deaths due to cancers associated with SLT use[89]. A monograph on SLT and Public Health in India reported that 90 per cent of oral and pharyngeal cancers were caused by tobacco in some form and 50 per cent of these are attributable to SLT[90]. However, the multitude and heterogeneity of products have raised doubts on these associations. Due to significant differences in composition, production and usage practices of SLT, the levels of most important carcinogens such as TSNA, vary widely across different SLT products[91].

A systematic review of health effects of SLT published in 2003 reported significant risk of oral cancers due to betel quid and tobacco chewing in India while studies from the US and Scandinavian countries did not report significant positive association[1]. Since this review, there have been a few region-specific or cancer-specific systematic reviews and meta-analyses on SLT[7,89,92]. However, review on association of various cancers with SLT products in a global perspective has not been conducted recently.

Risk of cancer occurrence in SLT users

The present review re-emphasizes the strong association between SLT use and occurrence of oral cancer with risk estimates ranging from 1.48 (1.03-2.13)[9] to 27.4 (10.0-74.7)[15], especially for studies originating from SEAR. Occasional studies from SEAR did not find significant positive association of oral cancer with SLT use[22,23,28]. This could partly be attributed to the fewer number of controls in one study[22]. Studies from EUR, fewer in number compared to those from SEAR, have not found a significant positive association between SLT use and cancer[12,13,35]. An earlier meta-analysis showed overall 34 per cent higher risk of oral cancer in SLT users although regional variation was evident[6]. Sinha *et al*[7], in their meta-analysis of Indian studies, gave a risk estimate of 5.67 (3.83-8.40) for oral cancer in SLT users (Table IV).

A review of studies from the USA found significantly higher risk of oral cancer with chewing tobacco as well as snuff[93]. Meta-analysis of studies from South Asia and Pacific concluded increased risk of oral cancer in tobacco chewers (7.46, 5.86-9.50) although need for conducting studies focussing on different types of tobacco and eliciting dose–response relationship was emphasized[94]. An Indian study has demonstrated a linear dose–response association of oral cancer and chewing tobacco[95]. This regional variation in risk estimates can partly be explained by the chemical composition of SLT products, especially levels of TSNAs, and their usage practices. The SEAR has the maximum diversity in SLT products as well as their usage methods, varying from chewing tobacco alone to a mixture of tobacco with ingredients such as betel quid and/ or areca nut (both recognized

Table IV. Results of published meta-analyses on association of smokeless tobacco use with cancer occurrence and mortality

Risk of cancer occurrence		
Authors/yr (global/regional)	OR	95% CI
Oral cancer		
Siddiqi *et al*, 2015[6] (global)	3.43	2.26-5.19
Wyss *et al*, 2016[93] (USA)	3.01 snuff 1.81 chew	1.63-5.55 snuff 1.04-3.17 chew
Sinha *et al*, 2016[7] (India)	5.67	3.83-8.40
Gupta and Johnson, 2014[94] (South Asia and Pacific)	7.46	5.86-9.50
Khan *et al*, 2014[92] (South Asia)	4.7	3.1-7.1
Pharyngeal cancer		
Siddiqi *et al*, 2015[6] (global)	2.23	1.55-3.20
Wyss *et al*, 2016[93] (USA)	1.22 snuff 1.04 chew	0.65-2.27 snuff 0.62-1.73 chew
Sinha *et al*, 2016[7] (India)	3.07	1.94-4.86
Oesophageal cancer		
Siddiqi *et al*, 2015[6] (global)	2.17	1.70-2.78
Sinha *et al*, 2016[7] (India)	3.15	2.50-3.97
Stomach cancer		
Sinha *et al*, 2016[7] (India)	1.31	0.92-1.87
Laryngeal cancer		
Sinha *et al*., 2016[7] (India)	1.79	0.70-4.54
Lung cancer		
Sinha *et al*, 2016[7] (India)	0.93	0.71-1.22
Cancer-related mortality		
Upper aerodigestive tract cancer		
Sinha *et al*, 2016[7] (India)	2.17	1.47-3.22
Stomach cancer		
Sinha *et al*, 2016[7] (India)	1.33	1.12-1.59
Cervical cancer		
Sinha *et al*, 2016[7] (India)	2.07	1.64-2.61

OR, odds ratio; CI, confidence interval

as carcinogens), lime and other such products[96]. Some products are sucked, gargled/sipped or used as a dentrifice (Table V)[97]. A review of toxicology of SLT products available in India highlighted the disturbingly high levels of TSNAs in the most popular brands of SLT products such as *khaini*, *zarda* and *mishri*[99]. Various authors have also detected TSNAs in the saliva of tobacco chewers[100,101]. In addition, mutagenic effects of extracts of SLT products have also been demonstrated[102]. Formation of micronucleus as a genotoxic effect has been reported in exfoliated buccal epithelial cells from tobacco chewers[103]. A few studies in the present review reported a higher risk of cancer in female SLT users (OR ranging between 3.2 and 45.89)[14,32] compared to male users in the same study (OR ranging from 2.7 to 9.33)[27,39]. A previous meta-analysis of studies from India also showed a significantly higher risk of oral cancer in female users (pooled OR 12.09, 95% CI 9.49-15.25) compared to males (5.16, 95% CI 4.49-5.94)[7]. This difference may be attributed to the behavioural differences in the usage of SLT products between males and females.

Results on association of SLT use and pharyngeal cancer have been conflicting as can be seen from Table I. However, earlier meta-analyses have shown 22 and 30 per cent higher risk of occurrence of pharyngeal cancer in SLT users[6,7]. Unlike oral cancer where tobacco is the most important aetiologic agent, pharyngeal cancer, especially oropharyngeal, is causatively linked to human papillomavirus (HPV)[104]. Synergistic effect of smoking and HPV16 positivity on the causation of head and neck cancer have been demonstrated[104] though the same has not been proved for SLT products as yet.

Another significant positive association highlighted is that of oesophageal cancer and SLT products. Majority of studies from SEAR, the single study from EMR and one of two reports from EUR demonstrated positive association of oesophageal cancer with SLT use. A previous global review of SLT-related diseases reported an overall 20 per cent higher risk of oesophageal cancer in SLT users with maximum risk detected in the analysis of studies from EMR and SEAR[6]. Similar positive association was reported in a meta-analysis of Indian studies[7].

Studies on gastric cancer have reported conflicting results with reports from EUR not finding positive association while majority of SEAR and EMR studies demonstrating higher risk of gastric cancer with SLT use. However, a previous meta-analysis of Indian studies did not find significant positive association between gastric cancer and SLT use (1.31, 95% CI 0.92-1.87)[7]. The association of pancreatic cancer with SLT use has been demonstrated in Scandinavian reports though studies from America have not supported this association[12,13]. The Scandinavian studies have shown this increased risk in SLT users after adjustment for smoking and alcohol use[13] or in never-smoking stratum[12]. Animal model experiments have shown the occurrence of pancreatic adenocarcinoma in rats exposed to TSNAs or their metabolites as well as effect of TSNAs on point mutations in the *RAS* gene that is implicated in pancreatic carcinogenesis[105,106]. TSNAs have also been documented in human pancreatic juice at higher concentration in smokers compared to non-smokers[107]. However, the available evidence lacks detailed information regarding the chemical composition of the SLT products consumed in different Regions. Since the toxicity of SLT products differs according to their composition and manufacturing practices, effect of these products in causation of various cancers has been debatable in the studies from different Regions.

The role of SLT use in occurrence of cancers such as colorectal, lung, breast and cervix has not been established beyond doubt as yet and needs further exploration by well-controlled studies.

Cancer-related mortality and SLT use

In comparison with the number of studies evaluating cancer occurrence in SLT users, research into cancer-related mortality with SLT use has been scarce. In the present review, only 19 individual risk estimates were retrieved for mortality of various cancers in SLT users. A previous meta-analysis of SLT-attributable mortality showed significantly higher risk of deaths due to UADT, gastric and cervical cancers in SLT users. Regional variation was noted for mortality outcome of UADT cancer with significant positive association in estimates from SEAR while the same was not true for those from AMR[89]. However, a limitation of this analysis was the small number of estimates included for each cancer. In addition, mortality estimates were not available from all Regions.

A cohort study from south India on effect of tobacco chewing on cancer mortality did not find significant positive association (1.07, 95% CI 0.94-1.22) after adjustment for age, gender, socio-economic status and dietary variables. However, age-wise evaluation

Table V. Commonly used smokeless tobacco (SLT) products described in this review - Composition, usage practice and toxicology

Name of product	Region/country	Method of use	Form of tobacco	Additives	*p*H	Known carcinogens (TSNAs/NNK/NNN/NNAL (ng/g))
Betel quid with tobacco	SEAR: India, Sri Lanka, Bangladesh, Myanmar, Thailand, Indonesia, Nepal, Maldives; EMR: Pakistan, UAE; WPR: Lao Democratic People's Republic, Palau, Cambodia, Malaysia, Vietnam, Federal States of Micronesia	Oral - chewed	Plain or flavoured tobacco flakes	Areca nut, slaked lime (calcium hydroxide) or other alkaline agents, betel leaf and usually catechu. Can include cardamom, saffron, cloves, camphor, aniseed, turmeric, mustard, or sweeteners	Data NA	Data NA
Dry snuff	AMR: Canada, USA; AFR: South Africa, Nigeria; EUR: Germany	Oral - sucked	Fire-cured and fermented tobacco	Sweeteners, flavourings	5.71-6.25	10300-76500/1340-4600/6120-31300/47-1050
Gutka	SEAR: India, Bangladesh, Nepal, Myanmar, Sri Lanka; EMR: Pakistan	Oral - chewed	Powdered tobacco	Areca nut, slaked lime (calcium hydroxide), catechu, and other condiments, sweeteners, and flavourings	India: 7.43-8.61 Pakistan: 8.20-8.54	India: 264-23900/7.1-375/154-8600/10.8-1030 Pakistan: 83.9-560/11.6-208/45.4-913/7.02-53.5
Khaini	SEAR: India, Bangladesh, Nepal, Bhutan	Oral - chewed, sucked	Tobacco leaves	Slaked lime (calcium hydroxide), and sometimes areca nut	9.65-9.79	21600-23500/88-502/16800-17500/1350-1400
Mishri	SEAR: India	Oral- sucked, applied to teeth and gums, teeth, cleaning	Toasted powdered tobacco	-	6.54	___/4210/870/___
Moist snuff	AMR: Canada, USA, Mexico; AFR: South Africa	Oral - sucked	Tobacco leaves	Flavourings, inorganic salts, humectants	5.54-8.62	4874-90024/382-9950/2204-42554/21-1412
Nass	EMR: Pakistan, Iran, Afghanistan, UAE; AFR: South Africa; EUR: Turkmenistan, Kyrgyzstan, Uzbekistan	Oral - chewed, sucked	Sun- and heat-dried tobacco	Ash, cotton or sesame oil, water, and sometimes lime or gum	8.76-9.14	Pakistan: 478-1380/29.4-309/363-545/8.6-104
Shammah	EMR: Saudi Arabia, Yemen; AFR: Algeria	Oral - sucked	Sun-dried pulverized tobacco	Slaked lime, ash, black pepper, oil, flavourings, bombosa (sodium carbonate)	Data NA	Data NA

Contd...

Name of product	Region/country	Method of use	Form of tobacco	Additives	*p*H	Known carcinogens (TSNAs/NNK/NNN/NNAL (ng/g))
Snus	EUR: Sweden, Norway, Iceland, Finland, Denmark; AMR: USA, Canada, Brazil; AFR: South Africa	Oral	Air-cured tobacco	Moisturizers, sodium carbonate, salt (sodium chloride), sweeteners, flavourings	Swedish Match: 6.61-7.21 RJ Reynolds: 7.55-7.70	Swedish Match (Sweden): 601-723 /84.5-105/267-345/8.57-13.1 RJ Reynolds (USA): 761-884/84-146/369-425/20-21
Tuibur	SEAR: India	Oral - gargled	Tobacco smoke	Water		Data NA
Toombak	EMR: Sudan	Oral - sucked; Nasal	Sun-cured tobacco	Baking soda (sodium bicarbonate, locally called atrun or natron), water	7.38-10.1	295000-992000/14700-516000/115 000-368000/4550-6770
Zarda	SEAR: India, Bangladesh, Myanmar, Nepal, Bhutan; EMR: Yemen	Oral - chewed, in *paan*	Tobacco leaves broken and boiled	Lime, spices, vegetable dyes, and sometimes areca nut and/or silver flecks	India: 5.22 Bangladesh: 6.51	India: 5490/829/2910/390 Bangladesh: 53700/3840/28600/3460

NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N'-nitrosonornicotine; NNAL, 4-(methylnitrosamino) 1-(3-pyridyl)-1-butanol TSNAs, tobacco-associated nitrosamines. NA: not available
WHO Study Group on Tobacco Product Regulation (TobReg) recommended standard: TSNA limited to 2 µg/g dry weight[98]
Source: Ref. 97

showed detrimental effects on cancer mortality in the middle age group, 40-59 yr (1.26, 95% CI 1.03-1.55)[108].

Due to paucity of studies evaluating cancer-related mortality in SLT users, conclusive opinion on cancer-specific, Region-wise or product-related mortality risk for various cancers is currently not possible. Exploring this aspect would need well-designed studies with appropriate adjustment for confounding factors.

Strengths and limitations

The strengths of this review include the wide and comprehensive range of cancers included, thorough literature review and global coverage to the widest extent possible. Cancer sites not considered by previous reviews and meta-analyses were also included in the present review.

However, there were certain limitations also. Many of the observational studies included inadequate descriptions of SLT use as 'ever or never' without defining the type of SLT product or estimating the dose-response relationship. Second, biochemical validation of SLT use was not conducted in majority of the studies. Self-reporting of SLT use is fraught with recall bias as well as intentional hiding of facts by the subjects. Such bias can lead to misclassification of subjects as cases or controls, leading to confounding results. A significant limitation of this review was the lack of uniformity of case definition in accordance with the International Classification of Diseases (ICD-10) system, especially for oral cancers. Many studies included in the review failed to mention the case definition criteria. The definition of various outcomes was also not uniform across studies. This was of special concern in the evaluation of studies on mortality since the data from developing countries were usually lacking in the completeness and certification of cause of death. In such a scenario, confounding by other causes of death in a cancer patient could not be excluded with confidence. Absence of studies from WPR limited the evaluation of SLT and cancer association in this Region. From AFR, only two studies evaluating role of *toombak* in risk of oral cancer were retrieved. Other cancer sites were not examined in AFR for the association with SLT products. Another limitation pertained to countries like India with wide inter-State variations in SLT products. Studies reported from such countries are not distributed uniformly through the country; however, the results are considered to represent the country as a whole.

Conclusion & recommendations for the future

The present review highlights the significant positive association of SLT use with risk of oral and oesophageal cancer in SEAR and EMR. Higher risk of pancreatic cancer in SLT users has been emphasized in

studies from EUR. Association of SLT products with cancers of other sites and with cancer-related mortality is still an unresolved issue that requires robust studies from across the globe.

Although association of SLT and oral cancer is well accepted especially for SEAR, further studies with adequate power and control of confounding factors are required from other Regions, as well as for other cancers to establish their association with SLT. The studies should specifically address the product-specific association to enable clear policy decisions and also to refute the claims of tobacco industry regarding relative safety of SLT products as an alternative to quitting for smokers. To address the latter issue, studies also need to include a category of 'switchers' in their long-term follow up to obtain real estimates of adverse health consequences of SLT use compared to smoking.

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