Systematic Review

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

Sanjay Gupta¹, Ruchika Gupta¹, Dhirendra N. Sinha³ & Ravi Mehrotra²

¹Division of Cytopathology, ²WHO FCTC Global Knowledge Hub for Smokeless Tobacco, ICMR-National Institute of Cancer Prevention & Research, Noida & ³School of Preventive Oncology, Patna, India

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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.

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**Figure.** Flow chart showing search strategy for studies on association of SLT with cancer. OPMD, oral potentially malignant diseases.
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 1). Majority of these studies have been case-control (28 of 33) while only five (three from SEAR and two from EUR) were cohort studies.

**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 1). 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 SEAR9-11 showed a significant positive association with SLT intake while both studies from EUR12,13 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 cancer12,13 while both the studies evaluating risk with tobacco chewing reported higher risk of oral cancer in chewers10,11. 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 products17-19,24-27,29-33,37,39-41 while the remaining three did not concur with this association22,23,28. The single studies from EUR35 and AMR38 did not detect any significant positive association of oral cancer with SLT use. All five studies from EMR15,16,20,21,34 and two from AFR14,36 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 users14,25,27,32,39-41. 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 association12. 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 association14,15,34,36. Snuff was evaluated in five studies; two found significantly higher risk of oral cancer in users40,41 while three studies did not report similar risk18,35,38. Of the 28 case-control studies, eight did not adjust for smoking as a confounding variable.

**Cancer of pharynx (excluding nasopharynx)**: Six studies (Table 1) were found for risk of occurrence of pharyngeal cancer (all from SEAR17,30,33,42,44) in SLT users. There was one cohort study32 while the rest five were case-control in design17,30,33,43,44. All these studies evaluated this association with chewing tobacco. Three studies did not report significant association with SLT use17,33,42 while two showed positive association30,44. In the study by Sapkota et al31, 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 SEAR9,30,46-49,51,52,54-56, three EUR13,45,53 and one EMR50). Only three were cohort9,13,45 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<sup>a</sup> | India   | Cohort       | Men    | SLT              | 1.48 (1.03-2.13) | 88,658 | Age, education, religion, BMI, smoking |
| Jayalekshmi et al, 2011<sup>b</sup> | 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<sup>c</sup> | 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<sup>d</sup> | Sweden  | Cohort       | Men    | Snus             | 0.9 (0.4-1.8)    | 258       | Age, BMI, smoking |
| Boffetta et al, 2005<sup>e</sup> | India   | Cohort       | Men    | Snus             | 1.13 (0.45-2.83) | 10,136 | Age, smoking |
| Oral cancer: Case-control studies                                                                                                                 |
| Hassanin and Idris, 2017<sup>f</sup> | 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<sup>g</sup> | 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<sup>h</sup> | Pakistan | Case-control | NA     | Gutka            | 5.54 (2.83-10.83) | 134 cases, 134 controls | Not mentioned |
| Nair et al, 2016<sup>i</sup> | India   | Case-control | Men and Women | Chewing tobacco | 3.34 (2.00-5.57) | 518 cases, 83 controls | Smoking |
| Mahapatra et al, 2015<sup>j</sup> | 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 |
| Kodashetti et al, 2015<sup>k</sup> | India   | Case-control | NA     | Tobacco quid     | 2.8 (1.2-7.0)    | 35 cases, 100 controls | Smoking, alcohol, age, gender |
| Merchant and Pitiphat, 2015<sup>l</sup> | 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<sup>m</sup> | 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<sup>n</sup> | 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<sup)o</sup> | India   | Case-control | Men and women | Chewing tobacco | 1.12 (0.61-2.04) | 125 cases, 207 controls | Smoking, alcohol, IL-1beta |

Contd...
| Author/yr          | Country   | Study design     | Gender               | SLT type                  | OR (95% CI)              | Sample size          | Confounder adjusted                                                                 |
|-------------------|-----------|------------------|----------------------|---------------------------|--------------------------|----------------------|-------------------------------------------------------------------------------------|
| Amtha et al, 2014 | 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   | India     | Case-control     | Men and women        | Chewing tobacco           | 2.88 (1.53-5.42)         | 71 cases, 187 controls | Not mentioned                                                                       |
| Madani et al, 2012 | 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 | India     | Case-control     | Men and women        | Chewing tobacco           | 4.3 (3.1-6.1)            | 282 cases, 1410 controls  | Smoking, alcohol, education, religion                                               |
| Znaor et al, 2003  | India     | Case-control     | NA                   | Chewing tobacco           | 5.05 (4.26-5.97)         | 1563 cases, 3638 controls | Age, education, smoking, alcohol                                                    |
| Buch et al, 2002  | 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 | 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 | India     | Case-control     | NA                   | Tobacco quid             | 5.8 (3.6-9.5)            | 148 cases, 260 controls | Age, smoking                                                                        |
| Merchant et al, 2000 | 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 | Sweden    | Case-control     | Men and women        | Snuff                    | 0.7 (0.4-1.2)            | 410 cases, 410 controls | Smoking, age, gender                                                               |
| Idris et al, 1995 | 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   | India     | Case-control     | Men                   | Chewing tobacco          | 3.64 (2.51-5.67)         | 713 cases, 635 controls | Age, residence, smoking, alcohol                                                    |
| Mashberg et al, 1993 | 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                                                                      |

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

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

Contd...
| Author/yr            | Country | Study design | Gender          | SLT type                        | OR (95% CI)                  | Sample size          | Confounder adjusted                                                                 |
|---------------------|---------|--------------|-----------------|--------------------------------|------------------------------|----------------------|-------------------------------------------------------------------------------------|
| Malakar et al., 2014<sup>58</sup> | 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<sup>59</sup>    | India   | Case-control | Men and women   | Tuibur, chewing tobacco        | 2.1 (1.3-3.1) tuibur        | 329 cases, 665 controls     | Alcohol, smoking, education, occupation, income, tuibur/chewing                     |
| Rao et al, 2002<sup>60</sup>       | India   | Case-control | Men and women   | Paan with tobacco              | 1.03 (0.7-1.4)              | 170 cases, 2184 controls   | Not mentioned                                                                      |
| Randhawa et al, 2004<sup>61</sup>  | India   | Case-control | Men and women   | Guttar                         | 1.2 (0.8-1.8)               | 262 cases, 820 controls    | Alcohol, smoking, BMI, education, occupation, income, smoking                       |
| Phukan et al, 2005<sup>62</sup>    | India   | Case-control | Men and women   | Tuibur, chewing tobacco        | 2.6 (1.1-4.2) chewing       | 329 cases, 665 controls    | Alcohol, smoking, education, occupation, income, tuibur/chewing                     |
| Rao et al, 2002<sup>63</sup>       | India   | Case-control | Men and women   | Tuibur, chewing tobacco        | 2.1 (1.3-3.1) tuibur        | 329 cases, 665 controls    | Alcohol, smoking, education, occupation, income, tuibur/chewing                     |
| Phukan et al, 2005<sup>64</sup>    | India   | Case-control | Men and women   | Tuibur, chewing tobacco        | 2.6 (1.1-4.2) chewing       | 329 cases, 665 controls    | Alcohol, smoking, education, occupation, income, tuibur/chewing                     |
| Ye et al, 1999<sup>65</sup>        | Sweden  | Case-control | Men and women   | Snuff                          | 0.5 (0.2-1.1) cardia        | 567 cases, 1165 controls   | Age, gender, smoking, alcohol, education, BMI, fruit/veg, physical activity         |
| Ye et al, 1999<sup>66</sup>        | Sweden  | Case-control | Men and women   | Snuff                          | 0.8 (0.5-1.3) distal intestinal type | Age, gender, smoking, alcohol, education, BMI, fruit/veg, physical activity         |
| Ye et al, 1999<sup>67</sup>        | Sweden  | Case-control | Men and women   | Snuff                          | 0.6 (0.3-1.2) distal diffuse type | Age, gender, smoking, alcohol, education, BMI, fruit/veg, physical activity         |
| Gajalakshmi and Shanta, 1999<sup>68</sup> | 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<sup>69</sup>       | Sweden  | Pooled cohort | Men             | Snus                           | 1.40 (1.09-1.79) rectal    | 71,35,504              | Smoking                                                                             |
| Nordenwall et al, 2011<sup>70</sup> | Sweden  | Cohort       | Men             | Snus                           | 1.08 (0.91-1.29)            | 40,932                 | Smoking                                                                             |
| Aithal et al, 2017<sup>71</sup>  | 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<sup>72</sup> | India   | Cohort       | Men             | SLT                            | 1.95 (0.68-5.54)            | 88658                 | Age, education, religion, BMI, smoking                                              |
| Luo et al, 2007<sup>73</sup>     | Sweden  | Cohort       | Men             | Snus                           | 2.1 (1.2-3.6)               | 83 cases               | Age, BMI, smoking                                                                  |
| Boffetta et al, 2005<sup>74</sup> | Sweden  | Cohort       | Men             | Snus                           | 1.60 (1.00-2.55)            | 10136                 | Age, smoking                                                                        |

**Pancreatic cancer: Case-control studies**

| Hassan et al, 2007<sup>75</sup>   | USA     | Case-control | Men and women   | Chewing tobacco and snuff      | 0.6 (0.3-1.4) chewing       | 808 cases, 808 controls     | Age, sex, race, smoking, alcohol, diabetes, education, residence, marital status    |

Contd...
| Author/yr                        | Country | Study design | Gender | SLT type          | OR (95% CI)                      | Sample size                  | Confounder adjusted                                      |
|---------------------------------|---------|--------------|--------|-------------------|---------------------------------|------------------------------|----------------------------------------------------------|
| Alguacil and Silverman, 2004¹⁷ | 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, 2013²⁰       | India   | Cohort       | Men    | Tobacco chewing   | 1.1 (0.5-2.4)                  | 65,553                       | Smoking                                                  |
| Sapkota et al, 2007²⁰          | India   | Case-control | Men and Women | Khaini, Zarda, Mawa, Gutka | 0.79 (0.43-1.44), 0.81 (0.36-1.78), 0.59 (0.25-1.45), 1.11 (0.45-2.74) | 511 cases, 718 controls | Age, sex, socio-economic status, alcohol, snuffing, other types |
| Lung cancer: Cohort studies     |         |              |        |                   |                                 |                              |                                                          |
| Pednekar et al, 2011³⁰         | India   | Cohort       | Men    | SLT               | 1.71 (1.08-2.73)                | 88658                        | Age, education, religion, BMI, smoking                   |
| Luo et al, 2007¹²               | Sweden  | Cohort       | Men    | Snus              | 0.8 (0.4-1.3)                  | 154 cases                    | Age, BMI, smoking                                        |
| Boffetta et al, 2005⁵³         | Sweden  | Cohort       | Men    | Snus              | 0.80 (0.36-1.85)               | 10136                        | Age, smoking                                              |
| Lung cancer: Case-control studies |       |              |        |                   |                                 |                              |                                                          |
| Ihsan et al, 2011³⁰            | India   | Case-control | Men and women | Tobacco chewing   | 3.05 (1.79-5.20)               | 116 cases, 278 controls | Smoking, alcohol, p53                                    |
| Ganesh et al, 2011⁹³           | India   | Case-control | Men    | Tobacco chewing   | 0.6 (0.3-1.2)                  | 408 cases, 1383 controls    | Smoking, alcohol                                         |
| Gajalakshmi et al, 2003³⁰      | India   | Case-control | NA     | Tobacco chewing   | 0.74 (0.57-0.96)               | 778 cases, 1927 controls    | Age, smoking                                              |
| Dikshit and Kanhere, 2000³⁵    | 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\textsuperscript{30,46-56}. Of the cohort studies, one report each from SEAR and EUR showed significant positive association between SLT use and oesophageal cancer\textsuperscript{9,45}. The third study from EUR did not find an increased risk of oesophageal cancer in snus users\textsuperscript{13}.

Nine of ten case-control studies from SEAR demonstrated a higher risk of oesophageal cancer in SLT users\textsuperscript{30,46-49,51,52,54,56} while one study did not report any similar risk\textsuperscript{55}. The study from EMR reported a significant positive association between SLT use and oesophageal cancer\textsuperscript{50} while the report from EUR\textsuperscript{55} 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\textsuperscript{48}. On the other hand, three studies evaluated snuff; two of these (from SEAR\textsuperscript{49} and EMR\textsuperscript{50}) revealed significantly higher risk of oesophageal cancer in snuff users while the study from EUR\textsuperscript{51} 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\textsuperscript{58,60,62}, four in EUR\textsuperscript{13,45,53,61} and one in EMR\textsuperscript{57}, as depicted in Table I. Of these, two were cohort studies\textsuperscript{13,45} while seven were case-control in design\textsuperscript{33,57-59,61,62}. Of the cohort studies, the report by Zendehdel et al\textsuperscript{55} 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\textsuperscript{13}. Among the case-control studies, report from EMR (shammmah users)\textsuperscript{47} and those from SEAR evaluating the effect of tuibur intake\textsuperscript{58,59} reported a significantly higher risk of gastric cancer. However, the studies including users of chewing tobacco (shammmah, paan with tobacco, betel quid) or snuff did not reveal significantly positive association with gastric cancer\textsuperscript{43,60-62}.

**Colorectal cancer:** Three studies (one pooled cohort\textsuperscript{63} one cohort\textsuperscript{64}, and one case-control\textsuperscript{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\textsuperscript{12,13}, two AMR\textsuperscript{66,67} and one SEAR\textsuperscript{9}) have assessed the risk of risk of occurrence of pancreatic cancer in SLT users (Table I). Three studies were cohort\textsuperscript{49,12,13} while two were case-control reports\textsuperscript{66,67}. Two cohort studies, both from EUR\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{9,12,13} and four case-control studies\textsuperscript{33,68-70}. One of the cohort (SLT type not specified) and one of case-control studies (assessing chewing tobacco\textsuperscript{69}) 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\textsuperscript{21,72}, cervical cancer\textsuperscript{71}, lymphoma\textsuperscript{74}, genitourinary tumours\textsuperscript{13,75,76} liver\textsuperscript{75}, and others\textsuperscript{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\textsuperscript{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\textsuperscript{81} to 9.1\textsuperscript{86}), cervical (OR 2.0 and 2.2 for urban and rural females, respectively\textsuperscript{84}), prostate (OR 2.1, 95% CI 1.1-4.1\textsuperscript{87}) and UADT (OR between 1.9 and 3.8\textsuperscript{84}). Due to small number of studies on individual cancer and mortality risk, product-specific assessment was not attempted.
| Author/yr       | Country | Study design | Gender | SLT type               | Site of cancer  | OR (95% CI)                  | Sample size               | Confounders adjusted                      |
|-----------------|---------|--------------|--------|------------------------|-----------------|-----------------------------|---------------------------|------------------------------------------|
| Rajbongshi et al, 2015 | 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 | USA     | Census       | Women  | SLT                    | Breast          | 7.79 (1.05-66.0) younger onset | 1070                      | Not mentioned                        |
| Rajkumar et al, 2003 | 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 | 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 | 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     | USA     | Case-control | Men    | Snuff                  | Prostate        | 5.5 (1.2-26.2)             | 981 cases, 1315 controls        | Not mentioned                        |
| Pednekar et al, 2011 | India   | Cohort       | Men    | SLT                    | Liver           | 2.35 (1.08-5.10)           | 88658                     | Age, education, religion, BMI, smoking |
| Zhou et al, 2013 | 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 | Pakistan | Case-control | Men and women | SLT                  | Oropharyngeal   | 4.66 (3.92-5.54)           | 7292                      | Age, sex, smoking, ethnicity            |
| Lewin et al, 1998 | 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 | Sweden  | Cohort       | Men    | Snus                   | Kidney          | 0.47 (0.23-0.94)           | 10136                     | Age, smoking                          |
| Boffetta et al, 2005 | 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.
| Author/yr          | Country | Study design | Gender                  | SLT type                | OR (95% CI) | Sample size | Site of cancer                        | Confounder adjusted                                                                 |
|-------------------|---------|--------------|-------------------------|-------------------------|-------------|-------------|----------------------------------------|--------------------------------------------------------------------------------------|
| Gupta et al, 2005 | 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 | 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 | Sweden  | Cohort       | Men                     | Snus                   | 2.3 (0.7-8.3)            | 9956        | Oral and pharyngeal combined           | Smoking, residence, alcohol                                                          |
| Timberlake et al, 2017 | 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 | 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 | 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 | 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 | 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 | USA     | Cohort       | Men and women           | SLT                    | 0.70 (0.34-1.43)         | 349,282     | Pancreatic                             | Age, gender, race, education, family income                                           |
| Accoritt et al, 2002 | 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    |
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. Reviews in the mid-1980s as well as the US Surgeon General Report in 1986 concluded that SLT products had negative health implications. 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. Another meta-analysis calculated

| Author/yr | Country | Study design | Gender | SLT type | OR (95% CI) | Sample size | Site of cancer | Confounder | Adjusted |
|-----------|---------|--------------|--------|----------|-------------|-------------|---------------|------------|----------|
| Henley et al, 2005 | USA | Cohort | Men | Chewing tobacco | 1.26 (1.05-1.52) | 7745 CPS I 3327 CPS II | Digestive system | Age, race, education, BMI, exercise, alcohol, smoking, fat consumption, fruit/vegetable | |
| Timberlake et al, 2017 | 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 | USA | Cohort | Men | Chewing tobacco | 1.08 (0.64-1.83) | 7745 CPS I 3327 CPS II | Lung | Age, race, education, BMI, exercise, alcohol, smoking, fat consumption, fruit/vegetable | |
| Accortt et al, 2002 | USA | Cohort | Men and women | SLT | 0.0 males (no case in SLT users) | 1068 | Lung | Age, race, poverty index ratio, residence, alcohol, exercise, fruit/vegetable, smoking | |
| Gupta et al, 2005 | India | Cohort | Men and women | Mishri, betel quid | 2.23 (0.82-6.04) | 99570 | Respiratory | Age, smoking, education | |
| Gajalakshmi and Kanimozhi, 2015 | India | Case-control | Men and women | Chewing tobacco | 0.5 (0.3-0.8) urban females | 315 cases 429306 controls | Breast | Smoking, alcohol, age, education | |
| Gajalakshmi and Kanimozhi, 2015 | India | Case-control | Men and women | Chewing tobacco | 0.9 (0.5-1.7) rural females | 421 cases 429306 controls | Cervix | Smoking, alcohol, age, education | |
| Hsing et al, 1990 | USA | Cohort | Men | SLT | 2.1 (1.1-4.1) | 149 | Prostate | Age | |
| Henley et al, 2005 | USA | Cohort | Men | Chewing tobacco | 0.97 (0.77-1.22) | 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
3.6 million DALYs and 101,004 deaths due to cancers associated with SLT use\(^8\). 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\(^9\). 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\(^10\).

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\(^7,8,9,92\). 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\(^7\). Sinha \textit{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 TSNA, 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

| Authors/yr (global/regional) | OR (95% CI) |
|-----------------------------|------------|
| Oral cancer                 |            |
| Siddiqi \textit{et al}, 2015\(^\#\) (global) | 3.43 (2.26-5.19) |
| Wyss \textit{et al}, 2016\(^\#\) (USA) | 3.01 (1.63-5.55) |
| Sinha \textit{et al}, 2016\(^\#\) (India) | 5.67 (3.83-8.40) |
| Guptad and Johnson, 2014\(^\#\) (South Asia and Pacific) | 7.46 (5.86-9.50) |
| Khan \textit{et al}, 2014\(^\#\) (South Asia) | 4.7 (3.1-7.1) |
| Pharyngeal cancer            |            |
| Siddiqi \textit{et al}, 2015\(^\#\) (global) | 2.23 (1.55-3.20) |
| Wyss \textit{et al}, 2016\(^\#\) (USA) | 1.22 (0.65-2.27) |
| Sinha \textit{et al}, 2016\(^\#\) (India) | 3.07 (1.94-4.86) |
| Oesophageal cancer           |            |
| Siddiqi \textit{et al}, 2015\(^\#\) (global) | 2.17 (1.70-2.78) |
| Sinha \textit{et al}, 2016\(^\#\) (India) | 3.15 (2.50-3.97) |
| Stomach cancer               |            |
| Sinha \textit{et al}, 2016\(^\#\) (India) | 1.31 (0.92-1.87) |
| Laryngeal cancer             |            |
| Sinha \textit{et al.}, 2016\(^\#\) (India) | 1.79 (0.70-4.54) |
| Lung cancer                  |            |
| Sinha \textit{et al}, 2016\(^\#\) (India) | 0.93 (0.71-1.22) |
| Cervical cancer              |            |
| Sinha \textit{et al}, 2016\(^\#\) (India) | 2.07 (1.64-2.61) |

OR, odds ratio; CI, confidence interval
as carcinogens), lime and other such products\textsuperscript{96}. Some products are sucked, gurgled/sipped or used as a dentrifice (Table V)\textsuperscript{99}. 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\textsuperscript{99}. Various authors have also detected TSNAs in the saliva of tobacco chewers\textsuperscript{100,101}. In addition, mutagenic effects of extracts of SLT products have also been demonstrated\textsuperscript{102}. Formation of micronucleus as a genotoxic effect has been reported in exfoliated buccal epithelial cells from tobacco chewers\textsuperscript{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)\textsuperscript{14,32} compared to male users in the same study (OR ranging from 2.7 to 9.33)\textsuperscript{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)\textsuperscript{97}. 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\textsuperscript{6,7}. Unlike oral cancer where tobacco is the most important aetologic agent, pharyngeal cancer, especially oropharyngeal, is causatively linked to human papillomavirus (HPV)\textsuperscript{104}. Synergistic effect of smoking and HPV16 positivity on the causation of head and neck cancer have been demonstrated\textsuperscript{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\textsuperscript{6}. Similar positive association was reported in a meta-analysis of Indian studies\textsuperscript{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)\textsuperscript{7}. The association of pancreatic cancer with SLT use has been demonstrated in Scandinavian reports though studies from America have not supported this association\textsuperscript{12,13}. The Scandinavian studies have shown this increased risk in SLT users after adjustment for smoking and alcohol use\textsuperscript{13} or in never-smoking stratum\textsuperscript{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\textsuperscript{105,106}. TSNAs have also been documented in human pancreatic juice at higher concentration in smokers compared to non-smokers\textsuperscript{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\textsuperscript{99}. 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
| Name of product       | Region/country                        | Method of use | Form of tobacco | Additives                                                                 | pH         | 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 | 83.9-560/11.6-208/45.4-9/137/0.2-53.5          |
| 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 | 4874-90024/382-9950/2204-4255/421-1412         |
| 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 | 478-1380/29.4-309/363-5/458.6-104            |
| Shammah               | EMR: Saudi Arabia, Yemen; AFR: Algeria | Oral - sucked | Sun-dried pulverized tobacco | Slaked lime, ash, black pepper, oil, flavourings, bombossa (sodium carbonate) | Data NA | Data NA                                      |

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

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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For correspondence: Dr Sanjay Gupta, Division of Cytopathology, ICMR-National Institute of Cancer Prevention & Research, I-7, Sector-39, Noida 201 301, Uttar Pradesh, India e-mail: sanjaydr17@hotmail.com