INTRODUCTION

Oral cancer, often fatal disease, is the eighth most common cancer in the world. However, the incidence is even higher in some parts of the world, especially South-East Asia including Pakistan, India, Sri Lanka where the disease accounts for up to 40% of all malignancies.1 A number of risk factors have been recognized over the past decade including tobacco, alcohol and betel quid and more recently Human Papilloma virus.2,3 Although, the reasons behind the higher incidence of oral cancer in the South Asian countries have been researched, there is paucity in the data, particularly in terms of well-designed epidemiological studies.4 Smokeless tobacco (SLT) is associated with many heath hazards including oral cancer. Its use is more common in South Asian countries. The current paper aims to systematically review the South Asian studies to assess the association of SLT and oral cancer. Detailed automated literature searches of PubMed, Medline, EMBASE and ISI Web of Science from January 1980 to July 2015 were conducted using the key words “oral cancer”, “oral precancer”, “oral premalignant lesions”, “oral squamous cell carcinoma”, “smokeless tobacco”, “betel quid”, “areca nut”, “Gutkha” in various combinations. Letters to the editor, review articles, and case-reports were excluded. A total of 21 studies were included. Three studies were of cohort design while the remaining were of case-control design. Nine studies reported betel quid as a risk factor for oral cancer, while fifteen studies reported data on other types of chewing tobacco. The odds ratio (OR) for betel quid and risk of oral cancer varied from 3.1 to 15.7 (11.0-22.1); and for chewable tobacco and risk of oral cancer varied from 1.2 (1.0-1.4) to 12.9 (7.5-22.3). A strong association between different types of SLT and oral cancer was observed. Well-structured programmes should be employed in South Asian region, both in terms of educating the general public about the health hazards of SLT as well as providing cessation assistance.

reported exposure to SLT and oral cancer as an outcome were included.

Case reports, experimental studies, review articles, letters to the editor, unpublished data, and articles not published in English were excluded. Studies that reported oral potentially malignant lesions as an outcome, evaluated physiological outcomes of SLT, and reported oesophageal, base of the tongue, and salivary glands cancers were also excluded.

Two reviewers (KHA, SP), using a standardized guide, initially screened titles and abstracts of studies. Full texts of studies found relevant were retrieved and independently reviewed using a standardized and pilot-tested form. The studies were only included in the review after agreement of both the authors (Kappa score = 0.85).

For the ease of analysis, all the selected studies were systematically arranged in tables. The abstracted data included year of publication, study type, sample characteristics (age, gender, location), exposure outcome and adjustment for cigarette smoking and other confounding factors. On the basis of SLT, data were divided into two broad groups: 1) Betel quid with tobacco; 2) All other types of chewable tobacco. Adjusted odds ratios (aOR) along with their 95% confidence intervals (95% CI) were recorded. However, in cases of aOR not reported in the study, crude OR was recorded. Studies that reported odds ratio (OR) for males and females, and frequency and duration of SLT use were also recorded.

RESULTS
A total of 21 studies16-36 that met our eligibility criteria were included in the review (Figure 1). Three studies32-34 were of cohort design while the remaining were of case-control design.16-31,35,36 Nineteen of the studies16-21,23,24,26-36 were conducted in India and two in Pakistan.22,25 Majority of the studies (n = 13) were published in or after the year 2000.24-36 Table I summarises the characteristics of the studies included.

Nine studies reported betel quid as a risk factor for oral cancer, while 15 studies reported data on other types of chewing tobacco. Fourteen studies reported data in relation to gender difference, 13 on daily frequencies of SLT use, while 10 studies reported the data on the total duration of SLT.

Betel quid with tobacco and oral cancer: Nine studies reported OR for the risk of betel quid and oral cancer (Table II).16-18,26,31 The aOR of betel quid as a risk factor for oral cancer ranged from 3.1 to 14.1 (7.4 - 26.5), while the overall OR (adjusted and unadjusted) ranged from 3.1 to 15.7 (11.0 - 22.1).

Gender disparities: A total of 6 studies reported OR of betel quid in regard to gender differences (Table II).16-18,26,31,36 For males, the OR of betel quid as a risk factor for oral cancer varied from 1.5 to 10.9 (0.75 - 3.02), while for females OR varied from 6.5 to 45.8 (25 - 84.1).

Frequency and duration of use: Five studies16-18,26,31 reported the associated risk of frequency of betel quid use and oral cancer (Table II). The reported OR of betel quid use between chewers and non-chewers ranged from 3.3 (1.6 - 6.9) for 5 times a day chewers, to 24.7 (12.5 - 48.7) for those chewing more than 10 times a day. However, when adjusted for cigarette smoking and other confounding factors, the OR ranged from 3.3 to 15.7 (1.6 - 6.9).

Four studies reported the risk in relation to duration of betel quid use and the OR ranged from 3.4 for those chewing betel quid for 10 years to 14.6 for chewing 20 years or more (Table II).16-18,31 When adjusted for cigarette smoking and other confounding factors, the OR ranged from 3.4 to 14.6.

Chewable tobacco and oral cancer: A total of 15 studies reported other types of SLT (mainly Gutkha) and their associated risks with oral cancer (Table III).19,24-27,30,32-36 The OR reported varied from 1.2 (1.0 - 1.4) to 12.9 (7.5 - 22.3). Five studies also reported OR that was adjusted for cigarette smoking and other confounding factors and varied from 3.6 (3.5 - 5.6) to 8.3 (5.4 - 13).

Gender disparities: Eight studies reported data for the associated risk of chewable tobacco use and oral cancer among males and females (Table III).20,21,24,27,32,33,34,36 For males, the OR ranged from 1.2 (1.0 - 1.4) to 5.8 (3.6 - 9.5), whereas the OR for females ranged from 6.4 (3.3 - 9.0) to 25.3 (11.2 - 57.3).

Frequency and duration of use: Eight studies reported exposure-response relationship in terms of frequency and duration of use (Table III).19,20,23,24,27,32,33,34 The reported OR of chewable tobacco use between chewers and non-chewers ranged from 1.1 (1.0 - 1.4) for 5 times a day chewers, to 20.0 (8.1 - 48.9) for those chewing more than 10 times a day. Only one study reported the OR adjusted for cigarette smoking and other confounding factors and ranged from 2.0 (1.0 - 3.8) to 13.9 (7.1 - 27.2).

Six studies evaluated the outcome of oral cancer in relation to the total duration of chewable tobacco use (Table III).19,21,23,27,28,34 The OR reported ranged from 0.8 (0.4 - 1.7) for a habit less than 10 years to 10.9 (5.9 - 20.0) for one lasting 20 years or more.

DISCUSSION
This data shows a strong relationship between various types of SLT and oral cancer. It further reinforces the IARC’s inclusion of SLT into the list of risk factors associated with oral cancer.11,37 The authors found a
# Smokeless tobacco and oral cancer

**Table I: Characteristics of included studies.**

<table>
<thead>
<tr>
<th>Author, et al. (year)</th>
<th>Cancer type</th>
<th>Study design</th>
<th>Sample population</th>
<th>Exposure type</th>
<th>Adjustment for smoking and other confounding factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Santhanam et al. (1989)</td>
<td>Tongue and floor of mouth</td>
<td>Study Type: Case-control; Setting: Kerala, South India; Period: 1993-1994</td>
<td>Cases: 228 cases; Controls: 453 hospital-based controls; age, sex and religion matched; Gender included: Males and females</td>
<td>Smoking, smokeless tobacco and alcohol</td>
<td>Smoking and alcohol</td>
</tr>
<tr>
<td>Santhanam et al. (1989)</td>
<td>Buccal and labial mucosa</td>
<td>Study Type: Case-control; Setting: Kerala, South India; Period: 1983-1994</td>
<td>Cases: 187 cases; Controls: 895 hospital-based controls; Gender included: Males and females</td>
<td>Smoking, smokeless tobacco and alcohol</td>
<td>Smoking and alcohol</td>
</tr>
<tr>
<td>Santhanam et al. (1990)</td>
<td>Gingiva</td>
<td>Study Type: Case-control; Setting: Regional Cancer Centre, Trivandrum, Kerala, A local teaching hospital, India; Period: 1983-1994</td>
<td>Cases: 414 cases; Controls: 895 hospital-based controls having non-malignant conditions; Gender included: Males and females</td>
<td>Smoking, smokeless tobacco and alcohol</td>
<td>Smoking and alcohol</td>
</tr>
<tr>
<td>Goud et al. (1990)</td>
<td>Buccal cavity cancer</td>
<td>Study Type: Case-control; Setting: Sir Sunderlal Hospital, Banaras Hindu University, Varanasi, India; Period: Not reported</td>
<td>Cases: 102 cases; Controls: 102 hospital-based controls having non-malignant conditions; Gender included: Males and females; Follow-up period: 1 year</td>
<td>Different forms of smokeless tobacco</td>
<td>Not adjusted</td>
</tr>
<tr>
<td>Naik et al. (1990)</td>
<td>Oral cancer excluding base tongue</td>
<td>Study Type: Case-control; Setting: Cancer registry, Bangalore, India; Period: 1982-1994</td>
<td>Cases: 348 cases; Controls: 348 age-sex matched controls with no evidence of cancer; Gender included: Males and females; Mean age of cases: 54.8 years</td>
<td>Diet, smoking and chewing tobacco</td>
<td>Not adjusted</td>
</tr>
<tr>
<td>Rao et al. (1990)</td>
<td>Oral cancer</td>
<td>Study Type: Case-control; Setting: Tata Memorial Hospital, Mumbai, India; Period: 1980-1984</td>
<td>Cases: 713 cases; Controls: 835 hospital-based controls free from cancers, benign tumors and infectious diseases; Gender included: Males only; Mean age of cases: 50.35 years</td>
<td>Smoking, smokeless tobacco and alcohol</td>
<td>Smoking and alcohol</td>
</tr>
<tr>
<td>Khan et al. (1990)</td>
<td>Oral cancer</td>
<td>Study Type: Case-control; Setting: Karachi, Pakistan; Period: Not reported</td>
<td>Cases: 24 cases; Controls: 24 hospital-based controls; Gender included: Males and females; Mean age of cases: 54 years</td>
<td>Lifestyle risk factors</td>
<td>Not adjusted</td>
</tr>
<tr>
<td>Muralidhar et al. (1998)</td>
<td>Oropharyngeal cancer</td>
<td>Study Type: Case-control; Setting: Three tertiary care centers (Government Medical College Hospital, Government Dental College, Raktash Sand Tulsi) Cancer Hospital) in Nagpur city, India; Period: Not reported</td>
<td>Cases: 123 cases of Oropharyngeal cancer; Controls: 246 age-sex matched controls (two for each case: one from non-cancer patients and another from patients having cancer of other sites); Gender included: Males and females</td>
<td>Smoking, chewing and occupational exposures</td>
<td>Not adjusted</td>
</tr>
<tr>
<td>Dikshit &amp; Khare (2000)</td>
<td>Oral, oropharyngeal and lung cancers</td>
<td>Study Type: Case-control; Setting: Bhopal, India; Period: 1990-1992</td>
<td>Cases: 558 cases (146 oral cavity, 247 oropharyngeal and 165 lung cancers); Controls: 260 population-based controls; Gender included: Males only; Mean age of cases: 50.35 years</td>
<td>Smoking and smokeless tobacco</td>
<td>Smoking</td>
</tr>
<tr>
<td>Merchant et al. (2000)</td>
<td>Oral cancer</td>
<td>Study Type: Case-control; Setting: Three tertiary teaching centers in Karachi, Pakistan; Period: July 1993-March 1998</td>
<td>Cases: 79 diagnosed cases of oral cancer; Controls: 149 controls matched for age, gender, hospital and time of occurrence; no history of cancer; Gender included: Males and females; Mean age of cases: 49 years</td>
<td>Behel quit and without tobacco</td>
<td>Smoking and alcohol</td>
</tr>
<tr>
<td>Balaram et al. (2002)</td>
<td>Oral cancer</td>
<td>Study Type: Case-control; Setting: Three areas (Bangalore, Mysore and Trivandrum) in Southern India; Period: 1996-1999</td>
<td>Cases: 591 incidental cases of oral cancer; Controls: 582 hospital-based controls; age-sex matched; Gender included: Males and females</td>
<td>Smoking, smokeless tobacco, alcohol and occupational exposures</td>
<td>Not adjusted</td>
</tr>
<tr>
<td>Zinner et al. (2003)</td>
<td>Oral, pharyngeal and esophageal cancers</td>
<td>Study Type: Case-control; Setting: Tata Memorial Hospital; Period: 1993-1994</td>
<td>Cases: 2765 cases (1563 oral, 636 pharyngeal, 556 esophageal cancers); Controls: 3638 hospital-based controls; Gender included: Males only; Mean age of cases: 50.85 years</td>
<td>Smoking, chewable tobacco and alcohol</td>
<td>Smoking and alcohol</td>
</tr>
<tr>
<td>Subramanya et al. (2007)</td>
<td>Oral cancer</td>
<td>Study Type: Case-control; Setting: Rajiv Gandhi Dental College and Hospital, Annamalai University, Chidambaram, Tamil Nadu, India; Period: 1993-2003</td>
<td>Cases: 368 cases; Controls: 385 age-sex matched controls; Gender included: Males and females; Mean age of cases: 50.35 years</td>
<td>Lifestyle risk factors</td>
<td>Not adjusted</td>
</tr>
<tr>
<td>Gampala et al. (2007)</td>
<td>Oral cancer</td>
<td>Study Type: Case-control; Setting: Mahatma Gandhi Institute of Medical Sciences, Sawai Madhopur, Central India; Period: 2001-2002</td>
<td>Cases: 140 historically diagnosed cases of oral cancer; Controls: 360 hospital-based controls; age-sex matched; Gender included: Males and females; Mean age of cases: 50.85 years</td>
<td>Smoking, smokeless tobacco, diet and alcohol use</td>
<td>Not adjusted</td>
</tr>
<tr>
<td>Bhatia et al. (2008)</td>
<td>Head and neck cancer</td>
<td>Study Type: Case-control; Setting: Kolkata, India; Period: 1998-2006</td>
<td>Cases: 110 diagnosed cases of head and neck squamous cell carcinoma; Controls: 110 hospital-based controls; age-sex matched; Gender included: Males and females; Mean age of cases: 50.85 years</td>
<td>Smoking and smokeless tobacco</td>
<td>Not adjusted</td>
</tr>
<tr>
<td>Musonge et al. (2008)</td>
<td>Oral cancer</td>
<td>Study Type: Case-control; Setting: Trivandrum, India; Period: 1996-2004</td>
<td>Cases: 282 incident oral cancer cases; Controls: 1410 matched controls; Gender included: Males and females</td>
<td>Smoking, smokeless tobacco and alcohol</td>
<td>Smoking and alcohol</td>
</tr>
<tr>
<td>Jayadevshetti et al. (2009)</td>
<td>Oral cancer</td>
<td>Study Type: Cohort study; Setting: Karnataka, India; Period: 1990-1997</td>
<td>Sample: Cohort of 71140; 92 cases of oral cancer; Gender included: Females only; Age: 30-94 years; Follow-up period: 8 years</td>
<td>Chewable tobacco</td>
<td>Not adjusted</td>
</tr>
<tr>
<td>Jayadevshetti et al. (2011)</td>
<td>Oral cancer</td>
<td>Study Type: Cohort study; Setting: Karnataka, India; Period: 1990-1997</td>
<td>Sample: Cohort of 66277; 160 cases of oral cancer; Gender included: Males and females; Age: 30-94 years; Follow-up period: 8 years</td>
<td>Bidi smoking and chewable tobacco</td>
<td>Not adjusted</td>
</tr>
<tr>
<td>Padmakar et al. (2011)</td>
<td>Multiple cancer</td>
<td>Study Type: Cohort study; Setting: Mumbai, India; Period: 1991-1997</td>
<td>Sample: Cohort of 87222; 1267 cases of oral cancer; Gender included: Males and females; Mean age of cases: 54.8 years; Follow-up period: 849,226 person years</td>
<td>Smokeless tobacco</td>
<td>Not adjusted</td>
</tr>
<tr>
<td>Matani et al. (2012)</td>
<td>Oral cancer</td>
<td>Study Type: Case-control; Setting: Pune, India; Period: February 2005-September 2006</td>
<td>Cases: 350 cases; Controls: 350 hospital-based controls; Gender included: Males and females</td>
<td>Smoking, smokeless tobacco and alcohol</td>
<td>Not adjusted</td>
</tr>
<tr>
<td>Ray et al. (2013)</td>
<td>Oral cancer</td>
<td>Study Type: Case-control; Setting: Dr. H. Ahmed Dental College, Kolkata, India; Period: 2010-2011</td>
<td>Cases: 698 cases having either oral potentially malignant or malignant lesion; Controls: 949 hospital-based controls reported for different oral/dental problems: habit of tobacco, areca nut and/or alcohol usage for at least 1 year; Gender included: Males &amp; females</td>
<td>Smoking, smokeless tobacco and alcohol</td>
<td>Not adjusted</td>
</tr>
</tbody>
</table>

**Journal of the College of Physicians and Surgeons Pakistan 2016, Vol. 26 (9): 775-780**
seven-fold higher risk of oral cancers among betel quid chewers compared to non-chewers [OR 7.1, 95% CI (4.5 - 11.1)]. A similar higher risk [OR 4.7, 95% CI (3.1 - 7.1)] of developing oral cancer was noticed among those chewing other types of SLT. Even after adjusting the cigarette smoking and other confounding factors, the associated risk was still significant. These findings are in line with those from previous reviews.\(^{11,15,36}\)

The data showed a higher risk of betel quid with tobacco compared to other chewable tobacco products. This could be explained by the presence of other carcinogenic agents in betel quid such as areca nut and slaked lime, thereby having a synergistic effect with the already present tobacco in betel quid.\(^{38}\) Areca nut is a well-established carcinogen and has been associated with submucous fibrosis, a potentially malignant disorder. In addition, slaked lime aids in the production of reactive oxygen species (ROS) and hydrolysis of arecoline into arecaidine, resulting in increased collagen and fibroblast production, thus facilitating the malignant transformation of tissues.\(^{39}\)

A significantly higher risk of oral cancer in relation to SLT
was found among females than their male counterparts. This higher risk among females may be due to the nature of their oral mucosa, which is more susceptible to damage on tobacco exposure,26 and/or lack of awareness and knowledge towards tobacco use.5 In addition, a higher incidence of cervical cancer in India attributed to human papilloma virus, a risk factor for oral cancer, may also be the reason behind this higher risk among females.40,41 However, there was an inconsistency in the effect estimates of SLT as a risk factor for oral cancer among females in all the included studies, that may have resulted in an overestimation of the risk status among females. Regardless of the degree of effectiveness, all included studies confirmed SLT as a major risk factor among females. These findings necessitate future research that should be focused particularly towards effect of SLT among gender disparities.

A casual association was observed between SLT and oral cancer in terms of exposure response relationship. These findings are consistent with the IARC reports. However, some other reviews conducted on studies from North America and Europe have conflicting results.42-44 This may be attributed to the differences in the SLT types, ethnic and socioeconomic status, and environmental factors between South Asian population and North American/European population. There was a higher risk of developing oral cancer with longer duration of SLT exposure. A parallel can be drawn here with the use of other tobacco products, where longer duration of exposure has also been linked with higher risk of oral cancer.45

CONCLUSION

Within the limits of the present review, a strong association between different types of SLT and oral cancer was observed. Well-structured programmes should be employed in South Asian region, both in terms of educating the general public about the health hazards of SLT as well as providing cessation assistance.

REFERENCES


34. Pednekar MS, Gupta PC, Yeole BB, Hibert JR. Association of tobacco habits, including bidi smoking, with overall and site-specific cancer incidence: Results from the Mumbai cohort study. Cancer Causes Control 2011; 22:859-68.


