Review Article

Association between Smokeless Tobacco and risk of malignant and premalignant conditions of oral cavity: A systematic review of Indian literature

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Abstract

Causative linkages of tobacco use with oral potentially malignant disorders and cancers of oral cavity have been studied. Oral squamous cell carcinoma is one of the most common cancers in India. The International Agency for Research on Cancer (IARC) monograph found a significant association between smokeless tobacco (SLT) use and oral cancer. However, only a few limited studies have been represented on the IARC monograph. Published meta-analyses have provided pooled risk estimates for oral cancers caused by tobacco, both on global and regional levels. This systematic review was aimed at summarizing all the available studies exclusively in India by collecting data from PubMed and Medline. Emphasis was laid on cohort and case–control studies, and a few cross-sectional studies for premalignant lesions were also discussed. A significant association was noticed on SLT and premalignant and malignant oral cavity lesions.

Keywords: Case–control, cohort, oral cancer, oral premalignant lesion, smokeless tobacco

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INTRODUCTION

Epidemiological studies in India have shown that up to 80% of oral cancer patients are tobacco users.[1]

They are consumed either has smoking forms: beedi, cigarette, cigar, dhumti, gudakhu, hookah and hookli[2] and chewable forms or smokeless tobacco (SLT): paan, khaini, snuff, zarda, mawa, etc.[2]

SLT is a major public health problem in the Indian subcontinent, and India is considered the global capital of SLT use.[3]

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Unlike other countries where cigarettes and waterpipe smoking are the major form of tobacco used, in India, only less than one-fifth (19%) of tobacco consumed is in the form of cigarettes.[4]

As per the Global Adult Tobacco Survey (2010), more than one-third (35%) of adults in India are tobacco users. Of them, 21% are addicted only to SLT products whereas 9% are addicted to smoking alone. The rest 5% are addicted to both forms, i.e., smoking as well as SLT.[3,5]

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As per the World Health Organization report, the most significant risk factor for cancer is tobacco use, which alone is responsible for 22% of cancer deaths worldwide.[6] According to the International Agency for Research on Cancer (IARC) monograph of 2007 on SLT, among the different subsites of the head-and-neck region, tobacco chewing is associated with only cancer of the oral cavity.[7] The majority of the studies were from Europe and North American countries. Countable studies from India were discussed in the monograph due to limited data from the Indian subcontinent.[7,8]

Research studies conducted over the years have shown linkage of SLT use with oral potentially malignant disorders (PMDs) and cancers of oral cavity.

According to the population-based cancer registry published by the Indian Council of Medical Research, in India, oral cavity and pharynx cancers account for about 12%–32% of all cancers in males and about 3.5%–10% of all cancers in females.[8,9]

Oral cancer is by far the most common cancer in India; laryngeal cancers are common in the Western world and nasopharyngeal cancers in the Chinese and southeast population.[9] The difference of incidence and site-wise distribution of head-and-neck cancer between India and most parts of the world is believed to be due to the difference in tobacco consumption pattern, i.e., smoking and SLT use. According to a recently published study from India, the mortality rate in tobacco chewers has increased by five times due to oral cancer in comparison to the nonchewers.[8]

SLT products are known to contain more than thirty carcinogens.[10] The basic ingredients of SLT include sun-cured unprocessed or processed tobacco of *Nicotiana tabacum* and *Nicotiana rustica* species. Tobacco-specific N-nitrosamines (TSNAs) – N-nitrosonornicotine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and N-nitrosamino acids – are quantitatively the most prevalent strong carcinogens in SLT along with[11] heavy metals such as nickel, cadmium, chromium and copper.[10,11] They are formed by nitrosation of tobacco alkaloids. Hence, nitrate and nitrite levels in SLT determine the extent of carcinogenicity, toxicity and health risk associated with the product as their levels vary widely among the SLT products. This hinders the comparability of results of various studies evaluating the health effects of SLT use.[10,12]

The carcinogens cause the 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 tumor promotion.[13] 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. SLT-related carcinogenesis can also be caused by epigenetic mechanism, like promoter methylation of tumor suppressor genes leading to unregulated proliferation.[14]

The review aims to discuss the harmful effects of SLT leading to premalignant lesions and oral cancer throwing an insight on the premalignant lesions. The review includes a short briefing on SLT products along with analysis of various study results carried on the Indian population on establishing correlation between usage and malignant, premalignant lesions and oral cancers.

We have reviewed all articles, which have investigated for association of oral cancer and premalignant lesions with usages of chewable form of tobacco with or without areca nut.

METHODOLGY

A systematic literature search was conducted in PubMed and Google Scholar databases for articles using combination of keywords smoking, tobacco chewing and oral cancer, premalignant lesion, leukoplakia, erythroplakia, oral submucous fibrosis and oral squamous cell carcinoma from 1980 to 2020. The primary focus was on cohort and case–control studies published exclusively in India. To rule out any bias, we have reviewed all articles, which have searched for association of oral cancer and premalignant lesions with usages of chewable form of tobacco with or without areca nut. In tables, as applicable, the form of tobacco usage has been mentioned.

RESULTS AND DISCUSSION

Oral cancer is one of the most common forms of cancer in India. Most oral cancers are preceded by premalignant lesion such as leukoplakia, erythroplakia, oral submucous fibrosis (OSMF) and verrucous carcinoma which when neglected lead to Oral Squamous cell carcinoma. Microscopically, they are detected as oral epithelial dysplasia whose malignant transformation rate is as high as 36%.[15] It is well known that oral cancer is preceded by visible oral precursors. The most commonly seen

PMDs are leukoplakia, erythroplakia, oral submucous fibrosis (OSMF), palatal lesions in reverse smokers and oral lichen planus. The prevalence of OSMF ranged from 0.4% to 1.2%,[16] and the malignant transformation rate varies from 7.6% to 40%.[17] The prevalence of leukoplakia varied from 0.2% to 4.9%.[18] The malignant transformation of leukoplakia ranges from 3.6% to 17.5%.[19] Erythroplakia is rare and has an incidence of 0.02%–0.83%.[20] Villa *et al.* reported the global mean prevalence of oral erythroplakia to be 0.11%[21] and malignant transformation rate of 14.3%–66.7%.[15] Oral premalignant lesions (OPMLs) are relatively common, occurring in about 2.5% of the general population and are an important target for cancer prevention.[22] Tobacco is the major risk factor in oral cancer. In India, chewing tobacco in a mixture form along with areca nut and other ingredients such as[4] betel leaf, slaked lime and catechu is a very common practice. Areca nut is derived from a oriental palm Areca catechu. Arecoline, the major alkaloid in areca nut, has been found to stimulate collagen synthesis in fibroblasts;[11] the presence of copper upregulates lysyl oxidase, leading to excessive cross-linking and accumulation of collagen in patients with oral submucous fibrosis (OSF). Slaked lime is composed of calcium hydroxide that boosts the pH of a product and results in increased availability of free nicotine, the form that is most easily absorbed in oral mucosa.[11] Catechu contains tannins which serve as flavoring agents.[11] The use of unprocessed tobacco, the cheapest form, varies in different parts of India. It is sold in different forms and with different names. The various forms are chewed, sucked or used as dentifrice.[23] Commonly used SLT products with local names and their ingredients used across the country are enlisted in Table 1.[24]

In an evaluation of epidemiological studies on the carcinogenic risk to humans of tobacco habits other than smoking, the IARC Working Group concluded that there was sufficient evidence that the habits of chewing betel quid containing tobacco and tobacco mixed with lime were carcinogenic to humans.[25] We hereby report various studies in the country revealing strong association between oral cancer, premalignant lesions and chewing tobacco from 1980 to 2019.

Limited cohort studies are available in India, and Karunagappally cohort is the first study established in 1990 at a rural coastal area in Kollam district of Kerala covering 93% of population. The baseline data were collected between 1990 and 1997. The study analyzed cancer incidence in the period of 1990–2005.[26] A total of 79,593 eligible women aged 30–84 years were taken as a subject, and 102 female cases of oral cancer were identified by the end of 2005.[26] After excluding women without habit history, a total of 92 oral cancer cases were diagnosed. The study found tobacco chewing as a significant risk factor for oral cancer among females strongly related to

Table 1: Local smokeless tobacco products with ingredients used across the country

Common/native name	Ingredients	State
Paan/betel quid with tobacco (C/S)	Betel leaf, areca nut, calcium hydroxide, catechu: Flavoring agents include menthol sugar, rosewater, aniseed, cardamom, clove spices, etc.	All Indian states
Khaini (C/S)	Sun-dried or fermented coarsely cut tobacco leaves mixed with slaked lime	North and North-East states of India
Tambakoo (C/S)	Finely or coarsely shredded tobacco leaves	Used all over India
Guthka (C/S)	Areca nut, slaked lime, catechu and sun-dried, roasted, chopped tobacco with flavors	Predominantly in North India
Zarda/vizapatta (C/S)	Flavored chewing tobacco flakes mixed with saffron, silver flakes and lime	Predominantly in North India
Loose leaf/chadha/(C/S)	Air cured loose tobacco leaf used for chewing as well as for smoking	All Indian States
Mainpuri/kapoori (C/S)	Mixture of finely cut betel nut and small pieces of tobacco leaves in slaked lime and various flavoring agents	Manipuri district of U.P
Kharra (C/S)	Mixture of tobacco, areca nut, lime, catechu with additional ingredients	Maharashtra
Kiwam (C/S)	Thick paste of tobacco leaf extract, spices (e.g., saffron, cardamom, aniseed) and additives such as musk	India
Mawa (C/S)	It is a mixture of thin shavings of areca nut with some tobacco flakes and slaked lime	Gujarat and adjoining areas in Maharashtra
Dhora (C/S)	Wet mixture of tobacco, slaked lime, areca nut and ingredients like catechu and flavors	Allahabad, Jaunpur and Pratapgarh districts of U.P
Creamy snuff (C/S)	Finely grounded tobacco mixed with clove oil, flavoring agents, salts, water packed as paste	Used all over India
Tuibur/hidakphu (SIPPING)	It is tobacco smoke-infused water. Stored and sold in bottles	North East: Mizoram and Manipur
Gudakhu/gul (D)	Tobacco paste made using fine tobacco leaf dust, sheera (molasses), lime and gerumati (red soil)	Bihar, Chhattisgarh, Orissa, West Bengal, U.P and Uttaranchal, North-East India
Lal Dant Manjan/red tooth powder (D)	Fine red tobacco powder and herbs. Additionally ginger, pepper and camphor may be used	North India, Goa, Maharashtra, Manipur and Sikkim
Tapkeer/dry snuff/bajar (D)	Dry powdered tobacco available as unscented and scented varieties	Gujarat, Maharashtra, Goa and Eastern part of India
Mishri (D)	It is roasted and powdered tobacco	Gujarat and adjoining areas in Maharashtra

C/S: Chewed and sucked, D: Dentifrice, U.P: Uttar Pradesh

daily frequency of tobacco chewing was increased 9.2-fold among women chewing tobacco ten times or more a day though age did not pose any risk [Table 2].

A similar analysis was performed on males. The risk of having cancer of mouth and gum was very high (relative risk [RR]: 4.7) among the current tobacco chewers, whereas the risk of having tongue cancer was only slightly higher (RR: 1.1). Alcohol was not found to be a significant risk factor for oral cancer, whereas bidi smoking was a significant risk factor only for those who did not chew tobacco [Table 3].[27]

As per study conducted by Pednekar *et al*. in Mumbai, the incidence of oral cancer in bidi smokers (hazard ratio [HR] =3.55; 95% confidence interval [CI]: 2.40–5.24) was 42% higher than in cigarette smokers (HR = 2.50; 95% CI: 1.65–3.78). SLT use was associated with cancers of the lip and oral cavity[28] [Table 2].

All the case control studies available in India reveal a strong association between tobacco chewing and oral cancer. And majority of them confirm that risk involved in tobacco chewing is higher than smoking. Majority of these studies confirmed that the risks involved in tobacco chewing were higher than the risks associated with smoking. A study done by Subapriya *et al*. in Tamil Nadu indicated that the chewing of betel nut and tobacco, chewing of tobacco alone, bidi smoking and alcohol consumption (OR = 1.65) were all significant risk factors for oral cancer. People addicted to all three habits had a very high RR for oral cancer (OR = 11.34).[29] Majority studies on tobacco chewing has been done in South India .One such study done by Muwonge *et al*. in Kerala. Showed he OR of chewing tobacco was much higher than bidi smoking (3.3 vs. 1.9). A significantly increased risk was observed among all categories of tobacco chewers, i.e., ever chewer, past chewer or present chewer. The adjusted OR of chewing tobacco was much higher than bidi smoking (3.3 vs. 1.9). A significantly increased risk was observed among all categories of tobacco chewers, i.e., ever chewer, past chewer or present chewer.[30] A similar type of result was also depicted by other studies. Tobacco chewers had about 5-fold increased risk of oral cancer and smokers 2-fold risk. According to this study, the joint effect of smoking, chewing and drinking alcohol was greater than additive but less than multiplicative [Table 3].

However, alcohol and tobacco chewing showed multiplicative interaction, inducing a 24-fold increased risk of oral cancer.[31] A study by Nandakumar *et al*. in Bangalore reported that RR associated with smoking (OR = 1.9) was much lower than RR associated with tobacco chewing (OR = 14.6).[32] A study by Dikshit *et al*. found about 6-fold increase in the risk of oral cavity cancer among tobacco quid chewers. Population attributable risk percent was found to be 66.1% for tobacco chewers for the development of oral cancer.[33]

Another case control study done by Balram *et al*. also stated that Relative Risk of oral cancer among men caused by chewing tobacco was higher than smoking bidis.(RR being 2.5).[34] As per studies reported from Tata Memorial Hospital (TMH), Mumbai, one of these studies from TMH found tobacco chewing to be a significant risk factor for oral cancer among males (OR = 2.95, 95% CI: 2.34–3.71). This study also found bidi smoking and alcohol consumption as a significant risk factor for oral cancer among males.[35] Another study from TMH by Rao and Desai showed that the type of tobacco had a direct relationship with the site of cancer. According to this study, tobacco chewing was a significant risk factor for anterior tongue cancer, whereas bidi smoking was a significant risk factor for a base of tongue cancer.[36] A study by Gangane *et al*. in Wardha[37,26] and Madani *et al*. from Pune[4] found the habit of tobacco chewing to be significantly associated with oral cancer.

Thomas *et al*. in Kerala conducted Case control study considering risk associated with tobacco chewing in multiple OPMLs like leukoplakia, erythroplakia and OSMF. The cases were patients having at least two or all the three major OPMLs, i.e., leukoplakia, erythroplakia and OSMF. The adjusted OR for continuous tobacco chewers was very high (OR = 37.8, 95% CI: 16.2–88.1).

Table 2: Cohort studies in India

Reference/location	Gender	Sample size	Tobacco type	RR (95% CI)	Confounder adjustment
Jayalekshmi *et al*., 2009[26]/ Karunagappally cohort, Kerala	Female	78,140	Chewing tobacco	5.5 (3.3-9.0) current 9.2 (4.6-18.1) former	Age, family income
Jayalekshmi *et al*., 2011[27]/ Karunagappally cohort, Kerala	Male	66,277	Chewing tobacco	2.4 (1.7-3.3) all 1.1 (0.7-1.9) tongue 4.7 (2.8-7.9) gum/mouth	Age, smoking, alcohol
Pednekar *et al*., 2011[28]/ Mumbai	Male	88,658	ST Cigarette smokers: Bidi smokers	1.48 (1.03-2.13) HR=3.55 (2.40-5.24) HR=2.50 (1.65-3.78)	Age, education, religion, BMI, smoking

RR: Relative risk, CI: Confidence interval, HR: Hazard ratio, BMI: Body mass index

Table 3: Case-control studies in India

Reference/ Location:	Gender	Sample Size	Tobacco Type:	OR (95% CI)	Confounder Adjustment:
1. Dikshit *et al*.,[33] Bhopal, 1986-1992	NA	148 cases 260 control	Tobacco quid chewing	5.8 (3.6-9.5)	Age and Smoking
2. Sankaranarayanan *et al*, 1989[44]	Male/Female	187 cases 895 controls	Paan with tobacco, nasal snuff	5.95 (2.99-11.84) males 6.62 (2.48-17.66) females 3.90 (1.19-12.70) snuff males	Age
3. Sankaranarayanan *et al*, 1990[45] Kerala	Male /Female	414 cases, 895 controls	Paan with tobacco, snuff	9.33 (5.6-15.22) males paan tobacco	Smoking, alcohol
4. Nandakumar[32] *et al*, 1990 Bangalore	Male/ Female	399 cases 561 control	Chewing + tobacco Chewing without tobacco	14.6 (8.2-25.9) 1.7 (0.9-3.5)	Not Adjusted
5. Rao *et al*., 1994 TMH35	Male	713 cases, 635 controls	Chewing tobacco	3.64 (2.51-5.67)	Age, residence, smoking, Alcohol
6.Balaram *et al*,[34] 1996-1999 South India	Male/ Female	309 males 282 females 591 controls	Paan with tobacco	6.10 (3.84-9.71) males 45.89 (25.02-84.14) females	Age, education, smoking, Alcohol
7.Shah N *et al*. 1998 AIIMS[43]	Male /Female	236(OSMF) cases, 221 control	Chewing tobacco: 2-3 times 4-5 times Always	42.9(6.22-445.65) 53.6(8.98-526.59 175.5 (26.26-1767.55)	Age
8.Hashib *et al*. 2000, kerala[40]	Males/ Females	100 cases (erthroplakia) 47,773 controls	Chewing tobacco	19.8 (9.8-40.0)	Age, sex education, BMI
9. Gangane *et al*.,[20] Maharashtra[37] 2001-2002	Male /Female	140 cases 140 control 100 with habbit.	Tobacco quid chewing	18 (5.88-61.65)	Not Adjusted
10. Hashib *et al*. 2002[41]	Males/ Females	170(OSMF) cases 47,773 controls	Chewing tobacco	44.1 (22.0-88.2)	Not Adjusted
11. Znaor *et al*, [31] 2003	NA	1563 cases, 3638 controls	Chewing tobacco	5.05 (4.26-5.97)	Age, education, smoking, Alcohol
12.Thomas G *et al*. 2003[38]	Males/ Female	115 cases (PML) 47,773 control	Chewing tobacco (P<0.0001)	37.8 (16.2-88.1)	Age, sex education, BMI, smoking, drinking and fruit/vegetable intake.
13. Anantharaman[4]6 *et al*, 2007	Male /Female	283 cases, 366 controls	Chewing tobacco	0.49 (0.32-0.75)	Age, gender, smoking, Alcohol
14. Subapriya *et al*, [29] 2007 Tamil Nadu	Male/ Female	388 cases (oscc) 388 control	Betel quid with tobacco.	4.10 (3.66-7.93)	Age, sex, religion, diet, oral hygiene, occupation, restricted to non-smoking, nonalcohol group
15. Muwonge *et al*, [30] 2008 kerala	Male/ Female	282 cases, 1410 control	Chewing tobacco	4.3 (3.1-6.1) 2.7 (1.8-4.2) males 9.5 (5.0-18.0) females	Smoking, alcohol, Education
16.Bathi Rj *et al*. 2009 [42]	Males/ Females	220(OSMF) cases.	Chewing tobacco	RR highest for tobacco chewers (1,142.4)	Not Adjusted
17. Madani *et al*, [4] 2012 Pune	NA	350 cases 350 control	Chewing tobacco, gutka, supari, mishri	8.3 (5.4-13.0) 12.8 (7.0-23.7) 6.6 (3.0-14.8) 3.3 (2.1-5.4)	Other products, alcohol, non-veg habits, education
18. Krishna *et al*,[47]2014;[22]	Male /Female	190 cases, 189 controls	Betel quid with tobacco	0.53 (0.23-1.20)	Smoking Alcohol
19. Lakhanpal *et al*. [48] 2014	Male /Female	125 cases, 207 contro	Chewing tobacco	1.12 (0.61-2.04)	Smoking, alcohol, IL-1beta

OR: Odds ratio, CI: Confidence interval, OSMF: Oral submucous fibrosis, PML: Premalignant lesion, BMI: Body mass index, RR: Relative risk, OSCC: Oral squamous cell carcinoma, IL-1beta: Interleukin-1β

[38] Another study was conducted among patients with only oral leukoplakia (OL) revealing tobacco chewing as a significant risk factor for OL.[39] Hashibe *et al*. study was conducted among patients with only oral erythroplakic lesion. This study found tobacco chewing as a significant risk factor for erythroplakia (OR = 19.8) as compared to alcohol (OR = 3.0) and smoking (OR = 1.6) [Table 3].[40]

A study from Kerala by Hashibe *et al*. investigated the association of other habits with OSMF. This study found ever-tobacco

chewing as a strong risk factor for OSMF (OR = 44.1, 95% CI: 22.0–88.2) whereas alcohol drinking as a possible risk factor (OR = 2.1, 95% CI: 1.0–4.4).[41]

A hospital-based case–control study compared 220 patients of OSMF with matched controls with regard to dietary habits, smoking history and preference for chewing substrates. Its right, mentioned in Table 3: Bathiraj etal study 2009.[42]

A study from All India Institute of Medical Sciences, New Delhi, found chewing of areca nut/quid or pan-masala was directly related to OSMF [Table 3].[43]

Studies have been done for specific subsites of oral cancer. One study found that substantial cases of cancer of the buccal and labial mucosa were attributable to paan-tobacco chewing.[44] One study found there was a significant positive association between paan-tobacco chewing and cancer of the gingiva. The strongest predictor was daily frequency of paan-tobacco chewing. Four predictors of gingival cancer were yielded from stepwise logistic regression analysis; they were the daily frequency of paan-tobacco chewing, duration of bidi use and alcohol and snuff use (regular versus ever).[45]

Among all the case–control studies, three studies were done on genetic polymorphism using specific markers at specific sites of affected cases that did not infer a positive association[46-48] [Table 2].

Various notable cross-sectional studies are also available from India:

Narasannavar *et al*. in Belgaum[49] and Kumar *et al*.[50] in Indore reported the prevalence of OPML associated with tobacco. OSMF is the most common type in both studies. Pimple *et al*. also reported OPML association with tobacco usage.[51] Pahwa *et al*. in from Udupi taluk reported that the prevalence of OPML was found to be 3.73%.[52]

The recent data of cross sectional study in India include studies conducted in Chhattisgarh,[53] Puducherry[54] and Kanpur[55] All of them had shown a strong association of OMLs showed prevalence of OSMF and leukoplakia among the tobacco users. Other studies including those in Lucknow in Uttar Pradesh[56] showed that the prevalence was 13.2%, with a high incidence of OLs followed closely by oral submucous fibrosis (OSF) with a study from Gujarat by Joshi and Tailor.[57]

As prevalence study data do not provide the concrete evidence of cause of the disease and the duration of the studies done is arbitrarily chosen, much cannot be relied on their results which are diversified.

As per the data from a decade, few of the cross-sectional studies have been stated without much emphasis on the discussion of their results.

CONCLUSION

As the use of tobacco is very common in India as compared to the Western world, the high incidence of oral cancer in this part of the world is attributed to SLT use. Indian studies suggest a strong association between tobacco chewing and different premalignant lesions. As per the analysis, maximum prevalence studies have shown its association with tobacco pouch keratosis, leukoplakia or OSMF, the lesions are curable by habit cessation.

As per the data collected, there are very few cohort and case–control studies done in the country for premalignant lesions and oral cancer. Majority of them are reported from South India. Further studies with adequate power and control of confounding factors are required. 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.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Mubeen K, Chandrashekhar H, Kavitha M, Nagarathna S. Effect of tobacco on oral-health an overview. J Evol Med Dent Sci 2013;2:3523-35.
2. Peter S. Essentials of Preventive and Community Dentistry. 2nd ed. New Delhi: Arya (Medi). Publishing House; 2003. p. 472-3.
3. Global Adult Tobacco Survey, GATS India 2009-2010. Ministry of Health and Family Welfare, Govt. of India Fact Sheet. Available from: http://www.who.int/tobacco/surveillance/en_tfi_india_ gats_fact_ sheet.pdf. [Last acessed on 2013 May 20].
4. Madani AH, Dikshit M, Bhaduri D. Risk for oral cancer associated to smoking, smokeless and oral dip products. Indian J Public Health 2012;56:57-60.
5. Panchamukhi PR, Woolery T, Nayantara SN. Economics of bidis in India. Bidi smoking and public health. Ahmadabad, Gujarat 2008:167-95.
6. Cancer, Factsheet (WHO). Available from: http://www.who.int/mediacentre/factsheets/fs297/en/. [Last accessed on 2021 Jul 17].
7. International Agency for Research on Cancer (ARC) Working Group on the Evaluation of Carcinogenic Risks to Humans. Smokeless tobacco and some tobacco-specific N-nitrosamines. IARC Monogr Eval Carcinog Risks Hum 2007;89:1-592.
8. Datta S, Chaturvedi P, Mishra A, Pawar P. A review of Indian literature for association of smokeless tobacco with malignant and premalignant

diseases of head and neck region. Indian J Cancer 2014;51:200-8.
9. Sankaranarayanan R, Masuyer E, Swaminathan R, Ferlay J, Whelan S. Head and neck cancer: A global perspective on epidemiology and prognosis. Anticancer Res 1998;18:4779-86.
10. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Smokeless tobacco and some tobacco-specific N-nitrosamines. IARC Monogr Eval Carcinog Risks Hum 2007;89:1-592.
11. Bhisey RA. Chemistry and toxicology of smokeless tobacco. Indian J Cancer 2012;49:364-72.
12. Boffetta P, Hecht S, Gray N, Gupta P, Straif K. Smokeless tobacco and cancer. Lancet Oncol 2008;9:667-75.
13. Hecht SS. Tobacco carcinogenesis. In: Schwab M, editor. Encyclopedia of Cancer. Berlin, Heidelberg: Springer Berlin Heidelberg; 2011. p. 3717-9.
14. Gupta S, Gupta R, Sinha DN, Mehrotra R. Relationship between type of smokeless tobacco and risk of cancer: A systematic review. Indian J Med Res 2018;148:56-76.
15. Aroquiadasse M, Daniel MJ, Srinivasan SV, Jimsha VK. Correlation of degree of dysplasia in potentially malignant disorders with tobacco use: A cross-sectional study. Clin Cancer Investig J 2016;5:398.
16. Pindborg JJ, Mehta FS, Gupta PC, Daftary DK. Prevalence of oral submucous fibrosis among 50,915 Indian villagers. Br J Cancer 1968;22:646-54.
17. Murti PR, Bhonsle RB, Pindborg JJ, Daftary DK, Gupta PC, Mehta FS. Malignant transformation rate in oral submucous fibrosis over a 17-year period. Community Dent Oral Epidemiol 1985;13:340-1.
18. Mehta FS, Pindborg JJ, Gupta PC, Daftary DK. Epidemiologic and histologic study of oral cancer and leukoplakia among 50,915 villagers in India. Cancer 1969;24:832-49.
19. Pindborg JJ, Jolst O, Renstrup G, Roed-Petersen B. Studies in oral leukoplakia: A preliminary report on the period pervalence of malignant transformation in leukoplakia based on a follow-up study of 248 patients. J Am Dent Assoc 1968;76:767-71.
20. Reichart PA, Philipsen HP. Oral erythroplakia – A review. Oral Oncol 2005;41:551-61.
21. Villa A, Villa C, Abati S. Oral cancer and oral erythroplakia: An update and implication for clinicians. Aust Dent J 2011;56:253.
22. Carnelio S, Rodrigues GS, Shenoy R, Fernandes D. A brief review of common oral premalignant lesions with emphasis on their management and cancer prevention. Indian J Surg 2011;73:256-61.
23. Gupta PC, Ray CS. Smokeless tobacco and health in India and South Asia. Respirology 2003;8:419-31.
24. Commonly Used Smokeless Tobacco Products. FCTC, ICMR, NICPR. Available from: https://Untobaccocontrol.Org› Paan-Betel-Quid-Tobacco 19/05/2021.
25. Gupta PC, Ray CS. Smokeless tobacco and health in India and South Asia. Respirology 2003;8:419-31.
26. Jayalekshmi PA, Gangadharan P, Akiba S, Nair RR, Tsuji M, Rajan B. Tobacco chewing and female oral cavity cancer risk in Karunagappally cohort, India. Br J Cancer 2009;100:848-52.
27. Jayalekshmi PA, Gangadharan P, Akiba S, Koriyama C, Nair RR. Oral cavity cancer risk in relation to tobacco chewing and bidi smoking among men in Karunagappally, Kerala, India: Karunagappally cohort study. Cancer Sci 2011;102:460-7.
28. Pednekar MS, Gupta PC, Yeole BB, Hébert 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.
29. Subapriya R, Thangavelu A, Mathavan B, Ramachandran CR, Nagini S. Assessment of risk factors for oral squamous cell carcinoma in Chidambaram, Southern India: A case-control study. Eur J Cancer Prev 2007;16:251-6.
30. Muwonge R, Ramadas K, Sankila R, Thara S, Thomas G, Vinoda J, *et al*. Role of tobacco smoking, chewing and alcohol drinking in the risk of oral cancer in Trivandrum, India: A nested case-control design using incident cancer cases. Oral Oncol 2008;44:446-54.
31. Znaor A, Brennan P, Gajalakshmi V, Mathew A, Shanta V, Varghese C, *et al*. Independent and combined effects of tobacco smoking, chewing and alcohol drinking on the risk of oral, pharyngeal and esophageal cancers in Indian men. Int J Cancer 2003;105:681-6.
32. Nandakumar A, Thimmasetty KT, Sreeramareddy NM, Venugopal TC, Vinutha AT, Bhargava MK. A population-based case–control investigation on cancers of the oral cavity in Bangalore, India. British journal of cancer 1990;62:847-51.
33. Dikshit RP, Kanhere S. Tobacco habits and risk of lung, oropharyngeal and oral cavity cancer: A population-based case-control study in Bhopal, India. Int J Epidemiol 2000;29:609-14.
34. Balaram P, Sridhar H, Rajkumar T, Vaccarella S, Herrero R, Nandakumar A, *et al*. Oral cancer in southern India: The influence of smoking, drinking, paan-chewing and oral hygiene. Int J Cancer 2002;98:440-5.
35. Rao DN, Ganesh B, Rao RS, Desai PB. Risk assessment of tobacco, alcohol and diet in oral cancer – A case-control study. Int J Cancer 1994;58:469-73.
36. Rao DN, Desai PB. Risk assessment of tobacco, alcohol and diet in cancers of base tongue and oral tongue – A case control study. Indian J Cancer 1998;35:65-72.
37. Gangane N, Chawla S, Anshu GS, Sharma SM. Reassessment of risk factors for oral cancer. Asian Pacific Journal of Cancer Prevention 2007;8:243.
38. Thomas G, Hashibe M, Jacob BJ, Ramadas K, Mathew B, Sankaranarayanan R, *et al*. Risk factors for multiple oral premalignant lesions. Int J Cancer 2003;107:285-91.
39. Hashibe M, Sankaranarayanan R, Thomas G, Kuruvilla B, Mathew B, Somanathan T, *et al*. Alcohol drinking, body mass index and the risk of oral leukoplakia in an Indian population. Int J Cancer 2000;88:129-34.
40. Hashibe M, Mathew B, Kuruvilla B, Thomas G, Sankaranarayanan R, Parkin DM, *et al*. Chewing tobacco, alcohol, and the risk of erythroplakia. Cancer Epidemiol Biomarkers Prev 2000;9:639-45.
41. Hashibe M, Sankaranarayanan R, Thomas G, Kuruvilla B, Mathew B, Somanathan T, *et al*. Body mass index, tobacco chewing, alcohol drinking and the risk of oral submucous fibrosis in Kerala, India. Cancer Causes Control 2002;13:55-64.
42. Bathi RJ, Parveen S, Burde K. The role of gutka chewing in oral submucous fibrosis: A case-control study. Quintessence Int 2009;40:e19-25.
43. Shah N, Sharma PP. Role of chewing and smoking habits in the etiology of oral submucous fibrosis (OSF): A case-control study. J Oral Pathol Med 1998;27:475-9.
44. Sankaranarayanan R, Duffy SW, Padmakumary G, Day NE, Krishan Nair M. Risk factors for cancer of the buccal and labial mucosa in Kerala, southern India. J Epidemiol Community Health 1990;44:286-92.
45. Sankaranarayanan R, Duffy SW, Padmakumary G, Day NE, Padmanabhan TK. Tobacco chewing, alcohol and nasal snuff in cancer of the gingiva in Kerala, India. Br J Cancer 1989;60:638-43.
46. Anantharaman D, Chaubal PM, Kannan S, Bhisey RA, Mahimkar MB. Susceptibility to oral cancer by genetic polymorphisms at CYP1A1, GSTM1 and GSTT1 loci among Indians: Tobacco exposure as a risk modulator. Carcinogenesis 2007;28:1455-62.
47. Krishna A, Singh RK, Singh S, Verma P, Pal US, Tiwari S. Demographic risk factors, affected anatomical sites and clinicopathological profile for oral squamous cell carcinoma in a north Indian population. Asian Pac J Cancer Prev 2014;15:6755-60.
48. Lakhanpal M, Yadav DS, Devi TR, Singh LC, Singh KJ, Latha SP, *et al*. Association of interleukin-1β -511 C/T polymorphism with tobacco-associated cancer in northeast India: A study on oral and gastric cancer. Cancer Genet 2014;207:1-11.
49. Narasannavar A, Wantamutte AS. Prevalence of oral precancerous lesions and conditions among tobacco consumers in rural population around Belgaum. A community based cross sectional study. IOSR J Dent Med Sci 2014;1:31-4.
50. Kumar S, Debnath N, Ismail MB, Kumar A, Kumar A, Badiyani BK,

et al. Prevalence and risk factors for oral potentially malignant disorders in Indian population. Advances in preventive medicine 2015;2015.
51. Pimple S, Pednekar M, Majmudar P, Ingole N, Goswami S, Shastri S. An integrated approach to worksite tobacco use prevention and oral cancer screening among factory workers in Mumbai, India. Asian Pac J Cancer Prev 2012;13:527-32.
52. Pahwa V, Nair S, Shetty RS, Kamath A. Prevalence of oral premalignant lesions and its risk factors among the adult population in Udupi Taluk of coastal Karnataka, India Asian Pac J Cancer Prev 2018;19:2165-70.
53. Yunus GY, Sahni H, Naveen N, Tiwari R, Vasant B, Suman S. "Tobacco" – The silent slayer for oral premalignant lesions/conditions among beedi rolling workers of Durg City, Chhattisgarh, India: A cross-sectional study. J Indian Assoc Public Health Dent 2019;17:119.
54. Paulose S, Rangdhol V, Kavya L, Ezhumalai G. Prevalence of oral potentially malignant disorders associated with habits in Puducherry – A cross-sectional study. Braz J Oral Sci 2020;19:e201684.
55. Srivastava R, Sharma L, Pradhan D, Jyoti B, Singh O. Prevalence of oral premalignant lesions and conditions among the population of Kanpur City, India: A cross-sectional study. J Family Med Prim Care 2020;9:1080-5.
56. Rehan AD, Dar MS, George JJ, Kausar T, Bhargava A, Saigal S, et al. betel quid users in Lucknow. IJDHS 2017;4;444-52.
57. Joshi M, Tailor M. Prevalence of most commonly reported tobacco-associated lesions in central Gujarat: A hospital-based cross-sectional study. Indian J Dent Res 2016;27:405-9.