



# Smokeless Tobacco and Its Ill-Effects: Recent Literature Update

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## Abstract

According to the Global Adult Tobacco Survey part 2 (GATS-2), approximately 200 million adult Indians consume smokeless tobacco (SLT). Circumvention of SLT product ban has been observed. We conducted a review of the literature to summarize the ill effects of tobacco for the articles published from 2019 to 2020. A systematic search of the databases PubMed (2019 onward) and Web of Science (2019 onward), through February 2021 was done. Search yielded 1,061 articles and after excluding articles based on the inclusion criteria, 37 articles were taken in to consideration. The review shows that differential SLT product has specific odds of oral carcinogenesis. Review also indicates the emerging data of cardiovascular risk due to higher use of SLT products along with its known cause of oral cancer. It also cautions about the adverse consequences of pregnancy associated with SLT use.

## Keywords

- ▶ smokeless tobacco
- ▶ gutkha
- ▶ oral cancer
- ▶ cancer

## Smokeless Tobacco and Its Ill Effects: Recent Literature Update

Oral cavity cancers are among the most common cancers affecting males in India.<sup>1</sup> Tobacco, alcohol, and areca nut are the root causes for high incidence of oral cancer in India.<sup>2</sup> However, tobacco has widespread effects on oral health, apart from oral cavity cancers, it is also responsible for 7 million deaths worldwide.<sup>3</sup> Smokeless tobacco not only causes cancer of the oral cavity, it is also responsible for higher incidence of esophageal and pancreatic cancers.<sup>4</sup> It has been documented to increase the risk of stroke and cardiovascular diseases. Consumption of smokeless tobacco (SLT) during pregnancy can also lead to higher chances of reduced gestation age and birth weight.<sup>5</sup>

According to the Global Adult Tobacco Survey part 2 (GATS-2) India survey,<sup>6</sup> incidence of SLT use is significantly more than combustible tobacco product. It has also shown that in India, states like Madhya Pradesh, Odisha, Bihar, Jharkhand, Chhattisgarh, and Northwestern states have high incidence of SLT use (above 30%) while Maharashtra, Gujrat, and Uttar Pradesh fall in moderate category (20–30%) and North and South Indian states have incidence of SLT use ranging from 10 to 20%. More than 30 types of SLT are consumed in India. To curb its usage and production, government has enacted many tobacco control legislations. As of May 2013, few SLT product involving pan masala and gutkha are banned in 24 states and 3 union territories in India.<sup>7</sup> However, the Federal Food Safety and Regulation act 2011 allows harmful product to be banned for a year after which it needs to be renewed every year based on the current

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evidence. Thus, primary aim of the study was to update the literature with the latest available evidence on the ill effect of SLT in India, as well as globally.

## Methods

A systematic search of the databases PubMed (2019 onward) and Web of Science (2019 onward) through February 2021 was done. Relevant articles were identified. The search terms used were “smokeless tobacco,” “cancer,” “oral cancer,” “ill effects,” “cardiovascular disease,” “stroke,” “pregnancy,” “potentially malignant lesion,” “precancer,” “gutkha,” and “gutka.” These were searched as text, as well as in combination using Boolean “AND.” The cross-reference lists of relevant articles were also screened for suitable studies. This search yielded 1,061 articles. Inclusion criteria involved those articles which were published between the year 2019 and 2021, those published in English literature, studies including exposed individuals consuming SLT leading to oral cancer or cancer or any ill-health effects were included in the review. Articles were excluded from the review if they failed to describe the factors of interest of the study. Search strategy is described in ►Fig. 1. Among these articles, 37 articles were included in the narrative review which described SLT and its ill effects on health. ►Table 1 presents the recent studies showing relationship between SLT use and oral cancer/cardiovascular diseases.

## Recent Literature Updates

### Smokeless Tobacco and Cancer: Clinical Studies

India is one of the largest producers and the highest consumer of SLT product. Approximately, 20 crore Indians consume SLT.<sup>4</sup> Thus, India has the highest population of new oral cancer cases every year. Last year, a global systematic review was published to find an association of SLT use and oral cancer.<sup>8</sup> This study consisted of 37 studies all over the world with majority being from the South East Asian Region (SEAR). For this region, there was significantly higher risk (4.44 times) of oral cancer associated with SLT. Surprisingly, in this study, females had significantly higher risk of oral cancer. This study also looked at product-wise vulnerability to oral cancer. Gutkha has the highest odds of carcinogenesis to the scale of 860% more than the rest. Similarly, oral snuff (four times) also had higher odds to cause cancer. Another systematic review by Asthana et al analyzed 12 systematic review that found a strong association between SLT and oral cancer.<sup>9</sup> All type of SLT had association in causation of oral cancer but gutkha and pan masala had higher odds for it. An African and Middle East based systematic analysis reviewed six studies and found shammah (form of SLT) had higher odds (39 times) of developing oral cancer.<sup>10</sup> Global burden analysis of SLT was performed for 127 countries including India.<sup>11</sup> This study pointed out that South Asian Region (India accounting for 70% of the load) is plagued with SLT pandemic with the highest mortality rate. At least 2.5 million disability adjusted life years (DALYs) were lost in the year due to cancer associated with SLT. A case control prospective study aimed to evaluate the risk of oral

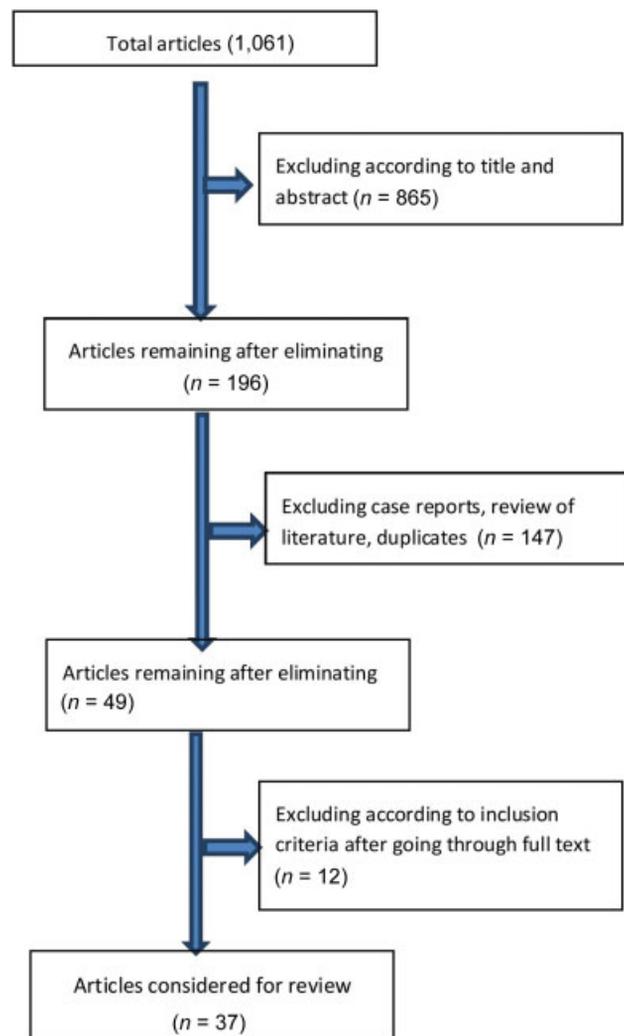


Fig. 1 A flowchart depicting the study selection.

cavity cancers among SLT users. This study enrolled oral cancer patients as cases and their attendants were enrolled as controls. It concluded that type, frequency, and duration of tobacco use were significantly high in cases as compared with controls. Individuals who ever consumed SLT product had an odds ratio of 4.98 (95% confidence interval [CI]: 2.76–9.01) while even when adjusting for smoking and age, snuff users were 4.6 times more vulnerable to oral cancers.<sup>12</sup>

A cross-sectional study conducted in Nepal consisting of 851 patients concluded high incidence of oral cancer (55.5%), premalignant lesion (12%), and the majority of them were SLT users.<sup>13</sup> This could be attributed to high incidence of SLT use in Nepal where one-third of the males (more than 30%) use SLT, betel quid with tobacco being the most common.<sup>14</sup> However, the study is subject to selection bias. Another study conducted among rural Indian population studied the pattern of tobacco use in oral cancer patients.<sup>15</sup> It was observed that more than 40% of all the rural Indian population consume SLT. Three-fourths of all the head and neck cancer patient enrolled in the study consumed SLT, while approximately 10% of all the tobacco chewers were independent users of gutkha.

**Table 1** Studies presenting the relationship between smokeless tobacco and oral cancer/cardiovascular diseases

Sl. no.	Author	Study type	Site	Outcome	Type of SLT	OR	HR	CI (95%)
1	Khan et al <sup>16</sup>	Case-control	India	OSMF	SLT	18	–	NA
2	Khan et al <sup>16</sup>	Case-control	India	OSMF	Gutkha + bidi	12.3	–	NA
3	Patil et al <sup>10</sup>	Systematic review	Africa	Oral cancer/OPMD	Shammah	–	38.74	19.50–76.96
4	Asthana et al <sup>8</sup>	Systematic review	SEAR	Oral cancer	SLT	4.44	–	3.51–5.61
5	Asthana et al <sup>8</sup>	Systematic review	EMR	Oral cancer	SLT	1.28	–	1.04–1.56
6	Asthana et al <sup>8</sup>	Systematic review	WHO (six)	Oral cancer	Gutkha	8.67	–	3.59–20.93
7	Asthana et al <sup>8</sup>	Systematic review	WHO (six)	Oral cancer	Pan masala	7.18	–	5.48–9.41
8	Asthana et al <sup>8</sup>	Systematic review	WHO (six)	Oral cancer	Oral snuff	4.18	–	2.37–7.38
9	Asthana et al <sup>8</sup>	Systematic review	WHO (six)	Oral cancer	Manipuri tobacco	3.32	–	2.32–8.36
10	Byhamre et al <sup>31</sup>	Cohort	Sweden	Cancer	Snus	–	1.12	1.00–1.26
11	Khan et al <sup>12</sup>	Case control	Pakistan	Oral cancer	Snuff	4.82	–	2.37–9.80
12	Khan et al <sup>12</sup>	Case control	Pakistan	Oral cancer	Betel leaf	4.42	–	1.66–11.91
13	Byhamre et al <sup>31</sup>	Cohort	Sweden	Cardiovascular	Snus	–	1.27	1.15–1.41
14	Gupta et al <sup>11</sup>	Systematic review	WHO	CHD (fatal)	Snus	1.1	–	1.00–1.20

Abbreviations: CHD, coronary heart disease; EMR, Eastern Mediterranean Region; HR, hazard ratio; OPMD, oral potentially malignant disease; OR, odds ratio; OSMF, oral submucous fibrosis; SEAR, South-East Asia Region; SLT, smokeless tobacco; WHO, World Health Organization.

According to National Cancer Registry Program of Indian Council of Medical Research at Bangalore in Karnataka, proportional increase in mouth cancer cases were significantly more in younger age group (third and fourth decades) as compared with fifth and second decades. This suspicious rise in the mouth cancers cases in the young cannot be sheer coincidence with the time period of popularization of gutkha and other factory-made tobacco products. This shows that time to carcinogenesis was significantly less in gutkha chewers as compared with loose tobacco product users, making such factory made tobacco product more dangerous than others, leading to development of cancer in young age.

### Smokeless Tobacco and Oral Potentially Malignant Disease

Study published in the year 2020 which evaluated medical records of 1,007 individuals coming to the tertiary care center in the South India assessed the pattern of tobacco use and corresponding oral mucosal alteration.<sup>16</sup> In this study, more than 50% were tobacco smokers and SLT user. About 18.2% of bidi smokers developed carcinoma and 15% developed leukoplakia. Various forms of SLT are strongly associated with development of oral submucous fibrosis (OSMF).<sup>17</sup> This study has shown that SLT including betel quid with tobacco and gutkha chewers lead to 18 times higher chances of development of OSMF as compared with those who do not chew SLT in any form. Oral submucous fibrosis is a systemic condition

which leads to irreversible reduction in mouth opening. One-third of all the betel quid tobacco and gutkha users developed tobacco pouch keratosis. The most important findings of the study were the combination of gutkha and bidi was even more lethal, leading to 12.3 times higher chances of oral cancer. Study conducted by Tata Memorial Hospital in Mumbai screened 12 slum clusters, consisting of approximately 11,000 tobacco chewing women. They found 327 (3.2%) were screened positive and 75% of the screen-positive women had precancerous or cancerous lesion.<sup>18</sup> Thus reaffirming the evidence that SLT users have a high incidence of precancerous lesion even in females. Another female-based study conducted in Bengal enrolled 155 women had high prevalence of SLT use (18.7%). They also found that there was a significant association between SLT use and unhealthy oral mucosal changes.<sup>19</sup> Another cross-sectional study conducted in Bhavnagar district of Gujarat concluded that every third of the population consumes SLT with majority being mawa and gutkha. This truly corresponds to high incidence of OSMF, OPMD (oral potentially malignant disease) and oral cancer in the South Gujarat.<sup>20</sup> Another study analyzing the effect of SLT user in migrant construction site workers in Chennai has shown alarmingly higher rates of potentially malignant disorders in the oral cavity. Inflammatory mucosal lesions in the oral cavity were 70.97% and more among SLT users compared with 22.58% among tobacco smokers and were significantly associated with up to 20 years of tobacco consumption.<sup>21</sup>

### Genetic and Molecular Studies: Preclinical Studies

A study led by Datta et al aimed at assessing the microscopic and the phenotypic changes in the oesophageal human cell lines.<sup>22</sup> In this study, oesophageal cell lines were treated with chewed tobacco for 8 months. They observed progressive increase in proliferative ability of cells and also increased invasive capabilities with increased duration of exposure to chewed tobacco. Last year, a study led by Pansare et al was also successful in identifying SLT-induced gingivobuccal carcinoma cell lines.<sup>23</sup> Thus, suggesting SLT-induced oral mucosa changes had genetically altered cell lines. An in vitro study observing the effect of prenatal gutkha chewing on the adult liver has shown that prenatal exposure to gutkha followed by a high fat diet in adulthood significantly increased the chances of fatty liver in males. Maternal exposure of gutkha raises the cytokine levels including interleukin (IL)-1b and IL-6 and m-RNA collagen expression. These experimental findings conclude that gutkha has the potential to induce fatty liver changes in a gender-dependent manner.<sup>24</sup>

Another genetic study assessed the effect of a type of SLT (Maras) on the deregulation of micro RNA. They found that SLT also leads to deregulation of miR-200b and miR-92a expressions. Deregulation of micro RNAs mediate process of tumorigenesis, such as inflammation, cell cycle regulation, stress response, differentiation, apoptosis, and invasion consequently leading to carcinogenesis.<sup>25</sup>

### Smokeless Tobacco and Cardiovascular Diseases

Apart from cancer, SLT-associated mortality due to heart disease contributed to 6 million DALYs and 258,000 lives were lost. A study analyzing cardiovascular risk among SLT users found to have significant association of SLT use and fatal coronary heart disease (CHD).<sup>11</sup> A case control study analyzing the cardiovascular effects of SLT on young individuals recorded significantly higher systolic blood pressure, mean arterial pressure, heart rate, and other component of heart rate variability and these were significantly deranged in the group of individuals consuming SLT. Thus this study shows that SLT adversely affects the cardiovascular parameters increasing the risk of cardiovascular disease.<sup>26</sup> Another study conducted on sub-Saharan women SLT user found higher differential blood pressure.<sup>27</sup> Similarly, an Indian study evaluating the inflammatory and thrombotic markers in SLT user found significantly higher levels of IL-6, tumor necrosis factor (TNF)- $\alpha$ , fibrinogen, and D-dimer. Higher inflammatory markers levels correspond with increased risk of thrombotic cardiovascular events among SLT users.<sup>28</sup> Another cross-sectional study found total cholesterol, triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) significantly higher in pan masala tobacco chewer.<sup>29</sup> In a prospective Swedish study with a follow-up of 8 years found 1.5 times higher risk of ischemic and 1.6 times risk of total stroke in nonsmoking Snus user as compared with non-users.<sup>30</sup> A Swedish study analyzed the all-cause mortality of falsely promoted safe product so called Snus.<sup>31</sup> This study stated that Snus leads to increased all-cause mortality (1.28 times higher) with higher cardiovascular mortality (1.27

times higher) and cancer mortality (1.1 times). Thus there is enough current evidence to prove that SLT use is associated with high cardiovascular risk.

### Smokeless Tobacco and Pregnancy

A systematic review was conducted to find the potential effects of SLT consumed during pregnancy. A systematic review of 21 studies concluded that SLT user probably increases the chances of poor outcome in pregnancy.<sup>32</sup> Studies have also shown that prenatal Snus (SLT) exposure is associated with higher systolic pressure and altered heart rate variability at 6 years of child's age. Another Australian study found that SLT (pituri) use is associated with possible complication like elevated glucose concentration which may lead to gestational diabetes.<sup>33</sup> Thus according to the current literature, SLT can potentially influence adverse maternal outcomes.

### Recommendation

We need to make research efforts to recognize the oral potentially malignant disorder and cancer risk according to the type, frequency, and duration of use of different type of SLT product. Current evidence highly recommends screening for high-risk individuals (SLT user) for prevention and early detection of oral potentially malignant lesion and oral cancer. It also recommends further research to find the direct association of cardiovascular disease and SLT use. Our review advocates screening pregnant women and creating awareness about the ill effects of SLT on postpregnancy adverse outcomes.

### Conclusion

There is strong evidence to suggest that SLT increases the risk of oral potentially malignant disorder, oral cancer, and it is detrimental to oral health. Evidence also indicates that it worsens the risk of cardiovascular disease and adverse maternal outcomes including low birth weight and gestational diabetes.

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### Conflict of Interest

None declared.

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