Oral mucosal disorders associated with habitual gutka usage: a review

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Objective. The aim of this study was to investigate the oral mucosal disorders associated with habitual gutka consumption.

Methods. Databases were searched from 1956 to June 2009 using the following terms: “gutka,” “gutkha,” “ghutka,” “guttkha,” “smokeless tobacco,” “areca nut,” “betel nut,” “slaked lime,” “dental,” “oral,” “periodontal,” “inflammation,” “submucous fibrosis,” “carcinoma,” and “cancer.” The eligibility criteria included: human and experimental studies, use of control subjects, and articles published in English. Unpublished data were not sought. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed.

Results. Twelve studies were included. Three studies associated gutka consumption with periodontal inflammation (ORs 1.64 [CI 1.2-2.1], 2.20 [CI 1.1-4.9], and 3.56 [CI 1.9-5.5]). Five studies showed a direct relationship between gutka usage and oral submucous fibrosis (ORs 1.65 [CI 1.2-2.3], 2.33 [CI 1.9-4.5], 2.98 [CI 1.5-3.9], 3.56 [CI 1.3-4.7], and 5.08 [CI 3.7-6.4]). An increased frequency of gutka usage was associated with malignant transformations in oral submucous fibrosis by 2 studies (ORs 4.59 [CI 2-5.6] and 18 [CI 5.8-61.6]). Two studies showed an extension of oral submucous fibrosis into the hypopharynx and esophagus in gutka users (ORs 4.59 [CI 2-5.6] and 33 [CI 2.2-46.6]).


Gutka (a form of smokeless tobacco) is chiefly a mixture of powdered tobacco, areca nut (fruit of Areca catechu), and slaked lime (aqueous calcium hydroxide). Other components of gutka include perfumery compounds such as sandalwood and musk ketones. The easy availability, low cost, and extensive marketing of gutka has resulted in an increase in its usage. Gutka is commercially available in colorful and glittery tins and sachets. Unlike cigarettes, gutka is commercially sold without a health warning, and lack of awareness of its negative impact on health increases its consumption. Gutka is initially placed between the teeth and gently chewed. It is then held against the buccal mucosa over a long duration and continued to be lightly chewed and sucked occasionally. The constituents may either be swallowed or spat out when desired. Other forms of smokeless tobacco products commonly used in the Indian subcontinent include betel quid/paan (a blend of areca nut, slaked lime, artificial sweeteners, and sometimes tobacco wrapped in Piper betel leaf) and khaini and zarda (mixtures of powdered tobacco and slaked lime).

Gutka usage is not restricted to the Indian subcontinent, but is also enjoyed by immigrant communities settled in Europe and the United States. The actual prevalence of gutka usage in southeast Asia and other countries is yet to be documented; however, varying results have been reported from community surveys. In a recent study, 46% of the residents of a local community in Karachi, Pakistan, reported using gutka habitually. Similarly, another study reported 35% of the patients visiting a health care center in Karachi to be habitual gutka users. In the Indian State of Wardha, the prevalence of gutka usage by men and women was reported to be 46.4% and 20%, respectively. In Tanzania, 6.9% of the native inhabitants have been reported to use gutka on a daily basis.

Habitual gutka use has been associated with the occurrence of several oral mucosal disorders, including oral submucous fibrosis (OSF), oral cancer, and periodontal disease. OSF is a chronic premalignant condition, characterized by progressive accumulation of

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collagen fibers in the oral submucosa, and its clinical presentation depends on the stage of the disease at detection. Most patients with OSF present with an intolerance to spicy food, with rigidity of lips, tongue, and palate leading to varying degrees of limitation of mouth opening and tongue movement. Habitual gutka users have also been shown to present with OSF at earlier ages compared with traditional betel quid users. This may be explained by the average weight and moisture content in a gutka sachet/pouch. A gutka sachet weighs ~3.5 g and contains 7% moisture, whereas the net weight of a betel quid is nearly 4 g (with ~1.14 g of tobacco) and contains 70% moisture. Because gutka users tend to consume more dry weight of tobacco, areca nut, and slaked lime, they may be exposed to oral mucosal disorders at earlier ages compared to betel quid users.

Oral cancer is the fifth most common cancer worldwide, and tobacco use has been thought to account for 30% of the global cancer load. In Karachi, oral cancer (mainly squamous cell carcinoma) ranks second in all malignancies among both men and women, with the highest reported incidence in the world. Bhurgri et al. identified areca nut and tobacco (which are also chief ingredients of gutka) as significant risk factors for the high oral cancer incidence in Pakistan. In a longitudinal study performed in India, 66 individuals with OSF were followed-up for malignant transformations over a period of 17 years. The results showed that oral cancer developed in 7.6% of the individuals, and the malignant transformation rate in the study group was reported to be 4.5% over a 15-year observational period. Malignant transformation rates up to 19.1% have also been reported in patients with OSF. Those results showed that a high degree of malignancy can be observed in patients with OSF.

Periodontal inflammatory parameters have also been reported to be higher among gutka users compared to control subjects (individuals not using tobacco in any form). In a recent study, Javed et al. measured the plaque index (PI), bleeding on probing (BOP), and periodontal probing depth (PPD) among habitual gutka users and control subjects. The results showed a significantly higher PI, BOP, and PPD (4-6 mm) in habitual gutka users compared with control subjects. In that study, self-perceived gingival bleeding also was more often reported by the gutka users than the control subjects. Similar results were reported in the study by Parmar et al., that showed an increased incidence of BOP, PPD, gingival recession, and oral ulceration in subjects chewing a mixture of areca nut and tobacco. Slaked lime is a strong alkali and has been shown to promote hyperplasia and irritation in the oral mucosal tissues. Chewing a mixture of slaked-lime, areca nut, and powdered tobacco has also been shown to facilitate the development of oral cancer. It may be postulated that gutka use intensifies the severity of oral mucosal disorders and exposes the consumers to severe oral health risks at earlier ages. Because gutka usage is increasing worldwide and its ingredients are hazardous to oral mucosal health, the aim of the present review was to evaluate the oral mucosal diseases associated with habitual gutka consumption.

MATERIALS AND METHODS

Rationale and focus question

Individuals who consumed ≥1 gutka sachet daily for ≥6 months were designated as “habitual gutka users/chewers.” The objective of the present review was to assess the negative effects of habitual gutka consumption on oral mucosal health. Therefore, our focus question was: What are the deleterious effects of habitual gutka consumption on oral mucosal health?

Eligibility criteria

The following eligibility criteria were imposed: 1) human studies; 2) test group: individuals consuming ≥1 gutka sachet/pouch daily for ≥6 months; 3) control group: individuals not using tobacco in any form; and 4) articles published in English.

The reference lists of potentially relevant original and review articles were also searched to identify articles that were not located in the original search. Table I presents the list of pertinent studies that were retrieved during the data extraction process. Letters to the editor, historical reviews, and unpublished articles were excluded. Table II shows the 13 studies that did not comply with the eligibility criteria and were excluded.

Search strategies

As a first step, the authors searched the National Library of Medicine, Washington, DC (Medline-Pubmed), for appropriate articles addressing the focus question. Databases were searched from 1956 up to and including June 2009 using the following terms in different combinations: gutka,” “gutka,” “gutkha,” “guttka,” “smokeless tobacco,” “areca nut,” “betel nut,” “slaked lime,” “dental,” “oral,” “periodontal,” “inflammation,” “submucous fibrosis,” “carcinoma,” and “cancer.”

The second step was to hand search the reference lists of original and review studies that were found to be relevant in the first step. Titles containing words suggesting smokeless tobacco consumption as an adjunct to oral health disorders were also sought.

After final selection of the papers, those studies that fulfilled the selection criteria were processed for data extraction. Full texts of the selected articles were re-
Table I. Investigators (year), study design, age, sample size, odds ratios, duration of gutka use and daily intake, and main results of selected studies

<table>
<thead>
<tr>
<th>Investigator(s), year</th>
<th>Study design</th>
<th>Age range (yrs)</th>
<th>Sample size</th>
<th>Male:female ratio</th>
<th>OR 95% CI</th>
<th>Duration of gutka use</th>
<th>Daily intake of gutka*</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Periodontal inflammation</strong></td>
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<tr>
<td>Javed et al., 2008¹</td>
<td>Case-control</td>
<td>45-64</td>
<td>1,000</td>
<td>1:1</td>
<td>2.20 (1.1-4.9)</td>
<td>8 years</td>
<td>8×</td>
<td>Periodontal inflammation was higher in gutka chewers than in nonchewers.</td>
</tr>
<tr>
<td>Doifode et al., 2000¹³</td>
<td>Case-control</td>
<td>14-59</td>
<td>110</td>
<td>1:1</td>
<td>3.56 (1.9-5.5)</td>
<td>NA</td>
<td>NA</td>
<td>Gutka chewing was significantly associated with OSF* and periodontal disease.</td>
</tr>
<tr>
<td>Parmar et al., 2008³²</td>
<td>Case-control</td>
<td>31-33</td>
<td>365</td>
<td>4:1</td>
<td>1.64 (1.2-2.1)</td>
<td>NA</td>
<td>NA</td>
<td>Periodontal inflammation and oral ulcers were higher in gutka-chewers compared to nonchewers.</td>
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<tr>
<td><strong>Oral submucous fibrosis</strong></td>
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<tr>
<td>Bathi et al., 2009¹⁰</td>
<td>Case-control</td>
<td>10-64</td>
<td>220</td>
<td>26.5:1</td>
<td>2.98 (1.5-3.9)</td>
<td>3-4 yrs</td>
<td>1-15×</td>
<td>Gutka is strongly associated with the development of OSF.*</td>
</tr>
<tr>
<td>Hazarey et al., 2007¹¹</td>
<td>Cross-sectional</td>
<td>9 to &lt;50</td>
<td>1,000</td>
<td>4:9:1</td>
<td>2.33 (1.9-4.5)</td>
<td>2-5 yrs</td>
<td>4×</td>
<td>Gutka consumption was a major pre-malignant lesions associated with OSF* and oral cancer.</td>
</tr>
<tr>
<td>Saraswathi et al., 2006¹²</td>
<td>Cross-sectional</td>
<td>13-84</td>
<td>2,017</td>
<td>1:7:1</td>
<td>5.08 (3.7-6.4)</td>
<td>NA</td>
<td>NA</td>
<td>OSF* was the most prevalent lesion among gutka chewers.</td>
</tr>
<tr>
<td>Doifode et al., 2000¹³</td>
<td>Case-control</td>
<td>14-59</td>
<td>110</td>
<td>1:1</td>
<td>3.56 (1.3-4.7)</td>
<td>NA</td>
<td>NA</td>
<td>Gutka-chewing is associated with periodontal disease and OSF.*</td>
</tr>
<tr>
<td>Misra et al., 1998¹⁴</td>
<td>Case-control</td>
<td>20-42</td>
<td>110</td>
<td>5.8:1</td>
<td>33 (2.2-46.6)</td>
<td>6 yrs</td>
<td>NA</td>
<td>Gutka usage was associated with oesophageal subepithelial fibrosis.</td>
</tr>
<tr>
<td>Babu et al., 1996¹⁵</td>
<td>Case-control</td>
<td>20-30</td>
<td>90</td>
<td>NA</td>
<td>1.65 (1.2-2.3)</td>
<td>3 yrs</td>
<td>4×</td>
<td>Gutka consumption was associated with the presentation of OSF.*</td>
</tr>
<tr>
<td>Bansode, 2002¹⁶</td>
<td>Retrospective</td>
<td>31-40</td>
<td>336</td>
<td>2:1</td>
<td>3.33 (2.5-5.3)</td>
<td>NA</td>
<td>10-12×</td>
<td>Gutka usage was associated with OSF,* oral ulceration and stomatitis.</td>
</tr>
<tr>
<td>Ahmad et al., 2006¹⁷</td>
<td>Case-control</td>
<td>11-54</td>
<td>292</td>
<td>2.7:1</td>
<td>9.25 (3.1-15.5)</td>
<td>2-4 yrs</td>
<td>2-10×</td>
<td>Gutka chewing was positively associated with OSF*.</td>
</tr>
<tr>
<td><strong>Oral cancer</strong></td>
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<tr>
<td>Gangane et al., 2007²⁶</td>
<td>Cross-sectional</td>
<td>29-70</td>
<td>520</td>
<td>2.1:1</td>
<td>18 (5.8-61.6)</td>
<td>20-49 yrs</td>
<td>NA</td>
<td>Gutka consumption was significantly associated with oral cancer cases.</td>
</tr>
<tr>
<td>Sapkota et al., 2007²⁷</td>
<td>Case-control</td>
<td>34-75</td>
<td>1,742</td>
<td>14:3:1</td>
<td>4.59 (2-5.6)</td>
<td>≥1 yr</td>
<td>NA</td>
<td>Gutka use was associated with an increased risk of hypopharyngeal cancer.</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; OSF, oral submucous fibrosis; NA, not available.
*Each sachet/pouch contains ~3.5-3.8 g dry weight gutka.¹¹

Retrieved. The following data were extracted from all the selected studies: investigators and year of publication of the study, study design, age/age range of the participants, gender of the participants, total number of study participants, number of male and female participants (male:female ratio), daily frequency of gutka usage (number of times gutka was consumed daily), duration of gutka usage (years), oral mucosal disorders associated with habitual gutka usage, and odds ratio (OR) and 95% confidence interval (CI). The structure of this review was customized to mainly summarize the relevant information.

**Statistical analysis**

The statistical analysis was performed using a software program (statistica v. 6.0; Statsoft, Tulsa, OK).
The ORs were computed and 95% CIs were constructed using logistic regression to assess the association between oral mucosal diseases among gutka chewers and control subjects.

RESULTS

Characteristics of the publications

The initial Medline-Pubmed search resulted in 25 citations. Titles of all articles obtained were screened by each author and all abstracts of related articles were screened further. The full text of articles fulfilling the eligibility criteria was assessed. Eventually, 12 studies (which varied by population characteristics and research methodology) were included in the present review (Table I). Thirteen studies, which did not comply with the selection protocol, as shown in Table II, were excluded.

All of the 12 studies included in the present review were carried out at either universities or health care centers. The sample sizes ranged from 90 to 5,061 individuals. The ages of the participants varied between ≥9 years to ≤75 years. In 2 studies, the male:female ratio was 1:1; and in the remaining 10 studies there were at least twice as many men than women in the study population.

The duration of gutka-chewing habit was reported in 8 studies and ranged between ≥1 year and 49 years. Daily gutka consumption by participants was reported by 5 studies. In those studies, the daily consumption of gutka by its consumers ranged from 1 time to 15 times.

Eleven studies were performed in India and 1 was conducted in Pakistan. Eight studies were clinical and 4 were epidemiologic. Three studies showed a significant association between habitual gutka consumption and periodontal inflammatory conditions, including gingivitis, gingival recession, and formation of periodontal pockets (ORs 1.64 [CI 1.2-2.1], 2.20 [CI 1.1-4.9], and 3.56 [CI 1.9-5.5]). Results by Javed et al. also reported self-perceived gingival bleeding to be significantly higher in gutka chewers than in nonchewers (OR 2.20 [CI 1.1-4.9]). Seven stud-
ies\textsuperscript{10,13,15,17} (4 clinical\textsuperscript{10,13,15,17} and 3 epidemiologic\textsuperscript{11,12,16}) showed that OSF was more common in gutka chewers than in nontobacco users (ORs 1.65 [CI 1.2-2.3], 2.33 [CI 1.9-4.5], 2.98 [CI 1.5-3.9], 3.33 [CI 2.5-5.3], 3.56 [CI 1.3-4.7], 5.08 [CI 3.7-6.4] and 9.25 [CI 3.1-15.5]). Hazarey et al.\textsuperscript{11} (OR 2.33) and Gangane et al.\textsuperscript{26} (OR 18 [CI 5.8-61.6]) reported oral cancer to be more prevalent in gutka users than in individuals not using tobacco products. An increased frequency of gutka usage was associated with malignant transformations in OSF cases in 2 studies (ORs 2.33 [CI 1.9-4.5] and 1.65 [CI 1.2-2.3]).\textsuperscript{11,15} Studies by Misra et al.\textsuperscript{14} (OR 33 [CI 2.2-46.6]) and Sapkota et al.\textsuperscript{27} (OR 4.59 [CI 2-5.6]) demonstrated an extension of oral mucosal fibrosis into the hypopharynx and esophagus in gutka users. Two studies demonstrated an association between gutka consumption and oral mucosal ulcerations (ORs 3.33 [CI 2.5-5.3] and 1.64 [CI 1.2-2.1]).\textsuperscript{16,22}

DISCUSSION

The deleterious effects of areca nut, smokeless tobacco, and slaked lime on oral health have been well documented; however, a more severe and intense pathogenic response may be expected when these substances are consumed as a mixture (gutka).\textsuperscript{28,29} A summary of the oral pathophysiologic events induced by habitual gutka chewing is presented in Fig. 1.

The duration of smokeless tobacco usage has been associated with the development of oral mucosal disorders. The Eipe study\textsuperscript{30} reported that habitual use of betel quid for \(\geq 5\) years predisposes the oral mucosa to oral premalignant disorders including OSF. Maher et al.\textsuperscript{31} also reported that individuals using smokeless tobacco products for up to a decade are more susceptible to develop OSF compared with subjects using such products for a shorter duration. However, habitual gutka use has been shown to expose its consumers to OSF at a much faster pace compared to betel quid usage.\textsuperscript{15} Results by Babu et al.\textsuperscript{15} showed that gutka users with OSF had consumed it for \(~3\) years compared with betel quid users with OSF who had started the habit nearly 8 years before. Similarly, a recent case-control study reported that gutka-chewing habit for up to 4 years increases the relative risk of developing OSF.\textsuperscript{10} A possible explanation for this may be that habitual gutka users consume more dry weight of tobacco, areca nut, and slaked lime, which causes nicotine to act synergistically on the cytotoxicity induced by arecoline (a major areca nut alkaloid), thereby increasing the vulnerability of buccal mucosal fibroblasts to damage and enhanced collagen production (up to 170%).\textsuperscript{15,32-37}

To our knowledge from the indexed literature, there is no consensus regarding the influence of daily frequency of gutka consumption on the occurrence of oral mucosal disorders. According to results by Javed et al.,\textsuperscript{1} the frequency of gutka consumption among individuals with oral mucosal disorders ranged from once a day to 10 times daily (average frequency 8 times daily). On the other hand, Bathi et al.\textsuperscript{10} reported that the risk of developing OSF is significantly higher in individuals consuming gutka at least 15 times daily. A direct association between oral inflammatory conditions and age of the subject has been reported.\textsuperscript{38} However, it seems that gutka can expose its consumers to severe oral mucosal disorders at any age. In a study by Javed et al.,\textsuperscript{1} gutka chewers presenting with periodontal inflammation had a mean age of \(~51\) years (range 45-64 years). In the study by Bathi et al.,\textsuperscript{10} the mean age of gutka users was \(<34\) years and ranged from 10 to 64 years. OSF has also been reported in children as young as 4 and 11 years of age who rapidly developed submucosal fibrosis within 3 years of starting the chewing abuse.\textsuperscript{17,37,39}

Gutka contains fine grains of areca nut, which besides causing mechanical injury to oral tissues, also allow ground tobacco to adhere to the traumatized mucosa, leading to morphologic changes and membrane damage. Thus, areca nut in combination with
tobacco may cause cross-links and accelerate the onset of OSF in habitual gutka chewers. This may be an explanation for clinical reports that have shown habitual gutka users to present with OSF at earlier ages compared with traditional betel quid users.\textsuperscript{10-15} However, there are several other factors that may influence the induction of OSF at younger ages regardless of the frequency and quantity of daily gutka usage. Rajendran\textsuperscript{30} reported that vitamin and iron deficiency together with malnourished state of the host leads to derangement in the inflammatory reparative response of the lamina propria, resulting in impaired healing and scarification, which eventually leads to OSF. Nutritional deficiency, deprived socioeconomic status (SES), poor education, as well as the duration of placement of gutka in the oral cavity may play cumulative roles on the induction and severity of oral mucosal disorders.\textsuperscript{13,17,38-41} In studies by Ahmad et al.\textsuperscript{17} and Shiau and Kwan,\textsuperscript{41} the majority of gutka users presenting with OSF were malnourished and had a deprived SES. In the study by Javed et al.,\textsuperscript{1} gutka users cited the chewing habit to be “beneficial” because it helped them to control hunger. Simultaneously, the role of a poor education status, which may compel tobacco chewers to continue with the abuse despite being aware of their impaired oral mucosal health, can not be overlooked. In the Eipe study,\textsuperscript{30} individuals with OSF were aware of their oral mucosal disorder, but they continued the tobacco-chewing habit until the diagnosis of oral cancer was made. Regarding duration of placement of gutka in the oral cavity, Ahmad et al.\textsuperscript{17} reported that 74.5\% of the individuals with OSF were placing gutka in their buccal vestibule for 2-10 minutes. In another study, individuals with oral inflammatory disorders were placing gutka in their buccal vestibule for 5-30 minutes.\textsuperscript{1} Therefore, it seems that the duration of the insult (in combination with the factors mentioned above) may also influence the occurrence and progression of oral mucosal disorders among gutka users. Although OSF is irreversible and persists even after cessation of the chewing habit, it may be hypothesized that cessation of the gutka-chewing habit may help to reduce the severity of the condition and may also prevent its progression to malignancy. However, gutka prevention and cessation research and interventions are not yet documented.

A relationship between oral inflammatory conditions and gender has been reported.\textsuperscript{42} However, the influence of gender in relation to oral mucosal disorders among gutka chewers remains debatable. Anwar et al.\textsuperscript{43} conducted a pilot study which aimed to investigate the attitudes and practices concerning habitual gutka use in a town in India. That study reported gutka usage to be more common among men than women.\textsuperscript{43} Similarly, results by Saraswathi et al.,\textsuperscript{12} Ahmad et al.\textsuperscript{17} and Gan-gane et al.\textsuperscript{26} have reported oral mucosal diseases (including OSF and oral cancer) to be more prominent among male than female gutka chewers. However, it is noteworthy that there were at least twice as many men than women in those studies.\textsuperscript{12,17,26} It may therefore be argued that the reported gender might have been due to the increased number of male compared with female participants. However, results by Hazarey et al.\textsuperscript{11} showed that the severity of OSF was more prevalent in women than men even though the male:female ratio was 4.9:1. In that study, an underprivileged SES and poor education was significantly higher in women than men.\textsuperscript{11} These factors may have contributed to the increased severity of OSF in women compared with men with OSF participating in that study.\textsuperscript{11} From the literature reviewed, we believe that the question “Does gender have any influence on oral mucosal disorders among gutka chewers?” is yet to be answered and further studies are warranted to investigate this relationship.

A study that investigated the effect of smokeless tobacco on blood flow responses showed that smokeless tobacco significantly increases the heart rate, arterial blood pressure, and gingival blood flow.\textsuperscript{44} Furthermore, gutka chewers have been shown to have reduced salivation and mucous formation, thereby reducing the normal commensal oral microflora and exposing their oral cavities to pathogens (\textit{Aspergillus} species).\textsuperscript{45} Thus, a reduced salivary flow may allow the pathogenic bacteria to stagnate in the supra- and subgingival areas, thereby inducing periodontal inflammation in gutka chewers compared with nonchewers. Areca nut extracts have also been associated with the expression of matrix metalloproteinase 9 in gingival epithelial cells, which might help to promote periodontal pathosis in gutka users compared with control subjects.\textsuperscript{46} These might be possible explanations for the raised periodontal inflammatory parameters (including PI, BOP, PPD, and self-perceived gingival bleeding) among gutka users compared with controls.\textsuperscript{1,22} Nevertheless, the role of confounding factors such as a low SES and poor education that may also trigger periodontal inflammation can not be overlooked.\textsuperscript{40}

In conclusion, it is apparent that habitual gutka consumption can rapidly devastate the oral mucosa, and the consequences may extend beyond the oral cavity.

**RECOMMENDATION**

It is highly recommended that the department of health and consumer protection should restrict access to gutka for adolescents and prohibit its sale to minors to curtail gutka usage. There should also be a health hazard label on gutka products. By raising public awareness about the negative effects and health hazards
of gutka, the prevalence of oral cancer and other mucosal disorders might decrease among gutka users. This may also assist in improving the quality of life in these individuals.

REFERENCES


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