The role of smokeless tobacco in the etiology of OPMDs
LEARNING OBJECTIVES

• To differentiate between OSCC and OPMDs
• To describe the epidemiological data related to OPMDs
• To appreciate the role of SLT in OPMD pathogenesis.
• To explain the causal nature of association between SLT and OPMD
• To recognize the differences in potential carcinogenicity of SLT products used in South Asia.
• To identify cost-effective strategies for SLT quitting among OPMD patients.
Estimated age-standardized incidence rates (World) in 2018, lip, oral cavity, both sexes, all ages
What are OPMDs

• Historical perspective, pre-cancers vs potentially malignant?

• Conditions & Lesions

  • A precancerous lesion is a morphologically altered tissue in which oral cancer is more likely to occur than its apparently normal normal counterpart.
  • A precancerous condition is a generalized state associated with significantly increased risk of cancer.

• Lesions: Leukoplakia, Erythroplakia, and the Palatal lesions of reverse smokers.

• Conditions: include Submucous Fibrosis, Lichen Planus, Epidermolysis Bullosa, and Discoid Lupus Erythematosus.

• WHO 2007 The distinction between potentially malignant lesions and conditions be abandoned in favor of a common term, oral potentially malignant disorders
COMPREHENSIVE DEFINITION

“It is a group of disorders of varying etiologies, usually tobacco; characterized by mutagen associated, spontaneous or hereditary alterations or mutations in the genetic material of oral epithelial cells with or without clinical and histomorphological alterations that may lead to oral squamous cell carcinoma transformation”. [1]
Sites of OPMD
Epidemiology of OPMDs

- The prevalence of OPMDs is reported to be from 1% to 5%.
- The overall pooled prevalence of OPMD is 4.47% (95% CI; 2.43 - 7.08) [2]
- The average age of patients with OPMDs is 50–69 years.
- 5% of OPMDs in age < 30 years. [3]
- Leukoplakia is the most common type. [1]
- In South Asia OSMF is comparatively higher [4]
- 3.3 (Buccal mucosa) – 24 .2 (Tongue) [3]
- Erythroplakia has the highest progression rate to malignancy [5]
Etiology of OPMDs

- Genetic predisposition
- Alcohol
- Diet
- Oral Hygiene
- Trauma
- Infections (HPV and Candida)
More than 40 types of smokeless tobacco products (e.g. gutkha, pan masala, snus, chew, etc.) are consumed by nose or mouth, by more than 300 million people around the world, most of whom live in South Asia.
Adult Use
Prevalence of Adult Smokeless Tobacco Use: 2016 or Most Recent

*55 countries have never collected smokeless tobacco use data, leaving them with an incomplete picture of tobacco use in their country. Such information needs to be collected in future tobacco surveillance efforts.
Carcinogenic potential of Naswar

<table>
<thead>
<tr>
<th>Product name</th>
<th>pH</th>
<th>Total nicotine*</th>
<th>Free nicotine*</th>
<th>TSNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naswar (Pakistan)</td>
<td>8.76–9.14</td>
<td>10.5–14.2</td>
<td>8.84–13.2</td>
<td>478–1,380</td>
</tr>
<tr>
<td>Nasway (Uzbekistan)</td>
<td>8.43</td>
<td>8.89</td>
<td>6.36</td>
<td>1,100</td>
</tr>
<tr>
<td>Gutkha (Pakistan)</td>
<td>8.20–8.54</td>
<td>0.16–2.08</td>
<td>0.12–1.08</td>
<td>83.9–1,560</td>
</tr>
<tr>
<td>Gutkha (India)</td>
<td>8.46–8.88</td>
<td>1.09–2.33</td>
<td>0.86–1.78</td>
<td>370–2,250</td>
</tr>
<tr>
<td>Mainpuri (Pakistan)</td>
<td>7.65</td>
<td>1.28</td>
<td>0.38</td>
<td>219</td>
</tr>
<tr>
<td>Mawa (India)</td>
<td>8.31</td>
<td>0.16</td>
<td>0.11</td>
<td>96</td>
</tr>
<tr>
<td>Snus (Sweden)</td>
<td>7.9</td>
<td>16.7</td>
<td>7.6</td>
<td>6.0-25.2</td>
</tr>
</tbody>
</table>

TSNA = Tobacco specific nitrosamines,
### Factors Associated with Progression to OSCC [6]

<table>
<thead>
<tr>
<th>Feature</th>
<th>Parameter</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size of lesion</td>
<td>&gt;200 mm²</td>
<td>Strong</td>
</tr>
<tr>
<td>Texture</td>
<td>Nonhomogeneous</td>
<td>Strong</td>
</tr>
<tr>
<td>Color</td>
<td>Red (or speckled)</td>
<td>Strong</td>
</tr>
<tr>
<td>Site</td>
<td>Tongue and floor of mouth</td>
<td>Strong</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Medium</td>
</tr>
<tr>
<td>Age</td>
<td>&gt;50 years</td>
<td>Medium</td>
</tr>
<tr>
<td>Habits</td>
<td>Nonsmoker</td>
<td>Weak</td>
</tr>
<tr>
<td><strong>Histologic features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysplasia</td>
<td>Severe</td>
<td>Strong</td>
</tr>
<tr>
<td>HPV</td>
<td>HPV-16 +</td>
<td>Medium</td>
</tr>
<tr>
<td>DNA content</td>
<td>Aneuploidy</td>
<td>Medium</td>
</tr>
<tr>
<td>LOH</td>
<td>Many genes involved</td>
<td>Medium</td>
</tr>
</tbody>
</table>
SLT & OPMD: An association or causation

- Bradford Hill criteria
  - Strength of the association
  - Consistency
  - Specificity
  - Temporality
  - Biological gradient
  - Plausibility/Coherence
  - Experiment
  - Analogy
• mOR (Overall, n = 18) = 15.5 (95% CI, 9.9 - 24.2)

• mOR (Alc+smok adjusted, n=12) = 13.1 (95% CI, 8.3– 20.7)

• mOR (India, n = 15) = 14.5 (95% CI, 8.9–23.5)

• mOR (India adjusted, n = 9) = 11.4 (95% CI, 6.9–18.8)

• mOR (Population controls, n = 6) = 15.0 (95% CI, 9.1–24.8)

• mOR (Females, n = 5) = 22.2 (95% CI, 9.1–54.1)

• mOR (Males , n = 5) = 8.7 (95% CI, 2.1–34.8)
mOR (OSMF, adjusted n = 9) = 16.2 (95% CI, 8.7–30.0)
mOR (LKP) = 4.33 (95% CI 1.4–13.2).
OR (Multiple OPMD) = 37.8 (95% CI, 16.8–88.1)
OR (EP) = 19.8 (95% CI, 9.8–40.0).
mOR (betel quid) = 16.1 (95% CI, 7.8–33.5)
mOR (Gutkha) = 4.9 (95% CI, 2.6–9.4)
mOR (Adjusted, multi) = 13.8 (95% CI, 5.5–34.9)
• mOR (20 years-non users) = 29.3 (95% CI, 20.3–42.1)

• mOR (40 years-non users) = 41.9 (95% CI, 27.4–64.1)

• mOR (10/day –non users) = 33.7 (95% CI, 23.6–48)

• mOR (20/day –non users) = 55.7 (95% CI, 35.2–88.3)
Very long latency period, but in almost all cases the initiation of habit is at a very early stage.

Mumbai cohort 16 year revisit = 64% had lesions [7]
Silencing of tumor suppressor genes in the genome-wide DNA methylation study.

Identified a unique set of hypomethylated immunoresponse genes among OSCC patients in India, which might be attributed to different oral habits observed in Indian patients.
High risk of OPMD with Paan use compared to other habits.

Areca nut, which in itself is considered carcinogenic is combined with slaked lime and tobacco in the preparation of betel quid.

The slaked lime works 2-fold:

(1) It helps in the release of Arecoline and its conversion into Arecaidine, which in turn trigger fibroblast proliferation and increase collagen synthesis in the oral mucosa, and

(2) It also facilitates the production of Reactive Oxygen Species, which causes oxidative stress by increasing the pH of the oral microenvironment.

Thus pose a higher risk of oral premalignancy and malignancy due to a synergistic effect, compared to other SLT products.
Other criteria

- Experimental evidence
  - Warnakulasurya & Straif, 2018 [8]

- Specificity

- Analogy
Public Health & Tobacco control Implications

“Early detection is the key”

Early detection → Early intervention → Favorable outcome

Patients with OPMDs are more motivated for tobacco cessation (odd's ratio = 2.30, \( P = 0.002 \)) [9]

“The absence of oral malignant lesions in the follow up of the Mumbai cohort, even after a long period of 16 years, may possibly be attributed to repeated, effective counseling to the tobacco and alcohol users regarding cessation of the same” [7]
REFERENCES

Main Sources


- https://tobaccoatlas.org/
THANK YOU FOR YOUR ATTENTION

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