Addictions Causing Head-and-Neck Cancers

Abstract

Background: Head-and-neck cancers pose a serious economic burden, with most countries investing significant resources to reduce the incidence, primarily focusing on understanding addictive etiologies. The traditional literature focused on tobacco and alcohol use, with few studies on contemporary factors such as e-cigarette, waterpipe smoking, and human papillomavirus. This article attempts to collate and present an update on the globally identified etiologic factors. Aims: The aim of this study was to identify and review the addictive etiologic factors causing head-and-neck cancers. Methods: An electronic search was performed on Medline, Embase, and Google Scholar to identify the etiologies causing head-and-neck cancers and narrowed down on those driven by addiction. Further, we identified their constituents, mechanism of action, and the risks attributable to various forms of products. Results: Substances identified included smoked and chewed tobacco, alcohol, mate, marijuana, areca nut and betel quid, and viruses. An alarming majority of youth are now utilizing these substances. Furthermore, migrant movements have led to the spread of traditional practices across the regions, especially from the Asian subcontinent. Conclusion: Ironically, despite modern advances and technology, we still see that a large proportion of population succumb to these cancers, emphasizing the need for more effective and targeted policies to combat this menace at the grassroots level.

Keywords: Addictions, alcohol, areca nut, betel quid, head-and-neck cancer, marijuana, tobacco, virus

Introduction

A significant contribution toward the global health burden is from head-and-neck squamous cell carcinoma (HNSCC) – the highest from the lip and oral cavity followed by larynx and oropharynx.[1] In an effort to reduce this load, countries often spend a significant portion of their health-care budget to understand the associated etiology and risk factors. The traditional risk factors include the use of tobacco, alcohol, and areca nut, while the more recent include poor oral hygiene, varied sexual practices, chronic trauma, and dietary deficiencies.[2] A majority of these are addiction driven, and about 75% are caused by tobacco, alcohol, and substance use alone.[3] The joint effects of lifestyle-related factors lead to approximately 35% of the cancer population.[4] An alarming majority of youth are now utilizing these substances developing a shift in the mean age of disease burden in emerging markets even more than adults.[5] There has also been a surge of novel products, such as the e-cigarette and waterpipe smoking, with companies investing gigantic amounts in branding them to be less hazardous, the effects of which still have to be recognized longitudinally.[6] Kandel popularized the concept of tobacco being a “gateway substance” for alcohol consumption and other substances such as marijuana and cocaine.[7] Studies have shown that adolescents who smoked were 3 times more likely to drink alcohol, 8 times more likely to also smoke marijuana, and 20 times more likely to use cocaine than nonsmoking peers.[8] On the contrary, it is interesting to see that many countries’ economies are crippingly dependent on the production of these leading causes of cancer, especially tobacco.[9] With these addictive substances being used across all strata of society, it is important to understand their varied carcinogenic potential. This article attempts to collate and present an update on these substances used globally that cause HNSCC.
Methods

We performed an electronic search on Medline, Embase, and Google Scholar to identify the various etiologies causing HNSCC. Our initial search results comprised 284 articles that suggested the role of a substance causing HNSCC. On identifying these agents, we further cross-searched the same databases to narrow down on those driven by addiction and identified studies according to the PRISMA guidelines. On reviewing these articles and their references, we concluded with 54 articles that were categorized into those who identified their constituents and mechanism of action and enlisted the various forms of use globally, along with their associated carcinogenic potential to cause HNSCC.

Results

Tobacco and its forms

Tobacco use in all its forms accounts for nearly a third of the global cancer mortality.[1] The initial association was made only for oral cavity, oropharynx, larynx, and hypopharynx but was later extended to include other subsites of the head and neck.[10] The overall risk is proportional to lifetime substance exposure, including the age of initiation, quantity, frequency, number of pack-years, and exposure to secondhand and thirdhand tobacco smoke.[11] Nicotine, a potent parasympathomimetic stimulant, usually constitutes 0.6%–3.0% of the dry weight of tobacco.[12] After inhalation of the smoke, nicotine crosses the blood–brain barrier in 10–20 s and has a half-life of about 2 h.[13]

Carcinogenic compounds

There are 60 confirmed carcinogenic chemicals in tobacco smoke out of its 4000 constituent chemicals, with a majority being Tobacco-Specific Nitrosamines (TSNAs).[13] Once metabolized, they cause DNA alkylation initiating a series of mutagenic events. Others include the polycyclic hydrocarbons, aromatic hydrocarbons, and catechols, all of which supplement the TSNAs.[13]

About 28 carcinogens have been identified in smokeless tobacco, formed during aging and curing. Others present include volatile aldehydes, benzo[a] pyrene, urethane, certain lactones, arsenic and nickel, uranium-235 and uranium-238, and polonium-210.[14] The overall nicotine absorption is slower compared to cigarettes, but about 3–4 times greater nicotine per dose is absorbed. Chewing or dipping smokeless tobacco 8–10 times per day may deliver a similar amount of nicotine as smoking 30–40 cigarettes per day.[15]

Mechanism of action

Once these carcinogens are absorbed, they require activation by cellular enzymes, such as the cytochrome p450 group, while detoxifying enzymes offset these effects. The induction of somatic genetic mutations is equally important to drive the tumor pathogenesis, which are either proto-oncogenes or inhibitors of tumor suppressor genes.[13] The common molecular enzyme signaling pathways affected are the p53 pathway, retinoblastoma pathway, epidermal growth factor pathway, and the PI3-kinase pathway. All of these events along with local mucosal changes due to chronic trauma or injury lead to the eventual development of a cancerous lesion.[13]

Smoked tobacco

Smoking is the single most preventable cause of cancer with the highest users in the WHO European region (75.3%).[15] The association of smoked tobacco and cancer was initially studied in 1915, where the habit was commonly seen among oral cavity lesions [Table 1].[16] Countries having more adolescent than adult smokers among males include Ethiopia, Nigeria, Qatar, and Senegal, while in females, include Argentina, Costa Rica, Egypt, Kenya, Mexico, Pakistan as well as the countries mentioned before. Countries with a very high human development index have shown a reduction in the rate of tobacco use among the youth.[15] A meta-analysis has shown that the odds of getting oral cancer was 4.65 times higher than nonsmokers, with the highest rates in the American continent (odds ratio [OR] = 7.65) and the lowest in Asia (OR = 1.88).[17]

Cigarettes

Blond variety of tobacco is the most commonly used form globally, with around 8 mg of total nicotine available in a commercial cigarette. Menthol cigarettes have become popular due to their flavor and increased half-life due to the inhibition of nicotine-to-cotinine metabolism.[18] The tonsillar crypts, glossosollicul sulcus, and base of the tongue are commonly affected due to the prolonged exposure of the pooled saliva. The relative risk for developing cancers in the upper aerodigestive tract increases with the number of cigarettes smoked daily and the duration of years. The risk is also proportional to the number of years after quitting, with the exception of esophageal cancers.[17] Lubin et al. found that a greater number of cigarettes smoked per day for a short duration were less deleterious than fewer cigarettes per day for a longer duration.[19]

Cigar and pipes

A typical cigar is made of dried dark tobacco leaves that are rolled into a bundle which is available in a variety of grades and sizes. The most common forms include the coronas or parejo that are predominantly manufactured in Southeast Asian and South American countries. The smoke from cigars is not inhaled and often rolled around the mouth. Similarly, pipe smoking was also traditionally meant for tobacco tastings. This may lead to a stronger association with oral cancer than other forms of smoked tobacco. Parkin et al. have found that pipe use had a similar risk of developing oral and oropharyngeal cancers as that

Another study by Wyss et al. from the INHANCE consortium found that the risk for HNSCC was higher in exclusive cigar (OR = 3.49) and pipe smokers (OR = 3.71), suggesting their independent association with these cancers.[21]

Beedi

This is a hand- or machine-rolled form of cigarette wrapped in tendu or temburni leaf used most commonly in the Indian subcontinent. It commonly causes cancers of the oral commissure and entire tongue. Rahman et al.’s meta-analysis showed that beedi smoking had a higher OR of 3.1 compared to cigarette smoking (OR = 1.1) in causing oral cancer.[22]

Waterpipe smoking or hookah/shisha/narghile

With its origins in the Middle East, this form of tobacco smoking has gradually gained popularity among the youth subsequent to the introduction of flavored tobacco (maassel).[23] Waterpipe smoking is the most common method of tobacco smoking than any other form in the Arab world.[24] Overall, the prevalence rates range from 0.9% in Oman to 34.2% in Lebanon.[25] A meta-analysis found that its association increased the risk of HNSCC (OR = 2.97), esophageal cancer (OR = 1.84), and lung cancer (OR = 2.22).[24]

Reverse chutta/addapoga

This form is more common in the rural indigenous population of the Asian subcontinent. It is related to cancers of the hard palate and associated structures due to maximum local exposure of heat with carcinogen, seen especially higher among women.[26]

E-cigarettes

E-cigarette is a contemporary form of noncombustible nicotine use. There is no clear evidence whether they aid in tobacco cessation. While population studies have shown that smokers have successfully quit smoking with the help of e-cigarettes, randomized trials and cohort studies have not been able to demonstrate the same. It is also associated with many side effects such as dry mouth or sore throat, cough, dizziness, headache, mouth or tongue sores, sleeplessness, palpitations, breathing problems, allergies, fatigue, nose bleeding, chest pain, stress, and gum bleeding.[27] There is also evidence of substantial experimentation among the youth, even among never-smokers, suggesting a possibility of a new “gateway” substance.[28] The epidemiological evidence of its long-term health effects is still to be seen and might take decades to make final conclusions. India has recently banned the manufacturing, distribution, import, and sale of all electronic nicotine delivery systems. Not only India but also other countries such as Argentina, Taiwan, Singapore, Jordan, Lebanon, Malaysia, Cambodia, Columbia, Egypt, Mexico, Singapore, Brazil, Thailand, and Vietnam have imposed ban with varying levels of success.[29]

Secondhand or passive smoking

More than 7 million people die due to tobacco smoking every year, while about 12% of these are due to secondhand smoke exposure.[30] Most studies available show a relation between environmental tobacco smoke and lung cancer, while few are present indicating a link to HNSCC.[31] Although the duration was not specified, Lee et al. showed that a long period of passive smoking increased the risk of HNSCC by 1.55–1.6 times that was stronger for pharyngeal and laryngeal cancers.[32]

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Table 1: Smoked forms of tobacco

<table>
<thead>
<tr>
<th>Product</th>
<th>Region</th>
<th>Preparation</th>
<th>Site of cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarettes</td>
<td>Worldwide</td>
<td>Blended tobacco (most often blond) packed into paper rolls + filter</td>
<td>Upper aerodigestive tract, Lung, Oral</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>UK, Australia, Mediterranean</td>
<td>Dark tobacco + packed into binder leaf and rolled</td>
<td>Oropharynx, Lung</td>
</tr>
<tr>
<td>Cigar and pipes</td>
<td>North and South America</td>
<td>Tobacco + special waterpipe</td>
<td>Oral, Oropharynx, Lung</td>
</tr>
<tr>
<td>Beedi</td>
<td>Asian subcontinent</td>
<td>Tobacco + packed into tendu leaf rolls</td>
<td>Oral commisure, Tongue</td>
</tr>
<tr>
<td>Waterpipe/hookah</td>
<td>Arab world</td>
<td>Tobacco + special waterpipe</td>
<td>Oral, Oropharynx, Lung</td>
</tr>
<tr>
<td>Reverse chutta smoking</td>
<td>India, Bangladesh, Pakistan</td>
<td>Any of above smoked with cherry reversed</td>
<td>Hard and soft palate</td>
</tr>
<tr>
<td>Secondhand/passive smoking</td>
<td>Worldwide</td>
<td>-</td>
<td>Pharynx, Larynx, Lung</td>
</tr>
</tbody>
</table>

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of cigarettes (OR = 3.8 and 3.9, respectively) while cigar smoking was double (OR = 8.3).[20] Another study by Wyss et al. from the INHANCE consortium found that the risk for HNSCC was higher in exclusive cigar (OR = 3.49) and pipe smokers (OR = 3.71), suggesting their independent association with these cancers.[21]
**Thirdhand smoking**

Residual tobacco pollutants including tobacco-specific nitrosamines, 3-ethenylpyridine, phenols, cresols, naphthalene, and formaldehyde remain in dust or on surfaces after smoking, and these react with oxidants to yield secondary pollutants or are re-emitted into gaseous state. Thirdhand smoke is pervasive and ubiquitous and its presence on surfaces and dust creates multiple routes of exposure. Because of increased exposure and sensitivity to various pollutants, children and infants account for the most vulnerable population.[33]

**Smokeless oral**

Cancers arising in these smokeless tobacco (SLT) users are more often at the site of quid placement, usually being the oral and oropharynx [Table 2]. Over 250 million people in the Southeast Asia region use SLT, representing about 17% of the population (82% live in India).[14] Siddiqi et al. studied the burden of SLT consumption across 113 countries and found that they were 3.43 times more likely to develop oral cancers, commonly of the tongue and lips.[34] Even the potentially malignant lesions have a higher incidence among SLT users.

A product with a higher pH delivers more protonated nicotine that adds to a higher potential of toxicity. The highest pH values are seen in naswar from Uzbekistan and toombak from Sudan.[14] Over the years, the pH values are declining possibly leading to reduced habitual behaviors. Ammonium and sodium carbonate (chunna) are often added as alkylating agents to the tobacco products to enhance absorption. With high use in the South Asian countries, a strong association has been found for oral cancers varying among the betel quid users from 3.1 to 15.7, while for other types of smokeless tobacco from 1.2 to 12.9.[35] Among

### Table 2: Smokeless forms of tobacco

<table>
<thead>
<tr>
<th>Product</th>
<th>Region</th>
<th>Preparation</th>
<th>Site of cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loose leaf chew</td>
<td>USA</td>
<td>Shredded tobacco leaf with sweeteners, licorice</td>
<td>Oral</td>
</tr>
<tr>
<td>Moist plug</td>
<td>Arab countries</td>
<td>Similar preparation wrapped into fine tobacco pressed into bricks</td>
<td>Oropharynx</td>
</tr>
<tr>
<td>Shammah</td>
<td></td>
<td>Catha edulis leaves</td>
<td>Nasopharynx</td>
</tr>
<tr>
<td>Qat</td>
<td>Arab</td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td>Khat</td>
<td>Northern Africa</td>
<td>Nass - tobacco with ash, sesame or cotton oil, and/or gum</td>
<td>Oral</td>
</tr>
<tr>
<td>Nass</td>
<td>Iran</td>
<td>Naswar - same mix with slaked lime, cardamom oil, or menthol</td>
<td>Oral</td>
</tr>
<tr>
<td>Naswar</td>
<td>Uzbekistan-Afghanistan</td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td>Paan</td>
<td>Southeast Asia</td>
<td>Tobacco with betel leaf, slated lime, areca nut</td>
<td>Alveolobuccal</td>
</tr>
<tr>
<td>Paan masala</td>
<td></td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td>Oral snuff</td>
<td>India - khaini</td>
<td>Snus - Moist ground tobacco with aqueous solution of water, other blended solutions</td>
<td>West - vestibule of the upper lip</td>
</tr>
<tr>
<td></td>
<td>Sudan - toombak</td>
<td>Toombak sp. Nicotiana rustica with soda bicarbonate</td>
<td>Southeast Asia and African - inferior gingivobuccal sulcus</td>
</tr>
<tr>
<td></td>
<td>Sweden - snus</td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Tunisia - neffa</td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td>Gutkha</td>
<td>Asian subcontinent</td>
<td>Premixed dried form of areca nut with slaked lime, spices, flavoring agents, and tobacco</td>
<td>Alveolobuccal</td>
</tr>
<tr>
<td>Gudaku</td>
<td>Central and Eastern India</td>
<td>Creamy preparation of tobacco</td>
<td></td>
</tr>
<tr>
<td>Mishri</td>
<td>Bangladesh</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bajjar</td>
<td>Some parts of the UK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mawa</td>
<td>Western India</td>
<td>Mawa - Rubbed mix of sun-cured areca nut with tobacco and slaked lime</td>
<td>Oral</td>
</tr>
<tr>
<td>Zarda</td>
<td>Bangladesh</td>
<td>Zarda - Same mix with spices</td>
<td>Lower gingivobuccal sulcus</td>
</tr>
<tr>
<td>Chimó</td>
<td>Venezuela - chimo</td>
<td>Tobacco leaf is crushed and boiled, sodium bicarbonate, brown sugar, ashes from the mamón tree, vanilla, and anisette</td>
<td></td>
</tr>
<tr>
<td>Kimam</td>
<td>Brazil - Asian and African - kimam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iq’mik</td>
<td>Alaska</td>
<td>Fire-cured tobacco with punk ash</td>
<td>Oral</td>
</tr>
<tr>
<td>Nasal snuff</td>
<td>Sweden</td>
<td>Fire-cured tobacco leaves crushed into a powder</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td></td>
<td>Nasal</td>
</tr>
<tr>
<td></td>
<td>UK</td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Bhutan</td>
<td></td>
<td>Larynx</td>
</tr>
<tr>
<td></td>
<td>India</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
the subsites, the highest OR of 5.5 has been shown to be among oral cancers while it is almost half for the pharynx and larynx (2.69 and 2.84, respectively).\[36\]

**Loose leaf chew/shammah and qat**

Sold primarily in the USA, loose leaf chew is the simplest form of chewed tobacco. Moist plug is the same preparation that is pressed into brick-like forms. The Arab equivalent is shammah. It causes oral, oropharyngeal, and nasopharyngeal carcinomas as it is commonly held at the posterior aspect of the oral cavity.\[37\] Qat or khat (Catha edulis) is a shrub whose leaves are chewed to deliver euphoric effects due to the amphetamine and cathinone. It is consumed in the Arab region and North Africa and can lead to hysteria and even psychosis. Qat-related oral cancer is often initiated by mucosal keratosis. Its carcinogenic effects are established by inducing mutations along with various embryogenic and teratogenic effects.\[14\]

**Nass and naswar and mishri**

Nass is a mixture of tobacco and ash with flavorings such as sesame or cotton oil with little water. Gum is sometimes added to make it chewy. When the same is rubbed with slaked lime and cardamom oil or menthol, it is referred to as a naswar.\[38\] Products used in the rural parts of Central and East India and Bangladesh are gul or mishri, often used as teeth cleaning abrasive, while bajjar is used on the gums. Central Asian countries such as Iran, Afghanistan, and Pakistan have a high consumption of these substances. Hence, alveolar cancers are common among these users. Ipco, as marketed in the Indian subcontinent, is also popular among migrant communities in some parts of the UK as a creamy snuff, primarily among women.\[33\]

**Paan and gutkha**

A customary form of SLT use called “paan” is tobacco, slaked lime, and areca nut mixed on a betel leaf. In Southeast Asia, a flavoring agent or sweetener is added and consumed as a mouth freshener. The release of alkaloids is accelerated due to the reduction of pH by the lime. Paan chewing is associated with high rates of alveolarbuccal cancers and premalignant lesions.\[14\]

Gutkha is a premixed form of the above ingredients available either in manufactured or indigenous packaging. It is the most advertised form of tobacco in the Asian subcontinent making it increasingly popular among the youth. Gutkha has been shown to cause genotoxicity and carcinogenesis.\[39\] Due to this, Indian states have started restricting the manufacture and distribution of these substances.\[40\]

**Oral snuff**

In India, a mix of ground moist tobacco and lime is referred to as khaini, while toombak is the Sudanese form of the same preparation. Sweden has the highest consumption and sale of snuff per capita in the world. It is available either as a portioned loose product, often rolled into a ball called a “saffa, weighing about 10 g.” Each pinch or dip is placed in the vestibule of the upper lip in Western countries and in the inferior gingivobuccal sulcus in Southeast and African countries.\[34\] The pH and the unprotonated nicotine are brand specific, ranging from 5.4 to 8.4.\[42\] The traditional Tunisian “neffa” has a similar content. Approximately 90% of the tobacco products in Algeria are used in the manufacture of snuff.\[43\] Low TSNA snuff is being marketed as a safe product as hard snuff or lozenges.

**Chimó or kimam and iq’mik**

The most common form of SLT in Venezuela is Chimó. Tobacco leaves are crushed and boiled with sodium bicarbonate, brown sugar, and ashes from the mamón tree to make a thick paste which is seasoned with a flavoring agent. Its use has increased exponentially among young children with a study showing one in ten among 13–16-year-old boys using it.\[44\] A similar paste is used in Africa made with cardamom or saffron called kimam or qwam. It is placed in the lower gingivobuccal sulcus that causes cancers of the lower alveolus. Iq’mik is a form of fire-cured tobacco mixed with punk ash, used by almost half of Alaskan natives, which includes teething babies.\[45\] A small piece is chewed until soft that often lasts throughout the day.

**Smokeless nasal**

**Dry snuff**

The snuff is prepared by fire curing the tobacco leaves and crushing them into a powder. Since it is sniffed, it is associated with sinonasal or nasopharyngeal cancers. It is very popular in Sweden and the USA. Approximately 8% of Bhutanese use oral or nasal snuff in a country where tobacco sale is prohibited.\[46\] Sankaranarayanan et al. found that a 3 times higher relative risk of developing tongue, floor of mouth, gingiva, and buccal mucosa cancers exists among snuff users compared to nonusers. They also found a 1.2 times higher risk of developing laryngeal cancers among snuff inhalers.\[14\]

**Alcohol**

After tobacco, alcohol is the second most common preventable cause of cancer. It has a multiplicative effect when used with tobacco, establishing a strong role as a co-carcinogen.\[47\] The National Institute on Alcohol Abuse and Alcoholism reports that alcohol is responsible for 5.9% of the total deaths globally.\[48\] Binge drinking, especially among teenagers and students, contributes three-quarters of the total misuse cost in the USA.\[49\]

Goldstein et al. studied the association between alcohol use and oral/oropharyngeal cancer and found that beer had the highest risk in the USA while wine had the lowest. In Italy and Switzerland, the highest risk was associated with...
wine, while among the Swedish, beer and liquor were the highest. Cuba and Brazil had the highest risk among hard liquor drinkers, while in Uruguay, it was wine. Arrack had the highest risk in India.\footnote{47} The hypopharynx has the strongest association, while the glottis and subglottis have the least.

*Mechanism of action*

On ingestion of alcohol, its metabolism to acetaldehyde is important for its carcinogenic effect. Acetaldehyde exerts its effect by binding to DNA and altering the methyl transfer pathways resulting in genetic hypomethylation, eventually leading to transcription of multiple genes. The reactive oxygen species further contribute to the mutations promoting the p540 cytochrome activity similar to tobacco. Locally, it acts as a solvent to increase the permeability of mucosa. Chronic alcoholics also have a lowered immunity and nutritional status, which further aggravates the process. Consumption causes a release of excitatory and inhibitory neurotransmitters such as dopamine and GABA. Some studies have also shown a direct increase in the release of endorphins on consumption.\footnote{14}

*Quantity of alcohol*

The relative risk of developing oral cancer among alcohol users ranges from 3.2 to 9.2 for people who consume >60 g/day (equivalent to 4 drinks/day).\footnote{47} Zhang et al. in their meta-analysis divided 13,830 patients into light drinkers (≤12.5 g/day), moderate drinkers (12.6–49.9 g/day), and heavy drinkers (≥50 g/day). They found that the OR for developing HNSSC was 1.29, 2.67, and 6.63, respectively, for the previously mentioned quantities.\footnote{80} It is also shown that more number of drinks per day over a shorter duration are more deleterious than fewer drinks consumed daily for a longer duration. They also found a stronger relation proportional to drink-years than drinks consumed daily for oral cavity and pharyngeal cancer risk.\footnote{19}

*Maté or chimarrão*

Maté is a popular beverage mainly consumed in South America. It is similar to tea in that it is made from fermented leaves and stems of *Ilex paraguariensis* or yerba maté. Most of its carcinogenic potential comes from phenolic compounds, tannins, and N-nitroso compounds.\footnote{14} It is mainly consumed in the South American continent and in lesser amounts in Syria, Northern Israel, and Lebanon. A meta-analysis calculated an increased risk (OR = 2.11) of developing oral cancer in mate users.\footnote{51} A dose–disease relation study by Stefani et al. showed that the highest risk of developing upper aerodigestive tract cancer and laryngeal cancer was with consumption of >2 l/day (OR = 1.37 and OR = 1.54, respectively) and in mouth cancers was with 1–1.9 l/day (OR = 1.03), while the highest overall risk was for esophagus (OR = 3.09).\footnote{52} Brazilian group found that maté at a very hot temperature had a 3-fold increase risk of oropharyngeal cancers than when consumed hot.\footnote{53}

*Marijuana*

After tobacco, marijuana is the most commonly smoked recreational substance. It has been associated with similar upper and lower respiratory pathologies and cancers. Their carcinogenicity is due to the cytogenetic changes that are induced after activation.\footnote{54} There are very few studies linking HNSSC with long-term marijuana use and all point toward a younger age of incidence resulting in more aggressive disease. Contrary to this notion, a meta-analysis by de Carvalho et al. suggested no strong association between exposure and disease with a relatively low OR of 1.021.\footnote{55}

*Areca nut and betel quid*

The areca nut is the seed of the fruit of the areca palm that is predominantly consumed in Africa, South America, Taiwan, and the Indian subcontinent. Its consumption is deeply integrated into cultural and religious activities in these regions. The Taiwanese usually do not add tobacco and have reported a relative risk of 58.4 of developing oral cancer among their population.\footnote{56} A higher risk of developing esophageal cancer is present in this population because they swallow the liquid extract, as opposed to tobacco chewers who spit it out in other parts. The risk further increases by 8.4 times when tobacco is added.\footnote{57} In certain parts of India, 87% of women chew areca nut as compared to only 49% of men.\footnote{58} The habit has a strong association with potentially malignant disorders such as submucous fibrosis. The areca nut contains alkaloids (arecoline, arecaidine, guvacine, and guvacoline) and flavonoids (tannins and catechins) that have a cytotoxic effect on cells and promote collagen synthesis. The constant irritation from the chewing habit leads to a T-cell and transforming growth factor-beta-mediated chronic inflammation, further adding to the fibrosis.\footnote{59}

During areca nut chewing, the oral mucosa is persistently stimulated by the areca nut extracts and arecoline, which causes induction of c-Jun proto-oncogene. This proto-oncogene encodes a nuclear protein (39 kDa) which is a major component of the mammalian transcription factor activator protein-1 (AP-1), and it is involved in cellular transformation, multiplication, and apoptosis. c-Jun activation or overexpression has been found in many human malignancies. This may be one of the mechanisms for causing oral cancers.\footnote{60}

*Viruses*

Majority of the literature on HPV-associated HNSSC comes from the west, with the highest association with oropharyngeal subsites, independent of tobacco and alcohol.\footnote{59} This association has been shown across numerous case–control studies globally, with risk ranging from 3.6 to 230 for oral oncogenic HPV infection.\footnote{61} The typical presentation of a HPV-positive HNSSC is in a young male, having a small primary tumor and a large
regional nodal metastasis, without the traditional risk factors (tobacco, alcohol, etc.). Tobacco-related HPV-positive cancers might be a different entity altogether as reported by their atypical behavior in many Indian studies. A systematic review suggests a significantly increased risk of developing oral and oropharyngeal cancers proportional to the number of lifetime sexual partners and practice of oral sex and homosexual relations. The other parameters, though inconsistent, included younger age at first engagement, lifetime oral and oral-anal sex partners, and ever performing anal sex.

**Discussion**

**Summary of key findings**

Despite the overwhelming evidence against tobacco, over a billion people still smoke today. Early on, a significant contributor included the media. Magazines such as Cigar Aficionado and Smoke and advertising campaigns such as the Marlboro Man revolutionized the marketing of tobacco products by associating it with a desirous lifestyle. While smoking has declined in high-income countries, it is constantly on the rise in low- or middle-income countries accounting for 80% of burden.

These habitual practices have also seen wide international adoption. Due to rapid migration, traditional practices are spreading across borders. The majority of quid consumption is made up of Asian and Arab immigrants. Similarly, the practice of waterpipe/hookah smoking is also emerging to be the next big killer. Administrations need to focus their resources in understanding these culture-centric habits and design tailored programs to redress their usage. Another approach is to create awareness of these less popularized indigenous habits by including them in the national list of health hazards.

The use of novel products such as e-cigarettes has increased recently. In 2014, they were the most commonly used tobacco product by the youth, with a third having tried them at least once. Among these, 25% are dual and 21% are multiple product users [Table 3].

**Implications**

These factors underscore the need for youth-centered addiction awareness and control programs. An increase in taxation of these substances has proved successful as the youth are most sensitive to these measures. The Cigarettes and Other Tobacco Products Act (COTPA) 2003 enacted by the Indian Parliament bans the sale of tobacco products near an educational institution. According to Section 6, it is deemed illegal to sell these products within a 100-yard radius of an educational institution. In order to protect children from the harms of tobacco addiction, the Juvenile Justice Act was amended in 2015 that now includes 7-year imprisonment and/or 100,000 fine and enforcement of other provisions of COTPA related to tobacco. Opportunistic screening programs stressing on lifestyle modifications are the most important key in reducing the burden of oral cancers, especially in less developed countries.

**Conclusion**

A large proportion of the population is still at risk of these cancers driven by addiction. It is of the utmost importance that policy decisions be taken based on the evidence provided in this review as more numbers of youngsters are being driven towards these habits without known the dire consequences.

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**Conflicts of interest**

There are no conflicts of interest.

**References**


the forum of international respiratory societies. Am J Respir Crit Care Med 2014;190:611-8.


13. IARC. Tobacco Smoke and Involuntary Smoking. IARC Monogr Eval Carcinog Risks Hum 2004a; 83-1,1438.


41. Idris AM, Ibrahim SO, Vassstrand EN, Johannessen AC, Lillehaug JR, Magnusson B, et al. The Swedish snus and...


