Smokeless Tobacco Lesions

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Background

The term smokeless tobacco, also known as dip, plug, chew, or spit tobacco, refers to both chewing tobacco (coarse cut) and snuff (fine cut). Three types of smokeless tobacco are commonly manufactured: loose-leaf chewing tobacco, moist snuff, and dry snuff.[1] Dry snuff, which is inhaled nasally, or in the more commonly used moist form, which is placed in the oral cavity. In 2006, pouch-type tobacco products were marketed in the United States. This type of tobacco is positioned along the gum line, and the user may swallow the juices, making chewing and spitting unnecessary. In the United States, clean indoor air acts and cigarette excise tax increases have resulted in a coincidental increase in smokeless tobacco use.[2] In addition, unlike cigarettes, the majority of smokeless tobacco products are sold without a health warning, and lack of awareness of its negative impact on health increases its consumption.[3]

Worldwide, several names are used to denote different smokeless tobacco products. These include plug, gutkha, khiwam, khaini, iq'milk, zarda, naswar, nass, chimo, toombak, shamma, gudhaku, gul, mishri, maras, and moist snus.[4]

The use of smokeless tobacco is associated with a spectrum of oral cavity lesions, including leukoplakia, speckled leukoplakia, erythroplasia, tobacco-associated keratosis, carcinoma in situ (CIS), verrucous carcinoma, and invasive squamous cell carcinoma (SCC). It can cause smokeless tobacco – induced keratosis, gingival inflammation, periodontal inflammation, alveolar bone damage, dental caries, and tooth abrasion. In addition to oral lesions, smokeless tobacco users are at increased risk for stomach and pancreatic cancers, although the data regarding the risks for pancreatic cancer are mixed, with some studies showing a statistical association.[5, 6, 7, 8, 9, 10]

Tobacco-related lesions (smokeless tobacco–related and nicotine stomatitis) comprised 4.7% of all lesions found in 17,235 people examined as part of the Third National Health and Nutrition Examination Survey. Smokeless tobacco users had one of the highest odds of having a lesion present (odds ratio, 3.9).[11]

Gingival inflammation and alveolar bone damage

Studies from the United States report high rates of gingival recession in smokeless tobacco users, and, ultimately, periodontal disease and bone loss. There appears to be an association between the quantity of smokeless tobacco used and the severity of disease. Periodontal pathology is most likely related to long-term use of smokeless tobacco and is more typical in adult populatiosn than in teenagers. However, although gingival and periodontal inflammation and bone damage can clearly be seen in association with smokeless tobacco use, there have not been studies that have been able to eliminate confounding factors such as the use of other forms of

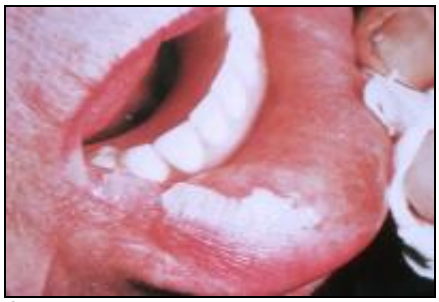
tobacco, preexisting periodontal disease, or other systemic diseases such as diabetes that may affect oral hygiene.[12]

Dental caries

Dental caries have been associated with the use of loose-leaf chewing tobacco, and studies have observed that the amount of dental caries has been shown to increase with the amount of chewing tobacco used. Other studies have found a minimal relationship between the 2 factors, and it has been speculated that the relative lack of dental caries may be secondary to the accelerated salivary flow the tobacco stimulates, which washes away the bacteria that induce the formation of the caries.[12]

Oral leukoplakia

Oral leukoplakia (white plaques) is a common physical finding in 40-50% of people who use smokeless tobacco. Oral leukoplakia is a premalignant lesion, with the risk of malignant transformation to oral cancer varying in relation to the product used. In relation to snuff products, differences in the tobacco species, fermentation processes, nicotine content, tobacco-specific *N* -nitrosamines content, and pH may account for the differences in the reported risk. With most products, the risk appears quite low, whereas toombak dipping (a regional term for snuff) has been associated with a high incidence of oral cancer in the Sudan.[13, 14] Oral leukoplakia has been shown to regress in as few as 6 weeks with smokeless tobacco cessation.[15] Note the image below.



Oral leukoplakia.

Erythroplasia

Erythroplasia (ie, erythroplakia, red plaques) is associated with severe dysplasia or malignancy in 80-90% of cases. Because of the high malignancy rate, the threshold for histologic evaluation of erythroplasia should be low.

Speckled leukoplakia

Speckled leukoplakia is much less common than either leukoplakia or erythroplasia and is distinguished, as the name suggests, by a speckled appearance.

Tobacco-associated keratosis

Tobacco-associated keratosis is a predictable lesion that manifests as an area of thickening at the site of habitual placement of snuff or chewing tobacco. Two distinct grading systems are used to classify lesion stage by degree of clinical thickening. The development of a lesion is dependent on the amount, frequency, type, and brand of smokeless tobacco used.

Carcinoma in situ

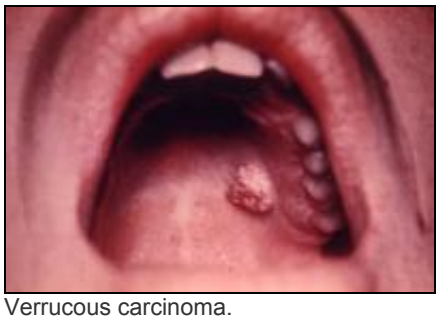
CIS may manifest clinically as leukoplakia, erythroplasia, speckled leukoplakia, or tobacco-associated keratosis.

Squamous cell carcinoma

SCC may arise in areas of oral or speckled leukoplakia, erythroplasia, or verrucous carcinoma. More than 80% of patients with oral SCC smoke, although those who smoke pipes or cigars are at the greatest risk. Overall, SCC accounts for more than 90% of all oral cancers.

Verrucous carcinoma

Verrucous carcinoma (also known as snuff dipper's cancer) is a type of low-grade, slow-growing, exophytic SCC that arises from regions in the mouth where smokeless tobacco is consistently placed. Lesions rarely metastasize but may recur, and, rarely, they transform into invasive SCCs. Although verrucous carcinoma is not the most common oral lesion found in users of smokeless tobacco, most cases of verrucous carcinoma are diagnosed in habitual users of smokeless tobacco. Note the image below.


Verrucous carcinoma.

Pathophysiology

Oral smokeless tobacco contains numerous carcinogens, including polonium 210, tobacco-specific *N* -nitrosamines, volatile aldehydes, and polycyclic aromatic hydrocarbons.[16]

In experimental in vitro systems, smokeless tobacco has shown effects on cell proliferation, apoptosis, and activation of inflammatory mediators. In animal models, evidence of carcinogenesis has been reported for the chewing tobacco and snuff products commercially available for human consumption in Europe and in North America. The mutational spectrum reported a high incidence of H-*ras* mutations in tobacco chewing oral carcinomas in the Indian population compared with smokers from Western populations.[4]

Pure nicotine and smokeless tobacco extract have been compared for their oxidative stress actions by measuring the generation of reactive oxygen species. Pure nicotine has been found to be less toxic than smokeless tobacco extract with equivalent amounts of nicotine.[17]

An analysis of the nicotine content of 11 brands of popular smokeless tobacco products found that moist snuff has the highest nicotine content, whereas loose-leaf chewing tobacco has the lowest nicotine content.[18]

In 2006, the International Agency for Research on Cancer (IARC) concluded that smokeless tobacco is carcinogenic in human beings, causing cancer of the oral cavity and pancreas.[19] The IARC noted wide variability between geographic regions in the type and extent of disease caused by use of smokeless tobacco, and that the disease dissimilarities were accompanied by large differences in the concentrations of carcinogens in the tobacco used in different regions. The World Health Organization (WHO) Study Group on Tobacco Product Regulation concluded that the scientific evidence suggests that the differences in carcinogenicity of smokeless tobacco in various regions is due, at least in part, to differences in carcinogen concentrations in the products used.[20]

Approximately twice as much nicotine is absorbed per dose from smokeless tobacco compared with cigarettes (4 mg vs 2 mg); orally absorbed nicotine also stays longer in the bloodstream. The average can of smokeless tobacco has an estimated nicotine content of 144 mg, equal to 80 cigarettes. Smokeless tobacco that is placed in the mucobuccal folds causes direct damage to the periodontium (eg, gingivitis, periodontal recession) and oral soft tissue.

Epidemiology

Frequency

United States

Smokeless tobacco products include chewing tobacco, dry snuff, and moist snuff. Consumption of chewing tobacco in the United States decreased from 47 million to 36 million pounds, and dry snuff from 3.5 million pounds to 2.2 million pounds, from 2000-2006. However, during the same period, consumption of moist snuff increased from 61.5 million pounds to 77.4 million pounds.[21]

Smokeless tobacco and its associated lesions affect a large number of persons in the United States, with an estimated 6-22 million people who use smokeless tobacco annually.[22, 23] The popularity of oral forms of snuff and chewing tobacco has rapidly increased in North America, especially among white adolescent males. The National Youth Tobacco Survey of 2004 noted 3.1% of male middle school students and 9.5% of male high school students used smokeless tobacco on at least one of the 30 days preceding the survey.[24]

The percentage of male high school students who used smokeless tobacco on at least 1 of the 30 days preceding a Youth Risk Behavior Survey published in 2003 by the US Centers for Disease Control and Prevention (CDC) varied by state. State prevalence rates in order of descending frequency were 21-30% for Alabama, Kentucky, Tennessee, West Virginia, Arkansas, Montana, Wyoming, and Oklahoma; 11-20% for South Dakota, North Dakota, South Carolina, Kansas, Idaho, Mississippi, Alaska, Colorado, Iowa, Indiana, Nebraska, New Mexico, Wisconsin, Ohio, Texas, Missouri, New Hampshire, Michigan, and Maine; and less than 10% for Florida, Arizona, Massachusetts, Delaware, Nevada, New York, Rhode Island, and Maryland.

The Adult tobacco survey of 2003-2007 of 19 states reported an average of 3.5% of adults used smokeless tobacco, with the highest state surveyed with the use of 14.2% in Oklaholma.[25] In 1999, the *Journal of the American Medical Association* published state-specific prevalences of cigarette and smokeless tobacco use among adults compiled by the CDC from the 1997 Behavioral Risk Factor Surveillance System.[2] . Results of 17 states were published, revealing more than a 6-fold difference in prevalence rates between Arizona and West Virginia (1.4% vs 8.8%, respectively). The states with the highest prevalence rates were West Virginia and Wyoming (the prevalence rates in males were 18.4% and 14.7%, respectively). Smokeless tobacco use among women was less than or equal to 1.7% in all 17 states.

A 2010 study reported an elevated use of smokeless tobacco among the US military personnel, and, in particular, 13.1% of military aviators reported using smokeless tobacco within the past month of the survey, which is much higher than the US national civilian average of 3.5%.[26]

According to the American Cancer Society, estimates for 2007 were that approximately 34,360 new cases (24,180 in men and 10,180 in women) of oral cavity and oropharyngeal cancer would be diagnosed in the United States in 2007, and approximately 7,550 people (5,180 men and 2,370 women) would die in 2007 as a result of these cancers. The death rate for oral cancer is higher than that for malignant melanoma, Hodgkin disease, brain cancer, testicular cancer, or cervical cancer, but it has been decreasing over the past 30 years. Oral cancer is 4 times more likely to occur in users of smokeless tobacco than in those who do not use tobacco products. The annual incidence of oral cancer is estimated at 26 cases per 100,000 users of smokeless tobacco.

International

Worldwide, more than 350,000 new cases of oral and laryngeal cancers are diagnosed each year. According to statistics from the WHO, the incidence of oral cancer shows extensive variation, but is the eleventh most common cancer worldwide.[27] Incidence and mortality rates are higher in men than in women. Differences across countries particularly relate to distinct risk profiles and availability and accessibility of health services.[28] Hungary and France have higher incidences than the United States, and Japan and Mexico have much lower rates.

Mortality/Morbidity

The survival rates associated with oral SCCs vary from 30-100%, depending on the size of the tumor, the time of diagnosis, and the location of the lesion. Leukoplakia is benign, while invasive SCC metastasizes via lymphatic spread, usually to the cervical lymph nodes.

In 1993, Wray and McGuirt[29] described a 5-year survival rate of 37% in patients who used smokeless tobacco for 40 years or more.

Decreased survival rates from smokeless tobacco use are not likely due to oral cancer alone but include many other causes of morbidity and/or mortality. Small studies in specific ethnic populations have shown an increased risk of cardiovascular disease.[30]

Race

Currently, the incidence of oral cancer is slightly more common in blacks than in whites. The latest statistics from the Surveillance, Epidemiology, and End Results (SEER) database indicate a rate of 17.2 cases per 100,000 black

males and 15.7 cases per 100, 000 white males.[31]

Sex

Oral cancer is more commonly diagnosed in men than in women. In 2004, 10,270 new male cases of oral and tongue cancer were reported in the United States, compared with 7,130 new female cases.

Age

Smokeless tobacco use usually begins between ages 9 and 16 years. Although the use of smokeless tobacco frequently starts at school age and may continue in middle age, oral cancer is most commonly diagnosed in patients aged 65 years or older. Verrucous carcinoma, specifically, is most commonly diagnosed in men older than 50 years.

The average age of most people diagnosed with cancer of the oral cavity is 62 years, but approximately 30% of these cancers occur in patients younger than 55 years.

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