

Health Effects of Smokeless Tobacco

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DOI: <http://dx.doi.org/10.5915/19-1-12833>

Abstract

Smokeless tobacco is used all over the world. It is usually used orally either as chewing tobacco or as snuff. In 1985, 12 million persons in the United States used smokeless tobacco and the trend is increasing among young males. There is strong association between smokeless tobacco use and cancers of the oral cavity. There may be a fifty-fold increased risk of oral cancers among long term snuff dippers. Potent carcinogens including nitrosamines, aromatic hydrocarbons and radiation-emitting polonium are found in tobacco. Smokeless tobacco is associated with oral leukoplakia at the site of tobacco placement. Some leukoplakias undergo dysplastic changes and may become cancerous. Nicotine dependency is very similar to other drugs such as morphine. The effects of nicotine from smokeless tobacco are similar to those as seen in cigarette smoking and are not discussed in this review.

Introduction

The use of smokeless tobacco has been increasing during the past decade particularly among young men. Oral cancer, leukoplakia and nicotine related side effects are strongly associated with the use of smokeless tobacco. In this article, we will review the various medical aspects of the use of smokeless tobacco.

Historical aspects

The use of tobacco was established in Mexico and Peru as early as 3500 B.C. Smokeless tobacco was thought to have many medicinal uses. People used to chew tobacco to alleviate hunger pains¹. Native Americans used to chew tobacco to alleviate toothaches, disinfect cuts, and relieve the effects of snake, spider and insect bites². In the 19th and 20th centuries in America, dental snuff was advertised to treat toothaches, neuralgia, bleeding gums, and scurvy.³

Tobacco use has had negative connotations for quite some time³. Tobacco use was prohibited in Japan in 1590 and users lost their property and were jailed. In the early 1600's, King James VI of Scotland was a strong anti-smoking advocate and increased

taxes on tobacco by 4,000 percent. In 1633, Sultan Murad of Turkey believed that tobacco caused infertility and reduced the fighting spirit of his soldiers. He made any tobacco use a capital offense. A Chinese law in 1683 stated that anyone who possessed tobacco would be beheaded. Many religious groups also banned snuff used. John Wesley, the founder of Methodism attacked its use in Ireland. The Mormons, Seventh-Day Adventists, Parsees and Sikhs of India, Buddhist monks of Korea, members of the TSAI LI sect of China, and some Ethiopian Christian sects forbade the use of tobacco.

Harmful effects of smokeless tobacco were first described by Hill who reported five cases of polypuses, a "swelling in the nostril that was hard, black and adherent with the symptoms of an open cancer"⁴. He suggested that nasal cancer could develop due to tobacco sniffing. In the late 1930's, Ahblom observed in Sweden that patients with buccal, gingival and mandibular cancer used snuff or chewing tobacco more frequently than patients with other types of cancers⁵. The first report of oral cancers due to snuff or chewing tobacco in the United States appeared in 1941⁶. A brief review of the health consequences of smokeless tobacco was presented in the 1979 Surgeon General's report on smoking and health⁷. Recently, a comprehensive report on this subject has been published.⁸

Products used

Smokeless tobacco is produced in two main forms, chewing tobacco and snuff^{9,10}. Chewing tobacco is chewed or held in the mouth against the cheek or lower lip. Snuff has a finer consistency than chewing tobacco and is usually held in the mouth without

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chewing.

Chewing tobacco is available in three forms, loose leaf, plug and twist. Pennsylvania and Wisconsin grown loose leaf chewing tobacco is made from air-cured, cigar leaf tobacco and consists of stripped and processed tobacco leaves. Many brands are sweetened and flavored with licorice. This is available either in 1.5 ounce or 3 ounce pouches. Plug chewing tobacco is made from enriched tobacco leaves or fragments wrapped in fine tobacco and pressed into bricks. Plug tobacco is available either in firm or moist (>15% moisture) forms and is sweetened with licorice. Twist tobacco is handmade from dark, air-cured leaf tobacco treated with a tarlike tobacco leaf extract and is twisted into strands, usually without added sweeteners.

Snuff is available in moist and dry forms. Moist snuff is made from air-cured and fire-cured tobacco and consists of tobacco stems and leaves. The dry snuff is made from fire-cured tobacco which is grown in Kentucky and Tennessee. The tobacco is fermented and processed into a dry powdered form. The dry snuff has less than 10 percent moisture and moist snuff may have up to 50 percent moisture. A small "pinch" is placed between the lip or cheek and gum and is held for 30 minutes or longer. Dry tobacco is also used for sniffing.

Tobacco production

In the United States, there has been a progressive increase in smokeless tobacco production during the last 15 years¹¹. The total production of smokeless tobacco in the United States in 1944 was 150.2 million pounds. The production declined to 92.5 million pounds in 1968, but has progressively increased to a high of 135.6 million pounds in 1985. The total production of chewing tobacco increased from 63.9 to 86.9 million pounds between 1970 and 1985. The total production of snuff increased from 31.3 million to 48.7 million pounds between 1970 and 1985.

Prevalence

The National Center for Health statistics survey in 1971 estimated that 3.8 percent of males used chewing tobacco and 1.4 percent used snuff⁸. The 1985 data of the Census Bureau indicated that 3.9 percent of males used chewing tobacco and 1.9 percent used snuff. The highest rates of use are seen among teenage and young adult males. The 1985 National Household Survey on drug use reported that 16 percent of males under the age of 21 had used chewing tobacco or snuff the previous year⁹. The usage among females was much lower. Smokeless tobacco is used across the United States but, the highest rates of usage are reported from major cities such as Atlanta (23 percent), Detroit (20 percent), and in the state of New Mexico (20 percent).

Carcinogens in smokeless tobacco

At least 2,500 compounds have been identified in processed tobacco¹³. Three classes of carcinogens are known to occur in smokeless tobacco: N-nitrosamine, polynuclear aromatic hydrocarbons and polonium 210.

Tobacco leaves contain amines in the form of proteins and alkaloids. Tobacco also contains up to 5 percent nitrates and nitrite. There is the potential for the formation of N-nitrosamine from the nitrate, nitrite and amines during the processing of the smokeless tobacco products. Of the 19 nitrosamine identified in smokeless tobacco, the carcinogen nitrosamines with the highest concentration are N-nitrosonornicotine (NNN) and methylnitrosoamino-pyridyl-butanone (NNK), both of which are chemically related to nicotine. Snuff contains 1.6 to 135mg/kg of NNN and 0.1 to 14mg/kg of NNK. Loose leaf and plug tobacco contain 0.2 to 8.2mg/kg of NNN and 0 to 1.0mg/kg of NNK. It is interesting to note that foods and beverages in the United States are not allowed to contain more than 0.01mg/kg of nitrosamine. Both NNN and NNK have been shown to produce cancer of the nose, trachea, esophagus, and liver in rats and hamsters. Benign papillomas can be produced in rat's mouth by direct application of NNN and NNK.

A number of polynuclear aromatic hydrocarbons have been identified in smokeless tobacco. These include classical carcinogens such as benzo(a)pyrene, dibenzo(a,h)anthracene and dibenzo(a,h)pyrene. The concentration of benzo(a)pyrene in the 'tar' of cigarettes has been used as an indicator of the carcinogenic potential of tobacco on mouse skin. In the five most popular snuff brands in the United States that were analysed in 1985, the benzo(a)pyrene level ranged from 0.1 to 63 part per billion.¹⁴

Polonium 210 is an alpha emitting element that has long been incriminated as a human carcinogen. In five of the leading snuff brands in the United States, the level of polonium ranged from 0.16 to 1.22 pCi/g.¹⁴

Cancer and smokeless tobacco

Many epidemiologic studies have shown the association of the occurrence of oral cancers, at the site of exposure, to chewing tobacco and snuff. Cancer of the ear and nose has been reported and suggests the possibility that direct contact may increase the risk of neoplasms. Other tissues that come in contact with the tobacco include those of the esophagus, larynx and stomach, but no consistent evidence of increased risk for cancer has been found in these organs.

Oral cancer

In the United States, the incidence for cancers of the buccal cavity and pharynx is approximately 11 cases per 100,000 population per year. The use of

smokeless tobacco has been strongly linked to oral cancer. Ahblom, in the 1930's, reported on the possible association of smokeless tobacco to cancer in Sweden⁷. The use of chewing tobacco or snuff was reported in 70 percent of the patients with buccal, gingival and mandibular cancer as compared to 16-37 percent of patients with cancer in other oral sites, the larynx, pharynx, and esophagus. Rosenfeld and Callaway reported 566 oral cancer patients from Tennessee¹⁵⁻¹⁶. Women constituted 61 percent of the patients and approximately 90 percent of the women with buccal or gingival carcinoma had used snuff for 30-60 years. In contrast, only 22 percent of the women with other oral cavity cancers had used snuff.

Many controlled studies have confirmed the association between the use of smokeless tobacco and oral cancer. The first case-control study in the United States was conducted in Minnesota. From the data reported, a crude relative risk estimate of 4.0 can be calculated for mouth cancer among smokeless tobacco users¹⁷. Peacock et al found a relative risk of 2.0 for mouth cancers and also suggested that the risk increased with age; an estimate of 3.7 for the age group 60 to 69 was made¹⁸. In these and other studies, the confounding factors of alcohol intake and cigarette smoking have not been addressed. Winn et al have recently reported a series of 255 women with oral and pharyngeal cancer from North Carolina¹⁹. There was a four-fold increase in risk for oral pharyngeal cancer among nonsmoking white women who dipped snuff. This data provided evidence for a strong relationship between the duration of snuff use and the risk for cancer, as well as striking localization of the carcinogenicity in the gum and buccal mucosa. For long term users of snuff, there was nearly a fifty-fold increase in risk for cancers of the gum and buccal mucosa. Almost all of the patients with cancer of the cheek and gums had dipped snuff. The authors concluded that 87 percent of oral cancers were due to the snuff-dipping habits of the patients.

Oral cancer is far more common in many Asian countries and many account for 25 percent or more of all cancers in Asia as compared to 3 percent in the United States²⁰. Smokeless tobacco products that are commonly used in Asia include tobacco with betel leaf, areca nut, and lime mixtures (popularly known as "pan"), Khaini (powdered tobacco and slaked lime paste), Mishri (powdered, partially burnt black tobacco), nass (tobacco ash and cotton or sesame oil), and various other preparations. Data from Pakistan, India, and Sri Lanka suggests considerably higher risks of oral cancer from the use of tobacco-containing quids as compared to nontobacco-containing quids.^{21,22}

Other cancers

Smokeless tobacco has been implicated in other than oral malignancies. One case of squamous cell

carcinoma developed in the ear of a man who habitually placed snuff in his ear for 42 years²³. The report raised the possibility of the carcinogenic potential of smokeless tobacco at other sites when the exposure is direct and prolonged.

Nasal cancer

Some people inhale snuff; consequently, the tissues of the nasal cavity come in contact with tobacco powder. An association between snuff inhalation and nasal cancer was reported two hundred years ago⁴. The incidence of nasal cancer is high among Bantu men where nasal inhalation of tobacco is common²⁴. A similar increase in posterior nasal tumors has been found in certain tribes in Kenya where liquid snuff is widely used²⁵. A study from Singapore, however, did not show an increase in the risk of nasopharyngeal cancer with snuff use.²⁶

Esophageal cancer

Data concerning the association between the use of smokeless tobacco and esophageal cancer is inconclusive. An increase in the risk of esophageal cancer has been suggested by some, but not all, studies. Although an earlier study²⁷ had suggested an increased risk of esophageal cancer among users of betel nut with tobacco (relative risk 11), as opposed to users of betel nut alone (relative risk 2), a more recent study in 649 patients with esophageal cancer found an increased risk of cancer among users of "pan" without tobacco²⁸. A case controlled study from an area of Iran that has the world's highest rate of esophageal cancer did not show an increased risk from chewing of nass.²⁹

Laryngeal cancer

Little data is available at the present time to show a definite casual relationship between the use of smokeless tobacco and laryngeal cancer. Williams and Horn found a relative risk for laryngeal cancer of 2.0 and 1.7 among individuals with high and low exposure to chewing tobacco or snuff, as compared to the controls¹³. Another case controlled study showed that the relative risks were 1.4 for those who chewed tobacco and 1.5 for snuff users³⁰. The increased risk of laryngeal cancer in these studies was not statistically significant.

Stomach cancer

Zacho et al, from Denmark, suggested that both gastric cancer and the use of chewing tobacco and/or snuff was directly related to age, more common in men, and more prevalent in rural areas³¹. A case control study of stomach cancer in coal miners of Pennsylvania did not show any increased risk of gastric cancer³². Another study found a relative risk of 1.7 in men with high use of chewing tobacco and snuff; there was no increase in women³⁰. The increased risk

of 1.7 was not statistically significant.

Urinary tract cancer

Since some constituents of smokeless tobacco are excreted in urine, the kidney and bladder are exposed to these agents. Many epidemiologic studies have evaluated the possible link between cancer of the renal pelvis and bladder and the use of smokeless tobacco; but no consistent evidence of increased risk has been found⁸. The 'National Bladder Cancer Study', the largest of these studies, included 2,982 cases of bladder cancer and 5,782 controls. Three hundred and forty patients with bladder cancer and 1,227 controls who had never smoked cigarettes. Eleven percent of those with bladder cancer and ten percent of the controls had used chewing tobacco, and three percent of the bladder cancer cases and four percent of the controls had used snuff.³³

Non cancerous lesions

Smokeless tobacco is strongly linked to oral leukoplakia in a dose dependent manner. Some oral leukoplakias can undergo dysplastic changes and may develop into squamous cell carcinomas. Many negative health problems related to teeth, gingival, and periodontal disease have been suggested, but these effects remain to be confirmed.

Oral leukoplakia

The World Health Organization (W.H.O.) defines oral leukoplakia as a white patch or plaque that cannot be characterized, clinically or pathologically, as any other disease³⁴. The W.H.O. has stated that tobacco is an etiologic agent in the formation of oral leukoplakia. A number of studies from different countries have demonstrated that oral leukoplakia is associated with smokeless tobacco use. There is strong evidence that leukoplakia plaques develop at the site of tobacco or snuff placement³⁵. A study from Atlanta, Georgia, in 75 adolescent male users of smokeless tobacco, found a 22.7 percent incidence of mucosal pathology. This was significantly different from the 4.7 percent incidence in nonusers³⁶. The mucosal lesions included morsicatio (cheek biter's lesion), ulcer, keratosis, leukoplakia, vesicubullous, petechiae, abscess, erythema, mucocele, and pericoronitis. About 50 percent of the smokeless tobacco users with mucosal pathology had leukoplakia, as compared to 3.8 percent of nonusers with mucosal pathology. A study of North Carolina textile workers showed a 34 percent incidence of leukoplakia in smokeless tobacco users, as compared to 7.4 percent for nonusers¹⁸. Smith et al reported a study of 15,500 snuff users and found that 11.3 percent had abnormal oral lesions³⁷. The oral lesions returned to normal appearance after the use of snuff was discontinued. Horsch et al reported their findings in 50 Swedes, 15 to 84 years of age, who used

snuff routinely³⁸. The prevalence of oral lesions directly correlated with the age of the patient and the duration of smokeless tobacco use, as well as the length of time it was used each day.

Lesions induced by smokeless tobacco may resolve, persist, or continue to enlarge, and have a higher malignant potential following cessation of tobacco use. Many different criteria used to define dysplastic changes and leukoplakia in various studies make comparative analysis difficult. Smith reported the 10 year follow up results on a group of patients with smokeless tobacco-induced leukoplakias and did not find dyskeratosis or carcinomas³⁹. A prospective study from India with ten years follow up showed a malignant transformation rate of 9.7/1,000 per year for patients with leukoplakia⁴⁰. The tobacco used in India however, contains many other ingredients that may have carcinogenic potential. A study from Tennessee suggested that carcinomas arising in the inner cheek and gingiva frequently start as leukoplakia¹⁵. Another study from Arkansas also found an evolution from leukoplakia to pseudoepitheliomatous hyperplasia to squamous cell carcinoma.⁴¹

Gingival and periodontal diseases

Only a few studies have evaluated the relationship between the use of smokeless tobacco and gingival and periodontal disease. One study of 75 smokeless tobacco users reported an incidence of 72 percent for gingivitis, which was similar to an incidence of 77 percent for nonusers³⁶. However, the 60 percent prevalence of gingival recession among smokeless tobacco users was significantly different from the 14.1 percent for nonusers. A study from Colorado noted a 25.6 percent incidence of smokeless tobacco use associated with periodontal degeneration³⁵. A study from Sweden also showed a direct correlation between the use of snuff and gingival inflammation⁴². In addition the gingival inflammation was related to the site of smokeless tobacco placement. Between 76.6 and 86.6 percent of smokeless tobacco users who had gingival recession also had concomitant mucosal pathology.^{35,43}

Salivary glands

Smokeless tobacco, or its components, have been implicated in causing degenerative changes and carcinoma of the salivary glands. Hirsch et al evaluated 50 male habitual snuff dippers³⁸. They found sialadenitis and degenerative changes in the minor salivary glands in 42 percent of the patients. There was the suggestion of more damage to the salivary glands than to the oral epithelium. Greer et al found evidence of sialadenitis and degenerative change in four of the 18 patients who used smokeless tobacco⁴⁴. They did not find a correlation between salivary gland fibrosis and the degree of clinical lesions. They

also suggested that the degree of sialadenitis, fibrosis, and degenerative changes may be associated with the brand of tobacco instead of a generalized response caused by all tobacco.

Teeth

Negative health effects on the teeth from smokeless tobacco use are suspected, but not confirmed. There is a suggestion that in individuals with existing gingivitis, the use of smokeless tobacco may increase the incidence of dental caries. A study evaluating 565 males found that dental caries rates, expressed as decayed, missing or filled teeth (DMFT), were higher among users of both snuff and chewing tobacco as compared to nonusers³⁶. Another study did not support these findings³⁷. Some case reports have suggested a causative effect for caries⁴⁵, while other reports have suggested a protective effective because the increased salivary flow may provide a buffering action.⁴⁶

Nicotine related effects

Nicotine addiction, similar to cigarette smoking, occurs in users of smokeless tobacco and is similar to other addictive drugs. A physiologic dependence on nicotine has been demonstrated. Nicotine is psychoactive and produces transient dose related euphoria. Since the exposure to nicotine from smokeless tobacco is similar to that of cigarette smoking, the health consequences are also similar. Nicotine related health effects have been recently reviewed.⁸

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Acknowledgements

The authors are thankful to I. Funches for her secretarial skills.