



Review Article

## Seduced by tobacco, killed by cancer

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### Abstract

The practice of placing a small amount of chewing tobacco or snuff in the oral cavity and leaving it in place for extended periods of time appears to be finding its way into young and middle aged adults as a socially acceptable and popular habit. Cancer development at the site of placement and other oral mucosal lesions caused by these products has been described from several population groups. As the composition and the pattern of use of the product vary, evaluation of each type of smokeless tobacco (ST) has to be undertaken with caution. This review thus, highlights the use of ST and its significance as the causative for oral cancer.

### Key words

Snuff, Oral cancer, Smokeless tobacco.

### Introduction

The word tobacco was originally used to denote a "Y" shaped piece of cone or pipe called tobago or tobaca that was used by Mexican Indians to inhale powdered leaves of a plant. Later, the plant came to be known by the name of the device, as "tobacco". The generic name of the tobacco plant, Nicotiana, is derived from the name of the French Ambassador to Portugal,

Jean Nicot, who introduced tobacco into the French Court in 1560. Nicotiana is one of the five large genera of Solanaceae and is represented by 68 recognized species, of which tabacum and rustica are cultivated, extensively [1].

Tobacco was introduced into Europe in the late 15<sup>th</sup> century. Sometime in the late 16<sup>th</sup> or early 17<sup>th</sup> century, Portuguese traders introduced it



into India. Since then, tobacco use has spread with remarkable rapidity, seeping into all sections of the society. Initially tobacco was smoked in India, but later it was used for chewing and application over the teeth and the gingiva as well (smokeless form). In the course of time, a large spectrum of methods of use was developed. It is estimated that among the 400 million individuals aged 15 years and over in India, 47% use tobacco in one form or the other [2]. Some 72% of tobacco users smoke bidis, 12% smoke cigarettes, and 16% use tobacco in the smokeless form. Of the 250 million kg tobacco cleared for domestic consumption in India, 86% is used for smoking, and 14% is used in the smokeless form (1% as snuff) [3].

### Smokeless tobacco and oral cancer

Smokeless tobacco (ST) is tobacco that is not burnt when it is used and is usually placed in the oral or nasal cavities against the mucosal sites that permit the absorption of nicotine into the human body. All forms of tobacco use are addictive and cause harm. There are two main types of ST: chewing tobacco; and snuff. It may be used alone or in combination with other substances [4]. Chewing tobacco comes in various forms, loose leaf, plug or twist. Loose leaf or dry powdered tobacco is often mixed with various ingredients according to the local custom. Snuff is commercially made in many different forms from fine cut or ground tobacco and can be dry or moist. Moist snuff is marketed as loose snuff in containers or as sachets (portion-bag) [5].

Many forms of ST are carcinogenic to humans as proved in various studies. Cancer development at the site of placement and other oral mucosal lesions caused by these products has been described from several population groups. As the composition and the pattern of use of the product vary, evaluation of each type of ST has to be undertaken with caution [6]. In the United

States, several studies have linked both tobacco chewing and snuff dipping to oral cancer. A case-control study from North Carolina estimated odds ratios (OR) of 4.2 (95% CI 2.6–6.7) among female non-smokers who regularly used snuff. The risk was greatest where snuff was habitually placed and the risk increased with longer duration of use. The US Surgeon General Cullen and the National Institutes of Health consensus statement (1988) have concluded that chewing tobacco and moist snuff available in the US increases the risk of mouth cancer [7]. An ecological study in West Virginia with high ST users, however, did not show a high rate of deaths from oral cancer. Leukoplakia – a precancerous lesion in the oral cavity – has also been strongly associated with ST use both among young adults and adolescents. In Africa, nasal and oral use of snuff is common. The pattern of use varies; in South African Bantu people (who inhale dry snuff nasally) an excess risk of maxillary antral carcinoma was reported nearly 50 years ago [8, 9]. Relatively high trace metal content (nickel and chromium) of snuff was linked to these cancers. Idris, et al. (1998) documented the widespread use of oral snuff in the Sudan called toombak – a mixture of tobacco and sodium bicarbonate. Both descriptive and analytical studies confirm an increased risk for mouth cancer particularly at the site of placement, mostly in the lower labial sulcus. Epithelial dysplasia in mucosal lesions induced by toombak is uncommon suggesting cancer development may arise de novo or genetic mutations caused by toombak may pass the dysplastic phenotype. This type of snuff contains high level of nitrosamines that is likely to be the procarcinogen acting at the target site. In Asia, chewing of finely cut tobacco is commonly practiced both by men and women mostly mixed with other chewing substances such as areca nut. The mixture is referred to as betel quid. IARC (1985) confirmed the carcinogenicity of betel quid with tobacco based



on a large body of evidence both from human and animal experimental studies [10]. The habit is also prevalent among Asian migrant communities in the UK who do have a higher risk for oral cancer compared with the native population whose custom does not generally include tobacco chewing. Gupta (1999) reported a rising trend of oral cancer among young Indians and related studies had shown a switch from traditional betel quid use to commercially prepared sachets of freeze-dried tobacco (Gutka). For women ST users in Mumbai India, the relative risk of mortality was 1.35 compared with a relative risk of 1.39 among cigarette smokers (mostly men). Several recently published case-control studies from India confirmed strong statistical associations and dose-response relationships for ST use and cancers of the oral cavity [11]. In one prospective cohort study all cancers that arose in a 10 year follow-up study was in tobacco users; estimated malignant transformation rate among ST users was 9.7 per 1000 person years. Considering the serious health consequences these products have recently been subjected to a state-wide ban in some parts of India. In Central Asia and the Middle East, use of nass – a mixture of tobacco, ash, lime and oil – is widespread. In Uzbekistan, the habitual use of nass is associated with oral leukoplakia, the relative risk reported for users in the highest category was 5.17. Shamma (also known as Yemeni snuff) is a ST product widely used in south west Saudi Arabia particularly in the Jizan province on the border of Yemen. Shamma is a mixture of powdered tobacco, carbonate of lime, ash and other additives is held in the mouth between the cheek and gum. Shamma has been implicated in the high incidence of oral cancer in the Jizan province. There is nearly 30-fold difference in oral cancer incidence rates in different regions of Saudi Arabia and this is linked to the practice of Shamma use in some regions [9]. In Europe, ST use is uncommon

except in Scandinavian countries where the use of oral snuff is a widespread habit, particularly in Sweden. Around 20% of the male population in Sweden use snus on a daily basis. In the year 2000 male oral cancer (age standardized) incidence in Sweden was 4.52 per 100 000, higher than rates reported for the UK (4.40 per 100 000). Of interest around that time smoking rates among adult males in Sweden was only 17% while in the UK smoking prevalence was close to 30%. Carcinogenic potential of Swedish snuff was demonstrated in animal studies. In Swedish males, oral carcinomas associated with snuff dipping were reported by Axell's group. These cancers were mostly of exophytic type and were reported as probably associated with the site of placement of moist Swedish snuff. In a 10-year period, about 10% of oral cancers reported to the Swedish National Cancer Registry occurred in snuff dippers. Two later studies from Sweden, both populations based and case-control in design, reported a lack of association of oral cancer with snus use. As cancer development occurs at the site of placement of ST, it is probable that the risk of intra-oral cancer is not significantly increased in users [12]. Most snuff induced cancers occur on the oral side of lip, which could be misclassified during registration. Schildt, et al. (1998), indeed reported that the most common tumour site in this material was the lip. When analyzed separately, an increased risk was found for lip cancer for ex-users. It is possible that users gave up the habit after noticing the hyper plastic lip lesion. Re-examination of the data among non-smokers in one study showed snuff use was associated with a statistically significant odds ratio of 4.7 for combined cancers of the upper aerodigestive tract including the oral cavity. Chronic wrinkling and thickening of oral mucosa at the site of placement of moist snuff has been described dipping of loose snuff being associated with varying degrees of cellular atypia (dysplasia) but their precancerous nature



has not been determined [13]. Axell, et al. commented that oral mucosal lesions caused by moist snuff as it is used in Scandinavia are reversible after cessation of the habit. Prospective studies on snuff-induced lesions are warranted to determine the risk of malignant change. Intermediate biomarkers such as keratin expression in basal layers may help to assess snus or other ST induced tissue damage in chronic users. Hoffmann's group had identified 28 known carcinogens in smokeless tobacco analysed by them [14]. Tobacco specific N-nitrosamines (TSNA) are the most abundant carcinogens identified in unburnt tobacco and are formed during the aging, curing and fermentation of tobacco. There is sufficient evidence for the carcinogenicity of 3-methylnitrosaminopropionitrile to experimental animals. A recent analysis of eight Swedish snuff products yielded a mean TSNA level of 1.5 mg/g of snuff. Smokeless tobacco is often viewed as a safe alternative to cigarette smoking and sales have increased both in USA and Sweden. Smokeless tobacco use not only leads to oral disease but increased mortality was reported in a cohort study among 6927 ST users of all ages in Swedish construction industry employees [15]. Potential benefit of snus use for smoking reduction has been discussed. In Sweden, 71% of men who quit smoking did so without the use of snuff. Introduction of snus also did not result in smoking cessation. Furthermore reduction in smoking cessation by Swedish women has not been through use of snus as tobacco replacement. Smokeless tobacco forms can serve as a gateway to cigarette smoking [16]. Haddock, et al. (2001) presented new evidence for smoking initiation following ST use in young adults. In the US, product switching is dominantly in the direction of snuff to cigarettes and not cigarettes to snuff. Dual tobacco-product use or switching from smoked tobacco to ST may also result in establishment of novel mutational spectra in the target organ that may

increase the number of genetic hits above a threshold considered essential for initiation and promotion of cancer in the oral cavity. Use of both products could also be far more toxic to oral mucosa than just one type of tobacco [17]. Pindborg, et al. (1991) had shown that in the setting of Indian villages it is possible to influence behaviors associated with tobacco use and to quit ST use [15]. A substantial drop in the incidence of oral leukoplakia was reported after cessation of chewing tobacco use in India (Gupta, et al., 1995) [18]. In a recent trial lasting a 4-week period among Bangladeshi residents in the UK 19.5% had stopped ST use, some with the help of nicotine replacement therapy (NRT) [19]. Six randomized control trials have shown benefit with bupropion, NRT and oral examination and feedback as all to be successful methods to assist quitting ST use. Further research and eventual implementation of such important health promotion programs will benefit populations addicted to ST use and contribute to the control of oral cancer.

The use of oral snuff (smokeless tobacco form) has a long tradition in the Asian countries. This is a moist form of snuff that consists of fermented tobacco with added salt and blending ingredients. The pinch of snuff is placed in the gingival fold under the upper lip, close to the midline frenulum, where it is kept in place for varying period of time. In recent years the snuff habit has become increasingly popular, owing both to extensive marketing and to increasing awareness of the detrimental effects of cigarette smoking. Sales of cigarettes have decreased by third during the past decade, while sales of oral snuff increased by 45%. The increase in snuff consumption is due primarily to the growing popularity of this habit among young and middle-aged men. It can be speculated that the common use of smokeless tobacco among athletes in our countries has given snuff dipping an image of a 'healthy'



tobacco habit. Snuff is considered a safe alternative to smoking and is socially widely accepted. Its popularity was further promoted by the introduction of the portion-bag pack, which makes the habit more discreet and easier to handle, than the earlier form of loose weight tobacco. Previous studies have shown that snuff causes typical lesions in the oral mucosa. To what extent these lesions pose a risk of becoming carcinomas is a subject still under debate. In general the development of snuff induced lesions is reversible if the snuff habit is discontinued. Snuff contains the same carcinogens as all tobacco, i.e., N-Nitrosornicotine (NNN), N-nitrosoanatabine (NNT), 4-(metylnitrosoamino)-1-(3-pyridyl)-1-butamine (NNK) and N-nitrosoanabasine (NAB). The risk of oral cancer from smokeless tobacco varies in different parts of the world. One possible explanation for this is the qualitative differences in the production of smokeless tobacco and differing contents of carcinogenic tobacco-specific N-nitrosamines.

## Conclusion

In conclusion, from the aspect of cancer prevention it would seem clear that snuff carries a lower cancer risk than smoking. In our opinion, however, the risk level for snuff remains to be conclusively determined. Whether snuff dipping alone can lead to malignant transformation or simply pave the way for other carcinogenic factors remains to be elucidated.

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