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EDITORIAL

Smokeless tobacco and oral cancer

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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. In this issue, Zatterstrom *et al* (2003) describe a case of an elderly man who developed cancer of the lip and gingivolabial sulcus following long term use of snus, the most common form of ST used in Sweden.

There are two main types of ST: chewing tobacco; and snuff. It may be used alone or in combination with other substances. 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).

Many forms of ST are carcinogenic to humans and in animal 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 varies, evaluation of each type of ST has to be undertaken with caution.

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 (Winn *et al*, 1981). The risk was greatest where snuff was habitually placed and the risk increased with longer duration of use. The US Surgeon General (Cullen *et al*, 1986) 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. An ecological study in West Virginia with high ST users, however, did not show a high rate of deaths from oral cancer (Bouquot and Meckstroth, 1998). Leukoplakia – a precancerous lesion in the oral cavity – has also been strongly associated with ST use both among young adults and adolescents (Wolfe and Carlos, 1987; Grady *et al*, 1990).

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 (Keen *et al*, 1955). 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 (Elbeshir *et al*, 1989; Idris, Ahmed and Malik, 1995). Epithelial dysplasia in mucosal lesions induced by toombak is uncommon (Idris *et al*, 1996) suggesting cancer development may arise *de novo* or genetic mutations caused by toombak may by pass the dysplastic phenotype. This type of snuff contains high level of nitrosamines (Murphy *et al*, 1994) 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 carcinogenecity of betel quid with tobacco based on a large body of evidence both from human and animal experimental studies. The habit is also prevalent among Asian migrant communities in the UK (Bedi and Jones, 1995; Warnakulasuriya, 2002) who do have a higher risk for oral cancer (Warnakulasuriya *et al*, 1999) 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) (Gupta and Mehta, 2000). Several recently published case–control studies from

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India confirmed strong statistical associations and dose–response relationships for ST use and cancers of the oral cavity (Dikshit and Kanhere, 2000; Balram *et al*, 2002; Zanor *et al*, 2003). 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 (Gupta *et al*, 1980). Considering the serious health consequences these products have recently been subjected to a state-wide ban in some parts of India (Kumar, 2002).

In Central Asia and the Middle East, use of nass – a mixture of tobacco, ash, lime and oil – is widespread. In Uzbekkistan, the habitual use of nass is associated with oral leukoplakia, the relative risk reported for users in the highest category was 5.17 (CI 3.10–8.61) (Evstifeeva and Zaridze, 1992). 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 (Papadakou-Sara, 1997). 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 (Brown A, personnel communication, 2003).

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) (IARC CancerBase No 5: http:/www-dep.iarc.fr/dataava/infodata.htm). 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 (Johansson *et al*, 1989). In Swedish males, oral carcinomas associated with snuff dipping were reported by Axell's group (Sundstrom, Mornsted and Axell, 1982). 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 (Axell, Mornstad and Sundstrom, 1978). Two later studies from Sweden, both population based and case–control in design, reported a lack of association of oral cancer with snus use (Lewin *et al*, 1998; Schildt *et al*, 1998). 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. 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 analysed separately, an increased risk was found for lip cancer (OR 1.8, CI 0.9–3.7) for ex-users. It is possible that users gave up the habit after noticing the hyperplastic lip lesion. Lewin *et al* (1998) did not separately report on lip cancer as a sub site of their series of head and neck cancers. 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 (Winn, 2002). Critichley and Unal (2003) examining the Scandinavian studies considered that they do not have sufficient power to detect moderately raised OR.

Chronic wrinkling and thickening of oral mucosa at the site of placement of moist snuff has been described (Andersson and Axell, 1989), dipping of loose snuff being associated with varying degrees of cellular atypia (dysplasia) (Andersson, Axell and Larsson, 1991) but their precancerous nature has not been determined. Axell (1993) 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 (Ibrahim *et al*, 1998).

Hoffmann's group had identified 28 known carcinogens in smokeless tobacco analysed by them (Brunnemann and Hoffmann, 1991). 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 (IARC, 1985). There is sufficient evidence for the carcinogenecity of 3-methylnitrosaminopropionitrile to experimental animals. A recent analysis of eight Swedish snuff products yielded a mean TSNA level of 1.5 $\mu g\ g^{-1}$ of snuff (Paccou, Jansson and Osterdhal, 2002).

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 (OR 1.4) was reported in a cohort study among 6927 ST users of all ages in Swedish construction industry employees (Bolinder *et al*, 1994). Less well recognized medical problems related to ST use are recently reviewed by Bolinder (2003); however, the range of diseases caused by ST appears narrow. 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 (Gilljam and Galanti, 2003). Introduction of snus also did not result in smoking cessation (Helgason and Gilljam, 2002). 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. Haddock *et al* (2001) presented new evidence for smoking initiation following ST use in young adults (OR 2.33, CI 1.84–2.94). In the US, product switching is dominantly in the direction of snuff to cigarettes and not cigarettes to snuff (Tomar, 2002). 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.

Pindborg *et al* (1991) have shown that in the setting of Indian villages it is possible to influence behaviours associated with tobacco use and to quit ST use. A substantial drop in the incidence of oral leukoplakia was reported after cessation of chewing tobacco use in India (Gupta *et al*, 1995). In a recent trial lasting a 4-week period among Bangladeshi residents in the UK 19.5% had stopped ST use (Croucher *et al*, 2003), some with the help of nicotine replacement therapy (NRT). Six randomized control trials have shown benefit with bupropon, NRT and oral examination and feedback as all to be successful methods to assist quitting ST use (Ebbert *et al*, 2003). 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.

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