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# Oral Mucosal Changes Related to Smokeless Tobacco Usage: Research Findings in Scandinavia

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**Smokeless tobacco is used in all Scandinavian countries. By far the highest consumption is recorded in Sweden, where the highest sales figures in the world can be found. Moist non-fermented snuff with a pH value of 8–9 comprises over 99% of the products. Only a few tons per year of chewing tobacco are sold. Moist snuff as it is used in Scandinavia today gives rise to oral mucosal changes which are reversible after cessation of the habit. The use of portion-bags, and even more so the use of chewing tobacco, seems to be associated with less pronounced changes than the use of loose snuff. The daily amount of snuff used and hours of daily use seem to have a greater impact on the risk for development of more pronounced changes as recorded clinically and histologically than the number of years with the habit and/or age of the subject. Gingival recessions are much more frequently found among users of loose snuff than among users of portion-bag-packed snuff and they seem to be irreversible.**
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SMOKELESS TOBACCO has been used orally in Sweden and the other Scandinavian countries for centuries. Snuff manufacturing in Sweden started in the early 18th century. Initially, it was inhaled through the nose but during the 20th century it has almost exclusively been used intraorally in the form of moist snuff. Sales figures reached a peak in 1919, when 7000 tons were sold, corresponding to about 1.5 kg per capita. They then decreased until 1969 and thereafter increased to 4632 tons (0.6 kg per capita) in 1990. About 15 years ago portion-bag-packed snuff was introduced on the Swedish market and it comprised about 16% (761 tons) of the total amount of smokeless tobacco sold in 1990. Only 14.5 tons of chewing tobacco was sold the same year. Swedish snuff is non-fermented moist snuff with a pH value of about 8–9 [1].

The first report in Scandinavia on smokeless tobacco-associated soft tissue changes was published by Ahlbom in 1937 [2]. Among 545 men with cancer of the oral cavity, pharynx, larynx or oesophagus, registered in 1931–1936 at a radiotherapy clinic, 496 (91%) used tobacco daily. Ahlbom found that 70% of 68 patients using any form of tobacco and with buccal/gingival/mandibular ("outer oral cavity") cancer used snuff or chewing tobacco while 30% smoked cigarettes or cigars. This preponderance of smokeless tobacco users among patients with, for example, gingival cancer could not be demonstrated by Wynder and coworkers [3] who analysed 36 cases of gingival cancer and 8 cases of buccal mucosal cancer from the same hospital as Ahlbom. They did not find any convincing association between "tobacco-chewing" and the tumours.

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Roed-Petersen and Pindborg [4] found 1 case of dysplasia and, at follow-up, 1 case of oral cancer among 32 snuff users. Axéll and coworkers [5] scrutinised the Swedish cancer registry for cancer cases registered during a 10-year period (1962–1971) to find cases which could possibly be associated with the habit of snuff taking. They found 33 such cases, corresponding to an annual incidence of 0.5 case per 100 000 daily users of snuff. For comparison, they also calculated the risk for developing lung cancer from smoking in the corresponding population and found the annual incidence to be 60–70 per 100 000. An inquiry to all university ENT clinics in Sweden carried out in 1990 indicates even lower figures of intraoral cancers possibly associated with the use of snuff and developed at the site where a snuff quid is regularly placed (Axéll and Andréasson, unpublished data, 1990).

In a monograph issued by the International Agency for Research on Cancer [6] it is stated that "There is *sufficient evidence* that oral use of snuff of the types commonly used in North America and western Europe is carcinogenic to humans," and that "There is *limited evidence* that chewing tobacco commonly used in these areas is carcinogenic." It seems highly doubtful whether this statement is valid for the present situation in Scandinavia. Opinions thus differ and it seems to be of importance to thoroughly analyse those snuff-induced changes associated with the use of smokeless tobacco products. Several analyses have been undertaken in Scandinavia and the following review gives a brief summary of pertinent findings.

A mucosal change can almost invariably be found at the site where a quid of snuff is regularly placed [7]. This change has been coined snuff dipper's lesion [1, 5, 7–9], snuff-induced oral leukoplakia [4] and snuff-induced lesion [10–12]. It has been described as wrinkled or folded and with or without a change of surface colour. Based on the clinical appearance, a four-point scale for classification of snuff dipper's lesion was published by Axéll and co-workers [8], with the following criteria:

*Degree* 1—A superficial lesion with a colour similar to the surrounding mucosa and with slight wrinkling. No obvious mucosal thickening.
*Degree* 2—A superficial, whitish or yellowish lesion with wrinkling. No obvious thickening.
*Degree* 3—A whitish–yellowish to brown, wrinkled lesion with intervening furrows of normal mucosal colour. Obvious thickening.
*Degree* 4—A marked yellowish to brown and heavily wrinkled lesion with intervening deep reddened furrows and/or heavy thickening.

Increasing daily consumption of snuff seems to be associated with development of changes of higher clinical degree [8–10]. Calculated by means of a cumulative index, the number of years with the habit seems to be of significant importance for the development of more pronounced clinical changes [4, 10]. However, in a recent study on 252 daily users of Swedish moist snuff (184 used loose snuff and 68 portion-bag-packed snuff) by Andersson and Axéll [13] it was shown, by means of stepwise logistic regression, that the following consumption factors influence the severity of changes in descending order: Package form (loose snuff versus portion-bag snuff), placement of the quid (one versus more sites), hours of daily snuff use, grams of snuff used daily, years with a regular snuff habit and age of the individual. The relatively slight importance of number of years with the habit was further supported by findings in a study on the impact of consumption factors based on analyses of biopsies taken in the above-mentioned study on 252 users of Swedish moist snuff [14].

Users of snuff may also show gingival recessions at the place where the quid is regularly placed. Frithiof and co-workers [11] found such recessions in 2 out of 25 male snuff users. Andersson and Axéll [13] found gingival recessions in 42 out of 179 men (23.5%) using exclusively loose snuff and 2 out of 68 men (2.9%) using exclusively portion-bag snuff. The relative impact of the consumption factors on the development of gingival recessions showed about the same descending order as for snuff dipper's lesion. These gingival recessions seem to be irreversible [1].

The most important factor for the development of snuff-induced changes thus seems to be the actual product used. In the thesis by Andersson [1], 2 men, using loose snuff and portion-bag snuff, 34 and 43 years of age, respectively, are compared and their clinical changes illustrated with colour plates. Their snuff consumption data are very similar. They have been regular snuff users for 10 years and they have used 15–16 g daily for 10 h per day. The man using loose snuff shows an extensive Degree 3 snuff dipper's lesion while the man using portion-bag snuff shows a discrete clinical Degree 1 lesion.

The histological features of snuff dipper's lesion in Scandinavia were first described by Pindborg and Renstrup [15]. The histological appearance has later been further analysed and described and the picture seems rather unequivocal [4, 8, 10–12, 16, 17]. It generally shows a hyperplastic epithelium with vacuolisation and a pattern which has been called a Chevron type of keratinisation. Varying degrees of inflammation have been recorded in most specimens.

Some difference has been found concerning the histological changes associated with the use of loose and portion-bag-packed snuff. Thus, among users with low daily consumption, biopsies from those using portion-bag-packed snuff showed less pronounced histological changes than biopsies from loose snuff users. This is in accordance with the clinical observations. However, the difference concerning histological changes could not be identified in specimens from subjects with comparatively high daily consumption [17].

Among other histological findings in Scandinavian reports are the presence of eosinophil granulocytes [8, 17] and koilocytosis-like changes in the epithelium [17], amorphous areas in the connective tissue [8, 10, 17–20] and salivary gland involvement [10].

The concept of dysplasia and finding of dysplastic features in oral mucosal changes associated with the use of Swedish moist snuff is thoroughly discussed in the thesis by Andersson [1]. The following Scandinavian studies have reported on findings or no findings of dysplasia. Axéll and co-workers [8] analysed 114 biopsies from snuff dipper's lesions of clinical degrees 1–4. No case of epithelial dysplasia was found. Roed-Petersen and Pindborg [4], in their series of 32 oral snuff users, found one with slight epithelial dysplasia. At a follow-up examination, another case of "snuff-induced leukoplakia" had developed into a carcinoma. On basis of these 2 cases the authors concluded that 6.2% of snuff induced-changes were associated with premalignancy or malignancy. Hirsch and co-workers [10] found 9 cases (18%) of mild dysplasia in biopsies from 50 habitual snuff users. Frithiof and co-workers [11] found 5 cases of mild epithelial dysplasia in 21 male snuff users. However, they stated that their dysplasias were probably nothing else but reactive changes due to inflammatory infiltration. Jungell and Malmström [12] were of a similar opinion after having analysed 21 snuff users among Finnish recruits. They found 1 case of mild dysplasia.

Dysplasia has been discussed for a long period of time between oral pathologists, and up to now there seems to be no general agreement or consistency concerning its application. It is therefore a matter of paramount importance that whenever reports including comments on epithelial dysplasia are published, applied parameters should be described in words and preferably also with illustrations. Only a very few studies have been published on snuff-associated changes where those requirements are satisfied.

Further, to evaluate irreversibility/reversibility, which probably are important parameters for evaluating dysplastic lesions, follow-up studies have been called for [21]. A few reversibility studies have been carried out on snuff-induced changes in Scandinavia. Pindborg and Renstrup [15] observed that such changes disappeared in 1 patient who discontinued snuff use for 3 weeks. Axéll and co-workers [8] registered changes of decreasing clinical degree on a four-point scale among 6 patients who had stopped using snuff for a few days. Clinical reversibility was also recorded by Jungell and Malmström [12]. They found no pathological alterations of the mucosa in 8 Finnish recruits who had stopped their snuff habits for 3 weeks. Larsson and co-workers [22] made a thorough analysis of changes in 20 subjects who had either stopped their snuff habit or changed from loose snuff to portion-bags and also changed the placement of the quids. Those 20 subjects were selected from 252 regular snuff users and they were selected because of observations in their biopsies of features compatible with the criteria of epithelial dysplasia as defined and illustrated by Smith and Pindborg [23]. At follow-up after about 6 months, all 20 subjects showed a clinically

healthy mucosa at the previous biopsy site and normal tissue at the histological examination of biopsies.

The observations made in Scandinavia and described above seem to differ from what has been found in, for instance, southeast U.S.A., Saudi Arabia [25] and Sudan [26], where to various degree the development of oral cancer has been attributed to the use of snuff. This discrepancy in findings may have many explanations including methodological ones. One most important factor is probably the large difference between the products including the contents of nitrosamines [27] and perhaps also the pH value and water content.

Chewing tobacco is also used in Sweden to a small extent. So far, only one study has been reported [28]. 20 subjects with exclusively a chewing tobacco habit were examined. They had been chewing tobacco for on average 10.7 hours per day for 11.3 years. The predominant clinical finding was an appearance of the buccal mucosa similar to leukoedema. 10 subjects also showed a change similar to snuff dipper's lesion of Degree 1 and 2. Histological findings were in agreement with the clinical observations. It was concluded that oral mucosal changes associated with Swedish chewing tobacco are discrete. This is in contrast to findings in India where tobacco is often used in betel quids consisting of betel leafs, areca nuts and lime. It has been claimed that chewing these tobacco containing quids may be a cause of oral cancer [29]. The contents of Indian and Swedish tobacco quids obviously differ a lot and any conclusions drawn from one of the habits may not at all be valid for the other.

This review has focused on *oral* tissue changes. It should though be emphasised that smokeless tobacco contains many substances which are absorbed and thus may exert distant biological effects. Only a few Scandinavian studies have been carried out and published on this matter. So far no valid publications are available on nicotine absorption from smokeless tobacco but indirect data, such as the impact on blood pressure, have been given in a recent report [30]. These data suggest that diastolic blood pressure is increased among construction workers with daily use of snuff. An accurate description of nicotine absorption and metabolism of various tobacco products is given in a recent study [31]. Saliva cotinine concentration showed the same level for snuff users as for smokers but was considerably higher in tobacco chewers. This parameter correlated well with total daily nicotine intake. The excretion profile was almost the same for users of loose snuff, portion-bag packed snuff and chewing tobacco. In this study it was also found that the clinical severity of oral mucosal changes did not relate to the snuff contents of nicotine or nitrosamines.

Serious cardiovascular effects from using snuff have not been demonstrated. One factor to investigate would be the effects on thrombocytes. By measuring excretion of the thromboxane $A_2$ metabolite some knowledge has been gained in this respect. Thus, increased amounts are excreted in smokers but no such increase has been observed in users of snuff [32].

In rapsodic and unconfirmed reports it has been claimed that there is an increased risk for smokeless tobacco users to contract pancreas cancer [33] and stomach cancer [34]. These data should be looked upon with great caution. In the report on construction workers mentioned above [30] it is claimed that snuff users have even less problems from the gastro-intestinal tract than smokers and non-tobacco users.

The question whether smokeless tobacco usage is carcinogenic to humans is perhaps the most important one and it seems to be a matter of dispute. The habits and the products prevailing in Scandinavia obviously give rise to reversible oral mucosal changes. However, this statement is based on research evaluating a limited number of cases and on a few retrospective population studies. To further elucidate the matter of carcinogenecity, it is recommended that (a) previous follow-up studies are repeated, and further that (b) case-control studies on oral and alimentary tract cancers and (c) case-control studies on other malignancies are implemented in Scandinavia.


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