The Swedish Snus and the Sudanese Toombak: are they different?


Abstract

In Sweden, snuff (locally known as snus), was introduced since the year 1637. Presently, Sweden has the highest per capita consumption and sale figures of snuff in the world, and the habit is becoming increasingly popular. Snus is manufactured into a dry form used in the nasal cavity and a moist form used in the oral cavity. Snus manufactured for oral use is a moist ground tobacco of Dark Kentucky or Virginia species mixed with an aqueous solution of water and other blending ingredients. This form of snuff is found in two types: (1) loose and (2) portion-bag-packed. These are the most widely used. The loose moist form (1–2 g a quid) is the most popular type consumed by 73% of the males, followed by the portion-bag-packed form (0.5–1 g a quid), consumed by 13% of the males, while 14% of the males are mixed users. The majority of snus users place the quid in the vestibular area of the upper lip, and the prevalence among persons 15 years of age or older is 15.9% among males and 0.2% among females. The pH of snus has declined from a previous range of 8–9 to a range of 7.8–8.5, moisture content ranges 35–60% and nicotine content is in the order of 5–11 mg/g dry wt tobacco-specific N-nitrosamines (TSNAs) in micrograms (NNN 5–9; 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanalone: NNN 1–2; N’-nitrosoanatabine: NAT 2–5). In the Sudan, snuff, locally known as toombak, was introduced approximately 400 years ago. It is always processed into a loose moist form, and its use is widespread in the country. Tobacco used for manufacture of toombak is of the species Nicotiana rustica, and the fermented ground powder is mixed with an aqueous solution of sodium bicarbonate. The resultant product is moist, with a strong aroma, highly addictive and its use is widespread particularly among males. Its pH range is 8–11, moisture content ranges 6–60% and nicotine content is from 8 to 102 mg/g dry wt, and TSNAs contents in micrograms (NNN 420–1 550; NNK 620–7 870; NAT 20–290). Snus and toombak dippers develop a clinically and histologically characteristic lesion at the site of dipping. Probably due to control of the TSNAs in snus, this type of snuff is associated with a lower risk of cancer of the oral cavity (relative risk: RR 5–6-fold), whereas the risk for cancer of the oral cavity among toombak users was high (RR 7.3–73.0-fold). In conclusion, the two snuff products significantly differ in many aspects. Most notable differences are tobacco species, fermentation and ageing, nicotine and TSNAs content, pH, expression of the p53 tumour suppressor gene, and keratin types 13, 14, and 19. It was, therefore, the object of the present study to highlight the oral health hazards of toombak, and to compare it with snus regarding the aforementioned differences. © 1998 Published by Elsevier Science Ltd. All rights reserved.

Keywords: Snus; Toombak; Sudan; Sweden

1. Introduction

Expert committees of the International Agency for Research on Cancer reviewed epidemiological studies from different countries who indulge in smokeless tobacco use and concluded that “the use of snuff can cause cancer in humans, and that the use of chewing tobacco may increase the risk for oral cancer development” [1]. Snuff is a term used to describe a wide variety of products containing finely ground tobacco as a principal constituent and other additives. Snuff is either inhaled to the nasal cavity or dipped in the oral cavity.
Epidemiological and laboratory studies have documented that use of snuff is associated with increased risk for cancer of the oral cavity [1,2]. Snuff contains a number of carcinogens, principally the most abundant ones, the tobacco-specific N-nitrosamines (TSNAs), which have been shown to be potent carcinogens in experimental animals [1–3]. In addition, snuff contains other carcinogens including aliphatic and aromatic hydrocarbons, formaldehyde, ketones, alcohols, phenols, amines, amides, alkaloids, metals, radioelements (e.g. polonium-210, uranium-235 and -238) and polynuclear aromatic hydrocarbons (PAHs) [1–3].

The use of snuff is common world-wide, but more common in the southern parts of United States, the Scandinavian countries, southern parts of the Kingdom of Saudi Arabia, southern African countries and the Sudan in northeast Africa. Scandinavian snuff (locally called snus), has been used for centuries. In Denmark, the habit of snus dipping is widely prevalent and the quid is usually placed between the lower lip and the alveolar process [4]. In Norway, the habit of snus dipping is uncommon, but presently is increasing particularly among young individuals, and the quid is placed under the upper lip [5,6]. In Sweden, the habit of snus dipping is the oldest in Europe and dates back to the year 1637. In Sweden, snus consumption declined for several decades during the period 1920–69 [7], increased by 92% during the period 1970–92, and currently is the only tobacco product with increasing sale figures [7]. Snus product for oral use is moist with a pH value in the range 7.8–8.5 [7], and many different brands are commercially available [7,8]. However, the majority of snus users prefer only one or two brands [7,8]. The most popular way of practising the habit is by placing the quid in the upper gingivolabial sulcus [7,8]. Sweden has the highest per capita consumption and sale figures of snuff in the world [7,8]. In Africa, consumption of snuff (locally called toombak) is particularly high in the Sudan where it has been used for over three centuries [9]. While cancer of the oral cavity is low in Sweden despite widespread use of snus [10], an increased risk for cancer of the oral cavity has been documented among toombak dippers in the Sudan [9].

1.1. Snus

Snus is manufactured from the Dark Kentucky or Virginia tobacco with relatively a high nicotine content compared to cigarettes [8]. The tobacco is selected according to the content of nicotine which may vary considerably. Both soil and climate where the tobacco is grown determine the quality of the product. The tobacco is dried in air or in barns by heating the air with open fires (dark-fired) [8]. The smoke affects both the aroma of the tobacco and its chemical composition [8]. After cutting and grinding of the leaves, water and salt are added to the dry flour to keep it fresh and thereafter the snus is heated at high temperature and humidity. To produce various brands, other ingredients are usually added. The purpose of heating is to eradicate micro-organisms and lower nitrate and subsequent nitrosamine formation [7]. Processing of the Swedish snus is a data controlled free-hands tobacco industrial process that involves several modifications through the different stages of processing. However, the exact composition of the blending additives remains a commercial secret [8]. Finally, and after repeated shifts, the snus is refrigerated until ready for packing, in waxed cardboard containers with plastic lids, and the product is then stored at +4°C [8].

Snus is primarily moist snuff with pH values previously 8–9 but presently 7.8–8.5, and is produced in various commercial brands [7,8]. Sweden has the highest prevalence of use of snuff in the European Union, with 21% of all males (900 000 persons) using moist snus [11]. Of the two forms, loose and portion-bag-packed snus, 73% of the males consume the loose form and 13% consume the portion-bag-packed form and the remaining 14% are mixed users [7,8]. The habit is practised by taking a pinch of 1–2 g of loose snus or sachets of portion-bag-packed of 1-g sachets, and place it in contact with the oral mucosa behind the upper lip [7,8]. The average snus dipper keeps the snus in the oral cavity for approximately 11–14 h/day, and consumes almost 75 g a week, corresponding to approximately 4 kg of snus a year [7,8]. Epidemiological studies have shown that changes of the oral mucosa and gingival margins are less pronounced among users of portion-bag-packed snus compared to users of loose snus who show more pronounced gingival recessions which seem to be irreversible [7].

1.2. N-nitrosamines

Snus leading brands were found to contain levels of TSNAs ranging from 5.5 to 106 ppm [8]. Waxed cardboard snus containers were found to contain morpholine. Diffusion of morpholine into snus and subsequent N-nitrosation may result in formation of N-nitrosomorpholines (NMOR), a potent experimental carcinogen [8]. On the other hand, snus portion bugs wrapped in aluminium foil have been reported to contain significantly fewer quantities of volatile N-nitrosamines (VNA) and N-nitrosodietanolamine (NDELA) and TSNAs [8], which demonstrates one possibility to reduce deleterious substances in snus. The levels of nicotine and TSNAs in snus have been reported during the period 1980–90 (Table 1), and were found in the range of 11.3–18.1 mg/g for nicotine, and 5.5–106 ppm for TSNAs.
1.3. Toombak

In the Sudan, nasal use of snuff is found only in the far southern parts of the country and only oral use which is widespread is described. Toombak is a native tobacco plant of the species *Nicotiana rustica* used for manufacture of snuff. Toombak is grown in silky or sandy soils which receive heavier rainfalls in the north-west of the Sudan. After the end of the rainy season (September/October), toombak is planted during the months November/December and never irrigated. Harvesting starts in the months February/March when the leaves turn yellow and brownish spots start appearing (called the smallpox stage). Harvested leaves are left in the field for uniform drying, tied into bundles, moistened with sprinkling of water and stored for fermentation for a couple of weeks at temperature ranging from 30 to 45°C, during which bundles are separated for uniform drying during the months April/May. Tobacco leaves are ground and stored for a year for ageing [12].

Processing of toombak for sale is usually carried out manually in toombak shops by toombak vendors [12]. It is performed by preparing four parts of a coarse powder of dried toombak leaves in a bowl and in another the concentrate of sodium bicarbonate is added gradually in small amounts to the tobacco [12]. While adding the solution, the product is mixed vigorously by both hands and concurrently tested by sensation of the tips of the fingers until it becomes moist and hardened. The output is then transferred to special air-tight tin-containers which are then covered firmly for about 2 h, thereafter the product becomes ready for sale or use. Before buying, users generally ask for a bit to smell or taste, since the aroma and taste decide the quality rank of the product. Currently, toombak is sold in small plastic bags each taking about 100 g. The toombak user carries round or box-shaped tin cans in his pocket, named hookah and is similar to plastic bags, though some people use king-size ones. Hookah is still used by some people, and it makes an indentation in the pocket of a user, thus one can easily guess and identify a user. This helps users to communicate with each other for exchange of brand or request of a dip. A regular user consumes an average of 10–20 dips per day, thus requiring a steady supply of toombak.

1.4. Natron (sodium bicarbonate)

Natron or atron (sodium bicarbonate, also called sodium hydrogen carbonate), is a mineral rock with the chemical formula Na₂H(CO₃)₂.2H₂O. Its colour is grey to yellowish white, and is of alkaline pH. There is no information on either the history or reasons behind use of atron as an additive to toombak. It may be used to homogenise the leaves to a fine sticky form as atron is used in the Sudan to homogenise vegetables during cooking.

Atron, opposed to lime in other parts of the world, is probably added to toombak for its alkaline effects. It has been shown that at high pH (11.0–11.8) nicotine is

### Table 1

<table>
<thead>
<tr>
<th>Sample&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Year</th>
<th>Nicotine (mg/g)</th>
<th>NNN (µg/g)</th>
<th>NNK (µg/g)</th>
<th>NAT (µg/g)</th>
<th>NAB (µg/g)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Snus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A(5)</td>
<td>1980–90</td>
<td>12.4–15.1</td>
<td>5.67–7.83</td>
<td>1.0–2.08</td>
<td>2.2–5.13&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>[19]</td>
</tr>
<tr>
<td>B(5)</td>
<td>1980–90</td>
<td>12.5–18.1</td>
<td>4.0–7.95</td>
<td>0.61–1.51</td>
<td>1.4–4.43&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(5)</td>
<td>1980–90</td>
<td>11.3</td>
<td>5.24–8.94</td>
<td>1.40–1.85</td>
<td>2.4–5.50&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Toombak</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D(4)</td>
<td>1990</td>
<td>17.9–40.6</td>
<td>850–1800</td>
<td>620–3830</td>
<td>50–130</td>
<td>90–230</td>
<td></td>
</tr>
<tr>
<td>I(5)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1993</td>
<td>241–369</td>
<td>188–362</td>
<td>21–42</td>
<td>14–43</td>
<td>[51]</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> All values are based on dry weight.
<sup>b</sup> Numbers in parentheses are numbers of samples analysed.
<sup>c</sup> NAT contains 5–10% NAB.
<sup>d</sup> Samples also contain 1.4–20.7 µg iso-NNAL, and up to 22.9 µg NNAL/g tobacco.
completely protonated and its rate of absorption is increased [13]. Studies of *nass*, a type of snuff used in the former USSR which contains lime and has high pH (11–11.8), have shown that when the product is placed in the mouth, nicotine reaches the central nervous system very quickly [14]. Thus, pH value in tobacco products can influence the absorption and thereby the extent of pharmacological activity of nicotine [14]. Atron probably quickens absorption of nicotine from *toombak* to the central nervous system.

1.5. The habit

*Toombak* can be bought from innumerable shops in the market, and the product is advertised extensively at points of sale where vendors tend to use commercial names to attract buyers [12]. The habit of *toombak* dipping is practised by taking a small portion from the bag or hookah with the three fore-fingers, usually of the right hand, putting it in the palm of the left hand, and manipulating it by the thumb and middle fingers of the right hand until it forms a ball called *saffa* which is of about 10 g in weight [12]. The saffa is not chewed but dip and retained between gum and lip or cheeks or floor of mouth, and sucked slowly for about 10–15 min. Generally, men prefer dipping between the lower lip and gum, while women prefer dipping between cheeks and gum. The dipping continues for a period ranging from a few minutes to several hours, until the saffa becomes bland. Men periodically spit the insoluble debris that is freed from the bullous and the saliva which is secreted during *toombak* use, whereas women retain the saffa, without spitting because of social unacceptability. The mouth is usually rinsed with water after the quid is removed. The *toombak* quid is sometimes retained in the mouth during sleep [12].

1.6. N-nitrosamines

Using gas chromatography with thermal energy analysis, the TSNA types; *N*'-nitrosornornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), *N*'-nitrosoanatabine (NAT) and *N*'-nitrosouanabasine (NAB) were quantified in *toombak* and saliva of *toombak* users [15,16]. Exceptionally high levels (mean; range, mg/g *toombak*/dry wt) of NNN (1.13; 0.50–3.08), NNK (2.31; 0.62–7.87; 31), NAT (0.08; 0.02–0.2) and NAB (0.22; 0.02–2.37) were found (Table 1). Previously, the highest levels of NNN and NNK in any oral tobacco found were 0.154 and 0.014 mg/g dry wt, respectively [17]. Two additional TSNAs, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and 4-(methylnitrosamino)-4-(3-pyridyl)-1-butanol (iso-NNAL) were found in the saliva of *toombak* users for the first time and were confirmed by gas chromatography mass spectrum [16]. Exposure to TSNAs has also been assessed by measuring the content in the saliva of 21 *toombak* users, where nine out of 10 subjects had detectable levels of TSNAs in their saliva before dipping (total TSNAs: 0.01–1.0 mg/ml). During *toombak* use, TSNAs concentrations have reached g/ml levels (range: number of positive subjects) for NNN (0.6–1.2, 12/12), NAT (0.6–6.7, 2/12), NAB (0.05–1.9, 12/12), NNK (0.06–6.7, 8/12), NNAL (0.05–3.3, 11/12) and iso-NNAL (0.07–0.4, 8/12). These high levels of TSNAs found in *toombak* were partially attributed to the use of tobacco Species, *Nicotiana rustica*, fermentation of *toombak* at elevated temperature, prolonged storage, and contamination during processing [18–20].

Levels of nicotine and TSNA concentrations in *snus* and *toombak* were previously compared [21]. Tables 1 and 2 show quantitative data on nicotine and TSNAs in various *snus* brands and saliva of *snus* dippers and compare that with concentrations of nicotine and TSNAs in various samples of *toombak* and saliva of *toombak* dippers. These data clearly document that *toombak* contains concentrations of TSNA 100-fold higher than those found in *snus* (Table 1). The level of NNN and NNK in the saliva of *toombak* dippers is also significantly higher than those found in the saliva of *snus* dippers (Table 2). It has been estimated that more than 80% of the carcinogenic TSNAs are extracted from the *toombak* by saliva and negative pressure during sucking of dipped *toombak* quid [20]. The concentrations of TSNAs in the saliva of *toombak* dippers exceeded their concentration in a solution that produced mouth tumours in rats swabbed with this solution twice daily [22]. Whereas epidemiological studies suggest low incidence of oral cancer in Sweden [10], both high relative frequencies of oral cancer as well as increased risk of oral cancer development among *toombak* dippers in the Sudan have been reported [9,21]. These data strongly support the widely held idea that the TSNAs NNN and NNK play an important role in carcinogenicity of *toombak*.

1.7. Prevalence

Large-scale surveys from Sweden in comparison with similar surveys from the Sudan have shown that *snus* is increasingly used by young individuals whereas *toombak* is increasingly used as persons get older. Use of *snus* by young individuals in Sweden suggests an alternative to smoking of cigarettes. Table 3 shows a large-scale survey in Sweden and its comparison with similar surveys from the Sudan. An informative report on prevalence of *toombak* use and cigarettes smoking in a random population sample of 4535 (21,433 household members; 22.6% males, and 1.7% females), in the population of age 4 years or older, in the Nile Province north of Khartoum, Sudan, has been described [9]. Among individuals of age 18 years or older, the average prevalence rate for use of *toombak* was found to be 34% in males.
compared to 2.5% in females [9]. Use of toombak has ranged between 40 and 47% among males of 40 years of age or older, while among adults in rural areas, 40% of males were found to use toombak compared to 24% found in urban areas [9]. Rural populations were found to use home processed toombak whereas urban ones use more vendor-processed toombak. However, both groups follow a similar processing procedure [9].

Almost all snus-dippers in Sweden in the 15–65-year age group are males, implying about 17% of the population [8]. When stratified, prevalence of the habit accounted for 19% for the age group 15–30 years, and 10% for the age group 65 years and above. Only 1% of Swedish women used snus [8,23]. Among school children aged 13–16 years, 11–15% of the boys, but none of the girls used snus regularly [24,25]. There are regional differences in the habitual use of snus in Sweden. Accordingly, the habit is widely spread in the northern part of the country where almost 25% of the male population over 15 years use snus daily [23]. The habit is also more common in rural areas (20%) and in small towns (13%) than in larger towns (7%) [26]. It has been reported that people with a high consumption of snus smoked less (12 cigarettes/daily) than people with limited snus habits. Of the male snus dippers, 43% did not smoke at all, while 22% smoked occasionally and 35% were regular smokers as well as snus dippers [8]. Recently, it has been reported that about 21% of all males in Sweden use moist snus regularly, implying 900 000 persons, of which > 500 000 use only smokeless tobacco and about 335 000 use both cigarettes and smokeless tobacco, and only 8% of the users are women [11].

### 1.8. Oral cancer

The first study from Scandinavia on snus-associated soft tissue changes was published in 1937 [27]. In that report, among 496 men with cancer of the oral cavity, pharynx, larynx and or oesophagus registered between 1930–36, 91% were daily snus users, and 70% of 68 cases of outer oral cavity cancers used snus. In another case control study, it has been concluded that chewing of tobacco is common among men, with the cases being too small to suggest that it could be a risk factor. It has been stated that, snus dipping in Sweden apparently increases the risk of oral cancer at the site where snus is placed five- to six-fold [28]. In addition, the role of the Swedish snus alone or in combination with live HSV-1 as an aetiiological factor in development of oral cancer has been studied [29]. More recently, quite a number of studies have been carried out in Sweden to elucidate a possible risk of snus use and oral cancer [7,8,29–32].

#### Table 2

<table>
<thead>
<tr>
<th>Product</th>
<th>Year</th>
<th>No. of samples</th>
<th>NNN (ng/ml saliva)</th>
<th>NNK</th>
<th>NAT</th>
<th>NAB</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snus</td>
<td>1988</td>
<td>4</td>
<td>3–140</td>
<td>nd</td>
<td>4–85</td>
<td>[52]</td>
<td></td>
</tr>
<tr>
<td>Toombak</td>
<td>1991</td>
<td>12</td>
<td>582–21 000</td>
<td>63</td>
<td>nd</td>
<td>46</td>
<td>[16]</td>
</tr>
<tr>
<td></td>
<td>1993</td>
<td>6</td>
<td>14.8–105.7</td>
<td>20</td>
<td>2.3</td>
<td>2.6</td>
<td>[53]</td>
</tr>
</tbody>
</table>

nd, not detected.

a NAT contains 5–10% NAB.


### Table 3

<table>
<thead>
<tr>
<th>Survey</th>
<th>Year</th>
<th>Age (years)</th>
<th>No.</th>
<th>%</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snus University of Malmö</td>
<td>1970–73</td>
<td>15</td>
<td>20333</td>
<td>15.9</td>
<td>[39]</td>
</tr>
<tr>
<td>Toombak University of Kartoum</td>
<td>1992</td>
<td>≥20</td>
<td>2868</td>
<td>41.6</td>
<td>[21]</td>
</tr>
<tr>
<td>Toombak</td>
<td>1998</td>
<td>4–17</td>
<td>3795</td>
<td>1.7</td>
<td>(Dr A Idris, University of Khartoum, Sudan, personal communication)</td>
</tr>
<tr>
<td></td>
<td>18+</td>
<td>7237</td>
<td>34.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥4</td>
<td>11 068</td>
<td>23.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
However, this has been supported by some studies [8,29] and questioned by others [7,30–32]. According to disagreement between the results of these studies and others, the Swedish Board of Health and Welfare symposium, held in September 1996, questioned the law which orders the manufacturers to label the snus product with the text “Causes cancer”, adopted after the IARC statement [1]. Nevertheless, the IARC statement was based on intense epidemiological as well as laboratory findings identified from different populations. Thus, it is clear that there is a need for further research into the field before any further questioning of the IARC statement.

Although a high relative frequency of oral cancer in the Sudan has been observed since the years 1959 and 1963 [33,34], the earliest observation on the association between oral cancer and use of toombak was reported in 1980 [35]. Much later, it was found that 81% (50/62) of patients with oral squamous cell carcinoma (SCC) from the Sudan used toombak [36]. Recently, abundant information on toombak use and development of oral cancer has been reported, and the cancer was frequently found at the site where the toombak quid is placed [9,12,15,16,21]. Studies of a similar nature from Saudi Arabia have suggested the aetiological role of Shamma for development of oral cancer [37,38]. So far, only one case control study from the Sudan has quantified the risk associated with use of toombak [12]. In that study, the history of the use of toombak was compared in four case groups including: (1) 375 with SCC of the lip, buccal cavity and floor of mouth; (2) 271 with SCC of the tongue, palate and maxillary sinus; (3) 204 with benign neoplasms in the oral cavity and/or other sites of the body; and (4) 2820 with no malignancy selected from the general population [12]. The adjusted odds ratio (OR) associated with toombak dipping for the first case group (cancer of the lip, buccal and floor of mouth) in comparison with the other hospital and general population control groups was 7.3 and 3.9 (95% confidence limits, 4.3–12.4 and 2.9–5.3), respectively, and among long term users of toombak, the OR was 73.0 for the hospital controls (95% confidence limits, 9.8–542.2) [12].

The clinical and histological features of snus-induced lesions in Scandinavia have been the subject of several studies [4,7,8,39]. The clinical characteristics of snus-induced lesion at the site of quid placement have been described as white or yellowish to brownish colour changes, a wrinkled or folded surface and a clear demarcation to diffuse merging into surrounding normal mucosa [4,7,8,39]. A four-point scale of clinical grading of these lesions has been introduced [39]. The severity of the grade is correlated with increased consumption (h/day/year). Two major histological patterns of changes in the surface epithelium were recognised [7,39]. The first pattern is increased epithelial thickness with vacuolated cells. The second was frequent chevron type changes and variable thickness with evidence of keratinization. High daily use was associated with relatively more pronounced epithelial changes [7]. It has been concluded that tissue changes clinically as well as histologically including presence of epithelial dysplasia are reversible following cessation of the snus habit [7].

The clinical and histological features of toombak dippers’ lesions have been described [40]. The characteristics of the clinical and histological features of toombak dippers’ lesions were found to be similar to those of snus dippers’ lesions. This similarity is probably due to high alkalinity of both products, although the previous high alkalinity pH (8–9) of snus has recently reduced to 7.8–8.5 [7]. A positive correlation between severity of the lesion and longer life-time duration (> 10 years) but not daily frequency, of the habit of toombak use was found [40]. However, increased severity of the lesion in snus users, was found associated with both daily and longer life-time duration of use [7]. Similar to snus dipper’s lesion, increased epithelial thickness, Parakeratosis, pale surface staining and chevron type keratinization were observed in toombak dipper’s lesions, but epithelial dysplasia was found to be low [40].

1.9. p53, keratins (Ks) and human papillomavirus (HPV) infection

The p53 tumour suppressor gene encodes a nuclear phospho-protein that plays an important role in cell proliferation and differentiation [41,42]. The most common genetic alterations identified in human cancers are mutations in the p53 tumour suppressor gene [42]. A high frequency of p53 mutations has been observed in tobacco-related cancers [43], including head and neck [44]. Expression of p53 in premalignant oral lesions and oral squamous cell carcinomas from Swedish and Sudanese snuff dippers, as well as in premalignant and malignant oral lesions from non-snuff dippers from the Sudan, Sweden and Norway, have been investigated by immunohistochemistry [45]. Only 2/15 fibro-epithelial hyperplasia from snus dippers and 3/14 carcinomas from toombak dippers expressed p53, whereas expression of p53 in carcinomas from non-dippers from the Sudan, Sweden and Norway was found in 9/14, 39/60 and 28/41, respectively [45]. Although results of immunohistochemistry are not always conclusive, these findings suggested that the low expression of p53 found in toombak and snus-associated oral lesions may be due to formation of the p53 protein to cytoplasmic complexes with other proteins, mainly Ks and HPV proteins. In another study, toombak dippers’ lesions (49 including 40 dysplastic), and snus dippers’ lesions (15 fibro-epithelial hyperplasias) were examined by immunohistochemistry for expression of K types 13, 14, and 19 and for presence of HPV DNA by in situ hybridization [46].
Moderate to intense expression of K13 and K14 was seen in all toombak dippers’ lesions compared to moderate to weak expression of K13 in 12/15 (80%) and K14 10/15 (67%) in the snus dippers’ lesions [46]. K19 was expressed in the basal layer in 16/49 (33%) of the toombak dippers’ lesions compared to no expression in the snus dippers’ lesions [46]. All tissues were found negative for HPV except two dysplastic toombak dippers’ lesions. The low expression of these markers in snus dippers’ lesions suggests differences in the biological effects of these products on oral tissues as well as a lower rate of malignant transformation of snus dippers’ lesions [46]. Later, carcinomas from Sudanese (toombak dippers/non-dippers), Swedish and Norwegian (non-snuff dippers) were examined for expression of K13, K14 and K19 and HPV infection. For the oral carcinomas from toombak dippers, moderate to intense expression of K13 (71%; 10/14), K14 (86%; 12/14) and K19 (93%; 13/14) was found [47]. For the oral carcinomas from non-snuff dippers, weak to moderate expression of K13 (64%; 47/74), K14 (43%; 32/74) and K19 (45%; 33/74) was found [47]. HPV DNA was not detected in any of the carcinomas from the three countries [47]. The study suggested that high levels of expression of the Ks investigated in oral carcinomas from toombak dippers, compared to those from non-toombak dippers is perhaps due to dysregulation of keratinocyte proliferation and maturation caused by damaging effects of toombak [47]. Otherwise, it may explain the low level of p53 expression previously found in toombak-associated oral carcinomas which is currently under investigation at the gene level [45].

1.10. Other health effects

The increased popularity of toombak use in recent years seems to be due to it satisfying some psychosocial, pharmacological, economical and social demands. Regarding the psychosocial demands, toombak helps to alter mood, and ambiguously helps both concentration, and relaxation and distraction that is provided by both the intervals of preparation of the saffra and the dipping. The pharmacological effects are mainly attributed to nicotine which is a powerful pharmacological agent that changes the cardiovascular, neural, endocrine, and muscle function and induces effects in the gastrointestinal tract [48]. The cardiovascular changes include increased heart rate, blood pressure and decrease in skin temperature due to vasoconstriction in the extremities [48]. The neural effects in the brain and the peripheral nervous system are associated with changes in electrical cortical activity, i.e. induction of both stimulation and relaxation [48]. In the gastrointestinal tract, nicotine stimulates the parasympathetic autonomic ganglia and brain stem, causing the release of pharmacologically active substances which may produce nausea, vomiting and occasionally diarrhoea [48]. Therefore, it is now accepted that tobacco causes physical dependence, addiction and habituation [48]. A case control study from Sweden showed an odd ratio for myocardial infarction of 0.89 (95% confidence interval 0.62–1.29) in non-smokers who used snus daily [49]. On the other hand, smokers showed a clear increase in risk (odds ratio 1.87, 95% confidence interval 1.40–2.48), blood pressure and serum cholesterol levels were found similar in snus users and smokers among the controls. Another study (cohort) revealed a relative risk for death from cardiovascular disease of 1.4 (95% confidence interval 1.2–1.6) in snus users who had never smoked [50]. In non-snus using smokers of >15 cigarettes/day, the corresponding relative risk was found to be 1.9 (1.7–2.2). The results were unchanged when adjusted for cardiovascular risk factors, such as body mass index and blood pressure. An excess risk was indicated in those dying before 55 years of age in both snus users and smokers [50]. Recently, it has been concluded that snus use in Sweden involves as high exposure to nicotine as smoking causes release of sympathoadrenergic stimuli which may signify an elevated risk of cardiovascular events including higher heart rate and blood pressure levels, thus influencing the risk of fatal cardiovascular events [11]. In the Sudan, nicotine content estimated from a toombak sample was found to be 32.2–102.4 mg/g dry wt compared to 17.1–23.4 mg/g dry wt and 12.4–15.1 mg/g dry wt of snuff used in USA and Sweden, respectively [21]. These data clearly document that toombak contains a range of two- to five-fold higher concentration of nicotine than does the commercial snuff manufactured in the United States and in Sweden. Therefore, during dipping nicotine is extracted from toombak and immediately deprotonated in the alkaline media provided by the natron; thus its absorption to the central nervous system is accelerated. These data support the conception that non-smoked tobacco product is a highly addictive product and its self-administration cannot be resisted.

In conclusion, despite snus and toombak both being snuff forms, the two products differ in many respects, and on their biological impact. They differ in type of tobacco species, ageing, fermentation, methods of processing and manipulation, packaging, pH value, moisture, nicotine, and nitrosamines content and the way the habit is practised and age of predominant use. The major differences which are expected to have significant biological consequences, particularly addiction and carcinogenesis, are pH and levels of the TSNAs.

Clearly, quantitative risk estimates on occurrence of cancer among snus and toombak dippers in non-smokers are needed. This research program will document the role of snuff, particularly snus and toombak, as an inducer of cancer in humans and it will affirm the importance of nicotine, nor-nicotine, anatabine and
anabasine defined N-nitrosamines in snuff carcinogenesis. Such an intervention program will be useful for populations at high risk in the Sudan, Sweden, the rest of Europe and the USA which could also specifically contribute to a reduction of toombak and snus use, modification of the product or use of an alternative product.

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References


