# HEALTH EFFECTS OF SMOKELESS TOBACCO

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Aims:

1. To inform about the various types of smokeless tobacco and how they are used
2. To brief the participants about the magnitude of consumption
3. To give a short account of the chemical composition of moist snuff
4. To discuss local effects
5. To discuss carcinogenic risks
6. To discuss cardiovascular risks

## Smokeless tobacco – what it is

*Chewing tobacco*
The habit of placing a quid of more or less processed tobacco in the mouth seems to be at least as ancient as the habit of smoking. The explorer Amerigo Vespucci thought that the inhabitants of a small island off the coast of Venezuela chewed tobacco to quench their thirst because the island was very short of water, and chewing of tobacco induced profuse salivation. The true reason is that nicotine is absorbed through the mucous membranes of the mouth whereupon its pharmacological effects, including psycho-stimulation, are exerted. Chewing tobacco now exists in a wide variety throughout the world. In the United States, there are three kinds: *loose-leaf* (or *scrap leaf*), *plug* and *twist tobacco. Loose-leaf tobacco* accounted for more than 90% of all chewing tobacco sold in the US in 1995, and it consists mainly of air-cured tobacco heavily treated with licorice and sugar. *Plug tobacco* is produced from heavier grades of tobacco leaves that are harvested from the top of the plant and separated from stems. It is then immersed into a mixture of licorice and sugar, pressed into a plug, covered with a wrapper leaf, and reshaped. The chewer keeps the plug tobacco between cheek and gum and chews bits of it. *Twist tobacco* is the least common of US chewing tobacco and is made with air- and fire-cured burley and is flavoured and twisted to resemble a decorative rope or a pigtail. In developing countries, tobacco is mostly consumed mixed with other ingredients. *Pan* (*paan*) or *betel quid* is commonly used on the Indian subcontinent, Southeast Asia, Papua New Guinea, and part of South America. Quids are prepared from areca nut, cured or sun-dried, and chopped, then usually placed on a leaf of the Piper betel vine. Slaked lime is an essential ingredient. It increases pH and accelerates release of alkaloids from both tobacco (which may or may not be included) and nut, with enhanced pharmacological effect. A similar product is the Indian *Mawa*, which consists of tobacco, lime and areca. *Nass* is used in Central Asia, Iran, Afghanistan and Pakistan and is made with tobacco, ash, and cotton or sesame oil. *Nashwar* (*nishwar*) is used in the same areas and consists, among

other ingredients, of tobacco, lime, indigo, cardamom, oil, and menthol. *Khani*, commonly used in Bihar, India, contains tobacco and lime. *Shammah* consists of tobacco, ash, and lime and is used in Saudi Arabia. *Toombak* is a common variety of smokeless tobacco in Sudan and is made up of tobacco and sodium bicarbonate. Other common forms of chewing tobacco in India and Arab countries include *Zarda* (boiled tobacco), *Mishri* (burned tobacco) and *Gadakhu* (tobacco and molasses).

*Snuff*

The practice of inhaling powdered tobacco is thought to have originated among the Indians of Brazil. It was introduced into Europe by members of the second expedition of Columbus to the New World, and at first it was thought to possess medicinal properties, a belief presumably borrowed from the Indians. The inhalation of *dry snuff* gradually spread throughout the then known world and became a socially acceptable practice, particularly in Europe. Dry snuff use reached a peak in England during the reign of Queen Anne (1702-1714). Although the popularity has declined, dry snuff (<10% moisture) still exists. In Europe, it is inhaled (nasal snuff), while in the US it is taken orally. It is generally produced from Kentucky and Tennessee fire-cured tobaccos. After the initial curing process, which takes several weeks, the leaves undergo a fermentation process. They are then powdered and often enriched with flavour additives, including spices. *Moist snuff*, on the other hand, is manufactured from air- and fire-cured dark tobacco laminae and stems which are shredded. Water and salts are added, along with sodium carbonate (in order to increase pH). The final product contains from 20 to 60% moisture and is often flavoured with wintergreen, raspberry, cinnamon, cherry, or mint. After the tobacco is cut and packed, it undergoes aging or sweating for up to three years, a process that involves fermentation. Oral use of moist snuff was introduced in the US in the middle of the 19$^{th}$ century by Scandinavian lumberjacks working in the northern United States. "Snuff dipping" of loose snuff, or of snuff placed into sachets, is practised by placing the product between cheek (or lips) and gums or beneath the tongue. The ingredients are then continuously extracted with saliva. The quid is usually expectorated after use, but may also be swallowed. The total time per day with snuff intraorally is about 13 hours for a habitual user.

**Some sales statistics**

Around 1900, about 60,000 tons of chewing tobacco were consumed annually in the United States, but the consumption declined gradually to a low of about 30,000 tons in the mid-60's. After the first Surgeon General's Report on Smoking and Health (that warned about the health hazards of smoking) in 1964, chewing tobacco became increasingly popular, so that consumption reached a new high of 45,000 tons between 1980 and 1985. Since then, the popularity has dropped, and the consumption in 1995 was about 30,000 tons. However, the use of snuff, especially moist snuff, increased from 16,000 tons in 1975 to nearly 30,000 tons in 1995. This increase was driven to a large extent by a marked increase among male adolescents and young adults. Studies have reported that that 13% of third-grade boys had used smokeless tobacco. In 1997, however, the US consumption of smokeless tobacco dropped to the lowest level since the Federal Trade Commission began tracking the industry. Sweden has the highest consumption of moist snuff worldwide, with 0.68 kg per capita and year in the beginning of the 1990's. Approximately 20% of Swedish men aged 15-75 years, and 2% of women, use snuff regularly. The mean daily consumption among users is 19 grams. Sales data regarding the types of

smokeless tobacco used in the third world are scarce and unreliable, but the consumption in certain populations is clearly substantial.

## Chemical composition

Tobacco contains approximately 2500 chemical substances. They derive from the tobacco plant itself, but also from agents that are added during cultivation and/or harvest. Some of the compounds are formed during processing from raw tobacco into the final product. Nicotine is the principal addictive component of smokeless tobacco. The pharmacological effects of nicotine have been studied extensively and fall beyond the scope of this review. Suffice to say that the cardiovascular effects of nicotine are mainly attributed to sympathetic stimulation on the ganglionic level, and on effects mediated via the adrenals. The acute effects include an increase in heart rate, blood pressure, cardiac output, stroke volume, and coronary blood flow, arrhythmia and electrocardiographic changes. Further, nicotine induces peripheral vasoconstriction and increased muscular blood flow. The level of nicotine in Swedish moist snuff is usually 0.8-0.9% and in the corresponding American products it is 1.2-1.8%. The uptake of nicotine varies with snuff brand (pH, loose snuff versus portion snuff in sachets, etc.). Moreover, there is a considerable interindividual variation, which distorts the correlation between daily snuff consumption and nicotine levels in plasma. This limitation notwithstanding, it has been shown that the daily level of exposure to nicotine from smokeless tobacco is similar to that from cigarette smoking; the total urinary excretion of nicotine and its metabolites during 24 hours in snuff users (16 grams of portion snuff in sachets per day) was similar to that in smokers of 17 cigarettes per day. But plasma and saliva levels of cotinine (a metabolite of nicotine) are higher in snuff users than in cigarette smokers consuming the same amount of tobacco per day. It must be noted that with cigarette smoking, as opposed to snuff dipping, nicotine is delivered intermittently into the pulmonary circulation, resulting in transiently high levels of nicotine in arterial blood. These levels exceed manifold the ones seen in blood when nicotine is dosed gradually from smokeless tobacco. Thus, snuff dippers can maintain a moderately high and steady level of nicotine in plasma, quite in contrast to cigarette smokers.

It is worth noting that the absorption of nicotine through the oral mucosa of chewers and dippers is enhanced when the pH levels go above 6.0-6.2. At acidic pH, nicotine is present in protonated form as a salt with organic acids. However, 9% of the nicotine at pH 7.0 and 50% at pH 8 are present in chewing tobacco or snuff in unprotonated form as a free base. Free nicotine is absorbed more rapidly and thus reaches the central nervous system more quickly, whereby it enhances a sense of well-being, produces first arousal, then relaxation, helps maintain vigilance, and reduces anxiety. In the US, snuff brands that have 22% to 60% of the nicotine present in unprotonated form account for 92% of the sales, while the brands with less than 1% of the nicotine in unprotonated form account for only 3% of the market. These data support the suspicion that the formulation of the leading snuff brands may be aimed at creating and maintaining nicotine dependence.

*Carcinogenic substances*

About 30 carcinogens have been identified in chewing tobacco and snuff. Among these, the major contributors to the carcinogenic activity of these types of tobacco are the tobacco-specific N-nitrosamines (TSNA). These agents are formed exclusively from nicotine and from the minor

tobacco alkaloids, primarily during the processing, fermentation, and aging of tobacco. Nicotine or other tobacco alkaloids react with nitrite, which is formed through microbial reduction of the nitrate that comes with tobacco. The most important TSNAs are 4-(nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) and N´-nitrosonornicotine (NNN). Other TSNAs include N´-nitrosoanabasine (NAB) and N´-nitrosoanatabine (NAT). The TSNAs are organ-specific carcinogens, *i.e.*, independent of the route of their application, they induce mainly tumours in specific host tissues and organs. For example, NNN, which is formed by N´-nitrosation of nicotine and nornicotine, induces tumours of the oesophagus, and NNK elicits adenoma and adenocarcinoma of the lung in mice, rats, and hamsters. NNK has a carcinogenic potency that is comparable to that of benzo[a]pyrene, a strongly carcinogenic polycyclic aromatic hydrocarbon (PAH) that is present in fire-cured natural tobacco and snuff, but at concentrations 1000-fold less than those of NNK and NNN. Furthermore, snuff contains other N-nitrosamino acids and volatile N-nitrosamines, of which at least 5 have been shown to have a carcinogenic potential in animal models, but the levels are usually several orders of magnitude lower than those seen for NNK and NNN. Moreover, snuff contains formaldehyde and acetaldehyde, as well as traces of α-emitting Polonium-210. However, the activity of the latter results in a yearly dose among habitual snuff users corresponding to no more than the background radiation during one week.

Manufacturers of snuff have taken action to reduce the levels of TSNA and other potentially carcinogenic substances. Avoidance of fire-cured tobacco has resulted in a 5-fold reduction of the levels of benzo[a]pyrene. Swedish manufacturers have abandoned fermentation in favour of a carefully controlled heating process, resulting in a practically sterile product. Hence, the level of TSNA in Swedish snuff in 1992 (4.4 mg/kg) was only 50% of the level in 1983. Further, the NNN and NNK levels in two of the most popular American snuff brands were reduced by at least 70% between 1980 and 1992. In 1980, the nitrosamine levels in American snuff was up to 18-fold higher than in Swedish snuff, while the difference between American and Swedish snuff with regard to NNK and NNN levels was only twofold in 1990. Nonetheless, for the Swedish population, the widely used moist snuff is by orders of magnitude the most important source of carcinogenic nitrosamines. Exposure to TSNA is considerably higher in users of snuff even in comparison to an individual smoking 40 cigarettes per day for 40 years. Thus, the lifetime intake of NNK has been estimated to be about 2.5-fold, and for NNN, 33-fold higher.

The smokeless tobacco used in the Third World may contain considerably higher levels of carcinogenic substances. A recent comparison between Swedish moist snuff and Sudanese toombak revealed that the levels of NNN, NNK, and NAT, respectively, were 100-200-fold, 600-4000-fold, and 10-60-fold higher in the latter.

*Protective substances*

Like most other plant products, tobacco also contains substances that are potentially antimutagenic and anticarcinogenic, including ubiqinone, α-tocopherol, flavonoids, isoprenoids and certain fatty acids. It is, however, uncertain if the concentrations are sufficient for a genuine protective effect. Recent data further indicate that nicotine might inhibit the activating step in the biotransformation of NNK.

## Local effects

Unlike cigarette smokers, who experience widespread periodontal destruction, the oral changes in users of smokeless tobacco are localized to the site of placement. In general, gingival recession occurs in 25-30% of these users, while a more or less clear mucosal lesion develops at the site where the snuff is placed in practically all. These "snuff dipper's lesions" have been dived into 4 grades, from "a superficial injury with the same colour as the surrounding mucosa and with slightly wrinkled surface" to "injuries with distinct white-yellow to brown colour, markedly wrinkled, with interjacent normal tissue, deep reddish grooves and/or marked thickenings". The latter stage clearly overlaps with the concept of leukoplakia, which is defined as "a white lesion, which cannot be scraped off the mucosa, and which cannot be classified clinically or histologically as any other disease". White mucosal lesions occur in 40-60% of current users of smokeless tobacco, compared to approximately 1% among non-users of tobacco. These lesions seem to develop rapidly, even in otherwise healthy young individuals. In one study, 56% of smokeless tobacco users developed white lesions within seven days of placement of smokeless tobacco at a new site. These snuff-associated white lesions are almost always (97.5%) completely reversible upon long-term cessation of the tobacco use, and in one study, 22% of lesions resolved one week after tobacco exposure ceased. Some authors prefer to reserve the term leukoplakia to lesions that are permanent, either due to irreversible tissue damage or continued exposure. These lesions seem to have a malignant potential, but the incidence of malignant transformation varies markedly between studies. In one Indian study, 6/13 patients with nodular leukoplakia developed cancer within 2.8 years, while the incidence is much lower in other studies. The malignant potential of the smokeless tobacco-related white lesions is practically unknown. But given the transient nature of the lesions, the risk is likely to be small. This poses a problem in the evaluation of cancer risk among patients with genuine leukoplakia, since the admixture of transient tobacco-related lesions will dilute the risk. In fact, in most studies of the risk of malignant transformation of leukoplakia, tobacco use emerges as a protective factor. Apart from snuff dipper's lesions and gingival recession, there is some evidence that use of American chewing tobacco, but not snuff, is associated with an increased risk of dental caries. This latter risk may be attributable to the high content of sugar in these products.

## Carcinogenic risks – oral cancer

*Genotoxicity*

Given the presence of strong carcinogens in snuff, cancer is the prime concern among health authorities. The question about the carcinogenicity of snuff was addressed by several scientific and/or administrative bodies in the mid-80's, and they all reached essentially the same conclusion that "there is sufficient evidence that oral use of snuffs of the types commonly used in North America and Western Europe is carcinogenic to humans" (International Agency for Research on Cancer [IARC], 1985); "the scientific evidence is strong that the use of smokeless tobacco can cause cancer in humans" (Advisory Committee to the Surgeon General, 1986); "observations in humans provide convincing evidence for an increased risk of oral cancer in humans" (National Institutes of Health Consensus Development Conference, 1986). A critical review of the evidence, paired with more recent data, however, unveils a more complex picture. The six genotoxicological studies reviewed by IARC yielded varying results, but the conclusion was that there was "sufficient evidence" for genetic activity of ethanol extracts of tobacco, but not of ethyl

acetate extracts. However, a subsequent elaborate evaluation of Swedish snuff using 6 genotoxicity tests on two different extracts, with and without metabolising systems (in three of the tests), showed evidence of genetic activity in only 5 out of 17 tests. The probability of carcinogenicity due to genotoxic mechanisms was deemed to be low in this study. One reason for this essentially negative result may be a lower potential for genotoxicity of newer Swedish snuff, compared to other forms of smokeless tobacco, and/or the presence of antimutagenic substances in snuff. Similarly, in two other studies, no mutagenic activity in urine could be demonstrated during snuff use by healthy volunteers, while this activity was 5-fold increased when the same individuals smoked cigarettes.

*Animal data*

Animal data regarding snuff are also unimpressive, as reviewed by Grasso and Mann (1998). Seven studies using the hamster cheek pouch or oral mucosa were all negative. A rat model with a surgically created artificial lip canal has been used in several studies. Although it simulates the human snuff dipping situation, when stuff is mixed with saliva, the model has been criticized because the surgical trauma in itself causes a marked inflammatory response, which may be perpetuated by iterated snuff applications. Further, when the inflammation subsides, it is followed by a mild epithelial hyperplasia and a persisting scar tissue. It is well known that proliferative reactions of this sort are prone to lead to cancer induction in laboratory animals even when no carcinogens are applied. Nevertheless, none of several studies where snuff was inserted into the artificial canal for up to 116 weeks showed a statistically significant excess of tumours among the snuff-treated animals.

Several studies with the rat lip canal model have addressed the possibility of a promotional effect if snuff exposure is combined with exposure to other carcinogens. In one of these studies, a considerable number of sarcomas developed around the lip canal. Although the scar fibrosis may be responsible for a general tendency to develop connective tissue tumours, the excess was greater in snuff-treated animals. The results overall were, however, consistent with the conclusion that snuff does not possess any promotional activity in the development of oral squamous cell carcinoma.

One of two studies with the rat lip canal model addressing a possible synergistic effect between HSV-1 virus infection and snuff came out positive (tumours developed in 2/10 infected animals exposed to snuff, while no tumours were seen among rats exposed to HSV-1 only [n=10], or snuff only [n=10]). A third study performed in the golden Syrian hamster showed that approximately 50% of the animals infected with either HSV-1 or HSV-2 and then exposed to snuff twice a day for 6 months developed invasive squamous cell carcinoma of the cheek pouch, while no tumours developed in infected or uninfected controls without snuff exposure. Although the excess in the latter study may be an unspecific effect of the intense inflammatory reaction produced by the infection per se, the manipulation required to maintain continued presence of the virus (the animals had to be reinfected every 4 weeks), and the iterated snuff administration, these data provide evidence in support of a synergistic action of herpes virus infection and snuff dipping.

In one study, where rats and mice were fed with snuff, a kidney sarcoma occurred in one snuff-exposed rat and leukaemia developed in 3 snuff-treated mice, while no neoplasias developed in control animals. Another well-conducted 2-year study in which 500 hamsters were fed with either

snuff or cellulose amounting to 20% of the total dietary intake did not result in any excess of tumours among the snuff-exposed animals. Thus, there is no strong evidence of any significant carcinogenicity when snuff is administered via the dietary route.

Experiments with topical application of snuff to the oral mucosa of the rat did not produce any tumours, but an extract enriched by the addition of 10 times the naturally-occurring amounts of NNN and NNK produced a few benign tumours at the site of application. A higher incidence of tumours was produced when an equivalent amount of an aqueous solution of these two TSNAs was applied to the oral mucosa, suggesting, according to the authors, that snuff inhibits the carcinogenic activity and TSNAs.

*Epidemiological data*

The epidemiological evidence of a positive association between smokeless tobacco use and risk of oral cancer is also difficult to interpret. From a global perspective, it appears that oral cancer is particularly common in developing countries where the use of smokeless tobacco is widespread (third most common site among males and fourth among females). However, ecological comparisons in the Western world do not support an important role of smokeless tobacco. For example, the oral/pharyngeal cancer mortality rates in West Virginia, the state with the highest per capita consumption of smokeless tobacco in the US, are lower than the US average. Similarly, oral cancer is rare in Sweden, with the world's highest per capita consumption of snuff. Although the oral and pharyngeal cancer incidence rates have increased dramatically in the US among young white males ages 15 to 34 years (where the use of smokeless tobacco is particularly common), one would expect that gingival and buccal mucosal cancers would be increasing relative to other oral sites if smokeless tobacco would be an important contributor to this increase. This appears not to be the case. Also, upward trends in oral cancer among younger men have also been evident in European countries where smokeless tobacco use is rare.

Several of the analytical epidemiological studies cited by IARC in their 1985 evaluation had serious methodological flaws; case definition varied between studies, as did the exposure (various kinds of smokeless tobacco). The exposure prevalence in Western populations is usually low, which led to small numbers. Exposure information was often collected from substitute responders (next-of-kin), or worse, from hospital case records, with considerable risk for information bias. All studies were hospital-based, with an entailing risk of selection bias. Only two of the studies controlled for cigarette smoking and no more than two (of which one controlled for smoking) were reported in a way that allowed calculation of the relative risk.

The strongest evidence in the IARC evaluation (Winn *et al*, 1981) derived from a hospital-based case-control study conducted among women in North Carolina, where the mortality of oral cancer is high, as is the oral use of dry snuff. Exposure information was obtained from 91% of 255 living or deceased cases with oral or pharyngeal cancer, and from 82% of 510 matched hospital- or mortality controls (the information had to be collected from substitute responders in 51% of the cases and 21% of the controls). In an analysis confined to non-smoking women, the excess risk among snuff users was 3.6-fold (95% confidence interval 2.2-5.7). This excess was essentially confined to white women. When risk for buccal and gingival cancer (where the snuff was most frequently placed) was analysed separately, the risk among non-smoking women with more than 50 years of snuff use was 50-fold increased, relative to never-users of any tobacco.

Adjustment for alcohol use, or for source of exposure information (case patient personally or next-of-kin), did not materially change these associations.

Since the publication of the IARC report, several new Western studies have appeared. Two of them observed strong associations between the use of smokeless tobacco and oral cancer, but in one, smoking could not be ruled out, and in the other one, it could not be determined whether differential recording of tobacco use in the medical records of cases and controls could have been responsible for the findings. A third study using the National Mortality Followback Survey and the National Health Interview Survey did not support a link between smokeless tobacco use and risk of oral cancer mortality. However, the surveys involved independent national samples and did not directly study risk of oral cancer death among persons with particular demographic or behavioural habits. In a study emanating from the US National Cancer Institute, persons with oral or pharyngeal cancer, identified from four US population-based cancer registries and population-based controls, were interviewed about, among other things, the use of smokeless tobacco. The study revealed a 6-fold increased risk among non-smoking female users of smokeless tobacco, relative to non-smokers and non-users of smokeless tobacco. The observed numbers were, however, small and the confidence interval was wide. Moreover, a corresponding risk increase could not be verified among men.

Four recent, well-conducted case-control studies, three of them population-based (one among US veterans, two from Sweden (Lewin *et al*, 1998; Schildt *et al* 1998), with high exposure prevalence), and one large cohort study from Sweden, have all been completely negative.

Thus, the bulk of the evidence derived from Western populations weigh towards no association. These results are in glaring contrast to several hospital-based case-control studies conducted in high incidence areas for oral cancer in the Third World. There, the relative risk among tobacco chewers is typically of the order of 6-7. Although the prerequisites for epidemiological studies are generally less favourable in these countries, it would probably be a mistake to dismiss these studies as being flawed. It appears plausible to attribute the difference in effects to the considerably higher contents of carcinogenic substances contained in the local smokeless tobacco products used in the Third World high incidence areas. Thus, smokeless tobacco might, indeed, be carcinogenic to humans, but refinements of Western products, notably moist snuff, may have reduced the carcinogenicity to a subclinical level.

**Carcinogenic risks – other cancers**

Apart from oral cancer, data on carcinogenic risks at other sites are scarce. Total cancer mortality rate among non-smoking snuff users was similar to that among never-users of tobacco in a large Swedish cohort study, indicating that overall cancer mortality is not increased. The most compelling positive findings concern pancreatic cancer, where four prospective studies showed relative risks between 1.7 (non-significant) and 2.9 among users of smokeless tobacco. One case-control study showed a positive association between smokeless tobacco use and risk of cancer of the ampulla of Vater, but all cases in that study smoked as well. Oesophageal and gastric cancer should be of particular interest, but the few studies that have addressed their relation to smokeless tobacco showed inconsistent results. The strongest studies, conducted in Sweden, with high exposure prevalence, (Lagergren *et al*, 2000; Ye *et al*, 1999) were negative. Studied, with alas

inconsistent results, are also colorectal cancer, cancer of the nasal cavity and paranasal sinuses, renal cell cancer, bladder cancer, prostate cancer, leukaemia, multiple myeloma, and soft tissue sarcoma. Although more studies are clearly warranted, the positive studies have generally shown only moderate excesses that might have resulted from confounding or chance. Therefore, it appears that the probability of finding any important associations with the aforementioned cancers is small.

## Cardiovascular risks

*Blood pressure*

Given that smoking is an established risk factor for cardiovascular disease, and in view of the pharmacological effects of nicotine (which include heart rate and blood pressure increases, release of free fatty acids followed by formation of lipoproteins, and platelet hyperreactivity), an increased risk for serious cardiovascular outcomes among smokeless tobacco users might be suspected. Indeed, as opposed to cigarette smoking, which is generally associated with a decreased blood pressure, smokeless tobacco was weakly associated with chronic hypertension in most, but not all, cross-sectional studies that addressed this relationship. A notable exception was a study of young and fit major- and minor league baseball players. Likewise, a Swedish study using 24-h blood pressure monitoring found significant elevations (on average 5 mm Hg) in daytime diastolic blood pressure, but only among subjects ≥45 years old. The systolic blood pressure was not significantly different from that among non-users of tobacco, and night-time measurements showed only minor differences between smokeless tobacco users and non-users of tobacco. Interestingly, though, a strong relationship emerged between cotinine levels and blood pressure (systolic as well as diastolic) in smokeless tobacco users.

*Lipid profile*

Studies of other cardiovascular risk factors have yielded mixed results. Lipid profile was normal in one American study of young healthy sportsmen, and in two small Swedish studies of young (mean age 24 years) snuff-using volunteers and of healthy middle-aged (mean age 44 years) firemen, respectively. In contrast, a study of US employed men (41 years old on average) revealed a significant excess of hypercholesterolaemia (defined as cholesterol levels ≥6.2 mmol/L) among users of smokeless tobacco. After adjustments for age, education, physical fitness, body fatness, and other tobacco use, smokeless tobacco users had a probability of being hypercholesterolaemic that was 2.5 times higher than among non-users. Similarly, in a study from India, tobacco chewers had significantly lower levels of high density lipoprotein-cholesterol, and higher levels of total cholesterol, low density lipoprotein-cholesterol, very low density lipoprotein-cholesterol, and triglycerides, compared to controls who were non-users of tobacco.

*Other cardiovascular risk factors*

In a small Swedish study, young snuff users had increased serum insulin and plasma fibrinogen levels, compared with non-users, but in a larger cross-sectional study conducted in a randomly selected population sample, snuff use was not associated with plasma fibrinogen and fibrinolytic variables. Moreover, fasting and post-load insulin tended, if anything, to be lower than among non-users. However, a recent population-based cross-sectional Swedish study found an increased

risk of type 2 diabetes among heavy users of moist snuff. The relative risk for diabetes was 2.7 among those who consumed three or more boxes per week. This excess was even more marked if those who had been former smokers were excluded from the analysis. This novel finding needs to be confirmed in other studies.

*Indices of atherosclerosis*
In a recent Swedish study, B-mode ultrasonography of the carotid intima media thickness was performed on 143 healthy middle-aged men with different tobacco consumption habits. Long-term smokeless tobacco users (n=28) did not differ significantly from never-users (n=40) in any of the parameters studied, while smokers had significantly increased wall measurements. The snuff users in this study did not have any of the biochemical risk factors observed in some of the studies cited above.

*Physical performance*
The middle-aged men engaged in the ultrasonography study also underwent graded maximal exercise tests. Regular users of smokeless tobacco, with exposures of more than 20 years, showed similar maximal oxygen uptake to non-users. The mean blood pressure and heart rate values were higher in smokeless tobacco users at rest and during submaximal work, but during maximal work the values were similar to those recorded in non-users. Thus, it appears that long-term use of smokeless tobacco does not significantly influence exercise capacity.

*Cardiovascular disease outcomes*
Data regarding the risk of severe cardiovascular outcomes are conflicting. Despite the absence of indices of significant cardiovascular changes, follow-up of a large Swedish cohort of construction workers revealed a statistically significant 40% excess risk of cardiovascular disease *death* among never-smoking snuff users, relative to never-users of any kind of tobacco. The relative excess was even greater (110%) in the youngest age group at start of follow-up (35-54 years). Adjustments for body mass index, blood pressure, and history of heart symptoms left the relative risk estimates essentially unchanged. The risks for ischaemic heart disease death and stroke death were similarly increased. Moreover, the incidence of disability pensions due to cardiovascular disease showed an excess of the same magnitude (50%), indicating that cardiovascular disease *incidence* is also increased, and that differences in case fatality among snuff users may not explain the findings.

Opposing data derive from two large, carefully conducted Swedish population-based case-control studies of incident myocardial infarction among men aged 35-64 years. In one of these studies, with an unmatched design, the age adjusted odds ratio for myocardial infarction was 0.9 among snuff users and 1.9 among cigarette smokers, relative to non-users of tobacco. In the other one, with a matched design, the odds ratio, adjusted for multiple cardiovascular risk factors, was 0.6 (significantly decreased) among non-smoking snuff users, and 3.5 among regular smokers. Thus, these studies indicate that the risk for incident myocardial infarction is *not* increased among snuff users.

The reasons for the discrepant results in the construction workers cohort and the population-based case-control studies remain obscure. Differential misclassification of the outcome in the former study is conceivable, but is unlikely to explain the entire excess observed. It should be noted that in the most recent case-control study, restriction to fatal cases (including sudden death) tended to

shift the relative risk estimates among snuff users towards an excess (odds ratio 1.5). This seems to indicate that the case fatality, after all, may be higher among snuff users. Since exposure information was missing more often for deceased cases than for surviving ones, more than 30% of the fatal case-control pairs had to be excluded from the analysis. This may have contributed to a moderate under-estimation of the relative risk.

In summary, although it appears that smokeless tobacco use affects traditional cardiovascular risk factors only marginally, and less severely than smoking, and notwithstanding that snuff use seems to leave cardiovascular morphology and function intact, a moderately increased risk for cardiovascular death cannot be excluded. A possibility that should be entertained is that the incidence of myocardial infarction is not increased, but that the case fatality is higher among snuff users who sustain this disease.

**Risk of other diseases**

The relationship of smokeless tobacco to inflammatory bowel disease has been studied in one Swedish case-control study. Among non-smokers, no association was evident for smokeless tobacco, but smokeless tobacco in combination with cigarette smoking was associated with a risk of about three-fold for ulcerative colitis and Crohn's disease. The meaning of this finding is unclear.

In a pilot case-control study from India, betel nut with tobacco chewing was a significant risk indicator (adjusted odds ratio 7.4) for Meige's syndrome, which is a neurological disorder of unknown aetiology, consisting of spontaneous symmetrical dystonic movements of facial muscles causing blepharospasm and a variety of dystonic spasms of the lower face, jaw and neck muscles. Further evaluation seems warranted.

**Recommended reading**

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