Review for ASH Britain, 3rd revised version Oct 29, 2002

SNUFFING, SMOKING AND THE RISK FOR HEART DISEASE AND OTHER VASCULAR DISEASES

Kjell Asplund

Department of Medicine, University Hospital, Umeå, Sweden

Correspondence: Professor Kjell Asplund
Department of Medicine
University Hospital
S-901 85 Umeå, Sweden

Tel +46 90 785 00 00
fax +46 90 14 59 21

e-mail Kjell.Asplund@medicin.umu.se

Key messages

- Smoking increases the risk of myocardial infarction, sudden death, stroke and peripheral artery disease of the legs by 2-4 times.

- Whether or not snuff use is associated with an increased risk of myocardial infarction and sudden death is still controversial. If there is an excess risk, it is very much smaller than for smoking. For stroke or peripheral artery disease, there is no scientific information on possible risks of snuff use.

- Smoking and snuff use produces immediate increases in blood pressure and heart rate, but do not seem to increase the occurrence of chronically elevated blood pressure (hypertension).

- Smokers, but not snuff users, have more artery wall changes (atherosclerosis) than non-tobacco consumers when examined by ultrasound.

- Smoking adversely affects a number of biochemical mechanisms that may lead to atherosclerosis and clot formation. Much less is known about the effects of snuff use, but so far no similar adverse effects have been documented.

- Whether or not snuff serves as a gateway to smoking in young people is a matter of debate, as yet unresolved.

- Among adults, snuff is often used by former smokers as a nicotine substitute. It is controversial if this is a viable and ethically correct strategy to reduce the health hazards of smoking.

- Virtually all scientific information on health effects of snuff comes from two countries, USA and Sweden. The effects on the cardiovascular system of snuff from other parts of the world (often home-made and/or blended with various other substances) are unknown.

This review presents the scientific information currently available on the risks of cardiovascular diseases (myocardial infarction, stroke and peripheral artery disease of the legs) in smokers and users of snuff, a form of smokeless tobacco. It also presents what is known about the effects of smoking and snuff use on cardiovascular risk factors, such as elevated blood pressure, obesity, and diabetes. The biochemical mechanisms that make smoking so devastating for the cardiovascular system are briefly described in relation to what is known about the biochemical effects of snuff. Finally, tobacco policy implications are discussed: if smokeless tobacco is less dangerous than smoking, should it be introduced as a substitute for smoking in people addicted to nicotine (so-called harm reduction strategy), or should it be universally prohibited because of its adverse health effects (as in the European Union)?

The adverse effects of smoking on the heart and the vascular tree are well established and will only be summarised briefly here; emphasis will be on the effects of snuff. With regard to smoking, only cigarettes are covered. The little information that is available about the effects in people who smoke pipe or cigars, indicate that the risk of heart disease and stroke is similar (1) or somewhat lower (2, 3) than in cigarette smokers.

What is snuff?

Snuff is pulverised tobacco that, when it was first introduced in Europe in the 17th centrury, was inhaled in dry form through the nostrils (snuffed). Today, most snuff is moist and taken orally, either in a loose form or in tea-bag-like small packages (sachets) placed between the gum and the chin or under the upper lip.

Two countries dominate the commercial snuff market, USA and Sweden. In United States, snuff production involves a fermentation process, whereas Swedish snuff (locally called snus) is prepared by a heating process without traditional smoke-drying, yielding a semi-sterile product. Various blending ingredients are added to make various brands of snuff taste differently.

In other countries, complex additives are used. For instance, "natrone powder" is an important ingredient of the Sudanese snuff variant toombak. In South Africa, most snuff is homemade, being a mixture of tobacco and other plant leaves. Betel quid, frequently used in South Asia, is made with or without tobacco.

The complexity of snuff composition makes it difficult to make general statements about the effects of all forms of snuff on the cardiovascular system. Nearly all scientific studies on the health effects of snuff have been performed in the United States and Sweden, and the results should be regarded as representative only of the kinds of snuff available commercially in these countries (fermented and non-fermented, respectively).

Who uses snuff?

Cigarette smoking is pandemic, i.e. it is widely spread all over the word. The use of snuff can best be described as endemic, which means that it is restricted to particular populations or countries. Snuff use is quite common in North America, some of the Scandinavian countries, India, Bangladesh and Southeast Asia and parts of Africa. In the United States and Sweden, moist snuff is the only tobacco product with increasing sales during the last decade. Snuff is often used in certain subsets of a population, such as athletes, male adolescents and young adults and people in professions where smoking is not allowed (firemen!). As discussed below, a large proportion of adult snuff users are former smokers.

Snuff is banned for health reasons in the European Union, but Sweden with its strong tradition of snuff use is exempted. It may seem a paradox that cigarettes with their serious health hazards are not prohibited. The ban followed a WHO recommendation where the reasoning was that introducing another tobacco alternative to markets not yet exposed to snuff would just worsen the tobacco problem.

What health hazards have been discussed?

A multitude of adverse affects caused by smoking on the vascular system and on factors promoting clot formation are well documented. Does snuff involve the same risks? There are much fewer studies performed on the effects of snuff than on the effects of smoking. The research on potential health hazards of snuff has focussed on the risks of cardiovascular disease, cancer, oral diseases and addiction. Increased risks for diabetes and osteoporosis have also been discussed. Cardiovascular diseases are the main topic of this review. The current knowledge about the other disorders is briefly summarised later in this review.

Myocardial infarction and other forms of cardiovascular disease in snuff users – what is the evidence?

As shown in Table 1, smoking markedly increases the risk for myocardial infarction, sudden death, stroke and peripheral artery disease (claudication and sometimes gangrene in the legs). The risk increase is dose-dependent, so that high consumers of cigarettes have a higher risk than people with lower consumption. Yet, even at daily consumption below 5 cigarettes per day, there is a clearly increased risk for cardiovascular disease.

The possible relationship between snuff use and cardiovascular disease has been explored much less. In fact, there are only three studies that have studied the relationship, all of them performed in Sweden. The results are somewhat contradictory.

The first study investigating the relationship was done among 135,000 construction workers in Sweden (4). In the years 1971-74 they underwent a health examination and they were asked about tobacco habits, including the use of snuff. Twelve years later, the Swedish cause-of-death register was checked – had the workers who participated in the health survey died and, if so, what was the cause of death? Compared to non-tobacco users, those who used snuff in the beginning of the 1970s were found to have a 40% higher risk of cardiac death (from myocardial infarction or sudden death with a presumed cardiac cause), whereas the risk was 85% higher in smokers than in non-tobacco users (Construction workers in the figure).

Obviously, this finding was in agreement with what was previously known about cardiovascular hazards conferred by tobacco smoking.

In two more recent studies, it has been very difficult to confirm that snuff use increases the risk for myocardial infarction. Both were performed within the framework of the Northern Sweden centre of the WHO MONICA Project, which is a very large multinational study of cardiovascular diseases and their risk factors. In the first of these studies, patients who had suffered a myocardial infarction were interviewed about their tobacco habits and other risk factors and they were compared with people that had not had a myocardial infarction (so-called case-control study) (5). If the patient had died, a family member was interviewed. As shown in the figure (WHO MONICA I), smokers had a nearly 4-fold increase in the risk for myocardial infarction, whereas snuff users did not appear to have any excess risk.

The same research group performed another, larger case-control study and they collected more detailed information on tobacco habits (6). This time, the control persons were strictly matched – they were of the same sex, were born on the same day and were living in the same area as those who had had a myocardial infarction or who had died suddenly from a probable cardiovascular cause. This study also failed to show an increased risk of myocardial infarction in snuff users compared to men who had never used tobacco (WHO MONICA II in the figure). Based on the data given in the article, the risk for myocardial infarction is estimated to be about 3-4-fold higher in regular cigarette smokers than in regular snuff users (6).

The results of the three studies agree on one point: the risk for a severe cardiac event is much smaller in snuff users than in smokers. But in the comparison between snuff users and non-tobacco users the results are discrepant. The first cohort study on construction workers showed an increased risk whereas the ensuing two case-control studies did not. There are several possible explanations for this discrepancy. The construction worker study was based on causes of death recorded by official vital statistics. As discussed later, nicotine has immediate effects on the heart rate and there is a possibility that snuff causes disturbances of the heart rhythm (arrythmia). This could enhance the risk of sudden death. The two later studies were not designed to explore the risk for sudden death, and they did not have a sufficient number of patients to detect a small increase in this risk.

Also, there has been a change in snuff use among Swedish men during the last decades, the high-prevalence groups gradually shifting from elderly low-educated men to young and middle-aged men with a high level of education. In the construction worker study, snuff users had, as a group, an unfavourable risk factor profile at the health survey in the beginning of the 1970s with higher body mass index and higher resting blood pressure levels than non-tobacco users (4). Several studies performed during the 1990swere not able to confirm that snuff users have elevated resting blood pressure or increased body weight (7-11). Since a large proportion of adult snuff users in Sweden today are former smokers, it could be argued that they constitute the most health-conscious part of the population of tobacco consumers. Possibly, they have other more favourable health behaviours as well, not present among snuff users 30 years ago.

A third possible explanation for the apparent discrepancies between the results of the construction worker study and the more recent studies is that the composition of moist snuff has changed over the years. The content of some of the toxic products (tobacco-specific nitrosamines, see below) was reduced by half in Swedish snuff from 1983 to 1992 (12), and this could perhaps be associated with the reduced health hazards of snuff.

It has also been suggested that factors not measured in the studies may have influenced the results. For instance, a number of social factors and the alcohol consumption pattern (all known to affect the risk of myocardial infarction) may well have been different in snuff users among construction workers in the early 1970s and snuff users in the general population 20 years later.

As shown in table 1, smoking is a strong risk factor for both stroke and peripheral artery disease. As for myocardial infarction, the relative risk is highest in young and middle-aged people and then decreases with increasing age. However, as the risk in absolute numbers is much higher in old age (even in non-smokers), smoking causes just as many strokes or new cases with peripheral artery disease in the elderly as in middle-aged people.

There is a dearth of studies that have explored the risk of stroke or peripheral artery disease in snuff users.

Does snuffing promote artery lesions as much as smoking does?

Two studies, both conducted in Sweden, have used ultrasound to detect thickening of the artery wall and atherosclerotic changes among smokers, snuff users and non-tobacco users. In the first study, middle-aged firemen were investigated (13). Those who smoked regularly had considerably more signs of atherosclerosis when compared to non-tobacco users. However, their colleagues who were regular snuff dippers did not have more thickening of the wall of the main neck artery leading to the brain than non-tobacco users had.

In the second study, both the main arteries to the leg (femoral arteries) and the main neck arteries (carotid arteries) were investigated by ultrasound in a random sample of middle-aged men (14). Regular smokers, but not snuff users, had much more carotid or femoral lesions (atherosclerosis) compared with men who had never used tobacco.

Does smoking and snuffing affect factors causing artery lesions and clots?

Smoking accelerates the processes that lead to artery disease (atherosclerosis) and clot formation by many different mechanisms. Table 2 lists some of the most essential mediating factors.

The factor that has attracted most attention in relation to smokeless tobacco is blood pressure. Snuff causes a rapid rise in both systolic and diastolic blood pressure and in heart rate. This persists as long as the nicotine is absorbed. The rise in diastolic blood pressure is in the order of 5 mmHg (15). In one early study, average resting blood pressure was found to be elevated in snuff users compared to non-tobacco users (16), but none of the studies performed during the 1990s and early 2000s have been able to find elevated blood pressure or increased prevalence of hypertension among snuff users (7-11). It is possible that the change in sodium content of snuff could partly explain the discrepancy between early and later studies.

Smokers have low circulating levels of antioxidant vitamins, such as ascorbic acid, carotene and vitamin E (tocopherol). These levels are not lowered in regular snuff users (17). The reason for the low levels in smokers is partly their lower intake of antioxidant vitamins

with the food, and partly that they seem to consume antioxidants at a faster rate as a defence mechanisms against the free radical formation induced by tobacco smoke.

Smokers also usually have elevated plasma levels of a substance called C-reactive protein. This reflects ongoing inflammatory and infectious processes. Inflammation, perhaps also viral infections, plays a crucial role in the atherosclerotic process. Snuff users have the same levels of C-reactive protein as non-tobacco users have (14).

Another substance with an increased production during inflammation is fibrinogen (much of an elevated sedimentation ratio is due to high levels of fibrinogen in the blood). High levels of. fibrinogen, in turn, promotes clot formation. Smokers usually have high fibrinogen levels, whereas the levels are not elevated in snuff dippers when compared with non-tobacco users (10). In addition, smokers, in contrast to snuff users, have increased formation of thromboxane A2, that reflects activation of platelets and elevated risk of clot formation (18).

As a defence mechanism against clot formation, we have a fibrinolytic system that serves to dissolve clots as they are formed. Poor activity of the fibrinolytic system has been found to increase the risk of myocardial infarction, particularly in young and middle-aged people. Smoking adversely affects several steps in the fibrinolytic system, whereas snuff dipping does not seem to have the same adverse effects (10).

As a caveat, it should be mentioned that nicotine has been shown to accelerate biochemical and physiological processes that are involved in the development of atherosclerosis. Most of these effects have been demonstrated in tissue culture systems and experimental animals (18). If nicotine will be confirmed to be a culprit also in the atherosclerotic process in humans, this would seriously caution against the long-term use of both snuff and nicotine replacement therapy.

Snuff and the risk for disorders other than cardiovascular

Recently, the interest in snuff as a promoter of disease has turned to diabetes. Long-term use of nicotine replacement (gums, patches, nasal sprays, etc.) has been associated with insulin resistance and high levels of insulin in the blood (19). In other settings, insulin resistance may precede the development of diabetes, and it could well be that snuff has the

same effects as nicotine gums and patches. Indeed, one report on a very limited number of newly diagnosed patients found an increased risk for type 2 diabetes in snuff dippers compared to non-tobacco users (20). There are, however, studies that have failed to show that snuff users have higher levels of insulin than normal (10) or that they have an increased risk for diabetes (Rodu and Asplund, in manuscript). A possible explanation for the divergent results may be that many snuff users are former smokers, and that smokers seem to have an increased risk for diabetes. Anyhow, the finding of an excess risk of diabetes in snuff dippers need to be confirmed (or refuted) in new studies.

Substances that can cause cancer (so called tobacco-specific nitrosamines) can be absorbed from snuff to a considerable extent, and snuff dippers have as high levels of these substances incorporated into hemoglobin and DNA as cigarette smokers have. As early as 1937, it was described that the great majority (70%) of patients with cancer in the anterior part of the mouth used smokeless tobacco (21). When a consensus panel under the auspices of the US National Institutes of Health reviewed the available evidence in a report published in 1988, snuff and other forms of smokeless tobacco were pointed out as culprits in the causation of mouth cancer (22). In analogy with cigarette smoking, smokeless tobacco has also been implicated as a possible causative factor in cancer in the pharynx, the oesophagus, the stomach and the urinary bladder. For a number of years, all snuff packages sold in Sweden were carrying the label ”Snuff causes cancer”.

Several studies published in recent years have, however, failed to confirm the suspicion that snuff marketed in Western countries causes cancer (4, 23-26). The types of cancer being considered here are, however, not very common, and the studies have usually not had the statistical power to exclude a very modest excess risk. It may also be that different forms of snuff have different cancer-promoting effects. Thus, when all information available in the scientific literature is reviewed, it seems that dry snuff increases the risk for cancer in the upper respiratory tract considerably, whereas no increased risk has been documented in

people who use moist snuff (27). It may also be that the cancer-promoting effects of snuff studied in early reports were different from those in the kind of snuff that is manufactured today. Recently, the Swedish health authorities decided to remove the label "Snuff causes cancer" on the packages because of the lack of scientific evidence for the statement.

Betel quid, frequently used in India and other parts of South Asia, increases the risk of oral cancer (28). Many betel preparations contain also tobacco, and it is possible that tobacco may act together with alkaloids in the betel to cause oral cancer.

Even if it has been difficult to implicate snuff as a culprit in mouth cancer, it clearly has other effects on oral health. At the site where the tobacco is placed (for instance under the upper lip in Sweden, between the lower gum and the chin in United States) there are local tissue reactions with thickening and whitening (termed leukoplakia) of the mucous membranes (7). These changes are worse in heavy snuff users, particularly if it is in the form of loose snuff (i.e. not portion-bags). The changes are usually reversible after cessation of snuff use. Snuff users also often have gingival recessions (the part of the gums covering the teeth is retracted). These changes seem to be irreversible (29).

An increased risk of osteoporosis in people who use smokeless tobacco has been proposed but, so far, there is no scientific information that has confirmed this hypothesis.

The most obvious medical effect of snuff dipping is that of addiction. Soon after placing smokeless tobacco in the mouth, nicotine peaks in the circulation at very high levels, and snuff seems to be at least as addictive as cigarette smoking (30). Some snuff users replace the portion more or less continuously throughout the day and they constantly have high blood levels of nicotine. The success rate among people who try to quit using snuff is no better than that among cigarette smokers (31). Intervention programs to help people quit using smokeless tobacco have been used with reasonable success when compared with the effects of anti-smoking interventions (32, 33).

Why the difference between snuff and cigarettes?

Let us for a moment leave the issue of the possible health hazards of snuff dipping compared to non-tobacco use to concentrate on the comparison between snuff use and smoking.

All three studies on snuff and myocardial infarction agree that there is a marked difference in risk between cigarette smoking and snuff use (4-6). This occurs despite the fact that nicotine content, nicotine absorption, nicotine levels in the blood and the risk of nicotine addiction is about the same with cigarettes and snuff. It seems that tobacco constituents other than nicotine account for the differences in risk of myocardial infarction and atherosclerosis in other parts of the vascular tree. Nicotine is not an important contributor to myocardial infarction (and maybe not to atherothrombotic mechanisms in general, a caveat being nicotine effects observed in tissue culture experiments, see above).

Many of the components of tobacco smoke are produced when tobacco is burned and inhaled. To summarise some the evidence (for detailed references, see(25, 34, 35)):

- Some tobacco components are better absorbed through the airways than through the mucous membranes of the mouth.
- The process of burning tobacco produces toxic substances, for instance through a process called endogenous nitrosation.
- Among the about 2,500 chemical substances identified in tobacco smoke, several moieties (for instance tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons and a wide variety of oxidant gases) have been implicated as agents causing cardiovascular disease.
- A specific chemical compound, 1,3 butadiene, that accelerates atherosclerotic plaque formation has been identified in environmental tobacco smoke.
- Cigarette smokers have elevated levels of carbon monoxide in their blood and this has also been implicated in the pathogenesis of smoking-related cardiovascular disease. However, the clinical and experimental evidence to support this hypothesis is not very robust.

Further support for the contention that tobacco smoke is very different from smokeless tobacco in causing disease comes from the cancer field. The case of lung cancer is obvious. But also when it comes to cancer in the mouth and pharynx the difference between snuff and tobacco smoke, despite both having local effects on the mucous membranes, is striking. Smoking confers a marked increase in the risk for risk for cancer of the mouth and pharynx but, as discussed above, it has been difficult to implicate snuff as a causative agents in these types of cancer. As with atherosclerosis and myocardial infarction, it seems that burning tobacco produces the most deleterious substances.

It should be emphasised that the composition of smokeless tobacco varies greatly around the world. An abundance of substances are added to create local variants of snuff, and some of the additives may contain exceedingly high concentrations of cancer-promoting substances. In the two main snuff-producing countries, the manufacturing processes are different. In United States, it involves a fermentation process, whereas Swedish snuff is nowadays prepared by a heating process without traditional smoke-drying, yielding a semi-sterile product with a lower content of toxic substances like tobacco-specific nitrosamines than previously (25). It must also be noted that, even within a country, there are wide variations in the content of nicotine and cancer-promoting tobacco-specific nitrosamines between different brands of moist snuff (36).

Is snuff a gateway to smoking or a way out?

Even if the direct health hazards of snuff may be very modest, the habit of snuffing may still be detrimental to health if it serves as a gateway to smoking. Studies among US Air Force recruits (37) as well as among Swedish boys (38) have shown an increased risk to start cigarette smoking among those who have experimented with smokeless tobacco. Switching from smokeless tobacco to smoking is common in US college students (39). These observations together would suggest that snuff might indeed be a gateway to smoking.

There are, however, several problems in interpreting these results. Young people who take up smoking often have a drug- and risk-seeking lifestyle, and experimenting with snuff may be yet another expression of this lifestyle. The Swedish experience is also that the

prevalence of smoking is higher among teenager girls than among boys despite boys more often having tried snuff. The issue of snuff as a gateway to smoking is extremely difficult to explore scientifically, at least by the use of quantitative research.

In countries where snuff dipping is endemic, it is commonly used to quit smoking. The situation in Sweden is particularly illustrative. About half of middle-aged snuff users are ex-smokers (6, 40). In smokers, cigarette consumption is about half in those who concomitantly use snuff compared to those who only smoke cigarettes. In northern Sweden with a tradition of widespread snuff use, the prevalence of cigarette smoking among men is the lowest in Europe (and lower than in the south of the country with less use of snuff) (41). Lung cancer rates are also exceedingly low by international comparisons (42). Whereas the proportion of the population who are tobacco consumers has remained constant over the last 15 years, the number of smoking men has declined at the same rate as the number of snuff users has increased. Today, there are two snuff dippers for every man who smokes. Recently, the proportion of women who use snuff has increased. At the same time, the proportion of smokers among women has started to decline (Northern Sweden MONICA Study, unpublished).

A complicated message

It is evident that the use of snuff involves much lower risks of cardiovascular disease and cancer than cigarette smoking does. Proponents of snuff have applied the concept of *harm reduction*: Can snuff be tried in inveterate smokers who have failed to quit despite using nicotine replacement therapy or other medical interventions?

Only one intervention study of snuff as an aid to quit smoking has been reported so far. In an open, uncontrolled, small study performed in the United States, a quarter of heavy smokers that were recommended to use snuff instead of cigarettes were smoke-free at one year (43). Nearly all quitters had previously tried nicotine patches or gums. All of them still used snuff at the one-year follow-up. Clearly, if this disputatious strategy is to be tried further, high-quality, controlled intervention studies are needed.

We are confronted with extremely difficult questions: Are there circumstances that could justify doctors to recommend the use of smokeless tobacco? What about the smoking patient who asks if he/she should try snuff dipping instead? And even more challenging: in pragmatic public health work, is snuff friend or foe?

People involved in the fight against tobacco intuitively refute the idea of treating cigarette smoking with smokeless tobacco as being flawed. The anti-snuff position is sometimes worded even more dramatically: "To promote smokeless tobacco in place of cigarette smoking would be like encouraging sniffing cocaine as a safer alternative to mainlining heroin" (44).

So, the concept of harm reduction by use of snuff is complicated and controversial. Obviously, from a medical and moral point of view, the only reasonable norm is non-use of tobacco. The goal should be a tobacco-free society. On the route towards this goal, we face enemies that are more perilous than others. Smoking is the overwhelming threat to people's health. In countries with access to snuff, the controversy continues whether or not it should be used to reduce the health hazards of smoking in the individual and in the population.

Unresolved issues

As is evident from this review, the hazards of cigarette smoking for the heart and other parts of the vascular system are extremely well documented in the scientific literature. For snuff, our knowledge is much more limited. Among the issues that need to be resolved are:

- Can the results of the Swedish studies on the risk for myocardial infarction and sudden death be applied to all commercially available snuff brands, or are the hazards different?
- Does home-made snuff used in many poor countries of the world involve risks for cardiovascular disease that are different from those of snuff used in rich countries?
- Does snuff cause disturbances of the heart rhythm and, if so, does this increase the risk for sudden death?

- Does snuff use increase the risk for stroke and/or peripheral artery disease?
- Does the immediate rise in blood pressure and heart rate upon intake of snuff have any long-term deleterious effects on the heart and the vascular tree?

It emerges from this list of unresolved issues, that it is wise to be cautious when discussion the health hazards of snuff use and their impact on health policy – there is still much room for improved knowledge.

References

1. Carstensen J, Pershagen G, Eklund G. Mortality in relation to cigarette and pipe smoking: 16 years' observation of 25,000 Swedish men. J Epidemiol Community Health 1987;41:166-72.
2. Haheim LL, Holme I, Hjermann I, Leren P. Smoking habits and risk of fatal stroke: 18 years follow up of the Oslo Study. J Epidemiol Community Health 1996;50:621-4.
3. Kaufman D, Palmer J, Rosenberg L, Shapiro S. Cigar and pipe smoking and myocardial infarction in young men. Br Med J 1987;294:1315-6.
4. Bolinder G, Alfedsson L, Englund A, de Faire U. Smokeless tobacco use and increased cardiovascular mortality. Am J Publ Hlth 1994;84:399-404.
5. Huhtasaari F, Asplund K, Lundberg V, Stegmayr B, Wester PO. Tobacco and myocardial infarction: is snuff less dangerous than cigarettes? BMJ 1992;305:1252-6.
6. Huhtasaari F, Lundber gV, Eliasson M, Janlert U, Asplund K. Smokeless tobacco as a possible risk factor for myocardial infarction. A population-based study in middle-aged men. J Am Coll Cardiol 1999;34:1784-1790.
7. Ernster V, Grady D, Greene J, Walsh M, Robertson P, Daniels T, et al. Smokeless tobacco use and health effects among baseball players. JAMA 1990;264:218-24.
8. Eliasson M, Lundblad D, Hägg E. Cardiovascular risk factors in young snuff-users and cigarette smokers. J Intern Med 1991;230:17-22.
9. Siegel D, Benowitz N, Ernster VL, Grady DG, Hauck WW. Smokeless tobacco, cardiovascular risk factors, and nicotine and cotinine levels in professional baseball players. Am J Publ Hlth 1992;82:417-21.
10. Eliasson M, Asplund K, Evrin PE, Lundblad D. Relationship of cigarette smoking and snuff dipping to plasma fibrinogen, fibrinolytic variables and serum insulin. The Northern Sweden MONICA Study. Atherosclerosis 1995;113:41-53.

11. Bolinder G, Norén A, Wahren J, de Faire U. Long-term use of smokeless tobacco and physical performance in middle-aged men. Eur J Clin Invest 1997;27:427-33.
12. Nordgren P, Ramström L. Moist snuff in Sweden - tradition and evolution. Brit J Addict 1990;85:1107-12.
13. Bolinder G, Norén A, de Faire U, Wahren J. Smokeless tobacco use and atherosclerosis: an ultrasonographic investigation of carotid intima thickness in healthy middle-aged men. Atherosclerosis 1997;132:95-103.
14. Wallenfeldt K, Hulthe J, Bokemark L, Wikstrand J, Fagerberg B. Carotid and femoral atherosclerosis, cardiovascular risk factors and C-reactive protein in relation to smokeless tobacco use or smoking in 58-year old men. J Intern Med 2001;250:492-501.
15. Bolinder G, de Faire U. Ambulatory 24-h blood pressure monitoring in health, middle-aged smokeless tobacco users, smokers, and nontobacco users. Am J Hypertens 1998;11:1153-63.
16. Bolinder GM, Ahlborg BO, Lindell JH. Use of smokeless tobacco: blood pressure elevation and other health hazards found in a large-scale population survey. J Intern Med 1992;232:327-34.
17. Stegmayr B, Johansson I, Hihtasaari F, Moser U, Asplund K. Use of smokeless tobacco and cigarettes - effects on plasma levels of antioxidant vitamins. Int J Vitam Nutr Res 1993;63:195-200.
18. Wennmalm A, Benthin G, Granstrom E, Persson L, Petersson A, Winell S. Relation between tobacco use and urinary excretion of thromboxane A2 and prostacyclin metabolites in young men. Circulaton 1991;83:1698-704.
19. Eliasson B, Taskinen MR, Smith U. Long-term use of nicotine gum is associated with hyperinsulinemia and insulin resistance. Circulation 1996;94:878-81.
20. Persson P-G, Carlsson S, Svanström L, Östensson C-G, Efendic S, Grill V. Cigarette smoking, oral moist snuff use and glucose intolerance. J Intern Med 2000;248:103-110.

21. Ahlbom HE. Prädisponierende Faktoren für Plattenepithelkarzinom in Mund, Hals and Speiseröhre. Eine Stastische Undersuchung am Material des Radiumhemmets, Stockholm. Acta Radiol 1937;18:163-185.
22. Panel NCD. National Institutes of Health consensus statement. Health implications of smokeless tobacco use. Biomed Pharmacother 1988;42:93-98.
23. Schildt EB, Eriksson M, Hardell L, Magnuson A. Oral snuff, smoking habits and alcohol consumption in relation to oral cancer in a Swedish case-control study. Int J Cancer 1998;77:341-346.
24. Bouquot JE, Meckstroth RL. Oral cancer in a tobacco-chewing US population - no apparent increased incidence or mortality. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;86:697-706.
25. Nilsson R. A qualitative and quantitative risk assessment of snuff dipping. Regul Toxicol Pharmacol 1998;28:1-16.
26. Lagergren J, Bergström R, Lindgren A, Nyrén O. The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. Int J Cancer 2000;85:340-346.
27. Rodu B, Cole P. Smokeless tobacco use and cancer of the upper respiratory tract. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;93:511-5.
28. Thomas S, Kearsley J. Betel quid and oral cancer: a review. Eur J Cancer B Oral Oncol 1993;29B:251-5.
29. Axéll T. Oral mucosal changes related to smokeless tobacco usage: research findings in Scandinavia. Oral Oncol Eur J Cancer 1993;29B:299-302.
30. Benowitz N. Systemic absorption and effects of nicotine from smokeless tobacco. Adv Dent Res 1997;11:336-40.

31. Tillgren P, Haglund BJ, Ainetdin T, Holm LE. Who is a successful quitter? One-year follow-up of a National Quit and Win Contest in Sweden. Scand J Soc Med 1995;23:193-201.
32. Walsh MM, Hilton JF, Masouredis CM, Gee L, Chesney MA, Ernster VL. Smokeless tobacco cessation intervention for college athletes: results after 1 year. Am J Publ Health 1999;89:228-234.
33. Severson HH, Andrews JA, Lichtenstein E, Gordon JS, Barckley M, Akers L. A self-help cessation program for smokeless tobacco users: comparison of two interventions. Nicotine Tob Res 2000;2:363-370.
34. Nair J, Ohshima H, Nair UJ, Bartsch H. Endogenous formation of nitrosamines and oxidative DNA-damaging agents in tobacco users. Crit Rev Toxicol 1996;26:149-61.
35. Penn A, Snyder CA. 1,3 Butadiene, a vapor phase component of environmental tobacco smoke, accelerates arteriosclerotic plaque development. Circulation 1997;93:275-276.
36. Hoffmann D, Djordjevic MV, Fan J, Zang E, Glynn T, Connolly GN. Five leading U.S. commercial brands of moist snuff in 1994: assessment of carcinogenic N-nitrosamines. J Natl Cancer Inst 1995;87:1862-9.
37. Haddock CK, Weg MV, DeBon M, Klesges RC, Talcott GW, Lando H, et al. Evidence that smokeless tobacco is a gateway for smoking initiation in young adult males. Prev Med 2001;32:262-267.
38. Galanti M, Wickholm S, Gilljam H. Between harm and dangers. Oral snuff use, cigarette smoking and problem behaviours in a survey of Swedish male adolescents. Eur J Public Health 2001;11:340-345.
39. Glover ED, Laflin M, Edwards SW. Age of initiation and switching patterns between smokeless tobacco and cigarettes among college studuients in the United States. Am J Publ Health 1989;79:207-208.

40. Huhtasaari F, Asplund K, Lundberg V, Stegmayr B, Wester PO. Trends in cardiovascular risk factors in the Northern Sweden MONICA Study: who are the winners? Cardiovasc Risk Factors 1993;3:215-21.

41. Kuulasmaa K, Tunstall-Pedoe H, Dobson A, Fortmann S, Sans S, Tolonen H, et al. Estimation of contribution of changes in classic risk factors to trends in coronary-event rates across the WHO MONICA Project populations [see comments]. Lancet 2000;355(9205):675-87.

42. La Vecchia C, Lucchini F, Negri E, Boyle P, Maisonneuve P, Levi F. Trends of cancer mortality in Europe 1955-1989. II: Respiratory tract, bone, connective and soft tissue sarcomas, and skin. Eur J Cancer 1989;28:514-599.

43. Tilashalski K, Rodu B, Cole P. A pilot study of smokeless tobacco in smoking cessation. Am J Med 1998;104:456-458.

44. Mackay J. Comments on West and Krafona's 'Oral tobacco: prevalence, helath risks, dependence potential and public policy'. Br J Addict 1990;85:1099-1106.

Table 1. Effects of smoking and snuff use on the risk for cardiovascular diseases

Disease/condition	Smoking	Snuff use
Myocardial infarction	3-4-fold increased risk	No excess risk
Sudden death	2-fold increased risk	Possibly modest risk increase (40%)
Stroke	2-fold increased risk	No information available
Peripheral artery disease of the legs	3-4-fold increased risk in heavy smokers	No information available

Table 2. Effects of smoking and snuff use on physiological and biochemical factors that increase the risk for cardiovascular disease

Risk factor	Smoking	Snuff use
Blood pressure	Immediate increase, but not increased prevalence of hypertension	Same as smoking
Heart rate	Immediate increase, uncertain if this has any long-term effects	Same as smoking
Antioxidant vitamins	Low blood levels of vitamin C (ascorbic acid), carotene and vitamin E (tocopherol)	Normal
Fibrinogen	Elevated	Normal
Fibrinolytic system	High PAI-1 leading to impaired ability to dissolve clots	Normal
C-reactive protein	Elevated	Normal
Blood sugar	Normal	Normal, but one report on increased risk for diabetes
Body weight	Lower mean weight than non-tobacco users	Same body weight as non-tobacco users

LEGEND TO THE FIGURE

Results from three studies that have explored the risk of myocardial infarction and sudden cardiac death. The risk among non-users of tobacco is set at 1. An odds ratio of 3 means an approximately 3-fold increased risk for myocardial infarction. The three studies (4-6) are described in the text.