

Smokeless tobacco and cancer

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Use of smokeless tobacco products is common worldwide, with increasing consumption in many countries. Although epidemiological data from the USA and Asia show a raised risk of oral cancer (overall relative risk 2.6 [95% CI 1.3–5.2]), these are not confirmed in northern European studies (1.0 [0.7–1.3]). Risks of oesophageal cancer (1.6 [1.1–2.3]) and pancreatic cancer (1.6 [1.1–2.2]) have also increased, as shown in northern European studies. Results on lung cancer have been inconsistent, with northern European studies suggesting no excess risk. In India and Sudan, more than 50% of oral cancers are attributable to smokeless tobacco products used in those countries, as are about 4% of oral cancers in US men and 20% of oesophageal and pancreatic cancers in Swedish men. Smokeless tobacco products are a major source of carcinogenic nitrosamines; biomarkers of exposure have been developed to quantify exposure as a framework for a carcinogenesis model in people. Animal carcinogenicity studies strongly support clinical results. Cancer risk of smokeless tobacco users is probably lower than that of smokers, but higher than that of non-tobacco users.

Introduction

Use of oral and nasal smokeless tobacco products has been common in many countries for centuries (figure 1). During most of the 20th century, use of these products has been common in India and other Asian countries, as well as in parts of Africa, but has declined in northern Europe and North America. However, during the past decades, an increase in use has been seen in the USA and some northern European countries, especially by young people.

Products and patterns of use

Smokeless tobacco is consumed without burning the product, and can be used orally or nasally. Oral smokeless tobacco products are placed in the mouth, cheek, or lip, and are sucked (dipped) or chewed. Chewing tobacco can be classified as loose leaf (made from cigar leaf tobacco that is air-cured, sweetened, and loosely packed), plug (made from heavier grades of tobacco leaves harvested from the top of the plant, immersed in a mixture of licorice and sugar and pressed into a plug), or twist (air-cured or fire-cured burley tobacco leaves, flavoured and twisted in form of a rope). Snuff is a general term for finely cut or powdered, flavoured tobacco, which can be prepared as moist snuff (air-cured and fire-cured tobacco, flavoured and powdered into fine particles, containing 20–55% moisture by weight) and dry snuff (fire-cured, fermented tobacco powder that may contain aroma and flavour additives). Tobacco pastes or powders are also used orally and applied to the gums or teeth. Dry snuff can also be inhaled through the nasal passages.

Most smokeless tobacco products use *Nicotiana tabacum*, and sometimes *N. rustica*. The major components of tobacco are alkaloids, with nicotine as the main compound (85–95% of total alkaloids). During product manufacturing, tobacco leaves, stems, and other ingredients are blended to achieve a specific nicotine content, pH, taste, flavour, and aroma. The pH strongly affects the concentration of bioavailable nicotine,¹ whereas the nitrite content affects nitrosamine concentrations in the product.²

Globally, a wide variety of different smokeless tobacco products are used, which can be used on their own, mixed with other products (such as slaked lime [khaini]), or as ingredients to other products (such as betel quid). These facts complicate the interpretation of epidemiological results, since study participants might have been exposed to products with variable amounts of carcinogens.

The frequency of smokeless tobacco use can vary substantially not only across countries, but also within countries by sex, age, ethnic origin, and socioeconomic



Figure 1: Snuff has been used over many centuries

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characteristics. A detailed description of the different smokeless tobacco products worldwide and country-specific patterns of use is provided elsewhere.^{3,4} Here, we describe major trends and patterns of use for the USA, Sweden, and India, where most epidemiological studies have been done and which have the highest frequency of use.

In the USA, chewing remained the dominant form of tobacco use until the expansion of the cigarette industry in 1918. After a decline in use, a resurgence in tobacco chewing (predominantly loose leaf) occurred in the 1970s, when new moist snuff products were developed and, accompanied with an aggressive marketing campaign, resulted in a three-times increase in snuff sales between 1980 and 2003.⁵ In 2000, 4.4% of men and 0.3% of women in the USA were current users of smokeless tobacco products. Current use was more common in young men, non-Hispanic white people, people with a high-school diploma or a lower education, southern US states, and rural areas.⁶

The major form of smokeless tobacco used in Sweden is moist snuff (snus). In the 1950s and 1960s, use of moist snuff was decreasing and remained common only in older men. However, the development of new products and intensive advertisement and promotion led to a surge in use of moist snuff and consumption increased steadily from 393 g to 921 g per person between 1970 and 2002.⁷ In 2004, 20% of men and 3% of women aged 16–75 years used moist snuff daily; the frequency of use was increased in young adults and in manual workers.⁸

In India, a large variety of commercial or home-made smokeless tobacco products exist. The use of chewing tobacco (often chewed with betel quid or other preparations including areca nut) is more common than the use of snuff; individuals applying smokeless tobacco products as dentifrice is also common. According to a 1998–99 survey,⁹ 28% of adult men and 12% of women reported to chew tobacco. However, the prevalence could have been underestimated because of the use of household informants. The frequency of chewing tobacco varied greatly (8–60% in men, <1–61% in women) between states and was increased in rural, poor, and less educated groups. Use of smokeless tobacco in students aged 13–15 years varied between states from 3–56%.¹⁰

Smokeless tobacco products are also widely used in other countries in southeast Asia. Many other products are used in other regions and countries, including naswar in central Asia, zarda in western Asia, maraş in Turkey, toombak in Sudan, chimó in Venezuela, and iq'mik in Alaska.⁴

Carcinogens in smokeless tobacco

More than 30 carcinogens exist in smokeless tobacco, including volatile and tobacco-specific nitrosamines, nitrosamino acids, polycyclic aromatic hydrocarbons, aldehydes, metals.⁴ Smokeless tobacco use entails the

highest known non-occupational human exposure to carcinogenic nitrosamines, which is 100–1000 times greater than exposure in foods and beverages commonly containing nitrosamine carcinogens. Every gram of commonly used smokeless tobacco contains 1–5 µg of the tobacco-specific nitrosamines 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and NL-nitrosoanabasinone (NNN), two recognised human carcinogens.^{4,11} Furthermore, other carcinogenic tobacco-specific nitrosamines (eg, NL-nitrosoanabasine [NAB]) and nitrosamino acids (eg, 3-[methylnitrosamino] propionic acid) are found in these products.⁴ The contamination of smokeless tobacco products, especially oral snuff, with NNK and NNN was first shown in the 1970s and although the concentrations of these compounds in some products have decreased, they are still moderately high in all products including Swedish snus.^{12,13} The uptake of NNK and NNN by smokeless tobacco users has been clearly shown by the detection of their metabolites in urine. 20 years of smokeless tobacco use would expose users to an amount of NNK (75–150 mg, or about 1.5 mg/kg bodyweight) similar to that which has caused tumours in rats (1.8 mg/kg bodyweight), in addition to substantial exposure to NNN.¹⁴

Target tissues for cancer in smokeless tobacco users have shown some similarity with those seen in rats treated with NNK or NNN. Absolute consistency cannot be expected, since animals are treated with pure carcinogens in an experimental setting whereas people use product mixtures under many other environmental factors (eg, genetics, diet). Carcinogenicity in people affects the oral cavity, the oesophagus, the pancreas, and possibly the lung. A mixture of NNK and NNN swabbed in the rat oral cavity causes oral tumours,¹⁵ and NNK and its metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) causes pancreatic tumours in rats when added to drinking water.¹⁶ NNN added to the drinking water of rats has produced oesophageal tumours.¹⁷ The lung is the main target tissue when NNK is added to the drinking water of rats.¹⁷

Cancer risk in human beings

Oral use—studies from Europe and North America

13 separate risk estimates have been made available from 11 studies examining the risk of oral cancer (oral and pharyngeal cancer in six studies) in users of smokeless tobacco products (table 1). Summary relative risk was 1.8 (95% CI 1.1–2.9), with evidence of heterogeneity in the results (table 2). When stratified by geographic region, the increased risk was restricted to the studies from the USA, whereas no increased risk was reported in the studies from Norway and Sweden (four risk estimates). Results were similar in studies including only non-smokers. Within geographic regions, no evidence of heterogeneity was reported in results between cohort and case-control studies. In the case-control study by Winn and colleagues,¹⁸ in which US women were exposed

	Sex, study period	Study design	Exposure	Inclusion of smokers*	Exposure frequency	Cancer type (number of cases)	Relative risk (95% CI)	Comments	Ref
USA	Women, 1975–78	PCC	Snuff dipping	NS	White, 34.3%; black, 61.0%	Oral and pharyngeal cancer (132)	White, 4.2 (2.6–6.7); black, 1.5 (0.5–4.8)	Proxy interviews for many; mainly use of dry snuff with high nitrosamine concentrations	18
USA	Men/women, 1982	PCC	Smokeless tobacco use	SNS	0.4%	Oral cancer (755)	Tongue cancer, 2.3 (0.2–12.9); mouth cancer 11.2 (4.1–30.7)	Cancer controls; exposure data from hospital records	19
USA	Women, 1984–85	PCC	Smokeless tobacco use	NS	2.0%	Oral and pharyngeal cancer (50)	6.2 (1.9–19.8)	Mainly use of snuff	20
USA	Men, 1977–84	HCC	Smokeless tobacco use	NS	16.9%	Oesophageal cancer (4)	1.2 (0.1–13.3)	Proxy interview for many	21
USA	Men, 1972–83	HCC	Tobacco chewing	SNS	NA	Oral cancer (359)	1.0 (0.7–1.4)	Low response rate	22
USA	Men, 1966–86	Co	Smokeless tobacco use	SNS	NA	Pancreatic cancer (57)	1.7 (0.9–3.1)	..	23
USA	Men, 1970–90	HCC	Tobacco chewing	NS	2.2%	Oral and pharyngeal cancer (82)	2.3 (0.7–7.3)	Unadjusted relative risk	24
USA	Men, 1985–93	HCC	Tobacco chewing	NS	1.5%	Pancreatic cancer (146)	3.6 (1.0–12.8)	Low response rate	25
Sweden	Men, 1988–90	PCC	Oral snuff use	SNS	14.2%	Oral cancer (128); oesophageal cancer (123)	Oral cancer, 1.4 (0.8–2.4); oesophageal cancer, 1.2 (0.7–2.2)	..	26
Sweden	Men/women, 1980–89	PCC	Snuff use	SNS	20.3%	Oral cancer (410)	0.8 (0.5–1.3)	Proxy interview for most	27
Sweden	Men/women, 1995–97	PCC	Snuff use	SNS	15%	Oesophageal cancer (167)	1.4 (0.9–2.3)	Squamous-cell carcinoma	28
USA	Men/women, 1986–89	PCC	Smokeless tobacco use	NS	6.1%	Pancreatic cancer (130)	1.4 (0.5–3.6)	..	29
Norway	Men, 1966–2001	Co	Snus use	SNS	31.7%	Oral and pharyngeal cancer (34); oesophageal cancer (27); pancreatic cancer (85); lung cancer (343)	Oral and pharyngeal cancer, 1.1 (0.5–2.4); oesophageal cancer, 1.4 (0.6–3.2); pancreatic cancer, 1.7 (1.1–2.5); lung cancer, 0.8 (0.6–1.1)	..	30
USA	Men 1959–72	Co	Current spit tobacco use	NS	10%	Oral and pharyngeal cancer (13); lung cancer (134)	Oral and pharyngeal cancer, 2.0 (0.5–7.7); lung cancer, 1.1 (0.6–1.8)	..	31
USA	Men, 1982–2000	Co	Current spit tobacco use	NS	2.2%	Oral and pharyngeal cancer (46); lung cancer (396)	Oral and pharyngeal cancer, 0.9 (0.1–6.7); lung cancer 2.0 (1.2–3.2)	..	31
Sweden	Men, 1978–2004	Co	Snus use	NS	31%	Oral cancer (60); pancreatic cancer (83); lung cancer (154)	Oral cancer, 0.8 (0.4–1.7); pancreatic cancer, 2.0 (1.2–3.3); lung cancer, 0.8 (0.5–1.3)	..	32
USA	Men/women, 2000–06	HCC	Tobacco chewing	NS	4.8%	Pancreatic cancer (323)	0.6 (0.3–1.4)	Similar findings for use of snuff	33
Sweden	Men, 1971–2004	Co	Snus use	NS	29%	Oesophageal cancer (26)	3.5 (1.6–7.6)	Squamous-cell carcinoma	34

Co=cohort study. HCC=hospital-based case-control study. NA=not available. NS=non-smokers. PCC=population-based case-control study. SNS=smokers and non-smokers. *Relative risks that refer to both smokers and non-smokers are adjusted for tobacco smoking.

Table 1: Epidemiological studies of smokeless tobacco use and cancer risk of the oral cavity, oesophagus, pancreas, and lung in the USA and northern Europe

mainly to dry snuff with high nitrosamine concentrations, duration of smokeless tobacco use was strongly associated with risk of cancer of the gum and buccal mucosa; the association was weaker for cancer of other parts of the mouth and pharynx. Exclusion of that study resulted in a pooled relative risk of 2.6 (1.1–6.4, seven risk estimates). In a case-control study from Sweden,²⁶ a trend with the amount of smokeless tobacco was suggested.

With respect to oesophageal cancer, the summary relative risk was 1.6 (1.1–2.3), based on five studies (table 1) but with limited evidence of heterogeneity (table 2). Four of five studies were from northern Europe, thus limiting the possibility to explore differences in risk

between regions. The increased risk was present both in cohort and case-control studies, and both in studies of non-smokers and smokers (data not shown). Results on duration or dose of smokeless tobacco use were reported in two studies,^{26,28} both of which detected an increased risk in the category at highest exposure. Alcohol drinking did not seem to confound the association.

Results from six studies were available on the risk of pancreatic cancer (table 1). Summary relative risk was 1.6 (1.1–2.2), with limited evidence of heterogeneity (table 2). No clear increased risk was present in studies from the USA, whereas two cohort studies from Norway and Sweden reported a raised risk. In two studies,^{29,32}

	Countries	Number of risk estimates	p*	Relative risk (95% CI)	p†
Oral cancer	Overall	13	<0.001	1.8 (1.1-2.9)	..
	USA	9	<0.001	2.6 (1.3-5.2)	..
	Nordic countries	4	0.4	1.0 (0.7-1.3)	0.01
Oesophageal cancer	Overall	5	0.3	1.6 (1.1-2.3)	..
	USA	1	..	1.2 (0.1-13)	..
	Nordic countries	4	0.08	1.6 (1.1-2.4)	0.8
Pancreatic cancer	Overall	6	0.08	1.6 (1.1-2.2)	..
	USA	4	0.3	1.4 (0.7-2.7)	..
	Nordic countries	2	0.6	1.8 (1.3-2.5)	0.5
Lung cancer	Overall	5	0.005	1.2 (0.7-1.9)	..
	USA	3	0.07	1.8 (0.9-3.5)	..
	Nordic countries	2	1.0	0.8 (0.6-1.0)	0.02

Nordic countries include Norway and Sweden. *Test of heterogeneity in individual studies. †Test of heterogeneity between geographical regions.

Table 2: Summary relative risk of selected cancers for ever use of smokeless tobacco in the USA and northern Europe

results were reported by duration or amount of smokeless tobacco exposure, consistently suggesting an association between risk and exposure.

Five cohort studies had available results on risk of lung cancer for use of smokeless tobacco (table 1). Heterogeneity in the results was reduced when studies were stratified by region; although the results of the three US studies indicated an increased risk, two studies from Norway and Sweden suggested a decreased risk (table 2).

Results are sparse on other tobacco smoking-related cancers, such as cancers of the larynx, bladder, and kidney, but none strongly indicates an increased risk for use of smokeless tobacco.⁴ Furthermore, studies examining the risk of other neoplasms have mostly shown null results.⁴

In general, the available epidemiological studies indicate an increased risk of oral cancer for use of smokeless tobacco in the USA, whereas results of studies in the Nordic countries do not support such association. Available evidence for oesophageal and pancreatic cancer points to a causal association, mainly based on the studies from Nordic countries. Results on lung cancer risk are inconclusive, and data for other cancers are inadequate. Possible explanations for the heterogeneity of results by geographic area include the composition of the products used in the USA and northern Europe, the statistical power of the analyses based on few or imprecise risk estimates, and the variable presence of uncontrolled confounding or other sources of bias. Products historically consumed in the USA had, on average, higher nitrosamine content than those used in northern Europe, although the amount of nitrosamine (and other carcinogens) in the products used by the study participants in table 1 cannot be specified. In general, the precision of risk estimates is lower for the US studies than for the northern European studies, and is particularly low for oesophageal cancer. We addressed potential confounding by tobacco smoking,

by including only studies that controlled for confounding factors, and by repeating the meta-analysis on studies including only never smokers. Potential confounding by other risk factors (eg, alcohol drinking for oral and oesophageal cancer) was controlled for in most studies. Other sources of bias are difficult to rule out completely, but the general consistency of results between cohort and case-control studies is an argument against it.

Oral use—studies from Asia and Africa

Since the focus of this Review was on cancer risks of smokeless tobacco, we restricted the search to studies examining use of smokeless tobacco products without betel quid or areca nut. Betel quid without tobacco, as well as areca nut, the common ingredient of betel quid, have been classified as human carcinogens; they cause cancers of the oral cavity, pharynx, and oesophagus.³⁵

Several case-control studies from India, Pakistan, and Sudan provide strong and consistent evidence of an increased risk of oral cancer (or oral and pharyngeal cancer) for use of smokeless tobacco (or tobacco plus lime) products, with relative risk as high as 10.⁴ Another study³⁶ on naswar use from Pakistan reported an equally strong increase in risk for oral cancer after adjustment for tobacco smoking. Additional evidence comes from ecological studies showing positive correlations between use of smokeless tobacco products and increased oral cancer (eg, in Sudan, central Asia, and Saudi Arabia), as well as from case reports and case series from different regions worldwide, in which oral cancer cases reported high frequency of use of smokeless tobacco products.⁴

Data for other cancers are sparse. A study from India³⁷ reported a five-times increase in the risk of oesophageal cancer in non-smokers who chewed tobacco leaves; another multicentre study from India reported a raised risk of hypopharyngeal cancer (but not of laryngeal cancer) in non-smokers who used smokeless tobacco products.³⁸

Nasal use

A case-control study from India reported an association between nasal snuff use and risk of cancer at different subsites of the oral cavity as well as the oesophagus, with relative risks from 2.4 to 4.0 and suggesting a dose-response relation.³⁹⁻⁴² A similar association was not detected for laryngeal cancer.⁴³ In a case-control study of lung cancer from Tunisia,⁴⁴ a two-times increase in relative risk was reported for ever use of inhaled snuff, after adjustment for tobacco smoking. These studies either were restricted to non-smokers or were adjusted for tobacco smoking and other potential confounders.

Switch from tobacco smoking to use of smokeless products

Henley and colleagues⁴⁵ compared men who switched from cigarette smoking to use of spit tobacco (switchers) with men who quit using tobacco entirely (quitters). Switchers had a higher mortality from cancer of the

oral cavity and pharynx than quitters (relative risk 2.6 [95% CI 1.2–5.8]). Compared with quitters, the relative risk of lung cancer was 1.5 (1.2–1.7) for all switchers, 1.3 (1.1–1.6) for switchers to chew only, 1.9 (1.2–2.5) for snuff only, and 2.0 (1.2–3.0) for chew and snuff combined. Compared with men who never used any tobacco product, the relative risk of lung cancer was 3.9 for quitters and 5.6 for switchers.

Health effects other than cancer

Many cross-sectional studies from the USA, India, Saudi Arabia, Uzbekistan, and Sudan reported a higher occurrence of oral soft tissue lesions in smokeless tobacco users than in non-users.⁴ Most of the studies have accounted for tobacco smoking either by statistical adjustment or restriction to non-smokers. The lesions are described as leucoplakia, erythroplakia, snuff dipper's lesion, tobacco and lime user's lesion, verrucous hyperplasia, and submucosal deposits, and tend to be seen in the site of product application. Since these lesions are regarded as precursors of cancer, these findings support the carcinogenicity of smokeless tobacco products on the oral mucosa. Furthermore, a few studies have reported an increased occurrence of gingival recession, tooth wear, and dental caries in users of smokeless tobacco products.⁴ Fewer studies on oral precancerous lesions are available from Nordic countries;^{46,47} overall, an increased occurrence in snus users cannot be excluded.

Several studies have addressed the risk of cardiovascular diseases in users of smokeless tobacco products. Results generally indicate a small or non-existent increased risk of myocardial infarction and cerebrovascular diseases, with most relative risk estimates lower than 1.5.^{4,48} No evidence has shown an increased risk of chronic obstructive pulmonary disease in users of smokeless tobacco products compared with non-users. A few studies have investigated a possible effect of smokeless tobacco on insulin resistance, glucose intolerance, and diabetes, although they have limitations and inconsistent results.⁴

Burden of smokeless tobacco-related cancer

The fraction attributable cancers (AF) is a measure of the burden of smokeless tobacco use on human cancer. It refers to the role of past exposure on current cancer burden, and, if exposure has changed (as has occurred in the composition of smokeless tobacco products used in North America and Europe), it cannot be applied to the effect of current exposure on future cancer. Attributable cancers can be estimated based on the relative risk due to the habit (RR) and the proportion of the exposed population (P), according to the formula:

$$AF = \frac{P \times (RR - 1)}{P \times (RR - 1) + 1}$$

A global estimate of attributable cancers is complicated by heterogeneity in exposure circumstances and risk and

	Sex	Relative risk	Proportion of population exposed to smokeless tobacco (%)	Cases attributable to smokeless tobacco use (%)	n
Oesophageal cancer					
Denmark	Men	1.6	3.5% ⁴⁹	2.1%	5
Norway	Men	1.6	6% ⁵⁰	3.5%	5
Sweden	Men	1.6	20% ⁸	10.7%	31
Sweden	Women	1.6	1% ⁸	0.6%	1
Pancreatic cancer					
Denmark	Men	1.8	3.5% ⁴⁹	2.7%	10
Norway	Men	1.8	6% ⁵⁰	4.6%	12
Sweden	Men	1.8	20% ⁸	13.8%	62
Sweden	Women	1.8	1% ⁸	0.8%	4
Oral cancer					
USA	Men	2.6	4.4% ⁵¹	6.6%	948
Canada	Men	2.6	1% ⁵²	1.6%	24
Sudan	Men	7.3 ⁵³	34% ⁵⁴	68.2%	627
Sudan	Women	7.3 ⁵³	2.5% ⁵⁴	13.6%	79
India	Men	5.1 ^{55*}	27% ^{56†}	52.5%	27 304
India	Women	5.1 ^{55*}	26% ^{56†}	51.6%	8827
Other Asian countries‡	Men	5.1 ^{55*}	25% ⁵⁷	50.6%	9568
Other Asian countries‡	Women	5.1 ^{55*}	25% ⁵⁷	50.6%	6453

N=number of cases attributable to smokeless tobacco use in 2002 (total number of cancers derived from reference 58).
 *Other studies from India and other south Asian countries have provided similar risk estimates. †No stable risk estimates exist for non-smokers. ‡Other surveys from India have provided similar results. †Bangladesh, Bhutan, Indonesia, Burma, Nepal, Pakistan, Sri Lanka.

Table 3: Proportion of oesophageal or oral cancer cases attributable to smokeless tobacco use in selected countries

by the limitations in available data on patterns of use. We therefore calculated the attributable cancers for selected countries, to provide an indication of the order of magnitude of the problem. We calculated the attributable cancers for oesophageal and pancreatic cancer in northern Europe and for oral cancer in Canada, USA, Sudan, India, and other southern and southeastern Asian countries (table 3). The proportion of oral cancer cases attributable to smokeless tobacco use was more than 50% in south and southeast Asia, resulting in more than 50 000 cases of oral cancer attributable to the habit in the eight countries considered, with 36 000 in India alone. This proportion was 68% in Sudanese men and 4.4% in US men, resulting in an estimated number of 627 and 948 cases per year, respectively. The number of oesophageal and pancreatic cancer cases attributable to smokeless tobacco use in northern Europe was small, because of the rarity of the diseases. In particular, 31 cases of oesophageal cancer and 62 cases of pancreatic cancer were attributable to smokeless tobacco use in Swedish men.

These figures are probably underestimated because data for occurrence of exposure refer to the present or the recent past, whereas the exposure relevant for carcinogenesis would have occurred further back in the past and was probably higher. Furthermore, cases of

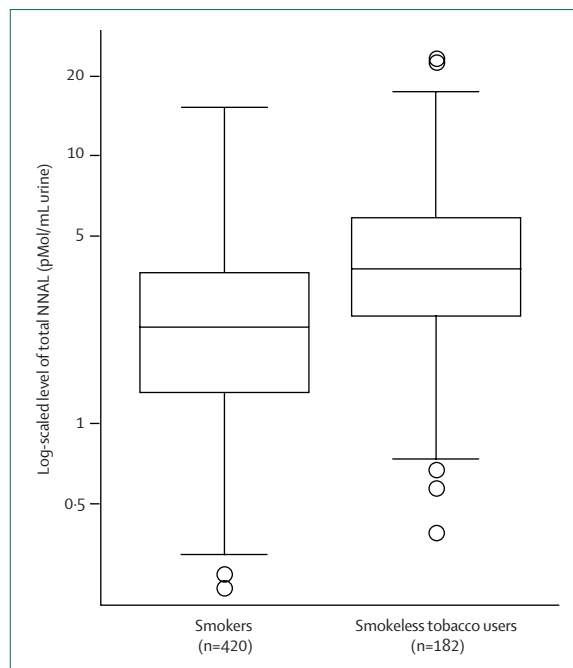


Figure 2: Whisker plots of total NNAL in urine of smokers and smokeless tobacco users
Summarised findings from reference 65.

pharyngeal cancer were not included in the calculation, despite the fact that an excess of this cancer was shown in several studies. Finally, the estimate excluded several populations in which smokeless tobacco is common, such as central and western Asian countries and Asian immigrants to Europe.

Biomarkers of carcinogen exposure in smokeless tobacco users

Biomarker studies clearly show the uptake and metabolism of tobacco carcinogens by smokeless tobacco users. These studies are crucial in linking smokeless tobacco use to cancer outcomes. Human beings and laboratory animals metabolise NNK into NNAL and NNK's glucuronides (NNAL-Glucs).¹⁷ These compounds are excreted in the urine, and the total amount, known as total NNAL, is a practical and widely used biomarker of NNK exposure.⁵⁹

The carcinogenic properties of NNAL are quite similar to those of NNK, whereas NNAL-Glucs are detoxification products.¹⁷ The NNAL biomarker has been extensively

used in studies of NNK exposure in smokers, smokeless tobacco users, and non-smokers exposed to involuntary tobacco smoke.⁵⁹ Advantages of this biomarker include its high reliability and specificity to tobacco products. Total NNAL in urine is not known to come from any source other than uptake of the tobacco-specific carcinogen NNK. Several small studies have clearly shown NNK uptake in smokeless tobacco users by measuring total urinary NNAL, including a study of Sudanese toombak users that recorded very high carcinogen exposures.^{60–64} In a recent study,⁶⁵ total NNAL in the urine of larger groups of smokeless tobacco users and smokers was compared. Total NNAL was substantially higher in smokeless tobacco users than in smokers (figure 2). Similarly, concentrations of the nicotine metabolite cotinine were substantially higher in smokeless tobacco users than in smokers, consistent with previous studies.⁶⁶ Although differences in the pharmacokinetics of NNK and nicotine in smokeless tobacco users and smokers could complicate interpretation of these data, the results nevertheless show substantial uptake of the NNK in smokeless tobacco users, consistent with its amounts in smokeless tobacco products. However, cancer risk is higher in smokers than in smokeless tobacco users because, in addition to NNK, cigarette smoke contains many other carcinogens, tumour promoters, oxidants, and co-carcinogens, mostly derived from combustion.⁶⁷

The tobacco-specific nitrosamines NNN, NAB, and NL-nitrosoanatabine (NAT) and their glucuronides have also been quantified in the urine of smokeless tobacco users, with generally higher concentrations than in smokers.⁶⁸ Total NNN could be a potentially useful biomarker of oesophageal carcinogen uptake in smokeless tobacco users. Tobacco-specific nitrosamines have also been quantified in the saliva of smokeless tobacco users.⁴

NNK and NNN are metabolically activated by cytochrome P450 enzymes resulting in the production of highly reactive pyridyloxobutyl (POB) diazonium ions and related species, which can react with DNA to form products that cause miscoding and mutations, initiating the carcinogenic process.^{17,69} These POB species react with haemoglobin to produce adducts that can be quantified in human beings by mass spectrometry of released 4-hydroxy-1-(3-pyridyl)-1-butanone (HPB). The highest concentrations of HPB-releasing haemoglobin adducts have been reported in snuff-dippers, nasal snuff users, and toombak users.^{64,70,71} These results have

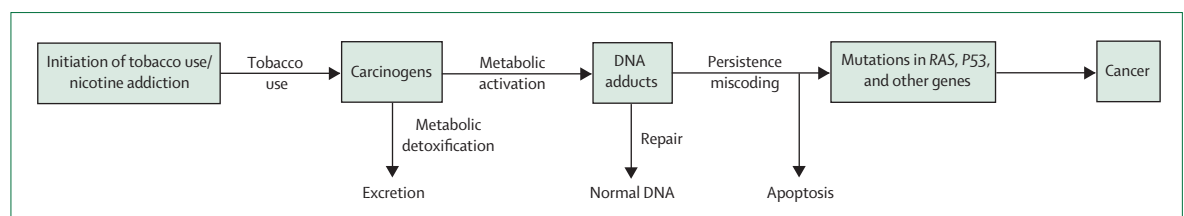


Figure 3: Conceptual model of smokeless tobacco carcinogenesis
Modified from reference 72.

shown that the metabolic activation of NNK and NNN, needed for carcinogenicity, occurs in smokeless tobacco users.

Mechanisms of carcinogenicity of smokeless tobacco

Figure 3 presents a conceptual framework for the carcinogenic mechanism by smokeless tobacco. People begin using these products generally at a young age, frequently because of effective marketing and peer pressure. These individuals become addicted to nicotine and cannot stop using the products. Nicotine is not a carcinogen, but as described above, every dip of smokeless tobacco contains more than 30 established carcinogens, with especially high amounts of the tobacco-specific nitrosamines NNK and NNN. These carcinogens are taken up, distributed, and metabolised in all smokeless tobacco users.

Few data exist about the levels of metabolic activation, detoxification, and DNA adduct formation in smokeless tobacco users,⁴ compared with the substantial volume of information in smokers that is available. However, DNA adducts are probably formed in the oral tissue and other tissues of smokeless tobacco users; sister chromatid exchanges, chromosomal aberrations, and micronuclei—consequences of DNA adduct formation—have also been reported.⁷² When DNA adducts persist unrepaired, by evading or overwhelming healthy cellular repair systems, the result can be miscoding, leading to permanent DNA mutations. If these mutations occur in crucial regions of specific genes, such as the *RAS* oncogene or the *P53* tumour suppressor gene, the result can be the loss of mechanisms of healthy cellular growth control, and ultimately the development of cancer. Many studies have demonstrated *RAS* and *P53* mutations in smokeless tobacco users.⁷³

Although figure 3 represents a useful and supportable conceptual framework, there are certainly other factors participating in the carcinogenic mechanism of smokeless tobacco.⁴ Oxidative stress and reactive oxygen species could have important roles, based on animal studies. Chronic local inflammation and irritation induced by smokeless tobacco and its constituents could have a tumour-promoting or co-carcinogenic effect. Upregulation of cyclo-oxygenase-2, involved in prostaglandin synthesis and inflammation, has been seen in animal studies on exposure to smokeless tobacco. Smokeless tobacco products have high amounts of sodium chloride, which could contribute to inflammation, tumour promotion, and co-carcinogenesis. Viruses have been shown to enhance the carcinogenicity of smokeless tobacco products in animal studies.⁷⁴

Conclusion

We do not intend to address explicitly the use of smokeless tobacco to reduce the risk from tobacco smoking—eg, by promoting smokers to switch to smokeless products or

Search strategy and selection criteria

We identified epidemiological studies of smokeless tobacco and cancer based on the IARC Monograph, which was prepared in October, 2004, and provides a very detailed review of the studies available at that time,⁴ and by searching Medline, PubMed, and references from relevant articles for reports published in any language between October, 2004, and September, 2007, using the search terms “snus”, “snuff”, or “smokeless tobacco”, and “cancer” or “neoplasm”. Meeting abstracts and reports were excluded. We also included one manuscript that was in press in September, 2007. If several reports covered the same population, we used the most recent or comprehensive paper. A similar strategy was used in the 2004 IARC Monograph⁴ to identify earlier publications. We did a quantitative review of epidemiological studies of smokeless tobacco use and risk of cancers of the oral cavity, oesophagus, pancreas, and lung. Results for other cancers were too sparse for a quantitative investigation. We included only studies restricted to non-smokers and studies that included smokers but were properly adjusted for the possible confounding effect of tobacco smoking.

by introducing these products in a population where the habit is not prevalent. Nevertheless, several conclusions can be reached based on the available data: use of smokeless tobacco products is widespread in many populations, but their health effects (especially with respect to cancer risk) need to be better characterised; such use results in exposure to carcinogens, notably nitrosamines; the risk of cancer depends on the type of product consumed, and the concentration of nitrosamines is the strongest factor to determine product-specific risk; the risk of cancer, especially that of oral and lung cancer, is probably lower in smokeless tobacco users in the USA and northern Europe than in smokers; and the risk of cancer is higher in smokeless tobacco users than in non-users of any form of tobacco. Available data for a possible benefit of switching from smoking to smokeless tobacco come from few studies and models from the USA and Sweden.⁷⁵ Comparative risk estimates depend on many assumptions, including the expected effect of the introduction of new smokeless products in populations where the habit has not been common.

Conflicts of interest

The authors declared no conflicts of interest.

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