Chapter 4

Health Consequences of Smokeless Tobacco Use

Chapter Contents

Tables and Figures

Introduction

The health risks associated with smokeless tobacco (ST) can vary substantially by product characteristics and ingredients, manner of use, and potential interactions with other tobacco use behaviors, such as cigarette smoking. Based on epidemiologic studies of traditional ST products, such as snuff, chewing tobacco, and betel quid, the International Agency for Research on Cancer (IARC) concluded that these products are carcinogenic to humans[1] and, specifically, that there is sufficient evidence that ST products cause precancerous oral lesions and cancers of the oral cavity, esophagus, and pancreas. Additionally, there is sufficient evidence that ST products cause addiction as well as reproductive and developmental toxicity. (IARC defines evidence as sufficient when "a causal relationship has been established and chance, bias, and confounding could be ruled out with reasonable confidence."[2,p.24]) Given that over 300 million people use ST worldwide, the total burden of ST use is likely to be substantial. Moreover, ST use in some regions appears concurrently with cigarette smoking, thus contributing to the total health burden of tobacco use.

Assessing the global magnitude or severity of the health effects of ST is complex primarily because of the variability of the products' chemical composition and other characteristics and the different ways in which these products are used around the world. (See chapter 3 for descriptions of ST products.) Conclusions about a product's use and risks in one country may not be transferable to similar products in other countries. Smokeless tobacco products differ considerably in their concentrations of nicotine and volatile and nonvolatile nitrosamines including the tobacco-specific nitrosamines (TSNAs), as well as polycyclic aromatic hydrocarbons (PAHs), toxic metals, and other compounds.[3–5] For example, nitrosamines are formed when secondary and tertiary amines in tobacco, including the alkaloids (nicotine, nornicotine, anatabine, and anabasine), react with nitrosating agents such as sodium nitrite. TSNAs are carcinogenic to humans and are formed primarily during tobacco processing, curing, fermentation, and storage.[2] PAHs, which are also carcinogenic to humans,[6] are formed by incomplete combustion of organic matter such as wood; most PAHs in ST are formed during the fire-curing process.[7] Toxic metals that have been detected in ST products include arsenic, beryllium, cadmium, chromium, cobalt, lead, nickel, mercury, and the radioactive metals polonium-210 and uranium.[2,8] All ST products contain nicotine, and virtually all contain TSNAs.

Some products also contain added plant materials such as tonka bean or flavoring agents that may contribute to adverse health consequences (see chapter 3). For example, additives such as the areca nut, a known carcinogen, are commonly used in products in India and other South-East Asian countries.[9] Areca nut, often used with tobacco or used prior to initiating tobacco use,[9] is considered an IARC group 1 carcinogen.[1] It is estimated that 10–20% of the world's population use areca or areca nut–containing products/preparations[1] (in 2001, this was estimated at 600 million people[9]). Examples of these products are betel quid, tombol, mawa, and gutka, which often contain tobacco.[1] Some users may intermittently switch between areca nut and areca nut plus tobacco.[10] The health implications of using tobacco mixed with areca nut warrant consideration because areca nut has been linked to oral submucosal fibrosis (OSF) and oral squamous cell carcinomas.[11] Areca nut–containing products are commonly used in South-East Asia (paan, mawa, mainpuri, gutka, etc.), the Middle East (tombol), and more recently in the United Kingdom,[12] South Africa,[11] and United States.[10]

The aim of this chapter is to provide a science-based summary of the association between the use of ST and a range of adverse health consequences. This chapter does not present an exhaustive review of the literature. Evidence was drawn from comprehensive reviews by authoritative bodies, particularly the IARC, the Office of the U.S. Surgeon General, and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), and supplemented by reviews and original research reports in the peer-reviewed literature. These sources should be consulted for additional in-depth information, including strengths and limitations of individual studies.

Adverse Health Consequences: Mechanisms

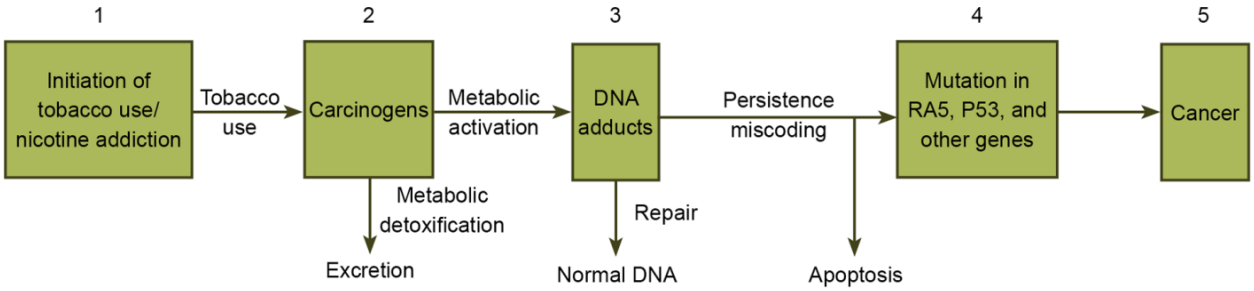
Evidence supports plausible mechanisms by which ST use can cause disease. Disease pathways and biologic mechanisms specific to ST (Table 4-1) may be similar in some respects to the pathways and mechanisms that underlie the pathogenicity of tobacco smoke and nicotine.[13] Higher concentrations of cotinine (a biomarker of exposure to nicotine uptake), nitrosamines, PAHs, and metals have been observed in the serum and urine of individuals who use ST products than in individuals who do not use tobacco.[8,14,15] Concentrations of some TSNAs are higher in ST users than in individuals who smoke cigarettes.[16] Constituents of ST cause local irritation and sensitization and are absorbed systemically through the oral or nasal mucosa and by swallowing saliva that contains tobacco particulates.[17] Smokeless tobacco carcinogens and other toxicants then circulate throughout the body and may damage multiple organs.

Adverse Health Consequences: Cancer

Conceptual Model

An adaptation by Boffetta and colleagues[18] of Hecht's conceptual model of carcinogenesis associated with tobacco smoke[19] is presented in Figure 4-1. The process begins with initiation of ST use and subsequent nicotine addiction (Box 1), leading to sustained use. Carcinogens present in ST are ingested and processed by the body (Box 2), which results in the metabolic activation of carcinogens and formation of DNA adducts, which are carcinogenic metabolites bound covalently to DNA (Box 3); and subsequent mutations (Box 4) which may ultimately lead to cancer (Box 5).

Figure 4-1. Conceptual model of carcinogenesis of smokeless tobacco use



Abbreviations: DNA = deoxyribonucleic acid; Hb = hemoglobin
Sources: Boffetta et al. 2008 (18); Hecht 1999 (19). Reproduced with permission.

Table 4-1. Smokeless tobacco products: Constituents, biologic mechanisms, and biomarkers

Product constituent	Biologic mechanism related to health consequences	Biomarker of human exposure (may not be specific to smokeless tobacco use)
Cancer		
Tobacco-specific nitrosamines (TSNA)*	Increase DNA adduct levels, cause oxidative DNA damage, cause gene mutations, disrupt mechanisms for cell growth control; systemic carcinogens	TSNAs and metabolites (NNAL) in urine TSNA–Hb adducts in red cells TSNA–DNA adducts in oral cells TSNAs in saliva
Volatile nitrosamines†	Form DNA adducts	N/A
Polycyclic aromatic hydrocarbons (PAH)‡	Form DNA adducts	PAH biomarkers in urine
Aldehydes§	Cause inflammation, increase cell proliferation	Aldehyde–DNA adducts in white blood cells
Metals¶	Cause inflammation and sensitization	Metal levels in urine, saliva, blood, and hair
Ethyl carbamate (urethane)	Form DNA adducts	N/A
Nicotine	Precursor to TSNAs	Nicotine and metabolites (cotinine) in urine
Arecoline	Inhibits cellular growth, depletes cellular glutathione	Arecoline in urine and blood
Areca-nut-specific nitrosamines (e.g., MNPN)	Form reactive oxygen species	MNPNs in saliva
Alkaline agents	Increases the absorption of carcinogens and contributes to chronic inflammation and tumor promotion	Sodium levels in urine
Cardiovascular disease		
Polycyclic aromatic hydrocarbons	Accelerate atherosclerosis	PAH biomarkers in urine
Aldehydes	Contribute to atherogenesis	Aldehyde–DNA adducts
Arsenic	Causes vasoconstriction	Arsenic levels in urine
Barium	Causes tachycardia, hypertension	Barium levels in urine and saliva
Cadmium	Disrupts endothelial function, increases blood pressure	Cadmium levels in urine, blood, and saliva
Nicotine	Acutely increases blood pressure and heart rate, may injure endothelial cells	Urine thromboxane A2 metabolites, atherosclerosis, elevated blood pressure
Arecoline	Acutely increases blood pressure and heart rate	Arecoline in urine and blood
Alkaline agents	Increase the fraction of nicotine and arecoline in free form that is most rapidly absorbed in the blood; increase blood pressure	Sodium levels in urine

Product constituent	Biologic mechanism related to health consequences	Biomarker of human exposure (may not be specific to smokeless tobacco use)
Addiction		
Nicotine	Elevates dopamine; releases endorphins	Nicotine and metabolites (cotinine) in urine
Arecoline	Elevates dopamine; releases endorphins	Arecoline in urine and blood
Acetaldehyde	Enhances reinforcing effects of nicotine	Aldehyde–DNA adducts in white blood cells
Reproductive health outcomes (neurodevelopmental toxicity, pregnancy complications)		
PAHs (e.g., BaP)	Causes anatomic and functional teratogenesis; prenatal, perinatal, and postnatal mortality; growth retardation; and developmental delay.	PAH–DNA adducts in umbilical cord blood
Cadmium	Causes oxidative stress, interferes with placental transfer of essential elements.	Placental cadmium levels
Nicotine	Binds nicotinic acetylcholine receptors in the developing lungs and impairs alveolar development and affects neurogenesis, migration, differentiation, and synaptogenesis in fetal developing neurites; also prune hippocampal and cortical neurons through effects of apoptosis.	Cord blood cotinine
Dental conditions		
Sugar	Causes dental caries	N/A
Arsenic, barium, mercury, nickel, cobalt	Cause dermal sensitization and irritation	Metal levels in urine, saliva, blood, and hair
Alkaline agents	Cause irritation	Sodium levels in urine
Silica	Wears down teeth	N/A

*Tobacco-specific nitrosamines (TSNAs): NNN (*N'*-nitrosonornicotine), NNK [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone], NAB (*N'*-nitrosoanabasine), NAT (*N'*-nitrosoanatabine). NNK is a metabolite of NNAL [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol].
†Volatile nitrosamines: NDELA (*N*-nitrosodiethanolamine), NDMA (*N*-nitrosodimethylamine), NMOR (*N*-nitrosomorpholine), NPIP (*N*-nitrosopiperidine), NPYR (*N*-nitrosopyrrolidine).
‡Polycyclic aromatic hydrocarbons (PAHs): Benz*[a]*anthracene, benzo*[a]*pyrene [BaP], benzo[*b*]fluoranthene benzo[*j*]fluoranthene, benzo[*k*]fluoranthene, 5-methylchrysene, dibenzo[*a,h*]anthracene, indeno[1,2,3-cd]pyrene, naphthalene.
§Aldehydes: Formaldehyde, crotonaldehyde, acetaldehyde.
¶Metals: Arsenic, beryllium, cadmium, cobalt, chromium, lead, mercury, nickel, polonium, uranium.
Abbreviations: N/A = information not available. DNA = deoxyribonucleic acid; Hb = hemoglobin; MNPN = 3-(methylnitrosamino)propionitrile.
Sources: U.S. Department of Health and Human Services 2010 (13); International Agency for Research on Cancer (IARC) 2004 (9); IARC 2007 (2); Pappas 2011 (8).

In this model, metabolic activation and DNA changes and subsequent mutations occur that may ultimately lead to cancer. During the metabolic activation stage, shown after Box 2, NNK and NNN are metabolically activated by cytochrome P450 enzymes. This activation induces primary DNA lesions including pyridyloxo-butylations and nucleotide methylations.[20] Permanent DNA mutations, such as in the RAS oncogene or the TP53 tumor suppressor gene, occur when DNA adducts persist unrepaired, leading to uncontrolled cell growth and cancer.[13] This model represents a simplified version of the complex process of carcinogenesis. Other mechanisms that may contribute to tumor promotion and co-carcinogenesis include chronic local inflammation and irritation, oxidative stress, and reactive oxygen species.[13]

Researchers have identified more than 30 carcinogens in various ST products, including volatile and nonvolatile nitrosamines, TSNAs, nitrosamino acids, PAHs, aldehydes, heavy metals, and radioactive metals (chapter 3, Table 3-2).

The most potent and abundant TSNAs in tobacco products include 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), the NNK metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), *N'*-nitrosonornicotine (NNN), *N'*-nitrosoanabasine (NAB), and *N'*-nitrosoanatabine (NAT).[21,22] The level of TSNAs varies depending on the type of tobacco used (for example, *Nicotiana rustica* has more TSNAs than *N. tabacum*), the method of curing, fermentation, products added to the tobacco for processing or flavoring, and the method of storing the product.[4] The TSNAs most strongly linked to cancer are NNN and NNK.[21] Although some products such as Swedish snus contain relatively low levels of NNN and NNK, some U.S. brands of moist snuff contain very high concentrations, and toombak, a product used primarily in Sudan, has the highest concentration of TSNAs (NNN, NNK, and NAT) identified to date.[14]

Some ST products have been found to contain PAHs, such as: BaP, classified by IARC as a Group 1 agent (carcinogenic to humans); dibenz[*a,h*]anthracene, classified by IARC as Group 2A agent (probably carcinogenic to humans); as well as several PAHs classified by IARC as Group 2B agents (possibly carcinogenic to humans) including benz[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, benzo[*k*]fluoranthene, 5-methylchrysene, indeno[*1,2,3-cd*]pyrene, dibenzo[a,i]pyrene, and naphthalene.[7,23] Smokeless tobacco is consumed without combustion, but some products contain fire-cured tobaccos; these products have higher concentrations of volatile aldehydes and PAHs, including BaP, than products that contain air-cured tobacco.[3,7] These PAHs may derive from the tobacco-curing process or from added ingredients such as punk ash.

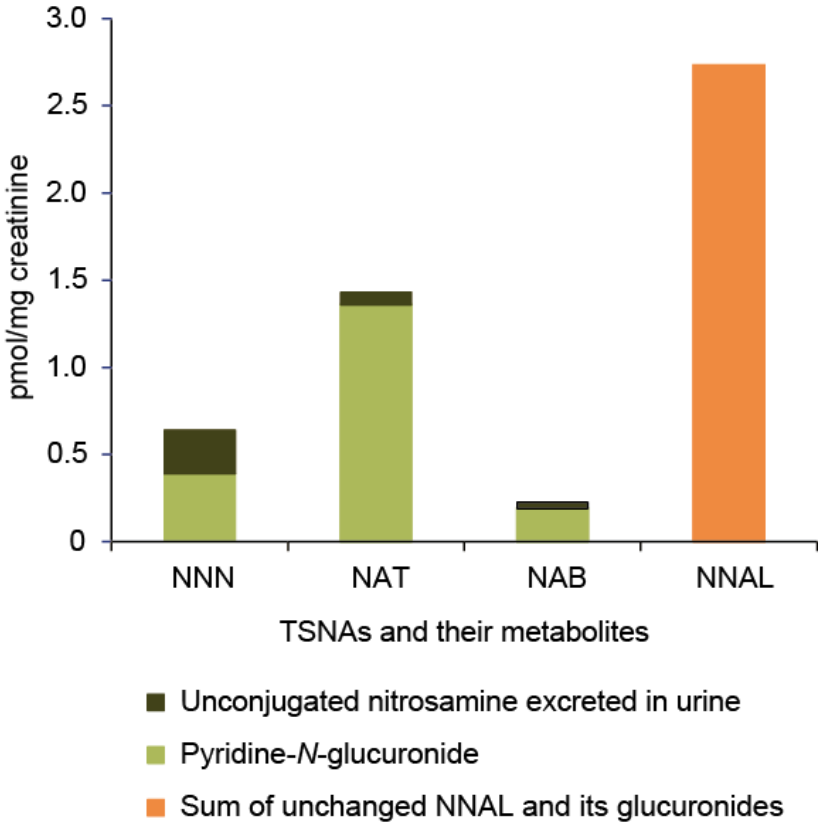
Other ingredients that are added to ST products also may have cancer-causing properties. Products commonly used in India and other parts of Asia often contain areca nut, which contains arecoline, a nicotine-like alkaloid, and the areca nut–derived nitrosamines 3-(*N*-nitrosomethylamino) propionaldehyde, 3-methylnitrosamino propionitrile, *N*-nitrosoguvacine, and *N*-nitrosoguvacoline.[9] Areca nut use can lead to the production of reactive oxygen species and may cause precancerous lesions including oral submucous fibrosis and oral cancer, cancer of the pharynx, and esophageal cancer.[9] Salts such as sodium chloride, added to ST as a flavor enhancer and antimicrobial agent, may damage the gastric epithelium, increase the absorption of carcinogens, and contribute to chronic inflammation and tumor promotion.[3]

Biomarkers

Users' exposures to carcinogens in ST are most accurately measured by looking at biomarkers in the body. Biomarkers such as serum cotinine levels, total NNAL, total NNN, NNK–DNA adducts, or hemoglobin (Hb) adducts of nitroaromatic compounds may provide a realistic assessment of carcinogen and toxic dose in an individual.[24] For example, studies suggest a dose–response relationship between total NNAL and serum cotinine (not a carcinogen itself, but a marker of tobacco exposure) and lung cancer[24] and between total NNN and esophageal cancer risk[25] in smokers.

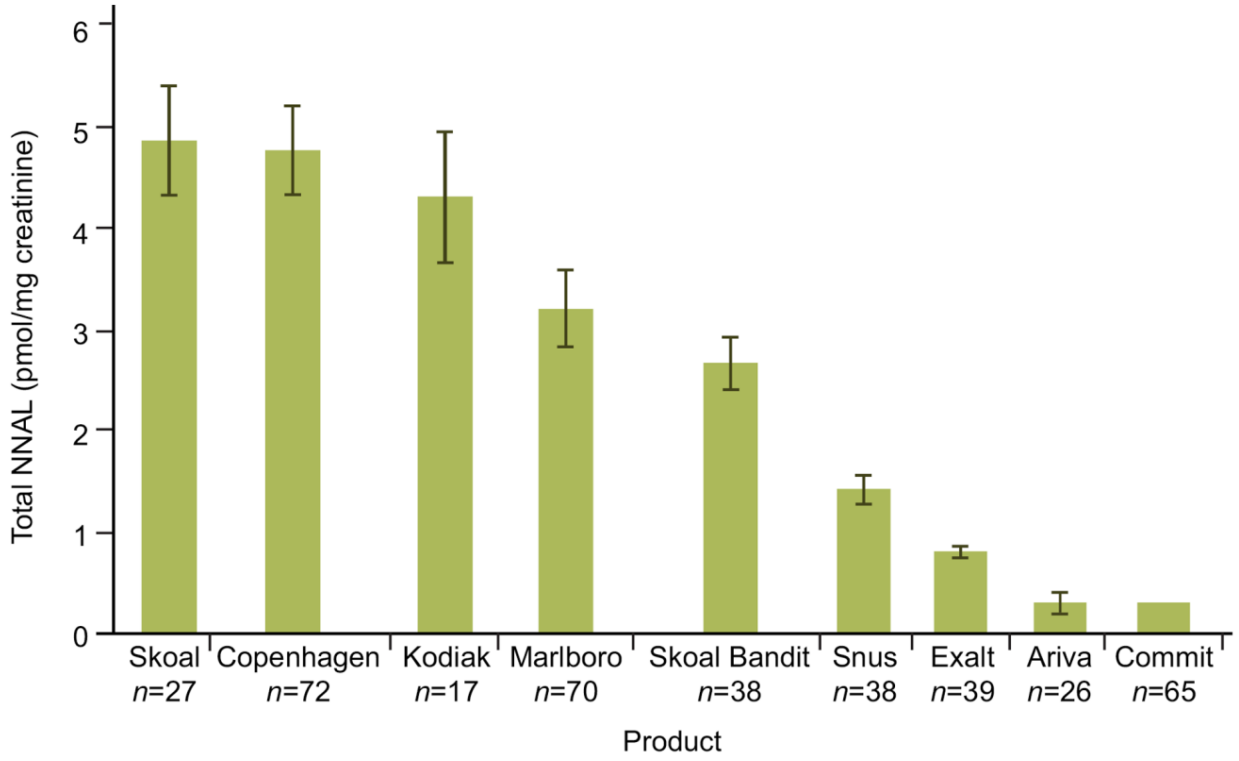
The metabolism of TSNAs can be measured in humans, as demonstrated by a study in which NNN, NAT, NAB, their pyridine-*N*-glucuronide metabolites, and NNAL were detected in the urine of ST users[26] (Figure 4-2). These metabolites can be used as biomarkers to provide realistic and direct assessments of a person's exposure to specific TSNAs.[24] The concentrations of total NNAL detected in urine parallel the level of NNK measured in these products.[14] A comparison of studies in the United States found that NNAL concentrations in the urine of users of moist snuff varied by brand used and, for some brands, were higher than levels seen in Marlboro cigarette smokers (Figure 4-3).[14]

Figure 4-2. Mean NNN, NAT, NAB, their pyridine-*N*-glucuronide metabolites (NNN-*N*-Gluc, NAT-*N*-Gluc, and NAB-*N*-Gluc), and NNAL in the urine of 11 smokeless tobacco users



Abbreviations: NNN = *N'*-nitrosonornicotine; NAT = *N'*-nitrosoanatabine; NAB = *N'*-nitrosoanabasine; NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; Gluc = glucuronide; pmol/mg = picomole per milligram.
Note: Total NNAL = NNAL + NNAL Glucs.
Source: Stepanov and Hecht 2005 (26).

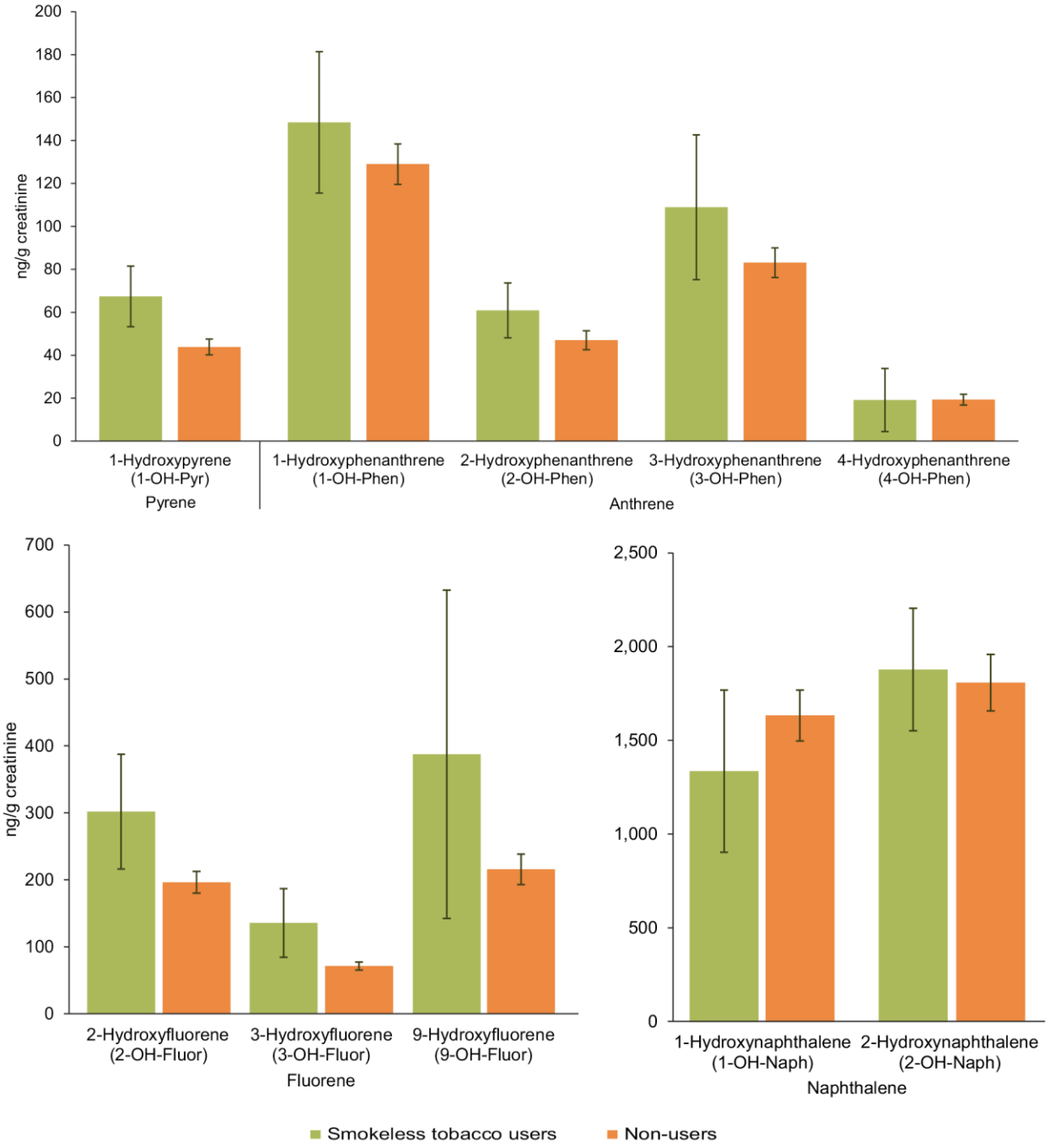
Figure 4-3. Total NNAL concentrations in the urine of users of Marlboro cigarettes, different brands of smokeless tobacco products, and medicinal nicotine



Abbreviations: NNAL = [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol]; pmol/mg = picomole per milligram.
Note: Total NNAL = NNAL + NNAL glucuronides.
Source: Adapted from Hatsukami et al. 2007 (14). Used with permission.

A study[15] using data from the U.S. National Health and Nutrition Examination Surveys from 1999 through 2008 to evaluate biomarkers of chemical exposure found that mean levels of PAHs (measured in urine) were higher among ST users than among people who did not use tobacco (Figure 4-4).

Figure 4-4. Polycyclic aromatic hydrocarbons in the urine of smokeless tobacco users compared to that of non-users, NHANES, 1999–2008



Abbreviations: NHANES = National Health and Nutrition Examination Survey; ng/g = nanogram per gram.
Note: 95% confidence interval.
Source: Naufal et al. 2011 (15).

Oral Cancer

Available evidence from multiple epidemiologic studies in the United States, Asia, and Africa supports a causal association between oral cancer and use of ST, including snuff, chewing tobacco, naswar, shammah, and toombak,[2,18,27] though observed relative risks (RR) vary substantially across products and regions, and with dosage and duration of use.[2] Summary RRs (adjusted for smoking) comparing ST users to non-users in the United States range from 1.65 (95% confidence interval [CI]: 1.22–2.25) for oropharyngeal cancer[27] to 2.6 (95% CI: 1.3–5.2) for oral cancer.[18] The RRs associated with some ST products may be especially high; for example, the RR associated with toombak is 3.9,[28] and relative risks ranged from 2 to as high as 14 for "tobacco chewers" (including users of pattiwala, naswar, khaini, and zarda) in India and Pakistan.[2] In contrast, although increased risks were observed in some studies of Scandinavian snus,[29] most evidence from Swedish studies does not support a causal association between snus use and oral cancer.[2,18,27]

Relative risk (RR): The likelihood of an event happening in one group/ country/region, etc., compared to another group.

RR = 1 (no difference between the groups)
RR >1 (increased risk in one group compared to the other)
RR <1 (decreased risk in one group compared to the other)

A relative risk of 1 indicates no difference between the groups, whereas a relative risk greater than 1 indicates an increased risk, and a relative risk less than 1 indicates a decreased risk.

Precancerous Lesions and Other Oral Conditions

Many studies from the United States, Scandinavia, and Asia provide conclusive evidence that ST products, including snus, snuff, shammah, and betel quid (paan), are strongly associated with the prevalence of oral mucosal lesions such as leukoplakia, erythroplakia, and verrucous hyperplasia.[2,18,30] These lesions are important because studies show a high risk of cancers arising from leukoplakia and oral submucous fibrosis.[9,31] Lesions tend to occur at the site of ST application and may vary depending on the product used. In comparison with use of chewing tobacco, use of snuff is associated with more frequent development of oral mucosal lesions and a greater variety of epithelial changes.[31] Chewing areca nut or betel quid with or without tobacco is also strongly associated with leukoplakia and oral submucous fibrosis.[9,32] Oral mucosal lesions are more severe in people who begin use at an earlier age, use ST for more hours per day, use greater dosages, or use on more days per month.[2] The lesions usually resolve when people stop using smokeless tobacco.[2]

Use of ST can lead to increased inflammation of the buccal and gingival mucosa.[33] The combination of ingredients in gutka—tobacco, areca nut, and slaked lime (calcium hydroxide)—may cause greater inflammation than one of these ingredients used alone.[34] Incidence of gingival recession, commonly adjacent to the area where the tobacco is held, is higher among individuals who use snus or snuff than among people who do not use smokeless tobacco.[30,33,35] Gingival recession can be observed within one year of beginning to use smokeless tobacco.[2] Prevalence of dental decay and caries is associated with the use of chewing tobacco.[33]

Esophageal Cancer

Available epidemiologic evidence from Scandinavia and Asia supports a causal association between esophageal cancer and use of ST, including snus, snuff, and chewing tobacco.[2,18,27] Summary RRs comparing ST users to non-users, based mainly on studies from Sweden, range from 1.13 (95% CI: 0.95–1.36; adjusted for smoking)[27] to 1.6 (95% CI: 1.1–2.3).[18] Evidence of a dose–response trend with amount and duration of use was reported in two studies.[2]

Pancreatic Cancer

The pancreas is one of the target sites of TSNAs.[2] Available epidemiologic evidence from Scandinavia and Asia supports a causal association between pancreatic cancer and use of ST, including snus and mishri.[2,18,36,37] Evidence of a dose–response trend with amount and duration of use was reported in two studies.[1]

Lung Cancer

Although the lungs are also a target site of TSNAs,[21] available evidence is inadequate to determine if ST use causes lung cancer.[2] Epidemiologic cohort studies comparing ST users to non-users from the United States (summary RR = 1.8; 95% CI: 0.9–3.5) and India (hazard ratio [HR] = 1.6; 95% CI: 0.9–2.9) reported an increased risk, but findings from cohort studies from Scandinavia have suggested no association (summary RR = 0.8; 95% CI: 0.6–1.0).[18,37]

Cervical Cancer

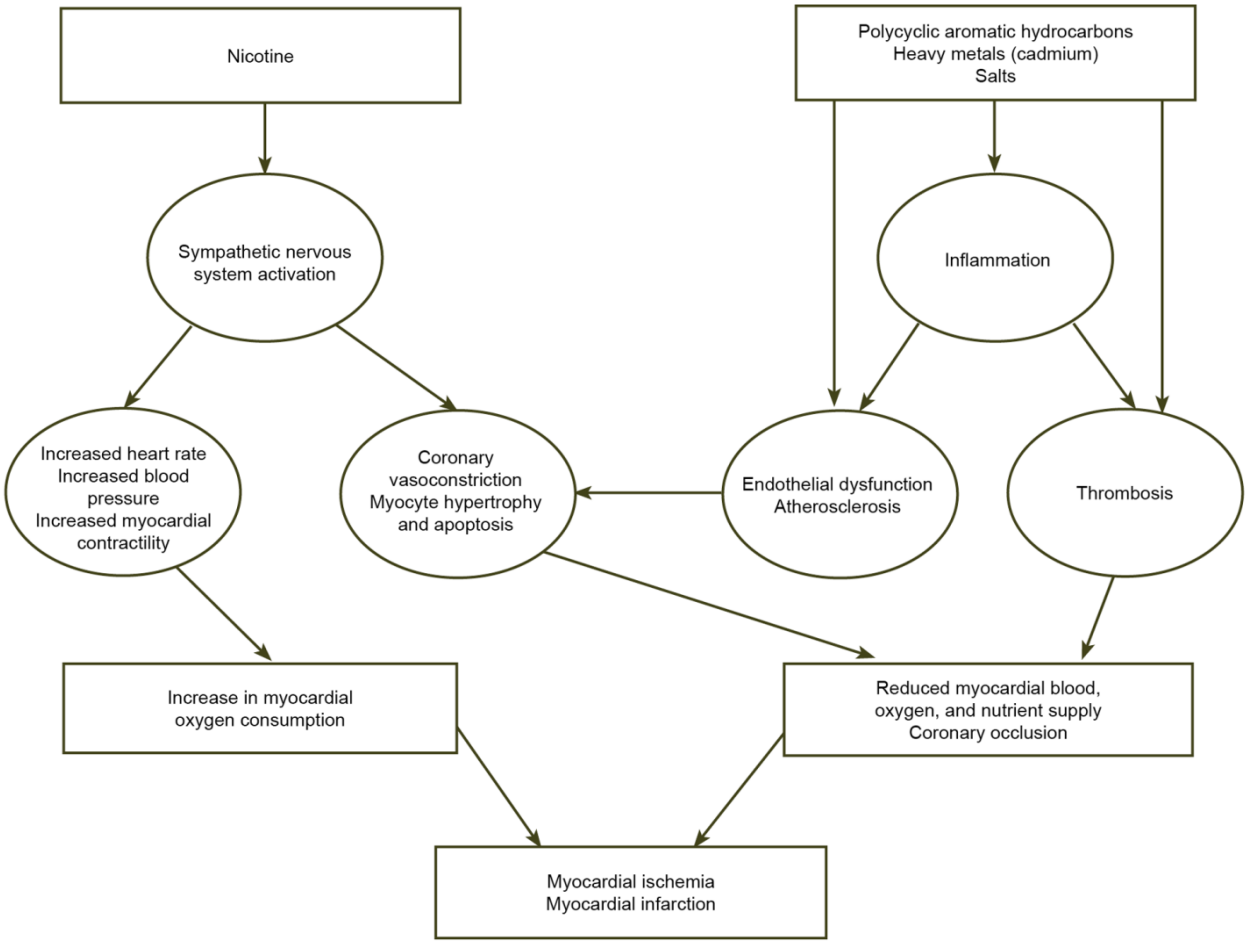
The evidence that ST use is associated with increased risk of cervical cancer is limited but plausible.[38] Although numerous epidemiologic studies have confirmed that smoking is an independent risk factor for cervical squamous cell carcinoma,[1] few epidemiologic studies have been conducted on the association between ST use and increased risk of cervical cancer. However, some research has shown that higher levels of carcinogen-DNA adducts have been measured in cervical cells of smokers than in those of non-smokers.[13] Both NNK and BaP have been detected in human cervical cells and are metabolically activated in cervical tissue.[2] Nicotine exposure alone can increase the expression of epidermal growth factor receptors (EGFRs) in cervical cancer cell lines; metabolites of BaP induce activation of EGFRs that promote cell proliferation.[13] Increased risk of cervical cancer with use of chewing tobacco and snuff was observed in a case-control study in the United States (RR for moderate use = 4.7, and heavy use = 3.6, compared to no use).[2] In a case-control study among non-smoking Indian women, women who had ever chewed tobacco (with or without areca nut) had a greater risk of cervical cancer mortality than women who did not chew tobacco; this association held true among women in both urban (OR 2.0, 95% CI: 1.5–2.7) and rural (OR 2.2, 95% CI: 1.5–3.2) areas.[38] Another case-control study in India observed a significant dose-response relationship between the number of betel quids with and without tobacco chewed per day and increased risk of invasive cervical cancer; ever use of betel quid was associated with a nonsignificant twofold increased risk.[9] In a study in Côte d'Ivoire, high-grade cervical squamous intraepithelial lesions were more common among women who chewed tobacco.[39]

Adverse Health Consequences: Cardiovascular Effects

Conceptual Model

Much of the work on the cardiovascular effects of tobacco and nicotine has focused on cigarette smoking[13]; some, but not all, of these mechanisms also may be applicable to ST use. Several of the constituents in cigarette smoke that are implicated in cardiovascular effects are also present in ST, although in differing amounts. These include nicotine, PAHs, and heavy metals such as cadmium.[40] PAHs have been shown to accelerate atherosclerosis in experimental animals.[13] Heavy metals such as cadmium catalyze the oxidation of cellular proteins, which may accumulate in the aortic wall and result in endothelial damage.[13] Additionally, some substances added to ST, such as punk ash or licorice, are reported to have adverse effects on the cardiovascular system.[13] Figure 4-5 presents a conceptual model of adverse cardiovascular effects associated with ST use (adapted from the conceptual model of adverse cardiovascular effects associated with cigarette smoking as described in Benowitz 2003[41]).

Figure 4-5. Conceptual model of adverse cardiovascular effects of smokeless tobacco



Source: Adapted from Benowitz 2003 (41). Used with permission.

As illustrated in the model, nicotine has a range of cardiovascular effects. Its effects mimic those of the body's sympathetic nervous system, acutely increasing blood pressure, heart rate, and the strength of the heart's contractions, all of which increase the heart's demand for oxygen and nutrients.[18] Nicotine also can contribute to inflammation, thus potentially contributing to atherogenesis.[41] Moreover, nicotine directly affects blood vessels and can contribute to the development of endothelial dysfunction.[41] In addition, nicotine in tobacco products may contribute to insulin resistance and hyperinsulinemia, both of which are linked to mitogenesis (cell proliferation), vasoconstriction, and inflammation, potentially contributing to the development of endothelial dysfunction and atherosclerosis.[42] Oral moist snuff users have shown decreased brachial artery flow–mediated dilation, a marker for endothelial dysfunction.[43] Because many of these studies have been conducted with individuals who use a range of tobacco products, the effects may be due to nicotine acting along with other tobacco constituents, rather than to nicotine alone. Additionally, safety studies have not shown any increased cardiovascular risk, even in people with existing cardiovascular disease who use nicotine replacement therapies.[13]

Hypertension

Several constituents of ST products, including nicotine, sodium, and licorice, can aggravate hypertension.[40,44] Although some ST products clearly cause acute, transient increases in blood pressure,[45] studies from the United States and Sweden do not provide evidence of increased prevalence of hypertension in ST users.[40] In a study in South Africa, women who used snuff had a higher prevalence of hypertension than women who did not use snuff, but this association was attenuated after controlling for other cardiovascular risk factors.[46] The prevalence of diastolic (but not systolic) hypertension was higher among Indian men who exclusively used ST products (mainly moist snuff, betel quid, and pan masala with tobacco) than among men who used no tobacco.[47] In another study, the prevalence of both diastolic and systolic hypertension was higher among Indian men who exclusively chewed tobacco (mainly gutka, paan, and khaini) than among men who used no tobacco.[48] One study from Sweden provides evidence that ST users may have a higher risk of developing hypertension.[40]

Heart Disease and Stroke

A substantial body of evidence from the United States, Sweden, and Asia indicates that ST use is associated with an increased risk of fatal ischemic heart disease and stroke, but is not associated with an increased risk of non-fatal myocardial infarction (MI) and non-fatal stroke.[2,40,49,50] This finding suggests that thrombosis is a major mechanism by which ST increases cardiovascular risk[44] and/or that ST use negatively affects survival after a cardiovascular event.[40] Some studies suggest an increased risk of non-fatal cardiovascular disease associated with use of ST including snuff, chewing tobacco, betel quid with tobacco, and mishri, but evidence is limited.[51–53] Data on dose–response trends are limited. Summary RRs for fatal ischemic heart disease range from 1.1 (95% CI: 1.04–1.19) in the United States and 1.1 (95% CI: 0.78–1.38) in Asia to 1.3 (95% CI: 1.07–1.52) in Sweden. Summary RRs for fatal stroke range from 1.3 (95% CI: 0.91–1.70) in Sweden and 1.3 in Asia (95% CI: 1.08–1.56) to 1.4 (95% CI: 1.22–1.60) in the United States.[49,50]

Adverse Health Consequences: Miscellaneous Other Diseases and Conditions

Diabetes and Insulin Resistance

Although nicotine increases circulating levels of insulin-antagonistic hormones and impairs insulin sensitivity,[13] the few studies that have examined the association between ST use and the development of insulin resistance, metabolic syndrome, and diabetes have yielded conflicting results.[2,40] Heavy use of Swedish snus appears to be associated with an increased risk of developing type 2 diabetes.[40]

Conditions of the Nasal Cavity

Some types of ST are inhaled nasally, including dry (powdered) snuff and Brazilian rapé[54] and products used in India and South Africa. Limited information is available about the effects of ST on the nasal cavity. Nasal use of snuff has been associated with edema of the mucosa and submucous conjunctive tissue of the turbinates, atrophy of the middle and inferior turbinates, inhibition of nasal mucociliary clearance, and chronic rhinitis.[54] Existing studies on nasal use of snuff have not provided conclusive evidence of a relationship with cancer.[2]

Reproductive Outcomes

Several constituents in ST have been shown to be reproductive or developmental toxicants, including nicotine, areca nut, PAHs, and several metals—particularly arsenic, cadmium, lead, and mercury.[9,13] Decreased perfusion from nicotine is not believed to be a major contributor to adverse fetal outcomes; rather, hypoxia is likely due to CO exposure. Metals may cause oxidative stress in cells and interfere with fetal nutrition.[13] Evidence suggests that infants born to women who use ST (including snus, betel quid, and mishri) during pregnancy have a higher risk of several adverse outcomes such as gestational age/pre-term birth and fetal growth restriction.[2,9,31,48,55–57]

Addiction

Research evidence shows that ST products initiate and sustain dependence and addiction.[2,58] Nicotine in tobacco causes addiction; other substances in ST products may reinforce nicotine's addictive effects.[13] Physiologic manifestations of ST addiction include tolerance with repeated use, symptoms of withdrawal upon cessation of regular use, and pleasurable psychoactive effects.[59] Smokeless tobacco users continue to crave and use ST despite harmful consequences, tend to switch to products with higher nicotine levels, and frequently relapse upon cessation.[2] Addiction to ST is related to age at initiation, amount of nicotine ingested per day, and years of use.[2]

Smokeless Tobacco Use as a Risk Factor for Cigarette Smoking

One important question is whether ST use promotes smoking initiation, particularly among youth. Smokeless tobacco products contain nicotine, and development of nicotine addiction may increase the risk of transitioning to smoking.[60] Some studies, but not others, have shown that young people in the United States who use ST are more likely to smoke cigarettes.[35,61] However, studies in Sweden have not observed that snus use among youth leads to cigarette use among adults.[31] Little evidence is available

about whether ST use precedes cigarette smoking in other countries, and transitioning from using ST to smoking is likely to depend heavily on social norms and tobacco industry marketing.

A second important question is whether cigarette smokers who may otherwise have quit using tobacco prolong tobacco use or engage in dual use by using smokeless tobacco.[1] For example, studies in the United States have found that smokers who may have otherwise quit using tobacco may switch to ST as a substitute for smoking or use both tobacco products concurrently (i.e., dual use).[13,62,63] A major concern about novel products like dissolvables—which have not been marketed long enough for epidemiologic data on health risks associated with them to become available—is that these products are marketed to provide smokers with an alternative source of nicotine in settings where smoking is prohibited.[64,65] People who both use ST and smoke cigarettes may have greater levels of toxicants, such as NNK, than people who use only one tobacco product, which suggests that a combination of ST use and smoking may have greater health risks than smoking alone.[13,51,60] Dual use of cigarettes and ST products may prolong rather than shorten the duration of smoking, thereby increasing the risks from continued smoking. It is also possible that some individuals substantially reduce cigarette smoking when they begin using ST, but the extent to which cigarette smoking would have to be reduced to result in lower health risks is unknown, especially when cigarettes are used in conjunction with smokeless tobacco. Additionally, evidence on the effectiveness of ST as a smoking cessation aid is insufficient.[66] Abstaining from all forms of tobacco use is the most effective way to prevent its morbidity and mortality.[13]

The Health Consequences and Disease Burden of Smokeless Tobacco Products

Understanding the global disease burden of ST use is important for informing tobacco prevention and control efforts. This impact is a function of the number of ST users multiplied by the magnitude of the risk. However, given the variety of products and conditions of use, in addition to limited product-specific data, estimating this total burden is not straightforward.

One way to measure the public health impact of an exposure to a risk factor is to calculate the *proportion* of cases of a given disease causally related to that risk factor, called the attributable fraction (AF). For example, the attributable fraction of lung cancer caused by cigarette smoking is over 90 percent.[67]

The AF due to ST use can be estimated using the RR associated with ST use and the percentage of people in the population who use ST (p) according to the formula[68]:

$$AF = \frac{p * (RR - 1)}{p * (RR - 1) + 1}$$

Then the attributable burden (AB), the number of cases (or deaths) attributed to ST use out of the *total* number of cases (or deaths) in the population, can be estimated by multiplying the AF by the total number of cases (or deaths) (D), according to the formula:

$$AB = AF * D$$

Because RR varies by type of ST and underlying disease prevalence varies by country, the attributable burden should be calculated for each country separately. As an example, this chapter includes estimates of the AB due to ST use in Sweden, the United States, and India. These countries were chosen as examples because much of the evidence on the associations between ST use and health consequences comes from studies conducted in these countries,[18,49] and because the ST products commonly used in these countries represent a wide range of products. (The prevalence of ST use was obtained from surveys reported between about 2008 and 2011; for descriptions of the ST products used and the prevalence of use in these three countries, see chapters 9, 10, and 13.) The RR estimates associated with ST use (Table 4-2) were obtained from reviews of studies in Scandinavia and the United States[18,49] and from studies in India and surrounding regions.[37,50] Cancer incidence data for 2008 were obtained from GLOBOCAN (http://globocan.iarc.fr/). These data were applied to the above formulas to estimate the attributable fraction and the annual attributable burden of disease due to ST use in Sweden, the United States, and India (Table 4-3). The estimated numbers of incident cancers of the oral cavity, esophagus, and pancreas attributed to ST use in 2008 ranged from about 130 in Sweden, to over 2,500 in the United States, and over 58,000 in India (Table 4-3). These estimates demonstrate the variability in public health impact caused by ST under different scenarios.

Table 4-2. Relative risks associated with smokeless tobacco use

Outcome	Country/region	Type of smokeless tobacco	Relative risk	Source*
Oral cancer	United States	Chew or snuff	2.6 (1.3–5.2)	Boffetta et al. 2008 (18)
	Scandinavia	Snus	1.0 (0.7–1.3)	Boffetta et al. 2008 (18)
	India	Smokeless tobacco†	5.1 (4.3–6.0)	Boffetta et al. 2008 (18)
Esophageal cancer	United States	Smokeless tobacco†	1.2 (0.1–2.3)	Boffetta et al. 2008 (18)
	Scandinavia	Snus	1.6 (1.1–2.4)	Boffetta et al. 2008 (18)
	India	Smokeless tobacco†	3.7 (1.6–8.4)	Pednekar et al. 2011 (37)
Pancreatic cancer	United States	Chew or snuff	1.4 (0.7–2.7)	Boffetta et al. 2008 (18)
	Scandinavia	Snus	1.8 (1.3–2.5)	Boffetta et al. 2008 (18)
	India	Mishri & other	2.0 (0.7–5.5)	Pednekar et al. 2011 (37)
Lung cancer	United States	Chew or snuff	1.8 (0.9–3.5)	Boffetta et al. 2008 (18)
	Scandinavia	Snus	0.8 (0.6–1.0)	Boffetta et al. 2008 (18)
	India	Mishri & other	1.6 (0.9–2.9)	Pednekar et al. 2011 (37)
Fatal ischemic heart disease	United States	Chew or snuff	1.1 (1.0–1.2)	Boffetta & Straif 2009 (49)
	Sweden	Snuff	1.3 (1.1–1.5)	Boffetta & Straif 2009 (49)
	Asia	Smokeless tobacco†	1.1 (0.8–1.4)	Zhang et al. 2010 (50)
Fatal stroke	United States	Chew or snuff	1.4 (1.2–1.6)	Boffetta & Straif 2009 (49)
	Sweden	Snuff	1.3 (0.9–1.7)	Boffetta & Straif 2009 (49)
	Asia	Smokeless tobacco†	1.3 (1.1–1.6)	Zhang et al. 2010 (50)

*Numbers in parentheses correspond to full citations in the References at the end of this chapter.
†Type of smokeless tobacco not specified.
Note: Relative risks associated with smokeless tobacco use are provided for the purposes of illustration, as some uncertainty still surrounds some of the values provided. Nevertheless, this table and Table 4-3 demonstrate the variability in public health impact from smokeless tobacco under different scenarios.

Table 4-3. Annual burden of disease attributable to smokeless tobacco use in three countries: Sweden, United States, and India

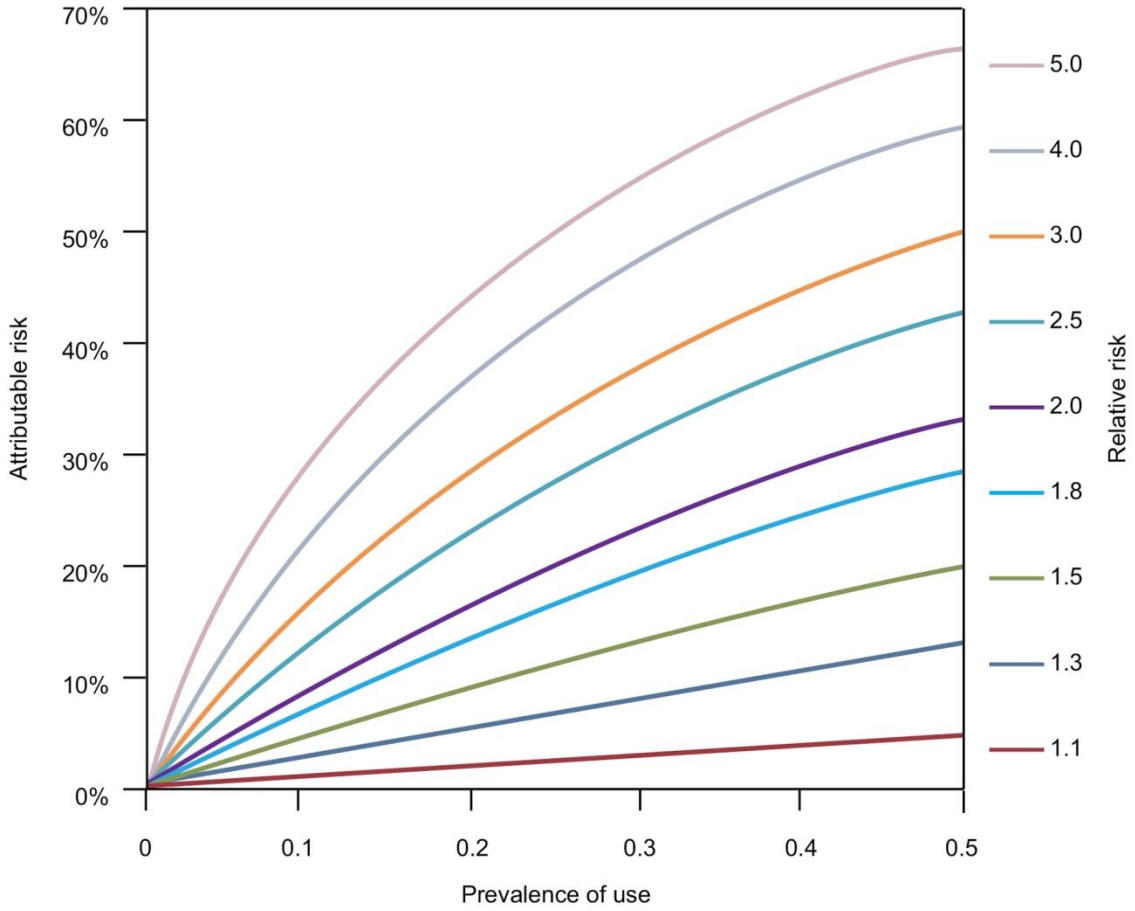
Country/disease	Sex	Relative risk	Prevalence of smokeless tobacco use	Attributable fraction	Attributable burden of disease (new cases per year)
United States					
Oral cancer	Men	2.6	6.9%	9.9%	1,566
	Women	2.6	0.3%	0.48%	35
Esophageal cancer	Men	1.2	6.9%	1.4%	182
	Women	1.2	0.3%	0.06%	2
Pancreatic cancer	Men	1.4	6.9%	2.7%	507
	Women	1.4	0.3%	0.12%	23
Sweden					
Oral cancer	Men	1.0*	26%	0%	0
	Women	1.0*	7%	0%	0
Esophageal cancer	Men	1.6*	26%	13.5%	39
	Women	1.6*	7%	4.0%	4
Pancreatic cancer	Men	1.8*	26%	17.2%	67
	Women	1.8*	7%	5.3%	23
India					
Oral cancer	Men	5.1	33%	57.5%	26,131
	Women	5.1	18%	42.5%	10,359
Esophageal cancer	Men	3.7	33%	47.1%	13,569
	Women	3.7	18%	32.7%	6,308
Pancreatic cancer	Men	2.0	33%	24.8%	1,260
	Women	2.0	18%	15.3%	593

*Relative risks for Sweden in these cases are not country-specific, but represent relative risks calculated for Scandinavia (see Table 4-2).

Sources: Relative risk of disease associated with smokeless tobacco use from Table 4-2; Sweden: prevalence of ST use from the 2012 National Survey on Public Health (70), Table 2-3; United States: prevalence of ST use from the 2009 National Survey on Drug Use and Health (71); India: prevalence of ST use from the 2009–2010 Global Adult Tobacco Survey (72); Cancer incidence data for 2008 from GLOBOCAN (73).

The differences between attributable burden rates reflect both the different RRs seen in studies of ST use in these countries (likely due to differences in products and how they are used) as well as differences in the number of ST users, disease incidence, and the size of the overall country population. The attributable burden will be large if any of the factors is large (Figure 4-6). That is, the AB will be great if the RR is high, if the proportion of people who use ST is large, or if there is a high background risk of disease. For example, oral cancer is a relatively rare disease among men in the United States (15,800 cases annually), and the association between ST use and oral cancer is moderate (RR = 2.6). With 6.9% of men using ST, the fraction of oral cancers attributed to ST use in men is 9.9%, and the attributable burden is about 1,600 cases. If more men began using ST, both the number of oral cancers would increase and the proportion attributable to ST use would increase. If future research determines that ST use is a cause of common diseases such as ischemic heart disease or stroke, even the relatively small RR associated with these diseases would result in a large number of deaths attributable to ST use. For example, the number of deaths from ischemic heart disease and stroke in 2008 potentially attributable to ST use would be approximately 1,000 in Sweden, 4,600 in the United States, and 300,800 in India.

Figure 4-6. Attributable risk increases with relative risk and prevalence of exposure/use



The health impact and disease burden of ST use may be influenced by other forms of tobacco use, particularly cigarette smoking, in at least three ways. First, some smokers who would otherwise have quit smoking because of restrictions on smoking may instead use ST as a situational substitute and continue to smoke. In such cases, ST products may prolong rather than shorten the duration of smoking, thereby increasing the risks from continued smoking.[13] Second, some epidemiologic studies show that dual use of ST and cigarette smoking could have greater health risks than smoking alone.[13,51] Third, although cigarette smokers who permanently switch to exclusive ST use may reduce their risks for some diseases specifically associated with smoke exposure, the single study that examined this issue found that smokers who quit all tobacco use had lower mortality rates from lung cancer, coronary heart disease, and stroke than those who switched to ST use.[69]

Gaps and Limitations in the Current Evidence Base

Compared with the vast amount of information linking adverse health effects to cigarette smoking, studies on ST use are not comprehensive. Epidemiologic studies of ST use have less information about what levels of use are associated with particular outcomes, and, in some countries, fewer numbers of ST users on which to base conclusions. Some, but not all, studies attempt to control for factors such as consumption of other tobacco products and alcohol, which may confound or modify the association with ST use. Also, given that the median time between smoking initiation and death from lung cancer may be as long as 50 years,[67] data on novel products such as Swedish snus may not have accumulated for a long enough period of time to fully characterize the associated risk.

Estimates of the proportion of the population using ST may not be available in all countries or may not reflect current prevalence. Prevalence may be difficult to estimate because of the variety of ST products and the possibility of multiple product use. Therefore, it may be necessary for countries to include measures of ST use in surveys, and to ensure that the information is product specific. Generic data on ST use will not provide the type of specificity necessary for accurate information on disease burden. Also, while reliable data on cancer incidence and mortality are available in many countries, there may be fewer resources for reliable data on incidence and prevalence of other conditions such as reproductive toxicity, cardiovascular disease, precancerous oral lesions, and diabetes. Current estimates of disease burden are critical for diseases that have an increasing trend (pancreatic cancer) or decreasing trend (heart disease). Chapters 9 to 14 in this report will help to fill in some of these data gaps.

Summary and Conclusions

Smokeless tobacco is used in various forms throughout the world. All ST products contain nicotine, and ST users exhibit characteristics of nicotine addiction similar to cigarette smokers. Smokeless tobacco products contain numerous known carcinogens, although in varying levels depending on product characteristics such as type of tobacco, additives, alkalinity, and processing methods. Many products also contain other plant materials (areca nut or tonka bean) or additives that may be carcinogenic or have other adverse health effects. For this reason, the assessment of health risks associated with ST products should include not only tobacco but also the more complex mixture of ingredients that may further increase risk.

Based on information from large, comprehensive reviews,[1,2,9,31,40,58] the following conclusions can be reached:

- The associations between ST use and adverse health consequences differ by type of product.
- There is sufficient evidence that ST products cause addiction, precancerous oral lesions, and cancer of the oral cavity, esophagus, and pancreas, as well as adverse reproductive developmental effects including stillbirth, pre-term birth, and low birth weight.
- The evidence suggests that some, but not all, ST products are associated with increased risk of fatal ischemic heart disease, fatal stroke, and type 2 diabetes; more studies are needed to clarify any causal associations.
- There is insufficient evidence to assess whether ST products are associated with increased risks of lung cancer, cervical cancer, and hypertension.

The public health impact of ST use depends on the disease risk associated with a given ST product, the prevalence and manner of ST use, and the background burden of disease in the target population. These elements may be difficult to quantify because of the lack of data specific to particular products and regions. Sample calculations of the attributable disease burden suggest wide disparities in the impact of ST across countries. Additionally, the role of ST use in shaping other tobacco use behaviors (such as smoking cessation or initiation) should be considered. Currently available data are insufficient to provide a robust estimate of the global disease burden due to ST use. In the long run, comprehensive monitoring of ST use and related health outcomes is needed, especially in those countries where use is high. Nevertheless, evidence is sufficient to conclude that on a global scale, the negative health effects of ST use are substantial and completely preventable.

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