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An epidemiologic review of smokeless tobacco health effects and harm reduction potential

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ABSTRACT

A systematic review of the epidemiologic literature on the health effects of smokeless tobacco (ST) and its relevance to the harm reduction model for smoking was undertaken. Published epidemiologic studies, from the US and European countries, meeting defined inclusion criteria and assessing the health effects of smokeless tobacco products were examined. ST use showed evidence of a slightly increased risk for all-cause mortality. Little evidence was found to support a causal relationship between ST use and risk of oral, pancreatic or lung cancer. ST use was not associated with an increased risk of cardiovascular disease or stroke incidence, but evidence suggested ST use was associated with increased mortality from these diseases. Clinical trials evaluating the effectiveness of ST products in smoking cessation have been sparse, and no standardized method for measuring ST dependence has been used, limiting the assessment of their relationship to ST use. Several studies have examined if ST use increases the risk of smoking initiation, but few have modeled this complex behavior appropriately. Overall, epidemiologic studies have not shown strong evidence of elevated tobacco-related disease risks with ST use. More research is necessary to assess the smoking behavioral consequences of ST use prior to its consideration as a harm reduction tool.

1. Introduction

Tobacco has been consumed in both smoked and smokeless forms by native Americans since ancient times; there is evidence of its use as early as 1 B.C.E. (Borio, 2007). Snuff was the predominant form of smokeless tobacco (ST)[1] used at the turn of 18th century in Europe and US (RCP, 2007). ST use declined after the US Civil War, and cigarettes gained widespread popularity (RCP, 2007). By the turn of 20th century, spitting tobacco was regarded as unsanitary, and cigarettes became the predominant tobacco product used (IARC, 2007). In developed countries like US and Europe, ST use is currently less prevalent than cigarette smoking, although ST use may be increasing with the advent of bans on smoking in public spaces. Sweden has been the exception because snus, its moist snuff product, has become increasingly more popular over the last few decades than smoking (Rodu et al., 2002). Currently moist ST products, like snus are banned from being sold and imported in most European Union countries, except for Sweden (Bates et al., 2003).

The health effects of ST use have been examined in numerous studies and debated extensively in the literature. Investigations on the overall health effects of ST use have been controversial because even if its use presents a health risk, if ST use prevented or reduced cigarette smoking overall in a population, it might provide the opportunity for a net health benefit. In fact, it has been proposed by some in the public health community that ST might be used as part of a harm reduction strategy for cigarette smoking (Gartner et al., 2007; RCP, 2007; Rodu and Godshall, 2006; Stratton et al., 2001). If ST can be supported as an effective product for smoking harm reduction, several conditions must be met:

(1) ST use will have a lower overall health risk compared to smoking cigarettes;
(2) Smokers who use ST will quit smoking at a higher success rate than when using other available products;
(3) ST use will not initiate cigarette smoking in significant numbers of people who would not have become smokers had they not used ST. The degree to which ST use leads to tobacco dependence is also linked to this issue.

The published literature on these topics is inconsistent and meaningful interpretation has been challenging, because although numerous epidemiologic studies have estimated health effects of

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[1] *Abbreviations used:* ST, smokeless tobacco; CI, confidence interval; RR, relative risk/ratio; HR, hazard ratio; NA, not available.

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ST use, many of these studies were not designed to examine the effect of ST use specifically, and do not account for other lifestyle factors (i.e. smoking, alcohol use and oral health) which may confound the true estimate of risk between smokeless tobacco and disease. Even less has been published examining the behavioral consequences of ST use, including its effectiveness as a smoking cessation tool, its dependence potential, and the degree to which ST use leads to the development of a regular smoking habit.

Another challenging aspect in assessing the health effects of ST use is that different types of ST products are available for use in different countries. In the US, chewing tobacco and moist snuff are most commonly used today; nasal dry snuff typically being used in older, more rural populations (Rogozinski, 1990). In Sweden, snus, a moist snuff product in a pouch placed in the oral cavity, has been the tobacco product of predominant use (Rodu et al., 2003). Other populations manufacture their own types of ST products, and may have additives such as betel quid or areca nut, which are considered more highly carcinogenic and were not included in this review. Different types of ST products may confer different health risks and many papers have not examined risks by ST type. Also, carcinogenic tobacco-specific *N*-nitrosamine (TSNA) levels in ST products may have changed over time in some ST products, as has been documented in Swedish snus since the 1980s (Osterdahl et al., 2004). All of these factors have complicated the assessment of health risk from the use of ST products in the epidemiologic literature.

This systematic epidemiologic review is designed to examine the strength of the epidemiologic evidence currently available about health effects from ST use in the US and Scandinavian countries, and assess where future research efforts are needed to determine if ST products could play a role in smoking harm reduction.

2. Methods

A comprehensive literature search using the terms 'smokeless tobacco', 'snus' or 'snuff' and tobacco-related diseases: oral cancer, lung cancer, pancreatic cancer, cardiovascular disease and stroke and all-cause mortality was conducted using Medline and other literature databases to find all epidemiologic studies published through March 31, 2009. To retrieve publications about ST use and smoking behavior and dependence, published manuscripts were also extracted from the databases, using the above ST search terms in conjunction with the terms: "smoking cessation", "tobacco dependence", "addiction", and "smoking initiation". In addition to the online database literature search, bibliographic references from two recent summary publications on the health effects of ST were also examined for studies which may not have been originally retrieved (IARC, 2007; RCP, 2007).

Careful assessment of study design is necessary since the published literature on ST use spans more than 50 years. Many of the published studies were not originally designed to evaluate the health effects of ST and have several design or analytical weaknesses such as: poor ST exposure measurement, only a baseline assessment of tobacco use in cohort studies, not accounting for dual use of tobacco products or other confounders of outcome, unspecified product type and small sample sizes because of the low prevalence of ST use in US or the rarity of some tobacco-related diseases such as oral and pancreatic cancer.

Studies included in this review had to meet the following criteria: published in English in a peer-reviewed journal, have an appropriate analytic epidemiology study design (i.e. case-control, cohort or clinical trial), have an adequate sample size (for case-control study, >100 cases and controls, for a cohort, >20 cases), used appropriate statistical methods, accounted for smoking habits and age in analysis (either by exclusion of smokers or by statistical adjustment), included a study population located in US or Scandinavia, included a homogeneous outcome measure of a tobacco-related disease, and reported primary data analysis (not a review or duplicate presentation). No paper was excluded based on small sample size alone.

3. Disease risk from smokeless tobacco use

Case-control and cohort studies which estimated a tobacco-related disease risk from ST use and met the inclusion criteria are presented in Tables 1 and 2, respectively. Studies which were retrieved through our literature search and which did not meet these criteria for at least one tobacco-related outcome are presented in a Supplementary Table with their corresponding reasons for exclusion.

3.1. All-cause mortality

All-cause mortality is the most robust endpoint to follow in a cohort study when estimating the health effects of smokeless tobacco (Table 3). Four cohort studies from the US and Scandinavia estimated the risk of all-cause mortality with ST use (Accortt et al., 2002; Bolinder et al., 1994; Henley et al., 2005;Roosaar

Table 1
Case-control studies of tobacco-related disease and smokeless tobacco use included in this review.

References	Population studied	Gender	Case-control study type	Time period	Number of cases/control	Case definition
Winn et al. (1981)	From five hospitals in North Carolina, USA	F	Hospital-based	1975–1978	232/410	Oral and pharyngeal cancer
Huhtasaari et al. (1992)	Northern Sweden, MONICA study	M	Population-based	1989–1991	585/589	First acute MI
Mashberg et al. (1993)	U.S. veterans from hospital in New Jersey	M	Hospital-based	1972–1983	359/2280	Oral cancer
Lewin et al. (1998)	Stockholm and southern region	M	Population-based	1988–1991	545/641	Oral cancer
Schildt et al. (1998)	4 Northern Swedish counties	M, F	Population-based	1980–1989	354/354	Oral cancer
Huhtasaari et al. (1999)	Northern Sweden, MONICA study	M	Population-based	1991–1993	687/687	First MI, fatal MI
Asplund et al. (2003)	Swedish MONICA and vaserbotten (VIP) studies	M	Population-based nested C–C	1985–2000	276/551	Stroke incidence
Hergens et al. (2005)	Stockholm heart epidemiology and vasternorrland heart epidemiology Studies	M	Population-based	1992–1993; 1993–1994	1432/1810	First MI, fatal MI
Rosenquist (2005)	Swedish population Southern region	M, F	Population-based	2000–2004	132/320	Oropharyngeal cancer
Wennberg et al. (2007)	Vasterbotten Intervention Program and MONICA study	M, F	Population-based	1985–1999	525/1798	First acute MI, cardiac mortality
Hassan et al. (2007)	University of Texas, M.D. Anderson Cancer Center	M	Hospital-based	2000–2006	808/808	Pancreatic cancer

Abbreviations: MI: myocardial infarction, C-C: case-control.

Table 2
Cohort studies of tobacco-related disease and smokeless tobacco use included in this review.

Reference	Population studied	Gender	Sample size	Follow-up time/ measure	Health outcome(s)
Zheng et al. (1993)	Lutheran Brotherhood Insurance Society in 8 U.S. states	M	17,633 subjects	1966–1986 Mortality	Pancreatic cancer
Bolinder et al. (1994)	Swedish Construction Worker's Study	M	6297 ST users 32,546 never tobacco	1974–1985 Mortality	All-cause mortality Cardiovascular disease Stroke
Accortt et al. (2002)	U.S. NHANES-1 Follow-Up Survey	M, F	414 ST users 2986 non-tobacco users	1971–1992 Mortality	All-cause mortality Circulatory disease Stroke
Johansson et al. (2005)	Swedish population SALLS national survey	M	107 daily ST users 1036 never smokers	1988–2000 Incidence	Cardiovascular disease
Henley et al. (2005)	U.S. volunteers Cancer Prevention Study I AND U.S. volunteers Cancer Prevention Study II	M M 	7745 current ST users 69,622 never ST users 2488 Current ST users 111,482 Never ST users	1959–1972 Mortality 1982–2000 Mortality	All-cause mortality Oral/pharyngeal cancer Cardiovascular disease Cerebrovascular disease Lung cancer
Boffetta et al. (2005)	Norwegian population sample and Norwegian relatives of U.S. migrants (includes smokers)	M	37,883 p-yrs, current snus user 158,672 p-yrs, never snus user	1964–2001 Incidence	Oral/pharyngeal cancer Pancreatic cancer Lung cancer
Luo et al. (2007)	Swedish Construction Worker's Study[a]	M	34,818 current snus only users 87,821 never tobacco users	1978–1992 Incidence	Oral cancer Pancreatic cancer Lung cancer
Haglund et al. (2007)	Swedish Survey of Living Conditions Study	M	721 daily ST users 2759 non-tobacco users	1988–2003 Incidence	Cardiovascular disease Stroke
Hergens et al. (2007)	Swedish Construction Worker's Study[a]	M	118,395 never smokers 32,321current snuff users	1978–1993 Incidence/Mortality	Cardiovascular disease
Hergens et al. (2008)	Swedish Construction Worker's Study[a]	M	118,395 never smokers 31,986 current snuff users	1978–1993 Incidence/mortality	Stroke
Roosaar et al. (2008)	Central Sweden population cohort	M	1548 ever daily snus users 8311 never daily snus users	1973–2002 Mortality	All-cause mortality Oral/pharyngeal cancer Cardiovascular disease

[a] Extension of earlier cohort reported by Bolinder et al. (1994).

Table 3
Risk estimates for all-cause mortality and smokeless tobacco studies in never smokers.

Reference	Observed number of deaths (ST users/ non-ST users)	Exposure	Multivariate relative risk (95% C.I.)	Adjusted covariates in model
Bolinder et al. (1994)	440/1322	Current ST user	**RR: 1.4 (1.3–1.8)**	Age, region of origin
Accortt et al. (2002)	NS	All ST users Male ST users Female ST users	RR: 1.1 (0.9–1.3) RR: 1.0 (0.8–1.3) RR: 1.3 (0.9–1.7)	Age, race, gender, poverty index Age, race, poverty index
Henley et al. (2005)	CPS-I: 2052/9819	Current ST user	**RR: 1.17 (1.11–1.23)**	Age, race, education, BMI, exercise, alcohol, diet, aspirin use
	CPS-II: 567/18,824	Current ST user	**RR: 1.18 (1.08–1.29)**	All the above + employment status
Roosaar et al. (2008)	641/2988	Ever daily snus users	**RR: 1.23 (1.09–1.40)**	Age, residence, alcohol

Bolded text represents risk estimates which were statistically significant at an $\alpha = 0.05$ level.
Abbreviations: BMI: body mass index, ST: smokeless tobacco, NS: not specified, and RR: relative risk.

et al., 2008). A Swedish study that followed 84,781 male construction workers from 1974–1985, found an increased risk for all-cause mortality in exclusive ST users compared to never tobacco users (RR:1.4, 95%CI 1.3–1.8), largely attributable to a significantly increased cardiovascular death rate in the ST users (RR:1.4, 95%CI 1.2–1.6). Despite its large sample size, this study has limitations. Tobacco exposure status and duration were self-reported at study entry and not verified again during the 11 year follow-up. There was no adjustment for potential confounders associated with increased mortality (such as BMI), and it is unclear to what extent the results can be generalized to other occupations or the general population in Sweden. No dose–response effect of ST use and mortality risk was assessed.

The First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (NHANES), a US cohort study, examined all-cause mortality rate and ST use (Accortt et al., 2002). A random sample of NHANES-I subjects ($n = 3847$) and all NHEFS participants were asked about ST use and were followed for 20 years from 1971–1992. The all-cause mortality rate ratio for exclusive ST users was 1.1 (95%CI 0.9–1.3), after adjusting for age, race, gender and poverty index. Limitations of this study were its ascertainment of subjects from two different cohorts, its small sample size, and its lack of adjustment for some mortality-associated confounders (i.e., BMI).

All-cause mortality risk was also measured in two US Cancer Prevention Studies, CPS-I and CPS-II (Henley et al., 2005); partici-

pants were followed up to 12 years and 18 years, respectively. The analysis was restricted to men and excluded participants who reported use of any other tobacco products besides ST. CPS-I found an increased hazard ratio for all-cause mortality, HR:1.17 (95%CI 1.11–1.23), after risk adjustment for age, race, education, BMI, exercise, alcohol consumption, fat consumption, fruit/vegetable intake and aspirin use. CPS-II also found a similarly elevated risk for current users of any ST (HR:1.18, 95%C.I. 1.08–1.29) after similar risk adjustment. No dose–response relationship was found for any cause of death with either frequency, or duration of ST use, which might give rise to uncertainty regarding the likelihood of a causative role between ST use and disease mortality. This study adjusted for many potential confounders, but only assessed tobacco use at the beginning of study.

Another population-based cohort study in Central Sweden began enrollment in 1973–1974 followed subjects until 2002 (Roosaar et al., 2008). This study found an increased risk of all-cause mortality with daily snus use among never smoking men (HR:1.23, 95%CI 1.09–1.40). Dose–response results were not reported.

The published literature provides evidence of an increased albeit small risk for all-cause mortality for ST users compared to never tobacco users, ranging from 20–40% excess risk across four cohort studies. Mortality risks may vary by product type, but many of these studies did not have the ability or statistical power to discriminate risk variation by ST product type. For the Swedish studies, it is important to note the time period over which the cohorts were followed because ST products in Sweden prior to the mid-1980s contained higher levels of carcinogenic TSNAs than in the standard ST products (snus) sold today, which may affect mortality rates (Osterdahl et al., 2004). It is also worth noting that although all-cause mortality risk from exclusive ST use is slightly increased compared to non-tobacco users, the risk is considerably lower than the mortality risk for men who currently smoke cigarettes (Doll et al., 2005; Enstrom, 1999).

3.2. Oral cancer

Since ST products are typically placed in the mouth or sniffed, there has always been a concern that their use will cause the development of cancer in the oral cavity, pharynx or larynx. Concerns about the risk of oral cancer from ST use likely developed because oral lesions such as leukoplakia, a white patch in the oral mucosa, tend to occur at the ST placement site and are commonly prevalent in snuff users. The degree to which these oral lesions are potentially pre-cancerous remains uncertain, as most tobacco-induced oral lesions regress and disappear after discontinuing ST use (Martin et al., 1999), and oral dysplasia has not shown evidence of progressing to oral cancer at the placement site in some studies (Roosaar et al., 2006). Numerous studies examining the risk of oral cancer from ST use have been summarized in recent documents (IARC, 2007; RCP, 2007; Weitkunat et al., 2007). The oral cancer studies that met the quality-based inclusion criteria for this review are presented in Table 4.

Table 4
Risk estimates from smokeless tobacco use and oral cancer studies.

Reference	Health outcome (*N*)	ST exposure[a] (number of exposed cases)	Multivariate	
			OR/RR (95% C.I.)	Adjustment factors
Winn et al. (1981)	Oral and pharyngeal cancer cases (232)	In non-smokers: White snuff dippers (90) Black snuff dippers (17)	 **OR: 4.2 (2.6–6.7)** OR: 1.5 (0.5–4.8)	 Stratified by smoking
Mashberg et al. (1993)	Oral squamous cell carcinoma cases (359)	All subjects (52): Ever snuff use Ever chew tobacco	 OR: 0.8 (0.4–1.9) OR: 1.0 (0.7–1.4)	 Age, race, smoking, alcohol
Lewin et al. (1998)	Incident oral cancer cases only (128)	All subjects: Ever use ST (25) Current use ST (10)	 RR: 1.4 (0.8–2.4) RR: 1.0 (0.5–2.2)	 Age, region, smoking, alcohol
Schildt et al. (1998)	Squamous cell oral cancer cases (354)	All subjects: Ever oral snuff user (67)	 OR:0.8 (0.5–1.3)	 Age, gender, county, smoking, alcohol
Rosenquist (2005)	Oropharyngeal squamous cell carcinoma cases (132)	All subjects: Ever snuff use (20) Current snuff use (13)	 OR: 0.7 (0.3–1.3) OR: 1.1 (0.5–2.5)	 Age, gender, county, smoking, alcohol
Henley et al. (2005)	CPS-I: Oropharynx cancer mortality (13)	In never smokers: Current ST use (4)	 RR: 2.02 (0.53–7.74)	 Age, race, education, BMI, exercise, alcohol, diet, aspirin use
	CPS-II: Oropharynx cancer mortality (46)	In never smokers: Current ST use(1)	 RR: 0.90 (0.12–6.71)	 Above factors + employment status
Boffetta et al. (2005)	Oral/pharyngeal cancer cases (34)	All subjects: Ever snus use (9) Current snus use (6)	 RR: 1.10 (0.50–2.41) RR: 1.13 (0.45–2.83)	 Age, smoking of cigarettes, pipes and cigars
Luo et al. (2007)	Oral cancer cases (60)(no pharyngeal, laryngeal or salivary cancer)	All subjects: Ever snus use (NS) In never smokers: Current snus use (9) Ever snus use (10)	 RR: 0.7 (0.5–1.9) RR: 0.9 (0.4–1.8) RR: 0.8 (0.4–1.7)	 Age, BMI, smoking Age, BMI
Roosaar et al. (2008)	Oral and pharyngeal cancer cases (34)	All subjects: Ever daily snus use (11) In never smokers: Ever daily snus use (5)	 **RR: 3.1 (1.5–6.6)** RR: 2.3 (0.7–8.3)	 Age, residence area, alcohol, smoking Age, residence area, alcohol

Bolded text represents risk estimates which were statistically significant at an $\alpha = 0.05$ level.
Abbreviations: BMI: body mass index, ST: smokeless tobacco, NS: not specified, OR: odds ratio, RR: relative risk.
[a] Studies exclude ever smokers unless otherwise specified.

3.2.1. Case-control studies

In 1981, a North Carolina study ascertained female oral/pharyngeal cases from hospital discharges and matched female hospital controls on age, race and region of residence (Winn et al., 1981). This study reported a strong relationship between snuff dipping and oral/pharyngeal cancer in white non-smokers (RR = 4.2, 95%CI 2.6–6.7) and non-significantly increased risk for black non-smokers (RR = 1.5, 95%CI 0.5–4.8). A strong dose–response relationship was found between years of snuff use and increased risk for mouth and gum cancers. This study was one of the first to assess the risk of ST use independently from smoking, but the many of ST users in this study used dry snuff, which has been reported to have a higher concentration of carcinogens and is consumed differently than moist snuff (Rodu and Godshall, 2006). The degree to which the results from this study can be generalized remains uncertain because the study sample was hospital-based, and risk of oral cancer was not examined by ST subtype, nor adjusted for alcohol use.

Another US case-control study, with cases ascertained from a New Jersey VA hospital and compared to non-cancer VA patient controls, did not find an increased risk for oral and oropharynx cancer in either snuff users or tobacco chewers, after adjusting for age, race, smoking, alcohol intake and other social variables, nor a trend in oral cancer risk with duration of ST use (Mashberg et al., 1993). This study did find significantly elevated risks for oral cancer (OR > 4.0) in both smokers and heavy alcohol drinkers, along with evidence for an interaction between these two risk factors, suggesting power may have been adequate to detect strong associations but again, this study sample was hospital-based, limiting the generalizability of the results to general population.

The risk of ST use was examined in a population-based case-referent study of 605 incident cases of squamous cell head and neck carcinoma ascertained in Sweden from 1988–1990 (Lewin et al., 1998). The risk of head and neck cancer from ST use was not elevated compared to never users, regardless of adjusted covariates, starting age, or duration. The risk for cancer of the oral cavity alone was also not different for current users of ST (RR = 1.0, 95%CI 0.5–2.2) or ever users of ST (RR = 1.4, 95%CI 0.8–2.4) compared to never users. This study did show evidence of an significant interaction between the effects of current smoking and high alcohol consumption on the risk of head and neck cancer (RR = 22.1, 95%CI 13.0–37.8), suggesting that smoking and alcohol are stronger risk factors for head and neck cancer than oral snuff use in Swedish men.

Two additional Swedish population-based case-control studies reported no association between oral cancer and ever ST use after multivariate adjustment for smoking and alcohol; one from a Northern region (OR:0.8, 95%CI 0.5–1.3) (Schildt et al., 1998) and another from a Southern region (OR:0.7, 95%CI 0.3–1.3) (Rosenquist, 2005). The second study estimated an elevated risk for heavy users of ST (>14 g/day), but this risk estimate did not achieve statistical significance (OR:1.7, 95%CI 0.5–5.7). The estimate from this study may have been limited by a relatively small sample size and by the use of proxy reports for alcohol and tobacco consumption for some subjects.

3.2.2. Cohort studies

In 2005, the CPS-I and CPS-II studies compared cancer mortality risk in ST users to never tobacco users, after excluding ever smokers (Henley et al., 2005). Despite the large number of subjects in each cohort and over 12–18 years of follow-up, neither study found a statistically significant increased risk of death from oral/pharyngeal cancer in male never smokers who exclusively used ST at enrollment (CPS-I HR:2.02 95%CI 0.53–7.74; CPS-II HR:0.90 95% C.I 0.12–6.71). These results suggest little effect of ST use on oral cancer mortality, although only a small number of cases were observed in CPS-I cohort, limiting power to detect a small association. Improved survival, despite increased incidence of disease, might be proposed to explain the lack of an association, but this seems unlikely as the survival rate from oral cancer has remained steady at 50% for the past 3 decades (Neville and Day, 2002). One limitation of this study, as with most of the cohort studies, was that exposure status for ST use was assessed only at baseline and was not updated for changes in tobacco consumption over the follow-up period. In addition, concerns have been raised that alcohol consumption may have been underestimated (or alcohol habits changed in ST users since baseline measurement) because of significantly high death rate of cirrhosis in current ST users found in CPS-II (RR:3.02, 95%CI 1.60–5.69) (Foulds and Ramstrom, 2006). Nonetheless, this was a large cohort with a long follow-up period, increasing the robustness of the findings.

In a cohort of 12,341 Norwegian men followed between 1966–2001 (Boffetta et al., 2005), there was no excess risk of oral/pharyngeal cancer in ever ST users (RR:1.10, 95%CI 0.50–2.41) or current ST users was found (RR:1.13, 95%C.I. 0.45–2.83). Although the number of person-years was large, the number of cases that were observed was small ($n < 35$), limiting the power to detect a small association.

Recently, Luo and colleagues examined the risk of oral cancer with Swedish snus use in almost 280,000 male Swedish construction workers followed from 1978–1992 (Luo et al., 2007). No association was found between oral cancer and ever use of ST among the never smokers (RR:0.8, 95%CI 0.4–1.7); similar results were found for ex-ST users and current ST users. No dose–response relationship was found between the amount of ST consumed and the risk of oral cancer. The challenge in interpreting results from this study is that tobacco use was assessed only at enrollment, and the analysis failed to control for potential confounding by alcohol consumption. However, given the large sample size and the high prevalence of snuff use, along with a homogeneous case definition limited to oral cancer only, this study had the most power to detect a small association compared with the previous studies. The results should be generalized with caution because the study subjects, employed construction workers, may have been healthier than the general population.

An extension of a population-based survey examining the risk of cancer among daily snus users and daily cigarette smokers in Central Sweden was recently published (Roosaar et al., 2008). In contrast to other studies from Sweden, this cohort of 9976 men, followed from 1973–2002, showed a significantly increased risk of oral/pharyngeal cancer in men who used ST daily compared to never smokers (HR:3.1, 95%CI 1.5–6.6), after adjustment for age, residence area, alcohol consumption and smoking. When the analysis was restricted to never smokers, the ever daily ST use risk decreased and did not achieve statistical significance (RR:2.3, 95%CI 0.7–8.3). Interestingly, daily ST use did not have a significant effect on overall cancer risk, smoking-related cancers (including oral/pharyngeal) or cancer deaths, but was significantly associated with an increased risk of respiratory death (HR:1.7, 95%C.I. 1.2–2.3), suggesting a potential residual effect of smoking unaccounted for in the analysis. No dose–response analysis between ST use and oral cancer was reported in this study. These results are difficult to interpret because of the poor classification of tobacco consumption (for both smoking and ST use) and cancer outcome measures (multiple cancer categories were grouped together), along with limited power and low participation rate.

A recent meta-analysis did not find evidence of a strong association between smokeless tobacco use and oral cancer (Weitkunat et al., 2007). Out of 38 study-specific estimates a relative risk random-effects estimate for oral cancer from any ST use was 1.87 (95%CI 1.40–2.48). When the meta-analysis was restricted to the seven studies which adjusted for potential confounding by smoking cigarettes and alcohol use, the relative risk estimate was

greatly reduced, to a non-significant 1.02 (95%CI 0.82–1.28). Given the variability of estimates for risk of oral cancer and ST use, and the fact that the majority of the high-quality studies have not found an association between ST use and oral cancer, it is likely the association between ST use and oral cancer is weak at best, particularly for the low *N*-nitrosamine products commonly used in Sweden (Hatsukami et al., 2004). However, caution should be used when interpreting a single point estimate from a meta-analysis that mixes very heterogeneous studies with varying study designs, outcome measures and exposures. Results in never smokers from most recent studies have been consistent with the conclusion that there is little evidence of a significantly increased risk between ST use and oral cancer (Luo et al., 2007; Roosaar et al., 2008).

Results from the oral cancer studies, in general, have been inconsistent, likely stemming from study design issues, small samples with limited power to detect weak/moderate associations, and the failure to control for confounders such as alcohol use, smoking history, and SES. In addition, the risk of oral cancer may depend on the level of TSNAs, which can vary significantly across ST brands and product types (Hatsukami et al., 2004; Osterdahl et al., 2004; Richter et al., 2008). Commonly used US-manufactured moist snuff may contain 15–23 times higher TSNA levels than those found in Swedish snus, and this may explain why the Swedish studies, in general, report lower risks of oral cancer than other studies of ST use (Hatsukami et al., 2004).

The risk of oral cancer appears to depend on type of ST used. From evidence available, it appears that the regular use of low-TSNA moist snuff and US chewing tobacco poses minimal risk of oral cancer. Many US studies, where different types of ST products are used, did not estimate risk independently by type of ST consumed complicating their interpretation. Dry snuff has shown more evidence of an increased risk of oral/oropharyngeal cancer, particularly in studies of US women (Rodu and Jansson, 2004). It would be of particular interest to assess if the risk of oral cancer differs between US ST products and the low *N*-nitrosamine ST products currently used in Sweden, but currently there is little literature examining this question. ST products produced outside the US and Scandinavia are also different. In Asian and African countries, ST products have been found to contain more carcinogens due to their processing and additives, such as areca nut (Merchant et al., 2000; Nair et al., 2004; Sham et al., 2003). Full consideration of these types of ST products are beyond the scope of this review, but risks of cancer may be vary greatly.

The majority of recent US and Scandinavian studies have not found a significantly increased risk of oral cancer, although some of these studies may have been underpowered to detect a weak association. The few studies which did find an increased risk of oral cancer observed subjects over 15 years ago, when ST products may have contained higher nitrosamine levels than in those currently used today or included studies with individuals using a combination of tobacco products. In addition, many of these earlier studies did not adequately control for strong confounders, such as smoking history and alcohol consumption.

3.3. Pancreatic cancer

Several studies have suggested an association between ST use and an increased risk of pancreatic cancer (Table 5). Two cohort studies have estimated that ST users have about a twofold increased risk of pancreatic cancer compared to non-ST users, but both had methodological limitations regarding the classification of non-smokers and the study design or analysis (Boffetta et al., 2005; Luo et al., 2007). Since smoking cigarettes is a known risk factor for pancreatic cancer, residual confounding from tobacco smoking along with misclassification of smoking habits raises concerns (Ghadirian et al., 1991; Harnack et al., 1997; Nilsson, 2006).

Another cohort study that followed 17,633 white men from a US life-insurance company found an elevated risk of pancreatic cancer (Zheng et al., 1993), albeit not statistically significant, among ever users of ST (RR:1.7, 95% CI 0.9–3.1) compared to never tobacco users, after adjustment for age, smoking, and alcohol consumption, but did not find any excess risk in those who used tobacco products other than cigarettes (RR:0.8, 95%CI 0.3–2.5). Such disparate results indicate that when assessing the effect of ST use on a disease, adjusting for smoking history may not have the same effect as limiting the analysis to never-smokers. In addition, alcohol consumption has been considered a risk factor for pancreatic cancer (Bueno de Mesquita et al., 1992; Ghadirian et al., 1991; Go et al., 2005; Heuch et al., 1983; Lin et al., 2002; Michaud

Table 5
Risk estimates from smokeless tobacco use and pancreatic cancer studies.

Reference	Health outcome (*N*)	ST exposure (number of exposed cases)	Multivariate OR/ RR (95% C.I.)	Adjustment factors
Zheng et al. (1993)	Pancreatic cancer mortality (57)	All subjects:		
		Ever use of ST (16)	RR: 1.7 (0.9–3.1)	Age, smoking, alcohol
Boffetta et al. (2005)	Pancreatic cancer cases (105)	All subjects:		
		Current snus use (27)	**RR: 1.60 (1.00–2.55)**	Age, smoking of cigarettes, pipes and cigars
		Ever snus use (45)	**RR: 1.67 (1.12–2.50)**	
		In never smokers:		
		Current snus use (3)	RR: 0.85 (0.24–3.07)	Age
Luo et al. (2007)	Pancreatic cancer cases (83)	All subjects:		
		Ever snus use (NS)	RR: 0.9 (0.7–1.2)	Age, BMI
		In never smokers:		
		Current snus use (18)	**RR: 2.1 (1.2–3.6)**	Age, BMI
		Ever snus use (20)	**RR: 2.0 (1.2–3.3)**	
Hassan et al. (2007)	Histologically confirmed pancreatic cancer cases (808)	All subjects:		
		Ever use chewing tobacco (34)	OR: 0.7 (0.4–1.1)	Age, gender, race/ethnicity, cigarette smoking, diabetes, alcohol, education, state of residency, marital status
		Ever snuff use (18)	OR: 0.6 (0.3–1.1)	
		Excludes cigarette smokers:		
		Ever use chewing tobacco (10)	OR: 0.6 (0.3–1.4)	
		Ever snuff use (4)	OR: 0.5 (0.1–1.5)	

Bolded text represents risk estimates which were statistically significant at an $\alpha = 0.05$ level.
Abbreviations: BMI: body mass index, ST: smokeless tobacco, NS: not specified, OR: odds ratio, and RR: relative risk.

et al., 2001; Silverman et al., 1995); none of these cohort studies adjusted for alcohol consumption.

More recently, a US case-control study, conducted from 2000–2006, did not find an increased risk of pancreatic adenocarcinomas with either chewing tobacco use or snuff consumption, but did find a twofold increased risk with cigar smoking (Hassan et al., 2007). There were only a small number of pancreatic cancer cases who had ever used ST ($n = 52/808$), but neither the never smoking, chewing tobacco users (OR:0.6, 95%CI 0.3–1.4) nor snuff users, (OR:0.5, 95%CI 0.1–1.5) had elevated risks of pancreatic cancer compared to never ST users. The analysis including all subjects found similar odds ratio estimates. Importantly, this analysis adjusted for alcohol consumption and a history of diabetes, both potential risk factors for pancreatic cancer (Gapstur et al., 2000; Go et al., 2005; Heuch et al., 1983). This was also the only study that ascertained pathologically confirmed pancreatic cancer cases, which helps minimize disease misclassification, a particular limitation for studies of pancreatic cancer.

The relatively low number of cases studied, the infrequency of ST use among the cases, and the potential confounding by smoking and alcohol consumption all combine to make pancreatic cancer and ST use a difficult association to investigate. Overall, there is little consensus in the literature concerning the risk of pancreatic cancer with ST, however it is interesting to note that the two studies which did not adjust for alcohol consumption were also the same studies which reported a significantly increased risk. A more robust study design, larger study sample, standardized histological confirmation of pancreatic cancer cases, along with appropriate statistical adjustment for all potential confounders will be needed to determine if current, low nitrosamine ST products pose an increased risk for pancreatic cancer. The public health significance of an association, if present, is unclear.

3.4. Lung cancer

The risk of lung cancer would not be expected to be increased in exclusive ST users compared to never tobacco users, as ST is not an inhaled tobacco product. However, some cohort studies have reported significant associations between lung cancer and ST use (Accortt et al., 2002; Henley et al., 2005), and some researchers have postulated that the certain TSNAs (i.e., NNAL) secreted from ST products are lung cancer-specific carcinogens (Hecht, 2006). In the NHANES-I and NHEFS studies, an increased risk of death from lung cancer was found in women who had ever used ST compared to non-tobacco users, although the number of deaths was very small (<10 deaths per group), the confidence intervals correspondingly wide, and the results were not consistent across genders.

In the CPS-II study, ST users who were never smokers (2% of subjects at baseline) had a hazard ratio of 2.0 for lung cancer (95%CI 1.23–3.24) compared to never ST users. No dose–response relationship was detected with either increasing consumption of ST or duration of use, and an increased risk was not found in the earlier CPS-I cohort study reported in the same paper, in which 10% of participants used ST (HR:1.08, 95%CI 0.64–1.83). While the authors excluded current and former smokers from their analysis, the exposures were measured at baseline and tobacco habits may have changed in some ST users who may have starting smoking or were not accurately categorized at baseline. In these studies, ST use had elevated hazard ratios for COPD, an established smoking-related disease, suggesting the potential for smoking exposure misclassification (Foulds and Ramstrom, 2006). Confounding by smoking is of particular concern, since lung cancer risk is highly elevated with cigarette smoking.

The Swedish cohort studies have failed to find any association between ST use and lung cancer (Boffetta et al., 2005; Luo et al., 2007). This relationship may depend greatly on the relationship between ST use and smoking, and could go in either direction depending on whether ST use increases or decrease long-term smoking rates. None of these cohort studies reassessed tobacco use at the time of diagnosis or death, so it is unclear if smoking exposure classification recorded at baseline continued uniformly throughout the long follow-up in these studies.

The relationship between ST use and lung cancer appears tenuous at best, and more detailed and accurate long-term tobacco exposure classification will be necessary before a causal relationship can be determined.

3.5. Cardiovascular disease (CVD)

ST use has been associated with some cardiovascular risk factors such as increased blood pressure (Benowitz et al., 1988; Bolinder and de Faire, 1998; Bolinder et al., 1992; Fant et al., 1999; Hirsch et al., 1992; Westman, 1995; Wolk et al., 2005), hyperlipidemia (Ernster et al., 1990; Norberg et al., 2006; Tucker, 1989; Wallenfeldt et al., 2001), overweight (Hergens et al., 2005), waist-to-hip ratio (Wallenfeldt et al., 2001), diabetes (Eliasson et al., 1991; Persson et al., 2000) and impaired endothelial function (Granberry et al., 2003; Rohani and Agewall, 2004), but these associations have not been found consistently across studies (Eliasson et al., 2004; Lee, 2007; Siegel et al., 1992; Wandell et al., 2008). On the other hand, levels of some biochemical CVD risk factors such as fibrinogen (Eliasson et al., 1995; Wallenfeldt et al., 2001), C-reactive protein(Wallenfeldt et al., 2001) and fasting plasma glucose (Eliasson et al., 1995), have been similar in ST users and non-tobacco users in several studies (Asplund, 2003). Most published studies have had difficulty differentiating if ST use itself causes increased cardiovascular risk or if other lifestyle habits correlated with ST use contribute to increased risk. The studies of cardiovascular outcomes included in this review are shown in Table 6.

3.5.1. Case-control studies of myocardial infarction and ST use

A Swedish case-control study (MONICA) examined the risk of myocardial infarction (MI) in 36–49 year old males and population controls between 1989–1991 (Huhtasaari et al., 1992) and found no increased risk of MI with regular ST use compared to non-tobacco users in this population (age-adjusted OR:0.89, 95%CI 0.62–1.29). A second case-control study of the same population prospectively ascertained from 1991–1993 (Huhtasaari et al., 1999), estimated an even lower risk of MI in male non-smoking, ST users compared to current users of tobacco after adjustment for age, hypertension, diabetes, high cholesterol, family history of MI, education and marital status (OR:0.58, 95%CI 0.35–0.94). The odds ratio for fatal MI was elevated but did not achieve statistical significance (OR:1.50, 95%CI 0.45–5.03). A limitation of both of these studies is that neither of them accounted for former smoking in the analysis, which could be a confounder when estimating the risk of MI.

Similar results were found in a larger Swedish case-control study of men aged 45–70, who had an MI between 1992 and 1994, resulting in an adjusted odds ratio of 0.93 (95%C.I. 0.77–1.3) for all subjects and 0.73 (95%CI 0.35–1.5) for in never smoking current snuff users (Hergens et al., 2005). In the control population, current use of ST was significantly associated with smoking, hypertension, and high BMI ($p < 0.05$), all independent risk factors for MI. It is unclear from case-control studies if ST use increases the prevalence of such MI risk factors or if other lifestyle habits (i.e. poor diet, sedentary lifestyle) in ST users may contribute to an increased risk of MI or MI death in some studies.

Interestingly, a nested case-control study from the Northern Swedish MONICA cohort (Wennberg et al., 2007), did not find evidence of increased risk of myocardial infarction (MI) or fatal MI in

Table 6
Risk estimates from smokeless tobacco use and cardiovascular disease (CVD) studies.

Reference	Health outcome (*N*)	ST exposure (number of exposed cases)	Multivariate risk	
			Estimate (95% C.I.)	Adjustment factors
Huhtasaari et al. (1992)	First acute MI (585)	In non-smokers: Daily snuff use (59)	OR: 0.89 (0.62–1.29)	Age
Bolinder et al. (1994)	CVD mortality (641)	In never smokers: Current ST use (220)	**RR: 1.4 (1.2–1.6)**	Age, region of origin
Huhtasaari et al. (1999)		Excludes present smokers:		
	All acute MI (658)	Regular snuff use (59)	OR: 0.58 (0.35–0.94)	Age, hypertension, diabetes, heredity,
	Fatal MI Only (106)	Regular snuff use (NS[a])	OR: 1.50 (0.45–5.03)	cholesterol, education, marital status
Accortt et al. (2002)	Circulatory disease mortality (includes stroke) (NS)	In never smokers: Males, ST use (NS)	HR: 1.0 (0.7,1.5)	Age, race, poverty index
		Females, ST use (NS)	HR: 1.2 (0.7–1.9)	
	Mortality from ischemic heart disease (NS)	Males, ST use (NS)	HR: 0.6 (0.3–1.2)	Age, race, poverty index, alcohol, exercise, diet, blood pressure, cholesterol, BMI
Henley et al. (2005)	CPS-I: CVD mortality (7777)	In never smokers: Current ST use (1399)	**RR: 1.18 (1.11–1.26)**	Age, race, education, BMI, exercise, alcohol, diet, aspirin
	CPS-II: CVD mortality (8689)	In never smokers: Current ST use (278)	**RR: 1.23 (1.09–1.39)**	All the above + employment status
Hergens et al. (2005)	First acute MI (1432)	All subjects:		
	First acute MI (310)	Current snuff use (147)	OR: 0.98 (0.77–1.3)	Age, hospital area, smoking
		In never smokers:		
	Fatal MI (259)	Current snuff use (10)	OR: 0.73 (0.35–1.5)	
		All subjects:		
	Fatal MI (49)	Current snuff use (25)	OR: 1.0 (0.65–1.6)	
		In never smokers:		
		Current snuff use (3)	OR: 1.7 (0.48–5.5)	
Johansson et al. (2005)	Incident CVD (NS)	In never smokers: Daily snuff use (107)	RR: 1.41 (0.61–3.28)	Age, physical activity, BMI, diabetes, hypertension
Haglund et al. (2007)		In non-smokers:		
	Incident MI (436)	Daily snuff use (28)	RR: 0.77 (0.51–1.15)	Age, SES, residence, health status,
	Fatal MI (130)	Daily snuff use (8)	RR: 1.15 (0.54–2.41)	chronic illness, physical activity
Hergens et al. (2007)		In never smokers:		
	All MI (3651)	Ever snuff use (453)	RR: 0.99 (0.90–1.10)	Age, BMI, residence region
		Current snuff use (416)	RR: 1.02 (0.92–1.14)	
	Fatal MI (841)	Ever snuff use (128)	**RR: 1.28 (1.06–1.55)**	
		Current snuff use (118)	**RR: 1.32 (1.08–1.61)**	
Wennberg et al. (2007)	First MI (426)	Never smoker, current snuff use (21)	OR: 0.82 (0.46–1.43)	Age, sex, BMI, activity level, education,
		Former smoker, current snuff use (37)	OR: 1.25 (0.80–1.96)	cholesterol
	Fatal MI in 28 days (103)	Never smoker, current snuff use (7)	OR: 1.12 (0.38–3.29)	
		Former smoker, current snuff use (7)	OR: 1.24 (0.44–3.53)	

Bolded text represents risk estimates which were statistically significant at an $\alpha = 0.05$ level.
Abbreviations: BMI: body mass index, ST: smokeless tobacco, CVD: cardiovascular disease, NS: not specified, SES: socio-economic status, OR: odds ratio, RR: relative risk, and HR: hazard ratio.

ST users who never smoked (OR:0.82, 95%CI 0.46–1.43 and OR:1.12, 95%CI 0.38–3.29, respectively) after adjustment for sex, age, BMI, physical activity, education and cholesterol, but did find a slightly higher risk of MI and cardiac death for men who were former smokers and currently used snuff (OR:1.25, 95%CI 0.80–1.96 and OR:1.24, 95%C.I. 0.44–3.53, respectively). Statistical significance was not achieved for these risk estimates. This study did confirm participants' tobacco use habits in a second survey during follow-up to assess if tobacco habits had changed since baseline. Heavy snuff use may be a marker for a less healthy lifestyle which may lead to poorer survival after a MI. Future studies will need to be designed to clarify if the observed increased risk of CVD death may be related to previous smoking or actual ST use; standardization of risk adjustment for confounders will be important in such studies.

3.5.2. Cohort studies of myocardial infarction and ST use

One of the first cohort studies to examine risk of cardiovascular mortality with ST use followed 135,036 male Swedish construction workers and found a significantly increased risk for cardiovascular death (RR:1.4, 95%CI 1.2–1.6) in ST users after adjustment for age and region of origin (Bolinder et al., 1994). Limitations for this study include one-time assessment of tobacco exposure at baseline and lack of adjustment for additional confounders of MI.

A US cohort study examined the 20-year mortality of ST users, age 45+, who participated in the NHANES-I (Accortt et al., 2002), and found no increased risk of death from all diseases of the circulatory system (including stroke) among male (HR:1.0, 95%CI 0.7–1.5) and female (HR:1.2, 95%CI 0.7–1.9) exclusive ST users, after adjustment for age, race, and poverty index. This study also found no association between risk of ischemic heart disease (IHD) and exclusive ST use (HR: 0.6, 95%CI 0.3–1.2) in males (female data not reported). This is the only cohort study which estimated CVD mortality risk in female ST users, however the authors did not report the number of deaths for any outcome in this paper making it unclear how much power this study had to detect such an association.

Slightly increased risks of CVD death with ST use were found in the two large US cohort studies: CPS-I (HR:1.18, 95%CI 1.11–1.26) and CPS-II (HR:1.23, 95%CI 1.09–1.39) after adjustment for age,

race, educational level, body mass index, exercise, alcohol consumption, fat consumption, fruit/vegetable intake and aspirin use (Henley et al., 2005). Concerns have been raised about the presence of residual confounding and/or misclassification of tobacco exposure measured only at baseline in this analysis (Foulds and Ramstrom, 2006).

In a 11-year follow-up study of ST and coronary heart disease from a Swedish national survey (SALLS) (Johansson et al., 2005), daily ST users who never smoked had a non-significantly increased hazard ratio of 1.41 (95%CI 0.61–3.28) for MI compared to never smokers after adjustment for age, physical activity, BMI, diabetes and hypertension. This study included only 107 daily ST users, limiting its power to detect a small relative risk that reaches statistical significance.

Another report from the Swedish Construction Workers cohort, extending follow-up to 19 years (Hergens et al., 2007), found no evidence of an increased risk of acute MI (RR:0.99, 95%C.I. 0.90–1.10) after adjustment for age, body mass index, and region of residence. There was an increased risk of fatal MI (RR:1.28, 95%C.I. 1.06–1.55), particularly among heavy ST users (those consuming $\geqslant$ 50 grams per day: RR:1.96, 95%CI 1.08–3.58). Survival analysis also showed that ST users had a higher probability of dying from all causes ($p = 0.01$) or from cardiovascular disease ($p = 0.005$) when compared to non-users. This cohort was not population-based, limiting the generalizability of these results, because lifestyle factors which affect MI risk in male construction workers may differ from those in the general population.

Recently, another Swedish cohort study, of 5002 men, examined the risk of hospitalization for ischemic heart disease in snuff users and smokers compared to non-tobacco users during 1988–2003 (Haglund et al., 2007). Daily ST use (with no daily smoking) was not associated with the risk of incident ischemic heart disease (RR:0.77, 95% 0.51–1.15), but daily smoking was significantly associated with increased risk for heart disease (RR:1.74, 95%C.I. 1.41–2.14) after adjustment for age, SES, residential area, self-reported health, number of longstanding illnesses and physical activity. Similarly, no association was found between daily ST use and death from ischemic heart disease (RR:1.15, 95%CI 0.54–2.41) in the multivariate model. Daily smokers had a significantly increased risk of death from ischemic heart disease (RR:1.98, 95%CI 1.35–2.91) compared to non-tobacco users. While tobacco habits were assessed more recently than other Swedish cohorts, the data collected about tobacco use were broad and did not provide any information on dose or duration. Despite these limitations, this is another cohort study with no evidence that ST use increases the risk for cardiovascular events.

3.6. Stroke

One nested case-control study and several cohort studies have examined ST use and the risk of ischemic stroke (Table 7). From the Northern Sweden MONICA cohort between 1986 and 1996 and the VIP cohort from 1985 to 2000, a nested case-control study was developed (Asplund et al., 2003), and no association was found between never smoking, regular snuff users and stroke after matching for age, sex, region, and adjusting for blood pressure, cholesterol, diabetes, education, and marital status (OR:0.87, 95%CI 0.41–1.83).

Risk of death from stroke was also not increased in the never smoking ST users in the Swedish male construction worker study (RR:1.9, 95%CI 0.6–5.7 for men aged 35–45 years, and RR:1.2, 95%CI 0.7–1.8 for men aged 55–65 years) (Bolinder et al., 1994),

Table 7
Risk estimates from smokeless tobacco use and stroke studies.

Reference	Health outcome (*N*)	ST exposure (number of exposed cases)	Multivariate	
			OR/RR (95% C.I.)	Adjustment factors
Bolinder et al. (1994)	Stroke mortality (86)	Never smoker, current ST use		
		Age 35–54yrs (4)	RR: 1.9 (0.6–5.7)	Age, region of origin
		Age 55–65 yrs (26)	RR: 1.2 (0.7–1.8)	
Accortt et al. (2002)	Mortality from stroke (NS)	Ever smokers, ever ST use:		
		Males (NS)	HR: 0.7 (0.3–1.5)	Age, race, poverty index, alcohol, exercise, diet, and blood pressure
		Females (NS)	HR: 1.7 (0.4–7.0)	
		In never smokers, ever ST use:		
		Males (NS)	HR: 0.7 (0.2–2.0)	
		Females (NS)	HR: 1.0 (0.3–2.9)	
Asplund et al. (2003)	All stroke incidence (219 case-control triplets)	In never smokers:		
		Regular snuff use (30)	RR: 0.87 (0.41–1.83)	Age, gender, region, exam year, cohort, blood pressure, education, marital status, diabetes, cholesterol
Henley et al. (2005)	CPS-I: cerebrovascular mortality (1911)	In never smokers:		
		Current ST use (460)	**RR: 1.46 (1.31–1.64)**	Age, race, education, BMI, exercise, alcohol, diet, aspirin use
	CPS-II: cerebrovascular mortality (1958)	In never smokers:		
		Current ST use (71)	**RR: 1.40 (1.10–1.79)**	All the above + employment status
Haglund et al. (2007)	All stroke incidence (232)	In non-smokers:		
		Daily snuff use (19)	RR: 1.07 (0.65–1.77)	Age, SES, residence, health status, chronic illness, physical activity
	Fatal stroke (50)			
		Daily snuff use (4)	RR: 1.01 (0.35–2.92)	
Hergens et al. (2008)[a]	All ischemic strokes (2283)	In never smokers:		
		Current snuff use (284)	RR:1.07 (0.94–1.22)	Age, BMI, and region of residence
		Ever snuff use (304)	RR: 1.03 (0.91–1.16)	
	Fatal ischemic stroke (114)	In never smokers:		Age, BMI, and region of residence
		Current snuff use (21)	**RR: 1.72 (1.06–2.78)**	
		Ever snuff use (22)	**RR: 1.63 (1.02–2.62)**	

Bolded text represents risk estimates which were statistically significant at an $\alpha = 0.05$ level.
Abbreviations: BMI: body mass index, NS = not specified, SES: socio-economic status, RR: relative risk, HR: hazard ratio.
[a] Extension of earlier study in Bolinder et al. (1994)

or in the US NHANES-I cohort of never smoking men (multivariate HR:0.7, 95%CI 0.2–2.0) (Accortt et al., 2002).

In contrast, the CPS studies (Henley et al., 2005) found significant associations between current ST use and risk of cerebrovascular death (CPS-I HR:1.46, 95%CI 1.31–1.64; CPS-II HR:1.40, 95%CI 1.10–1.79). In CPS-II, the risk was also elevated for current ST use but the risk varied by ST subtype: (snuff users HR:0.62, 95%C.I. 0.23–1.67; ST chewers HR:1.38, 95%C.I. 1.02–1.86). Caution needs to be used when interpreting these point estimates as the number of exclusive snuff users was low ($n = 4$). The potential for inadequate reassessment and adjustment for baseline alcohol and tobacco exposures remains a methodological issue of these studies.

A recent population-based cohort study, from the Swedish Survey of Living Conditions Study of men aged 16–74 years (Haglund et al., 2007), found that stroke incidence was not significantly elevated in daily ST users (RR:1.07, 95%CI 0.65–1.77) nor was the risk for stroke death in this population (RR:1.01, 95%CI 0.35–2.92). Also, in another analysis of the Swedish construction worker cohort study (Hergens et al., 2008), a significantly elevated risk of mortality from ischemic stroke (RR:1.72, 95%CI 1.06–2.78) but not for ischemic stroke incidence (RR:1.07, 95%CI 0.94–1.22) or for mortality from all types of stroke combined (RR: 1.38, 95%CI 0.99–1.91) was found, suggesting that risk may vary by type of stroke.

In a meta-analysis of these studies (Lee, 2007), the random-effects relative risk estimate for stroke was estimated at 1.42 (95%CI 1.29–1.57), for heart disease at 1.12, (95%CI 0.99–1.27), and for circulatory disease at RR: 1.25 (95%CI 1.14–1.37) in non-smoking ST users (Lee, 2007). These increased risks were weighted heavily by the positive results found in the US CPS mortality studies, which had the largest sample sizes. The strongest risks of CVD were found in the US studies, whereas the risk for heart disease (RR:1.06, 95%C.I. 0.83–1.37) and stroke (RR:1.17, 95% 0.80–1.70) were substantially weaker when limited to studies in Sweden. If ST use were to increase blood pressure or cholesterol levels, there may be an elevated risk of circulatory disease death with ST use. However, evidence of a causal association between ST use and circulatory disease is not well supported, as no dose–response has been found between ST use and CVD. Meta-analyses, such as this one, which include the mixing of study designs and permit the inclusion of both incidence and mortality data, should be interpreted with caution.

While there is some evidence of elevated risk of mortality from both MI and ischemic stroke with ST use, there is very little supporting evidence for an increased risk of the incidence of these diseases. This suggests that some component of ST use may increase the risk of mortality after a thrombolytic event or possibly that other cardiovascular risk factors are more common in ST users than in never ST users which may decrease the survival after an event. More research will be needed to discern if an increased risk results directly from ST use or if other lifestyle habits of ST users may contribute to circulatory disease incidence or death.

4. Smokeless tobacco use and smoking cessation

A question related to the public health impact of ST is whether ST affects the likelihood of achieving smoking cessation. There is also the concern that smokers will adopt the use of ST in addition or concurrently with smoking cigarettes, effectively becoming dual users.

Ecological evidence from Sweden has shown that as the prevalence of smoking in men has declined over last two decades, the prevalence of snus has increased (Stegmayr et al., 2005). This observation has been noted primarily in Swedish men, but a similar, albeit smaller, change may now be occurring in Swedish women smokers. Also, several cross-sectional studies have shown that ST use is associated with higher rates of smoking cessation, although the majority of these studies were conducted in Sweden, which may limit the generalizability of their results to other countries (Furberg et al., 2005; Gilljam and Galanti, 2003; Lindstrom and Isacsson, 2002; Ramstrom and Foulds, 2006; Rodu and Cole, 2004; Rodu and Phillips, 2008).

Results from cross-sectional Swedish studies suggest that snus has been a successful aid for smoking cessation in men, with ex-smokers 2–3 times more likely to use this ST product than not (Lindstrom, 2007). In Sweden, demographics also suggest that younger men (<55 yrs) use snus significantly more to quit smoking than older men in Sweden (Lindstrom, 2007; Rodu et al., 2002). However, this study also shows that ex-smokers who switch to snus continue to use it daily (73% men, 83% women), suggesting that snus may act as a nicotine replacement product rather than an aid for cessation of tobacco use (Lindstrom, 2007).

Drawing causal inferences from cross-sectional studies is challenging, in particular, because (1) the temporality of exposure and cessation outcome is unknown, (2) the data on smoking cessation was self-reported and not biologically verified, (3) the definition of former smokers and current smokers varies across studies and (4) because it is difficult to measure success rates for smoking cessation, as important factors such as number of repeated quit attempts are missed.

A recent national survey followed tobacco cessation rates in a US population for 1 year to assess if ST use affects smoking cessation (Zhu et al., 2009). In this relatively short longitudinal study, a couple of important observations were made. First, tobacco cessation rates were significantly lower for smoking than for smokeless tobacco (18% vs. 50%). Second, the quitting of one tobacco product and switching to another was infrequent; ST users switched to smoking cigarettes more commonly than vice versa (3.9% vs. 0.3%). This pattern of smoking cessation and ST use in US men differs from that reported in the Swedish experience (Furberg et al., 2006; Rodu et al., 2003), perhaps due to ST product composition differences (Foulds et al., 2003), cultural acceptance of ST use, or the cost differential between ST and cigarettes, which is much greater in Sweden (Zhu et al., 2009). Limitations of this study include the fact that tobacco cessation rates were not examined by age groups and that such a short follow-up may not reflect stable cessation rates.

A longitudinal study of Swedish twins (SALT) assessed the association between smoking cessation in ever regular smokers and their history of ST use (Furberg et al., 2008). ST use was found to be the strongest predictor of being a former regular smoker (HR:2.7, 95%CI 2.3–3.2) out of 12 possible covariates associated with cessation including strong predictors such as education, marital status, SES and nicotine dependence. One of the limitations of this study was that the cross-sectional design of longitudinal data does not actually measure smoking cessation rates but rather estimates the probability of having used ST in a lifetime and being a former regular smoker. Only a randomized, controlled clinical trial can provide evidence that ST products effectively increase smoking cessation rates.

A couple of smoking cessation clinical trials have been conducted with an ST intervention (Table 8), but only one large, open, randomized controlled trial testing the effectiveness of ST for smoking cessation has been published (Tonnesen et al., 2008). In Denmark, 263 healthy smokers were randomly allocated into either a treatment group with suggested use of ST product (tobacco pellet) for 7–12 weeks and group therapy or a placebo group which only offered smoking cessation therapy. At 7 weeks, quit rates differed significantly between the two groups, with ST users having a higher prevalence of smoking cessation (36.4% vs. 20.8%, $p = 0.001$). The difference in smoking cessation rates between the groups, however, did not persist at the 6 month follow-up (23.1% vs.

Table 8
Smoking cessation intervention trials with smokeless tobacco use.

Reference	Study design/sample size	Follow-up time	Intervention	Success Rate (%)	Comments
Tilashalski et al. (1998, 2005)	Smoking cessation interventional pilot study; 63 smokers At 7 yr follow-up:58 subjects, 41 smokers	1 yr; 7 yrs	All subjects introduced to ST and given smoking cessation education	*1 yr point prevalence* 25% quit used ST 10% quit without ST *7 yr prevalence* 44% Quit smoking overall 43% Quit using ST 57% Quit using other methods	No statistical tests or control group used
Tonnesen et al. (2008)	Open, randomized clinical trial for smoking cessation; 263 healthy smokers	7 weeks; 6 months	Two groups: ST product use with group support vs. group support only	*7 weeks prevalence* ST group: 36.4% No ST group: 20.8% **OR: 2.52** ***p* = 0.001** *6 months abstinence* ST group: 11.9% No ST group: 8.3% OR: 1.48 *p* = 0.344	Subjects were advised to taper use of ST product by 12 weeks time point 11% subjects stopped using ST due to adverse events

Bolded text represents risk estimates which were statistically significant at an $\alpha = 0.05$ level.
Abbreviations: ST: smokeless tobacco, OR: odds ratio.

20.8%, NS). This study shows that ST use can effectively substitute for smoking cessation in the short-term, but it may not increase smoking cessation in long-term, particularly if ST use is discontinued. More clinical trials, with longer interventions and follow-up, are needed to determine if changing to ST products will increase the probability that an inveterate smoker will be able to stop smoking long-term.

5. Smokeless tobacco use and dependence

While the epidemiologic literature addressing ST use and dependence is very limited, it has been generally assumed from pharmacological and basic research that ST is an addictive substance: it is tobacco product and contains a significant amount of nicotine which is absorbed in similar quantities as cigarettes and provides bioavailable nicotine, similar to cigarettes (Benowitz et al., 1988; Kozlowski, 2007; Richter et al., 2008). Nicotine absorption from ST is slower than from smoking cigarettes and elevated serum nicotine from ST use persists much longer than from smoking (Benowitz et al., 1988). Typically, ST users consume quantities of nicotine similar to smokers, with comparable peak serum nicotine levels (Ramstrom, 2003). Like cigarettes, nicotine content varies by ST product, which presents a challenge in dose–response assessment.

Part of the difficulty in providing evidence of the dependence potential of a ST product in epidemiologic studies is that no standardized measure of dependence of ST use has been implemented in human studies. While there is a medical standard to assess dependence in cigarette smokers, this criterion has not been established as a validated measure of ST dependence. Some studies have adapted the Fagerstrom Tolerance Questionnaire, developed for smokers, for ST users (Boyle et al., 1995) and a few other researchers have created further modification of this measure (Ferketich et al., 2007; Thomas et al., 2006). One 3-month clinical cessation trial found that higher FTQ-ST scores correlated significantly with reduced ST abstinence, and moderately with the amount of tobacco used and serum cotinine levels (Thomas et al., 2006).

However, few studies have been published examining the dependence potential of ST using any epidemiologic or medical measure. One study, using DSM-IV criteria similar to those used with smokers, found 69% of treatment-seeking male ST users exhibited enough withdrawal symptoms after cessation to meet criteria for nicotine withdrawal (Hatsukami et al., 1999). A better measure for true nicotine dependence for all types of tobacco use needs to be developed, as a recent study shows that nearly 40% of moderate to heavy daily smokers failed to meet the standard of nicotine dependence by DSM-IV criteria (Donny and Dierker, 2007). Another survey has found that 50% of current smokers do not meet any DSM/ICD dependence criterion (Hughes et al., 2006). Thus, the only currently available tools to measure dependence in ST users have not been validated.

6. Smokeless tobacco use and smoking initiation

One of the greatest concerns for public health researchers in recommending the use of ST products for smoking harm reduction, is that this endorsement of ST use will increase the risk of smoking initiation in individuals who might not otherwise use tobacco, also known as the 'gateway' drug hypothesis (Haddock et al., 2001; Hall and Gartner, 2009; Kozlowski et al., 2003; Tomar, 2003).

There have been several studies attempting to assess if ST use is associated with cigarette smoking (Furberg et al., 2005; Galanti et al., 2008; Haddock et al., 2001; Haukkala et al., 2006; O'Connor et al., 2003; Severson et al., 2007; Timberlake et al., 2009; Tomar, 2003). Most of these studies have focused on young teenage or adult populations as these are the most susceptible to the marketing efforts from the tobacco industry and most likely to initiate a smoking habit (Tables 9 and 10). Different estimates of the risk of starting to smoke cigarettes have been generated, depending on study design variations, population studied and the method of modeling of smoking predictor variables.

It has been difficult for researchers to develop an appropriate conceptual model that accurately represents a 'gateway hypothesis' paradigm. Establishing a uni-directional causal relationship in which ST use itself leads to cigarette smoking and its adoption as a regular behavior is challenging because of the complex interplay of psychosocial and behavioral factors that affect a teenager's decision to start smoking. Some of the most challenging aspects to model this process involve: (1) establishing which type of tobacco is adopted first when experimentation may involve multiple substances, (2) what constitutes a robust definition of a regular smoker (or ST user) for young adults or teens, (3) who should

Table 9
Studies examining smokeless tobacco use and smoking initiation.

Reference	Population studied	Study design/sample size	Time period	Odds ratio (OR) for smoking initiation (95% C.I.)	Adjusted covariates in model
Severson et al. (2007)[a]	Project 16 community intervention to prevent adolescent tobacco use 7th and 9th grade boys in Oregon schools	Cohort/2263 non-smokers ST user = any ST in last 30 days Smoker = weekly cigarette smoking	1994–1999 2 yr F/U	Weekly smoking: **OR: 2.62 (1.31–5.22)**	School grades, parent/sibling/friends smoke, deviant behavior index, low school grades, alcohol use
Galanti et al. (2008)	BROMS cohort includes adolescents who live in Stockholm region of Sweden 5th grade to 9th grade	Cohort/2938 total Mean age: 11.6 yrs current cigarettes or ST user = reported use at least once a month	1998; at least 1 yr F/U	ST starters: OR: 1.95 (0.96–3.80) Cigarettes starters: OR: 1.42 (0.98–2.10) Starts with both types tobacco: **OR: 2.54 (1.63–3.91)**	Age, gender, age at tobacco initiation
Timberlake et al. (2009)	National Longitudinal Study of Adolescent Health (Add Health) Middle to high school aged students	Cohort/498 ST users; 10,322 non-users Ever-daily smoking = smoked 1 or more cigarettes on 30 + consecutive days; ST user = used ST in past month	1995; 1 yr F/U and 6 yr F/U	With no matching, OR range: **1.3–2.0, $p < 0.001$** Matched on propensity score, OR range: 1.03–1.14, $p > 0.05$	Propensity score included: age, gender, race, US region, smoking exposures in friends/relatives, behavioral risk factors, delinquency and depression scores

Bolded text represents risk estimates which were statistically significant at an $\alpha = 0.05$ level.
Abbreviations: ST: smokeless tobacco, F/U = follow-up, and OR: odds ratio.
[a] Same study as Forrester et al. (2007).

represent an appropriate reference group (teens who have never tried tobacco at all or those who have tried it at least once?), and (4) how to appropriately model for the other psychosocial, behavioral, and cultural variables that affect a person's decision to smoke (access to tobacco, parental smoking habits, high-risk taker, cultural bans on smoking and tobacco marketing efforts, etc.) A recent paper illustrates how different results can be generated from the same cohort. When a propensity score which accounts for multiple predictors (i.e., demographic, smoking-related exposures, and behavioral risk factors) for becoming a daily smoker is included

Table 10
Additional studies examining smokeless tobacco use and smoking initiation[a].

Reference	Population studied	Study design/sample size	Time period	Odds ratio (OR) of smoking initiation in current ST users (95% C.I.)	Adjusted covariates in model
Haddock et al. (2001)	U.S. Air Force recruits mean age 19.8 yrs	Cohort/403 ST users 7264 never users	1 yr. after basic training	**OR: 2.33 (1.84–2.94)**	Age, ethnicity, income, education, marital status
Tomar (2003)	Teenage Attitude and Practices Survey – U.S. national survey 12–18 yr. olds	Cohort/60 regular ST users 373 occasional ST 2232 never users	1989–1993	Regular ST use: **OR: 3.45 (1.84–6.47)** ST use, not regularly: **OR: 2.01 (1.38–2.93)**	Age, ethnicity
O'Connor et al. (2003)	Teenage Attitude and Practices Survey – U.S. national survey 12–18 yr. olds	Cohort/58 regular ST users378 occasional ST 378 occasional ST 2245 never users	1989–1993	Regular ST use: OR: 1.68 (0.83–3.41) Not regular ST use OR: 1.41 (0.96–2.05)	Age, race, school performance, smoking in household, depression, fighting, riding motorcycles
Haukkala et al. (2006)	School smoking prevention program in Helsinki, Finland 7th–9th graders[b]	Cohort/910 boys	3 yr F/U	Tried ST once: **OR: 2.68 (1.55–4.62)** Weekly smoker:[c] **OR: 10.03 (4.70–21.4)**	School, sports activity, school achievement
Furberg et al. (2005)	Swedish Twin Registry (SALT) Ages 42–64 yrs.	Cross-sectional/case = smoker Ever smoker with snus use: 262 Ever smoker w/o snus use: 5466	NS; Swedish twins born before 1959	Regular ST use: OR: 0.2 (0.2–0.3) Now and then ST use: OR: 0.5 (0.3–0.7)	Age

Bolded text represents risk estimates which were statistically significant at an $\alpha = 0.05$ level.
Abbreviations: NS: not specified, ST: smokeless tobacco; F/U: follow-up.
[a] Each of these studies had different definitions for what represented a 'regular' smoker or ST user making comparisons across studies difficult.
[b] ST products are banned in Finland.
[c] Risk of using ST if had smoked cigarettes first. Comparatively lower risk of becoming regular smoker if use ST first prior to smoking cigarettes.

in the analysis, ST use is no longer associated with risk of becoming a ever daily smoker (Timberlake et al., 2009). A similar observation was found between two different analyses of a U.S. survey of teenagers on tobacco use (Tomar, 2003); (O'Connor et al., 2003). Clearly, different modeling leads to different answers to the question of whether ST use increases smoking initiation in youth.

The literature supporting the 'gateway' hypothesis has been inconsistent and, for the most part, not robust enough to permit causal inferences. Recent studies which have attempted to address the temporality issues between ST use and smoking initiation either by adjusting for additional environmental/behavioral variables associated with smoking initiation (Furberg et al., 2005), by accounting for additional covariates in a propensity score (Timberlake et al., 2009), or by using complex modeling of tobacco use in adolescence (Galanti et al., 2008). None of these studies have found that ST use is strongly associated with the probability of becoming a daily smoker. Results from the Swedish adult studies have suggested that snus use is associated with a reduced risk of becoming or continuing to be a regular cigarette smoker (Furberg et al., 2005; Ramstrom and Foulds, 2006), while the US studies have focused primarily on whether teenage ST use may increase the risk of becoming a smoker in adolescence (Haddock et al., 2001; O'Connor et al., 2003; Tomar, 2003). Given that adolescents tend to experiment and engage in risky behaviors, it is hard to predict which ones will become regular cigarette smokers, and particularly difficult to parse out which of the many psychosocial, cultural and environmental factors will contribute not only to smoking initiation, but also to the development of a long-term cigarette smoking habit.

Of all the studies published, only one paper attempted to examine the complex relationship between initial tobacco use in early adolescence and its use after a 6-year long follow-up (Galanti et al., 2008). Rather than comparing ST users to non-tobacco users, the authors used a unique approach and compared the current tobacco use (at 6 years follow-up) by the type of tobacco product used at baseline. Interestingly, adolescents who had used both ST and cigarettes at baseline were 2.5 times more likely to be current smokers 6 years later than those who had used ST as their first tobacco product. This may suggest that an adolescent's psychosocial milieu might be as important as the specific tobacco product initially used.

At this time, the current literature suggests there may be an association between ST use and cigarette smoking, however the evidence has not been adequate to support a causal relationship between the two factors, given the complex nature of behavioral factors which youth exhibit with initiation of any tobacco use. More sophisticated models of the complex environmental and behavioral relationship between adolescent behavior and tobacco initiation and dependence will prove to be necessary to accurately determine the true nature of this relationship.

7. Conclusion

More research is clearly needed to understand if ST products will fit into a smoking harm reduction model. Many of the currently available studies share methodologic challenges that complicate their interpretation. More standardized research, including studies that adjust for known potential confounding factors, use appropriate controls, accurately and consistently classify ST use and disease outcome, is needed to accurately evaluate the true risk of tobacco-related diseases from the use of various ST products. Cohort studies with long follow-ups have an additional challenge: the consumption of smoking tobacco and alcohol, strong confounders of several tobacco-related diseases, may change over a 10–20 year follow-up period, presenting the potential for misclassification of exposure if such changes were to occur disproportionately in ST users. Reassessment of lifestyle and dietary factors may be necessary periodically through the follow-up to accurately document an individual's exposure over time. Better planned study designs which implement the biological confirmation of tobacco exposures and include clear case definitions would also improve the quality of studies trying to assess the true health risk from ST use.

While the current epidemiologic literature does not provide much evidence for significant health risks with ST use, particularly when compared to the health risks associated with cigarette smoking, whether ST products would be an effective smoking cessation tool (either as a replacement product or for tapering off all tobacco use) has not been well investigated. More sophisticated and complex studies are needed to examine and monitor the public health consequences if ST products are adopted as a harm reduction tool. It is important to recognize the risks of promoting any tobacco product, even if only as a smoking cessation aid, particularly if it there is a potential to increase adolescent use of ST in those who would otherwise not use tobacco products at all. Politics aside, if the majority of inveterate smokers were to switch to ST use, and the majority of them quit smoking, it seems certain that public health overall would benefit.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.yrtph.2009.09.017.

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