LIPPINCOTT
WILLIAMS & WILKINS

EUROPEAN
SOCIETY OF
CARDIOLOGY

Original Scientific Paper

Smokeless tobacco and coronary heart disease: a 12-year follow-up study

Sven-Erik Johansson[a], Kristina Sundquist[a], Jan Qvist[b] and Jan Sundquist[a]

[a]Center for Family Medicine, Karolinska Institute, Huddinge, Sweden and [b]Statistics Sweden, Stockholm, Sweden.

Received 10 February 2005 **Accepted** 13 April 2005

Background **Cigarette smoking has declined whereas the use of smokeless tobacco is increasing. There is an ongoing debate as to whether smokeless tobacco is a recommendable strategy to help smokers to quit. However, very few studies have examined the association between smokeless tobacco, namely snuff, and coronary heart disease, which implies that it has not been possible to provide scientific results for public health policies and clinical guidelines concerning the use of smokeless tobacco.**

Design **A follow-up study.**

Methods **A random sample of 3120 healthy men aged 30–74 years was interviewed in 1988 and 1989 and followed up to the year 2000 with regard to coronary heart disease. Cox regression was used to estimate the relative risk of coronary heart disease in six categories of smoking and snuffing habits, after adjustment for established risk factors for coronary heart disease.**

Results **Smokers, former smokers, and those who combined smoking and snuffing had significantly higher hazard ratios than never-smokers. The very highest hazard ratio was found among individuals combining smoking and snuffing. Daily snuffers had a hazard ratio of 1.62 (95% confidence interval 0.70–3.03) after adjustment for age.**

Conclusions **Even though the association between daily snuffing and coronary heart disease was non-significant, the hazard ratio was markedly increased. Therefore, smokers should not use smokeless tobacco in order to quit smoking, especially as safer alternatives are available. Further studies in different settings are required to provide scientific results for public health policies and clinical guidelines.** ***Eur J Cardiovasc Prev Rehabil*** **12:387–392 © 2005 The European Society of Cardiology**

European Journal of Cardiovascular Prevention and Rehabilitation 2005, 12:387–392

Keywords: coronary heart disease, follow-up studies, smokeless tobacco, snuff

Sponsorship: This work was supported by the National Institutes of Health (grant no. R01-H271084-1), the Knut and Alice Wallenberg Foundation, the Stockholm County Council, the Karolinska Institute, the Swedish Research Council (grant no. K2004-21X-11651-09A to Dr Jan Sundquist and grant no. K2005-27X-15428-01A to Dr Kristina Sundquist), and the Swedish Council for Working Life and Social Research (grant no. 2001-2373).

Introduction

Cigarette smoking has declined during the past three decades in most industrialized countries. Paradoxically, the use of smokeless tobacco has greatly increased in some industrialized countries, such as Sweden. The characteristics of smokeless tobacco products vary by country and region and their use can be described as endemic. However, users of smokeless tobacco are found most frequently in the United States and Sweden, where the market is dominated by moist snuff, taken orally.

In the USA, a national survey conducted in 1999 showed that 9% of male college students were current users of smokeless tobacco [1]. In Sweden, 19% of Swedish men aged 30–74 years were current users of snuff in 1996–1997 compared with 14% in 1988–1989.

Although the evidence for the adverse cardiovascular effects of cigarette smoking is overwhelming, very little is known about the association between smokeless tobacco and cardiovascular disease (CVD). Only four studies have

Correspondence and requests for reprints to Kristina Sundquist, Center for Family Medicine, Karolinska Institute, Alfred Nobels allé 12, SE-141 83 Huddinge, Sweden.
Tel: +46 8 524 887 08; fax: +46 8 524 887 06;
e-mail: kristina.sundquist@klinvet.ki.se

examined the relationship between smokeless tobacco, namely snuff, and the risk of myocardial infarction [2–5]. All four studies were conducted in Sweden and the results are inconclusive. The first study was a classic case–control study in which patients who had had a myocardial infarction were interviewed about their tobacco habits [2], and compared with individuals who had not suffered a myocardial infarction. The second case–control study, conducted by the same research group, included a total of 687 patients with myocardial infarction [3]. The third study was also a case–control study that was performed in two Swedish counties in 1992–1994 [5].

None of these studies was able to detect an increased risk of myocardial infarction among snuff users. In contrast, a Swedish cohort study from the beginning of the 1970s included a total of 135 000 construction workers. The workers were asked detailed questions about their tobacco habits and were followed up for 12 years regarding death from CVD. Compared with non-tobacco users, the snuff users exhibited a significantly increased relative risk of 1.4 for dying of CVD [4]. However, the composition of snuff has changed substantially over the years. For example, smokeless tobacco bought on the Swedish market is now practically free from nitrosamines [6,7]. The change in the composition of snuff could imply that the results from the construction worker study are no longer valid.

The few and inconclusive findings from previous studies imply that it has not been possible to provide scientific results for evidence-based public health policies and clinical guidelines concerning the use of snuff. This is important, especially as there is an ongoing debate as to whether snuff is a safer alternative to smoking among inveterate smokers. A recent review article stated that it is advisable to counsel all current users of smokeless tobacco to quit, although the evidence for the adverse cardiovascular effects of smokeless tobacco use is not conclusive [8]. Another review article found that there may be an association between smokeless tobacco and CVD, and that further rigorous studies are required [9]. Asplund [10] stated that as a result of the many unresolved issues, it is wise to be cautious when discussing the health hazards of snuff use and their impact on health policy because there is still much room for improved knowledge.

In the present study, we had the opportunity to address some of the limitations in previous research because we used a random sample of adult men representative of all socio-economic groups and adjusted the results for several established CVD risk factors. In addition, smoking and snuffing habits were categorized into six groups in order to eliminate the confounding caused by the admixture of former smokers among snuff users, which has not been addressed sufficiently in the few studies conducted so far.

The first aim of this study was to analyse the association between six categories of smoking and snuffing habits and the incidence rate of coronary heart disease (CHD). The second aim was to examine whether these hypothesized associations remain after adjusting for socio-economic status and the four CHD risk factors: physical inactivity, obesity, diabetes and high blood pressure.

Methods

This follow-up study was based on data from the Swedish Annual Level-of-Living Survey (SALLS), a large national survey conducted annually by the Swedish Government-owned statistics bureau, Statistics Sweden. SALLS consists of a simple random sample of the entire adult, non-institutionalized Swedish population. The participants are interviewed face-to-face by trained interviewers about their living conditions, including highly complete information on socio-economic, lifestyle and health indicators. Our sample included all men aged 30–74 years who were surveyed in 1988 and 1989. In order to identify CHD events, these data were linked to the Swedish National Hospital Discharge Register and the Cause-of-Death Register. Participants were followed until the first event CHD, death, or the end of the study on 31 December 2000 (a mean follow-up time of 11.2 years). In total, there were 277 CHD events.

Exclusion criteria

In order to minimize residual confounding caused by unknown disease processes, participants with poor self-rated health were excluded. For this purpose, we used the following question in SALLS: 'How would you describe your general health?' There were three response alternatives: 'good', 'bad', or 'anywhere between good and bad'. Those who answered that their general health was 'bad' or 'anywhere between good and bad', were excluded, altogether 907 participants. Participants with a CHD hospitalization 2 years before the start of the study and participants who were interviewed with the aid of relatives were also excluded. Participants who lacked information about weight or height were excluded from the study in order to avoid self-report bias. The final sample included 3120 men.

Outcome variable

The time to first hospitalization for fatal or non-fatal CHD event was classified according to the International Classification of Diseases, ICD 9 (410–414) and ICD 10 (I20–I25).

Explanatory variables

Age was used as a continuous variable, centered around its mean. Socio-economic status was categorized into four

groups according to occupational status: (i) manual workers; (ii) lower-level employees; (iii) middle-level employees and professionals; (iv) self-employed and farmers. Smoking and snuffing habits were divided into six groups: (i) never-smokers; (ii) former smokers; (iii) daily smokers; (iv) daily snuffers and never-smokers; (v) daily snuffers who were former smokers; and (vi) daily snuffers and smokers. Leisure-time physical activity was initially categorized into five levels in the analysis. Because hazard ratios (HR) in levels iii–v were almost identical (data not shown), levels iii–v were collapsed so that, in the final analysis, three levels of physical activity remained: (i) practically no exercise at all; (ii) occasionally; and (iii) at least once a week. The five initial levels were based on five response alternatives: (i) I get practically no exercise at all; (ii) I exercise occasionally (e.g. one-hour walks, skiing a couple of times every year, swimming, picking mushrooms); (iii) I exercise about once a week (e.g. fast walks, skiing, swimming, jogging, and cycling); (iv) I exercise about twice a week (e.g. fast walks, skiing, swimming, jogging, and cycling); (v) I exercise vigorously at least twice a week (e.g. skiing, swimming, running, cycling for quite a while, ball games). As already mentioned above, levels iii–v were collapsed.

Body mass index (BMI) was calculated as weight (kg)/height (m^2), according to the World Health Organization recommendations, and comprised three categories: (i) BMI less than 25.0 (normal weight and underweight); (ii) BMI of 25.0 to less than 30 (overweight); and (iii) BMI of 30 or over (obesity).

Diabetes and hypertension assessments were based on the following questions: 'Do you suffer from any long-standing disease?', 'If so, what kind of disease?', 'Do you suffer from diabetes/hypertension?', and 'Do you take medicine for your diabetes/hypertension?' If diabetes or hypertension were reported as a disease or medicine was taken for diabetes or hypertension, the respondent was judged to have diabetes or hypertension. All others were judged not to have diabetes or hypertension.

Statistical analysis

The SAS software package was used in the statistical analyses [11]. Age-adjusted CHD incidence rates (per 10 000 individuals per year) were calculated between 1988–1989 and 31 December 2000 by standardization [12]. A Cox regression model [13] was used to estimate the HR of CHD in the different models. The results are shown as HR with 95% confidence intervals (CI). Risk time was calculated from the date of the interview to the first admission for CHD or death from CHD, whichever occurred first. Individuals who died from other causes during the follow-up were censored at the time of death, and all others were censored on 31 December 2000. The proportional hazards assumption was tested by including an interaction between each of the explanatory variables and time. All variables met the assumption.

Ethics

This study was approved by the Ethics Committee of the Karolinska Institute, Stockholm, Sweden, in accordance with the principles of the Declaration of Helsinki.

Results

Table 1 shows the distribution of the explanatory variables by smoking and snuffing habits. The lowest mean age was observed among daily snuffers. The highest percentage of 'no physical activity' was found among daily smokers and those combining snuffing and smoking. The lowest percentage of overweight and obesity was found among daily smokers. However, the highest percentage of overweight and obesity was found among those combining snuffing and smoking.

Table 2 shows the age-adjusted incidence rate of CHD. The higher the BMI, the higher the incidence rates of CHD irrespective of smoking and snuffing habits. As expected, individuals with diabetes or hypertension had higher incidence rates of CHD than those without diabetes or hypertension. Unexpectedly, among never-smokers the highest incidence rate was found among those who were physically active on a regular basis.

Table 1 Distribution (%) of the explanatory variables by smoking and snuffing habits

Variable	Level	Smoking and snuffing habits					
		Never-smoker	Former smoker	Daily smoker	Daily snuffer and never-smoker	Daily snuffer and former smoker	Daily snuffer and smoker
n		1036	854	793	107	245	85
Age (years)	Mean	47.0	51.0	47.1	41.4	44.2	43.5
Physical activity	1 (none)	9.9	6.9	15.9	13.1	10.2	19.6
	2 (occasionally)	30.9	34.6	41.0	33.1	32.4	42.9
	3 (at least once a week)	59.2	58.5	43.1	53.8	57.4	37.5
BMI	1 (normal weight, underweight)	58.2	51.3	63.3	58.5	52.8	42.5
	2 (overweight)	37.0	43.1	30.1	34.0	41.3	48.5
	3 (obesity)	4.8	5.6	6.6	7.5	5.9	9.0
Diabetes	Yes	1.2	1.6	2.1	1.9	3.4	0
Hypertension	Yes	6.9	7.7	4.5	4.2	6.2	4.4

BMI, body mass index.

Table 2 Age-adjusted incidence rates (per 10 000 person-years) of coronary heart disease by smoking and snuffing habits

Variable	Level	Smoking and snuffing habits					
		Never-smoker	Former smoker	Daily smoker	Daily snuffer and never-smoker	Daily snuffer and former smoker	Daily snuffer and smoker
n		1036	854	793	107	245	85
Physical activity	1 (none)	52	137	127	–	72	54
	2 (occasionally)	44	104	109	48	55	96
	3 (at least once a week)	57	89	97	63	57	116
BMI	1 (normal weight, underweight)	36	75	89	43	27	72
	2 (overweight)	69	117	130	47	98	111
	3 (obesity)	133	159	173	118	66	120
Diabetes	Yes	80	375	116	–	387	–
	No	53	93	107	50	48	95
Hypertension	Yes	180	333	337	207	426	856
	No	44	82	97	43	38	76

BMI, Body mass index.

Table 3 Hazard ratios with 95% confidence intervals for coronary heart disease in the Cox regression models

Variable	Level	Model 1	Model 2	Model 3
		HR (95% CI)	HR (95% CI)	HR (95% CI)
Smoking and snuffing habits	1 (never-smoker)	1 (Reference)	1 (Reference)	1 (Reference)
	2 (former smoker)	1.45 (1.05–1.99)	1.46 (1.06–2.02)	1.47 (1.07–2.03)
	3 (daily smoker)	2.19 (1.59–3.03)	2.27 (1.64–3.14)	2.30 (1.66–3.19)
	4 (daily snuffer and never smoker)	1.62 (0.70–3.75)	1.52 (0.66–3.53)	1.41 (0.61–3.28)
	5 (daily snuffer and former smoker)	1.38 (0.80–2.39)	1.31 (0.76–2.38)	1.18 (0.67–2.06)
	6 (daily snuffer and smoker)	2.66 (1.32–5.36)	2.53 (1.25–5.10)	2.73 (1.35–5.53)
Physical activity	1 (none)		1 (Reference)	1 (Reference)
	2 (occasionally)		0.76 (0.51–1.11)	0.76 (0.52–1.12)
	3 (at least once a week)		0.75 (0.52–1.09)	0.77 (0.53–1.12)
BMI	1 (normal, underweight)		1 (Reference)	1 (Reference)
	2 (overweight)		1.38 (1.07–1.77)	1.29 (1.00–1.66)
	3 (obesity)		2.07 (1.35–3.16)	1.84 (1.20–2.83)
Diabetes	1 (Yes)			1.43 (0.77–2.65)
	2 (No)			1 (Reference)
Hypertension	1 (Yes)			2.04 (1.49–2.78)
	2 (No)			1 (Reference)

BMI, Body mass index; CI, confidence interval; HR, hazard ratio. Model 1 is adjusted for age. Models 2 and 3 show the HR after stepwise inclusion of the other explanatory variables.

Table 3 shows three proportional hazard models after stepwise inclusion of the explanatory variables: Model 1 is adjusted for age, model 2 is also adjusted for physical activity and BMI, and model 3 is also adjusted for diabetes and hypertension. Smokers, former smokers, and those combining smoking and snuffing had significantly higher HR than never-smokers. The very highest HR was found among individuals combining smoking and snuffing (HR 2.73; 95% CI 1.35–5.53). Daily snuffers had an HR of 1.62 (95% CI 0.70–3.03) in model 1, which decreased to 1.41 (95% CI 0.61–3.28) in model 3. The lowest HR was observed among daily snuffers who were former smokers. Socio-economic status was included in an additional analysis. However, the risk estimates remained essentially the same as in model 3 (data not shown).

Discussion

The main finding of this study was that the association between daily snuffing and CHD was non-significant. However, the HR was markedly increased (HR 1.62; 95% CI 0.70–3.75). The lack of statistical significance could be explained by insufficient statistical power because of a small sample size, which was also one of the main limitations in two of the previous studies on the association between smokeless tobacco and CVD [2,3]. In addition, the lack of statistical significance does not necessarily mean that there is no association between exposure and disease. According to Rothman [14], it is a fallacy to infer a lack of association from a single *P* value, that is in this case a 95% CI that includes the Figure 1.

Limitations and strengths

The main limitation of this study was the relatively small sample size of 107 daily snuffers. However, we believe that our study is of interest because there is still much room for improved knowledge on this topic. Further studies in a new context are needed, especially as the same research group conducted two of the four studies performed so far. Another limitation was the non-response rate of 22.1%. However, we examined this non-response bias and found that approximately 70% of the non-respondents were refusals, and 30% involved non-respondents who could not be located or were too ill

to participate. Then we included both non-respondents and respondents in a proportional hazard model that adjusted for sex, age, marital status and residential region with all-cause mortality as the outcome. The 70% who refused had the same mortality risk as the respondents, and the remaining 30% had a significantly higher mortality risk. Moreover, residual confounding is likely to occur because individual socio-economic status cannot be measured precisely and completely [15]. Another limitation was that we only had a baseline measurement, which means that individuals might have changed their habits during the follow-up, resulting in too low a risk estimate of snuffing. In addition, we had data on former smokers but not on former snuffers. This implies that former snuffers were categorized as never-smokers. Finally, the prevalence of hypertension or diabetes was based on self-reported data, and therefore it is likely that the true prevalence was underestimated. However, we have no reason to believe that this self-report bias differed between the different categories.

The limitations of this study are balanced, however, by its strengths. First, this is the first follow-up study of a random sample of adult men representative of all socio-economic groups. The construction worker study [4] did not include individuals from different socioeconomic groups, and therefore the general applicability of the results was limited. Second, we adjusted the results for several established CVD risk factors. Third, smoking and snuffing habits were categorized into six groups in order to eliminate the confounding caused by a mixture of former smokers among snuff users, which has not been addressed sufficiently in previous research. In addition, we analysed the association between concomitant snuffing and smoking and CHD and found a nearly threefold increased risk of CHD among individuals combining smoking and snuffing, compared with never-smokers. Fourth, the prospective nature of our study design allowed us to calculate incidence rates of CHD, rather than prevalence rates. Furthermore, the validity of the diagnosis for myocardial infarction was high in an evaluation for 1987 and 1995 by the Swedish National Board of Health and Welfare [16]. Fifth, the reliability of the survey questions, collected in face-to-face interviews by well-trained interviewers, was high. Re-interviewing a sample of the participants (test–retest method) yielded kappa coefficients of 0.71–0.78 for socio-economic status and 0.96–0.99 for cigarette smoking [17]. Finally, there was little or no loss to follow-up as the Swedish registration system provides a personal identification number for each individual, which was used to follow each individual during the entire study period.

Although the possible association between smokeless tobacco and the endpoint CVD/CHD is unclear, several previous studies have found an association between smokeless tobacco and intermediate endpoints; namely established CVD factors. Acute cardiovascular effects include an increased heart rate and blood pressure [18]. Smokeless tobacco is also associated with a long-term adverse effect on blood pressure levels [19], cholesterol levels [20] and insulin levels [21]. These findings are alarming because the use of smokeless tobacco is increasing. For example, in a recent study from northern Sweden, 27% of middle-aged men used snuff [22]. Many of the daily snuffers are former smokers. Among Swedish middle-aged men, approximately half of the snuff users are former smokers [3], and we know that several of our colleagues recommend snuff to inveterate smokers. However, whether or not snuff is a useful strategy to help smokers to quit is a matter of debate. Our results indicate that this is not recommendable because it is possible that such a strategy could lead to a concomitant use of both snuff and cigarettes, which was the most hazardous category of tobacco habits in this study. In addition, smokeless tobacco may be associated with cancer of the mouth, urinary bladder, and the upper respiratory tract [23,24]. There are also indications that snuff could act as a gateway to cigarette smoking, especially among young men [25,26].

Conclusion

Even though the association between daily snuffing and CHD was non-significant, the heart rate was markedly increased. Therefore, smokers should not use snuff in order to quit smoking, especially as safer alternatives are available [27]. In order to provide scientific results for public health policies and clinical guidelines concerning the use of snuff, further studies in different settings are required.

Acknowledgements

The authors wish to thank Sanna Sundquist at the University of California, San Diego, California, USA, for her technical assistance.

References

1 Rigotti NA, Lee JE, Wechsler H. US college students' use of tobacco products: results of a national survey. *JAMA* 2000; **284**:699–705.
2 Huhtasaari F, Asplund K, Lundberg V, Stegmayr B, Wester PO. Tobacco and myocardial infarction: is snuff less dangerous than cigarettes? *BMJ* 1992; **305**:1252–1256.
3 Huhtasaari F, Lundberg V, Eliasson M, Janlert U, Asplund K. Smokeless tobacco as a possible risk factor for myocardial infarction: a population-based study in middle-aged men. *J Am Coll Cardiol* 1999; **34**:1784–1790.
4 Bolinder G, Alfredsson L, Englund A, de Faire U. Smokeless tobacco use and increased cardiovascular mortality among swedish construction workers. *Am J Public Health* 1994; **84**:399–404.
5 Hergens MP, Ahlbom A, Andersson T, Pershagen G. Swedish moist snuff and myocardial infarction among men. *Epidemiology* 2005; **16**:12–16.
6 Nilsson R. A qualitative and quantitative risk assessment of snuff dipping. *Regul Toxicol Pharmacol* 1998; **28**:1–16.
7 Nordgren P, Ramstrom L. Moist snuff in Sweden – tradition and evolution. *Br J Addict* 1990; **85**:1107–1112.
8 Gupta R, Gurm H, Bartholomew JR. Smokeless tobacco and cardiovascular risk. *Arch Intern Med* 2004; **164**:1845–1849.

9 Critchley JA, Unal B. Is smokeless tobacco a risk factor for coronary heart disease? A systematic review of epidemiological studies. *Eur J Cardiovasc Prev Rehabil* 2004; **11**:101–112.

10 Asplund K. Smokeless tobacco and cardiovascular disease. *Prog Cardiovasc Dis* 2003; **45**:383–394.

11 SAS Institute Inc. *SAS/STAT user's guide*, version 6, 4th ed, vol. 1. Cary, NC: SAS Institute Inc.; 1989.

12 Breslow NE, Day NE. *Statistical methods in cancer research, vol. ii – the design and analysis of cohort studies*. Lyon: International Agency for Research on Cancer; 1987.

13 Kleinbaum DG. *Survival analysis*. New York: Springer; 1995.

14 Rothman KJ, editor. Random error and the role of statistics. In: *Epidemiology – an introduction*. New York: Oxford University Press; 2002. pp. 113–129.

15 Kaufman JS, Cooper RS, McGee DL. Socioeconomic status and health in blacks and whites: the problem of residual confounding and the resiliency of race. *Epidemiology* 1997; **8**:621–628.

16 The National Board of Health and Welfare. *Validity of the diagnoses from the Swedish in-care register 1987 and 1995* [in Swedish]. Stockholm: Epidemiologiskt Centrum, Socialstyrelsen; 2000.

17 Statistics Sweden. *Re-interviews in the survey of living conditions (ulf). Appendix no 12*. Stockholm: Statistics Sweden; 1989.

18 Westman EC. Does smokeless tobacco cause hypertension? *South Med J* 1995; **88**:716–720.

19 Bolinder G, de Faire U. Ambulatory 24-h blood pressure monitoring in healthy, middle-aged smokeless tobacco users, smokers, and nontobacco users. *Am J Hypertens* 1998; **11**:1153–1163.

20 Tucker LA. Use of smokeless tobacco, cigarette smoking, and hypercholesterolemia. *Am J Public Health* 1989; **79**:1048–1050.

21 Eliasson M, Lundblad D, Hagg E. Cardiovascular risk factors in young snuff-users and cigarette smokers. *J Intern Med* 1991; **230**:17–22.

22 Rodu B, Stegmayr B, Nasic S, Asplund K. Impact of smokeless tobacco use on smoking in northern Sweden. *J Intern Med* 2002; **252**:398–404.

23 Rodu B, Cole P. Smokeless tobacco use and cancer of the upper respiratory tract. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; **93**:511–515.

24 Thomas S, Kearsley J. Betel quid and oral cancer: a review. *Eur J Cancer B Oral Oncol* 1993; **29B**:251–255.

25 Haddock CK, Weg MV, DeBon M, Klesges RC, Talcott GW, Lando H, *et al.* Evidence that smokeless tobacco use is a gateway for smoking initiation in young adult males. *Prev Med* 2001; **32**:262–267.

26 Galanti MR, Wickholm S, Gilljam H. Between harm and dangers. Oral snuff use, cigarette smoking and problem behaviours in a survey of Swedish male adolescents. *Eur J Public Health* 2001; **11**:340–345.

27 Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease. Nicotine replacement therapy for patients with coronary artery disease. *Arch Intern Med* 1994; **154**:989–995.