Int. J. Cancer: **114,** 992–995 (2005)

Smokeless tobacco use and risk of cancer of the pancreas and other organs

Paolo Boffetta[1,2]*, Bjarte Aagnes[2], Elisabete Weiderpass[1–4] and Aage Andersen[2]

[1]*International Agency for Research on Cancer, Lyon, France*
[2]*Norwegian Cancer Registry, Oslo, Norway*
[3]*Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden*
[4]*Finnish Cancer Registry, Helsinki, Finland*

Limited data are available on the carcinogenicity of smokeless tobacco products in organs other than the mouth. Snus is a smokeless tobacco product widely used in Norway. We studied 10,136 Norwegian men enrolled since 1966 in a prospective cohort study, 31.7% of whom were exposed to snus. The relative risk of pancreatic cancer for snus use was 1.67 (95% confidence interval [CI] = 1.12, 2.50); that of oral and pharyngeal cancer was 1.10 (95% CI = 0.50, 2.41), that of esophageal cancer was 1.40 (95% CI = 0.61, 3.24), and that of stomach cancer was 1.11 (95% CI = 0.83, 1.48). The relative risks of cancers of the lung (either all histological types or adenocarcinoma), urinary bladder and kidney were not increased among snus users. The increase in the relative risk of pancreatic cancer was similar in former and current snus users and was restricted to current tobacco smokers. Our study suggests that smokeless tobacco products may be carcinogenic on the pancreas. Tobacco-specific *N*-nitrosamines are plausible candidates for the carcinogenicity of smokeless tobacco products in the pancreas.

Key words: smokeless tobacco; pancreatic cancer; lung cancer; epidemiology; N-nitrosamines

Use of smokeless tobacco products is common in many regions of the world and is increasing in the United States and Northern Europe.[1,2] Tobacco chewing is a major risk factor for oral and pharyngeal cancer in Asia,[3,4] but a similar increase in risk has not been shown consistently among users of smokeless tobacco products in the United States or Europe.[5,6] Smokeless tobacco might cause other cancers, in particular those linked to tobacco smoking, but limited data are available.[2,4,5] In particular, an increased risk of pancreatic cancer has been suggested in studies based on few exposed cases.[7,8] A detailed assessment of the risk of pancreatic and other cancers entailed by smokeless tobacco use is needed before conclusions on the overall health risks of this group of products can be reached.

Although tobacco snuff and chewing entail very little exposure to polycylic aromatic compounds, exposure to *N*-nitrosamines is substantial.[9–11] Tobacco-specific nitrosamines are experimental carcinogens and are heavily suspected to cause cancer, in particular adenocarcinoma, in humans.[12]

Snus is a smokeless tobacco product widely used in Norway; it is usually placed behind the upper or lower lip. The average sale of snus in the mid-1960s was around 200 g/year/Norwegian adult. It decreased to 80 g/year in the 1980s, and has remained stable since.[13]

We conducted a detailed analysis of cancer incidence in a cohort of Norwegian men to estimate the risk of cancer of the pancreas and other organs from use of smokeless tobacco products.

Material and methods

The cohort under study consists of 2 groups of subjects: a systematic sample of the general adult population of Norway identified from the 1960 census, and relatives of Norwegian migrants to the United States.[7,14] Study subjects completed questionnaires on lifestyle habits in 1964 and 1967. The participation rate varied by study and location, but was above 75%. The questionnaire collected information on use of smokeless tobacco, as well as information on dietary habits, tobacco smoking, alcohol drinking and anthropometric parameters.

A total of 12,431 men who were alive on 1 January 1966 were included in the study. Information on snus use was missing for 2,295 of them (18.5%); the remaining 10,136 cohort members were classified as regular current users (N = 1,999, 19.7%), regular former users (N = 1,216, 12.0%), or never or occasional users (N = 6,921, 68.3%). The age distribution of subjects with information on snus was very close to that of subjects with missing information (χ^2 test with 7 *d.f.*, p = 1.0). Tobacco smoking was classified as never/current/former smoking of cigarettes/cigars/pipe. Amount of current smoking was classified in 3 categories for cigarettes (1–9, 10–14 and 15+ cigarettes/day) and in 2 categories for cigars and pipe (1–4 and 5+ g/day). Information on amount of smoking was not available for former smokers. No reassessment of snus use or tobacco smoking was carried out during the follow-up.

Cohort members were followed until date of diagnosis of cancer, date of emigration, date of death or 31 December 2001, whichever occurred earliest. The follow-up was carried out *via* linkage with nationwide residence, mortality and cancer incidence registries, using unique personal identification numbers. Fifteen cohort members were lost to follow-up (0.15%). For the purpose of this analysis, we considered the incidence of cancers of the oral cavity and pharynx (ICD7, 141–148), esophagus (ICD7, 150), stomach (ICD7, 151), pancreas (ICD7, 157), lung (ICD7, 162), kidney (ICD7, 180) and urinary bladder (ICD7, 181). In addition, cases of esophageal and lung adenocarcinoma were considered separately. Cases diagnosed on the basis of a clinical examination or death certificate only were excluded. The analysis of pancreatic cancer risk was based on 220,007 person-years of observation. Censoring the follow-up at the time of first diagnosis resulted in a slightly different number of person-years in the analysis of each cancer.

Cox proportionate hazard regression models, including attained age as time variable, were fitted to the data to estimate relative risks (RR) and 95% confidence intervals (CI) of each cancer. The regression models used in the main analysis included terms for never, former and current smoking of cigarettes, cigars and pipe. In sensitivity analyses, alternative approaches were used to control for the potential confounding effect of tobacco smoking. Additional models included a term for body mass index (BMI).

Results

The number of incident cases was 34 for oral and pharyngeal cancer, 27 for esophageal cancer (4 cases of adenocarcinoma), 217

Grant sponsor: U.S. National Cancer Institute with the Cancer Registry of Norway; Contract number: PH 43-64-499.
***Correspondence to:** Gene-Environment Epidemiology Group, International Agency for Research on Cancer (IARC), 150 cours Albert-Thomas, 69008 Lyon, France. Fax: +33-4-72738320.
E-mail: boffetta@iarc.fr
Received 13 August 2004; Accepted after revision 1 October 2004
DOI 10.1002/ijc.20811
Published online 11 January 2005 in Wiley InterScience (www.interscience.wiley.com).

for stomach cancer, 105 for pancreatic cancer, 343 for lung cancer (of whom 50 cases of adenocarcinoma), 88 for kidney cancer and 238 for bladder cancer.

There was an increased RR of pancreatic cancer among ever users of snus, and the RR of oral and pharyngeal, esophageal and stomach cancer showed a modest, non-significant increase. There was no increase in the RR of lung cancer (all histological types and adenocarcinoma) and of other cancers included in the analysis (Table I). No difference in the RR of pancreatic cancer was evident between former and current use. The number of cases of esophageal adenocarcinoma was too small to justify a separate analysis. Table II shows the RRs of pancreatic and lung cancers for ever snus use, estimated separately according to smoking habit. The number of cases among never and former smokers was small, and there was no evidence of an increased RR of pancreatic cancer in these 2 groups.

Different approaches to control for the potential confounding effect of tobacco smoking resulted in risk estimates that were similar to those reported in Table I. For example, the RR of pancreatic cancer for ever snus use, derived from a model including a continuous term for amount of tobacco smoking, was 1.66 (95% CI = 1.06, 2.62). Further adjustment for body mass index did not affect the RR (not shown in detail).

Discussion

Our study provides evidence for a carcinogenic effect of smokeless tobacco products on the pancreas, thus confirming the findings of an early report from this cohort, which was based on only 14 cases among snus users.[7] None of the other available studies, all from the United States, included more than 10 cases of pancreatic cancer among users of smokeless tobacco products.[8,15–17] Despite the low statistical power, an association was suggested in two of these studies.[8,17]

Arguments in favor of a causal effect of snus on pancreatic cancer in our study are the strong statistical significance, the likely exclusion of selection and information bias because of the prospective nature of the investigation, and the lack of an apparent confounding effect of tobacco smoking and BMI. Residual confounding by tobacco smoking or by other potential risk factors for pancreatic cancer, such as heavy alcohol intake and a diet poor in fruits and vegetables, cannot be completely ruled out. The lack of a corresponding increase in risk of lung cancer detracts from the hypothesis of residual confounding by tobacco smoking.

Lack of information on snus use and tobacco smoking after enrollment in the cohort is a matter of concern, in particular given the long-term follow-up of the study. Given the decrease in the prevalence and use of snus among Norwegian men during the study period, it is likely that change in snus use status mainly affected current users who quit rather than non-users and formed users who took up the habit. Because misclassification is unlikely to have occurred differentially with respect to outcome (*i.e.*, future cases of pancreatic cancer having changed their habits during the follow-up differently from other cohort members), it should have resulted in an underestimate of the difference of carcinogenic effect of snus between current and former snus users. Additional limitations of our study are the lack of information on amount and duration of snus use, which preempted dose-response analyses, and the small number of cases of pancreatic cancer among never and former smokers.

N-nitroso compounds, specifically *N*-nitrosamines, are plausible candidates for the carcinogenicity of smokeless tobacco products in the pancreas. Tobacco-specific nitrosamines have been identified in the pancreatic juice of smokers and, to a lesser extent, of non-smokers.[18] Experimental studies have shown the ability of tobacco-specific nitrosamines to produce pancreatic cancer in exposed rats,[12] and, in one experiment, oral administration of NNK (one of the main tobacco-specific nitrosamines) was more effective in causing pancreatic cancer than other routes of exposure.[19] Furthermore, a high proportion of G to A transitions in K-ras mutations detected in nitrosamine-induced animal pancreatic cancers represents further evidence for a central role of tobacco-specific nitrosamines and other *N*-nitrosamines in pancreatic carcinogenesis, although results on mutations in human cancers are not consistent.[12,20]

The lack of an increased risk of lung cancer among smokeless tobacco users confirms previous reports.[21–23] The relatively large size of the cohort confers a power of 80% to detect as significant a relative risk of 1.28 or greater. The analysis of lung adenocarcinoma was limited by the small number of cases, however, and our study had 80% power to detect as significant a relative risk of 1.85 or greater. We therefore cannot exclude some carcinogenic effect of smokeless tobacco on lung adenocarcinoma.

A weak, non-significant association was detected between use of snus and cancer of the oral cavity. The statistical power of our study for oral cancer was similar to that for lung adenocarcinoma (80% power to detect as significant a relative risk of 1.8–1.9). Chewing of tobacco products is an important cause of oral and pharyngeal cancer in several developing regions of the world, including in particular India,[3,9] other South Asian countries such as Pakistan, Bangladesh and Myanmar,[24–26] Central Asia,[27] and Sudan.[28,29] Studies conducted in the United States provided evidence for a carcinogenic effect of smokeless tobacco products on the oral cavity,[30–33] although these findings were not confirmed by other investigations conducted in the United States[34,35] or in Sweden.[36,37] The inconsistencies of results from previous studies can

TABLE II – RR OF PANCREATIC CANCER AND LUNG CANCER FOR EVER USE OF SMOKELESS TOBACCO (SNUS), ESTIMATED SEPARATELY ACCORDING TO SMOKING STATUS

Smoking	Pancreatic cancer			Lung cancer		
	Cases	RR[1]	95% CI	Cases	RR[1]	95% CI
Never smokers	3	0.85	0.24–3.07	3	0.96	0.26–3.56
Former smokers	14	1.37	0.59–3.17	7	0.64	0.24–1.68
Current smokers	28	1.86	1.13–3.05	62	0.68	0.51–0.90

[1]RR, relative risk adjusted for age and, among current smokers, for amount of tobacco smoking. Reference category: never users.

TABLE I – RR OF SELECTED CANCERS FOR USE OF SMOKELESS TOBACCO (SNUS)

	NU Cases	Ever users (PY = 61,335)			Former users (PY = 23,452)			Current users (PY = 37,883)		
		Cases	RR[3]	95% CI	Cases	RR[3]	95% CI	Cases	RR[3]	95% CI
Oral/pharyngeal cancer	25	9	1.10	0.50–2.41	3	1.04	0.31–3.50	6	1.13	0.45–2.83
Esophageal cancer	18	9	1.40	0.61–3.24	5	1.90	0.69–5.27	4	1.06	0.35–3.23
Stomach cancer	143	74	1.11	0.83–1.48	32	1.29	0.87–1.91	42	1.00	0.71–1.42
Pancreatic cancer	60	45	1.67	1.12–2.50	18	1.80	1.04–3.09	27	1.60	1.00–2.55
Lung cancer (all types)	271	72	0.80	0.61–1.05	28	0.80	0.54–1.19	44	0.80	0.58–1.11
Lung adenocarcinoma	39	11	0.83	0.42–1.65	4	0.86	0.30–2.43	7	0.81	0.36–1.85
Kidney cancer	66	22	0.72	0.44–1.18	13	1.17	0.63–2.16	9	0.47	0.23–0.94
Bladder cancer	169	69	0.83	0.62–1.11	30	0.98	0.66–1.47	40	0.72	0.52–1.06

[1]NU, never users (reference category, 158,672 person years).–[2]PY, person-years of observation (analysis of pancreatic cancer risk).–[3]RR, relative risk adjusted for age and smoking of cigarettes, cigars and pipe.

be explained by methodological aspects such as adequacy of control for tobacco smoking and statistical power; in any case, our results are consistent with previous evidence in supporting the conclusion that it is unlikely that the use of smokeless tobacco products in Europe and United States entails a substantial increase in the risk of oral and pharyngeal cancer. The reasons for the difference in carcinogenic risk entailed by smokeless tobacco products used in Europe, as compared to those used in developing countries, are not fully understood, but they might be related to tobacco species, fermentation and ageing.[38]

No effect of snus use on esophageal[36,39,40] and stomach cancer[41] was detected in previous studies, and our results might be attributed to chance. Previous studies of cancers of the bladder[42,43] and kidney[44,45] do not suggest an association with use of smokeless tobacco products, which is in agreement with our findings.

There is controversy on whether the use of smokeless tobacco products that are common in Northern Europe should be encouraged as an alternative to tobacco smoking, due to the apparent lack of a strong carcinogenic effect on organs such as the lung and the oral cavity.[3,46] Although the risk of cancer of the lung and some other organs in this population was lower among snus users than among non-users, the decrease was of small magnitude and not statistically significant, and there was no clear evidence of a beneficial effect among non-smokers. Our study does not offer arguments in favor of the use of smokeless tobacco products to reduce the burden of tobacco-related cancer incidence or mortality. Furthermore, it provides evidence of a carcinogenic effect on the pancreas, which should be taken into account in the assessment of the health effects of this group of products.

References

1. Everett SA, Husten CG, Warren CW, Crossett L, Sharp D. Trends in tobacco use among high school students in the United States, 1991–1995. J Sch Health 1998;68:1137–40.
2. Vainio H, Weiderpass E. Smokeless tobacco: harm reduction or nicotine overload? Eur J Cancer Prev 2003;12:89–92.
3. Gupta PC, Ray CS. Smokeless tobacco and health in India and South Asia. Respirology 2003;8:419–31.
4. Critchley JA, Unal B. Health effects associated with smokeless tobacco: a systematic review. Thorax 2003;58:435–43.
5. Winn DM. Epidemiology of cancer and other systemic effects associated with the use of smokeless tobacco. Adv Dent Res 1997;11:313–21.
6. Foulds J, Ramstrom L, Burke M, Fagerström K. Effect of smokeless tobacco (snus) on smoking and public health in Sweden. Tobacco Control 2003;12:349–59.
7. Heuch I, Kvale G, Jacobsen BK, Bjelke E. Use of alcohol, tobacco and coffee, and risk of pancreatic cancer. Br J Cancer 1983;48:637–43.
8. Alguacil J, Silverman DT. Smokeless and other non cigarette tobacco use and pancreatic cancer: a case-control study based on direct interviews. Cancer Epidemiol Biomarkers Prev 2004;13:55–8.
9. IARC. Tobacco habits other than smoking. In: IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans, vol. 37. Tobacco habits other than smoking; betel-quid and areca-nut chewing; and some related nitrosamines. Lyon: IARC, 1985. 37–140.
10. Hoffmann D, Djordjevic MV, Fan J, Zang E, Glynn T, Connolly GN. Five leading U.S. commercial brands of moist snuff in 1994: assessment of carcinogenic N-nitrosamines. J Natl Cancer Inst 1995;87:1862–9.
11. Nilsson R. A qualitative and quantitative risk assessment of snuff dipping. Regul Toxicol Pharmacol 1998;28:1–16.
12. Hecht SS. Biochemistry, biology, and carcinogenicity of tobacco-specific N-nitrosamines. Chem Res Toxicol 1998;11:559–603.
13. Lund KE. Samfuunsskapte endringer i tobakksbruk i Norge i det 20. Århundre. Dr Polit, Thesis. Oslo: University of Oslo, 1996.
14. Magnus K, Hougen A, Andersen A, Pedersen E. A study of disease in migrants and their siblings: development of sibling rosters. J Chronic Dis 1970;23:405–10.
15. Williams RR, Horm JW. Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the Third National Cancer Survey. J Natl Cancer Inst 1977;58:525–47.
16. Farrow DC, Davis S. Risk of pancreatic cancer in relation to medical history and the use of tobacco, alcohol and coffee. Int J Cancer 1990;45:816–20.
17. Muscat JE, Stellman SD, Hoffmann D, Wynder EL. Smoking and pancreatic cancer in men and women. Cancer Epidemiol Biomarkers Prev 1997;6:15–9.
18. Prokopczyk B, Hoffmann D, Bologna M, Cunningham AJ, Trushin N, Akerkar S, Boyiri T, Amin S, Desai D, Colosimo S, Pittman B, Leder G, et al. Identification of tobacco-derived compounds in human pancreatic juice. Chem Res Toxicol 2002;15:677–85.
19. Rivenson A, Hoffmann D, Prokopczyk B, Amin S, Hecht SS. Induction of lung and exocrine pancreas tumors in F344 rats by tobacco-specific and areca-derived N-nitrosamines. Cancer Res 1988;48:6912–7.
20. Li D. Molecular epidemiology of pancreatic cancer. Cancer J 2001;7:259–65.
21. Dikshit RP, Kanhere S. Tobacco habits and risk of lung, oropharyngeal and oral cavity cancer: a population-based case-control study in Bhopal, India. Int J Epidemiol 2000;29:609–14.
22. Accortt NA, Waterbor JW, Beall C, Howard G. Chronic disease mortality in a cohort of smokeless tobacco users. Am J Epidemiol 2002;156:730–7.
23. Gajalakshmi V, Hung RJ, Mathew A, Varghese C, Brennan P, Boffetta P. Tobacco smoking and chewing, alcohol drinking and lung cancer risk among men in Southern India. Int J Cancer 2003;107:441–7.
24. Merchant A, Husain SS, Hosain M, Fikree FF, Pitiphat W, Siddiqui AR, Hayder SJ, Haider SM, Ikram M, Chuang SK, Saeed SA. Paan without tobacco: an independent risk factor for oral cancer. Int J Cancer 2000;86:128–31.
25. Ahmed F, Islam KM. Site predilection of oral cancer and its correlation with chew and smoking habit—a study of 103 cases. Bangladesh Med Res Counc Bull 1990;16:17–25.
26. Sein K, Maung KK, Aung TH. An epidemiologic study of 70 oral cancer cases at the Institute of Dental Medicine, Yangon, Myanmar, 1985-1988. Odontostomatol Trop 1992;15:5–8.
27. Zaridze DG, Blettner M, Trapeznikov NN, Kuvshinov JP, Matiakin EG, Poljakov BP, Poddubni BK, Parshikova SM, Rottenberg VI, Chamrakulov FS. Survey of a population with a high incidence of oral and oesophageal cancer. Int J Cancer 1985;36:153–8.
28. Elbeshir EI, Abeen HA, Idris AM, Abbas K. Snuff dipping and oral cancer in Sudan: a retrospective study. Br J Oral Maxillofac Surg 1989;27:243–8.
29. Idris AM, Ahmed HM, Malik MO. Toombak dipping and cancer of the oral cavity in the Sudan case-control study. Int J Cancer 1995;63:477–80.
30. Winn DM, Blot WJ, Shy CM, Pickle LW, Toledo A, Fraumeni JF Jr. Snuff dipping and oral cancer among women in the southern United States. N Engl J Med 1981;304:745–9.
31. Stockwell HG, Lyman GH. Impact of smoking and smokeless tobacco on the risk of cancer of the head and neck. Head Neck Surg 1986;9:104–10.
32. Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, Bernstein L, Schoenberg JB, Stemhagen A, Fraumeni JF Jr. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res 1988;48:3282–7.
33. Spitz MR, Fueger JJ, Goepfert H, Hong WK, Newell GR. Squamous cell carcinoma of the upper aerodigestive tract: a case comparison analysis. Cancer 1988;61:203–8.
34. Sterling TD, Rosenbaum WL, Weinkam JJ. Analysis of the relationship between smokeless tobacco and cancer based on data from the National Mortality Followback Survey. J Clin Epidemiol 1992;45:223–31.
35. Mashberg A, Boffetta P, Winkelman R, Garfinkel L. Tobacco smoking, alcohol drinking, and cancer of the oral cavity and oropharynx among U.S. veterans. Cancer 1993;72:1369–75.
36. Lewin F, Norell SE, Johansson H, Gustavsson P, Wennerberg J, Biorklund A, Rutqvist LE. Smoking tobacco, oral snuff, and alcohol in the etiology of squamous cell carcinoma of the head and neck. Cancer 1998;82:1367–75.
37. Schildt EB, Eriksson M, Hardell L, Magnuson A. Oral snuff, smoking habits and alcohol consumption in relation to oral cancer in a Swedish case-control study. Int J Cancer 1998;77:341–6.
38. Idris AM, Ibrahim SO, Vasstrand EN, Johannessen AC, Lillehaug JR, Magnusson B, Wallstrom M, Hirsch JM, Nilsen R. The Swedish snus

and the Sudanese Toombak: are they different? Oral Oncol 1998;34: 558–66.
39. Pottern LM, Morris LE, Blot WJ, Ziegler RG, Fraumeni JF Jr. Esophageal cancer among Black men in Washington, D.C. I. Alcohol, tobacco, and other risk factors. J Natl Cancer Inst 1981; 67:777–83.
40. Lagergren J, Bergström R, Lindgren A, Nyrén O. The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesphagus and gastric cardia. Int J Cancer 2000;85:340–6.
41. Hansson LE, Baron J, Nyrén O, Bergström R, Wolk A, Adami HO. Tobacco, alcohol and the risk of gastric cancer: a population-based case-control study in Sweden. Int J Cancer 1994;57:26–31.
42. Advisory Committee to the Surgeon General. The health consequences of using smokeless tobacco. NIH Publ. No. 86-2874. Bethesda, MD: National Institutes of Health, 1986.
43. Slattery ML, Schumacher MC, West DW, Robison LM. Smoking and bladder cancer: the modifying effect of cigarettes on other factors. Cancer 1988;61:402–8.
44. Goodman MT, Morgenstern H, Wynder EL. A case-control study of factors affecting the development of renal cell cancer. Am J Epidemiol 1986;124:926–41.
45. Muscat JE, Hoffmann D, Wynder EL. The epidemiology of renal cell carcinoma: a second look. Cancer 1995;75:2552–7.
46. Fagerström KO, Schildt E-B. Should the European Union lift the ban on snus? Evidence from the Swedish experience. Addiction 2003;98: 1191–5.