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Use of Oral Moist Snuff and Inflammatory Bowel Disease

PER-GUNNAR PERSSON,* ** GÖRAN HELLERS[†] AND ANDERS AHLBOM* **

Persson P-G (Division of Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Box 210, S-171 77 Stockholm, Sweden), Hellers G and Ahlbom A. Use of oral moist snuff and inflammatory bowel disease. *International Journal of Epidemiology* 1993; 22: 1101-1103.

We examined the association between oral moist snuff use and inflammatory bowel disease in a case-control study based on the population in Stockholm County. The relative risk (RR) associated with ever use of moist snuff was 2.1 (95% CI : 1.0-4.6) for Crohn's disease, and 2.2 (95% CI : 1.1-4.4) for ulcerative colitis. Cigarette smoking indicated a synergistic relation with moist snuff: the RR estimate of Crohn's disease was 3.7 (95% CI : 1.1-13.1) and of ulcerative colitis 3.3 (95% CI : 1.0-10.9) for snuff dippers who were also current cigarette smokers, but only 0.9 and 1.1 respectively for snuff dippers who had never smoked.

Oral moist snuff is a smokeless tobacco product used by about 30% of Swedish men in the age group 16-35 years. The proportion of users among young men has markedly increased during the 1980s.¹ Although epidemiological findings on health effects associated with snuff are relatively sparse,² Health Ministers of the European Community recently decided that sales of snuff will be prohibited in the 12 member countries.³

Cigarette smoking has been shown to increase the risk of Crohn's disease and decrease the risk of ulcerative colitis.⁴ In a recent case-control study we found similar results but the associations were weak among men.⁵ The purpose of the present investigation was to evaluate the relationship of inflammatory bowel disease (IBD) to oral moist snuff use and to examine the role of cigarette smoking as a possible confounder or synergistic factor.

MATERIAL AND METHODS

A case-control study of IBD was carried out in Stockholm, Sweden. Details of the design and collection of data for this study were given in a previous paper.⁵ In short, the study base consisted of residents in Stockholm County who were aged 15-79 years between 1980 and 1984 and had listed phone numbers. The cases were selected from a central register of all

hospital admissions in Stockholm County. Medical records for all potential cases were examined to confirm the diagnosis. Strict diagnostic criteria were applied to define Crohn's disease⁶ and ulcerative colitis.⁷ We identified 236 cases of Crohn's disease and 247 cases of ulcerative colitis. Those cases whose medical records could not be reviewed within 4 years of diagnosis were excluded ($n = 52$ cases of Crohn's disease and $n = 66$ cases of ulcerative colitis), resulting in 184 cases of Crohn's disease and 181 of ulcerative colitis. As controls, a random sample, stratified by age (5-year age groups) and gender, of 390 subjects was selected via a register of the inhabitants of Stockholm County. Information on oral moist snuff use, cigarette smoking, and other lifestyle factors were collected by a postal questionnaire and a supplementary telephone interview. (The results on smoking,⁵ diet,⁸ and some other potential risk indicators⁹ have already been presented.) Completed questionnaires were obtained for 152 (83%) cases with Crohn's disease, 145 (80%) with ulcerative colitis, and 305 (78%) controls. The present investigation was restricted to men and included 63 cases of Crohn's disease, 82 cases of ulcerative colitis, and 147 controls.

Questionnaires were sent to the subjects up to 4 years after the date of diagnosis (1984-1987). The subjects were provided with retrospective questions covering a period of time 5 years previously. For 94% of the cases, this corresponded to a period of time of more than 1 year before the diagnosis. Cigarette smokers were classified as never, former or current according to their consumption 5 years previously. Subjects who smoked only a pipe or cigars were excluded from the

* Division of Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Box 210, S-171 77 Stockholm, Sweden.

** Epidemiologic Unit, Stockholm County Council, Sweden.

[†] Department of Surgery, Huddinge University Hospital, Stockholm, Sweden.

analyses ($n = 3$ of Crohn's disease and $n = 2$ of controls). Information on oral moist snuff use was obtained by two simple questions: 'Have you used oral moist snuff regularly?' and 'Do you still use oral moist snuff?' The respondents were classified into never users and ever users.

The two groups of cases were compared with the entire group of controls. Multiple logistic regression analysis with indicator variables for different strata was used to obtain unconditional maximum likelihood estimates of the relative risk (RR). Estimated standard deviations of the regression coefficient estimates were used to obtain 95% confidence limits.¹⁰

RESULTS

Ever users of oral moist snuff had a twofold increase in RR of both Crohn's disease (Table 1) and ulcerative colitis (Table 2). The estimated RR persisted after taking cigarette smoking into account. A synergistic effect of cigarette smoking and snuff use was suggested: use of moist snuff alone did not indicate any clear increased risk. However, compared to those who had neither used snuff nor cigarettes, ever users of snuff who were current cigarette smokers had more than a threefold increased risk of both diseases.

TABLE 1 Relative risk (RR) estimates^a and 95% confidence intervals (CI) of Crohn's disease for users of oral moist snuff and cigarettes.

Cigarette smoking:	Moist snuff use:		All ^b
	Never No. of cases/controls RR (95% CI)	Ever No. of cases/controls RR (95% CI)	
Never	22/61 1.0	5/11 0.9 (0.3-3.1)	27/72 1.0
Former	6/17 1.1 (0.4-3.3)	3/5 1.8 (0.3-8.9)	9/22 1.2 (0.5-3.1)
Current	16/46 1.1 (0.5-2.3)	8/5 3.7 (1.1-13.1)	24/51 1.3 (0.7-2.7)
All ^c			
	44/124	16/21	
adjusted	1.0	2.1 (1.0-4.6)	
unadjusted	1.0	2.1 (1.0-4.6)	

^a Multiple logistic regression estimated RR adjusted for age in three age groups (≤ 29 , 30-49, 50+).

^b Multiple logistic regression estimated RR adjusted for age and oral moist snuff.

^c In addition to age, multiple logistic regression estimated RR are adjusted or unadjusted for cigarette smoking.

TABLE 2 Relative risk (RR) estimates^a and 95% confidence intervals (CI) of ulcerative colitis for users of oral moist snuff and cigarettes.

Cigarette smoking:	Moist snuff use:		All ^b
	Never No. of cases/controls RR (95% CI)	Ever No. of cases/controls RR (95% CI)	
Never	31/61 1.0	9/11 1.1 (0.4-3.1)	40/72 1.0
Former	10/17 1.3 (0.5-3.4)	6/5 2.3 (0.6-8.9)	16/22 1.5 (0.7-3.4)
Current	17/46 0.7 (0.3-1.5)	9/5 3.3 (1.0-10.9)	26/51 0.9 (0.5-1.8)
All ^c			
	58/124	24/21	
adjusted	1.0	2.2 (1.1-4.4)	
unadjusted	1.0	2.3 (1.1-4.5)	

^a Multiple logistic regression estimated RR adjusted for age in three age groups (≤ 29 , 30-49, 50+).

^b Multiple logistic regression estimated RR adjusted for age and oral moist snuff.

^c In addition to age, multiple logistic regression estimated RR are adjusted or unadjusted for cigarette smoking.

DISCUSSION

The levels of plasma nicotine experienced daily by snuff users are as high as those of smokers.² Moist snuff also contains a vast number of carcinogenic compounds.¹¹ Epidemiological observations of biological effects associated with snuff use include cancers of the oral cavity and pharynx,¹¹⁻¹³ nasal cavity and sinuses,¹⁴ pancreas,¹⁵ and urinary bladder¹⁶ as well as hypertension, increased heart rate, and increased levels of certain blood lipids.² A recent report on myocardial infarction and tobacco use,¹⁷ however, did not present any increased RR associated with snuff dipping.

Although the exposed numbers were small in this study, we found a strikingly increased RR of both Crohn's disease and ulcerative colitis among ever users of oral moist snuff. Cigarette smoking was a suspected confounder of this association, but this proved false.

A synergistic effect between cigarettes and snuff was indicated: The RR were not increased for snuff use alone, but a marked potentiation was found among snuff dippers who were also cigarette smokers.

These results are striking particularly when considering that several studies have found that cigarette smoking is protective against ulcerative colitis.⁴ The explanation of the synergistic effect between snuff and cigarettes observed in this study is not known. One

possibility is that the use of snuff is suspected to be a basic cause of disease after being smoked. The synergistic effect between snuff and cigarettes is a possibility.

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- ¹ Nordgren P, et al. The evolution of the National Council for Medical Research from a research council to a research organization. *Scand J Public Health* 1990; 19: 622-623.
- ² The National Council for Medical Research. *Report from the National Council for Medical Research*. June 1990.
- ³ Council Director. *Report from the National Council for Medical Research*. June 1990.
- ⁴ Calkins B M, et al. *Report from the National Council for Medical Research*. June 1990.

possibility is that the use of moist snuff differs from the use of cigarettes with respect to exposure to suspected causes: smoke compounds from cigarettes are basically inhaled whereas compounds in oral moist snuff are absorbed in the mouth or in the intestines after being swallowed. Some compounds in cigarette smoke may act protectively, whereas some others may cause disease and the latter compounds may also exist in oral moist snuff thereby causing the observed synergistic effect in those who are exposed to both cigarettes and snuff.

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REFERENCES

- ¹ Nordgren P, Ramström L. Moist snuff in Sweden—tradition and evolution. *Br J Addict* 1990; **85**: 1107-12.
- ² The National Board of Health and Welfare. *Snus—en Hälsorisk. Rapport från ett expertmöte.* (Snuff—A Health Risk. Report from an Expert Meeting) (Swedish). Stockholm, 1988.
- ³ Council Directive 92/41/EEC of 15 May 1992 amending directive 89/622/EEC on the approximation of laws, regulations and administrative provisions of the Member States concerning the labelling of tobacco products. *Off J Eur Commun* L158, 11 June 1992, pp. 30-33.
- ⁴ Calkins B M. A meta-analysis of the role of smoking in inflammatory bowel disease. *Dig Dis Sci* 1989; **34**: 1841-54.
- ⁵ Persson P-G, Ahlbom A, Hellers G. Inflammatory bowel disease and tobacco smoke—a case-control study. *Gut* 1990; **31**: 1377-81.
- ⁶ Lennard-Jones J E. Definition and diagnosis of Crohn's disease. In: *Skandia International Symposia: Regional Enteritis*. Stockholm: Nordiska Bokhandels förlag, 1971.
- ⁷ Nordenvall B, Broström O, Berglund M *et al.* Incidence of ulcerative colitis in Stockholm county 1955-79. *Scand J Gastroenterol* 1985; **20**: 783-90.
- ⁸ Persson P-G, Ahlbom A, Hellers G. Diet and inflammatory bowel disease: a case-control study. *Epidemiology* 1992; **3**: 47-52.
- ⁹ Persson P-G, Leijonmarck C-E, Bernell O, Hellers G, Ahlbom A. Risk indicators for inflammatory bowel disease. *Int J Epidemiol* 1993; **22**: 268-72.
- ¹⁰ Epilog. *Epidemiology and Clinical Trials Statistics Package*. Pasadena, CA: Epicenter Software, 1988.
- ¹¹ IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans. *Tobacco habits other than smoking; Betel-quid and Areca-nut chewing; and some related nitrosamines*. IARC scientific publication no. 37. Lyon: IARC, 1985.
- ¹² Winn D M, Blot W J, Shy C M, Pickle L W, Toledo A, Fraumeni J F. Snuff dipping and oral cancer among women in the Southern United States. *N Engl J Med* 1981; **304**: 745-49.
- ¹³ Zahm S H, Heineman E F, Vaught J B. Soft tissue sarcoma and tobacco use: data from a prospective cohort study of United States veterans. *Cancer Causes Control* 1992; **3**: 371-76.
- ¹⁴ Brinton L A, Blot W J, Becker J A *et al.* A case-control study of cancers of the nasal cavity and paranasal sinuses. *Am J Epidemiol* 1984; **119**: 896-906.
- ¹⁵ Heuch I, Kvåle G, Jacobsen B K, Bjelke E. Use of alcohol, tobacco and coffee, and risk of pancreatic cancer. *Br J Cancer* 1983; **48**: 637-43.
- ¹⁶ Kabat G C, Dieck G S, Wynder E L. Bladder cancer in nonsmokers. *Cancer* 1986; **57**: 362-67.
- ¹⁷ Huhtasaari F, Asplund K, Lundberg V, Stegmayr B, Wester P O. Tobacco and myocardial infarction: is snuff less dangerous than cigarettes? *Br Med J* 1992; **305**: 1252-56.

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