

Oral Cancer in Swedish Snuff Dippers

JAN M. HIRSCH¹, MATS WALLSTRÖM², ANDERS-PETTER CARLSSON³ and LARS SAND¹

¹*Department of Surgical Sciences, Oral and Maxillofacial Surgery,
Medical Faculty, Uppsala University, Uppsala, Sweden;*

²*Department of Oral and Maxillofacial Surgery, Institute of Odontology,
Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden;*

³*Department of Oral and Maxillofacial Surgery, Västerås Hospital, Sweden*

Abstract. *Over recent decades there has been debate over whether or not Swedish snuff is carcinogenic in humans. Animal studies and molecular biological and experimental studies have shown the carcinogenic potential of Swedish snuff, but this has not been proved in prospective randomized studies. We present a case series of patients with oral squamous cell carcinomas diagnosed at the sites where the patients had used Swedish snuff for several years. Sixteen male patients were referred to and treated at Oral and Maxillofacial Surgery Departments and Ear, Nose and Throat clinics at seven different hospitals in Sweden. The mean age of the patients at the time of diagnosis was 72.9 years and the mean time of snuff use prior to cancer diagnosis was 42.9 years. This case series shows that Swedish snuff may not be a harmless alternative to smoking.*

According to the International Agency for Research on Cancer (IARC), the United States National Institutes of Health, and the US Surgeon General, the moist snuff used in Western Europe is carcinogenic in humans (1-3). In the US, snuff dippers were found to have a significantly greater risk for oral cancer than did smokers (4). Data from Sudan also reveal a number of cases of oral cancer in users of Sudanese toombak (5), a fermented tobacco produced and consumed in a way similar to Swedish snuff (6). Animal studies have demonstrated the carcinogenic potential of snuff (7, 8), and shown that Langerhans cells decrease in number while small salivary glands are irreversibly destroyed in snuff-induced lesions (9, 10). Molecular biological studies have shown an overexpression of p53 in snuff-induced lesions (11), and in

an experimental study, snuff was shown to reduce natural killer-cell activity in peripheral blood (12). However, data in another study showed low probability for a genotoxic mechanism in the carcinogenic toxicity of aqueous and methylene chloride extracts of Swedish snuff (13). Furthermore, two publications from Sweden challenged the cancer hypothesis and rejected conclusions that Swedish snuff is carcinogenic in humans (14, 15). Roosaar *et al.*, however, reported a statistically significant increase in the combined incidence of oral and pharyngeal cancer among daily users of snuff in Sweden (16). Overall mortality was also slightly increased, and their population-based prospective study provided evidence of snuff-related risks for oral and pharyngeal cancer. In this study we present data from 16 patients who developed oral squamous cell carcinoma (OSCC) at the exact anatomical location where the snuff quid was placed daily.

Materials and Methods

This study followed the guidelines of the Helsinki Declaration. Sixteen patients presenting with neoplastic oral lesions in the vestibular mucosa were referred for specialist evaluation at the Departments of Oral and Maxillofacial Surgery and Ear, Nose, and Throat clinics; incisional biopsies were obtained, and a diagnosis of OSCC was established in all 16 patients. We obtained the patients' medical records from the Uppsala University Hospital and from the seven other Swedish hospitals where the patients were initially seen, including photographs (Figures 1-3) showing the location and the clinical presentation of the primary tumours, smoking and snuff habits, as well as pathology reports.

Results

All 16 patients in this case series were male and all were diagnosed with OSCC (Table I). The mean age at the time of cancer diagnosis (N=16) was 72.9 years (range: 48-91 years) and the median age was 75 years. The mean duration of snuff use prior to cancer diagnosis (15 cases) was 42.9

Correspondence to: Jan-Michael Hirsch, Department of Surgical Sciences, Oral and Maxillofacial Surgery, Medical Faculty, Uppsala University, SE-751 85 Uppsala, Sweden. Tel: +46 186116450, Fax: +46 18559129, e-mail: jan.michael.hirsch@akademiska.se

Key Words: Oral squamous cell carcinoma, oral snuff, Sweden.

Table I. Clinical data of the 16 patients with oral cancer who used snuff.

Case no.	Age (years)	Location	Snuff use (years)	Smoking
1	75	Maxilla	61	No
2	91	Mandible	70	5 years prior to snuff use
3	72	Maxilla	42	No
4	75	Maxilla	71	No
5	50	Maxilla	8	10-15 years prior to snuff use
6	85	Maxilla	20	No
7	79	Mandible	45	Pipe-smoking 30 years ago
8	89	Maxilla	69	No
9	52	Maxilla	20	Concomitant to snuff for 30 years
10	67	Maxilla	18	15 years prior to snuff use
11	78	Mandible	n/a	No
12	81	Maxilla	66	No
13	74	Maxilla	40	No
14	84	Maxilla	30	No
15	67	Maxilla	49	4 years prior to snuff use
16	48	Maxilla	34	No

years (range: 8-71 years) and the median duration of snuff use prior to cancer diagnosis was 42 years. Ten of the patients had used oral snuff only and had no history of smoking. Five cases had a history of smoking but at the time of cancer diagnosis used snuff only. Three of the ex-smokers had ceased smoking more than 20 years earlier and the other two had stopped smoking 4 and 18 years prior to diagnosis. One patient used both snuff and smoking tobacco at the time of diagnosis. The mean age of starting snuff use was 30.4 years (median 30 years).

Discussion

Snuff contains carcinogenic tobacco-specific nitrosamines (TSNA) (17) and even though the amount of TSNA in Swedish snuff has been reduced (18), it probably might not be considered harmless. All the patients in our case series were diagnosed with OSCC, which was expected, since approximately 90% of all diagnosed oral carcinomas are OSCC (19). Generally, OSCC occurs more often in men (20) and this is considered to be an effect of men's heavier consumption of cigarettes and alcohol (21). The most common anatomical sites of intraoral OSCC are the floor of the mouth, the ventral or lateral tongue, and the soft palate complex (22). Tabah *et al.* found that in non-tobacco users, significantly more non-tobacco associated tumours were found in women whose mean age was significantly higher than that of tobacco users (23). In the patients presented here, the OSCC was developed in the buccal fold, where the snuff quid was placed for a long period of time, which is a fairly uncommon location for OSCC. All the patients were male, which is similar to the development of OSCCs in

smoking patients. The patients in this case series had been using snuff for a mean time of 43 years, which means that the carcinogenic content of the substances they used for much of that time, was most probably higher than in the products currently marketed today. The risk for snuff dippers in Sweden to develop oral cancer was pointed out as early as 1978 by Axéll *et al.*, who reported a five- to six-fold increased risk for snuff users to develop oral cancer (24), and also animal studies have indicated that snuff has carcinogenic potential (7, 8). In two studies noted in the IARC analysis, a borderline statistically significant increase was found for the risk of oral cancer in former snuff dippers (1). Roosaar *et al.* found a stronger association between oral cancer and Swedish snuff and concluded that the risk of snuff-induced oral cancer should not be dismissed lightly (16). In contrast, three studies from Sweden found no correlation between Swedish snuff use and head and neck cancer (14, 15, 25). However, further analysis of the statistical evaluation of data in the second of these studies revealed a nearly five fold increased risk of head and neck cancer in men with former snuff use but no previous history of smoking (15). Numerous recent studies from Scandinavia have shown that Swedish snuff may be used as a method for giving up smoking (26-28). Furthermore, cigarette smoking is considered more hazardous to general health than snuff use (29). Our case series is not a randomized clinical trial but an observational study based on our daily clinical practice. As demonstrated by our 16 cancer cases, oral cancer may develop in Swedish snuff dippers. Whether this is a pure coincidence or may be the effect of prolonged snuff use cannot be answered by a case series like this. However, it indicates that snuff should not be regarded as a harmless product, and we advice against



Figure 1. OSCC in the central part of the maxillary vestibulum in a 85-year-old man who used snuff for 20 years, without a history of smoking.



Figure 2. OSCC of the left maxillary alveolar mucosa and vestibulum in a 84-year-old man who used snuff for 30 years, without a history of smoking.

snuff use and against recommending snuff as a nicotine replacement therapy. It is especially unwise to recommend patients with diagnosed oral cancer to switch from smoking to using snuff, bearing in mind the constant exposure to carcinogens that snuff use involves. Second primaries are common phenomena in oral cancer (30) and additional exposure to carcinogens might very well enhance such events. Smokeless tobacco has also been shown to cause cancer of the pancreas in a Norwegian study (31) that was also confirmed by a Swedish study two years later (32). The Norwegian study also reported a modest, although not statistically significant, increase in oral, pharyngeal, oesophageal, and stomach cancer in users of smokeless tobacco.

Conclusion

In this study we present a case series of 16 patients who had used Swedish snuff for many years. All these patients developed OSCC at the exact anatomical location where the snuff quid was placed daily. These cases, plus the earlier consensus regarding snuff as being carcinogenic to humans in the way it is consumed in Western Europe, underline that Swedish snuff is not as harmless as argued by some, and in our opinion, the recommendation to use Swedish snuff in general or to use snuff as a nicotine replacement therapy is questionable.

Conflicts of Interest

There were no conflicts of interest for the Authors in this study. The study was supported by grants from Thuréus Foundation.



Figure 3. OSCC of the right maxillary alveolar mucosa and vestibulum in a 74-year-old man who used snuff for 40 years, without a history of smoking.

References

- 1 Smokeless Tobacco and Some Tobacco-specific N-Nitrosamines. IARC Monogr Eval Carcinog Risks Hum 89: 1-592, 2007.
- 2 National Institutes of Health consensus statement. Health implications of smokeless tobacco use. NIH Consensus Development Panel. Biomed Pharmacother 42: 93-98, 1988.
- 3 Cullen JW, Blot W, Henningfield J, Boyd G, Mecklenburg R and Massey MM: Health consequences of using smokeless tobacco: summary of the Advisory Committee's report to the Surgeon General. Public Health Rep 101: 355-73, 1986.
- 4 Winn DM: Tobacco chewing and snuff dipping: an association with human cancer. IARC Sci Publ pp. 837-849, 1984.

- 5 Elbeshir EI, Abeen HA, Idris AM and Abbas K: Snuff dipping and oral cancer in Sudan: a retrospective study. *Br J Oral Maxillofac Surg* 27: 243-248, 1989.
- 6 Idris AM, Ibrahim SO, Vasstrand EN, Johannessen AC, Lillehaug JR, Magnusson B, Wallstrom M, Hirsch JM and Nilsen R: The Swedish snus and the Sudanese toombak: are they different? *Oral Oncol* 34: 558-566, 1998.
- 7 Johansson SL, Hirsch JM, Larsson PA, Saidi J and Osterdahl BG: Snuff-induced carcinogenesis: effect of snuff in rats initiated with 4-nitroquinoline-N-oxide. *Cancer Res* 49: 3063-3069, 1989.
- 8 Johansson SL, Saidi J, Osterdahl BG and Smith RA: Promoting effect of snuff in rats initiated by 4-nitroquinoline-N-oxide or 7,12-dimethylbenz(a)anthracene. *Cancer Res* 51: 4388-4394, 1991.
- 9 Daniels TE, Chou L, Greenspan JS, Grady DG, Hauck WW, Greene JC and Ernster VL: Reduction of Langerhans cells in smokeless tobacco-associated oral mucosal lesions. *J Oral Pathol Med* 21: 100-104, 1992.
- 10 Hasseus B, Wallstrom M, Osterdahl BG, Hirsch JM and Jontell M: Immunotoxic effects of smokeless tobacco on the accessory cell function of rat oral epithelium. *Eur J Oral Sci* 105: 45-51, 1997.
- 11 Wedenberg C, Jonsson A and Hirsch JM: Assessment of p53 and Ki-67 expression in snuff-induced lesions. *Br J Oral Maxillofac Surg* 34: 409-413, 1996.
- 12 Johansson SL, Hirsch JM, Johnson DR: Effect of repeated oral administration of tobacco snuff on natural killer-cell activity in the rat. *Arch Oral Biol* 36: 473-476, 1991.
- 13 Jansson T, Romert L, Magnusson J and Jenssen D: Genotoxicity testing of extracts of a Swedish moist oral snuff. *Mutat Res* 261: 101-115, 1991.
- 14 Schildt EB, Eriksson M, Hardell L and Magnusson A: Oral snuff, smoking habits and alcohol consumption in relation to oral cancer in a Swedish casecontrol study. *Int J Cancer* 77: 341-346, 1998.
- 15 Lewin F, Norell SE, Johansson H, Gustavsson P, Wennerberg J, Biorklund A and Rutquist LE: Smoking tobacco, oral snuff, and alcohol in the etiology of squamous cell carcinoma of the head and neck: a population-based case-referent study in Sweden. *Cancer* 82: 1367-1375, 1998.
- 16 Roosaar A, Johansson AL, Sandborgh-Englund G, Axell T and Nyren O: Cancer and mortality among users and nonusers of snus. *Int J Cancer* 123: 168-173, 2008.
- 17 Hoffmann D and Djordjevic MV: Chemical composition and carcinogenicity of smokeless tobacco. *Adv Dent Res* 11: 322-329, 1997.
- 18 Osterdahl BG, Jansson C and Paccou A: Decreased levels of tobacco-specific N-nitrosamines in moist snuff on the Swedish market. *J Agric Food Chem* 52: 5085-5088, 2004.
- 19 Hogmo A, Kuylenstierna R, Lindholm J and Munck-Wikland E: Predictive value of malignancy grading systems, DNA content, p53, and angiogenesis for stage I tongue carcinomas. *J Clin Pathol* 52: 35-40, 1999.
- 20 Nylander K, Nilsson P, Mehle C and Roos G: p53 mutations, protein expression and cell proliferation in squamous cell carcinomas of the head and neck. *Br J Cancer* 71: 826-830, 1995.
- 21 Ide R, Mizoue T, Fujino Y, Hoshiyama Y, Sakata K, Tamakoshi A and Yoshimura T: Cigarette smoking, alcohol drinking, and oral and pharyngeal cancer mortality in Japan. *Oral diseases* 14: 314-319, 2008.
- 22 Mashberg A and Meyers H: Anatomical site and size of 222 early asymptomatic oral squamous cell carcinomas: a continuing prospective study of oral cancer. II. *Cancer* 37: 2149-2157, 1976.
- 23 Tabah RJ, Razack MS and Sako K: Early oral and oropharyngeal cancer in nontobacco users. *J Surg Oncol* 38: 22-25, 1988.
- 24 Axell T, Mornstad H and Sundstrom B: Snuff and cancer of the oral cavity-a retrospective study. *Lakartidningen* 75: 2224-2226, 1978. (in: Snusning och munhålecancer – en retrospektiv studie).
- 25 Rosenquist K, Wennerberg J, Schildt EB, Bladstrom A, Hansson BG and Andersson G: Use of Swedish moist snuff, smoking and alcohol consumption in the aetiology of oral and oropharyngeal squamous cell carcinoma. A population-based case-control study in southern Sweden. *Acta Oto-laryngologica* 125: 991-998, 2005.
- 26 Scheffels J, Lund KE and McNeill A: Contrasting snus and NRT as methods to quit smoking. An observational study. *Harm Reduct J* 9: 10, 2012.
- 27 Lund KE, McNeill A and Scheffels J: The use of snus for quitting smoking compared with medicinal products. *Nicotine Tob Res* 12: 817-822, 2010.
- 28 Ramstrom LM and Foulds J: Role of snus in initiation and cessation of tobacco smoking in Sweden. *Tob Control* 15: 210-214, 2006.
- 29 Daniel Roth H, Roth AB, and Liu X: Health risks of smoking compared to Swedish snus. *Inhal Toxicol* 17: 741-748, 2005.
- 30 Schwager K, Nebel A, Baier G and Hoppe F: Second primary carcinomas in the upper aerodigestive tract in different locations and age groups]. *Laryngorhinootologie* 79: 599-603, 2000. (in: Das Auftreten von Zweitkarzinomen im oberen Aerodigestivtrakt bei unterschiedlichen Tumorlokalisationen und Altersgruppen)
- 31 Boffetta P, Aagnes B, Weiderpass E and Andersen A: Smokeless tobacco use and risk of cancer of the pancreas and other organs. *Int J Cancer* 114: 992-995, 2005.
- 32 Luo J, Ye W, Zendejdel K, Adami J, Adami HO, Boffetta P and Nyren O: Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study. *Lancet* 369: 2015-2020, 2007.

Received March 14, 2012

Revised May 8, 2012

Accepted May 9, 2012