



ORAL SURGERY

ORAL MEDICINE

ORAL PATHOLOGY

REVIEW ARTICLE

Smokeless tobacco use and cancer of the upper respiratory tract

Brad Rodu, DDS,^a and Philip Cole, MD, DrPH,^b Birmingham, Ala
UNIVERSITY OF ALABAMA AT BIRMINGHAM

The most recent epidemiologic review of the cancer risks associated with smokeless tobacco use appeared in 1986, when 10 studies were available. This review describes 21 published studies, 20 of which are of the case-control type. We characterize each study according to the specific anatomic sites and according to the type of smokeless tobacco products for which it provides relative risks of cancer. The use of moist snuff and chewing tobacco imposes minimal risks for cancers of the oral cavity and other upper respiratory sites, with relative risks ranging from 0.6 to 1.7. The use of dry snuff imposes higher risks, ranging from 4 to 13, and the risks from smokeless tobacco, unspecified as to type, are intermediate, from 1.5 to 2.8. The strengths and limitations of the studies and implications for future research are discussed. (*Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002;93:511-5)

Smokeless tobacco (SLT) is well recognized as a cause of cancer of the oral cavity.¹ The most recent review of the epidemiology of this issue appeared in 1986 and described 10 studies.² The present review uses data from the 21 studies now available to estimate the relative risks (RRs) of each major type of oral and upper respiratory tract cancer associated with use of several types of SLT products.³⁻²³

We identified reports from the United States and western Europe that provided data potentially usable for estimating SLT-related RRs of cancer. We excluded studies from India and other eastern countries where processed tobacco is not comparable to that used in the West. Furthermore, in eastern countries, SLT is commonly used in combination with betel leaf, areca nut, and powdered slaked lime.¹

Twenty of the 21 available studies are of the case-control type. These provide RR estimates (or data that

allow RRs to be estimated) for cancers of several anatomic sites. The Mantel-Haenszel summary odds ratio²⁴ was used to estimate the pooled RR for cancer of each anatomic site related to each type of SLT. The 95% 2-sided confidence interval (CI) of each RR was estimated using the test-based interval estimator.²⁵ Two-tailed *P* values were obtained from the Mantel-Haenszel summary chi-square statistic.

SMOKELESS TOBACCO TYPES

Three types of SLT commonly are used in the oral cavity.²⁶ Chewing tobacco is air-cured tobacco that is shredded into flakes and treated with sweet flavoring solutions; moist snuff consists of fire- and air-cured dark tobaccos that are finely cut and fermented; dry snuff is a fire-cured tobacco that is pulverized into powder. Chewing tobacco and moist snuff are used primarily by men, whereas dry snuff is used by women, especially in the southern United States.^{27,28} All products are placed in contact with the oral mucosa, usually in the cheek or between the cheek and gum. We also present data for a fourth exposure category, SLT unspecified with respect to type, because the type of SLT used could not be determined in several studies.

CANCER OF THE ORAL CAVITY AND OTHER SITES

Oral cavity cancer (OCC) designates cancer of the tongue (International Classification of Diseases, Ninth Edition [ICD-9] code 141), gum (143), floor of the mouth (144), or of other or unspecified parts of the

Supported in part by an unrestricted gift from the United States Tobacco Company to the Tobacco Research Fund of the University of Alabama at Birmingham.

^aDepartment of Pathology, School of Medicine, University of Alabama at Birmingham.

^bDepartment of Epidemiology, School of Public Health, University of Alabama at Birmingham.

Neither author has any other financial involvement with the manufacturer of any product mentioned in this paper.

Received for publication Nov 14, 2001; returned for revision Jan 4, 2002; accepted for publication Jan 10, 2002.

© 2002 Mosby, Inc. All rights reserved.

1079-2104/2002/\$35.00 + 0 7/14/123497

doi:10.1067/moe.2002.123497

Table I. Characteristics of epidemiologic studies of smokeless tobacco and several forms of head and neck cancer

Reference number	First author	Year	Cases/controls	Tobacco type
3	Wynder	1957A	27/115	ST
4	Wynder	1957B	412/207	ST
5	Peacock	1960	45/146	ST
6	Vogler	1962	324/693	CT, DS
7	Vincent	1963	89/100	ST
8	Martinez	1969	170/510	ST
9	Williams	1977	*	ST
10	Wynder	1977	978/2560	CT, MS
11	Browne	1977	46/92	CT
12	Winn	1981	132/274	DS
13	Stockwell	1986	*	ST
14	Blot	1988	1114/1268	CT, DS
15	Spitz	1988	131/131	MS, CT
16	Maden	1992	131/136	ST
17	Zahm	1992	*	ST
18	Mashberg	1993	359/2280	ST, CT, MS
19	Kabat	1994	1560/2948	CT, MS, DS
20	Muscat	1996	1009/923	MS, CT
21	Schildt	1998	354/354	MS, CT
22	Schwartz	1998	165/302	ST
23	Lewin	1998	423/550	MS

ST, Smokeless tobacco—unspecified; CT, chewing tobacco; DS, dry snuff; MS, moist snuff.

*These studies provided relative risk estimates, but no case-control enumerations.

mouth (145). Code 145 includes the cheek, vestibule, palate, uvula, and retromolar region. Cancer of the lip (140) was excluded from all but 5 studies^{6,8,10,17,21} and cancer of the major salivary glands (142) from all but two studies.^{10,17}

Cancer of the pharynx includes cancer of the oropharynx (146) and hypopharynx (148) but excludes cancer of the nasopharynx (147). However, in 3 studies,^{8,10,17} data for cancer of the nasopharynx could not be separated from that for other pharynx sites. Some studies provided data specific for cancer of the larynx (161), whereas others did not separate it from cancer of the oral cavity and pharynx.

FINDINGS BY TYPE OF SLT

For each study reviewed, Table I lists the first author, year of publication, number of cases and controls, and the types of SLT for which data are provided. Eight studies appeared in the 1990s, twice as many as appeared in any other decade.

Eighteen case-control studies supplied data that were used in at least 1 of the summary RRs. The remaining 3 studies provided an RR estimate but no primary data; they are described separately. Summary RRs for the 4 categories of SLT and several forms of cancer are given in Table II.

Chewing tobacco

Eight studies contributed to summary RRs for use of chewing tobacco. For OCC, the summary RR of 0.6

(95% CI = 0.3-1.3) was derived from 2 studies. For cancer of the oral cavity/pharynx, the summary RR was 1.1 (0.8-1.6). The RR was 1.3 (0.9-1.8) for cancer of the larynx and 1.7 (1.2-2.4) for the combined disease entity oral cavity/pharynx/larynx. For all sites combined, the summary RR for chewing tobacco was 1.2 (1.0-1.4).

Moist snuff

Five studies specified RRs for various forms of cancer among moist-snuff users. The RRs ranged from 0.7 both for cancer of the pharynx (0.4-1.4) and for oral cavity/pharynx (0.4-1.2) to 1.2 (0.9-1.7) for cancer of the larynx. For all sites combined, the RR was 1.0 (0.8-1.2).

Dry snuff

Four studies provided RRs for cancer related to dry snuff use. Data from 3 yielded a summary RR of 4.0 (2.7-5.9) for cancer of the oral cavity and pharynx combined. The fourth study reported an RR of 13 (8.0-21) for cancer of the oral cavity, pharynx and larynx combined. The overall RR for all sites combined was 5.9 (1.7-20).

One OCC subsite, gingiva and buccal mucosa (not included in Table II), is of special interest because it is the location where SLT products are held. One study¹² reported a RR of 26 (7.6-92) for cancer of the gingival and buccal mucosa among dry-snuff users.

SLT—unspecified

Seven studies contributed to the summary RRs for use of SLT unspecified as to type. OCC was evaluated in 4

Table II. Relative risk of several forms of cancer according to type of smokeless tobacco product used

<i>Form of cancer</i>	<i>CT</i>	<i>MS</i>	<i>DS</i>	<i>SLT-unspecified</i>
<i>Oral cavity</i>				
No. of studies	2	2	—	4
Cases/controls	283/296	482/995	—	581/798
Relative risk	0.6	1.1	—	2.8
95% Confidence interval	0.3-1.3	0.8-1.6	—	1.9-4.1
References	11,21	21,23	—	4,5,7,8
<i>Pharynx</i>				
No. of studies	—	1	—	3
Cases/controls	—	138/641	—	169/472
Relative risk	—	0.7	—	2.3
Confidence interval	—	0.4-1.4	—	1.2-4.4
References	—	23	—	4,7,8
<i>Oral/pharynx</i>				
No. of studies	4	3	3	3
Cases/controls	2113/4454	1682/3931	298/947	655/2718
Relative risk	1.1	0.7	4.0	1.5
Confidence interval	0.8-1.6	0.4-1.2	2.7-5.9	1.1-2.0
References	10,14,19,20	10,19,20	12,14,19	16,18,22
<i>Larynx</i>				
No. of studies	1	2	—	1
Cases/controls	387/2560	544/3201	—	23/100
Relative risk	1.3	1.2	—	1.8
Confidence interval	0.9-1.8	0.9-1.7	—	0.3-9.3
References	10	10,23	—	7
<i>Oral/pharynx/larynx</i>				
No. of studies	2	—	1	—
Cases/controls	362/457	—	93/393	—
Relative risk	1.7	—	13	—
Confidence interval	1.2-2.4	—	8.0-20	—
References	6,15	—	6	—
<i>All sites</i>				
No. of studies	8	5	4	7
Cases/controls	3145/5245	2846/4926	391/1340	1428/3681
Relative risk	1.2	1.0	5.9	1.9
Confidence interval	1.0-1.4	0.8-1.2	1.7-20	1.5-2.3

CT, chewing tobacco; MS, moist snuff; DS, dry snuff; SLT, smokeless tobacco.

studies, yielding a statistically significant RR of 2.8 (1.9-4.1). RRs for cancer of the pharynx (2.3) and of the oral cavity and pharynx combined (1.5) were lower than that for OCC, but both were statistically significant. A single study reported elevated RRs for cancer of the larynx (1.8, 0.3-9.3). For all cancers combined, the 7 studies yielded a summary RR of 1.9 (1.5-2.3).

Two studies^{3,4} reported a combined RR of 2.3 (1.3-4.1) for cancer of the gingival and buccal mucosa in users of SLT-unspecified.

OTHER FINDINGS

Three studies that reported relevant RRs did not provide primary data, so they could not be included in the summary RRs. Williams and Horm⁹ reported RRs

for users of SLT-unspecified for OCC (RR = approximately 5, CI not available), pharynx (0.7), and larynx (2.0). Stockwell and Lyman¹³ reported RRs for users of SLT-unspecified: oral cavity (11.2, 4.1-31), pharynx (4.1, 0.9-18), and larynx (7.3, 2.9-18). Data from the one retrospective follow-up study¹⁷ could not be combined with those from the case-control studies. This study reported a standardized mortality ratio of 3.0 (2.0-4.5) for OCC and 8.7 (4.1-18) for cancer of the pharynx among users of SLT-unspecified.

Two studies contributed data to some summary RRs and also reported other findings that could not be included. Spitz et al¹⁵ reported a RR of 3.4 (1.0-11) for cancers of the oral cavity, pharynx, and larynx combined among moist-snuff users. Mashberg et al¹⁸

reported on cancer of the oral cavity and pharynx among users of moist snuff (0.8, 0.4-1.9) and chewing tobacco (1.0, 0.7-1.4).

DISCUSSION

This review indicates that the increased risks of cancers of the upper respiratory tract associated with the use of SLT generally are modest and differ depending on the type of product used. The lowest RRs are found among users of chewing tobacco (0.6-1.7) and among users of moist snuff (0.7-1.2). Users of dry snuff have higher risks, with RRs from about 4 to 15. Risks are intermediate for SLT-unspecified, possibly reflecting use of either the lower- or higher-risk products among different individuals.

The distinctive risk profiles of moist snuff and chewing tobacco on the one hand, and dry snuff on the other, have gone largely unnoticed. One article²⁹ did suggest that the use of chewing tobacco may be associated with a lower risk of oral cancer than is the use of snuff. No distinction in risks has been made previously between dry snuff and moist snuff, even though these products differ considerably. For this review, however, we separated dry snuff as a distinct exposure because it is essentially the only SLT product used by women, especially in the southern United States.^{27,28}

A strength of the data available now is that because most of the summary RRs presented are based on rather large numbers of cases and controls, they are reasonably precise. However, most of the studies do have limitations. The majority of them did not control confounding by 2 strong determinants of oral cancer, cigarette smoking and alcohol use. Seven studies partially controlled for smoking.^{8,9,12,14,19,21,23} Confounding by smoking would occur if SLT users smoke more than do nonusers. On the other hand, negative confounding is plausible and would occur if smoking rates are lower among SLT users than among nonusers. Three studies^{12,21,23} controlled for alcohol use, where only positive confounding is likely. Control for alcohol consumption probably would have reduced somewhat many of the RRs presented.

Another limitation of these studies, and this area of research, is the lack of clarity with regard to the anatomic sites studied. Although the major site of interest in epidemiologic studies of SLT is the oral cavity, in many studies RRs were reported only for cancers of the oral cavity and pharynx combined, or even for the oral cavity, pharynx, and larynx combined. Nomenclature was not particularly consistent, even for such a seemingly well-defined entity as OCC. For example, although most studies used the same subsites to comprise OCC, 5 included the lips, major salivary glands, or both.^{6,8,10,17,21} Furthermore, 4 studies^{12,16,20,22}

specify oral cancer in their titles but in fact report on cancer of the oral cavity and pharynx combined. Future studies should provide data for specified subsites in addition to designating SLT product types. However, even with these limitations, there is reasonable consistency among the results of these studies that span 45 years.

Twenty-nine reviews or broadly based articles published since 1985 have discussed oral cancer and SLT use. Surprisingly, all of these cited 6 or fewer of the relevant epidemiologic studies, and few presented actual risk estimates. Rather, they focused on issues such as the initiation and prevalence of SLT use. Although these are genuine public health concerns, the abundance of data now available indicates that commonly used SLT products increase the risk of oral and upper respiratory tract cancers only minimally.

REFERENCES

1. Baron JA, Rohan TE. Tobacco. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer epidemiology and prevention*. 2nd ed. New York: Oxford University Press; 1996; p. 269-89.
2. Cullen JW, Blot W, Henningfield J, Boyd G, Mecklenburg R, Masey MM. Health consequences of using smokeless tobacco: summary of the Advisory Committee's report to the Surgeon General. *Public Health Rep* 1986;101:355-73.
3. Wynder EL, Hultberg S, Jacobsson F, et al. Environmental factors in cancer of the upper alimentary tract: a Swedish study with special reference to Plummer-Vinson (Patterson-Kelly) syndrome. *Cancer* 1957;10:470-87.
4. Wynder EL, Bross IJ, Feldman RM. A study of the etiological factors in cancer of the mouth. *Cancer* 1957;10:1300-23.
5. Peacock EE, Greenberg BG, Brawley BW. The effect of snuff and tobacco on the production of oral carcinoma: an experimental and epidemiological study. *Ann Surg* 1960;151:542-50.
6. Vogler WR, Lloyd JW, Milmore BK. A retrospective study of etiological factors in cancer of the mouth, pharynx, and larynx. *Cancer* 1962;15:246-58.
7. Vincent RG, Marchetta F. The relationship of the use of tobacco and alcohol to cancer of the oral cavity, pharynx, or larynx. *Am J Surg* 1963;106:501-5.
8. Martinez I. Factors associated with cancer of the esophagus, mouth, and pharynx in Puerto Rico. *J Natl Cancer Inst* 1969;42:1069-94.
9. 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.
10. Wynder EL, Stellman SD. Comparative epidemiology of tobacco-related cancers. *Cancer Res* 1977;37:4608-22.
11. Browne RM, Camsey MC, Waterhouse JAH, Manning GL. Etiological factors in oral squamous cell carcinoma. *Community Dent Oral Epidemiol* 1977;5:301-6.
12. 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.
13. Stockwell HG, Lyman GH. Impact of smoking and smokeless tobacco on the risk of cancer of the head and neck. *Head Neck Surg* 1986;9:104-110.
14. Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, et al. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res* 1988;48:3282-7.
15. Spitz MR, Fueger JJ, Goepfert H, Hong WK, Newell GR. Squamous cell carcinoma of the upper aerodigestive tract. *Cancer* 1988;61:203-8.

16. Maden C, Beckmann AM, Thomas DB, McKnight B, Sherman KJ, Ashley RL, et al. Human papillomaviruses, herpes simplex viruses, and the risk of oral cancer in men. *Am J Epidemiol* 1992;135:1093-1102.
17. Zahm SH, Heineman EF, Vaught JB. Soft tissue sarcoma and tobacco use: data from a prospective cohort study of United States veterans. *Cancer Causes Control* 1992;3:371-6.
18. Mashberg A, Boffetta P, Winkelman R, et al. Tobacco smoking, alcohol drinking, and cancer of the oral cavity and oropharynx among U.S. veterans. *Cancer* 1993;72:1369-75.
19. Kabat GC, Chang CJ, Wynder EL. The role of tobacco, alcohol use, and body mass index in oral and pharyngeal cancer. *Int J Epidemiol* 1994;23:1137-44.
20. Muscat JE, Richie JP, Thompson S, Wynder EL. Gender differences in smoking and risk for oral cancer. *Cancer Res* 1996;56:5192-7.
21. 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.
22. Schwartz SM, Daling JR, Doody DR, Wipf GC, Carter JJ, Madeleine MM, et al. Oral cancer risk in relation to sexual history and evidence of human papillomavirus infection. *J Natl Cancer Inst* 1998;90:1626-36.
23. Lewin F, Norell SE, Johansson H, Gustavsson P, Wennerberg J, Björklund A, et al. 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* 1998;82:1367-75.
24. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22:719-48.
25. Miettinen O. Estimability and estimation in case-referent studies. *Am J Epidemiol* 1976;103:226-35.
26. Wahlberg I, Ringberger T. Smokeless tobacco. In: Davis DL, Nielsen MT, eds. *Tobacco: production, chemistry and technology*. Oxford, UK: Blackwell Science; 1999; p. 452-460.
27. Rogozinski J. Smokeless tobacco in the Western world. New York: Praeger Publishers; 1990; p. 42-4.
28. McGuirt WF, Wray A. Oral carcinoma and smokeless tobacco use: a clinical profile. In: *Smokeless tobacco or health: an international perspective*. NIH Publication No. 93-3461. Washington, DC: US Department of Health and Human Services; 1993; p. 91-5.
29. Mattson ME, Winn DM. Smokeless tobacco: association with increased cancer risk. *Natl Cancer Inst Monogr* 1989;8:13-6.

Reprint requests:

Brad Rodu, DDS
LHRB 156
University of Alabama at Birmingham
Birmingham, AL 35294-0007
rodu@uab.edu