SCHOOL OF
MEDICINE

Department of Pathology
Oral Pathology

August 5, 2002

The Honorable Donald S. Clark
Secretary
Federal Trade Commission
600 Pennsylvania Avenue, NW
Washington, DC 20580

Re: U.S. Smokeless Tobacco Company's Request for Advisory Opinion

Dear Secretary Clark,

I am a professor of pathology at the University of Alabama at Birmingham School of Medicine, and I have conducted research on the differential risks of various forms of tobacco use with Dr. Philip Cole, professor emeritus in the Department of Epidemiology at the UAB School of Public Health. We have published two peer-reviewed scientific manuscripts in the time period since the USSTC request that provide additional information for its evaluation.

1. Impact of the American Anti-Smoking Campaign on Lung Cancer Mortality. ***International Journal of Cancer*****, Volume 97, pages 804-806, 20 February 2002.**

In this manuscript we used mortality from lung cancer, the sentinel disease of cigarette smoking, to evaluate changes in smoking among birth cohorts of white men born from 1901 to 1942. Our analysis demonstrated that the 35-year old American anti-smoking campaign has produced moderate declines in smoking among younger individuals, but it has not been as successful among smokers above age 40, a group comprised disproportionately of inveterate smokers who are irreversibly addicted to nicotine and consequently at high risk of dying from a smoking-related disease. Our research documented that there are as many as 24 million inveterate smokers age 40-59 who are unresponsive to traditional quit-smoking messages emphasizing nicotine abstinence.

The University of Alabama at Birmingham
156 Lyons Harrison Building •701 South 19th St.
Birmingham, Alabama 35294-0007 • (205) 934-3380 • FAX (205) 975-5200

2. Smokeless Tobacco Use and Cancer of the Upper Respiratory Tract. ***Oral Surgery, Oral Medicine, Oral Pathology*****, Volume 93, pages 511-515, May 2002.**

In the debate over the risks of smokeless tobacco use, the substantial epidemiologic research data available in peer-reviewed scientific studies is cited only infrequently or very selectively. For example, of twenty-nine reviews or broadly based articles published since 1985 on oral cancer and SLT use, all cited 6 or fewer of the relevant epidemiologic studies, and few presented actual risk estimates. Our review described all 21 published studies, and we characterized each study according to specific anatomic sites and according to the specific type of smokeless tobacco products for which it provided risk data. The use of moist snuff and chewing tobacco imposes minimal risks for cancers of the oral cavity and 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.

I request that this letter and the enclosed manuscripts be placed on the public record relating to the request from USSTC.

Sincerely,

Brad Rodu
Professor
Department of Pathology

The University of Alabama at Birmingham
156 Lyons Harrison Building •701 South 19th St.
Birmingham, Alabama 35294-0007 • (205) 934-3380 • FAX (205) 975-5200

Int. J. Cancer: **97**, 804–806 (2002)

DOI 10.1002/ijc.10108

Publication of the International Union Against Cancer

IMPACT OF THE AMERICAN ANTI-SMOKING CAMPAIGN ON LUNG CANCER MORTALITY

Brad RODU[1]* and Philip COLE[2]

[1]*Department of Pathology, School of Medicine, The University of Alabama at Birmingham, Birmingham, AL, USA*
[2]*Department of Epidemiology, School of Public Health, The University of Alabama at Birmingham, Birmingham, AL, USA*

Customary statistics on smoking practices are limited because they do not correlate well with the frequency of smoking-related diseases. Our study developed outcome measures based on lung cancer mortality and used them to assess the anti-smoking campaign. Changes in mortality from lung cancer were used to assess significant smoking among 5-year birth cohorts of white men born from 1901 to 1942. We used each cohort's lung cancer mortality rate at ages 40–44 to indicate its earlier smoking. A lung cancer mortality ratio was developed to describe each cohort's continued smoking from ages 40–44 to 55–59. These ratios were then compared with the durations of the cohorts' exposure to the anti-smoking campaign that began in 1965. Lung cancer mortality in white men ages 40–44 peaked in 1970 and declined continuously thereafter, indicating that the anti-smoking campaign promptly reduced significant smoking among younger men. However, the lung cancer mortality ratio indicates that only half of smokers in the specified birth cohorts were able to quit by ages 55–59, despite receiving ever more intense anti-smoking messages. The anti-smoking campaign produced moderate benefits among younger white male smokers but fewer benefits among older smokers because of the existence of a large number of inveterate smokers.

Key words: *smoking; lung cancer mortality; inveterate smokers*

The anti-smoking campaign is intended to prevent morbidity and mortality caused by smoking. Yet, the campaign usually is evaluated by changes in measures such as population smoking rates and per-capita cigarette consumption. These statistics provide an overview of the amount of smoking in society, but they are only process measures. Both rely on surveys with inherent limitations including selection bias and progressive underreporting as smoking becomes less acceptable socially.[1,2] Specifically, neither measure describes the amount or duration of smoking by individuals or migration in and out of the "current smoker" category. Per-capita cigarette consumption data are limited further because the composition of cigarettes (*e.g.*, filters, tobacco and tar content) has changed considerably over time.[3,4]

In fact, neither smoking prevalence nor cigarette consumption is well correlated with the amount of disease that smoking causes. This is true even when accounting for an appropriate lag time. For example, smoking prevalence was 42% in 1965 and declined to 26% in 1990.[5] During that interval the prevalence of former smokers increased from 14% to 25%. Per capita cigarette consumption fell by one third from 4,258 in 1965 to 2,817 in 1990. Yet lung cancer mortality increased 78% from 23 per 100,000 person-years (py) in 1965 to 41 in 1990.[6] Thus, there is a need for outcome measures that describe meaningful changes in smoking. Our study develops such measures and uses them to describe the effects of the anti-smoking campaign.

METHODS

We used mortality from lung cancer, the sentinel disease of cigarette smoking, to describe changes in smoking patterns among white men. This group long has had the highest smoking rates and the highest frequency of smoking-related diseases in the United States. Lung cancer is smoking's "sentinel" disease because *(i)* smoking causes about 90% of the disease; *(ii)* lung cancer risk for smokers rises sharply by the relatively young age of 40; *(iii)* a group's lung cancer rate rises after age 40 in direct relation to the amount of its continued smoking and *(iv)* 10 years after quitting, the relative risk of lung cancer in former smokers is as much as 50% lower than that in continuing smokers.[7] We used mortality rather than incidence to describe lung cancer patterns because comparable mortality statistics have been available for much longer than incidence data, and the disease always has had a case-fatality greater than 90%. Moreover, 60% of deaths occur within 1 year of diagnosis.

Using age-specific population estimates and numbers of lung cancer deaths from National Center for Health Statistics (NCHS) publications.[8–10] we calculated "A", the lung cancer mortality rate (LCMR) at ages 40–44, and "B", the rate at ages 55–59 for 9 successive 4-year birth cohorts of white men. The first cohort was that of 1901–1905 and the last that of 1938–1942. (The last 2 cohorts partially overlap as shown in Table I.) We used the International Classification of Diseases category "Malignant Neoplasms of the Respiratory System" (ICD-9: 160–165). Deaths from malignancies of the trachea, bronchus, lung or larynx make up 99% of this category.

We used the term "significant smoking" to refer to the smoking experience of each cohort that leads to lung cancer and, implicitly, to other serious diseases. A birth cohort's LCMR at ages 40–44 reflects its significant smoking in youth and young adulthood, since the rate among nonsmokers is virtually nil at this age.[2,11] A cohort's B/A ratio describes its increase in LCMR from ages 40–44 to 55–59 and reflects its continued smoking over this 15-year age span. If all smokers age 40–44 in a particular birth cohort continued smoking, that cohort's B/A would be the maximum value of about 12, according to longitudinal follow-up studies of smokers.[2,11] In contrast, if all smokers in a cohort quit at ages 40–44, its B/A would be at a minimum of 4.[2,12] A B/A of 4 reflects the persisting rise in lung cancer from prior smoking and other causes.

A cohort's reduction in significant smoking is described by the extent to which its B/A ratio is below 12 and approaches 4. Thus, the largest possible reduction in a cohort's B/A ratio is 12 − 4 or 8. We estimated each cohort's percent reduction from this maximum possible value as (12 − CS B/A)(100%)/8, where CS B/A is each cohort's specific B/A.

We then related each cohort's percent reduction in significant smoking to its duration of exposure to the anti-smoking campaign.

Neither author has any conflict of interest relating to the research, preparation or publication of this article.

Grant sponsor: United States Tobacco Company.

*Correspondence to: SDB 81, University of Alabama at Birmingham, Birmingham, AL 35294-0007, USA. Fax: +205-975-5200.
E-mail: rodu@uab.edu

Received 17 May 2001; Revised 22 August 2001; Accepted 31 August 2001

Published online 5 November 2001

TABLE I – AGE-SPECIFIC LUNG CANCER MORTALITY AND DURATION OF EXPOSURE TO ANTI-SMOKING MESSAGES AMONG NINE BIRTH COHORTS OF WHITE MEN

Birth cohort	Lung cancer mortality[1] at age:		B/A	Exposure to anti-smoking messages[2]	
	40–44 (A)	55–59 (B)		Year	Years exposed
1901–1905	10.2	124	12.2	1960	0
1906–1910	11.6	140	12.1	1965	0
1911–1915	12.9	163	12.6	1970	5
1916–1920	15.0	157	10.5	1975	10
1921–1925	19.0	171	9.0	1980	15
1926–1930	22.6	178	7.9	1985	20
1931–1935	19.3	166	8.6	1990	25
1936–1940	18.1	131	7.3	1995	30
1938–1942	15.9	120	7.6	1997	32

[1]Deaths per 100,000 man-years.–[2]By ages 55–59.

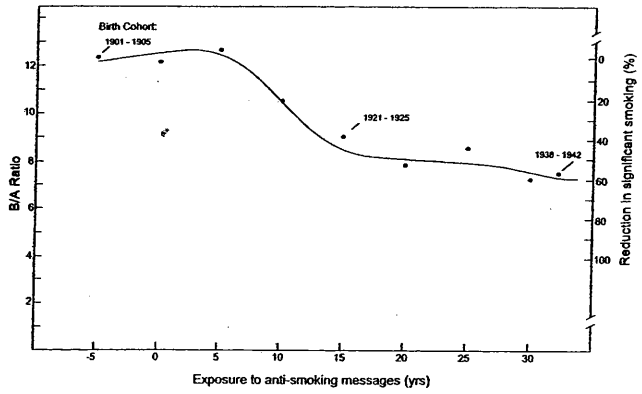

FIGURE 1 – The B/A ratio and the percent reduction in significant smoking by birth cohort, according to duration of exposure to anti-smoking messages, of white men in the US.

We used 1965 as the first year of the anti-smoking campaign because it was the first full year of publicity after the landmark 1964 report of the US Surgeon General on Smoking and Health. Also, in 1965 the majority of cigarettes consumed were filtered, and the transition to low tar brands was beginning. By 1985 most American smokers would be smoking low tar products. We tabulated the duration of each cohort's exposure to the campaign when it had reached ages 55–59. For example, the cohort of 1921–1925 (average year of birth, 1923) reached ages 55–59 (average, 57) in 1980, 15 years after the anti-smoking campaign began.

RESULTS

Table I shows LCMRs at ages 40–44 and at ages 55–59 for each of the 9 birth cohorts of white men. At ages 40–44 LCMRs increased from 10.2 deaths per 100,000 man-years in the 1901–1905 cohort to a peak of 22.6 for the 1926–1930 cohort in 1970, and then declined by 30 per cent to 15.9 for the cohort of 1938–1942. Virtually the same pattern occurred at ages 55–59, with the cohort of 1926–1930 again experiencing the peak LCMR of 178. Each cohort's B/A ratio also is given in Table I. This ratio exceeded 12 in the 3 oldest cohorts. However, the B/A declined in the next 2 cohorts and was 9.0 among white men born in 1921–1925. It decreased further and averaged 7.9 among the 4 youngest cohorts.

Table I also shows each cohort's duration of exposure to anti-smoking messages, and the figure relates this duration to each cohort's percent reduction in significant smoking after ages 40–44. The 2 oldest cohorts were not exposed to anti-smoking messages and the third was exposed for just 5 years. These 3 cohorts had no reduction in significant smoking. The next 2 birth cohorts were exposed to these messages for 10 and 15 years, and their respective reductions in significant smoking were 19% and 38% (Fig. 1). The next 4 cohorts, those of 1926–1930 to 1938–1942, were exposed to anti-smoking messages for 20 to 32 years, and their significant smoking declined an average of 52%. There was little variation in the reduction of significant smoking among these 4 youngest birth cohorts.

DISCUSSION

The major advantage of using LCMR and its derivative, the B/A ratio, to evaluate the anti-smoking campaign is that these measures reflect all determinants of a cohort's exposure to lung carcinogens from smoking. The American anti-smoking campaign can be viewed as consisting of anything that reduces the LCMR and the B/A ratio, including elements as diverse as changes in cigarette design (filters and low tar), educational messages and warnings, advertising limits, the availability of nicotine substitution, reduced accessibility by young persons and restrictions on smoking in public. The campaign can be judged by its impact on both the initiation of smoking among non-smokers and the continuation of smoking among older smokers.

A cohort's LCMR at ages 40–44 reflects its significant smoking in youth and young adulthood. The peaking of this measure in 1970 and its subsequent decline indicate that the anti-smoking campaign had an impact on young white men 5 years after starting in 1965. Furthermore, more recent data show that the LCMR at ages 40–44 decreased 55% from 1970 to 1996, suggesting that this measure will continue to decline for the foreseeable future.

Since the magnitude of a cohort's LCMR at ages 55–59 depends in part upon its LCMR at ages 40–44, the former cannot be used to compare smoking among cohorts after age 40. However, the B/A ratio allows evaluation of a cohort's continued significant smoking during this 15-year age period by, in effect, compensating for its LCMR at ages 40–44. The B/A ratios of about 12 in the oldest 3 cohorts indicate that prior to and early in the anti-smoking campaign there was no decline in significant smoking from ages 40–44 to 55–59. However, when the campaign reached its 10-year mark in 1975, the birth cohort of 1916–1920 showed a 19% reduction in its significant smoking up to ages 55–59. By 1985, the cohort of 1926–1930 had reduced its significant smoking by 51%. However, the youngest 3 cohorts reduced their smoking no further (52% on average), despite being subjected to anti-smoking measures of increasing intensity for ever-longer periods, up to 32 years.

The fact that white men born after 1925 had a reduction in significant smoking of only 50% after age 40 represents a public health problem. If half of smokers over age 40 do not quit, then they must be considered at least somewhat unresponsive to anti-smoking messages. We described these individuals as "inveterate" smokers who do not quit because they are addicted to nicotine.[13] If only half of smokers quit after age 40, then surely at any given point in time most of the 24 million current smokers between age 40–44 and 55–59 are inveterate. The proportion of inveterate

smokers probably is lower at younger ages and very high among those above age 59.

Inveterate smokers are not a uniquely American problem. Data from a recent British study of smoking and lung cancer[14] reveal cohort-specific declines in LCMRs among white men that are similar to those we report. More importantly, the B/A ratio in British men has been stable at about 7.6 from the mid-1980s through the 1990s, indicating that the anti-smoking campaign's effect reached a plateau similar to that in the US.

Our study indicates that the American anti-smoking campaign has reduced significant smoking in younger smokers. However, the campaign now should more directly address inveterate smokers over age 40, of whom 420,000 die annually from smoking-related diseases.[15] A recent report from the Institute of Medicine focuses on a harm reduction strategy emphasizing nicotine maintenance with reduced-risk products such as nicotine medications, smokeless tobacco and redesigned cigarettes.[16] Innovation is overdue, and the implementation of harm reduction may serve to lower the appallingly high number of deaths among inveterate smokers.

ACKNOWLEDGEMENT

Dr. Rodu was 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.

REFERENCES

1. Jackson R, Beaglehole R. Secular trends in underreporting of cigarette consumption. Am J Epidemiology 1985;122:341–4.
2. Thun MJ, Myers DG, Lally C, et al. Age and exposure-response relationships between cigarette smoking and premature death. Cancer Prevention Study II. In: Changes in cigarette-related disease risks and their implication for prevention and control. Smoking and control monograph 8. Bethesda, MD: US Department of Health and Human Services, Public Health Service, NIH Publication No. 97-4213.
3. Walker WJ, Brin BN. US lung cancer mortality and declining cigarette tobacco consumption. J Clin Epidemiol 1988;41:179–85.
4. Lee PN, Forey BA. Trends in cigarette consumption cannot fully explain trends in British lung cancer rates. J Epidemiol Community Health 1998;52:82–92.
5. Centers for Disease Control and Prevention. Achievements in public health, 1900–1999: Tobacco use: United States, 1900–1999. MMWR 1999;48:986–93.
6. Cole P, Rodu B. Declining cancer mortality in the United States. Cancer 1996;78:2045–8.
7. Centers for Disease Control. The Health Benefits of Smoking Cessation; A report of the Surgeon General. Rockville, MD: US Department of Health and Human Services, 1990.
8. Vital Statistics of the United States, Volume II: Mortality, Part A, 1945 to 1992. Rockville, MD.
9. US Department of Health, Education and Welfare, National Center for Health Statistics. Monthly Vital Statistics Report, Volumes 42–45. Hyattsville, MD: US Department of Health and Human Services, National Center for Health Statistics, 1993–1996.
10. National Vital Statistics Reports, Volume 47, Number 25. US Department of Health and Human Services, National Center for Health Statistics. October 5, 1999.
11. Doll R, Peto R, Wheatley K, et al. Mortality in relation to smoking: 40 years' observation on male British doctors. Br Med J 1994;309:901–11.
12. Halpern MT, Gillespie BW, Warner KE. Patterns of absolute risk of lung cancer mortality in former smokers. JNCI 1993;85:457–64.
13. Rodu B, Cole P. Nicotine maintenance for inveterate smokers. Technology 1999;6:17–21.
14. Peto R, Darby S, Deo H, et al. Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. BMJ 2000;321:323–9.
15. Centers for Disease Control and Prevention. Cigarette smoking-attributable mortality and years of potential life lost. MMWR 1993;42:645–9.
16. Stratton K, Shetty P, Wallace R, et al. Clearing the smoke: assessing the science base for tobacco harm reduction. Washington, DC: Institute of Medicine, National Academy Press, 2001.

Vol. 93 No. 5 May 2002

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 ratio[24] 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.
[a]Department of Pathology, School of Medicine, University of Alabama at Birmingham.
[b]Department 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.

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 study[12] 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

Form of cancer	*CT*	*MS*	*DS*	*SLT–unspecified*
Oral cavity				
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
Pharynx				
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
Oral/pharynx				
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
Larynx				
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
Oral/pharynx/larynx				
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	—
All sites				
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 Horm[9] reported RRs for users of SLT–unspecified for OCC (RR = approximately 5, CI not available), pharynx (0.7), and larynx (2.0). Stockwell and Lyman[13] 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 study[17] 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 al[15] 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 al[18]

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 article[29] 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, Biorklund 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