TABLE A16.—*Experiments concerning the effect of the inhalation of cigarette smoke or its constituents upon the respiratory tract of animals (cont.)*

(Figures in parentheses represent total number survivors in specific group)

Author, year, country, reference	Animal and strain	A. Type of exposure B. Duration C. Material	Results	Comments
Leuchtenberger et al., 1960, U.S.A. (*167*).	Female CF_1 mice: C. 243. E. 360.	A. Chamber. B. ½–6 cigarettes per day for 1 month to 2 years. C. Cigarette smoke.	*Number of mice* / *Number of cigarettes* / *Exposure length (months)* / *Number with severe bronchitis; peribronchitis; atypical epithelial proliferation* 151 ..... 25–1,526 1–23 30 150 ..... 0 0 2 36 ..... 100– 200 1– 3 7 36 ..... 250– 500 4– 8 7 34 ..... 600–1,600 9–23 8 51 ..... 100– 400 3– 6 4 63 ..... 100– 400 3– 6 17	
Leuchtenberger et al., 1960, U.S.A. (*168*)	Female CF_1 mice: C. 166. E. 231.	A. Chamber. B. ½–8 cigarettes per day for 17–600 days. C. Cigarette smoke.	*Number of mice examined* / *Exposure (days)* / *Percent of mice with pulmonary adenomatous tumors* 81 ..... 0 56 39 ..... 17– 99 41 35 ..... 100–199 37 51 ..... 200–600 66	Presence of tumors showed an age-relationship independent of smoking exposure.
Ito, 1963, Germany (*206*).	Albino mice. C. 60. E. 189.	A. Chamber. B. Approximately 12 cigarettes per day for varying intervals. C. Cigarette smoke.	*Number of mice examined* C. 60 E. 189 *Exposure* None. Varying up to 24 months. *Number with lung tumors* 3 pulmonary adenomas. 21 pulmonary adenomas. 2 epithelial carcinomas.	

TABLE A16.—*Experiments concerning the effect of the inhalation of cigarette smoke or its constituents upon the respiratory tract of animals (cont.)*

(Figures in parentheses represent total number survivors in specific group)

Author, year, country, reference	Animal and strain	A. Type of exposure B. Duration C. Material	Results	Comments
Dontenwill and Wiebecke, 1966, Germany (77).	Golden hamsters. C. — E. 320	A. Chamber. B. Up to 4 cigarettes per day for up to 2 years. C. Cigarette smoke.	*Number of animals dead at 540 days* / *Daily average exposure (cigarettes)* / *Histologic findings in dead animals* 40 ..... 1 — 8/ 40 MET des 40 ..... 2 — 8/ 40 MET des 80 ..... 1–2 — 44/ 80 MET des (3 MET bronch, 2 PAP trach) 143 ..... 1–4 — 67/143 MET des (13 MET bronch, 8 PAP trach)	MET des = desquamative metaplasia. MET bronch = bronchial papillary metaplasia. PAP trach = tracheal papillomata or intense tracheal metaplasia.
Leuchtenberger and Leuchtenberger 1966, Switzerland (164).	CF_1 mice.	A. Chamber. B. Up to 1,000 hours. C. Cigarette smoke, exposure to influenza virus (PR8).		†Epithelial tissues of these animals showed an increased frequency of cellular atypism. The authors concluded that PR8 influenza virus may act as a cofactor in malignant transformation.

	Marked squamous cell metaplasia (percent)	*Marked dysplasia (percent)*	*Marked transgression of lung parenchyma (percent)*
Controls (*100*):			
Male	—	—	—
Female	—	—	—
Smoke exposed (*59*):			
Male	—	6.0	3.0
Female	—	—	—
Virus exposed (*59*):			
Male	11.0	21.0	13.0
Female	—	—	5.0
Smoke and virus exposed (*68*):			
Male	9.0	43.0	†18.0
Female	29.0	54.0	†33.0

TABLE A16.—*Experiments concerning the effect of the inhalation of cigarette smoke or its constituents upon the respiratory tract of animals (cont.)*

(Figures in parentheses represent total number survivors in specific group)

Author, year, country, reference	Animal and strain	A. Type of exposure B. Duration C. Material	Results	Comments
Rockey and Speer, 1966, U.S.A. (*223*).	Mongrel dogs: C. 11. E. 19.	A. Tracheal fenestration (*10*). Nostril inhalation (*9*). B. Tracheal fenestration—284 treatment days. Nostril inhalation—180 treatment days. C. Cigarette smoke.	Inflammation; Hyperplasia with atypical features; Squamous metaplasia with atypical features; Precancerous changes; Carcinoma in situ Controls (*11*) . 9 1 1 0 0 Tracheal fenestration (*10*) ... 10 5 6 1 †1 Nostril inhalation (*9*) . 6 0 0 0 0	†Carcinoma *in situ* noted in 5 separate sites in this animal.
Auerbach et al., 1967, U.S.A. (*10*).	Beagle dogs: C. 10 (2 with tracheostoma). E. 10.	A. Tracheostoma. B. Up to 12 cigarettes per day for up to 421 days. C. Cigarette smoke.	Controls, experimental: No histologic change in bronchial epithelium: *a.* 1 animal died at 24 days and no histologic change noted. *b.* 5 animals sacrificed at 421 days and nuclear atypism noted in all. *c.* 2 animals died at 229 and 278 days and nuclear atypism was noted but of lesser severity than in those sacrificed at 421 days.	
Harris and Negroni, 1967, England (*121*).	C57BL mice: C. 200. E. 1,437.	A. Chamber. B. Smoke—12 cigarettes per 20 mice for 12 minutes every other day for lifetime. C. Cigarette smoke, influenza virus aerosol, benzpyrene aerosol.	*Treatment* — *Number* — *Number of lung carcinomas* Controls ..... 200 0 Influenza aerosol alone ..... 682 15 Benzpyrene aerosol (4 exposures) ..... 200 2 Smoking ..... 200 8 (all adenocarcinomas) Influenza and benzpyrene ... 200 3 Influenza and smoking 155 3	This strain of mice is noted for its lack of spontaneous lung tumor formation. Animals exposed to cigarette smoke showed no hyperplastic epithelial changes such as those noted by Leuchtenberger.

TABLE A16.—*Experiments concerning the effect of the inhalation of cigarette smoke or its constituents upon the respiratory tract of animals (cont.)*

(Figures in parentheses represent total number survivors in specific group)

Author, year, country, reference	Animal and strain	A. Type of exposure B. Duration C. Material	Results	Comments
Wynder et al., 1968, U.S.A. (*327*).	Male C57BL6 mice: C. and E.—more than 40.	A. Chamber. B. Up to 315 cigarettes. C. Cigarette smoke, nitrogen dioxide, volatile acids and aldehydes found in cigarette smoke, swine influenza virus.	Conclusions:† No squamous cell respiratory cancer noted. This is attributed to the limitation of inhalation time (CO and nicotine acute effects) and to the anatomically and physiologically intricate nasal passage defense system. Exposure to cigarette smoke, NO_2, or volatile acids and aldehydes leads to reactive hyperplasia and metaplasia, both of which were noted to be reversible. Swine influenza virus exposure produced hyperplastic and metaplastic effects which could not be enhanced by subsequent exposure to cigarette smoke.	†Results not provided in tabular form.
Laskin et al., 1970, U.S.A. (*159*).	Rats: C. 45. E. 3.	A. Chamber. B. 1 hour per day for up to 690 days. C. Benzo(a)pyrene aerosol, SO_2 atmosphere (3.5 p.p.m.).	*Exposure* — *Number* — *Squamous cell carcinomas* Atmosphere controls ..... 3 0/3 Atmosphere plus benzo(a)-pyrene exposure ..... 21 2/21 SO_2 controls ..... 3 0/3 SO_2 plus benzo(a)-pyrene exposure 21 5/21	
Hammond et al., 1970, U.S.A. (*119*).	Beagle dogs.	See text	See text.	

TABLE A21.—*Outline of retrospective studies of tobacco use and cancer of the larynx*

Author, year, country, reference	Cases			Controls		Collection of data
	Sex	Number	Method of selection	Number	Method of selection	
Schrek et al., 1950, U.S.A. (246).	M.	73	Referrals from V.A. hospitals in "entire midwest" to V.A. Cancer Center, Hines, Illinois, during 1942-44; patients with larynx-pharynx tumors clinically or histologically diagnosed: *Percent* Nonsmokers ..... 13.7 Cigarettes ..... 79.5 Cigars ..... 3.7 Pipes 6.8	522	From same set of referrals, patients with tumors other than lip, lung, larynx-pharynx: *Percent* Nonsmokers ..... 23.9 Cigarettes ..... 59.2 Cigars ..... 10.0 Pipes 11.5	Random sample of 6,003 admissions; questionnaires from Hines referrals for 1942-44; records included smoking history.
Valko, 1952, Czechoslovakia (292).	M-F	226	Clinic patients with cancer of the larynx: *Percent* Nonsmokers ..... 7.5 Cigarettes ..... 83.2 Cigars ..... 4.4 Pipes 10.6	108	Clinic patients of same age group with other diagnoses: *Percent* Nonsmokers 22.2	Medical history and questionnaire in clinic.
Sadowsky et al., 1953, U.S.A. (232).	M.	273	White male admissions to hospitals in New York City, Missouri, New Orleans, Chicago; patients with diagnosed laryngeal tumors, 1938-43: *Percent* Nonsmokers ..... 4.0 Cigarettes only ..... 60.1 Cigars only ..... 2.2 Pipe only ..... 4.8 Some combination 28.9	615	From same set of admissions, patients with illnesses other than cancer: *Percent* Nonsmokers ..... 13.2 Cigarettes only ..... 53.3 Cigars only ..... 3.4 Pipe only ..... 7.0 Some combination 23.1	Sample of 2,605 out of 2,847 interviews (including smoking history) by trained lay interviewers.

TABLE A21.—*Outline of retrospective studies of tobacco use and cancer of the larynx (cont.)*

Author, year, country, reference	Cases			Controls		Collection of data
	Sex	Number	Method of selection	Number	Method of selection	
Blümlein, 1955, Germany (*26*).	M.	241	Clinic patients with cancer of larynx: *Percent* Nonsmokers ..... 0.8 Heavy smokers ..... 79.3 Inhalers 95.0	200	Patients with no laryngeal disease: *Percent* Nonsmokers ..... 18.0 Heavy smokers ..... 4.3 Inhalers 17.0	Personal history taken in clinic. Patients and controls over 40 years of age.
Wynder et al., 1956, U.S.A. (*312*).	M.	209	White male inpatients Memorial Cancer Research Center during 1952 to 1954, with benign or malignant epidermoid tumors of larynx: *Percent* Nonsmokers ..... 0.5 Cigarettes ..... 86.0 Cigars ..... 7.5 Pipes ..... 5.0 Cigars/pipes 1.0	209	Patients with other than epidermoid cancer, individually matched controls in same institutions: *Percent* Nonsmokers ..... 10.5 Cigarettes ..... 73.7 Cigars ..... 10.1 Pipes ..... 3.8 Cigars/pipes 1.9	Trained lay interviewers.
Wynder et al., 1956, India (*312*).	M.	132	Laryngeal cancer patients at Tata Memorial Hospital, 1952–54: *Percent* Nonsmokers ..... 13.6 Bidis ..... 78.8 Cigarettes ..... 5.3 Hookah ..... 1.5 Chilum 0.8	132	Controls individually matched as for U.S.A. data above: *Percent* Nonsmokers ..... 30.3 Bidis ..... 62.1 Cigarettes ..... 4.5 Hookah ..... 0.8 Chilum 2.3	Interviews for smoking and medical histories.
Schwartz et al., 1957, France (*248*).	M.	121	Patients hospitalized from 1954 through 1956 with laryngeal cancer, in Paris and other large cities: *Percent* Smokers ..... 96 Inhalers ..... 58 Roll their own cigarettes 44	242	Same time and sources; patients hospitalized for non-cancerous conditions or trauma: *Percent* Smokers ($p<0.05$) ..... 84 Inhalers ($p<0.05$) ..... 47 Roll their own cigarettes 31	Cases and controls individually matched within institutions; each member of a set questioned by the same trained lay interviewer.

TABLE A21.—*Outline of retrospective studies of tobacco use and cancer of the larynx (cont.)*

Author, year, country, reference	Cases			Controls		Collection of data
	Sex	Number	Method of selection	Number	Method of selection	
Wynder et al., 1957, Sweden (*322*).	M.	60	Patients at Radiumhemmet with squamous-cell cancer of larynx, from 1952 through 1955:	271	Patients from same source and time, with cancer other than squamous-cell of larynx:	By trained lay interviewers in hospital.
			Percent		*Percent*	
			Nonsmokers 5		Nonsmokers 24	
			Cigarettes 47		Cigarettes 36	
			Cigars 17		Cigars 9	
			Pipes 16		Pipes 16	
			Mixed 17		Mixed 13	
Wynder et al., 1958, Cuba (*325*).	M. F.	142 32	Clinic patients in Havana during 1956-57, with histologically diagnosed epidermoid cancer of larynx.	220 214	Same source and time; apparently patients with cancers other than larynx, lung, or oral cavity, matched for age:	Interview of patients in clinic.
			Percent *Male* *Female*		*Percent* *Male* *Female*	
			Nonsmokers 1 13		Nonsmokers 16 66	
			Cigarettes 62 72		Cigarettes 45 27	
			Cigars 20 6		Cigars 22 6	
			Pipes ..... 1 ..		Pipes ..... 1 ..	
			Mixed 16 9		Mixed ..... 16 ..	
Dutta-Choudhuri et al., 1959, India (*86*).	M-F	582	Patients in Calcutta cancer hospital during 1950-54, with laryngeal tumor diagnosed and confirmed by biopsy or smear:	288	Not specified	Tobacco histories obtained during 1951-54, apparently by interviewer.
			Percent		*Percent*	
			Nonusers 14.1		Nonusers 41.7	
			Cigarettes or bidi 77.8		Cigarettes or bidi 52.1	
			Chew 3.1		Chew 3.8	
			Both 5.0		Both 2.4	

TABLE A21.—*Outline of retrospective studies of tobacco use and cancer of the larynx (cont.)*

Author, year, country, reference	Cases			Controls		Collection of data
	Sex	Number	Method of selection	Number	Method of selection	
Staszewski, 1960, Poland (259).	M. F.	207 13	Patients admitted to chronic disease hospital during 1957 and 1958 with histologically confirmed squamous-cell carcinoma of the larynx: *Percent* Nonsmokers ..... 0.5 Cigarettes only ..... 87.9 Pipes and/or cigars ..... 1.9 "Heavy smokers" ..... 88.4 Inhalers ..... 96.1 Female smokers 30.8	912 1,813	Patients admitted during 1957 and 1958 to chronic disease center for cancerous and noncancerous conditions presumably not related to tobacco consumption: *Percent* Nonsmokers ..... 17.3 Cigarettes only ..... 60.5 Pipes and/or cigars ..... 11.1 "Heavy smokers" ..... 49.0 Inhalers ..... 66.8 Female smokers 8.4	Author interviewed patients suspected of lung cancer for smoking history and background.
Rozenbilds, 1967, Australia (229).	M. F.	191 21	Patients admitted to 3 major hospitals with cancer of larynx and hypopharynx: *Percent* Nonsmokers ..... 8 Smokers ..... 92 Heavy smokers 30		No controls.	Patient interviews.
Terracol et al., 1967, France (274).	M.	961	Private service and clinic patients of ENT hospital: *Percent* Nonsmokers ..... 12.1 Smokers 87.9		No controls.	Patient interviews.
Svoboda, 1968, Czechoslovakia (271).	M. F.	205 10	Patients admitted to a regional hospital over a period of 6 years all confirmed histologically: *Percent* Nonsmokers ..... 2.93 Cigarettes ..... 94.63 Pipes 2.44	320	Male controls *Percent* Nonsmokers ..... 22.0 Cigarettes (approximately) . 71.0 Pipes (approximately) 7.0	Cases: patient interviews. Controls: not stated.

TABLE A22.—*Summary of results of retrospective studies of tobacco use and cancer of the larynx*

(Figures in parentheses represent ratios based on less than 5 case nonsmokers.)

Investigator reference	Relative risk ratio [1] all smokers to nonsmokers
Schrek et al., U.S.A. (*246*)	2.0
Valko, Czechoslavakia (*292*)	3.5
Sadowsky et al., U.S.A. (*232*)	3.7
Blumlein, Germany (*26*)	27.5
Wynder et al., U.S.A. (*314*)	23.6
Wynder et al., India (*312*)	3.1
Schwartz et al., France (*254*)	4.6
Wynder et al., Sweden (*322*)	6.0
Wynder et al., Cuba (*325*)	(18.9) (males only)
Datta-Choudhuri et al., India (*86*)	4.3
Stazewski, Poland (*259*)	(40.0) (males only)
Svoboda, Czechoslavakia (*271*)	8.3

[1] Computed according to method of Cornfield, J. (*61*).

TABLE A23.—*Number and percent distribution by relative frequency of atypical nuclei among true vocal cord cells, of men classified by smoking category*

(100 percent atypical cells defined as carcinoma)

Percent atypical nuclei	Never smoked regularly		Ex-cigarette smokers		Cigar/pipe smokers		Current cigarette smokers					
							Less than 1 pack a day		1-2 packs a day		2 or more packs a day	
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
Total	88	100.0	116	100.0	94	100.0	125	100.0	329	100.0	190	100.0
None	66	75.0	86	74.1	1	1.1	1	.8	0	—	0	—
Less than 50	8	9.1	14	12.1	4	4.3	25	20.0	4	1.2	0	—
50-59	10	11.4	13	11.2	50	53.0	54	43.2	87	26.4	29	15.3
60-69	4	4.5	1	.9	23	24.5	21	16.8	116	35.3	75	39.4
70-79	0	--	2	1.7	9	9.6	9	7.2	44	13.4	38	20.0
80-89	0	—	0	—	2	2.1	2	1.6	19	5.8	11	5.8
90-99	0	—	0	—	1	1.1	0	--	5	1.5	0	--
100:												
Carcinoma in situ	0	—	0	—	3	3.2	13	10.4	52	15.8	35	18.4
Invasive carcinoma	0	--	0	--	1	1.1	0	--	2	.6	2	1.1

Source: Auerbach, O. et al. (9).

TABLE A24.—*Number and percent distribution, by highest number of cell rows in the basal layer of the true vocal cord, of men classified by smoking category*

Number of cell rows	Never smoked regularly		Ex-cigarette smokers		Cigar/pipe smokers		Current cigarette smokers					
							Less than 1 pack a day		1–2 packs a day		2 or more packs a day	
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
Total	88	100.0	116	100.0	94	100.0	125	100.0	329	100.0	190	100.0
Less than 5 cell rows	30	34.1	7	6.0	4	4.3	3	2.4	1	0.3	0	...
5 cell rows	29	33.0	27	23.3	20	21.3	27	21.6	38	11.6	20	10.6
6 cell rows	8	9.1	15	12.9	15	6.0	25	20.0	51	15.4	24	12.6
7 cell rows	6	6.8	12	10.3	18	19.1	12	9.6	38	11.6	19	10.0
8 cell rows	8	9.1	14	12.1	9	9.6	13	10.4	30	9.1	23	12.1
9 cell rows	1	1.1	7	6.0	7	7.4	6	4.8	26	7.9	14	7.4
10 or more cell rows	6	6.8	34	29.4	21	22.3	39	31.2	145	44.1	90	47.4

Source: Auerbach, O. et al. (9).

TABLE A28.—*Outline of retrospective studies of tobacco use and cancer of the oral cavity*

(Data obtained from patient interview and other sources)

Author, year, country, reference	Sex	Cases: Number	Cases: Method of selection	Controls: Number	Controls: Method of selection	Comments
Borders, 1920, U.S.A. (*43*).	M. F.	526 11	Series of clinic patients with epithelioma of the lip: *Percent* Tobacco users ..... 80.5 Smokers ..... 75.1 Cigarettes ..... 0.9 Chewers ..... 24.0 Pipes ..... 59.0 Cigars 38.5	500	Series of clinic patients without epithelioma of the lip: *Percent* Tobacco users ..... 78.6 Smokers ..... 75.2 Cigarettes ..... 44.4 Chewers ..... 13.4 Pipes ..... 28.6 Cigars 44.0	
Ebenius, 1943, Sweden (*87*).	M. F.	439 33	Clinic patients with cancer of the lip: *Percent* *Male* *Female* Tobacco users ..... 79.7 — Tobacco users (all pipes) ..... — 57.6 Pipes ..... 61.8 — Chew or use snuff .... 47.4 — Cigars and cigarettes .. 12.9 —	300	Not defined. *Percent* *Male* *Female* Tobacco users ..... 68.7 — Tobacco users ..... — †1–2 Pipes ..... 22.9 — Chew or use snuff ..... 60.7 — Cigars and cigarettes .. 32.5 —	† Estimate of prevalence of use.
Levin et al., 1950, U.S.A. (*169*).	M.	143	Cancer Institute patients with cancer of the lip: *Percent* Smokers ..... 84.5 Cigarettes ..... 45.3 Pipes ..... 48.1 Cigars 26.5	51	Cancer Institute patients with non-cancer diseases of same site: *Percent* Smokers ..... 74.0 Cigarettes ..... 43.0 Pipes ..... 30.7 Cigars 34.9	

TABLE A28.—*Outline of retrospective studies of tobacco use and cancer of the oral cavity* (cont.)

(Data obtained from patient interview and other sources)

Author, year, country, reference	Cases			Controls		Comments
	Sex	Number	Method of selection	Number	Method of selection	
Mills and Porter, 1950, U.S.A. (*186*).	M.	124	Deaths from cancer of oral cavity in Cincinnati and Detroit, 1940-45 and 1942-46 respectively: *Percent* Cigarettes only ..... 35.5 Pipes, cigars, or combinations 54.8	185	Sample of population of Columbus, Ohio, in same proportion of color, sex, and age as in cases: *Percent* Cigarettes only ..... 32.4 Pipes, cigars, or combinations 29.7	
Moore et al., 1953, U.S.A. (*194*).	M.	112	Patients over 50 years old since 1951 with cancer of oral cavity: *Percent* Chewers ..... 58.0 Pipes ..... 42.0 Cigars and cigarettes 38.4	38	Patients of same age groups with benign oral lesions or benign surgical conditions: *Percent* Chewers ..... 31.6 Pipes ..... 47.4 Cigars and cigarettes 52.6	
Sadowsky et al., 1953, U.S.A. (*332*).	M.	1,136	Hospital patients with lip, oral, and pharyngeal cancer, 1938-44: *Percent* Cigarettes only ..... 42.3 Cigars only ..... 4.0 Pipes only ..... 17.8 Mixed 28.2	615	Patients with illness other than cancer: *Percent* Cigarettes only ..... 53.3 Cigars only ..... 3.4 Pipes only ..... 7.0 Mixed 23.1	
Sanghvi et al., 1955, India (*241*).	M. F.	657 81	Hospital patients with cancer of oral cavity and pharynx: *Percent* *Male* *Female* Smoke and chew ..... 38.8 3.7 Smoke only ..... 46.7 6.2 Chew only ..... 11.7 64.2 Neither 2.7 25.9	288 112	Hospital patients with diseases other than cancer: *Percent* *Male* *Female* Smoke and chew ..... 24.0 Smoke only ..... 50.0 6.3 Chew only ..... 8.7 23.2 Neither 17.3 70.5	Smoking is of bidis among both cases and controls.

TABLE A28.—*Outline of retrospective studies of tobacco use and cancer of the oral cavity (cont.)*

(Data obtained from patient interview and other sources)

Author, year, country, reference	Sex	Cases		Controls		Comments
		Number	Method of selection	Number	Method of selection	
Ledermann, 1955, France (*162*).	M.	240	Patients with cancer of oral cavity and pharynx: *Percent* Nonsmokers ..... 4.6 >20 cigarettes per day 23.4	62	Patients with cancer of skin, bone, and muscle: *Percent* Nonsmokers ..... 17.2 >20 cigarettes per day 18.6	Differences between cases and controls for both high and low alcohol intake are insignificant when smoking is controlled.
Wynder et al., 1957, U.S.A. (*313*).	M. F.	543 116	Patients with cancer of oral cavity: *Percent* *Male* *Female* Nonsmokers ..... 3 47 Cigars ..... 20 — Pipes ..... 11 — Mixed ..... 8 — Chew ..... 17 — Cigarettes ..... 57 53 >35 cigarettes per day ..... 20 — >16 cigarettes per day 34	207 232	Patients with cancer of other sites and benign diseases: *Percent* *Male* *Female* Nonsmokers ..... 10 70 Cigars ..... 13 — Pipes ..... 6 — Mixed ..... 8 — Chew ..... 8 — Cigarettes ..... 63 30 >35 cigarettes per day ..... 17 — >16 cigarettes per day 11	
Schwartz et al., 1957, France (*248*).	M.	332	Hospital patients with cancer of oral cavity and pharynx: *Percent* Nonsmokers ..... 16.4 Cigarettes only ..... 62.7 Pipes only 3.3	608	Hospital patients with non-cancer illness and accident cases, matched by age: *Percent* Nonsmokers ..... 23.4 Cigarettes only ..... 58.2 Pipes only 3.0	

TABLE A28.—*Outline of retrospective studies of tobacco use and cancer of the oral cavity (cont.)*

(Data obtained from patient interview and other sources)

Author, year, country, reference	Sex	Cases		Controls		Comments
		Number	Method of selection	Number	Method of selection	
Wynder et al., 1957, Cuba (*325*).	M. F.	178 34	Hospital clinic patients with cancer of oral cavity and pharynx: *Percent* *Male* *Female* Nonsmokers ..... 4 24 Cigarettes predominantly ..... 45 62 Cigars predominantly . 33 12	220 214	Patients in same clinics with non-malignant conditions, matched by sex and age: *Percent* *Male* *Female* Nonsmokers ..... 16 66 Cigarettes predominantly ..... 45 27 Cigars predominantly . 22 6	
Wynder et al., 1957, Sweden (*322*).	M.	115	Male patients with cancer of oral cavity and pharynx: *Percent* Cigarettes ..... 36.5 Cigars ..... 13.0 Pipes ..... 12.2 Mixed 15.7	115	Male patients in same hospital with cancer of sites other than oral, pharynx, larynx, lung, esophagus, breast: *Percent* Cigarettes ..... 36 Cigars ..... 9 Pipes ..... 16 Mixed 13	Alcohol data significant only for hypopharynx.
Peacock et al., 1960, U.S.A. (*210*).	M. F.	25 20	Hospital patients with oral cancer: *Percent* Chewed or used snuff over 20 years (all patients) 55.6	74 72	Patients in same hospital without oral cancer and 117 male and 100 female out-patients, randomly selected. 32.6 percent of first group, and 43.3 percent of second group chewed or used snuff over 20 years.	
Staszewski, 1960, Poland (*259*).	M.	383	Male patients with oral cancer: *Percent* Nonsmokers ..... 5.7 "Heavy" smoking index ..... 72.8 Cigarettes only ..... 72.3 Pipes and/or cigars 12.8	912	Male patients with other cancerous and non-cancerous conditions: *Percent* Nonsmokers ..... 17.3 "Heavy" smoking index ..... 49.0 Cigarettes only ..... 60.5 Pipes and/or cigars 11.1	

TABLE A28.—*Outline of retrospective studies of tobacco use and cancer of the oral cavity (cont.)*

(Data obtained from patient interview and other sources)

Author, year, country, reference	Sex	Cases: Number	Cases: Method of selection	Controls: Number	Controls: Method of selection	Comments
Vogler et al., 1962, U.S.A. (*298*).	M. F.	188 92	Clinic patients with cancer of lip and oral cavity: *Percent* Male / Female Chewers ..... †32.9 / — Excessive chewers .... 22.9 / — Snuff dippers ..... — / 72.0 Excessive snuff dippers ..... — / 41.3 Tobacco users ..... 90.0 / 90.0	521 1,064	Patients of same clinic with other cancer or non-malignant conditions: *Percent* Male / Female Snuff dippers .... †6.1 Tobacco users ..... 56.0 / 56.0	† Due to varying tabular treatment of data, percentages of tobacco users are not all based on the same number of cases.
Vincent and Marchetta, 1963, U.S.A. (*297*).	M. F.	66 16	Successive patients with lesions of buccal cavity and oropharynx: *Percent* Oral Cavity / Oro-pharynx Males: Nonsmokers ..... 3.0 / — <20 cigarettes per day ..... 18.3 / 15.1 >20 cigarettes per day ..... 78.7 / 84.9 Females: Nonsmokers ..... 55.5 / 28.6 <20 cigarettes per day ..... — / — >20 cigarettes per day ..... 44.5 / 71.4	100 50	Successive patients attending gastrointestinal clinic, age-matched; *Percent* 27.0 24.0 49.0 82.0 8.0 10.0	Male patients used considerably more alcohol than male controls. Data refers to all forms of smoking expressed as cigarette equivalents. Cigarette equivalents: 1 cigar = 5 cigarettes 1 pipe = 2 cigarettes † BN=Betel nut.

TABLE A28.—*Outline of retrospective studies of tobacco use and cancer of the oral cavity (cont.)*

(Data obtained from patient interview and other sources)

Author, year, country, reference	Sex	Cases: Number	Cases: Method of selection	Controls: Number	Controls: Method of selection	Comments
Shanta and Krishnamurthi, 1964, India (*256*).	M. F.	552 206	Patients with oral and pharyngeal cancer (unsure of confirmation):	300 100	Controls residing in same area matched for age, sex, and class:	
			Males: — *Lip*; *Buccal mucosa*; *Anterior tongue*; *Posterior tongue*; *Pharynx*; *Males* (Percent)			
			No tobacco habit .... — 2.0 7.2 2.0 5.3 39.1			
			Smokers 50.0 45.7 66.6 75.0 72.8 52.7			
			Number of cases .... (12) (203) (69) (48) (130) (300)			
			Females: — *Females*			
			No tobacco habit .... 14.3 11.0 33.3 — 40.0 88.8			
			Smokers ..... — 4.7 5.5 — 8.8 —			
			Number of cases .... (7) (162) (18) (4) (25) (100)			
Wahi et al., 1965, India (*302*).	M. F.	589 232	Patients with oral and pharyngeal carcinoma:	589 232	Patients matched for age, sex, religion, and social class.	
					Percent	
			Nonsmokers 9.62		66.5	
			Smokers 17.05		21.2	
			Chewers (Betel nut) 35.44		5.9	
			Both 37.88		6.4	
Hirayama, 1966, Central and South East Asia (*124*).	M. F.	369 176	Patients with oral and pharyngeal carcinoma:	277 163	Patients with other (unspecified) diseases:	Found only a suggestive association between alcohol-drinking and oral cancer in non-chewers only. † BN-Betel nut.
					Percent	
					Male *Female*	
			Nonusers 1.6 2.5		17.0 33.0	
			Smokers 17.1 2.5		23.8 1.2	
			Smokers, †BN and tobacco chewers 46.7 6.6		24.9 1.8	

TABLE A28.—*Outline of retrospective studies of tobacco use and cancer of the oral cavity (cont.)*

(Data obtained from patient interview and other sources)

Author, year, country, reference	Cases			Controls		Comments
	Sex	Number	Method of selection	Number	Method of selection	
Keller, 1967, U.S.A. (*140*).	M	408	Patients with squamous cell carcinoma of oral cavity and oropharynx confirmed histologically. Three New York City VA Hospitals 1953-63:	408	Next male patient admitted to same hospital within 5 year age range.	Excessive alcohol consumption noted for cases involving floor, mesopharynx, and tongue. Findings indicate the association of heavy drinking with cancer independent of the amount of tobacco used.
			Percent		*Percent*	
			Nonusers 5.1		14.2	
			Cigarettes 68.6		56.4 ($p<0.0001$)	
			Pipe only 4.0		2.9	
			Cigar only 6.9		6.1	
Martinez, 1969, Puerto Rico (*185*).	M. F.	38	Patients with epidermoid carcinoma of oral cavity and pharynx:	345 114	116 male and 38 female hospital or clinic patients without cancer; 330 male and 76 female residents of same region, age and sex matched.	Cases found to consume more alcoholic beverages than controls.
			Percent		*Percent*	
			Nonsmokers 13.7		19.2	
			Heavy tobacco users 24.8		12.2 ($p<0.0001$)	
Keller, 1970, U.S.A. (*141*).	M.	304	Patients with primary basal or squamous cell carcinoma of lip:	304	Patients from same hospital matched for age and race.	
			Percent		*Percent*	
			Nonsmokers 7.3		16.6 ($p<0.001$)	
			Cigarettes only 60.2		52.8	
			Pipe only 6.0		3.4	
			Pipe, other 6.3		0.4 ($p<0.01$)	

TABLE A28a.—*Summary of results of retrospective studies of smoking by type and oral cancer of detailed sites*

Author reference	Cigarettes	Cigarettes and cigars	Bidis	Pipes only	Pipes and other forms	Cigars only	Tobacco chewing	Betel nut chewing	Miscellaneous
Broders (*43*)	Lip (−)			Lip (+)		Lip (−)	Lip (+)		
Ebenius (*87*)		Lip (−)		Lip (+)			Lip (−)		
Levin et al. (*169*)	Lip (−)			Lip (+)		Lip (*)			
Mills and Porter (*186*)	Oral (*)								Pipes and cigars combined—oral (+).
Moore et al. (*193*)		Lip, mouth (−).		Lip, mouth (−)			Lip, mouth (+)		Snuff—lip, mouth (+).
Sadowsky et al. (*232*)	Lip, tongue, other oral, pharynx (−)			Lip, tongue, other oral (+)		Tongue, other oral (*)			
Sanghvi et al. (*241*)			Oral (+)				Oral (+)		If smokers and chewers—base of tongue, hypopharynx (+).
Lederman (*162*)	Oral (+)								
Wynder et al. (*313*)	Floor of mouth Male (*) Female (+)			Each site except tongue (+)		Each site (+)	Gingiva, lip (*)		
Schwartz et al. (*243*)		Pharynx (+)		Oral (−)					

TABLE A28a.—*Summary of results of retrospective studies of smoking by type and oral cancer of detailed sites (cont.)*

Author reference	Cigarettes	Cigarettes and cigars	Bidis	Pipes only	Pipes and other forms	Cigars only	Tobacco chewing	Betel nut chewing	Miscellaneous
Wynder et al. (325)	Oral and pharynx, Male (−) Female (+)	.....	.....	.....	.....	Oral and pharynx, Male (+), Female (+)	.....	.....	
Wynder et al. (325)	Pharynx (+), other sites (−).	.....	.....	.....	.....	Tongue, gingiva, pharynx (+).	.....	.....	Pipes and cigars combined—tongue (+).
Peacock et al. (210)	.....	.....	.....	.....	.....	.....	Oral (+)[1]	.....	Snuff—oral (+)[1]
Staszewski (259)	Lip, oral cavity (+)	.....	.....	.....	.....	.....	.....	.....	Pipes and cigars combined—lip, oral cavity (*).
Vogler et al. (293)	.....	.....	.....	.....	.....	.....	.....	.....	All forms combined (+), Female (+) Snuff—lip and buccal cavity in both cases.
Vincent and Marchetta (297)	.....	.....	.....	.....	.....	.....	.....	.....	All forms combined—oral (+), pharynx (+).
Shanta and Krishnamurthi (256	.....	.....	.....	.....	.....	.....	.....	Lip, buccal mucosa (+)	All smoking types—pharynx (+), post tongue (+). All forms combined—lip, oral cavity, pharynx (+).

TABLE A28a.—*Summary of results of retrospective studies of smoking by type and oral cancer of detailed sites (cont.)*

Author reference	Cigarettes	Cigarettes and cigars	Bidis	Pipes only	Pipes and other forms	Cigars only	Tobacco chewing	Betel nut chewing	Miscellaneous
Wahi et al. (*302*)	Anterior tongue and buccal mucosa, Males (+)							Anterior tongue and buccal mucosa, Males (+)	All forms combined—all sites (+).
Hirayama (*124*)				All sites (−)		All sites (−)	All sites (−)		All forms combined—base of tongue (+), oropharynx (+). Smoking only combined—buccal mucosa (+).
Keller (*140*)	All sites (+)			All sites (−)		All sites (−)			All types smoking combined, heavy—floor of mouth and tongue (+).
Martinez (*185*)	Oral cavity, pharynx (+)								All types of smoking, heavy, combined—oral cavity (+), pharynx (+).
Keller (*141*)	Lip (−)				Lip (+)	Lip (−)			All types of smoking combined—lip (+).

[1] Only in individuals of low economic status and over 60 years old.

Symbols: (+) = significant association.
(−) = association absent or not significant.
(°) = association of doubtful significance.

TABLE A29.—*Experimental studies concerning oral carcinogenesis*

Author, year, country, reference	Animal and strain	A. Method. B. Frequency and/or duration. C. Material.	Results
Kreshover, 1952, U.S.A. (*152*).	78 Swiss and C57 mice.	A. Painting of lower lip mucocutaneous region. B. 10 times in 76 days. C. Cigarette smoke "concentrate".	No macroscopic or microscopic changes in controls or experimental animals.
Salley, 1954, U.S.A. (*235*).	36 Syrian hamsters.	A. Painting of cheek pouch. B. 3 per week for 16 weeks. C. Benz(a)pyrene in acetone or benzene.	Treatment: — *Number of survivors*: Acetone solvent 5; Benzene solvent 4. *Number with benign tumors*: Acetone solvent 1; Benzene solvent —. *Number with carcinoma*: Acetone solvent 2; Benzene solvent —.
Holsti and Ermala, 1955, Finland (*130*).	60 Albino mice (40 controls).	A. Painting of lips and oral cavity. B. 140 times in 12 months. C. Tobacco "tar".	No oral or labial changes seen in controls or experimental animals.
Moore and Miller, 1958, U.S.A. (*192*).	80 Syrian Golden hamsters.	A. Material soaked onto wad and secured in cheek pouch. B. Wads replaced 8 times in 2 years. C. Smoke condensate Benz(a)pyrene.	Treatment: — *Original number*: Controls 30; Smoke condensate 80; Benz(a)pyrene 20. *Surviving over 1 year*: Controls 28; Smoke condensate 56; Benz(a)pyrene 16. *Number tumors*: Controls ..; Smoke condensate ..; Benz(a)pyrene .. *Inflammation and basal cell hyperplasia*: Controls 4; Smoke condensate 32; Benz(a)pyrene 9.
Guerin, 1959, France (*108*).	Strain IC and strain W rat.	A. Chamber inhalation of tobacco smoke. B. Daily (?). C. Up to 6½ months.	*Original number*: Controls 40; Experimental 100. *Survivors*: Controls 39; Experimental 68. *Buccal tumors*: Controls 0/39; Experimental 5/68 (3/5 definite epithelioma)

TABLE A29.—*Experimental studies concerning oral carcinogenesis (cont.)*

Author, year, country, reference	Animal and strain	A. Method. B. Frequency and/or duration. C. Material.	Results
Peacock et al., 1960, U.S.A. (210).	124 Syrian Golden hamsters.	A. Packing of cheek pouch. B. 1 year. C. Snuff, Tobacco, Bland material.	No tumors noted in any of the 42 animals surviving over 1 year.
Dunham and Herrold, 1962, U.S.A. (84).	Syrian Golden hamsters.	A. Packing of cheek pouch. B. Normal lifespan or 5–30 months. C. Betel quid ingredients 7-12 dimethylbenz(a)-anthracene (DMBA), Methylcholanthrene (MCA) in beeswax pellets.	Treatment: Betel quid — Original number 375 — Survivors 90% over 1 year — Hyperplasia and/or inflammation 19 — Malignant pouch tumors — Treatment: DMBA and MCA — Original number 71 — Survivors 56/71 over 5–30 months — Hyperplasia and/or inflammation — — Malignant pouch tumors 23/56
Moore and Christopherson, 1962, U.S.A. (191).	Albino hamster exteriorized oral pouch.	A. Painting oral mucosa. B. 3 per week for 683 days. C. Cigarette smoke condensate. DMBA in 0.5% petrolatum.	Treatment: — Animals with lesions (time) Controls — 0/18 (at 392 days). Smoke condensate — 0/20 (at 337 days) (10 showed hyperkeratosis). DMBA — 14/21 microscopic cancers (at 90 days) (invasive squamous cancer originating in the skin at the edge of the pouch).
Salley, 1963, U.S.A. (239).	CAF_1 strain mice.	A. Ultraviolet light exposure to and painting of lips. B. 3 per week for 98 weeks. C. B(a)P in acetone Cigarette smoke UV light.	Treatment: Ultraviolet light and cigarette smoke — Number 40 — Duration weeks 94 — Tumors — B(a)P and UV light — Number 40 — Duration weeks 48 — Tumors — UV light — Number 40 — Duration weeks 94 — Tumors — B(a)P — Number 40 — Duration weeks 48 — Tumors —

TABLE A29.—*Experimental studies concerning oral carcinogenesis (cont.)*

Author, year, country, reference	Animal and strain	A. Method. B. Frequency and/or duration. C. Material.	Results				
	Hamsters	A. Application to check pouch.	Treatment:	*Original Number*	*Survivors*	*Duration*	*Lesions*
		B. See results.	Cigarettes 5 per week	70	55	64	—
		C. See results.	DMBA once	13	6	128	2 hyperplasia
			Croton oil 3 per week	10	10	30	—
			DMBA once and cigarettes 5 per week	30	28	81	12 hyperplasia 4 dyskeratosis 1 carcinoma
			DMBA once then croton oil 5 per week	29	27	81	7 hyperplasia 6 dyskeratosis 3 carcinoma
Bock et al., 1964, U.S.A. (*90*).	ICR Swiss mice.	A. Painting mouse skin.					
		B. See results 36 weeks.			*Tobacco equivalent (cigarettes/daily)*		*Number tumors/number mice with tumors (small papillomas)*
		C. Various extracts of unburned tobacco DMBA.	Treatment:				
			DMBA once then:				
			Acetone benzene extract		2.5		16/7
			Concentrated $Ba(OH)_2$ extract		0.5		18/8
			Diluted $Ba(OH)_2$ extract		0.5		6/2
			DMBA only		—		—
			Acetone benzene extract		2.5		—
			Concentracted $Ba(OH)_2$ extract		0.5		—
			Diluted $Ba(OH)_2$ extract		0.5		—
			None		—		—

TABLE A29.—*Experimental studies concerning oral carcinogenesis (cont.)*

Author, year, country, reference	Animal and strain	A. Method. B. Frequency and/or duration. C. Material.	Results			
				Original number	*Percent at 13 months with* Papilloma	Cancer
Protzel et al., 1964, U.S.A. (*218*).	Swiss Webster mice with some having liver damage induced either by CCl4 or ethyl alcohol.	A. Swabbing of labial mucosa. B. Up to 13 months. C. B(a)P in acetone.	Alcohol and CCl_4 treated	40	74	46
			Alcohol treated	40	84	50
			CCl_4 treated	40	90	40
			No toxin	40	42	15
Reddy and Anguli, 1967, India (*219*).	Swiss female mice.	A. Intravaginal instillation. B. Daily for 324–380 days. C. "Pan" mixture of areca nuts, lime, and chewing tobacco.	*Original number*: 60	*Survivors*: 40	*Lesions*: 3/40 raised papillomatous malignant growths 4/40 possible carcinoma-in-situ.	
Elzay, 1969, U.S.A. (*90*).	Syrian Golden hamsters.	A. Application to cheek pouch. B. Daily for 200 days. C. See results.	Treatment:	*Original number*	*Mortality rate*	*Number animals*	*Percent with tumors*	*Percent with cancer*
			DMBA Alcohol Smoke	29	41.0	17	100.0	50.0
			DMBA Alcohol	29	66.0	10	60.0	40.0
			DMBA ..... Smoke	29	42.0	14	100.0	70.0
			DMBA	29	48.0	15	100.0	88.0
			..... Alcohol Smoke	29	42.0	14	—	—
			.... Smoke	29	42.0	14	—	—