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 acide 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 5,003 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 15		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		*Percent*	
			Male *Female*		*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	
Blümlein, Germany (*26*)	27.5	
Wynder et al., U.S.A. (*312*)	23.6	
Wynder et al., India (*312*)	3.1	
Schwartz et al., France (*248*)	4.6	
Wynder et al., Sweden (*322*)	6.0	
Wynder et al., Cuba (*325*)	(18.9)	(males only)
Dutta-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	10.5
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		Controls		Comments
		Number	Method of selection	Number	Method of selection	
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	Sex	Cases		Controls		Comments
		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. (*193*).	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. (*232*).	M.	1,136	Hospital patients with lip, oral, and pharyngeal cancer, 1938–43: *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 ihsignificant 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 ..... 29 — >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: Number	Cases: Method of selection	Controls: Number	Controls: Method of selection	Comments
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:	
				Percent		
			Males: *Lip* / *Buccal mucosa* / *Anterior tongue* / *Posterior tongue*		*Pharynx* / *Males*	
			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) / (293) / (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) / (152) / (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*	*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 1953–68: *Percent* Nonusers ..... 5.1 Cigarettes ..... 68.6 Pipe only ..... 4.0 Cigar only 6.9	408	Next male patient admitted to same hospital within 5 year age range. *Percent* 14.2 56.4 ($p<0.0001$) 2.9 6.1	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.
Martinez, 1969, Puerto Rico (*188*).	M. F.	38	Patients with epidermoid carcinoma of oral cavity and pharynx: *Percent* Nonsmokers ..... 13.7 Heavy tobacco users 24.8	345 114	115 male and 38 female hospital or clinic patients without cancer; 330 male and 76 female residents of same region, age and sex matched. *Percent* 19.2 12.2 ($p<0.0001$)	Cases found to consume more alcoholic beverages than controls.
Keller, 1970, U.S.A. (*141*).	M.	304	Patients with primary basal or squamous cell carcinoma of lip: *Percent* Nonsmokers ..... 7.3 Cigarettes only ..... 60.2 Pipe only ..... 6.0 Pipe, other 6.3	304	Patients from same hospital matched for age and race. *Percent* 16.6 ($p<0.001$) 52.8 3.4 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. (*248*)		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. (*323*)	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. (*298*)	.....	.....	.....	.....	.....	.....	.....	.....	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 (*183*)	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. (*238*).	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* — *Number with benign tumors* — *Number with carcinoma* Acetone solvent ..... 5 — 1 — 2 Benzene solvent ..... 4 — — — —
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* — *Surviving over 1 year* — *Number tumors* — *Inflammation and basal cell hyperplasia* Controls ..... 30 — 23 — .. — 4 Smoke condensate ..... 80 — 55 — .. — 32 Benz(a)pyrene ..... 20 — 16 — .. — 9
Guerin, 1959, France (*108*).	Strain IC and strain W rat.	A. Chamber inhalation of tobacco smoke. B. Daily (?). C. Up to 5½ months.	— *Original number* — *Survivors* — *Buccal tumors* Controls ..... 40 — 39 — 0/39 Experimental ..... 100 — 68 — 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: — *Number* — *Duration* weeks — *Tumors* Ultraviolet light and cigarette smoke — 40 — 94 — — B(a)P and UV light — 40 — 48 — — UV light — 40 — 94 — — B(a)P — 40 — 45 — —

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 cheek pouch. B. See results. C. See results.	Treatment:	*Original Number*	*Survivors*	*Duration*	*Lesions*
			Cigarettes 5 per week	70	55	64	—
			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. (*30*).	ICR Swiss mice.	A. Painting mouse skin. B. See results 36 weeks. C. Various extracts of unburned tobacco DMBA.	Treatment:		*Tobacco equivalent (cigarettes/daily)*		*Number tumors/number mice with tumors (small papillomas)*
			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
Protzel et al., 1964, U.S.A. (*213*).	Swiss Webster mice with some having liver damage induced either by CC14 or ethyl alcohol.	A. Swabbing of labial mucosa. B. Up to 13 months. C. B(a)P in acetone.	Alcohol and CCl_4 treated ..... Original number 40; Percent at 13 months with Papillomas 74; Cancer 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: DMBA Alcohol Smoke; Original number 29; Mortality rate 41.0; Number animals 17; Percent with tumors 100.0; Percent with cancer 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; —; —

TABLE A31.—*Summary of methods used in retrospectvie studies of tobacco use and cancer of the esophagus*

Author, year, country, reference	Cases			Controls		Collection of data
	Sex	Number	Method of selection	Number	Method of selection	
Sadowsky et al., 1953, U.S.A. (*232*).	M.	104	White patients admitted during 1938–43 to selected hospitals in New York City, Missouri, New Orleans, and Chicago.	615	White patients with illnesses other than cancer admitted to same group of hospitals during same period.	Obtained by 4 specially trained lay interviewers. 242 records out of a total of 2,847 excluded because of incomplete or questionable smoking histories.
Sanghvi et al., 1955, India (*241*).	M.	73	Consecutive clinic admissions to Tata memorial Hospital, Bombay.	288 107	Consecutive clinic admissions of patients without cancer. Consecutive admissions of patients with cancers other than intraoral or esophagus.	By means of "detailed questionary." No other details given.
Wynder et al., 1957, Sweden (*322*).	M. F.	39 35	Patients admitted to Radiumhemmet, Stockholm, during 1952–55.	115 156	Patients admitted to same hospital with cancer of skin, head and neck region other than squamous cell cancer, leukemia, colon, and other sites. No matching.	
Staszewski, 1960, Poland (*260*).	M.	24	Patients admitted to Oncological Institute during 1957–59.	912	Other patients sent to Institute with symptoms probably not etiologically connected either with smoking or with diseases of esophagus, stomach or duodenum.	No details given on method of data collection. No age adjustment or matching. Average age of cancer patients, 60.5; controls, 53.