



Cancer of the Larynx: Occupational and Environmental Associations

SALLY R. COWLES, MD, DrPH, Houston, Tex

ABSTRACT: This paper briefly reviews the available evidence for the influence of environmental and occupational factors in the development of cancer of the larynx. Although several occupational exposures have been suggested to play a role in the etiology of this disease, few have been convincingly confirmed. The strong association between smoking and cancer of the larynx, the weaker but still important association between alcohol consumption and cancer of the larynx, and the strong synergism between the two is emphasized. Other accepted or suspected environmental and occupational factors are also discussed.

IT HAS BEEN ESTIMATED that in 1982 roughly 10,900 new cases of cancer of the larynx will have occurred in the United States and that 3,700 deaths due to cancer of the larynx will have been recorded.¹ Although less than 1.5% of all new cancers are laryngeal, cancer of the larynx, in common with other cancers of the head and neck, has been strongly linked etiologically to environmental factors.² This makes it a good potential target for cancer control programs. Many of the identified environmental factors are related to life-style and personal habits, with only a few related to occupation. This review summarizes what is currently known or suspected about such factors in the development of cancer of the larynx.

One person in every 74 in the US will develop cancer of the larynx. The most common cell type is squamous cell carcinoma (over 90%), with most being moderately or well differentiated. The portion of the larynx most commonly affected is the glottic area (which also has the best prognosis); the least common cancers occur in the subglottic region and have the worst prognosis. The over 20-year survival for individuals with cancer of the larynx is 34%.³ Men are affected more than women, and the current male-female ratio of cases in the United States is roughly 4.5:1.0.⁴ The incidence for white men is highest in the northeastern United States,

Texas, South Carolina, and Georgia. Rates for white women are high in Maine, northern New York, and along the Gulf Coast. Worldwide, the highest rates are seen in Sao Paulo, Brazil, and Bombay, India. Cancer of the larynx is currently increasing in the United States and most other countries. Incidence in the United States has more than doubled since 1940.³

SMOKING

The evidence for a causal association between smoking and cancer of the larynx is particularly convincing. Studies from all over the world have found a marked predominance of smokers among patients with cancer of the larynx, and the relative risk for smokers has been calculated to be from three to 39 times greater than for nonsmokers.⁴⁻¹⁴ The striking correlation between studies, and the linear dose-response relationship between risk and amount smoked are well illustrated in a review by Rothman et al.³ The decline in male-female ratios for cancer of the larynx (14.9:1.0 in 1956 compared to 4.6:1.0 in 1974) is consistent with the increase, beginning before World War II, in the number of female smokers.¹⁵ In France, where cancer of the larynx is very common, the use of black tobacco cigarettes without filters when smoked without inhaling has been linked to increased risk.¹⁴ Cancer of the larynx is comparable to cancer of the lung in the strength of its association with smoking, and the relationship is far greater than for any other cancer.¹³ As with cancer of the lung, the risk to ex-smokers and smokers of filter cigarettes is less than to current smokers or smokers of unfiltered cigarettes. Ex-

From the Department of Family and Community Medicine, University of Texas Medical School, Houston.

Reprint requests to Sally R. Cowles, MD, Department of Family and Community Medicine, University of Texas Medical School, PO Box 20708, Houston, TX 77025.

smokers who have not smoked for ten to 15 years have approximately half the risk of a current smoker.⁴

The risks associated with smoking also appear to be age related. In new cases of laryngeal cancer, patients who smoked were an average of 15 years younger than those who did not smoke (age 58 compared to age 73, respectively), and long-term ex-smokers (more than ten years) were roughly ten years older than smokers.⁴ An Irish study showed similar results, with the risk of developing cancer of the larynx in a heavy smoker under age 60 being 18 times that of a nonsmoker, while only 5.5 times greater when the smoker was over age 60.⁷ In studies reviewed, the highest percentage of nonsmokers in cases of cancer of the larynx was only 4%.⁹ Smoking is a *potent* risk factor for cancer of the larynx. Because smoking is such a strong risk factor, it is a powerful confounder in any analysis of other possible associations with cancer of the larynx, and must be corrected for.

ALCOHOL INGESTION

Ethanol ingestion has also been shown to be associated with cancer of the larynx, but the relationship is far weaker than that with smoking. After adjustment for smoking habits, the ethanol risk has been estimated to be from 1.5 to 4.4 times that of nondrinkers.^{5-8,13,16} More important than the independent effect of ethanol, however, is the apparent potentiation and synergism seen when smoking and drinking are combined.^{4,5,7,8} Relative risks associated with heavy drinking and heavy smoking combined have been reported to be at least 50% greater than would be expected from additive effects of the two factors.¹⁷ Ethanol consumption and smoking have been found to be important in the development of double primary cancers of the head and neck as well, and the development of cancer of the larynx as a second primary shows an association with continued ethanol intake after discovery of the first primary.¹¹ As with smoking, the effects of alcohol appear to be greater at younger ages—heavy drinkers under 60 years of age had a relative risk of 5.8 compared to one of 2.3 for heavy drinkers over age 60.⁷ The mechanism of action of alcohol in the production of cancer of the larynx is not clear. Ethanol may be a cancer promoter, especially when combined with smoking.^{12,13} Benz-a-pyrene when diluted in ethanol will produce cancers in animal studies, whereas when diluted in oil it does not.¹² This would imply that the alcohol may serve as a vehicle to increase the carcinogenicity of other carcinogens. Poor nutrition is a frequent accompaniment of heavy drinking and may also contribute to cancer development. Specific nutritional deficits (vitamin B deficiency and iron deficiency) have been implicated in the increased numbers of laryngeal cancers seen in Scandinavian women (Plummer-Vinson disease)—cancers that are now rarely seen since efforts to correct the nutritional defi-

cits have been made.^{12,18} Low vitamin A and low vitamin C intake was associated with a slight increase in risk of laryngeal cancer in one study.⁶ Ethanol may have an effect on micronutrients or result in the production of proximate carcinogens within the oral cavity. Ethanol has been shown to increase the hydroxylation of nitrosamines.¹⁸ A recent preliminary report described ethyl nitrite (a potent mutagen) in the breath of two people who smoked and drank at the same time, but not after smoking or drinking alone.¹⁹ Ethanol ingestion, by whatever mechanism, is weakly associated with cancer of the larynx in the absence of smoking, and strongly associated when smoking is also present.

OTHER ENVIRONMENTAL FACTORS

Other nonoccupational environmental factors that have been linked to cancer of the larynx include such habits as chewing betel nuts, using "PAN" (a combination of tobacco, slaked lime, and betel leaf) in India, and chewing miang (fermented wild tea leaves) in northern Thailand.^{20,21} Phenols in tea have been suspected of cancer promotion as well, and have produced suggestive laboratory evidence.²¹ No study to date, however, has shown an increased risk of laryngeal cancer in heavy tea drinkers in the absence of other factors. Despite high levels of PAHs (polycyclic aromatic hydrocarbons) in south Los Angeles air, no association with laryngeal cancer has been demonstrated, though an increased incidence in lung cancer has been seen in this area.²² Studies are divided as to whether there is a rural or urban predominance for cancer of the larynx, so if such an effect exists, it is likely to be small compared to that of smoking, drinking, and other personal habits.

OCCUPATIONAL FACTORS—ACCEPTED

Much recent interest has been focused on possible occupational association of cancer of the larynx. The extremely strong association of cancer of the larynx with smoking makes it difficult to identify potential occupational exposures that may also be exerting an effect. Very few exposures to date have shown convincing and constant evidence of an association.

The strongest evidence for an occupational association with cancer of the larynx is found in studies of Japanese and English mustard gas workers, in whom an excessive incidence of laryngeal cancer was found in follow-up.^{23,24} Mustard gas is highly irritating to the respiratory tree, and the larynx receives an early concentrated dose. Acute laryngeal findings had been documented in some cases during mustard gas production as well,²⁴ so the cause-effect sequence is convincing and so far unchallenged. Numbers of cases were small, however, and no control for smoking or drinking was made in these studies.

Another fairly well accepted occupational association recognized since the early 1940s is that of isopropanol production and laryngeal cancer. Two cases of cancer of the larynx were found in operators at one plant using a strong acid process (in conjunction with several other cancers of the head and neck area).²⁵ Investigation at the time determined that isopropyl oil (an animal carcinogen) was the most likely culprit. A more recent study by Exxon of four cases of cancer of the larynx associated with a strong acid process for ethanol production has determined that diethyl sulfate is the more likely carcinogen.²⁶ The diethyl sulfate is a potent mutagen found in high concentrations during the strong acid process production of both ethanol and isopropanol. Levels are much reduced in the weak acid process currently used, and no associated laryngeal cancers have been seen in conjunction with it.

OCCUPATIONAL FACTORS—SUSPECTED

Other occupational associations with cancer of the larynx are based either on one unconfirmed and not entirely convincing report, or on conflicting reports. Better controlled studies are needed to definitively assess these possible associations. The association for which data continue to be conflicting, and around which the most controversy currently revolves, is that of occupational exposure to asbestos and cancer of the larynx. If there is an association, it is far less important than the potential link between occupational exposure to asbestos and cancer of the stomach. Several reports have suggested an association between asbestos exposure and cancer of the larynx. Three cases of cancer of the larynx occurred in Philadelphia shipyard workers who also had chest x-ray evidence of asbestos-related disease.²⁷ They ranged from 54 to 65 years old, and each was a current or ex-smoker. One cancer of the larynx occurred in a series of 879 cases of asbestosis in Italy, but smoking habits were not assessed and the paper reporting this case was more concerned with the significant excess of lung cancer and pleural mesothelioma in this population.²⁸

A retrospective case-control study in Liverpool, England, showed that more patients than controls had had occupational exposure to asbestos (including ten dockworkers who had unloaded raw asbestos), but smoking was not adequately controlled for. Questions also remain regarding possible selection bias in this study (three reports of the study each give different numbers of exposed patients), and only one patient showed chest x-ray changes related to asbestos exposure.²⁹⁻³¹ In addition, in the last report of this study³¹ a caveat was added pointing out that the report was based on a small number of male patients "who may have been influenced by the prospect of compensation." A similar case-control study in Toronto of 54 cases of cancer of the larynx found that more than

expected had worked with asbestos^{32,33}; but this study did not control for smoking (all asbestos workers were smokers), no clear dose-response was seen (nor was one seen in the Liverpool study), and all had had less than one year of exposure or only light intermittent exposures to asbestos. Another case-control study of 47 cases in Washington state (Puget Sound area) found a weak, insignificant correlation between asbestos exposure and cancer of the larynx, with no dose-response effect.⁸ A strong association between smoking and cancer of the larynx, with a strong dose-response effect, was seen. Only one patient was a nonsmoker.

A study of shipyard workers in Virginia also found no overall excess of cancer of the larynx in workers using asbestos, though an excess of lung cancer was found.³⁴ Numbers were small, but a strong smoking association that increased with ethanol intake was also seen. Black workers were found at higher risk than white workers in this study. A study of more than 900 chrysotile asbestos miners in Italy found six with cancer of the larynx compared to 1.9 expected cases (based on Italian cancer statistics), but the numbers were too small for statistical significance; all were smokers, and the area in which the study was done has a higher background rate of cancer of the larynx than the rest of Italy.³⁵

Two reviews of the asbestos and laryngeal cancer association mention two studies, one of London factory workers working with asbestos, and the other of American insulators, which showed potentially a 2:1 excess of deaths from cancer of the larynx in these populations, but again, smoking was not controlled for. Similar results have *not* been seen in Canadian chrysotile miners or millers, or in a prospective case-control study in an ENT hospital in London.^{36,37} At this point the association between asbestos exposure and cancer of the larynx is unproven, but evidence suggests there may be a mild synergism between smoking and asbestos exposure similar to that seen between smoking and ethanol intake (although possibly to a lesser degree). In cancer registry studies, both in the United States and the United Kingdom, occupations with high asbestos exposures do *not* consistently show greater risks for cancer of the larynx.³⁸⁻⁴³

Other occupations that have been linked in at least one report to cancer of the larynx, but for which confirming evidence is not currently available, include farmers and laborers in Croatia¹⁰; farmers, fishermen, and laborers in Japan⁹; barbers, chemical industry operatives, leather industry operatives, and paper workers in the US^{42,43}; leather workers, pulp and paper workers, sawyers, and woodworkers in Washington state⁴¹; persons exposed to wood dust in the US⁴; stevedores and dock laborers; recreation workers, laborers, machine tool operators, deck and

TABLE. Summary of Factors of Potential Importance in the Development of Cancer of the Larynx (in Relative Order of Importance)

Factors	Importance
1. Smoking	Increased risk 4-40x
2. Alcohol consumption	Increased risk up to 3x
3. Mustard gas	} Synergism between Occupational relationship well accepted
4. Isopropanol production (probably due to diethyl sulfate)	
5. Chewing betel, PAN, miang	Consistent results—probably relationship between these habits and increased risks seen in India, Southeast Asia
6. Dietary deficiencies (iron, vitamin B, vitamin A, vitamin C)	Suspected from several studies and by virtual elimination of Plummer-Vinson disease from Sweden through nutrition supplements
7. Asbestos	Conflicting reports; may be mild asbestos/smoking synergism
8. Nickel	Occupational relationship reported from one country—unconfirmed by other studies
9. Vocal abuse	Suggested from several studies
10. Soots, tars, mineral oil	Anecdotal reports—no confirming evidence
11. Pesticides	Anecdotal reports—no confirming evidence
12. Dental x-ray studies	Relationship in heavy smokers in one study
13. Naphthalene workers	Reported in one study—so far unconfirmed
14. Leather workers	Suggested from case registry data; unconfirmed by study of English leather workers
15. Wood dust	Suggested from case registry data but unconfirmed; not seen in English furniture workers
16. Bearing plant workers	Cluster reported—no follow-up
17. Air pollution	No evidence

engine room personnel, and barkeepers in England³⁸; farmers, gardeners, and forest workers in North Bohemia⁴⁴; gardeners in England⁴⁵; nickel workers in Norway⁴⁶; bearing plant workers⁴⁷ and thorium dioxide workers in the US⁴⁸; naphthalene cleaners in Germany⁴⁹; and brewery workers in Denmark.¹⁶ Cancer of the larynx was not found to be increased in a study of English furniture workers.⁵⁰

Vocal abuse has been proposed as a possible factor in the development of cancer of the larynx as well, and many of the occupations statistically linked to this cancer do have increased potential for vocal abuse.^{9,38,51,52} Agents potentially related to the increased risks seen in some of these occupations include mineral oil, pesticides, coal tar, and dental x-rays.^{8,45,53,54}

CONCLUSION

The Table summarizes the current status of various occupational and environmental factors of potential importance in the development of cancer of the larynx. Obviously, there is much still to be learned about cancer of the larynx. Smoking and the combination of smoking and drinking are the two major risk factors for this disease. Mustard gas workers and workers using the strong acid process for ethanol and isopropanol production are the two occupational groups with a well accented increased risk. The evi-

dence regarding asbestos is suggestive, but as yet unproven. Other occupational exposures may increase risk as well, but the relationships are even less clear than those for asbestos. Certainly more research in this area is needed.

As with other cancers strongly associated with smoking, smoking cessation and control are likely to produce the greatest dividends in the efforts to decrease the incidence of cancer of the larynx. Should such efforts be successful, other important environmental and occupational factors may become more readily recognized.

References

1. Silverberg E: Cancer statistics 1982. *Ca* 32:15-31, 1982
2. Decker J, Goldstein JC: Current concepts in otolaryngology: risk factors in head and neck cancer. *N Engl J Med* 306:1151-1155, 1982
3. Rothman KJ, Cann CI, Flanders D, et al: Epidemiology of laryngeal cancer. *Epidemiol Rev* 2:195-209, 1980
4. Wynder EL, Covey LS, Mabuchi K, et al: Environmental factors in cancer of the larynx: a second look. *Cancer* 38:1591-1601, 1976
5. Feldman JG, Hazan M, Nagarajan M, et al: A case-control investigation of alcohol, tobacco, and diet in head and neck cancer. *Prev Med* 4:444-463, 1975
6. Graham S, Mettlin C, Marshall J, et al: Dietary factors in the epidemiology of cancer of the larynx. *Am J Epidemiol* 113:675-680, 1981
7. Herity B, Moriarty M, Bourke GJ, et al: A case control study of head and neck cancer in the Republic of Ireland. *Br J Cancer* 43:177-182, 1981
8. Hinds MW, Thomas DB, O'Reilly HP: Asbestos, dental x-rays, tobacco, and alcohol in the epidemiology of laryngeal cancer. *Cancer* 44:1114-1120, 1979
9. Iwamoto H: An epidemiological study of laryngeal cancer in Japan (1960-1969). *Laryngoscope* 85:1162-1172, 1975
10. Krajina Z, Kulcar Z, Konic-Carnelutti V: Epidemiology of laryngeal cancer. *Laryngoscope* 85:1155-1161, 1975
11. Schottenfeld D, Gant RC, Wynder EL: The role of alcohol and tobacco in multiple primary cancers of the upper digestive system, larynx and lung: a prospective study. *Prev Med* 3:277-293, 1974
12. Wynder EL, Mabuchi K: Etiological and preventive aspects of human cancer. *Prev Med* 1:300-334, 1972
13. Wynder EL, Stellman SD: Comparative epidemiology of tobacco-related cancers. *Cancer Res* 37:4608-4622, 1977
14. Wynder EL, Mushinski MH, Stellman SD, et al: Tobacco usage in France: an epidemiological study. *Prev Med* 10:301-315, 1981
15. Wynder EL: Toward the prevention of laryngeal cancer. *Laryngoscope* 85:1190-1196, 1975
16. Jensen OM: Cancer morbidity and causes of death among Danish brewery workers. *Int J Cancer* 23:454-463, 1979
17. Flanders WD, Rothman KJ: Interaction of alcohol and tobacco in laryngeal cancer. *Am J Epidemiol* 115:371-379, 1982
18. McCoy GD, Hecht SS, Wynder EL: The roles of tobacco, alcohol and diet in the etiology of upper alimentary and respiratory tract cancers. *Prev Med* 9:622-629, 1980
19. MacDonald J: OT briefs. *Oncology Times* 4:18, 1982
20. Hiranandani LH: Panel of epidemiology and etiology of laryngeal carcinoma. *Laryngoscope* 85:1197-1207, 1975
21. Yang JA, Huber SA, Lucas ZJ: Inhibition of DNA synthesis in cultured lymphocytes and tumor cells by extracts of betel nut, tobacco, and miang leaf: plant substances associated with cancer of the ororespiratory epithelium. *Cancer Res* 39:4802-4809, 1979
22. Henderson BE, Gordon RJ, Menck H, et al: Lung cancer and air pollution in south central Los Angeles County. *Am J Epidemiol* 101:477-488, 1975
23. Kurozumi S, Harada Y, Sugimoto Y, et al: Airway malignancy in poisonous gas workers. *J Laryngol Otol* 91:217-225, 1977
24. Manning KP, Skegg DCG, Stell PM, et al: Cancer of the larynx and other occupational hazards of mustard gas workers. *Clin Otolaryngol* 6:165-170, 1981
25. Weil CS, Smyth HF, Nale TW: Quest for a suspected industrial carcinogen. *Arch Ind Hyg Occup Med* 5:535-547, 1952
26. Lynch J, Harris NM, Bird MG, et al: An association of upper respiratory cancer with exposure to diethyl sulfate. *J Occup Med* 21:333-341, 1979
27. Libshitz HI, Wershba MS, Atkinson GW, et al: Asbestosis and carcinoma of the larynx: a possible association. *JAMA* 228:1571-1572, 1974
28. Vigliani EC, Mottura G, Maranzana P: Association of pulmonary tumors with asbestosis in Piedmont and Lombardy. *Ann NY Acad Sci* 132:558-574, 1965
29. Stell PM, McGill T: Asbestos and cancer of head and neck (Letter). *Lancet* 804(1):678, 1973
30. Stell PM, McGill T: Asbestos and laryngeal carcinoma. *Lancet* 805:416-417, 1973

31. Stell PM, McGill T: Exposure to asbestos and laryngeal carcinoma. *J Laryngol Otol* 89:513-517, 1975
32. Shettigara PT, Morgan RW: Asbestos, smoking, and laryngeal carcinoma. *Arch Environ Health* 30:517-519, 1975
33. Morgan RW, Shettigara PT: Occupational asbestos exposure, smoking, and laryngeal carcinoma. *Ann NY Acad Sci* 271:308-310, 1976
34. Blot WJ, Morris LE, Stroube R, et al: Lung and laryngeal cancers in relation to shipyard employment in coastal Virginia. *J Natl Cancer Inst* 65:571-575, 1980
35. Rubino GF, Piolatto G, Newhouse ML, et al: Mortality of chrysotile asbestos workers at the Balangero Mine, Northern Italy. *Br J Ind Med* 36:187-194, 1979
36. Newhouse ML, Gregory MM, Shannon H: Etiology of carcinoma of the larynx. Biological effects of mineral fibers. *IARC Sci Publ* 30:687-695, 1980
37. Newhouse M: Epidemiology of asbestos related tumors. *Semin Oncol* 8:250-257, 1981
38. Chovil A: Laryngeal cancer: an explanation for the apparent occupational association. *Med Hypotheses* 7:951-956, 1981
39. Decoufle P: Cancer risks associated with employment in the leather and leather products industry. *Arch Environ Health* 34:33-37, 1979
40. Flanders WD, Rothman KJ: Occupational risk for laryngeal cancer. *Am J Public Health* 72:369-372, 1982
41. The evaluation of the carcinogenic risk of chemicals to humans: wood, leather and some associated industries. *IARC Sci Publ* 25:244, 296-299, 1981
42. NIOSH Research Report: *A Retrospective Survey of Cancer in Relation to Occupation*. NIOSH DHEW, 1977
43. Viadana E, Bross ID, Houten J: Cancer experience of men exposed to inhalation of chemical or to combustion products. *J Occup Med* 18:787-792, 1976
44. Svoboda V: An analysis of some possible epidemiological factors involved in carcinoma of the larynx. *Neoplasma* 15:677-864, 1968
45. Klayman MB: Exposure to insecticides (Letter). *Arch Otolaryngol* 88:116-117, 1968
46. Pedersen E, Hogerweit AC, Anderson A: Cancer of respiratory organs among workers at a nickel refinery in Norway. *Int J Cancer* 12:32-41, 1973
47. Kopelman J, Thind I, Lorina D: Investigating industrially-related diseases (Letter). *Am J Public Health* 70:436, 1980
48. *Assessment of Technologies for Determining Cancer Risks from the Environment*. Office of Technology Assessment, Congress of the US, 1981
49. Wolf O: Carcinoma of the larynx among naphthalene cleaners. *Z Gesamte Hyg* 24:737-739, 1978
50. Rang EH, Acheson ED: Cancer in furniture workers. *Int J Epidemiol* 10:253-261, 1981
51. Atkinson L: Some features of the epidemiology of cancer of the larynx in Australia and Papua, New Guinea. *Laryngoscope* 85:1173-1184, 1975
52. Wynder EL, Bross IJ, Day E: A study of the environmental factors in cancer of the larynx. *Cancer* 9:86-110, 1957
53. Hueper WC: Occupational and environmental cancers of the respiratory system. *Recent Results in Cancer Research*. New York, Springer-Verlag, Vol 3, 1966
54. Kipling MD, Waldron HA: Polycyclic aromatic hydrocarbons in mineral oil, tar, and pitch, excluding petroleum pitch. *Prev Med* 5:262-278, 1976

*Southern Medical Association's
Research Project Fund has distributed
over \$250,000 since it began in 1970*