Asbestos Exposure and Laryngeal Cancer: An Analysis of the Epidemiologic Evidence

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We conducted a critical analysis of the available epidemiologic investigations on the causal relationship between asbestos exposure and laryngeal cancer. A review of nine case-control studies indicates that the estimated risk (odds ratio) attributable to asbestos exposure alone is negligible when smoking and ethanol intake are appropriately controlled for. Six of the 12 cohort studies demonstrated no significant increase in the standardized mortality ratio due to asbestos exposure. The remaining six longitudinal studies showed an increased standardized mortality ratio from 1.91 to 5.41 but no adjustment was made for the confounding effects of smoking and ethanol consumption. In conclusion, the available epidemiologic evidence does not support a causal association between asbestos exposure and laryngeal cancer.

Asbestos, in spite of its technological and economic value to society at large, has been among the greatest occupational hazards of this century.[1] Asbestos has been clearly shown to be responsible for many cases of lung cancer, mesothelioma, and also for asbestosis.[2-4,6-11] Asbestos has also been inculpated in other malignancies, including laryngeal tumors.[3-11] The notion that asbestos could cause laryngeal cancer is suggested both by limited evidence of asbestos fibers being present in laryngeal tissue[12,13] and by the larynx being part of the respiratory tract. However, the larynx is, unlike lower airways, lined by squamous epithelium. We offer here a review of this latter relationship, which will suggest first that much of the evidence derives from epidemiologic studies which have simply examined the relation between asbestos and laryngeal cancer without any regard to other known potent carcinogenic factors, specifically cigarette smoking and ethanol consumption, and second that the evidence implicating asbestos is minimal or absent. Aside from the inappropriateness of the oft-quoted conclusions and some misplaced litigation, one result may be that physicians do not always advise asbestos workers on the proper personal preventive measures that they should take.

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Effects of Smoking and Alcohol

There has been a gradual increase in laryngeal cancer rates in the United States over the last four decades.[14] Part of the increase may be attributable to more accurate reporting of the disease or increased detection[14] but smoking and alcohol drinking have been consistently shown to be the two most important environmental factors for this neoplasm.[14-20] The dose-response relationships which support causality between smoking, alcohol, and laryngeal cancer (Table 1) have been elegantly demonstrated by Wynder et al[16] and Rothman et al.[19] Flanders and Rothman[20] also reported a synergistic effect between smoking and alcohol consumption for laryngeal cancer; the interaction being such that a one pack-a-day smoker who also consumes a moderate amount of alcohol (more than 6 ounces of liquor per day) has a greater than twenty-fold increased risk of developing laryngeal cancer.[18,20] A particularly detailed study by Elwood et al[21] reported on 374 cases of head and neck cancer and specifically separated the sites to include data on extrinsic and instrinsic laryngeal cancers. They found that both smoking and alcohol were separate risk factors for 46 extrinsic cancers, whereas smoking was the significant factor for 108 intrinsic laryngeal cancers. These workers were not able to distinguish between additive and multiplicative interpretations of the data for alcohol and smoking. All these studies demonstrate the necessity of adjusting for smok-

TABLE 1
Relative Risk Estimates for Laryngeal Cancer*

	Relative Risk
Smoking (cigarettes/day)	adjusted for alcohol
0	1.0
1–15	4.6
16–34	11.0
35+	14.0
Alcohol intake (oz liquor/day)	adjusted for smoking
<1.5	1.0
1.5–9	1.2
>10	2.2

* Modified from Wynder et al[16] and Rothman et al.[19]

ing and ethanol consumption when delineating other risk factors for laryngeal cancer. The need for such adjustment is underscored by the high prevalence (>90%) of smoking, frequently heavy, among asbestos workers.[22]

Effects of Asbestos

The available evidence on the causal relationship between asbestos and laryngeal cancer in the English literature can be divided into three main categories: retrospective case-control design,[21,23–30] cohort or longitudinal follow-up survey,[3–11,31–33] and case series.[34]

Case-control Studies

The pertinent results of the nine case-control studies[21,23–30] are summarized in Table 2 and are considered in two groups.

Studies Adjusted for Smoking and Alcohol. There were five well-executed case-control studies[23–27] that adjusted the crude estimates of relative risk (odds ratios) for cigarette smoking and alcohol consumption (Table 2).

Hinds et al[23] stratified their cases and controls and according to cigarette and alcohol consumption and found no increase in risk from asbestos exposure alone. An impressive and statistically significant dose-dependent increase in the odds ratios comparable to that reported in the general population[16,20] was demonstrated for both cigarette and alcohol intake in the asbestos population. The unadjusted odds ratio for laryngeal cancer associated with asbestos exposure was a statistically insignificant value of 1.75 (Table 2). When adjustments were made for cigarette and ethanol consumptions,[23] the ratio became one!

A similar but smaller case-control study by Blot et al[24] showed (Table 2), after adjustment for cigarette smoking, no significant increase in the odds ratio among asbestos workers for either black or white persons (Table 2). In spite of small numbers and with their inherent errors in relative risk estimates, clear relations between laryngeal cancer and both smoking and alcohol consumption were again observed.[24]

In a search for "occupational causes" of laryngeal cancer, Olsen and Sarbroe[25] found a slightly increased odds ratio for asbestos exposure (Table 2). However, since the 95% confidence limit for the odds ratio when adjusted for tobacco and alcohol consumption was 1.0 to 3.4, the conclusion is moot.

TABLE 2
Case-control Studies on Asbestos and Laryngeal Cancer

Authors	No. of Cases	Odds Ratio	P
Elwood et al[21]	154	—	NS*
Hinds et al[23]	47	1.75	NS
Blot et al[24]			
Blacks	11	2.4	NS
Whites	2	0.23	NS
Olsen and Sarbroe[25]	17	1.8	NS
Burch et al[26]	14	1.6	NS
Shettigara and Morgan[27]	43	∞	<.001
Morgan and Shettigara[28]	54†	13	<.001
Stell and McGill[29]	100	14.5	<.001
Stell and McGill[30]	119‡	14.8	<.001

* NS, not significant.
† Of the 54 cases, 43 were reported in Ref 27.
‡ Of the 119 cases, 100 were reported in Ref 29.

The case-control study of Burch et al[26] on 204 cases of newly diagnosed laryngeal cancer in Ontario, Canada, again showed strong associations between tobacco products and alcohol. A subanalysis of 14 cases and 9 controls with definite asbestos exposure showed a statistically insignificant odds ratio of 1.6 (Table 2).

The Elwood study[21] referred to earlier also failed to detect an influence of occupational factors including asbestos, but the numbers of asbestos workers were small.

Unadjusted Studies. Four case-control studies report significant increases in the odds ratio for laryngeal cancer due to asbestos exposure (Table 2). Lamentably, these studies lack adjustments for either smoking or ethanol consumption. Shettigara and Morgan[27] report an odds ratio of infinity for asbestos exposure in their original study of 43 cases with laryngeal cancer because none of their controls had an asbestos exposure. In a follow-up study, Morgan and Shettigara[28] added 11 cases and found an odds ratio of 13 for asbestos exposure and laryngeal cancer (Table 2). In spite of their own observed striking dose-response relationship for smoking and laryngeal cancer in both of their studies,[27,28] the authors made no adjustments but they indicated that "the risk imposed by asbestos is confined to smokers"[28] since no case of laryngeal cancer was found among nonsmokers with asbestos exposure only.[27,28]

Stell and McGill[29,30] twice reported the increase in odds ratio due to asbestos exposure in a contrived population of 119 patients with laryngeal cancer to be about 15. The crucial information on the smoking habit of a subgroup of 33 cases with asbestos exposure was not available. Although the authors pointed out that smoking might be a "cofactor in the development of laryngeal carcinoma,"[29] they made no adjustment since they believed that "smoking is unlikely to be very important."[29] Ethanol was not considered.

Thus these four studies[27–30] are seriously flawed.

Cohort Studies and Longitudinal Surveys

A number of retrospectively or prospectively assembled exposed asbestos populations have been carefully observed for an average of 20 or more years.[3-11,31-34] These longitudinal studies, in contrast to the case-control studies discussed earlier, provide a more precise assessment of exposure, including dose, time, and latency, thus permitting a more accurate estimate of the risk attributable to asbestos. Also, the confounding effects due to biased interviews or questionnaires, and the "recall bias" provided by the interviewer[35] frequently encountered in case-control studies are avoided in these prospective investigations. Such studies, if performed prospectively, would take at least 20 years, are very expensive, and require cohorts of several thousands of exposed individuals since laryngeal cancers[14] are relatively infrequent. Their results are summarized in Table 3.

In the birth cohort of 11,379 miners exposed to chrysotile fiber in Quebec, McDonald et al[3] found no excess deaths from laryngeal cancer (Table 3). However, a subanalysis of deaths due to laryngeal cancer and smoking revealed a convincing dose-response relationship. Specifically, the standardized mortality ratio (SMR) in nonsmokers was 0.46; in moderate smokers the SMR was 0.93, and in heavy smokers the SMR went up to 4.85. Similar linear exposure-response relationship was also found for asbestos with lung cancer and for pneumoconiosis.[3]

A cohort of 2,543 textile plant workers exposed to chrysotile in South Carolina was also studied by McDonald et al.[4] Life table analyses and "log-rank" statistical comparisons both indicated a much steeper exposure-response slope for lung cancer in the textile workers than that observed in miners.[3] The overall SMR was also elevated to 1.27.[4] However, over the 20 years, the major causes of death in these textile workers were lung cancer, asbestosis, and abdominal malignancies, whereas only three deaths were due to laryngeal cancers (Table 3).

In a follow-up survey of 1,970 workers employed at an asbestos cement factory with predominant exposure to chrysotile, Thomas et al[5] failed to find a single case of cancer of the larynx. However, over three quarters of this population had only worked in this factory for under 4 years.[5]

Hodgson and Jones[6] reviewed the British national survey of over 30,000 asbestos insulation workers in 1981. The length of time after exposure was highly variable in this cohort. Although they observed an SMR of 2.56 for lung cancer, no excess deaths from laryngeal cancer occurred.

In a quasi-cohort survey, Botha et al[7] calculated the SMRs in South African crocidolite mining districts from 1968 to 1980. Eleven contiguous districts with little crocidolite exposure were used as controls. In spite of elevated SMRs for asbestosis, mesothelioma, and cancer of the lung and stomach, no excess of laryngeal cancer (four deaths) occurred in this group of 18,000 persons of mixed race.

In a survey of cancer mortality between 1950 and 1969 in 49 US counties where shipyards were engaged in the construction and repair of large naval and cargo vessels during World War II, Blot et al[8] found "no upward trends in mortality for laryngeal cancer." The age-adjusted mortality rates for those counties in that period among whites was 1.18 for men and 1.16 for women. The obvious limitation in this type of large population survey is that major changes in the incidence of disease are needed before there is any noticeable increase in the relative risk in huge populations. Therefore, one cannot use these results to exclude confidently any causal relationship.

Selikoff et al[9] reported on a contrived cohort of 17,800 insulation workers in the United States and Canada. The length of time after exposure was also variable, ranging from less than 20 years to well over 35 years from onset of employment. An increase in the overall SMR to 1.37 was observed, and the major contributors to this increase in SMR were lung and abdominal cancers and asbestosis. Laryngeal cancer was reported in nine deaths, which elevated the SMR to 1.91 (Table 3), but no adjustment was made for cigarette or ethanol consumption.

TABLE 3
Cohort Studies on Asbestos and Laryngeal Cancer

Authors	Cohort Size	Years after Exposure	No of Cases of Laryngeal Cancer	SMR/RR*
McDonald et al[3]	11,379	>29	16	1.07
McDonald et al[4]	2,543	>20	3	—
Thomas et al[5]	1,970	Variable	0	—
Hodgson and Jones[6]	31,150	Variable	—	—
Botha et al[7]	18,278	Variable	4	—
Blot et al[8]	—	Variable	—	1.16–1.18
Selikoff et al[9]	17,800	Variable	9	1.91
Puntoni et al[10]	2,348	>10	8	1.57
Puntoni et al[11]	34,746†	Variable	15	1.96
Newhouse[31]	4,000	>20	2	5.41
Newhouse et al[32]	5,100‡	>20	3	3.70
Rubino et al[33]	900	Variable	6	3.16

* RR, relative risk.
† Person-years of observation.
‡ Of the 5,100 workers, 4,000 were included in Ref 31.

Puntoni et al[10,11] analyzed the causes of deaths among the shipyard workers in Genoa, Italy. The first report in 1977[10] included 2,348 dockyard workers observed for 10 or more years after asbestos exposure for a total of 22,188 person-years of observation. The 1.57 relative risk for laryngeal cancer was not statistically significant. In the follow-up report in 1979[11] of several thousand dockyard workers employed between 1960 and 1970, the investigators noted 15 deaths due to laryngeal cancer with a corresponding relative risk of 1.96. Their conclusion that asbestos exposure was a risk factor for laryngeal cancer is vitiated by failure to control for smoking and alcohol consumption.

Both studies of Newhouse et al[31,32] (Table 3), although useful in other ways, contain too few cases of laryngeal cancer (two and three cases) to provide stable estimates of the relevant SMR.

The report by Rubino et al[33] on the mortality of more than 900 North Italian chrysotile miners is particularly interesting. They report six deaths from laryngeal cancer (SMR of 3.16). Although all these six miners were smokers, no adjustment of the SMR was made for smoking. Surprisingly, no excess deaths from asbestosis or lung cancer were found, but the SMRs for nonmalignant respiratory diseases and cirrhosis were, respectively, 2.53 and 3.13. One may well ask what were the smoking and drinking practices of these miners?

Why should 12 cohort studies[3-11,31-33] arrive at SMRs or relative risk that ranged from 1.07 to 5.41? Even if we exclude Newhouse's data[31,32] because of the small number of cases and discard Rubino's anomalous results[33] the discrepancy in the SMR of 1.07 in McDonald's study[3] and 1.91 in Selikoff's cohort[9] and the conflicting results of Puntoni's two studies[10,11] needs comment. Aside from the failure to address the effects of smoking and ethanol consumption, two other potential confounding variables are the variable length of follow-up[36] and differences in the types and size of asbestos fibers exposed in these cohorts.[37,38]

Indeed, if we reanalyze Selikoff's data[9] for their older cohort of 623 insulation workers with 20 or more years after onset of work, the SMR in this subgroup was 1.18.[9] Since the average follow-up in McDonald's cohort[3] was over 20 years, the adjusted SMR of 1.18 in the "older" Selikoff cohort would be a more appropriate comparison, and supports the lack of association between asbestos exposure and laryngeal cancer shown in the case-control studies.[23-27] Furthermore, there are substantial differences in the occurrence of lung cancer among workers in various asbestos industries.[4,6] Such differences may reflect variation in the type, quantity, and size of the asbestos fiber in the various trades.[3-11,31,33-34]

Case Series

Libshitz et al[34] reported laryngeal cancer in three persons with asbestosis and so proposed a possible association between asbestosis and laryngeal cancer. However, it is worth noting that all three patients were cigarette smokers![34]

Conclusion

In sharp contrast to other incontrovertible hazards of asbestos,[1,2] the foregoing evidence inculpating asbestos in laryngeal cancer is weak or non-existent.[3-13,21-34] With a few exceptions,[9-11,27-33] discussed above, the SMRs for laryngeal cancer in asbestos workers are all small.[3-6,23-26]

The extraordinarily high odds ratios found by Shettigara and Morgan[27,28] and Stell[29,30] were not reproduced by the perhaps more accurate and somewhat less biased[35] SMR estimates obtained in the cohort studies.[3-11,31-33] Other than the major flaw of not adjusting for the effects of smoking and ethanol, the odds ratios in these studies[27-30] might also have been significantly confounded by the interviewer and interviewee bias, or ascertainment bias,[35] which is an innate weakness of case-control methodology.

If only 10% of an asbestos worker population were to smoke more than one pack a day or to smoke one pack a day and drink 6 oz of ethanol a day, then the SMR for laryngeal cancers in the *whole* population would approach three times that of a nonsmoking, nondrinking population. Although this is a theoretical estimate, it does highlight in numerical terms the limited value of the unadjusted SMRs. This same effect makes it impossible to exclude totally some interactive effects between smoking and asbestos in laryngeal cancer. However, we know of no case in the foregoing literature of asbestos workers with laryngeal cancer who did not smoke and there are no published data on their ethanol intake.

Other considerations include socio-economic factors and the beneficial influence of tea drinking[21]—the latter perhaps by the absence of other factors! An additional variable rarely considered in the asbestos cancer literature is diet, specifically the content of vitamin A and related materials. An inverse relation between vitamin A intake and lung cancer incidence has been reported in other populations.[39] Nutritional status may conceivably be important in the pathogenesis of the laryngeal cancer[40] because retinols have been shown to diminish asbestos-induced tracheal metaplasia in experimental animals.[41] A preliminary study[42] reports low serum β-carotene in asbestos workers. Dietary factors have not been otherwise examined in the asbestos worker, and this relationship to laryngeal cancer has not been critically assessed.

It is improbable that further evidence will be available on this asbestos-laryngeal cancer issue since the preventive measures are now generally in place, at least in most Western society. However, we suggest that the foregoing evidence will focus preventive measures on life style factors.

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