The Attribution of Lung Cancers to Asbestos Exposure

A Pathologic Study of 924 Unselected Cases

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Abstract

We studied a series of 924 nonselected surgical cases of lung carcinoma (without occupational history in clinical records) by histologic examination and light microscopic determination of asbestos body (AB) concentration to determine cancers attributable to asbestos exposure. Lower lobes showed higher concentrations, but no significant associations were recorded between concentrations and histologic type of the lung carcinomas. Histologic asbestosis was demonstrated in 56 cases considered definitely asbestos-related. In 12 of them, the demonstration of asbestosis was attained only after repeated examination of additional sections, suggested by the finding of more than 1,000 ABs per gram of dry weight (gdw), an indicator of occupational asbestos exposure. In the 56 cases, the median AB concentration was 3,281/gdw. In 5 other cases without demonstration of ABs in histologic sections, concentrations higher than this median and interstitial fibrosis were observed. The AB count after digestion of pulmonary tissue may show greater sensitivity than the search in histologic sections as an indicator of substantial asbestos exposure. Extrapolation of our estimate on a national scale suggests about 2,000 cases per year of asbestos-related cancers of the lung in Italy; 281 cases were reported (from all occupational causes) in the years 1990-1995.

Attributable risk for lung cancer in Europe has been reported as between 2% and 50% for asbestos exposure in males, but after exclusion of the extreme values, most of the remaining estimates are within the range of 10% to 20%.[1] The wide interval reflects the different extension of asbestos use and, therefore, the different prevalence of exposure and the different definition of exposure. The attributable fraction, evaluated with a method based on the correlation of incidence rates of lung cancer and mesothelioma, was estimated as 5.7% in Glasgow[2] and 3.9% in our region.[3] Surveys conducted in the Nordic countries and in the United Kingdom in general populations indicated a proportion of asbestos-related lung cancer in the range of 7% to 36% among men, with differences related to the age distribution of respondents and the economic profile of the area.[1] Since population studies suggest probabilities but do not allow conclusive evidence in individual cases, several criteria have been proposed for the attribution of a lung cancer to definite asbestos exposure. Despite this, a serious underreporting of these occupationally related cancers is being recognized.[4]

At present, the balance of evidence supports the proposition "the asbestos load itself in lung tissue is the main determinator of lung carcinogenesis,"[5] but forensic medicine still debates whether the asbestosis is a prerequisite for the attribution or whether it is just an indicator of substantial exposure. The discussion of this topic is beyond the purposes of this article. Anyway, the pathologic demonstration of asbestosis is considered, beyond dispute, as decisive proof of linkage (at least contributing if smoking is associated) between a lung cancer and previous exposure to asbestos: we have found no contradictory evidence in the literature. The criteria for the histologic diagnosis of asbestosis, therefore, are crucial in this respect.

The minimal features that permit the diagnosis of asbestosis have been described, in the Report of the Pneumoconiosis Committee of the College of American Pathologists (CAP) and the National Institute for Occupational Safety and Health (NIOSH), as discrete foci of fibrosis in the walls of respiratory bronchioles associated with accumulations of asbestos bodies.[6] Bellis et al[7] validated the applicability of these criteria in the Piedmont region (northwestern Italy). The fibrosis with possible pigmentation of the walls of respiratory bronchioles was defined as "small airway lesions" (SALs), and these features were considered as "asbestosis grade 1" (AG1) when associated with asbestos bodies (ABs) on the sections. In fact, similar lesions have been regarded as a form of interstitial fibrosis.[8,9] Fibrotic thickening with possible carbon and iron pigmentation of the walls of the respiratory bronchioles and of alveolar ducts has been observed in patients who had been exposed to asbestos and named "asbestos airway disease" by other authors.[10] In the series of Bellis et al,[7] the AG1 cases compared with subjects without SALs were associated significantly with indicators of asbestos exposure such as bilateral pleural plaques, high concentrations of ABs in the digested lung, and a history of occupational exposure.

The criteria settled by the International Expert Meeting on Asbestos, Asbestosis and Cancer convened in Helsinki in 1997[11] are not very much different in substance from those described by CAP and NIOSH for the diagnosis of asbestosis on histologic sections. However, a new concept was introduced by the Helsinki Criteria, that is, the acceptability of the diagnosis of asbestosis when, together with interstitial lung fibrosis, the count of lung asbestos fibers by electron microscopy was in the range recorded for asbestosis by the same laboratory. According to this statement, when interstitial fibrosis is present, the demonstration of a substantial asbestos burden in the digested tissue examined by electron microscopy may replace the finding of ABs in the histologic sections examined by light microscopy.

Even in absence of interstitial fibrosis, concentrations higher than 1,000 ABs per gram of dry weight of lung tissue (ABs/gdw) by light microscopy indicate exposures of the occupational type. This proposition results from pathologic studies in various countries, including our region,[12-15] and has been validated by international workshops.[16,17] But until now, the light microscopic counts of ABs have not been systematically taken into consideration along the diagnostic path for the recognition of asbestosis in a fibrotic lung.

The objective of the present study was the pathologic assessment of the prevalence in our region of asbestos-related carcinomas, recognized because of the association with histologic asbestosis according to CAP and NIOSH criteria, in a large surgical series of unselected lung cancers. In a previous study, Mollo et al[18] found histologic asbestosis in 6.7% of 165 hospital autopsy cases with lung carcinoma, but this result could seem to be biased by postmortem selection.

Materials and Methods

We studied 924 unselected cases of pulmonary carcinomas, consecutively examined at the Department of Biomedical Sciences and Human Oncology, Turin (northwestern Italy), after pneumonectomy or lobectomy, from December 1992 through December 1998. These surgical specimens were sent to the laboratory of pathology without records about occupational histories. There were 345 pneumonectomies and 579 lobectomies (359 upper lobes and 220 intermediate and/or lower lobes).

Pathologic Investigations

The identification of ferruginous bodies as true typical ABs was performed according to the criteria described on the basis of the comparison between light and electron microscopic findings.[19,20] The concentration of ABs/gdw was determined in samples of "normal" lung tissue taken from each available lobe. The optical count was performed after membrane filtration of the material obtained by hypochlorite digestion of the pulmonary tissue.[21] When 2 or 3 samples were examined, the count was expressed as the mean value resulting from the different counts. We screened 2 to 5 sections of lung tissue without neoplastic invasion for SALs and for features of histologic asbestosis according to the CAP and NIOSH criteria and previous experience[7] **Image 1**. When the diagnosis of histologic asbestosis was not justified according to these criteria because ABs were not evident on the sections, 2 to 4 additional sections were prepared and carefully screened if interstitial fibrosis (IF) was present and the AB count was higher than 1,000/gdw. As for minimal interstitial fibrosis, the CAP and NIOSH criteria[6] were applied; furthermore, particular attention was given to recommendations suggested for the differential diagnosis between interstitial fibrosis due to asbestos and that attributable to other diseases.[22]

Job Inquiries

In the cases of carcinoma that, through the aforementioned examinations, were associated with histologic asbestosis, an effort was made to obtain personal or proxy interviews, to examine official documents concerning the past jobs of the subjects, or both.

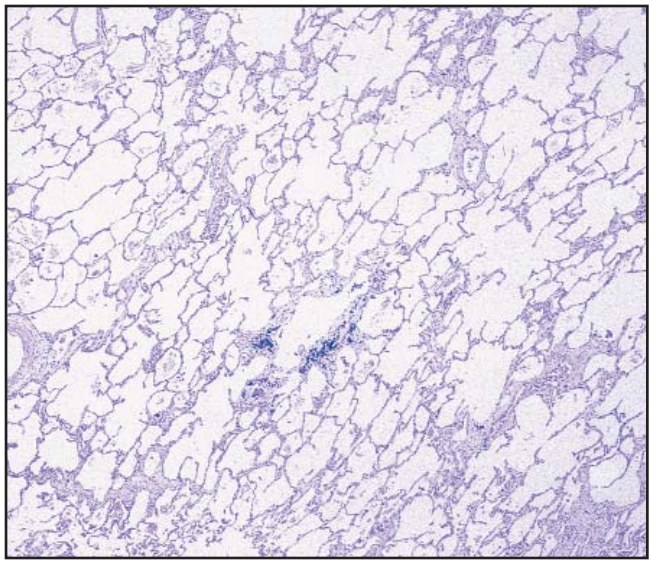

Image 1 In the center of the field, there is a respiratory bronchiole with a fibrotic and pigmented wall. At this magnification, no asbestos bodies are recognizable, and this pattern could be considered a "small airway lesion" (H&E, original magnification ×40).

Statistical Methods

The concentration of ABs was compared among the different categories of subjects, classified according to sex, age (10-year classes), pulmonary lobe sampled, histologic type of the neoplasm, and period of diagnosis (1995 or earlier or 1996 or after).

AB concentration is positively skewed; therefore, values were transformed to their logarithm before the analyses: For this purpose, zero values were substituted by a trivial value (0.1).

Analyses were conducted computing descriptive statistics and cumulative distributions and comparing subgroups using nonparametric statistics, such as the Wilcoxon-Mann-Whitney or the Kruskal-Wallis or the median test[23] as appropriate. Analyses were conducted using SAS, version 6.12 (SAS Institute, Cary, NC).[24]

Results

The range of AB concentrations in the whole series of 924 unselected lung cancers was 0 to 728,000. The concentrations were different in the two sexes: among men, the average concentration was 1,952 ABs/gdw (SD = 26,672; median, 188); among women, it was 382 ABs/gdw (SD = 763; median, 95). The difference was statistically significant ($P < .001$). **Table 1** shows the distribution of subjects by classes of AB concentration, separately for men and women. The cases of lung carcinoma with a concentration of ABs/gdw higher than 1,000 were 116: 106 of 806 men and 10 of 118 women, corresponding to 13.2% and 8.5%, respectively, of the corresponding totals **Table 2**. Histologic asbestosis was diagnosed at the first histologic examination in 44 cases and in another 12 after the examination of additional sections when the AB count was more than 1,000/gdw. These 56 cases (54 men and 2 women) were considered definitely asbestos-related. The median value of AB concentrations observed in these cases was 3,281/gdw. The AG1 cases were 34, or 63% of the histologic asbestosis cases and 3.7% of the whole series. In 5 cases of lung cancer, all in occupationally exposed subjects and associated with interstitial fibrosis and with a count of ABs higher than the median concentration recorded in histologic asbestosis, the diagnosis of histologic asbestosis could not be attained; in fact, no typical ABs were identified in the sections, despite the substantial concentration in the digested tissue and the repeated histologic examinations. Conversely, 2 cases (both men) with histologic asbestosis diagnosed at the first examination had fewer than 1,000 ABs/gdw.

Concentrations of ABs by pulmonary lobe are given in **Table 3** and by histologic type in **Table 4**. Samples from upper lobes showed lower AB concentrations than samples from lower lobes or from the total lung. The difference was significant ($P = .02$) by the Wilcoxon test (which compares the 2 frequency distributions), but not when only the median was considered. Differences by histologic type were not statistically significant.

Table 1
Cases of Lung Carcinoma by Sex and Asbestos Body Count*

		Asbestos Bodies/gdw						
	Total	≤1,000	1,001-2,000	2,001-3,000	3,001-4,000	4,001-5,000	5,001-9,000	>9,000
Men	806 (87.2)	700 (86.8)	48 (6.0)	22 (2.7)	9 (1.1)	7 (0.9)	9 (1.1)	11 (1.4)
Women	118 (12.8)	108 (91.5)	7 (5.9)	2 (1.7)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Total	924 (100.0)	808 (87.4)	55 (6.0)	24 (2.6)	9 (1.0)	7 (0.8)	10 (1.1)	11 (1.2)

gdw, gram of dry weight of lung tissue.
* Data are given as number (percentage). For the "Total" column, percentages are based on 924; percentages for the first, second, and third rows are based on the total numbers of men, women, and patients, respectively.

Table 2
Cases With More Than 1,000 ABs/gdw by Sex and Histologic Evidence of Asbestosis*

	No. of Subjects With >1,000 ABs/gdw	Asbestosis	
		Yes	No
Men	106	52 (49.1)	54 (50.9)
Women	10	2 (20)	8 (80)
Total	116	54 (46.6)	62 (53.4)

ABs, asbestos bodies; gdw, gram of dry weight of lung tissue.
* Data are given as number (percentage). Two additional cases of asbestosis showed fewer than 1,000 ABs/gdw (see text) and are excluded from the table.

Table 3
ABs/gdw by Pulmonary Lobe From Which the Sample Was Obtained*

Lobe	Mean	SD	Median	95th Percentile
Upper	615	1,697	162	2,447
Intermediate or lower	1,677	13,116	154	2,395
Multiple or unspecified	2,957	39,349	204	2,750

ABs, asbestos bodies; gdw, gram of dry weight of lung tissue.
* $P = .02$, Wilcoxon; $P = .11$, median test.

Reliable information about the occupational history was obtained in 25 cases (20 with histologic asbestosis and 5 with interstitial fibrosis and AB counts higher than those recorded in histologic asbestosis). This retrospective job inquiry confirmed definite asbestos exposure in all of them.

Discussion

In our material, no significant associations were recorded between the concentrations of ABs and the cancer histologic type, while lower lobes showed higher concentrations. One may find in the literature different statements about these topics.[5] In previous case-control investigations on autopsy material, Mollo et al[25] found a significant association between adenocarcinoma and asbestos exposure using a cutoff level of 10,000 ABs/gdw as an indicator of heavy exposure, but the pattern was much less evident using a cutoff level of 1,000 ABs/gdw. The present results, achieved using nonparametric analyses on the frequency distributions (and not just a cutoff level of 1,000 Abs/gdw) on unselected lung cancers from surgery, are consistent with remarks suggesting that the pathologic features of the lung cancer do not differ substantially between subjects exposed and subjects not exposed to asbestos.[26-28]

The median value of AB concentrations in our asbestos-related cases (3,281 ABs/gdw) is very much lower than that recorded by others.[29] These data may be related to possible differences concerning not only the technical procedures or the criteria for unquestionable identification of ferruginous bodies as typical ABs and for the pathologic diagnosis of minimal interstitial fibrosis compatible with asbestosis but also the severity of exposure, the type of fibers (mainly amphiboles or chrysotile), and the degree of asbestosis in the studied series.

The major outcome of the present investigation is that a thorough pathologic examination should be performed in all cases of pulmonary carcinoma (also when occupational history is not included in clinical reports). In our series, 34 cases of histologic asbestosis (of 56 asbestos-related cancers) were AG1, that is, they showed minimal features recognizable only by careful microscopic screening of the sections. Furthermore, to detect the asbestos-related cases among cancers presented for pathologic examination, the AB concentration should be determined in all cases in addition to an examination for histologic asbestosis. In particular, cases with interstitial fibrosis may call for more in-depth histologic study, even though the association between these findings may present some exceptions in single cases.

As a matter of fact, we observed 2 cases of lung carcinoma with minimal asbestosis in which the AB/gdw counts were lower than the concentration suggesting previous exposure of the occupational type. It may be an occasional

Table 4
ABs/gdw by Carcinoma Histologic Type*

Histologic Type	No. of Tumors	Mean ABs/gdw	SD	Median	95th Percentile
Squamous	459	1,037	9,111	173	1,887
Small cell	19	488	721	218	2,646
Large cell	63	12,469	91,642	155	6,442
Adenocarcinoma	298	1,000	4,359	185	3,058
Bronchioloalveolar	27	418	633	179	2,231
Other types	28	733	2,035	231	2,424
Not specified	30	302	653	129	689

ABs, asbestos bodies; gdw, gram of dry weight of lung tissue.
* $P = .88$.

finding. On the other hand, ABs form mainly on long fibers of amphiboles and not (or in negligible amount) on chrysotile fibers,[30,31] but also the latter may have pathogenic effects inducing interstitial fibrosis.[32]

Conversely, ABs may be masked in the histologic sections when heavy anthracosis is present, or they may be unrecognizable when perpendicularly oriented in respect to the plane of the section **Image 2**; when only a few ABs are occasionally present in the sections and they are not well oriented, the diagnosis of minimal histologic asbestosis may be missed. The optical examination of ABs obtained from the digested lung and observed lying on the membrane may be an easier method for their recognition and a more reliable light microscopic indicator of the previous asbestos exposure.

On the other hand, it is noteworthy in this regard that according to the Helsinki Criteria, interstitial fibrosis associated with a significant electron microscopic count of uncoated asbestos fibers may be regarded as asbestosis, and a good correlation has been demonstrated between ABs counted by light microscopy and uncoated fibers 5 μm or greater in length counted by electron microscopy.[33] Therefore, it seems reasonable to suggest that the interstitial fibrosis associated with a significant concentration of ABs in light microscopy could be regarded as an actual indicator of pneumoconiosis due to asbestos. From a conceptual viewpoint, asbestosis is a "pulmonary fibrosis caused by asbestos"[34]; the demonstration of a substantial AB burden in the fibrotic lung is important, but it could be proved in the digested tissue and not necessarily in the histologic sections.

Interstitial fibrosis without identification of ABs in histologic sections but with a concentration of ABs higher than the median recorded in histologic asbestosis was observed in 5 cases. Such a concentration in a fibrotic lung of an exposed subject is very significant from a forensic point of view, and in our opinion, these lung cancers are to be regarded as asbestos-related. Nevertheless, the criteria for the attribution of a lung cancer to asbestos exposure may be different in different countries, and sometimes (perhaps not only in Italy) they are matters of litigation. But apart from the medicolegal debates in the individual cases, even if we add these cancer cases to those associated with actual histologic asbestosis, the percentage of our definitely or reasonably asbestos-related lung cancers would not change very much, from 6% to 6.6% of the total series. Instead, more important underestimation (unfortunately not pathologically demonstrated in our material) may have occurred in our estimates. In fact, ABs form mainly on amphibole fibers,[30,31] so that the AB burden (both in sections and in digested tissues) may not adequately reflect a noxious exposure that possibly occurred in the past, and certainly was not negligible for the induction of the lung cancer.[32] In fact, the occupational exposure to chrysotile

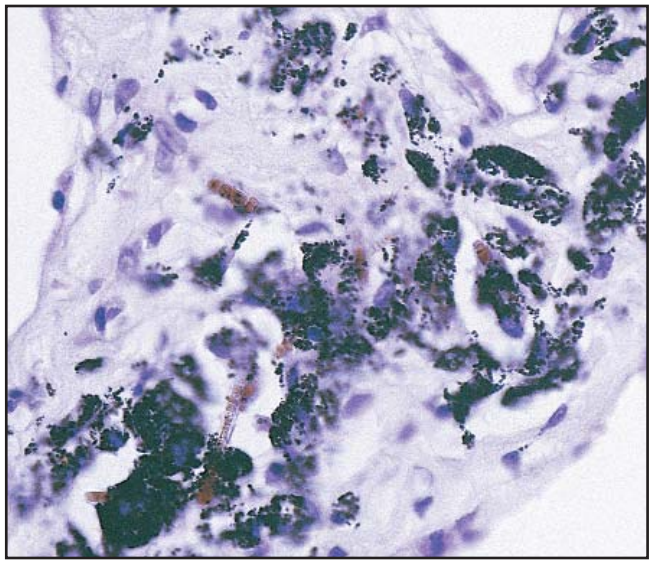

Image 2 At higher magnification, asbestos bodies are recognizable in the wall of the respiratory bronchiole showed in Image 1; this is "minimal histologic asbestosis" (H&E, original magnification ×400).

also is to be considered among the factors responsible (at least as a major contributing factor together with smoking) for the increased risk of pulmonary carcinoma.[35]

Our estimate of the fraction (about 6%) of lung cancers attributable to asbestos, based on this study of unselected surgical material and also on previous results from autopsies,[18] is on the same order of magnitude recorded in epidemiologic studies of general populations, such as those of the United States (5%),[36] of Scotland (5.7%),[2] and even of our region, Piedmont (3.9%).[3]

Furthermore, the present type of investigation allows the pathologist to recognize individual cases of lung cancer that should be considered for compensation owing to occupational exposure to asbestos (at least to amphiboles). It is noteworthy that since the incidence of the lung cancer in Italy during the 1990s was about 32,000 cases per year, the extrapolation of our pathologic estimate could suggest that in this country, about 2,000 cases per year should be linked with asbestos exposure. The number of cases of lung cancer reported during the period 1990-1995 to the Italian National Institute of Work Injuries Insurance as possibly due to the occupation (not only to asbestos exposure) was 281, and 91 persons eventually were compensated.

In our series, occupational histories had not been recorded before the study, and the lung fibrosis associated with several cancers had not been detected in x-ray chest films or suspected as a pneumoconiosis disorder. It might be supposed that the lung cancer cases related to asbestos exposure through the present work were otherwise destined to

remain unrecognized, while they have now given rise to the proper medicolegal actions.

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