CHEST

Official publication of the American College of Chest Physicians



Asbestos burden and the pathology of lung cancer.

M L Warnock and W Isenberg

Chest 1986;89;20-26
DOI 10.1378/chest.89.1.20

The online version of this article, along with updated information and services can be found online on the World Wide Web at:
http://chestjournal.chestpubs.org/content/89/1/20

Chest is the official journal of the American College of Chest Physicians. It has been published monthly since 1935. Copyright1986by the American College of Chest Physicians, 3300 Dundee Road, Northbrook, IL 60062. All rights reserved. No part of this article or PDF may be reproduced or distributed without the prior written permission of the copyright holder.
(http://chestjournal.chestpubs.org/site/misc/reprints.xhtml) ISSN:0012-3692

AMERICAN COLLEGE OF CHEST PHYSICIANS®

Downloaded from chestjournal.chestpubs.org by guest on November 10, 2011
© 1986 American College of Chest Physicians

388 ABS

Asbestos Burden and the Pathology of Lung Cancer*

Martha L. Warnock, M.D.;† and William Isenberg, B.S.‡

To determine whether we could distinguish asbestos-related lung cancers from unrelated ones, we typed and quantified by electron-optical methods the asbestos fibers in the lungs of 75 men with lung cancer. All but eight men had some history of asbestos exposure. On the basis of combined amosite and crocidolite (AC) concentrations, we divided the subjects into three groups (AC fibers per gram of dry lung): low ($<10^5$); intermediate (10^5 to 10^6); and high ($>10^6$). Age, smoking history, latent period, and type and location of tumors were similar in all three groups. Of 62 evaluated subjects, zero of 14 in the low group, seven of 29 in the intermediate group, and five of 19 in the high group had asbestosis. Epidemiologic studies suggest that persons exposed to concentrations of asbestos that can cause asbestosis are at increased risk for lung cancer. Thus, the subjects in our intermediate and high concentration groups may have been at increased risk for cancer, even when they did not have asbestosis. Because large burdens of asbestos do not always cause pulmonary fibrosis, asbestosis may be a poor marker of fiber-related lung cancer.

89 186 Chest

Asbestos was first suspected of causing bronchogenic carcinoma in the mid-1930s, but it was not until 1968 that it was postulated that asbestos and cigarette smoking together produce a greater incidence of lung cancer than either agent alone.[1,2] Because the link between smoking and cancer is well established, it is important to try to find criteria for distinguishing asbestos-related tumors from those related to smoking alone. There is a consensus that a diagnosis of asbestos-related cancer requires the presence of asbestosis as proof of substantial asbestos burden.[3-5] In postmortem examinations of persons whose occupations have not been monitored for asbestos, quantification of the burden of asbestos fibers in the lung can also provide objective evidence of exposure and perhaps indicate its magnitude.[6] Accordingly, using electron-optical methods, we have shown that subjects with pleural plaques,[6] asbestosis,[7] and mesothelioma[8] have higher concentrations of amosite and crocidolite fibers than control subjects. Even though the pulmonary burden of amosite and crocidolite is not directly proportional to exposure because of clearance of fibers over time, we used it as a measure of exposure, asking two questions: (1) Can tumors in lungs with a high burden be distinguished by type or location from those in lungs with a low burden? (2) Is the presence of asbestosis helpful in designating a tumor as asbestos-related?

Materials and Methods

Selection of Subjects

We analyzed pulmonary tissue from 75 men with a diagnosis of primary carcinoma of the lung. For 69 subjects a whole lung or lobe was available, but in six cases, only generous pieces of pulmonary tissue from upper and lower lobes were available. Twenty-nine lungs came from autopsies performed at the Solano County (California) Coroner's Office. This office serves a shipyard neighborhood, and the subjects all had a history of exposure to asbestos. Thirty additional subjects were referred to our laboratory from elsewhere because they had a history of exposure to asbestos. Sixteen lungs were from a series of men who underwent pulmonary resection or autopsy at Moffitt Hospital or Fort Miley Veterans Hospital between Sept 1, 1980 and Dec 31, 1983. Of the 75 specimens that we examined, 17 were from surgical resections. The 58 postmortem specimens were obtained from the lung without tumor. For all subjects, we reviewed the postmortem or surgical-pathology report, and we interviewed a relative by telephone to obtain the subject's occupational, residential, and smoking history.

Tissue Preparation and Histologic Analysis

We fixed the whole lungs or lobes by intrabronchial instillation of 10 percent buffered (pH 7.0) formalin, as we have described previously.[6] Fragments of tissue were fixed by immersion. After slicing the lungs parasagittally at 1-cm intervals, we evaluated each slice for parenchymal fibrosis by both inspection and palpation. Parenchymal fibrosis was graded from 0 to 3+. Fibrosis of 3+ involved more than 50 percent of the parenchyma, and fibrosis of 1+ and 2+ involved less than 25 percent and between 25 and 50 percent, respectively. We reviewed the histologic sections of tumor and classified the tumors according to the World Health Organization's classification.[9] When appropriate, we stained sections of the tumors by the PAS method, after diastase digestion, to detect neutral mucins.

We took at least four histologic sections of pulmonary parenchyma, one from the pleural region and one from more central alveolar parenchyma of both the upper and lower lobes. Areas of fibrosis were selected, if present. Sections were stained with hematoxylin and eosin, and the van Gieson stain for collagen. We evaluated the sections for microscopic evidence of fibrosis, which we graded from 0 to 3+ on each slide. The total score was divided by the total possible score for the slides evaluated. Fibrosis was designated 1+ if there was generalized fibrosis around respiratory bronchioles and alveolar ducts, with slight extension into the acinus. Fibrosis did not have to be present in every acinus, but it had to be present in many to warrant a designation of 1+. A grade of 3+ designated well-defined interstitial fibrosis throughout the acinus, with some revision of the

*From the Department of Pathology, University of California, San Francisco.
Supported by USPHS RO1 ES 02117.
Manuscript received March 11; revision accepted June 12.
†Professor of Pathology.
‡Graduate Student in Pathology.

Downloaded from chestjournal.chestpubs.org by guest on November 10, 2011
© 1986 American College of Chest Physicians

normal alveolar architecture. Grade 2+ was intermediate. We often observed other histologic features, including chronic alveolitis, characterized by macrophages and occasional neutrophils in alveolar spaces; patchy lymphoid interstitial infiltrations, sometimes in aggregates; and type 2 cell hyperplasia. We made no attempt to quantify these abnormalities for this study. Sections were evaluated by both authors to determine the reproducibility of the grading method. We had insufficient information about the presence of pleural plaques to analyze their significance.

Analysis of Asbestos Bodies and Fibers

The procedure for extracting asbestos bodies and asbestos fibers has been described previously.[6] As before, we counted asbestos bodies by light microscopy and counted and classified by type the asbestos fibers by electron-optical methods in four samples of each lung. One sample was taken from the central alveolar parenchyma and one from the pleura and underlying 0.5 cm of pulmonary parenchyma of both the upper and lower lobes. Blank preparations lacking tissue were run with each set of samples. The fibers counted were multiplied by a factor to obtain fibers per gram of dry lung. The results of each set of four analyses were averaged. The final concentrations were based on analysis of a total of about 60 asbestos fibers per case if the asbestos body concentration was less than 1,000/g of dry lung and about 100 asbestos fibers per case if the asbestos body concentration was over 1,000/g.

We classified the asbestos fibers as we have described previously[6] with one change. The mineral fiber, glaucophane, having an amphibole diffraction pattern and an elemental composition of 8 percent sodium, 7 percent magnesium, 9 percent aluminum, 53 percent silicon, and 23 percent iron, was added to the group of fibers comprising tremolite, anthophyllite, and actinolite (TAA), to form the group, TAAG.

Histologic Assessment of Asbestosis

To determine whether we could make a diagnosis of asbestosis by conventional histologic criteria, we selected lungs with macroscopic fibrosis from seven subjects with concentrations of amosite and crocidolite (AC) fibers in group 2 (discussed subsequently). Two histologic sections cut at a thickness of 6μ were stained for iron, and asbestos bodies were counted by scanning the slide serially at a magnification of 100 times. The area of the section was measured by planimetry, and the number of asbestos bodies was expressed as bodies per square centimeter of tissue.

RESULTS

We plotted the number of subjects against the logarithm of the combined amosite and crocidolite (AC) concentrations. After inspecting the data (Fig 1), we divided the subjects into three groups: (1) those with fewer than 100,000 AC fibers per gram of dry lung (group 1, with 15 subjects); (2) those with 100,000 to 1 million fibers per gram of dry lung (group 2, with 35 subjects); and (3) those with more than 1 million fibers per gram of dry lung (group 3, with 25 subjects). We then compared the data for the three groups in an effort to find differences that might distinguish asbestos-related cancers from unrelated ones.

Age and Smoking History

The subjects ranged in age from 35 to 82 years. The three groups did not differ significantly in mean age (Table 1), nor did they differ in the mean number of pack-years smoked (packages of cigarettes per day times number of years) (Table 1). We had no information about the smoking history of three subjects. Two subjects (one in group 1 and one in group 2) had smoked for fewer than ten pack-years. Although subjects in group 1 tended to smoke more heavily than those in groups 2 and 3, this difference was not significant (analysis of variance [ANOV][10]).

Occupation

Without knowledge of the asbestos concentrations in the lungs of the subjects, we classified them by occupation into the following four categories: (1) white collar worker; (2) blue collar manual laborer (not construction worker); (3) construction worker; or (4) shipyard worker. We classified subjects as shipyard workers if they had any history of such work, no matter how short. Similarly, subjects in construction trades

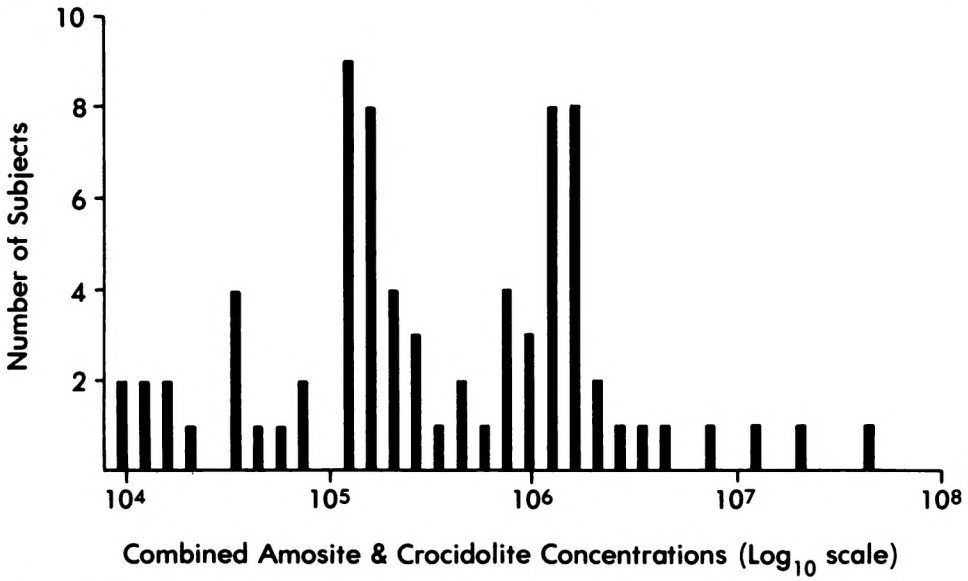

FIGURE 1. Combined amosite and crocidolite concentrations in 75 men.

Downloaded from chestjournal.chestpubs.org by guest on November 10, 2011
© 1986 American College of Chest Physicians

Table 1—*Age, Smoking History, Occupation, and Latency Period for 75 Subjects*

Group	Age, yr*†	Smoking, pack-yr*†	Occupational Category‡				Time from First Asbestos Exposure to Dx of Tumor, yr*§	Time Exposed, yr*§
			White Collar	Blue Collar	Construction	Shipyard		
1	62.7±9.6	67±38	5(33)	6(40)	1(7)	3(20)	35±16‖	24±12‖
2	62.6±9.9	51±23	0	4(12)	5(14)	26(74)	38±10	26±11
3	62.7±6.4	57±36	0	4(16)	3(12)	18(72)	35±6	24±10

*Mean ± SD.
†Differences among groups were not significant (analysis of variance).
‡No. of subjects (number within parentheses is percent of subjects in group).
§Difference among groups is not significant if the 8 unexposed subjects in group 1 are omitted.
‖Average for 7 subjects with exposure.

who had never worked in the shipyard were classified as construction workers, even if the history was brief. Other manual laborers were classified as blue collar workers. The distribution of subjects in each group by job category is shown in Table 1. Groups 2 and 3 were similar in this distribution and in the subjects' actual job titles (Table 2). Over 70 percent of the subjects in each of these groups were shipyard workers; however, of the subjects in group 1, some 73 percent (11/15) were classified as white-collar or blue-collar workers. The difference in distribution of subjects by job category between group 1 and groups 2 and 3 combined was significant ($p = 0.05$; χ^2 test with Bonferroni correction).

Total Years Exposed and Latency Period

When the eight subjects with no history of exposure to asbestos were omitted from group 1, the three groups did not differ significantly (ANOV) in the average number of years from first exposure to diagnosis of tumor (latency period) or the average number of years of exposure (Table 1).

Concentrations of Asbestos Bodies and Fibers

The combined concentrations of amosite and crocidolite fibers in the 75 subjects ranged from undetectable to 69 million/g; the range of chrysotile fiber concentrations was somewhat smaller (77,000/g to 28 million/g). Amosite fibers predominated over crocidolite fibers by a factor of 22 (group 2) to 32 (group 3). The median concentrations of asbestos bodies (AB) and of the various types of asbestos fibers in each group are listed in Table 3. Median values are given because neither the concentrations nor the log transforms of most of the concentrations were normally distributed. The median concentration of asbestos bodies in group 3 was 260 times that in group 1; the median concentration of amosite was 40 times that in group 1; but the chrysotile and TAAG concentrations were only 4 and 2.6 times as great, respectively. Asbestos body concen-

Table 2—*Major Occupations of 75 Subjects**

Group 1	Group 2	Group 3
Insurance sales	Longshoreman	Longshoreman
Physicist	Foundry worker (4)	Printer
Cook	Steel mill worker	Steel mill worker
Car salesman	Fire fighter (2)	Asbestos miner
Hardware salesman	House construction (2)	Asbestos pipe manufacturer (2)
Machinery salesman	Weapons assemblyman	Rigger (S)
Bartender	Auto mechanic	Sandblaster (S)
Carpenter	Aircraft construction	Shipfitter (S)
Foundry worker	Shipfitter (4) (S)	Chipper; caulker (2) (S)
Truck driver	Chipper; caulker (S)	Engineer (4) (S)
Aircraft mechanic	Engineer (3) (S)	Machinist (3) (S)
Machinist (2) (S)	Machinist (6) (S)	Sheet metal worker (S)
Shipwright (S)	Sheet metal worker (2) (S)	Maintenance worker (2) (S)
Maintenance worker	Maintenance worker (4) (S)	Electrician (S)
	Electrician (3) (S)	Pipefitter (6) (S)
	Pipefitter (4) (S)	Painter (2) (S)
	Painter (S)	Welder (4) (S)
	Welder (2) (S)	
	Tool and dye maker (S)	

*Some subjects had more than one occupation. No. in parentheses is number of subjects. (S) indicates work in shipyard.

Downloaded from chestjournal.chestpubs.org by guest on November 10, 2011
© 1986 American College of Chest Physicians

Table 3—*Median Asbestos Body and Asbestos Fiber Concentrations × 10^3 (25th and 75th Percentiles)**

Group	Asbestos Bodies[a]	Amosite[b]	Crocidolite[c]	AC[d]†	Chrysotile[e]	TAAC[f]‡
1	0.180	52.5	0	55.6	736	200
	(0.087; 0.608)	(12; 58.4)	(0; 3.39)	(17.4; 59.2)	(631; 964)	(65.7; 328)
2	3.75	272	12.4	316	1,510	309
	(0.811; 11.9)	(130; 547)	(0; 79.4)	(179; 610)	(417; 2,520)	(211; 578)
3	46.7	2,080	65.4	2,500	3,070	516
	(13.3; 124)	(1,210; 4,670)	(9.59; 171)	(1,390; 4,850)	(1,530; 5,140)	(334; 1,450)

*Group 1 differs significantly from group 2 (a; b; d; $p<0.003$). Group 2 differs significantly from group 3 (a; b; d; $p<0.003$) (e; $p<0.03$). Group 1 differs significantly from group 3 (a; b; c; d; e; $p<0.003$) (f; $p<0.03$) (Mann-Whitney test with Bonferroni correction).
†Combined amosite and crocidolite concentrations.
‡Tremolite, anthophyllite, actinolite, and glaucophane.

trations differed significantly among all three groups. For fibers classified as chrysotile or TAAG, the concentrations in group 3 were significantly greater than those in group 1.

Relation between Asbestos Body and Fiber Concentrations

Because the cores of most asbestos bodies are amosite or crocidolite[11] (unpublished data), we plotted the $\log_{10}$ of AC concentration against the $\log_{10}$ of asbestos body concentration (the latter was shown to be normally distributed[10]) for each subject (Fig 2). The slope of the regression line was 1.06, with an intercept of −2.3, if we eliminated the four cases (all in group 1) in which either asbestos bodies or AC fibers were not detected. The correlation coefficient for asbestos bodies and amosite or for amosite and crocidolite combined was 0.77 (Spearman rank test[10]). Although asbestos body concentration depended on AC concentration, the graph indicates that there is great variability among subjects in the frequency of fibers becoming coated. In fact, the ratio of AC fibers to asbestos bodies ranged from 136,000:1 to 4:1. The three groups did not differ in the range of this ratio (Kruskal-Wallis test[10]). Of all of the subjects, 55 percent (41) had AC/AB ratios less than 100:1, 27 percent (20) were between 100:1 and 500:1, and 18 percent (14) were over 500:1. The concentrations of other types of fibers were not closely correlated. The correlation coefficient for amosite and chrysotile concentrations was 0.45 and for amosite and TAAG concentrations was 0.47 (Spearman rank test).

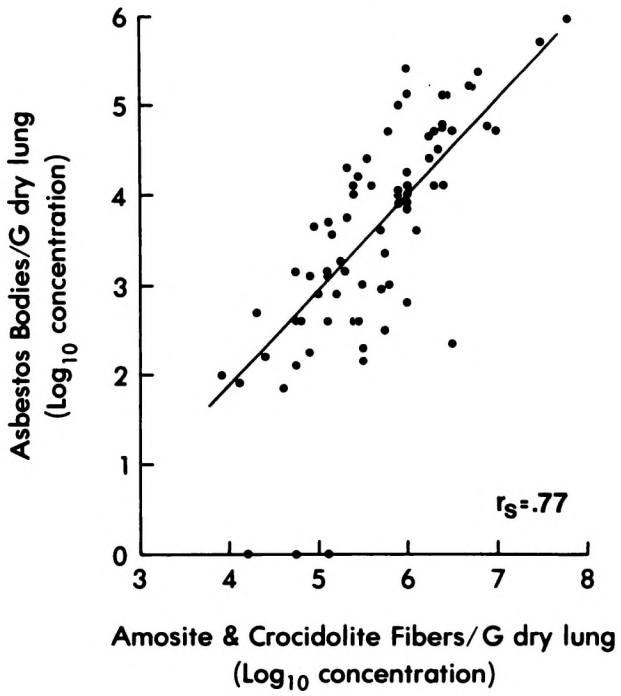

FIGURE 2. Plot of $\log_{10}$ of AC concentration against $\log_{10}$ of asbestos body concentration. Data for one subject with no AC fibers was omitted from figure. If more than 10^3 asbestos bodies per gram of dry lung is used as measure of concentration of AC fibers greater than 10^5, four (8 percent) of 49 cases with more than 10^3 asbestos bodies per gram have fewer than 10^5 AC fibers (false-positive), and 13 (54 percent) of 24 with fewer than 10^3 asbestos bodies have more than 10^5 AC fibers per gram of dry lung (false-negative).

Type and Location of Tumor

Forty-five percent of the tumors were adenocarcinomas, 42 percent were squamous cancers, and 13 percent were undifferentiated. If the surgically resected tumors were omitted, 42 percent (24) of the tumors were adenocarcinomas, 36 percent (21) were squamous tumors, and 22 percent (13) were undifferentiated. There was no significant difference among the three groups in the frequency of any of the tumor types, whether or not the surgically resected tumors were included (χ^2 test), (Table 4).

Similarly, there were no differences among the three groups in the location of the tumors. Of the 67 tumors whose locations could be determined, 69 percent were in the upper or middle lobes, 13 percent were in the lower lobes, and 18 percent were in the main bronchi.

Parenchymal Fibrosis

Fibrosis of the lung can be difficult to evaluate macroscopically in the presence of tumor, pneumonia, bleeding, or atelectasis. In most instances, we evaluated the lung contralateral to that with the primary tumor, and the majority of the lungs were fixed in an inflated state. No fibrosis was detected grossly in 13 of the 14 lungs in group 1 that could be evaluated (Table 5). In group 2, there was no fibrosis in 22 of 29 cases,

Downloaded from chestjournal.chestpubs.org by guest on November 10, 2011
© 1986 American College of Chest Physicians

Table 4—*Distribution of Subjects by Tumor Type and Site*

Tumor type	Subject group	Tumor site			
		Main bronchus	Upper & middle lobes	Lower lobes	Unspecified
Squamous carcinoma	1	2(13%)*	3(20%)	2(13%)	—
	2	5(14%)	7(20%)	2(6%)	—
	3	3(12%)	5(20%)	2(8%)	—
Adenocarcinoma	1	—	5(33%)	—	1(7%)
	2	—	12(34%)	1(3%)	3(9%)
	3	1(4%)	7(28%)	1(4%)	3(12%)
Small & large cell carcinoma	1	1(7%)	1(7%)	—	—
	2	—	4(11%)†	1(3%)	—
	3	—	2(8%)	—	1(4%)

*The percentages in parentheses are the frequency of tumors in each subject group.
†Three of these are the only large cell cancers in the study.

and 14 of 19 cases had no fibrosis in group 3. The earliest detectable fibrosis (1+) always occurred in subpleural regions in the lower lobes of the lung.

The histologic grading was reproducible. After a learning period, the slides were graded independently by both authors. There was concordance of the grading for 75 percent of the slides. In no case was the difference in grade more than 1. Sixteen subjects had no fibrosis. The median score (25th and 75th percentile) for group 1 was 0.05 (0; 0.29), for group 2 was 0.25 (0.08; 0.39), and for group 3 was 0.28 (0; 0.5). These scores were not significantly different (Kruskal-Wallis test). In group 1, six cases had no fibrosis, and in groups 2 and 3, ten had none.

Asbestos Bodies in Histologic Sections

Conventionally, the histologic diagnosis of asbestosis requires the presence of fibrosis and asbestos bodies.[12] The size of section to be searched is not specified. Table 6 shows the results of the search for asbestos bodies in histologic sections of lungs with macroscopic fibrosis from group 2. Three of the cases had more than one asbestos body and fibrosis.

Discussion

By dividing subjects with lung cancer and differing asbestos burdens in the lung into groups with low (group 1), intermediate (group 2), and high (group 3) combined amosite and crocidolite concentrations and by comparing the data for the groups, we hoped to find differences that would distinguish asbestos-related lung cancers from those not related to asbestos. A greater prevalence of asbestos-related occupations, increased asbestos body concentrations, and a trend, although not statistically significant, toward increased parenchymal fibrosis served to distinguish groups 2 and 3 from group 1. We detected no differences in the type or location of tumors among the groups. When we sorted cases by increasing chrysotile concentration, the subjects with no history of exposure were present in intermediate and high concentration groups. Therefore, we considered AC concentration the best marker of asbestos exposure.

Because previous investigators have concluded that a lung cancer can be designated as asbestos-related only if asbestosis is present,[3,4,5,13] we were particularly interested in the criteria for making the diagnosis of asbestosis. A committee of the College of American Pathologists has suggested that the minimal criteria should be peribronchiolar fibrosis and the presence of asbestos bodies.[12] In our series, grossly visible fibrosis was infrequent, but diffuse microscopic fibrosis was present in 50 of 60 cases in groups 2 and 3, and 9 of 15 cases in group 1. Because we were not able to find a statistically significant difference among the groups in

Table 5—*Distribution of Subjects by Grade of Macroscopic Fibrosis**

Group	Grade of Fibrosis			
	0	1+	2+	3+
1	13(93)	1(7)	0	0
2	22(76)	5(17)	0	2(7)
3	14(74)	3(16)	1(5)	1(5)

*No. in parentheses is percentage of cases in each group. For those subjects with macroscopic fibrosis in subject groups 2 and 3, the mean score for microscopic fibrosis was 0.46 in group 2 and 0.63 in group 3.

Table 6—*Asbestos Bodies in Tissue Sections from Seven Subjects in Group 2 with Grossly Visible Fibrosis**

Case	Asbestos Bodies per Gram	AC Fibers per Gram	Asbestos Bodies Counted	Total Area, sq cm	Asbestos Bodies per sq cm
1	444	284,000	1	6.96	0.14
2	825	128,000	0	9.12	0
3	1,400	202,000	1	6.96	0.14
4	4,000	461,000	1	5.08	0.2
5	5,640	210,000	12	6.47	1.85
6	8,000	949,000	4	8.36	0.48
7	13,000	412,000	14	7.1	1.97

*TAAG fibers ranged from 97,000/g to 699,000/g, except for cases 1 and 7, which had 2.05 million/g and 3.43 million/g, respectively. All cases had 1+ fibrosis, except cases 4 and 5, which had 3+ fibrosis.

Downloaded from chestjournal.chestpubs.org by guest on November 10, 2011
© 1986 American College of Chest Physicians

either macroscopic or microscopic fibrosis, we could not define the fibrosis of asbestosis more precisely than others.[12]

Asbestos bodies were sometimes very infrequent in histologic sections (Table 6). Our correlation coefficient for extracted and histologic asbestos bodies (0.90, Spearman rank test) was considerably lower than that of Roggli and Pratt,[14] who employed many correction factors to obtain their good correlation; but no matter how good the correlation is, the variation in the ratios of uncoated to coated fibers (4:1 to 136,000:1) precludes the use of asbestos bodies as the standard for diagnosing asbestosis. Many factors influence the number of asbestos bodies to be found in histologic sections.[14] The area scanned and the degree of distention of the lung tissue are important variables. (Our subjects' lungs, although distended, were not perfused at a constant pressure during fixation.) It is sometimes impossible to detect bodies within debris or to distinguish asbestos bodies morphologically from ferruginous bodies with cores of another mineral.[7] In other studies, we did not find a strong correlation between extracted and histologic asbestos bodies.[15] Although two asbestos bodies per histologic section (about 4 cm^2) may be a rough guide for diagnosing asbestosis, we would caution against its use as a necessary criterion.[12] For example, although conventional criteria would separate the cases in Table 6 into two groups (cases 1 to 4 without asbestosis and 5 to 7 with asbestosis), the actual AC burden places them all in the same group, and we propose that all of these subjects have asbestosis.

Because lungs may have a heavy burden of asbestos but no fibrosis, host factors are probably more important than asbestos burden in the development of asbestosis. The detection of antinuclear antibody or rheumatoid factor in subjects with asbestosis, but not in co-workers without asbestosis who are presumed to have had similar exposure,[16,17] the finding of abnormal cell-mediated and humoral immune responses in subjects with asbestosis,[18-20] and the poor correlation of fiber burden (as determined by phase-contrast microscopy) and fibrosis[21] all suggest that fibrosis may depend on factors other than the fiber burden.

The actual fiber composition of the asbestos to which our subjects were exposed is not known. Furthermore, the pulmonary asbestos burden is probably not an accurate indicator of the degree of asbestos exposure. A history of exposure to asbestos correlated best with amosite, not chrysotile, concentrations. Little crocidolite was present in our subjects. Nevertheless, we found no correlation between years of exposure and AC fiber burden. Correlations of chrysotile or TAAG with amosite fibers and years of exposure were poor. Preferential clearance of chrysotile or fragmentation of fibers after being inhaled into the lung may account for the only modest increase (four times) of chrysotile fibers in group 3 over group 1.[22,23]

Several other studies have addressed the pathology of lung cancers in asbestos workers. Whitwell et al[24] showed that adenocarcinomas were more prevalent in subjects with moderate asbestosis than in those with mild asbestosis, but not significantly so. Kannerstein and Churg[25] found no differences in tumor type between subjects with asbestosis and controls, but the tumors in subjects with asbestos exposure tended to be located in the lower lobes ($p<0.025$; χ^2 test). Others[24,26] also found that asbestos-associated tumors were usually in the lower lobes. Most of the subjects in these studies had asbestosis and not simply a history of exposure to asbestos. A recent study of 196 subjects with lung cancer and asbestos exposure noted that, as in the control subjects (without asbestos exposure), squamous cancers (49 percent) were more frequent than adenocarcinomas (15 percent). The subjects with asbestos exposure had tumors in the upper lobes more frequently than in the lower lobes (2:1).[27] The authors did not determine whether asbestosis was present. In our small series of 12 cases with asbestosis, three of four cases with 2+ or 3+ asbestosis had tumors in the lower lobes, but seven of eight cases with 1+ asbestosis had tumors in the upper lobes. The probability that the degree of fibrosis and tumor location are related approaches statistical significance ($p=0.06$, Fisher's exact test[10]). These findings suggest that the relation between fibrosis and cancer should be studied further, despite recent evidence indicating that some scarring associated with lung cancer may be a desmoplastic response to tumor.[28,29] Previous studies of the pathology of asbestos-related tumors do not specify whether the tumor was situated in a scarred area.

In summary, in our subjects neither the type nor the location of lung cancers was dependent on the degree of parenchymal fibrosis or on residual AC burden. The question of the usefulness of asbestosis as a marker of asbestos-related cancer remains. For the purpose of this study, it is perhaps sufficient to have shown that asbestosis was present in some subjects in groups 2 and 3. Epidemiologic studies indicate that persons exposed to concentrations of asbestos that cause asbestosis are at increased risk of lung cancer whether or not they have asbestosis.[30,31] We propose that persons with an asbestos burden heavy enough to cause asbestosis in some should be considered at increased risk for lung cancer. The magnitude of the risk of lung cancer in shipyard workers has been studied in other epidemiologic surveys that were controlled for smoking. These studies indicate that such workers (like 70 percent of our subjects in groups 2 and 3) have a risk of lung cancer about 1.7 times the risk in the general population,[32-34] meaning that, on average, two tumors in five are possibly attributable to asbestos.

The asbestos body concentration, which is techni-

Downloaded from chestjournal.chestpubs.org by guest on November 10, 2011
© 1986 American College of Chest Physicians

cally simpler to determine than the AC fiber burden, does not give an accurate estimate of the AC fiber burden because of the large variation of the AC/AB ratios (4:1 to 136,000:1). Nevertheless, it is apparent from Figure 2 that asbestos body concentrations over 1,000/g of dry lung are likely to be associated with concentrations of AC fibers over 100,000/g of dry lung. Few persons in the general population have asbestos body concentrations in this range.[35] In the absence of an amosite and crocidolite fiber determination, an asbestos body concentration over 1,000/g of dry lung in a person with a history of exposure to such fibers should be used in place of asbestosis as an indication that a lung cancer may be asbestos-related.

ACKNOWLEDGMENTS: We thank T. Kuwahara and G. Wolery for technical assistance and A. Warnock for writing the computer programs. We also thank Ms. B. Poetter for editorial assistance.

REFERENCES

1 Selikoff IJ, Hammond EC, Churg J. Asbestos exposure, smoking, and neoplasia. JAMA 1968; 204:104-10
2 McDonald JC. Asbestos-related disease: an epidemiological review. In: Wagner JC, ed. Biological effects of mineral fibres. Lyon, France: IARC Scientific Publications (No. 30), 1980; 2:587-603
3 Newhouse ML. Asbestos-related diseases. Practitioner 1983; 227:1399-411
4 Seal RME. Current views on pathological aspects of asbestosis (the unresolved questions and problems). In: Wagner JC, ed. Biological effects of mineral fibres. Lyon, France: IARC Scientific Publications, 1980; 1:217-35
5 Parkes WR. Occupational lung disorders. Boston: Butterworths, 1982, pp 294-95
6 Warnock ML, Prescott BT, Kuwahara TJ. Numbers and types of asbestos fibers in subjects with pleural plaques. Am J Pathol 1982; 109:37-46
7 Warnock ML, Kuwahara TJ, Wolery G. The relation of asbestos burden to asbestosis and lung cancer. Pathol Annu 1983; 18:109-45
8 Warnock ML, Kuwahara TJ, Wolery G. Asbestos fibers in lungs of subjects with mesothelioma. Lab Invest 1984; 50:66A
9 World Health Organization. The World Health Organization histological typing of lung tumours. Am J Clin Pathol 1982; 77:123-36
10 Zar JH. Biostatistical analysis. Englewood Cliffs, NJ: Prentice-Hall, Inc, 1974
11 Churg A, Warnock ML. Analysis of the cores of asbestos bodies from members of the general population: patients with probable low-degree exposure to asbestos. Am Rev Respir Dis 1979; 120:781-86
12 Craighead JE, Abraham JL, Churg A, Green FHY, Kleinerman J, Pratt PC, et al. The pathology of asbestos-associated diseases of the lungs and pleural cavities: diagnostic criteria and proposed grading schema. Arch Pathol Lab Med 1982; 106:544-96
13 Sluis-Cremer GK. The relationship between asbestosis and bronchial cancer. Chest 1980; 78:380-81
14 Roggli VL, Pratt PC. Numbers of asbestos bodies on iron-stained tissue sections in relation to asbestos body counts in lung tissue digests. Hum Pathol 1983; 14:355-61
15 Warnock ML, Prescott BT, Kuwahara TJ. Correlation of asbestos bodies and fibers in lungs of subjects with and without asbestosis. Scan Electron Micros 1982; 2:845-57
16 Turner-Warwick M, Parkes WR. Circulating rheumatoid and antinuclear factors in asbestos workers. Br Med J 1970; 3:492-95
17 Kagan E, Solomon A, Cochrane JC, Kuba P, Rocks PH, Webster I. Immunological studies of patients with asbestosis: 2. studies of circulating lymphoid cell numbers and humoral immunity. Clin Exp Immunol 1977; 28:268-75
18 Kagan E, Solomon A, Cochrane JC, Beissner EI, Gluckman J, Rocks PH, Webster I. Immunological studies of patients with asbestosis: 1. studies of cell-mediated immunity. Clin Exp Immunol 1977; 28:261-67
19 Lange A, Nineham LJ, Garncarek D, Smolik R. Circulating immune complexes and antiglobulins (IgG and IgM) in asbestos-induced lung fibrosis. Environ Res 1983; 31:287-95
20 Doll NJ, Diem JE, Jones RN, Rodriguez M, Bozelka BE, Stankus RP, et al. Humoral immunologic abnormalities in workers exposed to asbestos cement dust. J Allergy Clin Immunol 1983; 72:509-12
21 Ashcroft T, Heppleston AG. The optical and electron microscopic determination of pulmonary asbestos fibre concentration and its relation to the human pathological reaction. J Clin Pathol 1973; 26:224-34
22 McDonald AD, McDonald JC, Pooley FD. Mineral fibre content of lung in mesothelial tumours in North America. Ann Occup Hyg 1982; 26:417-22
23 Rowlands N, Gibbs GW, McDonald AD. Asbestos fibres in the lungs of chrysotile miners and millers—a preliminary report. Ann Occup Hyg 1982; 26:411-15
24 Whitwell F, Newhouse ML, Bennett DR. A study of the histological cell types of lung cancer in workers suffering from asbestosis in the United Kingdom. Br J Industr Med 1974; 31:298-303
25 Kannerstein M, Churg J. Pathology of carcinoma of the lung associated with asbestos exposure. Cancer 1972; 30:14-21
26 Hourihane DO'B, McCaughey WTE. Pathological aspects of asbestosis. Postgrad Med J 1966; 42:613-22
27 Auerbach O, Garfinkel L, Parks VR, Conston AS, Galdi VA, Joubert L. Histologic type of lung cancer and asbestos exposure. Cancer 1984; 54:3017-21
28 Madri JA, Carter D. Scar cancers of the lung: origin and significance. Hum Pathol 1984; 15:625-31
29 Shimosato Y, Hashimoto T, Kodama T, Kameya T, Suzuki A, Nishiwaki Y, et al. Prognostic implications of fibrotic focus (scar) in small peripheral lung cancers. Am J Surg Pathol 1980; 4:365-73
30 Weill H. Asbestos-associated diseases: science, public policy, and litigation. Chest 1983; 84:601-08
31 Newhouse ML. A study of the mortality of workers in an asbestos factory. Brit J Industr Med 1969; 26:294-301
32 Blot WJ, Harrington JM, Toledo A, Hoover R, Heath CW, Fraumeni JF Jr. Lung cancer after employment in shipyards during World War II. New Engl J Med 1978; 299:620-24
33 Blot WJ, Morris LE, Stroube R, Tagnon I, Fraumeni JF Jr. Lung and laryngeal cancers in relation to shipyard employment in coastal Virginia. J Natl Cancer Inst 1980; 65:571-75
34 Kolonel LN, Hirohato T, Chappell BV, Viola FV, Harris DE. Cancer mortality in a cohort of naval shipyard workers in Hawaii: early findings. J Natl Cancer Inst 1980; 64:739-43
35 Churg A, Warnock ML. Correlation of quantitative asbestos body counts and occupation in urban patients. Arch Pathol Lab Med 1977; 101:629-34

Downloaded from chestjournal.chestpubs.org by guest on November 10, 2011
© 1986 American College of Chest Physicians

Asbestos burden and the pathology of lung cancer.
M L Warnock and W Isenberg
Chest 1986;89; 20-26
DOI 10.1378/chest.89.1.20

This information is current as of November 10, 2011

Updated Information & Services
Updated Information and services can be found at:
http://chestjournal.chestpubs.org/content/89/1/20

Cited Bys
This article has been cited by 5 HighWire-hosted articles:
http://chestjournal.chestpubs.org/content/89/1/20#related-urls

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.chestpubs.org/site/misc/reprints.xhtml

Reprints
Information about ordering reprints can be found online:
http://www.chestpubs.org/site/misc/reprints.xhtml

Citation Alerts
Receive free e-mail alerts when new articles cite this article. To sign up, select the "Services" link to the right of the online article.

Images in PowerPoint format
Figures that appear in *CHEST* articles can be downloaded for teaching purposes in PowerPoint slide format. See any online figure for directions.

AMERICAN COLLEGE OF
CHEST
PHYSICIANS®

Downloaded from chestjournal.chestpubs.org by guest on November 10, 2011
© 1986 American College of Chest Physicians