資料6

Pleural Plaques and Risk for Bronchial Carcinoma and Mesothelioma*

A Prospective Study

Gunnar Hillerdal, M.D., F.C.C.P.

From the general population in the county of Uppsala, Sweden, 1,596 men with pleural plaques fulfilling strict radiologic criteria were identified from 1963 until June 1985. The men have been followed prospectively for 16,369 person-years. The number of mesotheliomas and bronchial carcinomas was compared with the age- and year-specific expected incidence from the official cancer registry of Sweden. Fifty bronchial carcinomas occurred, while 32.1 were expected after correction for smoking habits, a difference which was statistically significant. Patients with radiologic asbestosis were overrepresented among those with bronchial carcinoma. The risk for patients with pleural plaques without asbestosis was increased 1.4 times, which was statistically significant. There were 9 mesotheliomas, while only 0.8 were expected. The mean latency time from first exposure to diagnosis of bronchial cancer was 44.1 years and for mesothelioma was 48.1 years. Thus, pleural plaques on the chest roentgenogram indicate significant exposure to asbestos, with an increased risk for mesothelioma and possibly also for bronchial carcinoma. Any person found to have plaques on chest roentgenogram should be informed of them and should be persuaded to stop smoking. *(Chest 1994; 105: 144-50)*

Asbestos was extensively used in most industrialized countries during and especially after World War II. Only for the last one or two decades has there been a marked decline in the use of asbestos, as

For editorial comment see page 8

consequence of the health risks. Even before this decline in use, increasingly strict protective measures in the workplace were enforced in most countries. Thus, today there are large groups of workers who have been occupationally exposed to asbestos but generally to much lower levels than was the case before and during the war.

Since they can occur even after relatively low exposure, pleural plaques are nowadays by far the most common lesion seen in persons exposed to asbestos. Their clinical importance has been much discussed, with some researchers claiming that they are simply a sign of exposure without clinical importance while others believe them to be associated with other more serious diseases. One reason for these diverging opinions is disagreement about the radiologic definition of plaques and consequently a low reproducibility between readers.

Pleural plaques are a common finding in the population of industrialized societies and are seen mainly in those persons who have been occupationally exposed to asbestos; however, pleural plaques can also be found in persons without any known exposure, and they can be caused by environmental exposure to asbestiform minerals, as reported from Finland, Greece, Turkey, and other countries.

In the county of Uppsala, Sweden, a large number of persons with pleural plaques from the general population has been identified and followed for more than two decades. The county has a population of about 250,000 and is not heavily industrialized. There are no shipyards in the county and only one minor asbestos industry. A general health survey including a small size chest roentgenogram was done from 1963 until June 1985. All inhabitants of the county from 15 years of age were invited every third or second year. The overall participation was 64 percent, and among those aged 40 to 70 years, it was 70 percent.[1] Thus, serial roentgenograms are available for a large proportion of the population, giving ideal conditions to study slowly developing lesions such as pleural plaques.[2]

All persons with chest roentgenograms showing pleural plaques which fulfilled strict radiologic criteria were followed since discovery. In this paper, the occurrence of mesotheliomas and bronchial carcinomas in 1,596 men, observed prospectively for 16,369 person-years, is reported.

Material and Methods

Identification of Persons With Plaques

All persons found at the general health survey from Jan 1, 1970 to June 30, 1985, to have suspect pleural plaques were recalled for a full-size chest roentgenogram, clinical investigation, and a careful history including possible exposure to asbestos. There was very good agreement between the findings of the small- and the full-size roentgenograms in regards to the finding of plaques. If the findings at the full-size chest roentgenogram fulfilled the criteria in Table 1 for pleural plaques, the person was included in the study and offered a biyearly medical checkup with chest roentgenogram.[2] In

*From the Department of Lung Medicine, Uppsala University, Akademiska Sjukhuset, Uppsala, Sweden.
This study was supported in part by the Swedish Heart and Lung Foundation.
Manuscript received January 7, 1993; revision accepted April 21.
Reprint requests: Dr. Hillerdal, Department of Pulmonary Medicine, University Hospital, S-751 Uppsala, Sweden

addition to those found at the health survey, a number of persons who had been found accidentally to have pleural plaques at investigation for some other reason were also included. For inclusion in the study, there were no signs of malignant tumor or serious lung or other disease.

Attack Year

Chest roentgenograms were requested from other hospitals and earlier small-size roentgenograms were scrutinized. With this method, it was possible in the majority of cases to identify the first chest roentgenogram within a 5-year interval where the plaques fulfilled the criteria. This was termed the attack year of pleural plaques.

Asbestos Exposure and Latency Time

Asbestos exposure was graded from 1 to 3, where 1 was occasional and not very intense exposure (such as a building worker in general), and 3 was daily heavy exposure (for example an insulator working indoors applying asbestos, or the building worker spraying asbestos). The length of exposure in years was multiplied by this figure, giving a rough estimate of all persons' total exposure. This was based solely on the patient's history since in most instances no other information was available. Latency time (the time from the first year of asbestos exposure to the attack year) was calculated.

Asbestosis

At each visit, the chest roentgenograms were classified according to the International Labor Office (ILO) scale.[3] Asbestosis was defined as grade 1/0 or more.

Follow-Up

All patients were traced until Dec. 31, 1991. Their vital status, if not known, was checked in the central registry, where all persons living in Sweden can be traced. Only those who had emigrated to other countries could not be traced. For those who had died, death certificates were requested.

Calculations

Every full observed year was counted as a person year. The year of discovery and the year of death, diagnosis of lung cancer, or emigration was counted as half a year. For every year (1970 to 1991), the number of observation years in each 5-years age group (40 to 44 years old, 45 to 49 years old, etc) was calculated.

Since the lung department is the only one in the county, the majority of all bronchial carcinomas and mesotheliomas are referred there. Thus, in most patients with pleural plaques, even those alive with such tumors will be known by the department.

The number of observation years in each 5-year age group was multiplied by the expected incidence for bronchial carcinoma or malignant pleural mesothelioma for this particular age group of males the given year. This latter figure was taken from the official cancer registry of Sweden for each year. However, the latest year available was 1988. Therefore, for the years of 1989, 1990, and 1991, the figures for 1988 were used. The resulting figures of expected tumors for each year and age groups were added, giving the total expected number of bronchial carcinomas and mesotheliomas in the cohort. The average incidence of bronchial carcinomas in the County of Uppsala only was found to be not statistically different from the country as a whole though slightly lower, and therefore, the figures for all of Sweden were used.

The smoking habits of the cohort were compared to the expected, which was taken from official statistics. The expected incidence of bronchial carcinomas was corrected for this difference, assuming a linear dose-effect of smoking on the risk of lung cancer. Separate calculations of the actual and expected number of bronchial carcinomas as a function of time since first exposure and in relation to radiologic asbestosis were also made.

Table 1—*Criteria for Pleural Plaques (All Criteria to be Fulfilled)*

Bilateral lesions
At least 5 mm thick and/or calcified
Well demarcated
No remnants of pleurisy, *ie*, costophrenic angles not obliterated

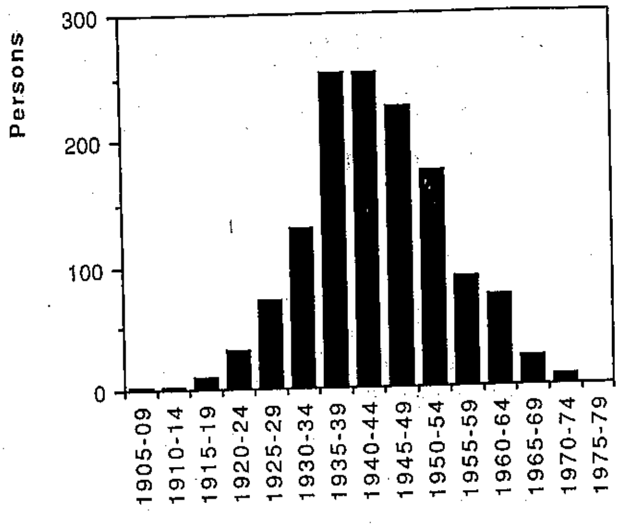

Figure 1. The first year of exposure to asbestos (or the first year of working in the particular occupation where exposure occurred).

Results

The total cohort consisted of 1,596 men. The majority, 1,350 (84.6 percent), was discovered in the health survey. The occurrence of pleural plaques in the county was steadily increasing until 1985 and by then reached 2.7 percent among the men over age 40.

Exposure to Asbestos

Of the 1,588 men whose histories were available, 1,408 (88.7 percent) had an occupational exposure to asbestos, 14 (0.9 percent) had a nonoccupational exposure, and 166 (10.5 percent) denied any exposure to asbestos. Information was missing for eight men (0.5 percent) who had refused to come for the checkup. The occupational exposure was not always available at the first visit. Eighty-six persons who denied having ever used asbestos at later visits confirmed such exposure, sometimes quite heavy, which they, however, had not remembered or even known about until they did some private research. The majority (84.0 percent) had an exposure of grade 1, 14.9 percent had grade 2 exposure, and only 1.1 percent had grade 3. The mean length of exposure was 23.8 years (range, 1 to 58 years).

The first year of exposure was in most cases in the 30s, 40s, or 50s (Fig 1). More than half of the exposed men had been in building and construction and most

Table 2—*Occupational Exposure*

	No.	Percent of Exposed	Percent of All
Building and construction			
Building workers	397		
Plumbers	169		
Electricians	80		
Painters	38		
Sheet metal workers	31		
Insulators	15		
Floor layers	10		
Total	740	51.6	46.4
Industry and free trades			
Automobile (repair and prod)	113		
Paper and chemical industry	84		
Supervisors	51		
Metal industry	44		
Repairmen	38		
Mechanics	34		
Welders	32		
Engineers	29		
Insulators	23		
Ceramic industry	16		
Steam engine workers (railroad)	9		
Shipyard workers	8		
Miners	4		
Other factories	47		
Total	532	37.8	33.3
Other occupations	136	9.7	8.5

of the others in industry of another kind (Table 2). A long list of other occupations completed the list (Table 3). In 1,090 men, the latency time from first exposure to asbestos to the attack year could be calculated and was 33.3 years (1SD=9.3, range 3 to 63 years) (Fig 2).

Table 3—*Other Occupational Exposure in Men*

Selling of asbestos	18
Sea engineers	16
Scrap iron workers	15
Transport of asbestos	13
Storage workers	12
Chimney sweepers	8
Gold/silversmiths	8
Custodians	8
Instrument technicians, laboratory work, *etc.*	5
Fire fighters	5
Railroad workers	3
Tile-stove makers	3
Glass worker	3
Municipal employees	3
Dental technicians	2
Farmers	2
Bicycle repairmen	2
Advertisers	2
Dairy workers	2
Laundry workers	2
Baker	1
Artist	1
Military officer	1
Radio repairman	1
Total	136

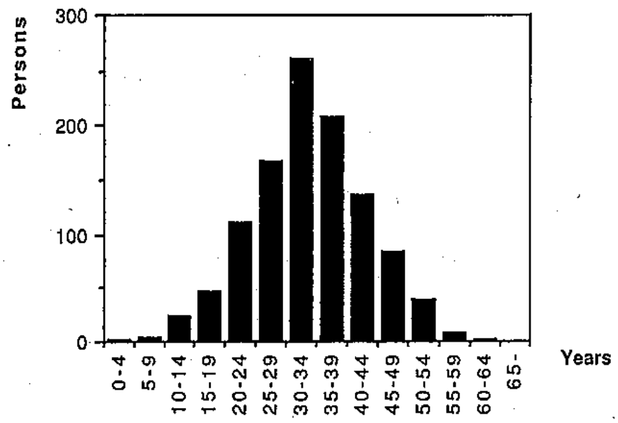

FIGURE 2. Latency time for pleural plaques (time from first known exposure to the attack year of bilateral plaques) in 1,090 men.

Smoking Habits

These figures were available for 1,538 persons out of the 1,596 (96.4 percent). Three hundred thirty-two (21.6 percent) had never smoked, 694 (45.1 percent) were exsmokers, and 512 (33.3 percent) were smokers at last observation.

Radiologic Parenchymal Lesions

At the year of discovery, only 11 patients (0.69 percent) had small size opacities on their chest roentgenogram (ILO 1/0 or more). However, during the observation time, a number of patients developed such changes, and at last observation, 166 patients (10.4 percent) had them. Of those, 151 (9.5 percent of total) had ILO grade 1 (1/0 to 1/2) and 15 (0.9 percent) had grade 2 (2/1 to 2/3). These increased interstitial markings could indicate an early asbestosis, but they are not specific and can be seen in elderly people, especiallly smokers, without any exposure to asbestos. In the following, however, the term "radiologic asbestosis" is used for these findings (*ie*, ILO 1/0 or more).

Those with such presumed radiologic asbestosis (grade 1 and 2) had a heavier exposure to asbestos when the grading was used ($p < 0.001$, Table 4) but not when the number of years exposed was calculated. Those without such lesions had a mean of 24.0 years of exposure, while those with them had been exposed 22.2 years. Patients with radiologic asbestosis had a

Table 4—*Grade of Exposure to Asbestos and Development of Asbestosis*

Asbestosis Grade (Range)	Exposure Grade 1	2	3
1 (0/-0/1)	1,027 (85.9)*	159 (13.3)	10 (0.8)
1 (1/0-1/2)	99 (71.7)	36 (26.1)	3 (2.1)
2 (2/1-2/3)	4 (28.6)	8 (57.1)	2 (14.3)

*Number of patients (%).

Table 5—*Observed and Expected Rates of Bronchial Carcinoma and Mesothelioma*

	Observed (O)	Expected (E)	E Corrected for Smoking	O/E	95 Percent Confidence Interval
Bronchial carcinoma	50	24.6	32.1	1.6	1.16-2.05
Mesothelioma	9	0.8	0.8	11.25	5.13-21.35

Table 6—*Risk for Bronchial Carcinomas Among Persons With Pleural Plaques With and Without Radiologic Asbestosis*

	Expected	Observed	Observed/Expected	95 Percent Confidence Interval
Asbestosis	3.9	9	2.3	1.05-4.38
No asbestosis	28.2	41	1.4	1.04-1.97

history of heavier smoking; of those who had no parenchymal lesions, 22.7 percent were never-smokers, while this figure for patients with radiologic asbestosis was 14.2 percent ($p < 0.001$)

The number of observation years was approximately the same for patients with or without radiologic asbestosis (10.8 ± 4.4 and 11.5 ± 4.9, respectively).

Bronchial Carcinomas

During the observation time, 50 bronchial carcinomas occurred, while 32.1 were expected after correction for smoking habits, a difference which was statistically significant (Table 5). Of the 50 patients who developed a bronchial carcinoma, 4 (8 percent) denied exposure to asbestos, but all of them had worked in occupations with potential exposure to the mineral. There was no significant difference in length of time exposed (23.8 years for both those with and those without cancer), nor in the degree (80.9 of those who developed bronchial carcinoma had an exposure of grade 1, while this figure for the others who were exposed was 83.9 percent, a nonsignificant difference).

All patients with bronchial carcinoma were smokers (29) or exsmokers (21 patients). The patients with bronchial carcinoma had a history of heavier smoking with more pack years than those smokers

Table 7—*Relative Risk of Bronchial Carcinoma From First Exposure**

Years From First Exposure	Observation Years	Expected Cancers†	Found Cancers	RR
20-29	1,624	0.5	3	6
30-39	4,105	4.0	11	2.8
40-49	5,712.5	13.1	16	1.2
50-59	2,446.5	9.3	11	1.2
60-69	428	1.6	4	2.5
Sum	14,316	28.5	45	1.6

*Calculated from cases where exposure was known.
†Corrected for smoking habits.

or exsmokers without bronchial carcinoma (mean, 34.7 ± 15.2, as compared to 24.9 ± 15.1, $p < 0.001$).

Patients with asbestosis were overrepresented among those with bronchial carcinoma: 9 (18 percent) of them had asbestosis, as compared to 10.2 percent of those who did not develop a bronchial carcinoma ($p<0.001$). When the risk ratio was recalculated for patients with and without asbestosis, the risk for patients with pleural plaques without asbestosis approached the lower limit of the confidence interval (Table 6). The figures were corrected for the higher smoking habits among those with asbestosis.

The mean latency time from first exposure to diagnosis of cancer was 44.1 years (range 8 to 62, 1SD = 11.5). There was a tendency for the relative risk of bronchial carcinoma to decrease with time from first exposure (Table 7).

Nine patients with carcinoma were still alive at the end of 1991. Five of them have lived more than 5 years after operation without signs of recurrence. In addition, 1 patient died 6 years after operation of myocardial infarction. The majority (32 patients) had a squamous cell carcinoma; 5 had small cell carcinoma; 8 had adenocarcinoma; 2 had large cell carcinoma; and 3 with undifferentiated carcinoma. The lower lobes were overrepresented (21 cases) and only 10 had their cancer in the upper lobes, 2 in the middle lobe, the rest being distributed in the main bronchi.

Mesotheliomas

There were 9 mesotheliomas while only 0.8 were expected (Table 5). Four patients had been exposed while working in the building industry, and a fifth had also been working in a similar setting but denied exposure. The remaining four had been exposed in various types of industry. Two had classified their exposure as grade 2 and six as grade 1. The length of exposure varied between 26 and 47 years (mean, 48.1 years). The mean latency time from first exposure was 48.1 years (range, 40 to 55 years).

Discussion

This prospective study, with patients from the general population included and followed over a time-span of more than 20 years on the basis of radiologically, strictly-defined pleural plaques, demonstrates that these persons have an increased risk of mesothelioma, cancer of the bronchi and the gastrointestinal tract, and pulmonary fibrosis. The risk of bronchial carcinoma was increased even among those who did not show any radiologic signs of asbestosis, even if it was substantially smaller than among those who had such signs. This is contrary to the currently most popular doctrine, which claims that the lung cancer risk is increased only in those who show radiologic asbestosis, and as a consequence, it has been claimed that the cancer is secondary to the fibrosis (for references, see below). The following discussion will focus on the diagnosis of plaques, the possible occurrence of asbestosis in patients with plaques, the effect of smoking on asbestosis and cancer, and review the data on asbestosis and lung cancer in the light of the findings from this study. Finally, some words about mesothelioma.

Diagnosis of Pleural Plaques

Pleural plaques are always more widespread and numerous at autopsy than those seen on the roentgenogram, and in fact, only 10 to 15 percent is seen with conventional radiography. Unfortunately, as soon as "possible" or "suspect" plaques are included in a study, the specificity will decrease substantially, and half or more of the radiologically diagnosed "plaques" will not be confirmed at autopsy.[4-7] Thus, strict radiologic criteria are essential. Those used in the present study have been compared to findings at autopsy and have a high specificity. In fact, there were no false-positives.[5] The good correlation between plaques found in the general population and the persons' occupational exposures further illustrates the value of these strict criteria. The ILO classification, which is commonly used for defining plaques, is unfortunately too unspecific, and using it as the "gold standard" will make scientific studies impossible by inclusion of too many false-positives.

The low sensitivity with strict criteria can be seen as a disadvantage, but in fact, it will probably cause only large plaques to be diagnosed. The longer and heavier the exposure, the more extensive plaques will generally develop,[2,5,8-11] and thus, by using these criteria, the more heavily exposed among the plaque carriers are selected. This hypothesis was confirmed in a recent study by Kishimoto et al[12] published in 1989. In 400 lungs obtained at autopsy, he found 71 with more than 500 asbestos bodies per 5 g of lung tissue. All patients had pleural plaques at autopsy. Those with a chest roentgenogram showing probably plaques had a mean of 960 and those with definite plaques, 32,560 asbestos bodies per 5 g of lung tissue. Others have also reported similar correlations.[13]

Of course, a certain percentage of the general population not having plaques fulfilling strict radiologic criteria will, in fact, be carriers of plaques, either too small or too badly located to be seen on a standard chest roentgenogram. An increased cancer risk even for these people would decrease the difference between the "plaque group" and the "nonplaque group." This is unavoidable, but the essential requirement is as few as possible false-positives, *ie*, the use of strict radiologic criteria, such as those used in this study.

Pleural Plaques and Asbestosis

Persons with pleural plaques have as a group a somewhat lower lung function;[14-21] which is probably best explained by a concurrent subclinical asbestosis.[19,22] Since both pleural plaques and asbestosis are due to asbestos exposure, it is not surprising that some patients with plaques develop a radiologically manifest asbestosis if they are followed, nor that pulmonary fibrosis is more common in plaque carriers than in those without plaques.[23,24]

The Effects of Smoking

Smoking has been shown in many studies to increase the risk of radiologic asbestosis,[18,23,25-27] which was further confirmed by the present study. Smoking is also by far, the greatest risk factor for bronchial carcinoma. Asbestos exposure seems to have a multiplicative effect on the lung cancer risk, which means that nonsmokers (who have a very low "basal" risk) have a low risk even if they are exposed to asbestos and very large materials would be needed to prove a risk of the magnitude seen in this study, *ie*, 1.6 times.[28-30] Consequently, as in this study, all or most patients with lung cancer (whether they are exposed to asbestos or not) will be smokers or exsmokers.

Smoking is more common among workers exposed to asbestos than in the general population. However, this difference is not so great that it can explain large differences in lung cancer risk between various occupational groups[31] and can be corrected for, as in the present study. In addition to quantitative differences, there might also be qualitative, *ie*, blue collar workers might smoke with greater intensity such as smoking the cigarette down to the filter and taking deeper drags. Such smoking habits would be difficult to adjust for but are also unlikely to have any greater impact on the figures.

A factor which might also affect the results is that quitting smoking will decrease the risk of cancer.[32] Consequently, the intense antismoking propaganda that these patients have been given each time they visited the department probably has reduced the risk.

Plaques and Bronchial Cancer

In many studies, the incidence of bronchial carcinoma is two or more times higher in those with plaques as in those without but with similar exposure.[33-35] Plaques occur twice as often in thoracotomies for malignancy as in those performed for other reasons[36,37] and are twice as common as expected as a radiographic finding in lung cancer patients.[38,39] There are, however, also studies that have shown that the frequency of bronchial carcinoma among plaque carriers is not higher than expected.[40,41] Variations in diagnostic criteria for plaques and perhaps exposure to different types of asbestos could explain these different results. However, as has been shown, there are many studies indicating an increased risk of lung cancer among patients with pleural plaques. This is not surprising since, as discussed above, plaques in most cases are an indication of an important exposure to asbestos.

Bronchial Carcinoma and Asbestosis

As mentioned above, the currently most popular doctrine is that the risk of lung cancer is increased only in those who show radiologic asbestosis, and indeed, it has been claimed that the cancer is secondary to the fibrosis, *ie*, it is a type of "scar carcinoma." This is based upon a number of studies which has shown an increase among patients with either radiologic[28,42,43] or pathologic[44,45] findings of asbestosis but not any significantly increased risk among exposed persons who failed to show signs of asbestosis. It should be stressed here that the pathologic studies often refer to a slight or moderate asbestosis, which most often would be undetected by ordinary radiologic techniques. The conclusion has been that in the absence of asbestosis at necrospy, a bronchial carcinoma in a man exposed to asbestos is not due to asbestos.

However, once again it must be stressed that both asbestosis and lung cancer are dose-related. Thus, that both diseases co-exist is exactly what one would expect, and it does not necessarily follow that one disease is the cause of the other. With lower grades of exposure (and consequently lower risk of asbestosis), the risk for lung cancer would also be low, so low that for simple statistical reasons, a large number of patients must be investigated to prove that risk. Statistics can suggest a causal connection, but a statistically nonsignificant finding does not prove that there is no connection. Further, a confounding factor is that smoking increases both the risk for asbestosis and the risk for bronchial carcinoma.

As discussed above, it is also quite probable that many patients with pleural plaques have a subclinical pulmonary fibrosis, seen only histologically.

Pathology of Bronchial Cancers

In asbestos workers the bronchial carcinoma is more often situated in the lower lobes than in the upper ones, while the reverse is generally found in nonexposed populations.[46,47] This was also found in the present study. Since the majority of the tumors were squamous cell cancers, the theory that asbestos-related lung cancers are scar carcinomas is not strongly supported.

Time-Related Risk

This study shows that the relative risk for lung cancer seems to decrease 35 to 40 years after first exposure. This is in accordance with other published data.[48,49]

Mesothelioma

The risk of mesothelioma is independent of smoking habits. Edge,[33] in 1976, estimated that plaque carriers had a risk of developing mesothelioma which was 1/377 per year. In the present study, the risk (9 cases in 15,000 person years, *ie*, 1/1,700) is considerably smaller, which is not surprising since Edge's patients were exposed to a higher degree to amphiboles and also, probably had a heavier exposure.

Conclusions

The finding of definite pleural plaques at chest roentgenogram indicates exposure to asbestos at a level which is of clinical importance. There is a definitely increased risk for mesothelioma, and the data suggest that there is possibly also an increased risk for bronchial carcinoma, though not very great. Any person found to have plaques on his chest roentgenogram should be informed of their significance and be persuaded to stop smoking.

References

1 Hillerdal G, Hillerdal O, Nöu E. Radiologically visible pleural plaques in a one-year material from a health survey in 1976: a cross-sectional study. Eur J Respir Dis 1980; 61(suppl 107):89-98

2 Hillerdal G. Pleural plaques in a health survey material: frequency, development and exposure to asbestos. Scand J Respir Dis 1978; 59:257-63

3 Guidelines for the use of the ILO international classification of radiographs of pneumoconioses, rev ed. ILO Office, Occupational Safety and Health series No. 22 (Rev). 1980

4 Hourihane DOB, Lessof L, Richardson PC. Hyaline and calcified pleural plaques as an index of exposure to asbestos: a study of 100 cases with a consideration of epidemiology. BMJ 1966; 1:1069-74

5 Hillerdal G, Lindgren A. Pleural plaques: correlation of autopsy findings to radiographic findings and occupational history. Eur J Respir Dis 1980; 61:315-19

6 Rubino GF, Scansetti G, Pira E, Piolatto G, Mollo F, Andrion A, et al. Pleural plaques and lung asbestos bodies in the general population: an autoptical and clinical-radiological survey. In: Symposium on radiological effect of mineral fibers. Lyon,