Pleural Plaques and Asbestos-associated Malignancy

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Pleural plaques are common in asbestos-exposed workers, affecting 15% to 60% of workers.[1] The finding of a pleural plaque is often a signal of abnormality and is frequently a cause of fear of additional disorders. However, the significance of these plaques is uncertain; is the plaque simply a "marker of exposure" or does it signify increased risk of disability or death? The large size of the population that has had asbestos exposure makes pleural plaques a frequent health concern for these workers' families, as well as to their employers and to the medical and legal personnel involved. Recent increases in public and health professional awareness of asbestos effects is increasing the vigor with which plaques are sought diagnostically.

Previous studies of the significance of pleural plaques have yielded conflicting results.[2-5] We have therefore conducted a nested case-control study of a cohort of asbestos-exposed workers to determine whether pleural plaques are a risk factor for development of asbestos-associated malignancy.

Methods

A total of 1,500 asbestos-exposed workers were examined for the detection of asbestos-associated disease between 1979 and 1983 by physicians in the departments of pulmonary and occupational medicine at three University of California, Los Angeles, medical centers (Center for Health Sciences, Cedars-Sinai, and Harbor-UCLA Medical Centers). Most of the workers examined were referred after filing a claim for compensation for asbestos-related lung disease.

Each subject was interviewed in a standard manner by a trained nurse and subsequently by a physician. Dates of exposure were determined from information supplied by subjects and employers. Particular care was taken to encourage accurate reporting of exposure and of smoking histories. Radiographic examination of the chest included four views (posteroanterior, lateral, and bilateral obliques) in almost all cases. The radiographs were read by radiologists but were not coded according to the International Labor Office (ILO) system.[6] Most had worked in shipyards, performing both new construction and refitting work. The median duration of work with asbestos exposure was 24 years. Industrial hygiene data describing fiber counts are unavailable, but work description suggests that asbestos exposure was heavy.

Members of this population were subsequently contacted to ascertain who had developed asbestos-associated malignancies detected after the initial examination. Malignant mesothelioma and carcinomas of the larynx, pharynx, trachea-bronchus-lung, kidney, and gastrointestinal tract were considered to be asbestos related based on reports confirming or suggesting such associations.[7] The average interval between initial examination and follow-up contact was 30 months.

Information about cancer status was sought from the subject or family members by telephone and by letter. A trained interviewer called the last known telephone number and administered a short interview if possible. Letters with a brief questionnaire were sent to the last known address. Information about 726 of the potential subjects was obtained.

Each patient, defined as a subject known to have developed an asbestos-associated malignancy, was individually matched to a control, a subject known to be free of cancer. Thus, subjects whose cancer status was unknown were ineligible to be a control. Only male

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subjects were included. Each patient was individually matched to a control of the same race, smoking status, and hospital of examination and with similar age, duration of asbestos exposure, and pack-years of smoking (if an ex-smoker or current smoker). Workers who had stopped smoking at least 6 months before examination were classified as ex-smokers, and persons who had smoked less than 1 pack-year with none for at least 5 years were considered nonsmokers. Although selection of more than one control per patient would increase the statistical power of the analysis, it would have required including controls who were less comparable to the patients. The matches were selected according to a prescribed protocol by an individual who had no knowledge of the subjects' radiographs.

The radiographs from the patients' and controls' initial examinations were then obtained for review. The readers were unaware of the identity and cancer status for each radiograph. Names and dates were masked to avoid any possible bias. Each radiograph was read independently by two readers familiar with the ILO system, one of whom was a certified B reader.

The radiographs were read by three systems, which are summarized in Table 1. First, posteroanterior films were interpreted according to ILO guidelines, modified to include four categories of certainty for plaque presence: "negative," "probably negative," "probably positive," and "positive."[6] Second, the ILO guidelines were used to interpret, but were applied to all four views (ILO-4 view). Third, the readers were asked to choose which of a pair of radiographs was most likely to show a plaque or interstitial disease. A forced choice was required for each of these questions, not allowing "neither" or "both" as answers. Each pair included a patient and his control; the readers were unaware of the identity. All radiographs were read by a single system before proceeding to the next system.

The choice of radiographic scoring methods and statistical analysis methods was made before collation of results. The interpretations based upon the ILO system were scored with the point system shown in Table 2 to yield a composite plaque score. This was done for both the ILO and ILO-4 view interpretations. The readings by the B reader and the non-B readers were analyzed separately to avoid counting each case-control pair twice.

Analyses were performed by the paired t test[8,9] and by the sign test (a nonparametric test depending only on the direction rather than magnitude of the case-control differences).[10] The paired readings for most likely pleural plaque (question 1) and most likely interstitial disease (question 2) were analyzed by the sign test, approximating the normal distribution. This was performed for both the interpretations of the B reader and of the non-B readers. Also, a 3-point scale was developed for the paired readings; the score is the number of readers (0 to 2) who felt the patient was more likely than the control to be positive. The investigators realized in advance that performance of multiple analyses increased the likelihood of finding a "statistically significant" result.

TABLE 1
Radiographic Reading Methods

Radiographs interpreted individually
PA only (ILO)
4 View (ILO—4 view)
Radiographs interpreted in pairs
Question 1. "Which of the pair is more likely to have a plaque?" (Pair-Plaque)
Question 2. "Which of the pair is more likely to have interstitial disease?" (Pair-Interstitial)

Results

Sixteen cases of asbestos-associated malignancy were identified. A total of 13 were bronchogenic carcinoma; other malignancies included colon, kidney, and throat. Age, smoking history, and duration of asbestos exposure were comparable between patients and controls, and pack-years and duration of exposure were similar.

Results of the analysis are shown in Table 3. The order of presentation of results for the B reader and the non-B readers has been varied. If a reader indicated that a radiograph was not of high quality, it was excluded from analysis, eliminating up to two pairs for some analyses. As shown in the table, there were no statistically significant differences ($P < .05$). Furthermore, there is no suggestion of a strong trend toward association of pleural plaque with subsequent malignancy.

Estimates of the power of several of these analyses were performed based upon a conditional sample size of 16 pairs. For the sign test, Fisher exact method showed that there was a 92% probability of finding a difference between patients and referrents (with a 10% chance of type II error) if 80% of the patients' radiographs showed plaque-like findings to a greater degree than the matched controls' radiographs. There was an 81%

TABLE 2
Composite Score = Plaque Score-Right (0, 1, 2, or 3) + Plaque Score-Left (0, 1, 2, or 3) + Profile Width Score-Right (0 or 2) + Profile Width Score-Left (0 or 2) + Calcification Score (0 or 2)

Plaque score = 0 if pleural abnormality (localized plaque or diffuse thickening) is definitely absent, 1 if pleural abnormality is probably absent, 2 if pleural abnormality is probably present, 3 if pleural abnormality is definitely present.

Profile width score = 0 if plaque width in profile <6 mm, 2 if plaque width in profile ≥6 mm.

Calcification Score = 2 if pleural calcification is present in either side, otherwise = 0.

Possible scores range from 0–12. For example, a radiograph with a 3-mm wide calcified probable plaque on right and a 7-mm calcified definite plaque on left would be scored as 9; plaque score-right = 2, plaque score-left = 3, profile width score-right = 0, profile width score-left = 2, calcification score = 2

TABLE 3
Results of Radiographic Interpretation*

System	Reader	Paired t test		Wilcoxon	Sign test	
		Mean Δ	P	P	% positive	P
ILO	1	−.10	.43	.34	50	0
	2	.07	.45	−.31	50	0
ILO-4 view	1	21	.31	.50	50	0
	2	−.03	.48	91	54	.11
Pair-plaque	1				47	−.10
	2				40	−.28
Pair-interstitial	1				50	0
	2				32	−.43
Pair-3 point-plaque	1 + 2			.67		

* These statistical analyses test the hypothesis that the patient is more abnormal than the control. No results were statistically significant. The order of readers is varied on the table. ILO and ILO-4 view results are based upon the plaque scoring system described in Table 2. Mean Δ, average case-control difference. % positive, percentage of pairs in which the patient received a higher score than his control. P value for the sign test is based upon a z score approximation.

chance of this finding if the true probability of the case having a more abnormal radiograph than the referent was .75. Power estimates for the 12-point scale readings paired differences were also performed for a reader. Variance of the difference between scores for cases and referents was estimated as twice the pooled variance for all readings, conservatively assuming no covariance. Power was then estimated using the t distribution for a one-sided $\alpha = 0.05$. A mean score difference of 2 points would be detected with 60% likelihood. A difference of 6 points would be detected with 81% power; this difference, for example, corresponds to finding bilateral plaques in the patient and normal pleura in the referent.

Discussion

Although pleural plaques are a common effect of asbestos exposure,[1,2] the medical significance of plaques is uncertain. At the very least, plaques serve as a marker of asbestos exposure, alerting clinicians to take a more detailed occupational history. Albelda et al[13] have shown the specificity of bilateral pleural plaques for asbestos exposure. Is there, however, additional significance? Are asbestos-exposed workers at higher risk of cancer or asbestosis if they have a plaque than if they do not?

Several previous studies have suggested that persons with plaques have increased risks of cancer relative to persons who do not have plaques. However, because asbestos causes both plaques and cancer, these studies do not demonstrate whether plaques per se imply any added risk. For example, Edge[3] matched on age but not on asbestos exposure. Hillerdal[4] also stated that his study did not show that knowledge of the presence or absence of plaques added any information about cancer risk that was independent of the extent of asbestos exposure. Hence, there is a need for studies such as the current one, in which the effect of the plaque per se is separated from that of asbestos exposure.

This nested case-control study was performed to determine whether pleural plaques are an independent risk factor for the subsequent development of an asbestos-associated malignancy. As shown in Table 3, despite the use of multiple analytic techniques to discern such a relationship, none was found. Thus, although asbestos exposure can cause plaques and can also cause cancer, plaques per se do not appear to be causally related to subsequent cancer development. Any apparent association between plaques and cancer is spurious, being a consequence of their associations with asbestos exposure.

The study design allowed control of confounding factors, matching each patient individually with a control subject (ie, without cancer) who had similar duration of asbestos exposure, smoking status, extent of smoking, and age. Each of these factors has been shown to lead to increased pleural plaque prevalence rates. Earlier studies have relied upon less certain information about these factors. For example, Wain et al[5] relied on occupational histories gleaned from the medical records of patients who underwent autopsies at a Veterans Administration hospital.

To assure close comparability between patients and controls and to overcome limitations of previous studies of the relationship between plaques and cancer, we selected only one control per patient. The nested case-control design used provided a unique ability to avoid biases that often affect cancer studies. First, smoking and exposure data were collected from the subject rather than from next of kin. Second, "recall" bias, due to selective remembering of risk factors after establishment of a diagnosis, was avoided because the information was collected before making the cancer diagnoses. Third, "diagnostic bias" is avoided; because the diagnosis of cancer and the ascertainment of plaques were accomplished independently, the presence of one is unlikely to affect the diagnosis of the other. Fourth, patients and controls were selected from the same population, enhancing comparability.

Inaccurate information about the confounding factors used for case-control matching are unlikely to affect the conclusions found. If anything, such inaccuracies would bias toward showing a spurious association of plaques and cancer. For example, if a subject understated his smoking experience, he would have been inappropriately matched with a subject with a lesser smoking exposure.

Because cigarette smoking causes both cancer[14] and an increased chance of radiologic abnormality, the "inaccurate" subject is more likely than his control to have both a plaque and cancer, thus biasing the study toward finding a positive plaque-cancer association.

The sample size for the statistical analysis is relatively small, although an initial cohort of 1,500 subjects was used for case identification. The limited sample size decreases the statistical power to find a low P value" in hypothesis testing but does not bias the mean result observed. There was no trend toward increased risk due to plaques, suggesting that lack of effect is the most likely true situation.

Although precise data about the duration of asbestos exposure were used, information about intensity of exposure was not available. Industrial hygiene data, describing fiber counts based on use of personal sampling pumps worn by the workers throughout the period of exposure, were not collected. The finding of no association is unlikely to be due to lack of exposure intensity data. Any effect, if present, would lead to a spurious association as discussed in the earlier example about smoking information. Furthermore, systematic interreader differences in radiographic interpretation would be unlikely to confound the results.

In summary, this study found no association between pleural plaques and asbestos-associated malignancies that were independent of other causative factors such as duration of asbestos exposure, age, and cigarette smoking. Although pleural plaques do indicate exposure, we do not believe their presence or absence should be used to allocate cancer screening resources among similarly exposed asbestos workers. If workers are known to have had significant exposure, it appears unwise to deny them appropriate examinations that they might otherwise receive simply because pleural plaque is not detected.

Acknowledgments

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Hazards of Early Pregnancy

The Director-General of WHO (World Health Organization) reminds us of something we know but tend to forget: that the inner-city teenager with two children by her 16th birthday has risked her own future health, has markedly reduced her chances of ever functioning effectively in our complex society, and has placed the babies themselves at risk of premature death. Early fertility in many subgroups of women in the United States is as much a barrier to the solution of our social problems as early fertility in undeveloped countries is to those countries' advancement into the modern world.

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PLEURAL PLAQUES AND ASBESTOS-ASSOCIATED MALIGNANCY

The presence of pleural plaques indicates a history of exposure to asbestos but is not an independent risk factor for the development of asbestos-associated malignant disease.

THE PROSPECTIVE IMPACT OF PSYCHOSOCIAL VARIABLES ON RATES OF ILLNESS AND INJURY IN PROFESSIONAL EMPLOYEES.

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In-house clinic usage, absenteeism, and tardiness were studied among 1505 employees at an automobile assembly plant. Less than 16 per cent of the workforce accounted for over 50 percent of the medical visits and more absence and tardiness, compared to the rest of the plant population.

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