The Clinical Diagnosis of Asbestosis in This Century Requires More Than a Chest Radiograph*

Robert M. Ross, MD, FCCP

Asbestosis can cause significant impairment and even death. It is also a well-recognized risk factor for the development of lung cancer. However, asbestosis is usually diagnosed on clinical grounds without the aid of pathology. Many physicians and researchers believe that in asbestos-exposed individuals with adequate latency, chest radiographic findings that are compatible with asbestosis are sufficient for the diagnosis. In order to determine whether this approach is reasonable, the positive predictive value of the chest radiograph for the diagnosis of pathologic asbestosis must be determined. This requires information about the prevalence of asbestosis, and the sensitivity and specificity of the chest radiograph in its diagnosis. In this article, the sensitivity and specificity of the chest radiograph in diagnosing asbestosis is determined from a literature analysis. The prevalence of asbestosis among present-day cohorts, such as construction workers and petrochemical workers, is assessed based on the relative risk of lung cancer in patients with asbestosis and the overall relative risk of lung cancer in these occupationally asbestos-exposed cohorts. The results indicate a positive predictive value for abnormal chest radiograph findings alone to be significantly < 50%. Therefore, the chest radiograph is inadequate as the sole clinical tool to be used to diagnose asbestosis in these cohorts. However, when rales and a low diffusing capacity of the lung for carbon monoxide are also present, the diagnosis of asbestosis on clinical grounds can be made with reasonable confidence. *(CHEST 2003; 124:1120–1128)*

Key words: asbestos; asbestosis; chest radiograph; diagnosis; diffusing capacity; lung cancer; rales

Abbreviations: DLCO = diffusing capacity of the lung for carbon monoxide; HRCT = high-resolution computed tomography; ILO = International Labour Organization

Asbestosis is a form of diffuse interstitial pulmonary fibrosis. It is caused by the inhalation of excessive amounts of asbestos fibers that are within certain size and aerodynamic shape ranges. It can cause significant impairment, or even death, and is a well-recognized risk factor for the development of cancer of the lung. However, frequently a diagnosis must be made in a particular person without the aid of pathology. That is, asbestosis must often be diagnosed on clinical grounds. The American Thoracic Society, in its 1986 position paper on the diagnosis of nonmalignant diseases related to asbestos,[1] reviewed, in a general way, the factors to consider when trying to diagnose asbestosis clinically. In a summary paragraph, it suggested that, in individuals with appropriate exposure and latency, the chest radiograph is the most important tool in diagnosis when pathology specimens are not available. Many physicians have thus concluded that the finding of a chest radiograph compatible with asbestosis in a patient with previous asbestos exposure is sufficient to diagnose asbestosis with all its attendant associated risks of morbidity and mortality. Furthermore, many epidemiologic studies have also used the finding of a chest radiograph compatible with asbestosis as a surrogate for asbestosis. In short, many people think that the presence of a mildly abnormal chest radiograph finding is compatible with asbestosis (International Labor Organization [ILO] grade, 1/0 or 1/1)[2] in asbestos-exposed individuals is, more likely than not, indicative of pathologic asbestosis. That is, in asbestos-exposed individuals with adequate exposure and latency a chest radiographic finding of ILO grade 1/0 or 1/1 has a positive predictive value for pathologic asbestosis of > 50%.

In order to calculate the positive predictive value of a test, it is necessary to determine the prevalence of the disease in the population at risk, as well as the sensitivity and specificity of the test. In this article,

From the Baylor College of Medicine; Houston, TX.
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Correspondence to: Robert M. Ross, MD, FCCP, 6550 Fannin, Suite 2403, Houston, TX 77030; e-mail: rross@bcm.tmc.edu

which is based on an analysis of the literature, the prevalence of pathologic asbestosis among present-day North American cohorts in the construction and petrochemical industries, the members of which have previously been exposed to asbestos, can be estimated. The sensitivity and specificity of the chest radiograph in diagnosing diffuse interstitial pulmonary fibrotic diseases such as asbestosis also can be approximated. Using these values, the positive predictive value of the chest radiograph for diagnosing pathologic asbestosis can be determined. The results show this to be significantly < 50% among individuals in these cohorts. Therefore, the chest radiograph should not be used as the sole diagnostic tool as it will be wrong more often than it will be right.

Mortality Risk From Lung Cancer in Various Asbestos-Exposed Cohorts

Occupational exposure to asbestos is a well-recognized risk factor for primary cancer of the lung. However, the size of the risk varies quite markedly depending on the cohort and the date of the study (earlier studies generally reflect the effects of much heavier exposure). For example, in a study of insulators published in 1979, lung cancer mortality was increased more than four times compared to control subjects,[3] whereas in a study[4] of shipyard workers in Hawaii, the incidence of lung cancer was only 40% greater among workers with at least 15 years of asbestos exposure compared to control subjects. A 1999 meta-analysis reviewed 69 asbestos-exposed occupational cohorts.[5] These cohorts consisted of individuals who often were involved in the mining or manufacturing of asbestos products or were members of heavily exposed groups, such as shipyard workers or insulators. The meta-standard mortality ratio increase for lung cancer, considering latency, was 63%. However, studies of other cohorts such as petrochemical workers[6] and steelworkers,[7] for example, often have found no increase in lung cancer.

Presently, the majority of workers who have been occupationally exposed to asbestos are not those in the primary asbestos industries, such as mining or the manufacture of asbestos-containing products, but are workers who used these products.[8] Table 1 lists the mortality risk ratios for lung cancer deaths among construction workers and petrochemical workers in North America obtained from a MedLine search of large cohorts published since 1990.[8,9–24]

Table 1—*Death From Lung Cancer From Various Studies of People Exposed to Asbestos**

Study/Year	Description	Patients, No.	Deaths, No.	Lung Cancer Deaths, No.	Mortality Ratio, %	Study Type
Robinson et al[9]/1995	Construction industry		61,532	5,944	114	PMR
Stern et al[10]/1995	Construction laborers		11,685	1,206	120	PMR
Robinson et al[11]/1996	Union carpenters		27,328	3,726	122	PMR
Satto et al[12]/1996	Oil refinery workers	17,844	6,799	423	92	SMR
Tsai et al[13]/1996	Maintenance employees in a refinery and petrochemical plant	2,504	725	68	81	SMR
Cooper et al[8]/1997	Texas refinery and chemical manufacturing workers	92,218		1,388	84	SMR
Rand et al[14]/1997	Pulp and paper mill workers	30,157	4,074	351	109	SMR
Stern and Hering-Sweeney[15]/1997	Construction operating engineers		15,843	1,915	126	PMR
Stern et al[16]/1997	Construction iron workers		13,301	1,523	125	PMR
Raabe et al[17]/1998	Maintenance refinery workers	5,360	1,539	109	120	SMR
Dement et al[18]/1998	Union refinery workers		2,985	203	105	PMR
Wang et al[19]/1999	North Carolina construction workers		29,544	3,023	113	PMR
Robinson et al[20]/1999	Electrical workers involved in construction		31,068	2,977	117	PMR
Stoealand and Palu[21]/1999	Union painters	42,179	18,239	1,746	123	SMR
Lewis et al[22]/2000	Refinery workers	9,266	2,905	221	95	SMR
Stern et al[23]/2000	Roofers and waterproofers		11,144	1,071	139	PMR
Stern et al[24]/2001	Plasterers and cement workers		13,573	1,366	139	PMR

*SMR = standard mortality ratio; PMR = proportional mortality ratio. Total Lung Cancer deaths from all studies, 26,255; expected lung cancer deaths, 22,569; mortality ratio, 116.

These studies find a range of about 0 to 40% increased risk of lung cancer in these cohorts with an average of about 16% over unexposed control subjects. However, it should be remembered that not all of this increased risk may be due solely to asbestos. Most of these studies were not controlled for smoking or other potential carcinogens in the workplace, which also could lead to increased mortality from lung cancer.

Risk of Lung Cancer Associated With Asbestosis

Pathologic asbestosis is associated with a significant increase in lung cancer risk. In one study, an approximate fivefold increase in lung cancer was found among an insulator cohort.[25] Later, autopsy studies[26] on this group of lung cancer patients found that virtually all had asbestosis. Hughes and Weill[27] found that in a cohort of workers producing asbestos-containing cement and pipe covering those with radiographic evidence of asbestosis had a lung cancer risk that was more than four times that of the control population, and Liddell and McDonald[28] found a risk of asbestosis that was 3.5 times that of control subjects among Quebec asbestos workers who had radiographic evidence of asbestosis. In a study[29] of people who had asbestosis and were reported to the Finnish Registry of Occupational Diseases, there was an increase of more than sixfold in the incidence of lung cancer. Other studies[30] of people who were "certified" to have asbestosis by various entities also have found a marked increase in mortality from lung cancer. A 1996 study[31] of asbestosis patients found an overall relative risk of 5.9.

Other forms of diffuse interstitial pulmonary fibrosis, which are pathologically similar to asbestosis, also are associated with an increased risk of lung cancer. For example, in a study[32] of people with diffuse interstitial pulmonary fibrosis associated with scleroderma, the lung cancer risk was five times that of control subjects. Another study[33] of people with cryptogenic fibrosing alveolitis also found a markedly elevated lung cancer risk.

The exact risk of lung cancer that is associated with asbestosis depends on many factors that have not yet been completely elucidated. These may include exposure amount, intensity, duration, and host factors. The degree of fibrosis, fiber type, and smoking history also play a significant role.[34,35]

Prevalence of Asbestosis

The prevalence of pathologic asbestosis has not been accurately determined for asbestos-exposed workers. This would require the examination of lung tissue from a large number of randomly selected people, which is not feasible. Furthermore, the definition of asbestosis has to be determined. Is it solely based on pathology or does there have to be some physiologic dysfunction? Furthermore, what is the minimal amount of pathologic abnormality that is associated with an increased risk of lung cancer? These issues have not been resolved. However, the relationship between asbestosis and an increased risk of lung cancer has been studied in some detail, as was discussed in the previous section. Using this knowledge, an estimate of the prevalence of this degree of asbestosis can be obtained. Based on the overall lung cancer risk, as well as on the risks related to asbestosis and to asbestos exposure alone, an assessment of the prevalence of pathologic asbestosis that leads to an increased risk of lung cancer in the population that is at risk can be obtained. Based on the articles previously cited, the overall increase in lung cancer risk among workers such as those in the construction industry and petrochemical industry is about 16%. In addition, as previously discussed, the presence of a diffuse interstitial pulmonary fibrotic disease such as asbestosis is associated with a 3.5-fold to more than sixfold increased risk of lung cancer over that of control subjects. Using an overall risk of lung cancer of 116% and a risk of lung cancer associated with asbestosis of 400%, then, if the rest of the asbestos-exposed population were at no increased lung cancer risk, about 5% of the workers would have asbestosis ($400X + 100[1 - X] = 116$, and $X = 0.053$). Whether asbestos exposure in itself is a cause of the increased lung cancer risk or whether it is through the development of asbestosis is a current subject of debate.[36–38] If the risk of developing lung cancer in asbestos-exposed workers who do not have asbestosis is greater than that for similar unexposed control subjects, that is, if asbestos increases lung cancer risk even without the presence of asbestosis, the number of asbestosis patients must be even lower than in the previous calculation. For example, if the lung cancer risk were 10% higher than normal for asbestos-exposed persons without asbestosis, then approximately 2% of that exposed population would have asbestosis ($400X + 110[1 - X] = 116$, and $X = 0.02$). If the risk of developing lung cancer among asbestosis patients were > 400% of unexposed control subjects, the prevalence of asbestosis would be lower than that in the previous examples. Similarly, if some of the increase in lung cancer risk were due to factors other than asbestos exposure, such as a higher prevalence of smoking, smoking more, or exposure to other potential carcinogens in the workplace, the prevalence of asbestosis would also be less. It is well-

recognized that construction workers smoke more than the general population.[39] If, for example, the prevalence of smokers in these cohorts were 5% greater than in the general population, if the increased risk of lung cancer that was associated with smoking were 15-fold compared to that in nonsmokers, and if the prevalence of smokers in the general population were 30%, then, utilizing calculations popularized by Axelson,[40] the relative risk of lung cancer for the group would be 113. Therefore, the increased risk due to asbestos exposure could be no > 3% and the prevalence of asbestosis would be ≤ 1%. Taking these factors into account, a reasonable estimate of the prevalence of asbestosis in these types of cohorts would be about 1 to 5%.

Sensitivity and Specificity of the Chest Radiograph in the Diagnosis of Asbestosis

The chest radiograph has long been used as an important tool in the diagnosis of diffuse interstitial pulmonary fibrotic diseases such as asbestosis. Extensive disease can usually be accurately detected by a well-trained radiologist or physician. Of course, it is necessary to exclude diseases that radiologically can be confused with diffuse interstitial pulmonary fibrosis, such as congestive heart failure or lymphangitic spread of malignancy. Also, the differential diagnosis of interstitial lung diseases must be kept in mind. It should be remembered that asbestos-exposed individuals are not immune from other forms of interstitial lung disease.[41,42] If doubt exists and a patient is significantly symptomatic, tissue biopsy is appropriate.

The chest radiograph is problematic, however, when trying to diagnose minimal or mild disease. Is a radiographic finding of a mild increase in interstitial lung markings (*ie*, a mild increase in small, irregular opacities [ILO grade, 1/0 and 1/1]) adequate by itself to diagnose asbestosis? Although chest radiographic findings usually are abnormal in patients with asbestosis, about 10 to 15% of the time they may be relatively normal,[28,43] which yields a sensitivity of 85 to 90%. Furthermore, many factors other than asbestos exposure can lead to a mildly abnormal chest radiographic finding, affecting its specificity. These factors include, for example, radiographic technique, aging, obesity, smoking, presence of COPD, and exposure to various other fibrogenic and nonfibrogenic dusts.[44] In addition, the radiologic diagnosis of *mildly abnormal* has a rather large interobserver variation. For example, in one study[45] in which 23 "B-readers" certified by the National Institute of Occupational Safety and Health evaluated 105,029 chest radiographs for the assessment of asbestosis among naval personnel, there was a 20-fold difference in the prevalence of positives findings (ILO grade, ≥ 1/0) between the extreme readers, and the average prevalence was 2.4%. Welch et al[46] reviewed the interobserver variation in chest radiograph interpretation of pneumoconiosis, finding that among the same 119 chest radiographs that were read by six qualified readers, the number that were read as being positive for asbestosis (ILO grade, ≥ 1/0) varied from 24 to 91%. This problem, of course, significantly affects sensitivity and specificity. If, in fact, 91% of the group actually had asbestosis, the individual who found it in only 24% would exhibit a very poor sensitivity of, at best, 24 of 91 patients (26%). Conversely, if 24% were the correct figure, the individual who diagnosed it in 91% of the people would exhibit very poor specificity of, at best, 9 of 76 patients (12%).

The chest radiograph may also be mildly abnormal among people who have never been exposed to asbestos and who do not have any type of diffuse interstitial pulmonary fibrosis. Epstein et al[47] found in a hospital study of 200 consecutive admission chest radiographs that were read according to the 1980 ILO scale, 11% of the radiographs were read as being positive for asbestosis (ILO grade, ≥ 1/0) with no documentable dust exposure or other specific medical etiology that would explain the presence of the lung opacities. Zitting et al[48] found in a radiographic survey of 7,095 radiographs that among the 3,494 people who were unlikely to have been exposed to asbestos there was an 11.7% incidence of their chest radiographs being read as having abnormal findings (ILO grade, ≥ 1/0). In a literature analysis of many studies performed in the United States and Europe, where radiographs were read according to the 1980 ILO standard, the number of radiographs that were read as being positive for asbestosis (ILO grade, ≥ 1/0) among people who had not been exposed to asbestos varied from 0.21 to 11.7%. A meta-analysis[49] of the published data yielded a population prevalence of 5.3%. These studies suggested that with qualified readers a specificity of 90 to 95% for the chest radiograph would be the best that could be expected.

Positive Predictive Value of the Chest Radiograph Alone

From these previous discussions, reasonable estimates of asbestosis prevalence among present-day construction or petrochemical workers, as well as the sensitivity and specificity of the chest radiograph in diagnosing asbestosis, can be made. From this, the positive predictive value of the chest radiograph can

be obtained. The prevalence of asbestosis in this at-risk population could be expected to be about 1 to 5%. In addition, from the previous discussion, at least 5 to 10% of the time the chest radiograph finding may be abnormal (ILO grade, ≥ 1/0) without the presence of asbestosis. This represents a specificity of approximately 90 to 95%. Furthermore, the sensitivity of chest radiographs for asbestosis is about 85 to 90%. From these values, the positive predictive value of a positive chest radiograph can be determined with the following formula:

$$PPV = \frac{1}{1 = \left(\frac{1-spec}{sens}\right)\left(\frac{1}{prev} - 1\right)}$$

where PPV is the positive predictive value, spec is specificity, sens is sensitivity, and prev is the prevalence in the at-risk population.

Using a prevalence of 5%, a sensitivity of 90%, and a specificity of 93%, the positive predictive value of a positive chest radiograph alone (ILO grades, 1/0 and 1/1) is about 40%. If the prevalence of asbestosis is 3%, the positive predictive value of the chest radiograph alone is only 28%. It should be mentioned that in cohorts with less exposure to asbestos, the prevalence of asbestosis will be even lower, and so the positive predictive value of an abnormal chest radiograph will also be lower. On the other hand, for cohorts with a high prevalence of asbestosis, such as the insulators studied by Selikoff and coworkers,[3] a radiograph with an ILO reading of 1/0 or 1/1 may have a positive predictive value > 50%. However, using a chest radiograph as the sole clinical determinant of asbestosis in most present-day asbestos-exposed cohorts such as construction or refinery workers is inaccurate at best, with well over half the people probably not actually having the disease.

Furthermore, a diagnosis of asbestosis made solely on the basis of a mildly abnormal chest radiograph may have adverse consequences. Patients may be labeled with a potentially serious disease that they do not have, which leads to unnecessary concern. These people also may ascribe symptoms to this incorrect diagnosis and may not seek medical assistance for potentially treatable problems such as COPD, asthma, or ischemic heart disease.

The mildly abnormal chest radiograph also adds confusion to the understanding of asbestos-related diseases. It is well-recognized that smokers have a higher incidence of chest radiographs showing mild increases in lung markings or so-called *dirty lungs*.[50] This, at least in part, results from the presence of chronic bronchitis and COPD. These are the people who are at highest risk for lung cancer, not only because they smoke but also because, among smokers, those with bronchitis and airflow obstruction are at a higher lung cancer risk than are comparable smokers without these findings.[51] In other words, the mildly abnormal chest radiograph tends to select people who are at higher risk for lung cancer even when controlled for smoking. Therefore, many people with a mildly abnormal chest radiograph (*ie*, ILO grade, 1/0 and 1/1) may have an increased risk of lung cancer but not because of asbestos or even because of asbestosis. This adds confusion to studies that attempt to assess the lung cancer risk from asbestosis that has been diagnosed solely on the basis of a chest radiograph.

In conclusion, utilizing the chest radiograph for the detection of asbestosis among asbestos-exposed cohorts such as construction and refinery workers has too low a true-positive rate to be relied on as the sole diagnostic tool in obtaining a reasonably accurate diagnosis.

Other Imaging Techniques

High-resolution CT (HRCT) scans of the chest are better than chest radiographs for the evaluation of asbestosis. They are more sensitive and more specific. However HRCT scans also can miss pathologic asbestosis. Furthermore, minimal changes on HRCT scans are nonspecific and often do not indicate fibrosis.[52,53] Even if the sensitivity and specificity increased to 95%, the positive predictive value of the HRCT scan alone would be only 50% if the prevalence of asbestosis were 5%, and 37% if the prevalence were 3%. Although HRCT scanning holds some promise, adequate information is not yet available to determine its positive predictive value in the diagnosis of asbestosis.

Usefulness of the History, Physical Examination, and Other Physiologic Tests in Diagnosing Asbestosis

In its position statement regarding nonmalignant disease related to asbestos,[1] the American Thoracic Society also mentioned that it is important to obtain a good occupational history and that rales, restriction, and a diffusing capacity of the lung for carbon monoxide (DLCO) below the limit of normal are of recognized value in diagnosing asbestosis. These will now be discussed.

History

Taking a good occupational history is important because it helps to place the patient in certain risk groups. By obtaining an adequate work history, a

reasonable estimate of lung cancer risk and, therefore, a prevalence of asbestosis for that person can be obtained from epidemiologic studies of similar cohorts.

Rales

Characteristic rales or crackles of "Velcro" or "dry" quality have been found in approximately 70 to 90% of patients with pathologic diffuse interstitial pulmonary fibrosis diseases such as asbestosis. Epler et al,[43] studying people with interstitial lung disease, even those with a relatively normal chest radiograph finding, found rales in 71% of cases. Tukjainen et al[54] found rales in 94% of people with diffuse interstitial pulmonary fibrosis. Bouros et al[55] found rales in 85% of his group of patients with fibrosing alveolitis associated with systemic sclerosis. Bjoraker et al[56] found rales in 80% of their group of patients with idiopathic pulmonary fibrosis, and Daniil et al[57] found rales in 87% of patients. Murphy and Sorensen[58] found rales in 63% of pipe coverers with clubbing (and asbestosis). Shirai et al[59] found rales in 95% of the asbestos workers with abnormal chest radiographic findings that they studied. Furthermore, rales are an early finding and often are present before the chest radiograph becomes significantly abnormal.[59,60] Rales are not under volition and, when found by a well-trained physician, are quite specific.[61] It is distinctly uncommon to have pathologic asbestosis without the presence of rales.

Restriction

With significant diffuse interstitial pulmonary fibrosis, the lungs shrink, leading to reduced vital capacity and lung volumes, such as total lung capacity (restriction). However, the normal range for these parameters is quite large, so small changes may not be detected on cross-sectional testing. Furthermore, the vital capacity test is voluntary, and results can be abnormal due to effort or understanding. Also, many other medical disorders other than diffuse interstitial pulmonary fibrosis lead to restriction. Therefore, although the finding of restriction on pulmonary function testing is seen in approximately 50 to 60% of patients with diffuse interstitial pulmonary fibrosis diseases, such as asbestosis, it is too nonspecific to be used as a sole diagnostic tool and is relatively insensitive for the detection of mild fibrosis.

DLCO

The DLCO test, however, is very sensitive for the presence of diffuse interstitial pulmonary fibrosis. This is because this disorder first and most extensively affects the smallest airways, alveolar ducts, alveoli, and microcirculation where gas exchange occurs. The disease alters the anatomy so that the matching of ventilation with pulmonary blood flow is less than optimal. The overall result is ventilation-perfusion mismatching and gas exchange abnormalities, which the DLCO test is exquisitely sensitive at assessing. Although it is not highly specific and many factors may lead to it being low, a normal diffusing capacity test result is rarely found with the presence of a pathologic diffuse interstitial fibrotic diseases, such as asbestosis. In fact, the DLCO is reduced in 70% to > 90% of cases.

In Table 2 the findings from several studies regarding rales and DLCO in patients with diffuse interstitial pulmonary fibrosis are reviewed.[62] It can be seen that rales and reduced DLCO are very frequently seen in patients with diffuse interstitial pulmonary fibrotic diseases, such as asbestosis. In fact, some studies have found them more sensitive than HRCT scanning,[62] and Markowitz et al[54] found that abnormal findings of pulmonary function tests

Table 2—*Findings From Studies of Patients With Interstitial Pulmonary Fibrosis**

Study/Year	Group	Patients, No.	Clubbing, %	Rales, %	Reduced VC, %	Reduced DLCO, %
Murphy and Sorensen[58]/1973	Asbestos pipecoverers with clubbing	12	100	83		
Epler et al[43]/1978	Various ILDs	458		71†	57	71
Tukjainen et al[54]/1983	IPF	100	46	94	70	90–95
Bjoraker et al[56]/1998	IPF (UIP/NSIP and other)	104	25	80	73	90–95
Daniil et al[57]/1999	IPF (UIP/NSIP)	30	67	93	Most	80–85
Shirai et al[59]/1981	Asbestosis	21		95		
King et al[64]/2001	IPF (biopsy-proven UIP)	85			70–75	80–85
Bouros et al[55]/2002	ILD (associated with systemic sclerosis)	74		85	57	97

*IPF = (idiopathic pulmonary fibrosis; UIP = usual interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; ILD = interstitial lung disease.
†Interstitial pneumonia.

and physical examinations significantly raised the risk of dying of asbestosis in a cohort of insulators.

The Clinical Diagnosis of Asbestosis

How can these various clinical diagnostic findings be used in order to diagnose asbestosis within a reasonable degree of certainty without too many false-positive diagnoses or too many false-negative diagnoses when lung tissue is not available? The chest radiograph is positive in approximately 90% of cases. Furthermore, pleural plaques are often present in patients with asbestosis.[63] Rales occur in approximately 70 to 90% of cases, and a reduced D_{LCO} occurs in about 80 to 90% of cases. Conversely, many chest radiographs will be interpreted as mildly abnormal (ILO grade 1/0 and 1/1) but will not be due to asbestosis or diffuse interstitial pulmonary fibrosis. *Dry or velcro rales are quite specific* for diffuse interstitial pulmonary fibrosis, but rales from mucus in the airways, congestive heart failure, or even mild basilar atelectasis occasionally can be confused with the rales of fibrosis. The D_{LCO} may be reduced secondary to technical factors or other medical problems and is by no means specific for diffuse interstitial pulmonary fibrosis. The goal in terms of clinical diagnosis is to find whether these tests together have a high enough specificity with adequate sensitivity so that the positive predictive value when all these test results are abnormal will be significantly > 50% without missing too many people who have the disease.

The sensitivity and specificity of chest radiograph, rales and D_{LCO} for the diagnosis of asbestosis can be estimated. For chest radiographs, the sensitivity is approximately 90%, while the specificity is 90 to 95% (therefore, 93% specificity will be chosen). For D_{LCO}, the sensitivity is approximately 85%. By definition, the lower limit of normal for the test is such that 95% of healthy people have a result equal to, or higher than, that value (*ie*, a specificity of 95%). However, technical factors and other disorders also lead to a reduced D_{LCO}. There are only a few disorders that lead to an increase in D_{LCO}, so the test is rarely falsely high. The actual specificity for D_{LCO} in diagnosing asbestosis is not known with certainty. However, even if 10% of the study population had other disorders leading to a reduced D_{LCO}, the specificity of the test would be about 85%. For rales, based on values from the studies presented, a sensitivity of 80% would be appropriate. Taking into account rales due to mucus in the airways, congestive heart failure, and technical factors, the specificity should be not much lower than 75 to 80%. So, a specificity of 75% will be chosen.

The interdependence of the various tests has not been carefully examined. If each test were independent of the others, the overall specificity of these tests together would be > 99%. For example, from the previous discussion the chest radiograph could be expected to be normal in about 93% of people who do not have asbestosis. If the tests were completely independent, D_{LCO} would be expected to be within normal limits in about 85% of the remaining 7%, leaving only about 1.05%. Rales would be absent in about 75% of these, leaving only 0.26% of people with asbestosis who would be missed by all three tests (*ie*, $0.93 + 0.85 \times 0.07 + 0.75 \times 0.0105 = 99.74\%$). It is reasonable to assume that the tests are relatively independent of each other because one is a visual anatomic assessment (*ie*, the radiograph), another is auscultatory (*ie*, rales), and the last is physiologic (*ie*, D_{LCO}). However, even if the specificity of rales and D_{LCO} dropped to 50% in patients in whom the chest radiograph findings were positive, the specificity would still be > 98% (*ie*, $0.93 + 0.5 \times 0.07 + 0.5 \times 0.035 = 98.25\%$). Therefore, an overall specificity of 98 to 99% if all three test results are normal is quite conservative. If the tests were independent, the overall sensitivity would be about 62% (*ie*, $0.9 \times 0.85 \times 0.8 = 0.62$). If there were some interdependence, it would be higher, more toward the 80% sensitivity of the presence of rales. It is reasonable to assume there is some interdependence because the same process of fibrosis leads to all three abnormalities. Therefore, a more appropriate estimate of sensitivity might be 70%.

Using these calculations, the positive predictive value if all three test results are abnormal can be determined. Using a sensitivity of 70% and specificity of 98.5% for all three tests together, if the prevalence of asbestosis were 5%, the positive predictive value when all three test results are abnormal would be about 70%. If the prevalence were 3%, the positive predictive value would be about 60%.

Although two tests could be used, the maximum sensitivity could not be greater than the lower test result value obtained (or about 80 to 85%). If the tests were somewhat independent of each other, the sensitivity would be less. If the overall sensitivity of two tests were 75%, the specificity required to give a positive predictive value of 50% can be calculated. For a prevalence of 5%, the specificity of the two combined tests must be at least 96%, and 98% if the prevalence is 3%. If there is some interdependence, then two tests may not provide this degree of specificity, while all three tests would provide it, with only a small loss of sensitivity.

Requiring the results of all three tests to be positive provides a reasonable combination of adequate sensitivity while assuring that, in the proper