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Asbestos Exposure Results in Asbestosis and Usual Interstitial Pneumonia Similar to Other Causes of Pneumoconiosis

Yoshinori Kawabata

Abstract

The progression of asbestosis is supposed to begin with the first order of respiratory bronchiole and extend outward. Recently, grade 4 asbestosis was reported to begin with the subpleural peripheral lobular area or the subpleural lobule. Grade 4 asbestosis is defined as diffuse pulmonary fibrosis caused by the inhalation of excessive numbers of asbestos fibers. Pathologically, the presence of more than two asbestos bodies/cm² on a glass slide is required. There are many cases of diffuse interstitial pneumonia, mainly usual interstitial pneumonia, that does not fulfill the above criteria among asbestos workers or high-grade environmentally exposed persons. I call these cases “usual interstitial pneumonia seen in asbestos workers” and not idiopathic pulmonary fibrosis. In this chapter, I discuss the above subjects, including the dose-response relationship for asbestos exposure, the heterogeneous response to asbestos exposure, and the relationship between asbestosis and idiopathic pulmonary fibrosis.

Keywords: pathological examination, usual interstitial pneumonia, atelectatic induration, asbestos body, idiopathic pulmonary fibrosis

1. Introduction

It is well known that moderate- to high-grade exposures to asbestos cause serious diffuse pulmonary fibrosis called diffuse asbestosis. Asbestosis is believed to start in the region of the first order of respiratory bronchiole (grade 1, **Figure 1**) and gradually extends outward to involve more and more of the lung acinus until separate foci of fibrosis link or attach to the pleura and the interlobular septum (grade 3), finally resulting in a diffuse pattern of the fibrosis (grade 4) [1, 2]. However, this description has not yet been proved. Asbestosis is defined as diffuse interstitial fibrosis of the lung as a consequence of exposure to asbestos dust. A histological diagnosis of asbestosis requires the presence of two or more asbestos bodies (ABs) in the tissue with a section area of 1 cm² [3]. Meanwhile, diffuse interstitial pneumonia, mainly usual interstitial pneumonia (UIP), that does not fulfill the above histological criteria is called idiopathic pulmonary fibrosis (IPF) even if the patient is a worker exposed to asbestos [4].

In this review, I discuss the process of asbestosis progression, the pathological definition and the features of asbestosis, the lower limit of asbestos fiber exposure

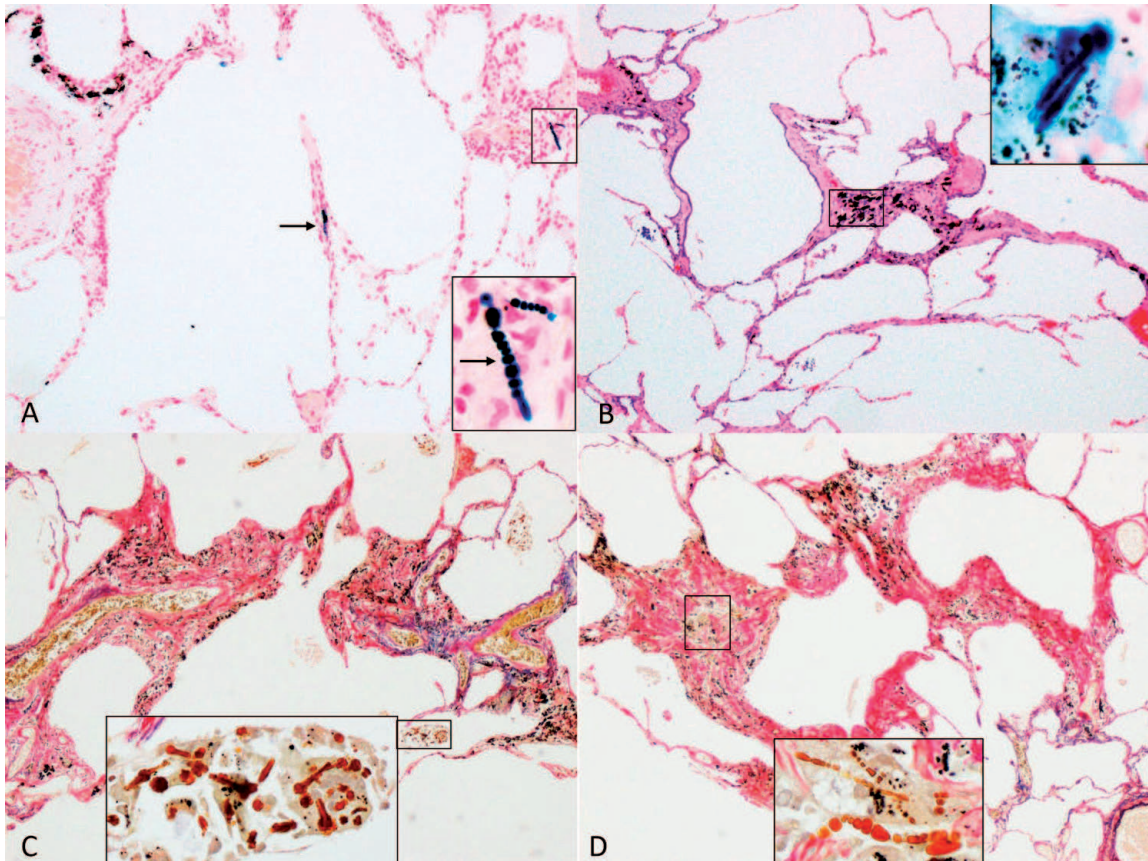


Figure 1. Grade 0 to grade 2 lesions. (A) Grade 0 lesion without respiratory bronchiolar fibrosis but with three asbestos bodies (arrows). Hematoxylin and eosin staining (HE), $\times 100$. Inset: enlarged asbestos bodies. (B) Grade 1 lesion with fibrosis of the respiratory bronchiole and surrounding lung. HE, $\times 60$. Inset: enlarged asbestos bodies. (C) Grade 2 lesion with fibrosis of the respiratory bronchiole and surrounding lung. Elastica van Gieson staining (EvG), $\times 60$. Inset: many enlarged asbestos bodies. (D) Grade 2 lesion with fibrosis of the respiratory bronchiole, alveolar duct, and surrounding lung including luminal organization. EvG, $\times 60$. Inset: enlarged asbestos bodies.

causing asbestosis and the dose-response relationship of asbestos exposure, various causes of UIP, and how to think about diffuse interstitial pneumonia or UIP that does not fulfill the histological criteria of asbestosis. The term “asbestosis” is used differently in the literature. I term diffuse interstitial fibrosis due to asbestos exposure as pathological grade 4 asbestosis and clinical diffuse asbestosis. The term asbestosis alone can indicate various extents of severity from grade 1 to grade 4 pathologically and early to diffuse asbestosis clinically.

2. Process of asbestosis progression

Under a normal environmental state, the numbers of ABs are thought to be up to 200 per gram of dry lung tissue (/g dry lung) [5, 6], and the presence of more than 1000 ABs/g dry lung is thought to indicate persons with a high probability of exposure to asbestos dust at work [3, 7]. As stated above, asbestosis begins in the first order of respiratory bronchiole (**Figure 1**), but how many ABs are needed to cause grade 1 asbestosis? The minimal numbers are different from study to study and range from “1,000 to 22,000” ABs/g dry lung [5, 6, 8–10]. Our data showed a maximum of “273,000” ABs/g dry lung in grade 4 asbestosis without grade 1 lesions [9], and this might be the upper limit. Meanwhile, there are reports showing the presence of grade 1 fibrosis of below 1 AB per 1 histological slide even in cases of diffuse asbestosis [11, 12]. Grade 1 lesions appear to begin at lowest numbers of less than 1000 ABs/g dry lung, but the upper limit is not precisely known yet except

for that in our data [9]. Thus, it is still necessary to determine how many ABs or asbestos fibers are needed to cause grade 1 and grade 2 lesions without progression to grade 4 asbestosis.

Meanwhile, one of the important pathological criteria of idiopathic UIP (IPF) is predominant subpleural and/or paraseptal distribution of fibrosis mainly in the lower lobes [13, 14]. This means that UIP begins in a peripheral area of the lobule with continuous extension inward and forms centrilobular honeycombing due to peripheral lobular dense fibrosis and structural destruction of the centrilobular area. An outward extension of asbestosis to form centrilobular honeycombing of grade 4 asbestosis is a logical contradiction. It might be logical to think that grade 4 asbestosis is not just a further outward extension of grade 3 asbestosis. We examined grade 4 asbestosis histologically and confirmed that UIP-type asbestosis begins with the subpleural peripheral lobular area as this area was the most densely fibrotic (intraluminal collagenosis with collapse) and the centrilobular area showed young fibrosis (**Figure 2**) including fibroblastic foci. We also observed inflammatory cell infiltration and lymphoid follicles in the fibrosis-like idiopathic UIP [9]. We also confirmed that atelectatic induration-type asbestosis also begins with the subpleural peripheral lobular area or the subpleural lobule (acinar or lobular intraluminal collagenosis with various degrees of collapse with inflammatory cell infiltration) (**Figure 3**) [9]. Yamamoto also stated nearly the same in terms of the starting point of grade 4 asbestosis [11]. Inflammatory cell infiltration was reported in humans [15, 16] and experimental sheep along with intraluminal organization [17].

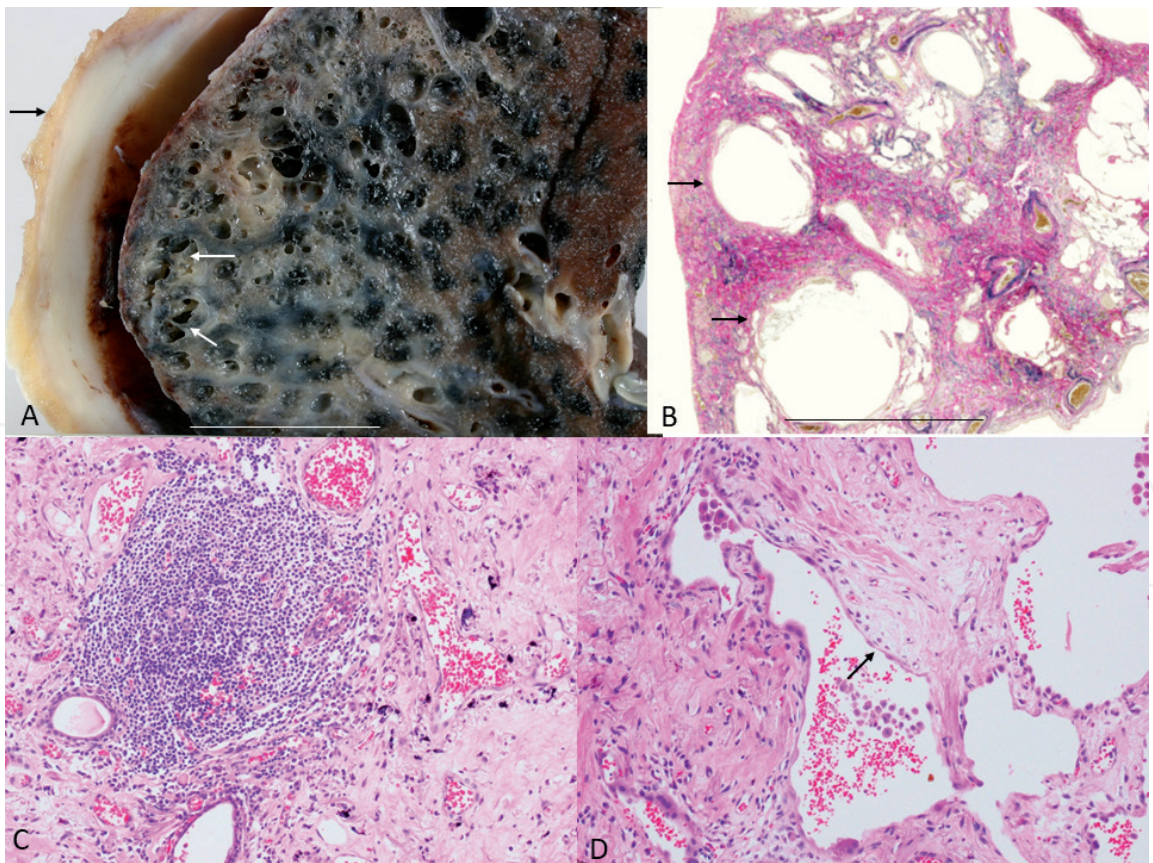


Figure 2.
Histology of usual interstitial pneumonia-type asbestosis in a 66-year-old man working with rock wool spray. A lobectomy was performed for lung cancer. Upon examination, the numbers of asbestos bodies (ABs) were 950,000 ABs/g dry lung and 108 ABs/cm². A grade 2 lesion was seen (Figure 1C, D). Macroscopic features of the right lower lobe showed diffuse formation of pleural plaques (black arrow) and honeycombing (white arrows) in the gray-colored fibrosis of the lung. Bar = 2 cm. Histological features showed subpleural dense fibrosis with ring-like honeycombing (arrow). Elastica van Gieson, $\times 10$. Bar = 5 mm. One lymphoid follicle was noted in the fibrosis. Hematoxylin and eosin (HE), $\times 150$. Young intraluminal fibrosis was noted between dense fibrosis and the normal lung. HE, $\times 150$.

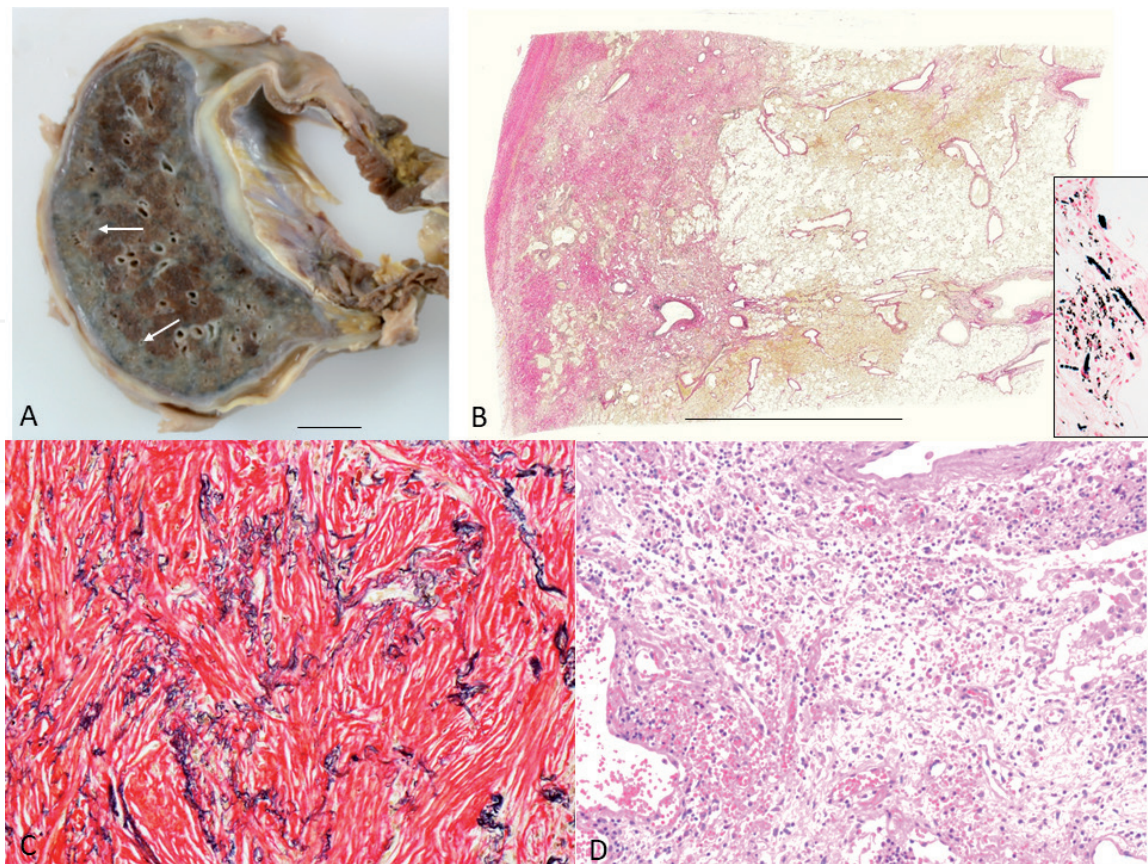


Figure 3. Atelectatic induration-type asbestosis in a 60-year-old man working in the asbestos cement industry for 30 years as a secretary. Bilateral diffuse pleural thickening with calcification and reticular shadows in the bilateral basal areas of the lower lobes. No grade 1 lesion was seen. (A) Macroscopic features of the right lower lobe showed pleural fibrosis and plaque at the diaphragmatic area with subpleural zonal atelectatic induration (arrow). Bar = 2.5 cm. (B) Panoramic view of the subpleural lung tissue showing 1-cm-thick subpleural atelectatic induration. Hematoxylin and eosin. Bar = 1 cm. Inset. Asbestos bodies stained with Persian blue. (C) Subpleural area showing intraluminal dense fibrosis and muscle proliferation with some collapse. Elastic van Gieson, $\times 200$. (D) Young intraluminal fibrosis with inflammatory cell infiltration next to normal lung.

3. Pathological definition of grade 4 asbestosis and its features

Grade 4 asbestosis is defined as diffuse pulmonary fibrosis caused by the inhalation of excessive numbers of asbestos fibers [1–3, 7]. The Helsinki criteria state that a histological diagnosis of asbestosis requires the identification of diffuse interstitial fibrosis in well-inflated lung tissue plus the presence of two or more ABs in tissue with a section area of 1 cm^2 [3, 7]. The previous histological definition of asbestosis was the presence of one or more ABs in one or another histological section in addition to lung fibrosis [1]. A subsequent study showed that more ABs are needed to cause grade 4 asbestosis [18]. Then, more than 2 ABs/ cm^2 were required in 1997 [3], and that was continued in the next Helsinki criteria [7]. Two ABs/ cm^2 on glass slides correspond to “8000–20,000” ABs or over/g dry lung [12, 19, 20]. The smallest numbers were less than “4000” ABs in our data [9].

Histological findings of grade 4 asbestosis show various forms: atelectatic induration type or accelerated asbestosis and UIP pattern (**Figures 2 and 3**) [2, 9, 11]. I described the histological features of atelectatic induration and UIP pattern in the previous chapter. The asbestos burden in atelectatic induration is more severe than that in the UIP pattern [9]. It is reported that atelectatic induration type is seen in undeveloped countries, and UIP is seen in developed countries [2]. It is also reported that fibrosis in asbestosis is always paucicellular, lacks any significant degree of inflammation, and is collagenous rather than fibroblastic, without

reference to other studies [2]. From this viewpoint, Kishimoto et al. reported the mean value of ABs for these cases was a mean of “2,133,000”/g dry lung [21], whereas Arakawa et al. reported a mean of “1,465,000” [22]. However, it is difficult to point out specific histological features seen only in asbestosis [3, 7, 9, 11, 23]. Yamamoto stated that some cases cannot be differentiated from that of IPF except for the presence of ABs [11]. Patterns of fibrosing nonspecific interstitial pneumonia and unclassifiable interstitial pneumonia were also reported [2, 22, 24].

What asbestos burden is required to cause grade 4 asbestosis? We reported it to be between “3,450 and 3,340,000” ABs/g dry lung [9], and Kishimoto et al. reported a value between “156,000 and 2,733,000” ABs [21]. Arakawa et al. reported a mean of “1,465,000” [22] with the highest number being “7,473,000” ABs (personal communication). Roggli et al. have reported the highest numbers, which range from “6,840,000 to 16,000,000” ABs/g dry lung [5, 8]. So, as with the beginning of grade 1 asbestosis, there are enormous differences from person to person in the number of ABs that indicate grade 4 asbestosis.

Chrysotile fibers (one of commercially produced and most used asbestos fibers) are difficult to coat with iron (during AB formation) and are easily dissolved and cleared from the lung [25, 26]. There are reports of asbestosis without ABs histologically but which show numerous asbestos fibers in the lung [27, 28]. In cases of asbestos exposure with diffuse pulmonary fibrosis that do not fulfill the Helsinki criteria, it is then necessary to determine the numbers of asbestos fibers in the lung using electron microscopy. Still, this may not be enough as most chrysotile fibers are cleared by the time of examination [25, 26], but long chrysotile fibers can become asbestos body [29].

4. Lower limit of asbestos fiber exposure causing asbestosis and the dose-response relationship

For clinical purposes, the following guidelines are recommended to identify persons with a high probability of exposure to asbestos dust: over “0.1 million” amphibole fibers ($>5 \mu\text{m}$)/g dry lung tissue, over “1 million” amphibole fibers ($>1 \mu\text{m}$)/g dry lung tissue as measured by electron microscopy in a qualified laboratory, or over “1000” ABs/g dry lung tissue, among others [3, 7]. The relationship between asbestos exposure and disease onset or early asbestosis is not settled yet. Precise estimation of the cumulative exposure amount is difficult and may actually be impossible.

It is reported that clinical asbestosis can be induced by cumulative asbestos exposure to around 25 to 200 fibers/mL-years [2, 23, 30–32]. However, there are many reports concerning the beginning of asbestosis. Green et al. reported that asbestosis was usually present in asbestos textile workers exposed to more than 20 fibers/mL-years [33]. Fischer et al. reported 42% of patients with asbestosis do not reach an exposure level of 25 fibers/mL-years [10]. The smallest exposure causing early asbestosis radiologically or histologically might be less than 2–5 fibers/mL-years [34–36]. Fischer et al. also reported that the clinical estimate of fibers/mL-years does not correlate with the numbers of ABs/g dry lung and the beginning of grade 1 lesions [10]. One reason might be differences in the ability to decompose or detoxify the inhaled asbestos fibers from person to person. Another reason is that chrysotile is easily cleared from the lung and is difficult to coat with iron as stated earlier [23, 24]. The development and progression of asbestosis are generally independently correlated with cumulative asbestos exposure and latency, and the dose–response curve is nonlinear [32, 37–45]. Heavy exposure shortens latency, and diffuse asbestosis has been reported with 13 years of latency [46, 47]. In contrast,

new lesions appear at a mean of 35 years of latency [48], and there is one report of rapidly progressive pulmonary interstitial fibrosis appearing with 40 years of latency [49].

Even a high level of environmental exposure (living near asbestos mines or asbestos factories, families of asbestos workers, and others) can result in mild or early asbestosis (either grade 1 or 2 lesions or early UIP-type fibrosis) [50–55]. From these previous studies [50–55], it is not clear whether such a level of exposure causes grade 4 asbestosis or diffuse UIP-type fibrosis.

As stated above, an exposure level of 20–25 fibers/mL-years is supposed to indicate the beginning of asbestosis, but actually a lower level of 2 fibers/mL-years can cause early asbestosis or early UIP-type fibrosis based on long-term follow-up. The main reason for the variable response to exposure might be the different abilities of humans to digest, clear, transport, and detoxify asbestos fibers, and thus their susceptibility can differ [56]. In addition genetic polymorphisms affect the fibrogenesis and carcinogenesis of asbestos fibers [57–60].

The beginning of grade 1 lesions occurs between “1,000 and 273,000” ABs/g dry lung, whereas grade 4 asbestosis satisfying the Helsinki Criteria is between “3,450 and 16,000,000” ABs/g dry lung. The dose-response relationship has been determined, but small numbers of people do not have asbestosis even when they suffered from near the upper limits of exposure. The essential question is whether there is a threshold asbestos dose that causes pulmonary fibrosis.

5. Relationship between IPF and asbestos exposure

Gaensler et al. reported a 5% incidence of IPF in workers exposed to asbestos [4]. This incidence is higher than that of 0.002% among American people 75 years or older [61]. Roggli et al. reported the mean ABs/g dry lung in IPF cases to be 90 (8–1480)/g dry lung, whereas it was 30 (2–220) in normal people [5]. We reported that asbestos exposure increases the incidence of UIP [62]. Barber et al. reported that for mesothelioma and IPF, there was a significant linear relationship between the number of male and female deaths each year and historic imports of asbestos in the UK, and for mortality from asbestosis, a similar relationship was found for male but not female deaths [63, 64]. They selected a latent period of 48 years based on a previously developed US asbestosis model [65]. Attanoos et al. also reported the presence of three cases of UIP without ABs among asbestos workers [24]. We need to reconsider that mild to moderate amounts of asbestos exposure might cause diffuse UIP. A schematic relationship between asbestos exposure and diffuse pulmonary fibrosis is presented in **Figure 4**. It might be more appropriate not to call IPF that does not fulfill the Helsinki Criteria but results from more than environmental exposure or low-grade occupational exposure level “diffuse pulmonary fibrosis or UIP seen in asbestos exposed person.”

Figure 5 illustrates such a case of short-term occupational exposure occurring more than 40 years ago that was followed up as IPF. Macroscopic and microscopic features are identical with those of IPF. Most of the analyzed asbestos fibers were chrysotile with not enough AB formation to call it asbestosis [66].

Many epidemiologic studies have reported the risk factors of IPF as being male, smoking, having a specific occupation (with exposure to wood dust, metal dust, sand/silica, mining, engineering, agriculture, animal dust, and others), or hobby (raising birds and others) [67–73]. These data suggest that IPF can be triggered by various inciting agents in genetically susceptible persons. Investigation into genetic risk factors such as telomere length and the *Muc5B* rs35705950 promoter polymorphism is now underway [74–78].

Schematic relationship between asbestos exposure
and diffuse pulmonary fibrosis

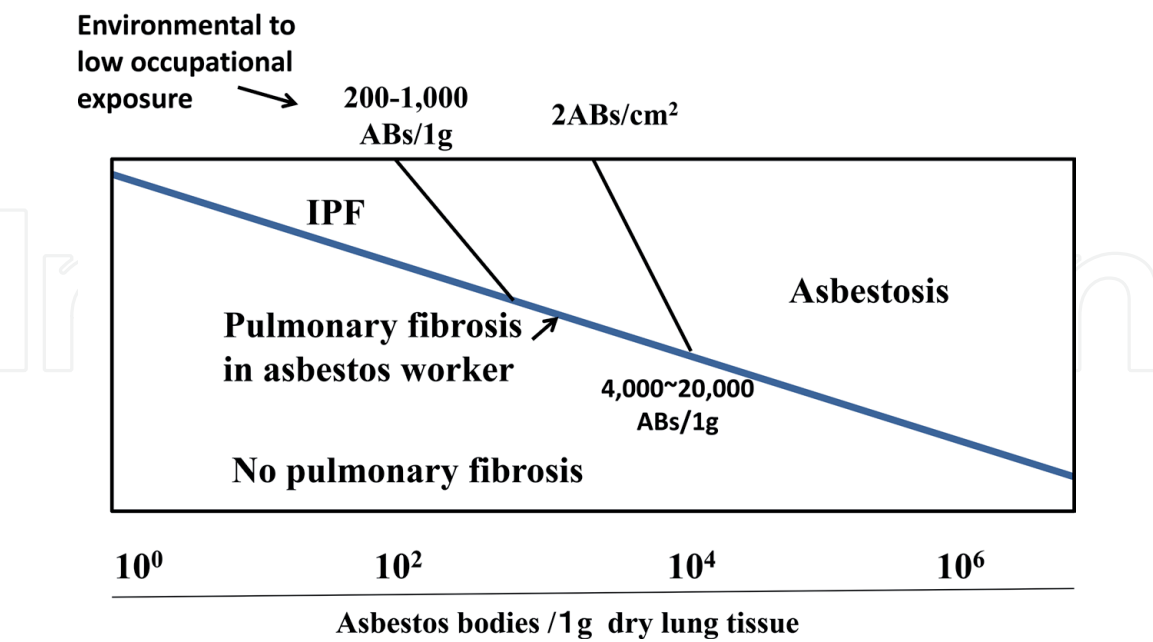


Figure 4.
Schematic of the suspected relationship between asbestos exposure and diffuse pulmonary fibrosis. By increasing asbestos exposure, the frequency of diffuse pulmonary fibrosis increases proportionately. When more than 2 asbestos bodies (ABs)/cm² are found histologically, this fibrosis can be termed asbestosis. When ABs in the digested lung are present between environmental and low occupational levels (200–1000 ABs/g) and less than 2 ABs/cm², this fibrosis can be termed idiopathic pulmonary fibrosis (IPF) when no cause is found. The boundary between asbestosis and IPF can be called “pulmonary fibrosis in asbestos workers.”

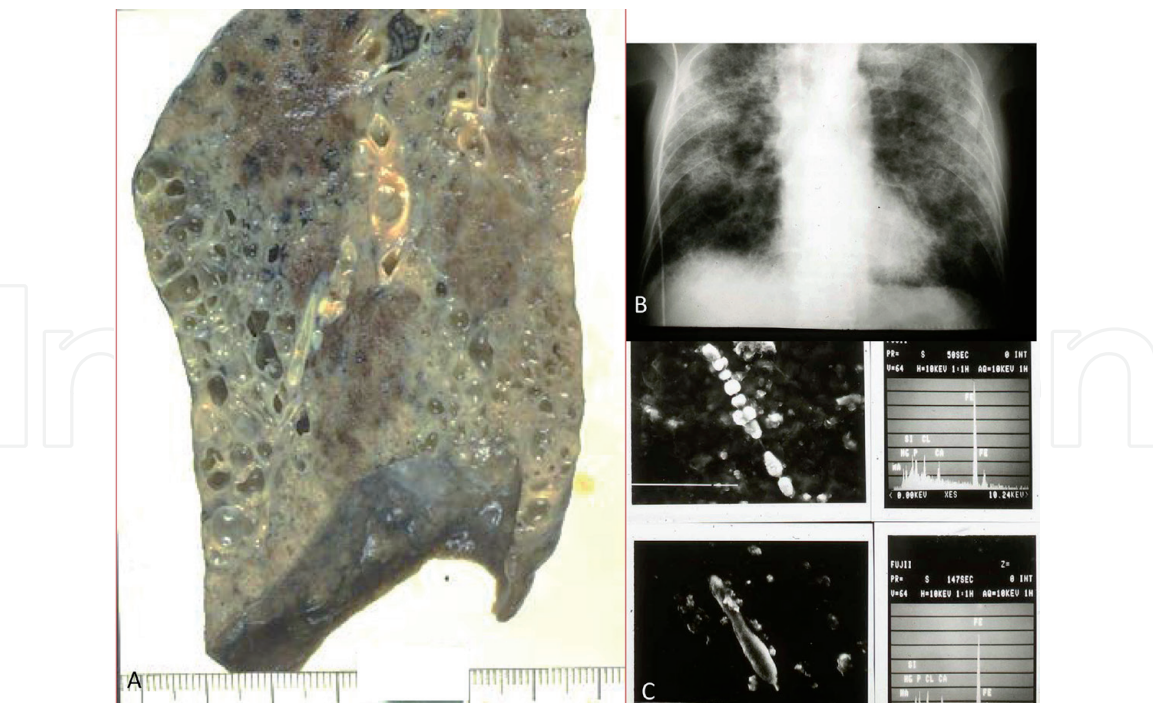


Figure 5.
Radiological and pathological features of an asbestos exposed worker that does not fulfill asbestosis criteria. A case of pulmonary fibrosis in a 73-year-old male asbestos worker who visited a hospital because of acutely progressive dyspnea. Clinically, this case was diagnosed as acute exacerbation of IPF. Usual interstitial pneumonia (UIP)-type fibrosis and pleural and pericardial plaques were found at autopsy. He had worked several months at a shipyard 40 years ago during war time. The number of asbestos bodies (ABs) was 740/g dry lung. Macroscopic features are typical for UIP with clear subpleural honeycombing in the right lower lobe, and no pleural fibrosis or adhesions were found. Plain chest X-ray showed diffuse infiltrative pulmonary shadows bilaterally. Typical (upper left) and atypical ABs (lower left) were found, but these were almost all composed of chrysotile as confirmed by energy-dispersive X-ray analysis (right).

6. UIP seen in various diseases

Various diseases cause UIP including various pneumoconioses, chronic hypersensitivity pneumonitis, and collagen vascular diseases. Histological features of pneumoconiosis are characterized by bronchiolocentric fibrous nodule formation predominantly in the upper lobes. Arakawa et al. reported a prevalence of chronic interstitial pneumonia in 243 pneumoconiosis cases of approximately 12% on CT, and three fourths of these cases showed a typical IPF pattern. Pathological data obtained by autopsy or lobectomy in 11 cases indicated UIP [79]. The prevalence of chronic interstitial pneumonia among pneumoconiosis cases is 10–20% [80–82]. Arakawa et al. reported that the earliest CT abnormalities (faint ground-glass opacity or coarse reticular opacity) of 14 cases appeared at the lung bases and then fibrosis progressed to honeycombing over a median period of 12.1 years in the silica-exposed patients, with autopsy in 8 cases confirming a diagnosis of typical UIP [83]. Generally, latent periods from occupational exposure to disease onset are quite long [79–83]. Occasionally, hard metal lung disease appears as UIP when the degree of exposure has been mild [84]. Histological features of acute and subacute hypersensitivity pneumonitis are characterized by bronchiolo-alveolitis with loose granulomas diffusely spread throughout both lungs. In contrast, most chronic hypersensitivity pneumonitis shows UIP pathologically, with points of differentiation from that of IPF being the presence of bronchiolitis, peribronchiolar fibrosis

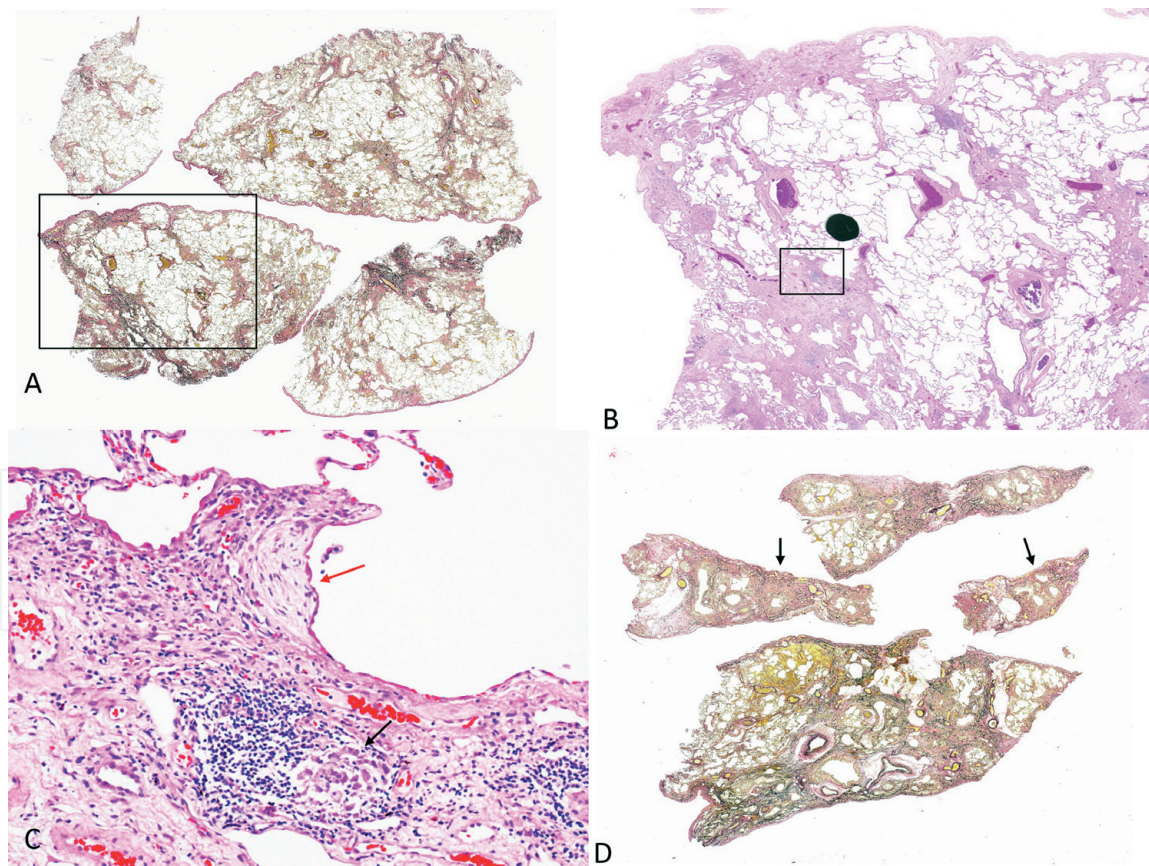


Figure 6.

Histology of chronic hypersensitivity pneumonia. A 66-year-old woman who had been breeding birds developed progressive dyspnea. Specific antigen for pigeon was markedly elevated. Surgical lung biopsy was performed from the left lingula and S8 (case from the Department of Respiratory Medicine, Kobe City Medical Center West Hospital). A panoramic view of the lingula showed mainly subpleural dense fibrosis. Elastica van Gieson staining (EvG). Patchy dense fibrosis was noted mainly in the subpleural area and peripheral lobular areas (next to an interlobular septum by EvG) of the lung. Box in A: hematoxylin and eosin (HE), $\times 40$. A clear fibroblastic focus was noted at the edge of the dense fibrosis (red arrow), and one loose granuloma was seen in the fibrosis (black arrow). Box in B: HE, $\times 200$. Panoramic view of the S8 showing subpleural dense fibrosis and honeycombing (black arrow). EvG.

or centrilobular fibrosis, bridging fibrosis, epithelioid cell granuloma, and giant cells [85–87]. Still, it is impossible to think of UIP as an extension of respiratory bronchiolar lesions as UIP begins within the subpleural peripheral lung. Typical histological features of chronic hypersensitivity pneumonitis are shown in **Figure 6**. Recently, telomere-related gene variants were reported in chronic hypersensitivity pneumonitis [88]. UIP is the one of the major pulmonary complications in cases of collagen vascular diseases, especially in rheumatoid arthritis (RA). As with IPF, the prevalence is higher in smokers and males [89]. UIP in RA shares a number of radiological and histopathological features with IPF [90–92]. An additional histological feature of UIP in RA is frequent germinal center formation [93]. RA-related UIP also begins within basal, subpleural peripheral areas as does IPF. Recently, the *MUC5B* promoter variant was reported in RA-related UIP [94].

7. Conclusion

Moderate to severe exposure to asbestos causes asbestosis. However, there are a number of cases of UIP in asbestos workers or high-grade environmentally exposed people that do not fulfill the Helsinki criteria. The susceptibility to asbestos exposure varies. UIP-type grade 4 asbestosis begins within the basal, subpleural peripheral areas as do cases of IPF, other pneumoconioses, chronic hypersensitivity pneumonitis, and RA. The suspected relationship between asbestos exposure, numbers of exposed persons, and the development of diffuse pulmonary fibrosis is shown in **Figure 7**. Cases of diffuse UIP with less than 200–1000 ABs/g dry lung

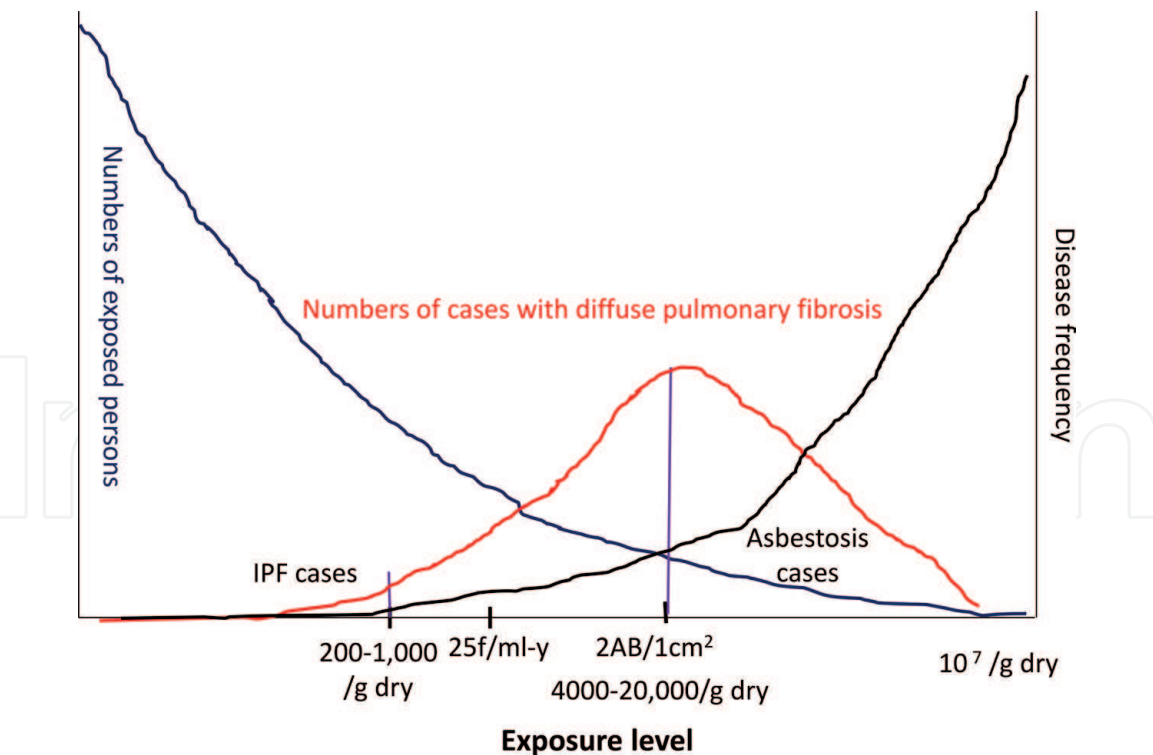


Figure 7. Schematic of suspected cases of diffuse pulmonary fibrosis related to asbestos exposure. The black line is the suspected dose-response curve related to the degree of asbestos exposure and disease frequency. The lower line indicates the degree of asbestos exposure, with 200–100/g dry lung indicating higher than the environmental or low occupational exposure level, 25 f/mL-y indicating the beginning of the asbestosis level, and 2 asbestos bodies/cm² or 4000–20,000/g dry lung indicating the beginning of the grade 4 asbestosis exposure level. The blue line indicates the numbers of people exposed. The red line indicates the numbers of diffuse pulmonary fibrosis. Disease in patients with less than the low occupational level can be called idiopathic pulmonary fibrosis, whereas that in patients between the low occupational exposure level and grade 4 asbestosis exposure level can be called diffuse usual interstitial pneumonia seen in asbestos workers (or a high-grade environmentally exposed person).

can be called IPF when there is no other etiology. Diffuse interstitial fibrosis with more than 2 ABs/cm² can be called grade 4 asbestosis. There might be significant numbers of cases of diffuse interstitial fibrosis that lie between IPF and grade 4 asbestosis, and these cases can be called diffuse interstitial pneumonia seen in asbestos workers or high-grade environmentally exposed persons.

I hope future more genetic research can reveal the phenotypes that can acquire diffuse pulmonary fibrosis through mild occupational and environmental exposure to dust.

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Conflict of interest

The author declares no conflicts of interest and no funding disclosures.

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